CLINICAL INVESTIGATION PLAN

A first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma undergoing non-penetrating glaucoma surgery

Reference Number: ARGOS-SC01

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Release Date:	June 25, 2019
Sponsor:	Implandata Ophthalmic Products GmbH Kokensstrasse 5 30159 Hannover Germany

Sponsor Signature Page

ARGOS-SC01

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ARGOS-SC01

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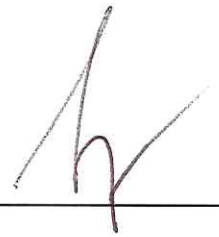
Prof. Dr. med. Peter Szurman



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Investigator Signature Page

ARGOS-SC01

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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.

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SYNOPSIS

Title	A first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma undergoing non-penetrating glaucoma surgery
Study Number	ARGOS-SC01
Sponsor	Implandata Ophthalmic Products GmbH
Name of IMD	**ARGOS-SC System** The ARGOS-SC system is a non-CE marked investigational medical device composed of the implant and its accessories: **Implant**: ARGOS-SC pressure sensor implant for suprachoroidal placement **Accessories:** MESOGRAPH reading device, telemetric Multiline Connector
Intended use	The sensor device is intended to be permanently implanted in the human eye and used in conjunction with the hand-held MESOGRAPH reading device to telemetrically measure the intraocular pressure (IOP) of the implanted eye.
Indication for use	Patients with glaucoma and scheduled for non-penetrating glaucoma surgery
Study Purpose	The purpose of this study is to evaluate both the safety and feasibility of the surgical implantation of the ARGOS-SC implant during non-penetrating glaucoma surgery and the safety and usability of the ARGOS-SC implant and system in the year following the implantation.
Study Design	This study is designed as a prospective, open-label, multicenter, single-arm clinical investigation. Subjects will be followed up at regular intervals for one year following implantation to collect safety and performance information. Enrollment will be halted at every serious adverse device event (SADE).
Sample Size Considerations	The sample size calculation was based on the study's dual purpose of establishing safety and comparability of IOP measurements with the ARGOS-SC system to those made with GAT and DCT. IOP measurements will be made with all devices at various time points, resulting in a within individual control for IOP variables. Based on these calculations (performance, safety) and considering possible drop-outs, the exploratory investigation will enroll 24 patients. The minimum number of measurements required to hold the performance claim is approx. 120. With multiple (>8) measurements with either method (ARGOS, GAT) per patient, a sufficient number of paired measurements (in total >>120 measurement pairs) will be available to show equivalence of the methods (primary objective)[2].

Subject Population	Patients with glaucoma who are scheduled to undergo non-penetrating glaucoma surgery.
Study Objectives	**Primary Objective** **Performance** To evaluate the limits of agreement between measurements with Goldmann Applanation Tonometry (GAT), Pascal Dynamic Contour Tonometry (DCT) and the ARGOS-SC system in the 12 months following implantation **Secondary Objectives** **Safety** To evaluate the safety and tolerability the ARGOS-SC pressure during implantation and throughout a 12 months follow-up period. **Performance** To evaluate the performance of the ARGOS-SC system up to 12 months after implantation
Patient Selection	**Inclusion Criteria** Eligible subjects must meet all the following inclusion criteria: 1. Subjects able to understand the informed consent and willing to participate as evidenced by providing informed consent. 2. Patients aged ≥ 18 on the day screening Female subjects of childbearing potential (not surgically sterilized or more than one year post-menopausal) must have a negative pregnancy test (urine beta-hCG) within 24 hours prior to ARGOS-SC pressure sensor implantation. 3. Diagnosis of open angle glaucoma requiring a non-penetrating glaucoma surgery (NPGS). The medical indication for a non-penetrating glaucoma surgery 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 non-penetrating glaucoma operation. 4. 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 prior to implantation: 1. Contraindications for a non-penetrating glaucoma surgery

- Neovascular glaucoma, primary and secondary angle closure glaucoma
- Condition after previous glaucoma incisional surgery
- IOP > 40 mmHg

2. Myopia (> -6 dpt) or hypermetropia (> +4 dpt)
3. Axis length < 22 mm or > 26 mm
4. Patient with single eye vision (monovision)
5. Exudative age-related macular degeneration, instable macular degeneration 30 days prior to inclusion, or macular edema
6. Acute retinal detachment
7. Uncontrolled Diabetes Mellitus (DM) with manifestation of moderate to severe non-proliferative diabetic Retinopathy (DR) or proliferative DR.
8. History or evidence of severe active inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-SC implantation
9. Ocular surgery procedure(s) (excluding selective laser trabeculoplasty and peripheral iridotomy) within 6 months (cataract surgery within 3 months) prior to ARGOS-SC implantation in the study eye that can affect the assessment of IOP by Goldmann Applanation tonometry
10. Ocular disease other than glaucoma that may affect assessment of visual acuity and/or IOP by Goldmann Applanation tonometry/Pascal Dynamic Contour Tonometry (e.g. choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy)
11. Existence of other active medical eye implant and/or other active medical implants in the head/neck region
12. Difficulties or complications during NPGS procedure or implantation of ARGOS-SC sensor, as assessed by surgeon (e.g. perforation of trabeculo-descement's membrane; excessive aqueous filtration through TDM leading to shallow anterior chamber; excessive bleeding; choroidal detachment)
13. Severe generalized disease resulting in a life expectancy shorter than a year
14. Currently pregnant or breastfeeding
15. 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
16. Patients who are not suitable for the study based on the surgeon's evaluation (e.g. patients affected by Parkinson's disease or essential tremor)
17. Patients unable or unwilling to understand or comply with required study procedures
18. Patients with psychiatric disorders influencing their judgement or autonomy

	19. 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. 20. 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> • Vision-related Quality of Life (VQoL) questionnaire • Visual acuity (ETDRS) • Perimetry • Concomitant medication • External eye photography <u>Anterior segment</u> • Optical coherence tomography (OCT) of cornea and anterior chamber • Slit lamp biomicroscopy • Gonioscopy <u>Posterior segment</u> • Slit lamp biomicroscopy • Optical coherence tomography (OCT) of macula and optic nerve • Fundus photography <u>IOP measurements</u> • Goldmann Applanation tonometry (GAT) • Pascal Dynamic Contour Tonometry (DCT) (if available) **<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 non-penetrating glaucoma surgery with ARGOS-SC pressure sensor implantation

	and standard clinical procedures. If it becomes apparent during the surgery that the subject is not a suitable candidate for the ARGOS-SC pressure sensor implant, the subject will be removed from the study and returned to standard of care. At Visit 01, data will be collected regarding: General • Implantation procedure questionnaire (surgeon) • AE/ADE/SAE/SADE/UADE • Concomitant medication • Device deficiency **Follow-up (V02 to V09)** The follow-up period after surgery will consist of 8 visits (Day 1 until Day 360). 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 • VQoL questionnaire (V06, V07, V09) • Visual acuity (EDTRS) • Perimetry (V06, V07, V09) • External Eye Photography (V04-V09) • Heidelberg Engineering ANTERION® (location of ARGOS-SC)(V04-V09), if available • User acceptance questionnaire (investigator) (V09) • User acceptance questionnaire (patient) (V09) • AE/ADE/SAE/SADE/UADE • Concomitant medication • Device deficiency Anterior Segment • Slit-lamp biomicroscopy • Optical coherence tomography (OCT) of cornea and anterior chamber (V04-V06) • Gonioscopy (V06, V07, V09) Posterior segment • Slit lamp biomicroscopy

	• Optical coherence tomography (OCT) of macula and optic nerve (V06, V07, V09) • Fundus photography (V06, V07, V09) <u>IOP measurements</u> • GAT • Pascal DCT (V05-V09) (if available) • ARGOS-SC system measurements • <u>Optional:</u> 24-hours measurements inpatient with ARGOS-SC and GAT (V06, V07, V09) • ARGOS-SC system self-measurement at home
Data Analysis and Statistics	**<u>Primary Endpoint</u>** **Performance** - Level of Agreement between measurements made using GAT, Pascal DCT and the ARGOS-SC system from V02 (day 1) through V09 (day 360). **<u>Secondary Endpoints</u>** **Safety** - Number of patients experiencing a device-related SAE (SADE) at any time during implantation and in the first 12 months (Day 0 to Day 360) following it - Incidence, nature, severity and seriousness of observed adverse events and adverse device events at any time during implantation and in the 12 months following it **Performance** - Repeatability of the ARGOS-SC measurement - Incidence, nature and seriousness of observed device malfunctions during implantation and in throughout a 12 months follow-up period. **Utility** - User acceptance of the ARGOS-SC implantation procedure by means of evaluation of implantation procedure questionnaires (investigators) - User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of patient acceptance questionnaires (by investigators) - User acceptance of the ARGOS-SC system at home by means of evaluation of patient acceptance questionnaires (patients)

	- Daily IOP self-measurement profiles (patients) **Definition of the analysis populations** The safety population comprises all subjects for whom ARGOS-SC pressure sensor implantation was attempted, whether or not the implantation was successful. The Per Protocol Set (PPS) will comprise all subjects in whom an ARGOS-SC pressure sensor was successfully implanted and for whom the full data set including IOP measurements made in the clinic and safety data according to protocol are available until 3 months (Visit 6) after surgery. **Statistical analysis** **Safety analysis** AEs, SAEs, ADEs and SADEs will be listed and analyzed by descriptive and explorative statistical methods. **Performance analysis** The probability distribution of the difference of the paired measurements grouped within 1 mmHg will be compared to the primary objective of the accepted 70% of the measurements to agree between +/- 5 mmHg. **Interim analysis** An interim analysis will be conducted to assess safety and performance after the last patient has completed the 6 months follow up visit.
Safety Monitoring	A Data Safety Monitoring Board (DSMB) will be established prior to enrollment of the first patient. The DSMB will review the safety data, including SAEs/SADEs, on a regular basis and will advise on any changes required in the conduct of this clinical investigation.
Data Collection	Data will be collected using a Case Report Form (CRF).
Study Duration	The overall study duration for each individual subject is up to 13 months. Subjects will undergo screening a maximum of 28 days prior to surgery and will be followed for 12 months afterwards. The overall recruitment period is expected to last a maximum of 12 months. At the start of the study, all patients enrolled in Switzerland will be requested to sign up for an additional follow-up of 2 years. These patients will automatically transition to the ARGOS-SC_Follow-up. The estimated total duration of the study from first patient screened to last patient last visit is 25 months.

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2. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
α	Type I error
ADE	Adverse Device Effect
AE	Adverse Event
AS	Anterior Segment
ASADE	Anticipated serious adverse device effect
ASIC	Application specific integrated circuit
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMO-MRW	Minimum rim width at Bruch membrane opening
CIP	Clinical Investigation Plan
D	Day
dB	Decibel
DCT	Dynamic contour tonometry
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
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
GSM	Global System for Mobile Communications
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
LAL	Limulus amebocyte lysate
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
NPGS	Non-penetrating glaucoma surgery
OCT	Optical coherence tomography
OU	Oculus uterque
P	Pressure or statistical significance
PIC	Patient informed consent
PS	Posterior Segment
RA	Regulatory Authority
Rev.	Revision
RNFL	Retinal Nerve Fiber Layer Thickness
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Suprachoroidal
SDV	Source Data Verification
T	Tesla
TDM	Trabeculo-descement’s membrane
TMF	Trial Master File
V	Visit
VQoL	Vision-related quality of life
USADE	Unanticipated serious adverse device effect

3. BACKGROUND INFORMATION

3.1 Nature and Incidence of Glaucoma

An estimated 1 in 40 adults over the age of 40 has glaucoma, a group of conditions characterized by a progressive thinning of the retinal nerve fiber layer of the optic nerve head and the neuroretinal rim that appears as a central depression in the optic disc. Glaucoma leads to loss of visual field and if not controlled in end-stage disease, also to blindness, of which it is the second most common cause worldwide [4–6]. In open angle glaucoma (OAG), which accounts for approximately 70% of the glaucoma cases seen, aqueous outflow from the eye is restricted, most likely due to increased resistance in the trabecular meshwork.

3.2 Treatment Options

Glaucoma treatment

Glaucoma often remains asymptomatic until late in the disease, when irreversible vision problems and vision field restriction become evident. Although it may be present with normal intraocular pressure (IOP), the higher the IOP, the more rapidly the damage progresses [4]. Reduction of IOP is the only known treatment to prevent visual disability in the patient's lifetime [6]. Lowering the IOP of patients with OAG by 20 to 40% can halve the rate of progressive nerve fibres damage [4]. However, the chronic nature of OAG necessitates a lifelong treatment.

Governed by the ultimate treatment objectives of maintaining quality of live and quality of vision while containing costs, treatment guidelines recommend a progression from single topically administered medications (prostaglandin analogues, beta blockers, carbonic anhydrase inhibitors, sympathomimetics and/or miotics) to combinations thereof, to laser therapy with or without medications to surgery, again with or without medications, to reduce IOP to an acceptable target range [7].

Surgical treatments expand the natural outflow pathway or create alternative routes for aqueous humor to drain from the anterior chamber. In deep sclerectomy, an intrascleral space is created by removing a lamellar band of the sclera, to expose the trabeculo-Descemet's membrane. The intrascleral space acts as an aqueous reservoir and as a filtration site. In viscocanalostomy, a high-viscosity sodium hyaluronate is additional injected left and right to the surgical incision in the

Schlemm's canal to improve the aqueous drainage by this route whereas in canaloplasty, a recent and more reproducible variation viscocanalostomy, the Schlemm's canal is dilated along its entire length utilizing a flexible microcatheter, and additionally tensioned by suture material [8].

If surgery alone is not sufficiently effective, use of IOP lowering medications is generally resumed and doses increased as needed to attain target IOP. However, these medications frequently cause systemic side effects that may be severe and can have a greater immediate impact on patients' quality of life than OAG itself (NICE). Consequently, there is a need to reduce medication use to the minimum needed to maintain the target IOP.

IOP measurement

Ensuring maintenance of target IOP is adequate requires frequent monitoring using a tonometric device. There are a number of tonometric devices on the market, of which the Goldmann Applanation Tonometer (GAT), which was first described in the 1950's, is considered to be the gold standard to which all others are compared.

The accuracy of most of these devices is limited to the degree that the secondary biometric parameters they measure, principally the force needed to applanate a section of the cornea or sclera, are affected by factors other than IOP, such as corneal thickness [9]. 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, in effect limiting 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 [10]. 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 [5, 11].

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

3.3 Advantages of Experimental Treatment

The ARGOS-SC system that is the subject of this investigation is anticipated to provide a feasible solution to these problems. It is a multicomponent system consisting of the ARGOS-SC device, an intraocular pressure sensor that is intended to be permanently implanted in the patient's suprachoroidal space during the non-penetrating glaucoma surgery, and the MESOGRAPH, an external handheld reader that powers and interrogates the ARGOS-SC implant telemetrically. Because the sensor itself is in direct contact with the choroid, it measures IOP directly from the vitreous throw the force on the choroid, without interference from either the cornea and sclera, or physical contact with the external eye. The device is easy to use, permitting patients or their immediate caregivers to measure IOP themselves in the home setting several times per day. The IOP measurements so obtained are stored in the Mesograph memory and can be accessed by the treating ophthalmologist, either directly from the Mesograph during patient visits or between visits when uploaded by the patient using the accessory Multiline Connector to a central database. The implantation itself, as a part of the non-penetrating glaucoma surgeries, doesn't elongate or complicate the surgery itself, as many other implantation procedures for IOP sensors do. Therefore, the sensor gives extra benefit with multiple feasible IOP-measurements without creating and extra risk for the patient by extended operating times and special implantation entrance or manipulation.

The related EYEMATE-IO system, which is implanted in the sulcus and received CE-mark approval in 2017, has been shown to effectively measure IOP in glaucoma patients who underwent cataract surgery [12], with an accuracy comparable to that of GAT.

Although developed using the same materials and technology as the EYEMATE-IO, the form and location of placement of the ARGOS-SC differ sufficiently to require independent clinical investigation. The present investigation, which is the first-in-human, will test its use in patients with glaucoma undergoing concurrent indicated NPGS. If shown to be safe and accurate, it is anticipated that the ARGOS-SC system will permit a detailed tracking of IOP levels in this patient population, thereby facilitating timely adjustments medication while at the same time, ultimately reducing the number of control visits required of patients.

The purpose of this clinical investigation, which will follow up all patients who receive an ARGOS-SC device for 12 months after implantation, is to determine the safety of implantation of the ARGOS-SC in conjunction with a non-penetrating glaucoma surgery, as well as to explore the agreement of the IOP measured with ARGOS-SC system and GAT and DCT (dynamic contour tonometry).

4. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

4.1 Summary description of the investigational device and its intended purpose

The ARGOS-SC system was developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor of the human eye (IOP, intraocular pressure). It is made up of two components: the ARGOS-SC implant and the external hand-held Mesograph reading device (with the later one already carrying CE mark as an accessory for the EYEMATE-IO posterior chamber IOP sensor implant). An additional component, the Multiline connector, can be used by the subjects between study visits to upload recorded measurement data from the Mesograph reading device to a secure centralized database that can be accessed by the investigator.

The ARGOS-SC implant is comprised of a micro-electromechanical system (MEMS) application specific integrated circuit (ASIC) bonded to a micro-wire wound coil of gold and encapsulated in a special silicone-rubber material that has been extensively proven to be well tolerated by the eye when silicone intraocular lenses (IOL) were still popular. It is intended to be implanted during otherwise required ocular surgery and to remain in place indefinitely. In the ARGOS-SC01 study, the implant will be introduced into suprachoroidal space of the eye during non-penetrating Glaucoma surgery, using the associated surgical access.

Activation of the Mesograph reading device in the near vicinity of the eye establishes an inductive link between the reader and the micro-coil. This induces a slight current in the otherwise electrically passive implant, supplying it with power and permitting data transmission. Pressure-sensor cells and an A/D converter incorporated in the ASIC measure IOP and the digitized data is then transmitted to the reader. Data is stored in non-volatile memory inside the reader device, preventing data loss in case of an error, and can be uploaded to a computer, or to an internet-based database through the Multiline connector.

Because the ARGOS-SC pressure sensor is implanted such that its pressure sensitive membranes are in unobstructed hydraulic contact with the interior of the eye, it measures IOP directly, without interference from corneal properties or examiner skill. This 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. This will provide an accurate, reproducible method of measuring IOP in Glaucoma patients that can be performed frequently without requiring more frequent clinic visits.

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

The ASIC and micro-wire wound coil components of the implant are hermetically encapsulated in a biocompatible silicone-rubber material (Nusil MED-6820) that has been extensively proven to be well tolerated by the eye when silicone intraocular lenses (IOL) were still popular, and with the EYEMATE-IO family of implants that received CE mark approval in May 2017. 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.

The ASIC itself contains silicon, silicon dioxide, silicon nitride, gold, and traces of aluminum, titanium, phosphorus, arsenic, borium, polyimide and tungsten-titanium, all of which have been previously used in ocular implants. Detailed risk assessments commissioned by the sponsor determined that, even in the event of a breach of the silicone barrier, none of the materials comprising the implant pose any risk of an adverse biological effect to the patient [13]. Cytotoxicity and chemical analyses of extracts obtained from final sensors detected no organic or inorganic leachables above the lower limit of quantification and no evidence that the sensors contained or would release any residues/contaminants in toxicologically relevant concentrations during clinical application [14]. Above described testing has been performed using EYEMATE-IO devices, which are technically equivalent to ARGOS-SC, with the exception of the telemetry coil being integrated within the electronic module (not patient contacting), which is a three-dimensional micro-wire wound coil instead of a galvanically

etched planar microcoil. The micro-wire has been tested to be non-cytotoxic according to EN ISO 10993-5. See the Investigator's Brochure for more information.

The implant is designed to be seated firmly within a surgically created artificial cyst between the inner layers of the sclera and the choroid. After healing, the cyst is tightly enveloping the implant, being no larger than necessary. Relative to the eyeball, the implant will be situated between the limbus and the equator of the eye, in a 12 o`clock position, hidden under the upper eyelid.

For non-penetrating Glaucoma surgery, a scleral flap and a smaller "scleral lake" are prepared down to or almost down to the choroid. A hyaluronic acid-based viscoelastic (e.g. Healon OVD, Abbott Medical Optics Inc.) will be injected using an atraumatic cannula, to separate the sclera from the choroid, which additionally serves as a safeguard against injuries of the surrounding tissue. The viscoelastic will be resorbed within a few days or weeks after surgery. A special designed implantation forceps padded with silicone coatings (Implandata Ophthalmic Products GmbH, Germany) facilitates the implantation and protects the ARGOS-SC implant from damage through mechanical irritation. The device will be implanted into the suprachoroidal space by pushing it gently through the scleral opening into the suprachoroidal space/the volume of viscoelastic material.

The back side of the implant that is interfacing with the innermost layer of the sclera has a spherical shape with a dihedral angle matching the average eye, which will ensure, together with the intraocular pressure acting onto the uveal layer, a firm seat of the implant within the newly created suprachoroidal space. The profile and thickness of the implant are minimized and its edges tapered and rounded to avoid causing trauma or damage to surrounding tissue even with direct long-term contact, and to minimize open space for deposition of fibrous material. The choroidal interface of the implant, which contains planar pressure sensor cells, is planar and slightly indenting the uveal layers, minimizing the risk of choroidal detachment. The indentation is necessary to remove all mechanical stress from the area covering and surrounding the pressure sensor cells, in order to facilitate the unobstructed translation of the mechanical force components induced by and directly proportional to the intraocular pressure.

Manufacturing, testing, cleaning, packaging and labelling process are carried out under monitored clean room conditions following international standards by ISO 13485 Implandata Opthalmic Products

GmbH itself or a certified contract manufacturer. Each implant is packaged in multiple protective layers: the implant is first wrapped in sturdy Tyvek and placed in a small plastic box, and then packaged in two SteriClin sterilization bags, in conformance with EN ISO 11607-1:2006. Labels identifying each individual implant are located on the inner SteriClin bag as well as on the outer layer. Following packaging, the implant are sent to another contract manufacturer where they are sterilized with ethylene oxide using processes validated according to AAMI TIR 28:2009 and ISO 11135-1:2014. Prior to release, samples from each batch undergo testing Limulus Amebocyte Lysate (LAL) testing using the gel clot method (United States Pharmcopeial Convention Procedure UPS 85) to detect any residual bioburden or endotoxins [15].

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.

4.4 Device and accessories identification

Each ARGOS-SC 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 can 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 subjects, 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 1 year under temperature conditions ranging from +5° C to +25° C.

4.6 Necessary training and experience requirements

It is assured that ophthalmic surgeons performing the surgery will be adequately trained on the ARGOS-SC 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

- The ARGOS-SC device will only be implanted by ophthalmic surgeons who are experienced in performing the non-penetrating glaucoma surgery and who have been familiarized with the handling and implantation of the sensor either through instruction by Sponsor representatives or by intensive consultation of the Implant Instruction for Use (IFU) [16].

Intraocular pressure measurement using the Mesograph Reading Device

- Intraocular pressure (IOP) measurement with the ARGOS-SC system may be carried out by any trained individual, including patients and care givers. Health care professionals will be trained by sponsor representatives or their delegates. Prior to hospital discharge following surgery, trial staff will instruct subjects on the use of the reading device for IOP self-measurement. Subjects will also be given separate written handling instructions provided by the Sponsor.

Setup of Mesograph and downloading of measurement data

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

Evaluation of data

- The data obtained by the ARGOS-SC system measurement will only be used for the evaluation of the trial outcome. Diagnosis, therapeutic assessments and decisions about additional medical treatments will be based primarily on IOP measurements made with the tonometry method(s) conventionally used by the investigator in this patient population. However, because study patients will perform regular self-monitoring of IOP, which is not currently possible, it is conceivable that detection of elevated IOP levels by the patients may lead to more frequent unscheduled visits.

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

Detailed implantation instructions are presented in the Instructions for Use (IFU) [16] and the Investigator's Brochure (IB) [17] and in Section 8.3.14 Surgery of this CIP.

Following completion of the IOP lowering portion of the non-penetrating glaucoma surgery, hyaluronic acid-based viscoelastics such as Healon OVD (Abbott Medical Optics Inc.) are used to separate the sclera from the choroid. The scleral flap is enlarged or an additional small incision made next to it to ensure a final flap width of at least 3.2 mm to 3.5 mm. The ARGOS-SC sensor is then gently pushed through the opening into the suprachoroidal space with the "pressure sensing side" of the ASIC facing the eye.

4.8 Pre-clinical testing/assessment

4.8.1 In vitro/Bench/Lab testing

4.8.1.1 First study in human cadaver eyes

On July 18, 2013, Prof. Szurman implanted 3 early ARGOS-SC demonstrators into 2 adult human cadaver eyes, using different methods and orientations of the implant.

As an initial effort to determine the required form factor for the implant, non-functional demonstrators were implanted into human cadaver eyes by Prof. Dr. med. Peter Szurman at Knappschaftsklinik Sulzbach [18]. The size of the demonstrators was about 7.5mm x 3.5mm x 1mm, and Prof. Szurman used a surgical approach where he opened the conjunctiva with a small incision in an oblique quadrant, and then prepared a laminated scleral incision with a width of about 4mm, about 2mm posterior of the limbus. All implants were easily inserted radially; one implant was turned 90° for a horizontal position parallel to the limbus. Eyes were sectioned in half, and the position of the implants underneath the choroid was inspected. All implants were securely positioned, without any sign of tissue damage, with a position starting from about 1mm anterior of the ora serata. In posterior direction, none of the implants reached the equator of the eye. Prof. Szurman determined that a pressurized vitreous body would secure the implant in place, securely preventing implant migration.

The bulbi were fixated in formalin, and sent for histology preparation in a special cutting-grinding technique to preserve the structure of the implanted structure. Macroscopic findings and histology results were assessed [19] and did not reveal any compromise to the eye's integrity, with the sclera (apart from the surgical wound) and especially the choroid being fully intact.

4.8.1.2 Functional Testing in Porcine Eyes

On April 26, 2013, a fully functional ARGOS-SC demonstrator was implanted in the suprachoroidal location as proposed by Prof. Szurman. Measurements showed very good concordance compared to water column and an electronic pressure gauge (both connected to anterior chamber using a 20G Lewicky anterior chamber maintainer through a tightly sealed off paracentesis), with an R2 of 0.99 or better. Results have been documented in [20].

4.8.1.3 Validation of implantation method/approach and validation of approach for surgical removal of implant in human cadaver eyes

On August 21, 2017, in an effort to develop/validate the surgical approaches for implantation, and, if necessary, explantation, have been performed by Prof. Peter Szurman and Dr. Sigfried Mariacher at Knappschaftsklinik Sulzbach in human cadaver eyes came from local eye bank. As in all prior experiments, it was easily possible to insert the implant through a full thickness scleral cut of about 4.5mm width, after preparing the surgical site in the same was as done throughout the pre-clinical studies; in a second approach, the implant was placed as it will be during non-penetrating glaucoma surgery. A superficial scleral flap was created measuring about 5.5 mm (lateral) by 5 mm (anterior-posterior). Due to the missing corneoscleral button (eyebank eyes), the anterior flap ended at the rim of the front hole of the globe. A 3 mm (wide, lateral) by 2 mm (anterior-posterior) deep scleral lake was then created within the borders of the superficial flap, dissecting down to the choroid. Hyaluronic acid was injected to form a cavity between the sclera and the choroid (towards the equator of the eye). The implant was easily inserted into its in-situ position, through the deep scleral lake, without any widening if the incision. The rounded sclera facing side of the implants fits the inner shape of the bulbus well.

4.8.1.4 Functional Testing

Accuracy, precision and long-term stability of measurement are being tested using the same processes that have been implemented for the CE marked EYEMATE-IO system. As ARGOS-SC is based on the exact same technology as EYEMATE-IO, it can be expected that the long-term measurement stability data derived with EYEMATE-IO is also applicable for ARGOS-SC. We have validated this assumption by comparing the accuracy and precision data of ARGOS-SC with that of EYEMATE-IO.

Both systems have a specified 3-sigma accuracy of 2 mmHg, and an annual drift rate not to exceed 2.5 mmHg. The output value of both systems is a pressure reading in mmHg. ISO 8612:2009 -- Ophthalmic instruments – Tonometers, the international standard that is specifying the requirements for conventional tonometers measuring intraocular pressures, is specifying a tolerance of +/- 5 mmHg.

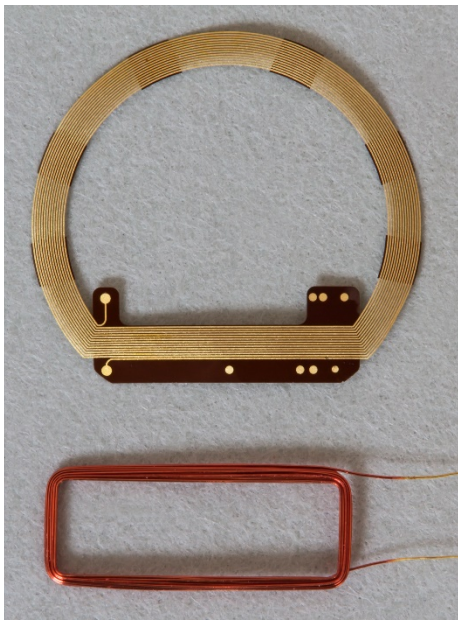
(Concordance with Goldmann Applanation Tonometry and with DCT Pascal Tonometer in human eyes is one of the objectives of this clinical investigation.)

In several test cycles, it has been shown that EYEMATE-IO devices exceed above mentioned specifications, especially long-term drift, where values below 1 mmHg/a over a time span of >10 years were accomplished in all tests that has been conducted to date.

4.8.1.5 Biocompatibility and Cytotoxicity

The outer layer composition of CE-certified EYEMATE-IO is exactly the same as for the experimental ARGOS-SC, with the exact same processing methods. The electronic modules of both devices are similar, with the exception that ARGOS-SC uses a gold wire wound antenna coil, with Polyimide as isolator, where EYEMATE-IO uses a planar, photogalvanically manufactured gold coil on a Polyimide substrate (Figure 1). From a material composition point of view, the only additional material in ARGOS-SC is a very thin layer of Polyvinylbutyral to stabilize the wire wound coil. However, the cytotoxicity profile of both electronic module variants does not differ.

Figure 1: Antenna coils of the EYEMATE-IO / ARGOS-SC pressure sensor



Top: Antenna coil EYEMATE-IO. Bottom: Antenna coil ARGOS-SC

4.8.1.6 Exclusion of possible adverse effects

Temperature Elevation (worst case estimation)

The theoretical temperature elevation of surrounding tissues due to the malfunction of the EYEMATE-IO implant was estimated for the worst-case scenario and found to be well below the acceptable limit defined in EN ISO 45502-1 and EN ISO 14708-1:2014 (section 17.1) [21]. Since the electronic modules of both devices are similar and share the same principle of power supply (and data transfer), the worst-case estimation also applies for the ARGOS-SC device.

Hazards due to RF Field Exposure during IOP Measurements with ARGOS-SC device

The risks associated with exposure of the patient to intended and unintended radio frequency fields and of the risk of interaction of the ARGOS/EYEMATE-IO, which also applies to the technical similar ARGOS-SC device, with other AIMDs were estimated based on available literature. It was concluded that:

- The risks due to exposure to heating effects and RF fields under normal use are negligible.
- Exposure of pacemakers or ICDs to the activated MESOGRAPH could interact with pacemakers and ICDs when in close proximity. The MESOGRAPH must not be activated closer than 22 cm from such devices.
- It is not known how the ARGOS-SC system will interact with cochlear implants, implantable hearing aids or implanted neurostimulators in the head/neck region. Use of the ARGOS-SC implant is contraindicated in these patients.
- The Mesograph was tested according to EN ISO 60601-1-2 and ETSI standards and should not interact with other medical devices.
- Foreign magnetic fields do not pose a risk of harm to the patient.

4.8.1.7 MRI Compatibility, Compatibility with other Implantable/Wearable medical devices

Non-clinical testing in accordance with the relevant standards (ASTM F 2052 (Displacement), F 2182 (Heating), F2119-07 (Artifacts)) by means of magnetic resonance tomography (MRT) devices on the technically similar EYEMATE-IO device demonstrated that ARGOS-SC device is “MRI conditional” (safe, but imaging artifacts likely) with a magnetic field strength up to 3 T [22]. 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.

4.8.1.8 Packaging, Cleaning, Sterilization

The packaging system used for ARGOS-SC is the same that is used for CE certified EYEMATE-IO. All packing related validation is adopted from EYEMATE-IO.

- Packaging Validation
- Cleaning Process
- Sterilization
- Manufacturing

4.8.2 In vivo Studies

4.8.2.1 Animal Studies

Prove-of-concept study: "Tübingen I"

Six ARGOS-SC telemetric pressure transducers were implanted into the suprachoroidal space of 6 eyes from 6 New Zealand White rabbits. Functionality of each device was verified 1, 4, 8, 12 and 30 weeks after implantation on May 23 and May 24, 2014. After cannulation of the anterior chamber different intracameral pressure levels were generated using a height adjustable water column. Telemetric assessed IOP and intracameral pressure were analyzed using scatter plots and Bland-Altman analysis (95% CI). Mean bias (limits of agreement) 1, 4, 8, 12 and 30 weeks after implantation was 0.14 mmHg (-2.04 to 2.31 mmHg), 0.01 mmHg (-2.83 to 2.86 mmHg), 0.62 mmHg (-2.08 to 3.32 mmHg), 0.47 mmHg (-3.04 to 3.98 mmHg) and 0.33 mmHg (-2.75 to 3.42 mmHg) respectively. A slight variability of offset and proportional bias was explained with the mechanical stress that was exerted onto the implants due to the fact that the posterior chamber of the rabbit's eye differs significantly from the larger structures of the human eyes. In rabbit eyes the anterior segment is proportional larger and the posterior segment smaller than in human eyes [23], so mechanical stress and dislocation of the implant due to altered conditions is more likely in rabbit eyes.

Ophthalmological examinations showed no signs of conjunctival, scleral, choroidal or retinal lesions. Histological analyses revealed a small band of fibrosis next to the implantation site but showed no signs of inflammation, necrosis or other pathologies. Implantable telemetric suprachoroidal pressure sensors provided promising concordance between telemetric and intracameral IOP values. Clinical and histological examinations revealed good biocompatibility 30 weeks after implantation.

Devices used for this exploratory study were technology demonstrators which outer shape was not 100% identical with the final design. The purpose of this study was to prove the long term feasibility of suprachoroidal measurement of intraocular pressure. Technically, from a sensor and material point of view, devices were identical to the final devices. The devices were of rectangular shape (Dimensions: x mm x y mm x z mm), and encapsulated in PDMS silicone polymer with rounded edges.

Devices tended to slightly extrude out of the suprachoroidal cavity towards the incision, which was addresses in a follow-up study (see below).

Biocompatibility study: "Tübingen II"

A second implantation study with 8 ARGOS-SC devices in the final design was performed at the University of Tübingen, Germany. The sensor device, ARGOS-SC was tested on local tolerance in a 6 months study in New Zealand White (NZW) rabbits. The objective of this implantation study was to evaluate possible adverse effects of ARGOS-SC device. The report [24] deals with the results of the pathology evaluation.

Testing has been carried out in lieu of DIN EN ISO 10993-6:2017-09: Although the rabbit eye is different from the human eye in many aspects, it is still the model of choice for pre-clinical testing of intraocular implants. Due to the smaller size of the rabbit eye, the implants are oversized relative to the structures of the posterior chamber. However, apart from intensified mechanical stress level between the tissue surrounding the implant and the implant itself, histology findings were assessed to be representative for implantations in humans. In our view, this test strategy if far more meaningful and significant than implanting the device into muscular tissue for a max. 12 weeks. The material the outer surface of the device consists of (Nusil MED 6820) is a well-known material for long term implantation in numerous regions of the body, including the eye. Such testing would not reveal specific issues that may be existing in direct contact with the delicate structures of the eye wall.

Purpose of this test was to assess the biocompatibility of the final design, as well as the tendency of the devices to migrate out of the suprachoroidal cavity.

Histology Findings

Images of the in-situ situation and during explantation were taken by digital microscopy (Keyence 2000). The implantation sites did not reveal any gross lesion. The implants were visible through the

overlaying tissue. In two samples (sample no. 2.2 and 4.2, right), there was distinct bubbles noted in the retina. Furthermore, on the inner eye surface, a striated tissue overlaying the implant was recorded in these samples. Histologically, these regions correlate to a partial replacement of a cyst-forming fibrotic reaction. They are deemed to represent remainders of a traumatic insult during surgery.

The histology examiner found the implant pouch (if visible on the section) to be located in all samples between choroidea and sclera. Further analysis did not reveal any indication of pathological changes in all samples. The implant was tolerated by the tissue fully. In some sample, even a fibrotic reaction was not traceable. In other samples, the fibrotic reaction consisted of an extremely thin rim of connective fibers. Only in two eyes, a few macrophages attached to the inner capsule surface were found. No other inflammatory reactions could be noted.

In three eyes, focally limited degeneration of the retina consisting of a partial replacement by a cyst-forming fibrotic reaction was noted by the histology examiner. By digital microscopy, it correlated to small bubbles and striations in the retina overlaying the implant. These findings were also assessed by the surgical team.

The surgeon performing all implantations reported difficulties forming a suprachoroidal cavity in rabbits, compared to the same task when performed in human eyes (surgeon has extensive experience in suprachoroidal implantation of Ologen implants of similar size). He presumed there are tissue adhesions between the rabbit sclera and choroidal, which he never experienced in human eyes. This is one likely explanation for the additional mechanical insult that have been reported by the histological examiner. Implantation in human eyes should be easier to perform, with significantly reduced mechanical irritation.

The reported retinal lesions may also have been caused by a reduced nourishment of retinal tissues. Similar effects can be found in cases of retinal detachment. However, since in human eyes, a large portion of the implant will be located in the pars plana region (a region without retinal coverage), and the remainder will be covered by the very peripheral retina (that portion of the retina does not contribute to the central vision of the eye).

A third factor may be the, compared to human eyes, the additional mechanical effect of the implant due to the strong curvature of rabbit eye, and the resulting short axial length: The relative size of the implant is larger compared to the rabbit eye than to the human eye.

All in all, both the implanting surgeon (Professor Dr. Peter Szurman, Chefarzt, ehemaliger Leiter der Sektion “Experimentelle Ophthalmichirurgie”Univ. Tübingen) and the histological examiner view the findings to be uncritical and most likely to be less prevalent in human eyes.

Implant integrity after explantation

Surface roughness measurements was performed on the explanted devices. No cell adhesion was observed on the implants. Overall the implants can be considered clean with minor adhesion of particles, likely fibrin. Overall the data shows very homogenous surfaces both between the defined areas within an implant as well as between different implants.

Implant migration

In one of the animals, the implant was dislocated into the vitreous cavity. Comparing the lesion of the retina from this eye, and in the absence of any further inflammatory or degenerative lesion, it is concluded that the migration took place during the necropsy/collection phase, but not during the in-life phase. The main supporting factor is the formation of a focally limited retinal alteration. In case of an in-vivo phase migration, a multifocal retinal lesion should be expected. Furthermore, the fibrotic reaction seen in both other animals are indicative for traumatic trauma (pressure). Since the lesion in the eye with migrated implant was qualitatively of a same character, there is no question on another cause than a focal traumatic insult (pressure).

4.8.2.2 Human cadaver eye study

Furthermore, two ARGOS-SC devices were implanted in a human donor eye by means of non-penetrating glaucoma surgery. One ARGOS-SC device was implanted at 12 o’clock and the other one at the opposite side. The eye was subsequently fixated and preserved in Formalin [25].

The eye was then examined by means of high resolution ANTERION® (Heidelberg Engineering) and 7T-MRT scan (Hannover Medical School). The ANTERION®®, a new development within the field of OCT imaging, works on a different wavelength compared to the commercially broad distributed OCT imagers, thus allows for a deeper visual scan of the eye structures, in particular within the area of the

sclera. With this novel imaging technique, the position of the implant within the suprachoroidal space as well as the state of the eye tissues can be assessed.

Neither the ANTERION® scans, nor the 7T-MRT scans revealed any damage to the eye tissue layers, i.e. choroid, and eye structures. The position of the implant was as expected. Furthermore, the back (convex) plane of the ARGOS-SC device is supported by the sclera as intended [17].

4.9 Clinical experience with similar devices

4.9.1 Method validation: Clinical experience with EYEMATE-IO

In the ARGOS-02 clinical trial, which involved the EYEMATE-IO device, surgical complications were reported in 7 of 23 patients. In five of those seven patients, complications occurred during the implantation of the EYEMATE-IO device. The complications most often (five times each) were Irisprolapse/floppy iris and pigment dispersion. Flat anterior chamber and “vis a tergo” (“pressure from behind”) were reported twice each.

Serious adverse events which were considered to be at least possibly related to either the implant or the implantation procedure were:

- Fibrin reaction in the anterior chamber (postoperative event which was resolved by medication)
- Increased intraocular pressure (was most likely caused by pigment dispersion)
- Corneal decompensation (was most likely caused by excessive surgical manipulation)

These complications are connected with the cataract surgical procedure and are possibly related to the implants position but not to the functional principle of the implant, and as such not associated with the ARGOS-SC device.

The EYEMATE-IO IOP measurement method showed an excellent level of concordance to the conventional GAT IOP measurement though a dependence of the differences between GAT IOP and EYEMATE-IO IOP on the respective IOP level was observed. In the range of physiological IOP (≤ 21 mmHg), the differences between both methods are in the range of the physiological variety of IOP. In IOPs considered to be higher as normal (> 21 mmHg) the differences between the two methods were higher than the average variety of IOP in human eyes. The higher the IOP the larger the difference between the methods, as also observed by other groups [26, 27].

4.9.2 Experience with Ologen and Esnoper V-2000 implant

Over the last decades, a large variety of implants were introduced in the market to facilitate the non-penetrating glaucoma surgery concept. The majority of the implants, which are implanted in the conjunction with the intervention, aim to maintain the intrascleral space and upkeep the aqueous outflow. The Ologen implant, a biodegradable collagen-glycosaminoglycan copolymer matrix implant, is unique in this sense. This implant - and most recently the Esnoper V-2000 - is, within the non-penetrating glaucoma surgery procedure, fully implanted into the suprachoroidal space to upkeep the aqueous humor outflow from the suprachoroidal space via the uveoscleral pathway across the sclera to the orbital vessels as well as via the uveovortex pathway across the choroid to the vortex veins [28]. With exception of the common surgery based (i.e. hyphema) and drainage based (i.e. transient hypotony) complications, no position based (suprachoroidal space) complications were observed with these implants.

5. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The suprachoroidal approach for placing an intraocular pressure sensor implant was developed in parallel with the EYEMATE-IO, which received CE-mark approval in 2017, for placement into the posterior chamber/ciliary sulcus placement. This parallel approach was chosen for several reasons:

- Access to the suprachoroidal space is part of or can be easily combined with surgery to lower intraocular pressure, either penetrating or non-penetrating surgery techniques. While high volume Cataract surgeon may be reluctant to operate in the posterior segment, Glaucoma surgeons routinely access this area.
- EYEMATE-IO requires crystalline lens removal. While Cataract and Glaucoma often coincide in the relevant age group, many patients will not be eligible for EYEMATE-IO implantation, or will, at younger age, not be willing to have their crystalline lens removed prior to end stage presbyopia. A major advantage of the suprachoroidal approach is that the anterior chamber stays unaffected during implantation. Therefore, the procedure can be performed regardless of the lens status and any anterior chamber pathologies.

EYEMATE-IO has been lauded to measure the actual intraocular pressure, b/c it is located within the anterior segment, immersed in aqueous humor. A concern was that the slightly indirect measurement of the pressure within the vitreous cavity with ARGOS-SC is not representative of the actual intraocular

pressure. However, in vitro and in vivo testing has shown that the pressure level set within the anterior chamber (via water column connected through cannula penetrating the cornea) is comparable to the pressure measured with ARGOS-SC.

Functionality of the ARGOS-SC device is independent of Glaucoma surgery, and could well be implanted in a standalone procedure. However, in order to mitigate initial risk, surgical consultants recommended to, in a first step, combine the implantation with non-penetrating Glaucoma surgery.
If it is demonstrated to be safe and reliable in humans, the ARGOS-SC system will provide in all postoperative phases an accurate method of measuring intraocular pressure that:

- Is not influenced by the condition of the cornea or the presence of sutures
- Is not limited to the use for pseudophakic patients, as EYEMATE-IO is
- Can be conducted frequently and conveniently in a non-clinic setting, by patients themselves or any assisting personnel.

The ARGOS-SC will thereby permit rapid detection of postoperative IOP changes and patterns between clinic visits, providing a complete and accurate IOP profile that allows treatment to be titrated up or down according to each patient's individual condition.

At this point in time, all technical risk factors, and risk factors that can be evaluated in bench testing or animal models have been assessed. A study in patients undergoing non-penetrating glaucoma surgery is needed to determine if concomitant implantation of an ARGOS-SC device is also safe in this population. Comparison of the IOP measurements obtained with the ARGOS-SC device to those obtained using methods standard in this population at various time points, resulting in a within individual control of IOP variables, will also allow initial conclusions to be made regarding the usefulness of the device.

6. RISK EVALUATION

6.1 Anticipated clinical benefits

Intraocular pressure (IOP) is one of the most important determinants of disease progression in glaucoma as IOP reduction remains, to date, the only proven therapeutic intervention for disease control and prevention [29, 30]. Despite the emergence of newer technology [31, 32], the Goldmann

Applanation Tonometry (GAT) is currently the most common method to routinely measure IOP [29]. The accuracy of Goldmann Applanation Tonometry is dependent on corneal biomechanics, curvature, and thickness [33, 34]. In some situations, Applanation Tonometry is not possible such as in eyes implanted with keratoprosthesis [35].

Current methods of IOP measurement do not permit frequent, round-the-clock, or continuous recording, or self-measurement of IOP by the patient in his home environment. Such measurements may be critical in understanding the progression of glaucomatous visual loss especially in normotensive or low-tension glaucoma [36–38].

Due to these facts, the treating Ophthalmologist is missing important information regarding the short- and long-term fluctuation of IOP. In clinical routine, IOP is measured once every 3 months. This is not sufficient to reach a good judgment regarding patients' therapy, or success of therapy, or to adequately adjust therapy. A further advantage of the non-invasive IOP measurement will be the possibility to acquire continuous IOP data in the patient's normal living environment.

An intraocular pressure sensor, which is delivering objective data with regard to the actual situation of the pressure within the eye will give the Ophthalmologist important information about the influencing factors of elevate IOP and Glaucoma.

Providing an easy-to-use way of self-measuring IOP will provide patients with a feedback about their therapy, which is especially important in Glaucoma, a disease with a very slow progression. The motivation for the patients to apply their eye drops according to the treatment plan is likely to be significantly improved by that fact (similar to e.g. self-measurement of blood pressure in hypertensive patients). To date, the patient compliance, which means the patients willingness to adhere to the treatment plan with eye drops and other medications is not optimal, which can jeopardize success of therapy [39, 40].

6.2 Risk Management Process

Potential risks related to the intended use and foreseeable misuse of the ARGOS-SC system were identified and mitigated on an ongoing basis according to the risk management analysis prescribed by ISO 14971:2013 and detailed in the document Risk Management Report [41].

Risk control measures were undertaken to reduce the probability of unacceptable and borderline acceptable risks. Where ever possible, priority was given to eliminating the risk first through design changes to eliminate it and if this was not feasible, mitigating it 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 were mitigated by including clear warnings and cautions in the literature and packaging accompanying the device and by limiting implantation use to experience ophthalmic surgeons. The resulting measures were finally reassessed to ensure that no new risks had been introduced during the mitigation process.

6.3 Possible complications and adverse events

Complications may occur due to additional surgical manipulation of the eye while implanting the ARGOS-SC device. While it is possible to implant the device in a standalone procedure, for a first-in-human trial, implantation will be combined with non-penetrating glaucoma surgery (NPGS). The complications which might occur during the implantation may also be associated with the standard non-penetrating glaucoma surgery. However, implantation of the additional device may increase their likelihood and/or severity. Nevertheless, it is assumed that these adverse events could be minimized or eliminated by surgeon training as well as following all of the instructions regarding implant handling and surgical procedure. Possible adverse events might be:

- Perforation/Rupture of the trabeculo-descement‘s membrane (TDM)
- Anterior chamber inflammation
- Hypotony
- Shallow anterior chamber
- Suprachoroidal hemorrhage
- Choroidal detachment
- Retinal detachment
- Hyphema
- Blebitis
- Iris incarceration in TDM
- Temporary visual impairment as a secondary effect caused by the adverse events described above.

It is assumed that in most cases, the complications that may arise following NPGS with combined ARGOS-SC implantation are expected to be temporary and manageable by medication.

For the clinical evaluation process, IOP management therapy and assessment of therapy success will be based solely on IOP values measured with Goldmann Tonometry and, when available, Dynamic Contour Tonometry. IOP values derived from the ARGOS-SC implant will in no case be used for therapy decisions as long as not validated.

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

- **ARGOS-SC system associated risks** – As described in Section 6.2, a full risk analysis was performed during the development of the ARGOS-SC system to anticipate and eliminate or at least minimize all foreseeable ARGOS-SC 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-SC 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-SC 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 Subject ID 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 NPGS at this time. To mitigate these risks, only patients who have already consented to NPGS 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-SC system.

- 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-SC implant with other medical treatments and devices is possible both during the implantation, which is intended to occur concomitantly with non-penetrating glaucoma surgery, 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-SC implant with other devices and/or substances used in treatments of the eye:

- **Instrumentation and substances used during the implantation procedure:**
  - Padded forceps for manipulation of the implant
  - Other instruments commonly used for the non-penetrating glaucoma surgery: 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. No instrument of any kind should come into contact with sensor at the ASIC.
  - Viscoelastic surgical devices
- **High energy ultrasound:** Do not use high energy ultrasound in the vicinity of the implant
- **Diathermy:** Do not use diathermy in the vicinity of the implant
- **Therapeutic ionizing radiation:** Do not use therapeutic ionizing radiation in the vicinity of the implant
- **Laser:** Do not expose the implant to direct laser energy impact to avoid 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.

- **Interaction of the device with topically applied ophthalmic medications:** Although the device could theoretically affect effectiveness of the medication, thereby compromising therapeutic success of medication could interfere with functionality of the device, these risks are considered very unlikely. No drug-device interaction was observed either during pre-clinical studies in rabbits [42] or during the ARGOS-02 study with the technical similar EYEMATE-IO device.

Interactions with other general medical procedures:

- **Magnetic Resonance Imaging (MRI):** it is safe to use MRI with the ARGOS-SC implant for MRI field strength of up to 3T (please refer to section 9 in the Implant IFU for details), however imaging artifacts are likely to be seen in the proximity of the implant.
- **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-SC implant because it will very likely erase the EEPROM.
- **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.

Interactions with other active implanted medical devices:

- **Pacemakers:** the ARGOS-SC reader must not be activated in direct proximity to a pacemaker generator
- **Implantable cardioverter defibrillator (ICD):** the ARGOS-SC reader device must not be activated in direct proximity to an ICD generator.
- **Cochlear Implants:** the ARGOS-SC is contraindicated in patients with cochlear implants
- **Other (head and neck region) nerve stimulators:** the ARGOS-SC is contraindicated in patients with other nerve stimulators

6.6 Possible Alternative Treatments

Only patients who require and have already consented to non-penetrating glaucoma surgery will be contacted regarding participation in this study. They will undergo the same non-penetrating glaucoma surgery regardless of whether they participate in the study or not. The only differences in their treatment will be any adaptations to the surgery required by the ARGOS-SC implant related procedures, such as placement of the ARGOS-SC implant, access to the suprachoroidal space and a slightly longer surgery time.

Treatment decisions during the follow-up period will be based primarily on IOP measurements obtained using conventional tonometry. Abnormalities in IOP detected through measurements obtained with the ARGOS-SC device may however result in additional clinic visits for further diagnosis. If potential subjects choose not to participate in the study, their IOP levels will be monitored using their physician's preferred method.

6.7 Risk/Benefit Assessment

Based on the risk management effort, and the resulting design implementation and user information, the Implandata management team concludes that the benefits for a patient from the implantation of an ARGOS-SC implant device outweighs the residual risks as described above. Predicate implantable ophthalmic medical devices and procedures, show that there is also residual risk with regard to the surgical procedure in general. The surgical placement method of the ARGOS-SC implant slightly differs from non-penetrating glaucoma surgery, but there is no significant difference in the risk profile for the patient. **The medical benefit of the implantation of the device, and resulting possibility of direct IOP measurement and frequent self-tonometry by the patients at home clearly outweighs the identified residual risks of the device. The residual risks and their probability of occurrence are within the acceptable range, compared to similar marketed devices in the ophthalmic field.**

Being able to monitor IOP quasi-continuously over extended periods of time will give the treating ophthalmologists valuable information about the individual disease of a patient and the effectiveness of the medication regimen. The ARGOS-SC system will help the patients to actively monitor their condition, which will in turn improve their motivation and ultimately compliance. This is particularly important in a disease where the loss of vision normally occurs gradually over long periods of time and is often only recognized in advanced cases.

7. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

7.1 Objectives

The purpose of this study is to evaluate the safety and performance of the ARGOS-SC suprachoroidal pressure sensor in patients with glaucoma undergoing non-penetrating glaucoma surgery.

7.1.1 Primary Objectives

Performance

- To evaluate the limits of agreement between measurements with the Goldmann Applanation tonometry (GAT), Pascal Dynamic Contour Tonometry (DCT) and the ARGOS-SC system in the 12 months following implantation.

7.1.2 Secondary Objectives

Safety

- To evaluate the safety and tolerability of the ARGOS-SC pressure sensor during the implantation and throughout a 12 months follow-up period.

Performance

- To evaluate the performance of the ARGOS-SC system up to 12 months after implantation

7.2 Claims and intended performance of the IMD to be verified

This study is designed to show agreement between IOP measurements obtained with the ARGOS-SC device, GAT and DCT at the same time point. Furthermore, it will allow initial assessment of the safety of implanting the ARGOS-SC sensor during non-penetrating glaucoma surgery.

7.3 Risks and anticipated adverse device effects to be assessed

Information will be collected on all AEs and ADEs to allow assessment of the safety of implantation and use of the ARGOS-SC sensor in humans undergoing non-penetrating glaucoma surgery. Particular attention will be paid to ophthalmic AEs, for which increased risks are considered possible. However, because these AEs are common in this patient population, an independent assessment of their relationship to the ARGOS-SC sensor implant will not be possible. Possible adverse device effects will be subject to evaluations of the DSMB. Incidence, nature and severity will be compared to literature of standalone NPGS. AEs of particular interest include:

- Perforation/Rupture of the trabeculo-descement's membrane (TDM)

- Anterior chamber inflammation
- Hypotony (IOP < 5 mmHg for more than one month or hypotony maculopathy (e.g. with signs of maculopathy))
- Shallow anterior chamber
- Suprachoroidal hemorrhage
- Choroidal detachment
- Retinal detachment
- Hyphema
- Iris incarceration in TDM
- Temporary visual impairment as a secondary effect caused by the adverse events described above

Procedures that are anticipated in the general patient population in the follow-up period include:

- 360°-suture removal after canaloplasty
- Nd:YAG membranectomy
- Nd:YAG goniopuncture
- Nd:YAG iridotomy
- Retinal detachment repair
- Transcleral cyclophotocoagulation
- Vitrectomy with epiretinal membrane peeling
- Choroidal drainage
- Anterior chamber infusion with or without recombinant tissue plasminogen activator
- Re-suturing of the scleral flap
- Subconjunctival injection of dexamethasone
- Inserting a therapeutic soft contact-lens

8. DESIGN OF THE CLINICAL INVESTIGATION

8.1 General Aspects

8.1.1 Description of the type of clinical investigation

This prospective, open-label, single-arm multicenter clinical investigation will enroll only adult patients who are planning to undergo indicated non-penetrating glaucoma surgery for the treatment of glaucoma.

Prospective patients will undergo informed consent and screening up to 28 days prior to the planned surgery. Following surgery, all patients who receive an ARGOS-SC implant will attend additional 8 scheduled follow-up visits during the 12-month post-surgical period (days 1, 3, 10, 30, 90, 180, 270 and 360).

To investigate the performance of the device and detect possible safety issues, patients will undergo ophthalmic examinations and be questioned regarding their health by the investigator at every visit.

Additional visits may be held as deemed appropriate by the investigator. The content and reasons for visits will be documented on a separate unscheduled visit CRF.

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

No randomization or blinding/masking procedures will be used in this study. To avoid bias resulting from patient selection, all consecutive patients who potentially meet the eligibility requirements will be informed of the study and asked to participate. Those agreeing will undergo the informed consent procedure and if they consent, will be screened. All eligible patients will be enrolled.

There will be no control group for safety events. Incidence, nature and severity will be compared to literature of standalone NPGS. To allow assessment of performance, measurements of IOP with the ARGOS-SC sensor will be compared to those obtained with the standard GAT method and Pascal DCT at the same time point. To prevent possible influence of prior knowledge of the IOP value obtained with the ARGOS-SC, which is objectively displayed, measurements will always be made first with GAT/DCT. Data on all device deficiencies will be recorded.

8.1.3 Primary and secondary endpoints

8.1.3.1 Primary endpoints

Performance

- Level of Agreement between measurements made using GAT and the ARGOS-SC system from V02 (day 1) through V04 (day 10) and with GAT, Pascal DCT and the ARGOS-SC system from V05 (day 30) through V09 (day 360).

8.1.3.2 Secondary endpoints

Safety

- Number of patients experiencing a device-related SAE (SADE) at any time during implantation and in the first 12 months (Day 0 to Day 360) following it.
- Incidence, nature, severity and seriousness of observed adverse events and adverse device events at any time during implantation and 12 months following it.

Performance

- Repeatability of the ARGOS-SC measurement
- Incidence, nature and seriousness of observed device malfunctions during implantation and in the 12 months follow-up

Utility

- User acceptance of the ARGOS-SC implantation procedure by means of evaluation of implantation procedure questionnaires (investigators)
- User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of patient acceptance questionnaires (by investigators)
- User acceptance of the ARGOS-SC system at home by means of evaluation of patient acceptance questionnaires (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 diagnostic devices. The study monitor 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 (i.e. consented patients withdrawn for any reason up to implant of the ARGOS-SC device) 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-SC pressure sensor is intended to be permanently implanted in the subject's suprachoroidal space concomitantly with a non-penetrating glaucoma surgery of the same eye. Subjects will be exposed to transient (2 seconds) low-levels of electromagnetic energy (0.25 W) emitted by the MESOGRAPH reading device during the reading sessions, at which time their skin may also be exposed to the MESOGRAPH outer surface.

IOP measurements will be made with the ARGOS-SC system at every follow-up visit. The values obtained at Visits 02 through 04 will be compared to those obtained using GAT and at Visits 05 through 09 with GAT and if available Pascal DCT. Patients will also be requested to make daily measurements with the ARGOS-SC system in the out-patient setting.

8.2.2 Justification of the choice of comparator

GAT, considered by the medical community to be the gold standard method of IOP measurement, will be used as comparator. However, GAT actually estimates IOP based on a measurement of the force needed to applanate a predetermined area of the cornea while the ARGOS-SC sensor will be in direct contact with the aqueous humor and measure IOP directly. Consequently, differences are anticipated between the IOP values obtained with the two devices. However, trends in IOP are expected to remain the same regardless of the method used. Therefore, to assess the accuracy of the ARGOS-SC system, IOP profiles obtained with ARGOS will be compared to those obtained with GAT.

Pascal DCT is designed to eliminate some of the measurement errors in GAT that come from variations in corneal thickness and rigidity. It is believed to be closer to true IOP, especially at higher IOPs. It is also less prone to "user error".

8.2.3 Other medical devices or medication to be used

The ARGOS-SC system is the only investigational medical device that will be used during this study. No other devices or medications will be used specifically for this clinical investigation. Standard devices will be used as required for ophthalmic diagnostics and treatment procedures, including if needed glaucoma treatment.

8.2.4 Number of investigational devices to be used

ARGOS-SC pressure sensor will be implanted in a maximum of 24 patients undergoing non-penetrating glaucoma surgery. Sites will be provided with implants at surgery. Approximately 48 devices including replacement devices, 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 enrollment in the study. The investigator may not apply any additional eligibility criteria.

Eligible subjects must meet all the following inclusion criteria:

1. Subjects able to understand the informed consent and willing to participate as evidenced by providing informed consent.
2. Patients aged ≥ 18 years on the day of screening

   Female subjects of childbearing potential (not surgically sterilized or more than one year post-menopausal) must have a negative pregnancy test (urine beta-hCG) within 24 hours prior to ARGOS-SC pressure sensor implantation.
3. Diagnosis of open angle glaucoma requiring a non-penetrating glaucoma surgery (NPGS). The medical indication for a non-penetrating glaucoma surgery 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 non-penetrating glaucoma operation.
4. 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. Contraindications for a non-penetrating glaucoma surgery
   - Neovascular glaucoma, primary and secondary angle closure glaucoma
   - Condition after previous glaucoma surgery
   - IOP > 40 mmHg
2. Myopia (> -6 dpt) or hypermetropia (> +4 dpt)
3. Axis length < 22 mm or > 26 mm
4. Patient with single eye vision (monovision)
5. Exudative age-related macular degeneration, instable macular degeneration 30 days prior to inclusion, or macular edema
6. Acute retinal detachment

7. Uncontrolled Diabetes Mellitus (DM) with manifestation of moderate to severe non-proliferative diabetic Retinopathy (DR) or proliferative DR.
8. History or evidence of severe active inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-SC implantation
9. Ocular surgery procedure(s) (excluding selective laser trabeculoplasty and peripheral iridotomy) within 6 months (cataract surgery within 3 months) prior to ARGOS-SC implantation in the study eye that can affect the assessment of IOP by Goldmann Applanation tonometry/Pascal Dynamic Contour Tonometry
10. Ocular disease other than glaucoma that may affect assessment of visual acuity and/or IOP by Goldmann Applanation tonometry (e.g. choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy)
11. Existence of other active medical eye implant and/or other active medical implants in the head/neck region
12. Difficulties or complications during NPGS procedure or implantation of ARGOS-SC sensor, as assessed by surgeon (e.g. perforation of trabeculo-descement's membrane, excessive aqueous filtration through TDM leading to shallow anterior chamber, excessive bleeding, choroidal detachment).
13. Severe generalized disease resulting in a life expectancy shorter than a year
14. Currently pregnant or breastfeeding
15. 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
16. Patients who are not suitable for the study based on the surgeon's evaluation (e.g. Persons affected by Parkinson's disease or essential tremor)
17. Patients unable or unwilling to understand or comply with required study procedures
18. Patients with psychiatric disorders influencing their judgement or autonomy
19. 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.
20. Enrollment of the fellow eye in this clinical study

8.3.3 Discontinuation or Withdrawal Criteria

8.3.3.1 Study stopping rules

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 study becomes available; and/or on the recommendation of 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 termination or suspension and the reason behind it. If the study is prematurely terminated for any reason, the investigator should promptly inform the site's 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 and either fail to meet eligibility criteria for enrollment e.g. they do not meet one or more of the inclusion criteria or do meet one or more of the exclusion criteria, and subjects who revoke their consent and agreement preoperatively. Such subjects will return to standard treatment.

The only data collected on subjects who fail to meet eligibility criteria prior to surgery 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 screening summary page 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 a cause that could raise 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 analysis. The data of all subjects who undergo implantation of the ARGOS-SC pressure sensor will be included in the efficacy analysis under the Full Analysis Set.

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

- The subject withdraws informed consent.

- It is determined during NPGS surgery that the subject is not feasible for ARGOS-SC pressure sensor implantation. Subjects withdrawn before implantation of the sensor will be replaced. For subjects determined to be ineligible during NPGS surgery, additional information will be collected about the procedure up to that point.
- The ARGOS-SC pressure sensor must be removed for any reason.

If the subject permits, all end-of-study assessments indicated in the visit schedule will 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 subject 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

The choice of keeping the implant or letting the implant be retrieved will be offered to the participating patients.

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 right, followed by mandatory contacts with the patient's treating doctor for exchange information on the patient's health status. Reasonable effort consists of at least three attempts to contact the subject by

phone or post. These efforts should be documented in both the subject's source documents and CRF. So that the monitor can verify if the study center's attempted contacts with the patient and patient's family doctor were adequate.

8.3.3.6 Pregnancy

If a subject 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 enrollment

A subject is considered as being enrolled into the clinical investigation when he/she gives written consent 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 25 months. At the start of the study, all patients enrolled in Switzerland will be requested to sign up for an additional follow-up of 2 years. These patients will automatically transition to the ARGOS-SC_Follow-up.

8.3.6 Expected duration of each subject's participation

The maximum duration of each subject's participation in this clinical intervention is 13 months. The point of enrollment 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 enrollment. The subject will be followed-up for 12 months post-surgery to obtain data on safety and performance. At the start of the study, all patients enrolled in Switzerland will be requested to sign up for an additional follow-up of 2 years. These patients will automatically transition to the ARGOS-SC_Follow-up.

8.3.7 Number of subjects required

This exploratory investigation will enroll 24 patients.

The overall recruitment time is expected to last a maximum of 12 months.

8.3.8 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.

8.3.9 Allocation of Patient Number

Each subject is uniquely identified in the study by a combination of his/her country identifier (e.g. DE for Germany and CH for Switzerland), site 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 abbreviation of suprachoroidal and 01 (SC01) (and a 3-digit string consisting of a 1-digit center identifier and a 2-digit patient identifier. This 2-digit patient identifier corresponds to the chronological order of enrollment in the center (e.g. the 3rd subject included in the study at site 1 in Germany will be patient DE-SC01-1-03). Once the patient number has been assigned to a subject, a number will not be reused even if the subject is a screen failure.

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

During the study, subjects will attend 10 clinic visits, including 1 screening visit (up to 28 days prior to surgery), 1 surgery visit (day 0), and 8 follow-up visits (days 1, 3, 10, 30, 90, 180, 270 and 360). The assessment schedule in Table 1 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.

At the start of the study, all patients enrolled in Switzerland will be requested to sign up for an additional follow-up of 2 years. These patients will automatically transition to the ARGOS-SC_Follow-up (V10 –V13).

8.3.11 Safety

At each follow-up visit, the Investigator will examine the subject 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 subject non-leading questions to ascertain if the subject experienced any adverse events or adverse device events between visits.

8.3.12 Performance

IOP level will be assessed at every follow-up visit in a series of 2 GAT standard measurements followed by 3 consecutive measurements with the ARGOS-SC system. From V05 (day 30) on, if available, additional 2 DCT measurements followed by 3 consecutive measurements with the ARGOS-SC system. **Optional:** At visits V06, V07 and V09, 24-hours measurements with GAT and ARGOS-SC will be done inpatient.

Patients will be given a MESOGRAPH reading device at Visit 01 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. At every follow-up visit, site staff will examine the subject's hand-held reader device and download all readings recorded since the last visit. In addition, they will ask subjects non-leading questions to determine if any device deficiencies occurred since the last visit. All device deficiencies will be recorded on the device deficiency page of the CRF.

To ensure accuracy and comparability of the recorded parameters, all responsible site personnel will be thoroughly instructed on the agreed measurement methods.

To access the user acceptance of the implantation procedure and the general usability of the ARGOS-SC system, surgeons and personnel performing the ARGOS-SC system measurements will be asked to complete user acceptance questionnaires. The aim of these questionnaires is to gain more information about the level of user-acceptance of the ARGOS-SC 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.

8.3.13 Assessments

8.3.13.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: year of birth, age, sex, race, pre-treatments and source of subject referral. This information will be collected at the Screening visit.

8.3.13.2 Medical history

Relevant medical history/current medical condition data includes data regarding ongoing or significant previous ophthalmic and general medical conditions and procedures until start of ARGOS-SC 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.

8.3.13.3 Concomitant medication, treatments and devices

There are no restrictions for the use of concomitant medications required for ophthalmologic or systemic diseases during this clinical investigation. All medications including non-prescription medications used by the subject during the trial and medications in use at enrollment, will be documented in the subject's file and in the CRF, as will all diagnostic procedures and medical interventions. There are following recommendations:

30 days prior to surgery (advisable, but not mandatory)

Modification of the glaucoma therapy:

- If possible, stop prostaglandin drops

On day of surgery

Treatment in the ward:

- 1x antibiotic eye drops (e.g. Polyspectran©)
- Topical Povidone-Iodine Solution
- Pilocarpine (1-2%) eye drops as required

Treatment in the Operation room

- 1x Local anesthetic eye drops (e.g. Oxybuprocaine)
- Acetylcholine or Carbachol solution as needed

Immediately postoperative:

- Steroid-antibiotic combination ointment or drop (e.g. Isopto-Max© or Tobradex©)
- Protective eyepatch

Postoperative follow-up:

Treatment after discharge:

- Avoid prostaglandin treatment until postoperative inflammation is resolved
- Non-steroidal anti-inflammatory or corticosteroid (surgeon's discretion) and antibiotic eye drops (e.g. Tobradex©)
- Artificial tears as required

Month 1

- Protective eye-shield at night for one week (also daily, if necessary. In case of monocular vision: use transparent eye-shield)
- Non-steroidal anti-inflammatory or corticosteroid (surgeon's discretion) and antibiotic eye drops (e.g. Tobradex©) 6x daily, degressive reduction over 1 month or frequency at surgeon's discretion
- Artificial tears as required
- Minimum 4 weeks non-steroidal anti-inflammatory or corticosteroid eye drops or ointment and minimum 2 weeks antibiotic eye drops or ointment

Month 2

- Non-steroidal anti-inflammatory drops (e.g. Acular© or Nevanac©), 4x daily or frequency at surgeon's discretion

8.3.13.4 AEs/ADEs/SAEs/SADEs

All AEs/ADEs/SAEs/SADEs will be recorded starting with the implantation of the ARGOS-SC pressure sensor.

8.3.13.5 Device Deficiencies

A device deficiency form will be completed and sent to the sponsor for all observed device malfunctions or deficiencies, including defects in devices that have not been implanted in a subject or used otherwise. Starting with the implantation of the ARGOS-SC implant, all relevant malfunctions will also be recorded in the subject's chart and CRF.

8.3.13.6 Acceptance Questionnaires ARGOS-SC

In the study, three types of questionnaires will be used to assess potential strengths and weaknesses of the ARGOS-SC system. Surgeons are asked to complete an implantation procedure questionnaire after each implantation at V01 (D0). At V09 (D360), the investigator responsible for IOP measurement

as well as the patients will be asked to complete a user acceptance questionnaires 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-SC 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.

8.3.13.7 National Eye Institute – Vision related Quality of Life Questionnaire-25 (VFQ-25)

The VFQ-25 is a standardized questionnaire about quality of life relating to the patient's vision. It should be completed by the patient at V06, V07 and V09.

8.3.13.8 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 character read and the reading distance will be recorded. The standard testing distance is 4 meters.

8.3.13.9 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. This should always be done on **both eyes** in order to compare study and fellow eye.

A change of the perimeter during the study should be avoided.

8.3.13.10 External Eye Photography

External eye photography will be performed through a slit lamp camera or equivalent in order to document potential changes to the outer eye at Screening and V04 through V09.

8.3.13.11 Heidelberg Engineering ANTERION® (if available)

The ANTERION® from Heidelberg Engineering will be used for determination of the ARGOS-SC location at V04 through V09 (only at sites where it is available).

8.3.13.12 Anterior eye segment measurement

Slit-lamp biomicroscopy (undilated, anterior segment)

At every visit, the external ocular structures and the front of the eye will be assessed using the slit-lamp biomicroscopy according to standard site procedures. Particular attention will be paid to the ocular surface and possible effects of the ARGOS-SC. The following structures will be assessed:

a) Lids
b) Conjunctiva *(irritation)*
c) Cornea
d) Anterior chamber *(cells/flares (SUN-Classification), fibrin, flattening)*
e) Iris
f) Pupil
g) Lens
h) Anterior vitreous body *(cells/haze (NIH-Grading))*

Optical Coherence Tomography (OCT)

Anterior Segment OCT will be used to evaluate effects on change in chamber angle and after non-penetrating glaucoma surgery and to assess the central corneal thickness (Screening, V04 through V09).

Gonioscopy

Standard gonioscopy will be used to confirm 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 gonioscopic grading system according to Shaffer is used in this study (Screening, V06, V07, V09).

8.3.13.13 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:

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 both macular structures and the peripapillary nerve fiber layer (RNFL) at Screening, V06, V07 and V09.
If available, the Heidelberg Engineering Spectralis Glaucoma-Module Premuim Edition (Minimum rim width at Bruch membrane opening ((BMO-MRW), RNFLT and macula) should be used. This should always be done on **both eyes** in order to compare study and fellow eye.

Fundus photography

Standard fundus photography will be performed at Screening and V06, V07, 08 and V09 to document potential changes to the interior surface of the eye, including the retina. Additionally, a photo of the optic nerve and nerve fiber layer will be performed in red-free illumination.

8.3.13.14 Intraocular pressure (IOP) measurement

Intraocular pressure will be measured using three techniques. Goldmann Applanation Tonometry (GAT) will be performed in the clinic at every visit and if available, Pascal Dynamic Contour Tonometry (DCT) at V05 through V09. ARGOS-SC measurements will be performed in the clinic at every visit and by the patient at home between the visits. Only GAT will be used to guide any treatment decisions. The GAT and DCT must be performed by as few dedicated investigators as possible at each site to reduce potential bias.

IOP measurement in the clinic

IOP measurement will be conducted at V02 through V09 as a series of 2x GAT (in case of a difference of more than 2mmHg, a third GAT-measurement is required) followed by 3x ARGOS-SC system. When series of measurements are made, GAT must always be used first to avoid potential operator bias. For the ARGOS-SC measurements the patient has to stay in the same position as for the GAT-measurements (chin on chin rest, forehead installed). From V05 through V09 additionally (if available), a series of 2x DCT (in case of a difference of more than 2mmHg, a third DCT-measurement is required)

followed by 3x ARGOS-SC will be performed after the series of GAT and ARGOS-SC measurements. For the ARGOS-SCmeasurements, the patient has to stay in the same position as for the DCT-measurements (chin on chin rest, forehead installed).

Optional: At V06, V07 and V09, the patient will be hospitalized for 24-hours measurements with GAT and ARGOS-SC. IOP measurements with ARGOS-SC will be done automatically via an external antenna. IOP measurements with GAT will be done every three hours, if it is possible even at night. If night measurements are not possible every three hours at night, the last measurement should take place between 22 and 24 o'clock and the three-hours rhythm should be resumed between 5 and 7 o'clock on the next morning.

ARGOS-SC system measurement by the subject at home

Subjects will receive detailed instruction in the use of the MESOGRAPH reading device. At V02, they will receive an individual MESOGRAPH reading device, a copy of the instructions for use and the Multiline Connector to perform self-tonometry at home. Subjects will be requested to perform at least 4 IOP measurements daily with the MESOGRAPH, one each in the morning after getting up, at noon, in the afternoon and in the evening before going to bed.

No data will be recorded manually by the subject. The MESOGRAPH reading device, which is capable of storing up to 3,000 measurements, 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.

The MESOGRAPH will also be brought to every visit, at which time site staff will assess its functionality and delete recorded IOP data from its memory.

8.3.14 Surgery

During the first implantations and if desired, a member of Implandata staff will be present at the surgery.

8.3.14.1 Non-penetrating glaucoma surgery and preparation for implantation

At the start of the procedure, the conjunctiva is excised over 2 clock hours around the limbus next to the proposed operation side after which the non-penetrating glaucoma surgery is performed using the surgeon's normal preferred procedure. Because the ARGOS-SC sensor will be placed in the suprachoroidal space following completion of the IOP lowering portion of the non-penetrating glaucoma surgery, hyaluronic acid-based viscoelastics such as Healon OVD (Abbott Medical Optics Inc.) should be used to separate the sclera from the choroid. This additionally serves as a safeguard against injuries of the surrounding tissue. Viscoelastics based on hydroxpropyl methylcellulose (HMPC) or other synthetic or semi-synthetic alternatives to hyaluronic acids are to be avoided.

8.3.14.2 ARGOS-SC pressure sensor implantation

To ensure proper function of the sensor when implanted, it is critical to confirm before implantation that the ASIC is in the proper orientation. Care must be taken throughout the process to avoid damaging the ASIC. The sensor may only be handled using the specially designed implantation forceps (Implandata Ophthalmic Products GmbH, Germany), the tips of which are padded with silicone to protect the microsensor from damage and facilitate its implantation.

A scleral window of at least 3.2 to 3.5 mm (maximum 4x4 mm) is necessary for the implantation of the sensor. If a narrower scleral flap was used for the IOP lowering surgery, the width of the flap will be enlarged or an additional small incision made next to it to ensure a final width of at least 3.2 mm.

Using the specially designed implantation forceps, the implant is pushed gently through the scleral opening into the suprachoroidal space with the "pressure sensing side" of the ASIC facing the eye. The sensor must not be forcibly inserted.

For the detailed ARGOS-SC implantation process, please see "*IFU ARGOS-SC Implant".*

8.3.14.3 ARGOS-SC pressure sensor explantation, if medically necessitated

In the event that the sensor must be explanted, a scleral incision of 4.5 to 5 mm is made above the pars plana at the short side of the sensor, preferably above it. The incision must be fully opened to

ensure a safe explantation procedure. A hyaluronic acid-based viscoelastic (see implantation) is then inserted in the suprachoroidal space to ensure complete separation of the sclera and the choroid. Following explantation, the scleral incision should be sealed using at least one suture.

The explanted device is to be returned to Implandata Ophthalmic Products GmbH for analysis.

For the detailed ARGOS-SC explantation, please see *"IFU ARGOS-SC Implant).*

8.3.15 Study Visits

Assessments and procedures to be performed at each visit are indicated with an X in the assessment schedule in Table 1 (see also Section 8.3.13 Assessments). The visits should be arranged as closely as possible to the specified visit day, accepted tolerances are set up for every visit (see Table 1).

Table 1: Assessment Schedule ARGOS-SC01

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09
Indicative Days (D) Visit window	**Up to 28 days before surgery**	**D0**	**D1**	**D3 - 1/+ 2 Days**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D90 +/- 10 Days**	**D180 +/- 15 Days**	**D270 +/- 15 Days**	**D360 +/- 15 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]								
Non-penetrating glaucoma surgery and ARGOS-SC pressure sensor implantation		X								
Vision related Quality of Life (VQoL) questionnaire	X						X	X		X
Visual acuity (ETDRS)[3]	X		X	X	X	X	X	X	X	X
Perimetry[4] (OU)	X						X	X		X
Heidelberg Engineering ANTERION®					X	X	X	X	X	X
External eye photography[5]	X				X	X	X	X	X	X
Implantation procedure questionnaire (surgeon)		X								
User acceptance questionnaire (patient)										X
User acceptance questionnaire (investigator)										X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
AE/ADE/SAE/SADE		X	X	X	X	X	X	X	X	X
Device malfunction		X	X	X	X	X	X	X	X	X
ANTERIOR SEGMENT										
Optical Coherence Tomography[6]	X				X	X	X	X	X	X
Slit-lamp biomicroscopy[7]	X		X	X	X	X	X	X	X	X
Gonioscopy[8]	X						X	X		X
POSTERIOR SEGMENT										
Slit-lamp biomicroscopy[9]	X		X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)[10] (OU)	X						X	X		X
Fundus photography[11]	X						X	X		X

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09
Indicative Days (D)	**Up to 28 days before surgery**	**D0**	**D1**	**D3 - 1/+ 2 Days**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D90 +/- 10 Days**	**D180 +/- 15 Days**	**D270 +/- 15 Days**	**D360 +/- 15 Days**
IOP Measurement										
Goldmann Applanation Tonometry[12]	X		X	X	X	X	X	X	X	X
Pascal Dynamic Contour Tonometry[12]	X					X	X	X	X	X
ARGOS-SC pressure sensor measurement[12]			X	X	X	X	X	X	X	X
Optional: 24-hours measurements inpatient with GAT and ARGOS-SC over 24h[13]							X	X		X
ARGOS-SC pressure sensor self-measurement[14]		X	X	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 best corrected visual acuity will be determined after objective and subjective determination of refraction with the ETDRS chart in accordance with the ETDRS protocol.

[4] 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.

[5] 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.

[6] Anterior segment OCT is performed to evaluate effects on change in chamber angle after non-penetrating glaucoma surgery and to assess corneal thickness.

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

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

[9] Posterior segment biomicroscopy is performed by means of indirect ophthalmoscopy on a slit lamp with the aid of a 90D or “Superfield” or comparable lenses. For this examination the pupil needs to be dilated by the use of mydriatic agents. 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.

[10] Posterior segment OCT is used to assess macular structures and the peripapillary nerve fiber layer thickness (RNFLT) and if possible Minimum rim width at Bruch membrane opening (BMO-MRW).

[11] The fundus should be photographed in order to document potential changes to the optic nerve (cup/disc ratio) and nerve fiber layer (red-free illumination).

[12] V02 to V09 IOP measurements will be made in series of 2 GAT measurements (in case of a difference of more than 2 mmHg, a third GAT measurement is required) followed by 3 directly consecutive ARGOS-SC system measurements; *if DCT is available:* V05 to V09 additionally followed by 2 Pascal DCT measurements (in case of a difference difference of more than 2 mmHg, a third Pascal DCT measurement is required) and 3 directly consecutive ARGOS-SC system measurements.

[13] Optional: Patient’s admission at the site for a 24h series of measurements with GAT and ARGOS-SC sensor. Measurements with EYEMATE-SC sensor will be done automatically via an externa antenna. GAT will be done every three hours, if it is possible even at night. If night measurements are not possible every three hours at night, the last measurement should take place between 22 and 24 o’clock and the three-hours rhythm should be resumed between 5 and 7 o’clock on the next morning.

[14] All patients will receive a MESOGRAPH reading device after implantation in order to measure the IOP daily at home. Measurements will 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.

8.3.16 Visit SC – Screening (Day -28 to 0)

Only patients who have already agreed to undergo non-penetrating glaucoma surgery will be approached by the trial team about participation in the study.

At the screening visit (SC), the Investigator will conduct the informed consent process (Section 12.1), ensuring that the subject has signed and received a copy of the patient informed consent (PIC) form before any study specific procedures are conducted. Once the PIC is signed, the subject will be assigned a patient number (Section 8.3.9) and the Investigator will determine if the subject meets the eligibility criteria, surgery (V01) will be scheduled and the sponsor will be informed.

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

- Collection of background information about the subject including: demographics, medical history with prior treatments and current medications and indication for non-penetrating glaucoma surgery.
- Pregnancy test, when applicable
- Vision-related Quality of Life (VqoL) questionnaire
- Visual acuity (ETDRS)
- External eye photography
- Anterior Segment assessments (slit-lamp biomicroscopy, AS-OCT, gonioscopy)
- Posterior Segment assessments (biomicroscopy, PS-OCT and fundus photography)
- IOP measurement with GAT and if available DCT
- Instruct subjects on the need to report as soon as possible any SAEs occurring at any time throughout the study (starting from Visit 02 surgery)
- Complete the CRF.

8.3.17 Surgery, Visit 01 (Day 0)

The following procedures may be carried out up to one day before surgery (in subjects already hospitalized for the surgery) or prior to surgery 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

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

- Updating medical history (up to start of ARGOS-SC implantation)
- Recording of concomitant medications, device deficiencies or malfunctions (including those detected during device preparation) and any Aes (starting from the point of inclusion/signing of the informed consent)
- Non-penetrating glaucoma surgery and ARGOS-SC pressure sensor implantation (described in Section 8.3.12)
- 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 immediately report any SAE that may occur at any time during the study.
- Schedule Visit 2 (V02).

The duration of the subject's hospitalization following surgery is at the discretion of the Investigator. Durations of up to 6 days will not be considered to be SAEs.

8.3.18 Follow-up visits (V02 to V09)

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

- Recording of Aes/SAEs/ADEs/SADEs, concomitant medications and device malfunctions
- VqoL questionnaire (V06, V07, V09)
- User acceptance questionnaire (investigator) (V09)
- User acceptance questionnaire (patient) (V09)
- Visual acuity (ETDRS)
- External eye photography (V04-V09)
- Heidelberg Engineering ANTERION® (optional V04-V09)
- Perimetry (V06, V07, V09)

- Anterior Segment assessments: slit-lamp biomicroscopy, AS-OCT (V04-V06), gonioscopy (V06, V07, V09)
- Posterior Segment assessments: biomicroscopy, PS-OCT (V06, V07, V09), fundus photography (V06, V07, V09)
- IOP Measurement: GAT and ARGOS-SC. Optional, if available V05 –V09 Pascal DCT;
  Optional: 24-hour measurements inpatient with ARGOS-SC and GAT (V06, V07, V09)
- Instruction of subjects on the use of the MESOGRAPH and Multiline Connector
- At V02, provide the patient with a MESOGRAPH and Multiline Connector for home-use for the rest of the study. Patient should bring both devices to all subsequent visits.
- Remind subjects to promptly report any SAE that may occur at any time during the study.
- Complete the CRF and arrange the next visit.

Visit 09 is the study discharge/end of study visit. At this visit, subjects will be informed about the planned surveillance registry and asked if they wish to participate (ARGOS-SC01_Follow-up) or they will return to standard of care. At the start of the study, all patients enrolled in Switzerland will be requested to sign up for an additional follow-up of 2 years. These patients will automatically transition to the ARGOS-SC_Follow-up.

9. STATISTICS

9.1 Statistical design, method and analytical procedures

The primary purpose of this investigation is to assess the performance of the investigational device.

9.1.1 Demographic and baseline characteristics

Demographic characteristics (age, sex, educational level), lens status, anti-glaucoma medication, and other previous and concurrent treatments will be tabulated for the safety set.

9.1.2 Subject Disposition

The number and percentage of screened, enrolled and implanted subjects, as well as those who complete the follow-up will be tabulated for the safety set. 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 incidence and nature of adverse events observed within the safety population will be analyzed by descriptive and explorative statistical methods.

Safety will be described in detail by frequency, seriousness, severity, nature and duration of events.

Number of adverse events as well as the number and relative frequency of patients reporting adverse events will be tabulated by system organ class and preferred terms. The same table will be prepared for serious adverse events. In addition, the number and relative frequency of patients reporting adverse events will be tabulated by system organ class and preferred terms in dependence on the worst severity and worst causal relationship. Furthermore, number of adverse device effects as well as the number and frequency of patients reporting adverse device effects will be tabulated by system organ class and preferred terms and not by event description as stated in the protocol.

9.1.4 Performance Analysis

The probability distribution of the difference of the paired measurements grouped within 1 mmHg will be compared to the primary objective of the accepted 70% of the measurements to agree between +/- 5 mmHg.

9.2 Sample Size Calculation

The sample size calculation was based on the study's dual purpose of establishing safety and comparability of IOP measurements with the ARGOS-SC system to those made with GAT and DCT. IOP measurements will be made with all devices at various time points, resulting in a within individual control for IOP variables. Based on these calculations (performance, safety) and considering possible drop-outs, the exploratory investigation will enroll 24 patients. The minimum number of measurements required to hold the performance claim is approx. 120. With multiple (>8) measurements with either method (ARGOS, GAT) per patient, a sufficient number of paired measurements (in total >>120 measurement pairs) will be available to show equivalence of the methods (primary objective)[2].

9.3 Level of significance and the power of the clinical investigation

Significance level is set to 0.10, Power to 80%.

9.4 Expected drop-out rates

The drop-out rate for this study following implantation is expected to be low. The ARGOS-SC is intended to remain in situ and the patient population generally requires close follow-up care by the ophthalmologist. Subjects who do not undergo implantation of an ARGOS-SC will be replaced.

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

This investigation will be considered a success if no more than one of the 24 patients experiencing SADEs during the follow-up period (SADEs evaluated by DSMB) and if 70% of the measurements agree between +/- 5 mmHg (limits of agreement from GAT and ARGOS-SC measurements are between +/- 5 mmHg).

9.6 Interim analysis

One interim analysis is planned for this study. It will take place when all patients have completed the first 6 months of the follow-up period.

9.7 Criteria for termination of the clinical investigation

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 judges it necessary for any reason. See also Section 8.3.3 Discontinuation or Withdrawal Criteria Early Patient Withdrawal and Section 12.11 Criteria for Suspension and Premature Termination of Study
- If, throughout the course of the study, the DSMB comes to the conclusion that further implantation of the ARGOS-SC pressure sensor would subject study patients to undue risk

Patients who already have an ARGOS-SC pressure sensor implanted by the time of premature termination will continue to be followed up. If the study is discontinued for safety reasons it will be

proven whether explantation of all ARGOS-SC sensors deems necessary or follow-up of patients is sufficient.

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 permit investigation of their impact on performance and safety, information will be collected prospectively on the following variables:

- Gender
- Post-surgical complications
- Successful implantation
- Age groups
- Country of investigational site
- Educational level
- Medical History (primary underlying ophthalmic illness or injury necessitating the non-penetrating glaucoma surgery)
- Pre-treatment
- Concomitant medications

Which subgroup analyses are actually performed will be decided at a final data review meeting preceding the statistical analysis, based on the actual distribution of subjects in the study population.

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

All data of the patients will be used as available. All analyses will be performed on observed cases only. Missing data will not be replaced. Implausible values will be only excluded from the analysis if reasonable. The reason for exclusion will be given in the footer of the table or description of the figure. Patients terminating the trial prematurely due to whatever reason will be evaluated like any patient completing the trial as per protocol, within the analysis sets they qualify for.

Subjects who dropped out during a scheduled visit will be counted for that visit.

9.11 Datasets to be analyzed

9.11.1 Safety set

The safety population comprises all subjects for whom ARGOS-SC pressure sensor implantation was attempted, defined as introduction of the ARGOS-SC pressure sensor into the eye, whether or not the implantation was successful.

9.11.2 Per protocol set

The Per Protocol Set (PPS) will comprise all subjects in whom an ARGOS-SC pressure sensor was successfully implanted and for whom the full data set including IOP measurements made in the clinic and safety data according to protocol are available until 3 months (V06) after surgery. Because IOP measurements conducted outside the clinic will be made at varying times under varying conditions, they are not anticipated to be comparable to those made in the clinic and will not be included in the Per-Protocol evaluation of agreement.

Additional information about the drop-outs: all subjects who revoke their consent and agreement preoperatively will be regarded as screen failures and will not be included in the statistical evaluation. All subjects who revoke their consent and agreement postoperatively will be considered withdrawals. Unless the subject also withdrew consent to use their data, they will be evaluated in the safety analysis.

9.12 Number of subjects at each site

It is planned to enroll an approximately equal number of subjects at each site. Due to the small sample size a stratified design / analysis will not have the power to detect center specific treatment effects.

10. DATA MANAGEMENT

10.1 Site Monitoring

The study will be monitored in compliance with the Declaration of Helsinki, ISO 14155, 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, 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. For each patient lost to follow-up, the monitor will verify if the study center's attempted contacts with the patient, followed by contacts with the patient's family doctor, were adequate.
Detailed monitoring procedures will be described in a separate monitoring plan.

10.2 Data collection

Data will be collected through a Case Report Form (CRF) provided by the sponsor or its designee to the centers prior to study start. Designated site staff will enter study data in the CRF during or as soon as possible after the visit (within 3 days at the latest).

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 privacy of participating subjects must be maintained. The sites will maintain a list of the subjects´ names and the Patient ID assigned to each individual subject. Subjects will not be identified except by Patient ID on any document submitted to the sponsor. All documents that could identify the subject beyond the Patient ID (e.g. the signed informed consent document) 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 review the completed CRFs for each subject and must confirm the accuracy of all data entered with his/her signature at the end of each documented subject's visit in the CRF within 3 days. Any corrections made to data entries will be GCP conform.

During data review, data management will generate queries for any missing, out of range or questionable data and send those to the investigator for resolution. 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

The sponsor will verify 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-SC 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 obtain written permission from the sponsor before destroying any study specific documentation. 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 subjects, 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 Definitions

The following definitions are taken from Global Harmonization Task Force Document GHTF/SG5/N5, and are based on ISO 14155 and MEDDEV 2.7/3.

11.2 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.

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.

11.2.1 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.

11.2.2 Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is defined as any Adverse Event that:

1. Led to death
2. Led to a serious deterioration in the health of a subject that:
   a) Resulted in a life-threatening illness or injury
   b) Resulted in a permanent impairment of a body structure or body function
   c) Required in-patient hospitalization or prolongation of existing hospitalization
   d) Required medical or surgical intervention to prevent permanent impairment to body structure or a body function
3. 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, or 3 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]: **For the purposes of this Regulation, 'serious adverse event' means any unintended event occurring in a clinical trial which has led, may have led or may lead, directly or indirectly, to the death or serious deterioration in the state of health of a subject, user or other person, without taking into account whether the event was caused by the medical device.**

11.2.3 Serious Adverse Device Effect (SADE)

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

11.2.4 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).

11.2.5 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).

11.2.6 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.

11.3 Recording of Adverse Events (AEs)

All AEs will be documented throughout the clinical trial as per ISO 14155, chap. 6.4.1, meaning from the point of inclusion/signing of the informed consent, until resolution or stabilization, or for a maximum of 7 days after the last subject has been discharged from the study.

All AEs will be reported on an Adverse Event Form, one for each Adverse Event, which is part of the CRF.

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. SAEs will be followed until resolution or stabilization. AEs will be followed until resolution or stabilization, or for a maximum of 7 days after the last subject has been discharged from the study.

11.3.1 Seriousness

Seriousness will be recorded as described in Section 11.2.2.

11.3.2 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).

Note: Severity is not seriousness. An AE may be severe but not serious, as in a severe headache, while an SAE may be mild, as in a mild myocardial infarct.

11.3.3 Relationship to study device

Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological or physical 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 about the study device supports a causal relationship although another cause cannot be ruled out.
- ***Definite:*** The criteria for probable relationship are fulfilled and no other possible causative factors exist.

11.3.4 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

11.3.5 Outcome

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

- Recovered
- Recovered with sequelae
- Recovering
- Death
- Unknown.

11.4 Reporting of Serious Adverse Events (SAEs)

The site must report the following events to the sponsor immediately after becoming aware of them:

1. Any SAE affecting a subject, regardless of its relationship to the device or the study-procedures (beginning with the implantation of the ARGOS-SC sensor)
2. A SADE affecting a user or third party (all)
3. A device deficiency that might have led to an SAE involving a subject, user or third party if suitable action or intervention had not been taken or if circumstances had been less fortunate (all)

If the site is uncertain as to whether an event is an SAE, they should report it to the sponsor as if it were.

The sponsor will report SAEs to the Competent Authority in accordance with ISO 14155, Annex X of Directive 93/42/EEC, its amendment Directive 2007/47/EC, Annex 7 of Directive 90/385/EEC, MEDDEV 2.7/3, the German Ordinance on Medical Device Vigilance (MPSV) and applicable local laws and

regulations. Reporting modalities defined in the MPSV and MEDDEV 2.7.3 will be followed. All SAEs will be documented completely. SAEs for which a relationship to the study device or diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial cannot be excluded will be reported to BfArM immediately using the SAE report form found on the BfArM website. A summary report for all other SAEs will be submitted to BfArM every three months or as requested by BfArM using the SAE summary table from MEDDEV 2.7.3.

Information reported on the SAE shall include:

- The date the event was reported to the sponsor
- The country
- Site and Patient ID
- The date the subject underwent implantation with the study device
- The date of event onset
- The affected organ system
- A description of the event
- Actions, treatments and patient outcome as a result of the event
- The date the event was first noticed by or reported to the investigator
- An assessment of the relatedness of the event to the procedure
- An assessment of the relatedness of the event to the device
- The expectedness of a SADE
- The event status
- The date of event resolution

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 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.

Regulatory authority and ECs will be informed about SAEs according to local regulations as described in Table 2.

Table 2: SAE reporting requirements

Reporting Party	Reports to	Causal Relationship to Study Devices or Procedures	Reporting Timeline	Reporting Method
Investigator	Sponsor	All SAEs, regardless of relationship	Immediately upon learning of the event	SAE Report Form
Sponsor	BfArM	Relatedness cannot be excluded	Immediately upon learning of the event	Submission of SAE report form for single events (BfArM website)
		Relatedness can be excluded	Summary report every 3 months or as otherwise requested by BfArM	Submission of MEDDEV 2.7.3 Summary Table

11.5 Recording and Reporting of Device Deficiencies

The investigator will record all observed device deficiencies by completing a Device Deficiency Form. The reporting modalities are defined in ISO 14155 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 as soon as possible. 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 2 following the SAE reporting modalities.

Any adverse device effect causing injury with the nature of a SADE to a person other than a study subject must be reported to the sponsor in accordance with the SAE reporting procedure.

11.6 Medical Care

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

11.7 Safety Monitoring

A Data Safety Monitoring Board (DSMB) will be established prior to enrollment of the first patient. The DSMB will review the safety data on a regular basis and will advise on any changes required in the conduct of this clinical investigation. The DSMB will consist of 2-4 independent clinicians with expertise in the treatment of glaucoma who are not otherwise involved in the study and will be designated to review safety related issues including reported SAEs/SADEs on a frequent basis and advise the sponsor on any changes required to the conduct of the study. It is anticipated that these clinicians may come to one of three types of binding 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-SC pressure sensors in subjects unethical.

11.8 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 2** and **Table 3** for details.

Table 3: Sponsor Reporting Responsibilities

Reporting Responsibility	Reports to	Description
Serious Adverse Events (SAEs)	Regulatory Authorities, ECs	See Section 11.2.2 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. GERMANY: According to MPG §23a, Abs. 1, the Sponsor is required to notify BfArM of the completion of the clinical investigation within 90 days after close-out. GERMANY: According to MPG §23a, Abs. 2, the Sponsor is required to notify BfArM of the premature termination of the clinical investigation within 15 days after termination.
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. Germany: According to MPG §23a, a CIR has to be submitted to BfArM within 12 months completion or premature termination of the clinical investigation.

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 CIP (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 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 safety, study procedures or any aspects of the study that could potentially influence a subject's willingness to continue in the study. After the new subject information documents have been approval by EC and regulatory authorities, the subject 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 subject is informed in a timely manner about any new safety-relevant information that could affect the subject's willingness to continue in the study and agrees to request the subject's consent again, if necessary.

12.2 Vulnerable Subjects

Only mentally competent subjects will be enrolled in this study.

12.3 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.

12.4 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 the start of the investigation. 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 (RA) 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 and RA for approval. The amendment will not be implemented until EC and RA approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the subjects.

12.5 Investigator Responsibilities for Ethics Committees and Regulatory Authorities

Prior to study start, the investigator is required to sign a CIP signature page confirming his or her agreement to conduct the investigation in accordance with all of the instructions and procedures found in this CIP 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.

12.6 Reporting responsibilities

12.6.1 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 AEs (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 11.3. Refer to Tables Table 2 and Table 3 for SAE reporting responsibilities.

12.6.2 Sponsor Reporting Responsibilities

The sponsor is responsible for reporting SAEs, interim or annual safety reports, premature termination or suspension of the clinical investigation, and the Final Study Report. Refer to Table 3 for details.

12.7 Insurance

The sponsor will maintain 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.

12.8 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 RA 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 subject included in this study, regardless of any need for approval of formal CIP amendments, even if this action represents a deviation from the CIP. In such cases, the sponsor should be notified of this action promptly and the Ethics Committee responsible for the study site should be informed.

12.9 Recording, Reporting and Analysis of CIP Deviations

Deviations 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
- SAEs or SADEs were not reported by investigators within the required timeframe as specified in the CIP
- Source data permanently lost
- Pregnancy of a subject

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 12.9 Recording, Reporting and Analysis of CIP Deviation. 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 an investigational site continues to deviate from the CIP despite retraining, 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 it is necessary to discontinue the study, 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 is an open-label study and will not be masked.

12.13 Subject follow-up requirements

All pregnancies will be followed up 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 non-penetrating glaucoma surgery. 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 performing non-penetrating glaucoma surgery and in the care of glaucoma patients
  - Access to the patient population
- Patient recruitment potential
  - Potential of 2 - 8 subjects in the given timeline
  - Patient enrollment and site commitment not expected to be impacted by any competing studies
- Clinical support staff
  - Study nurse/assistant/coordinator or equivalent with adequate training and time to perform study administration including data entry
- Time investment
  - Sufficient availability of the investigator to fulfill the study requirements, including reporting and attendance at 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 Investigation Report (CIR) for the study after the study is completed. This report, or parts of it, will be submitted to the relevant authorities as applicable.

A CIR will be submitted to BfArM within 12 months after completion or premature termination of the clinical investigation in accordance with the German MPG §23a. See Table 3 in section 11.8 for further details.

13.2 Publication of Study Results

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.

13.3 Registration in a Clinical Trial Database

The investigation will be registered in a clinical trial database such as clinicaltrials.gov prior to the start of enrollment. Following finalization of the final report, a summary of the investigation results will also be publicized on the database.

14. REFERENCES

1 Oehring D. (2017) ARGOS-02 vs. GAT Final Analysis V20a.

2 Implandata. (2018) ARGOS-SC01: Sample size determination.

3 Zou G. Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual. 1–13.

4 Quigley HA. (2011) Glaucoma. *Lancet*, 377(9774), 1367–1377.

5 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.*, 95(5), 627–629.

6 King A, Azuara-Blanco A, Tuulonen A. (2013) Glaucoma. *BMJ*, 346(jun11 1), f3518.

7 (2014) European Glaucoma Society. Terminology and Guidelines for Glaucoma (4th edition). *www.eugs.org*. Retrieved December 21, 2016, from http://www.eugs.org/eng/EGS_guidelines4.asp

8 Panday M, George R. (2010) Non-Penetrating Glaucoma Filtering Surgery-An overview. *Kerala J. Ophthalmol.*, 22(4), 319–321.

9 Krug A, Kompa S, Schrage NF. (2002) The Aachen-keratoprosthesis - a flexible KPro that permits intraocular pressure measurement. *Int. J. Artif. Organs*, 25(3), 238–242.

10 Rotchford AP, King AJ. (2012) Repeatability of measurements of effectiveness of glaucoma medication. *Br. J. Ophthalmol.*, 96(12), 1494–1497.

11 Liang SYW, Lee GA, Shields D. (2009) Self-tonometry in Glaucoma Management - Past, Present and Future. *Surv. Ophthalmol.*, 54(4), 450–462.

12 Implandata Ophthalmic Products GmbH. ARGOS-02 Clinical Investigation Report.

13 Cao M. (2010) Silicone-Coated Microship for Ocular Implantation. Atlanta, USA: NAMSA Asvisory Services.

14 Timme M. (2015) Biological safety-toxicology evaluation of the ARGOS-IO implant (second generation). Gilching, Germany: Medical Device Services.

15 Implandata Ophthalmic Products GmbH. 50-RE-75A LAL validation.

16 Implandata Ophthalmic Products GmbH. IFU ARGOS-SC Implant Rev. A.

17 Implandata Ophthalmic Products GmbH. Investigator's Brochure ARGOS-SC01 Rev. A.

18 Implandata Ophthalmic Products GmbH. Implandata Ophthalmic Products GmbH Mail - Szurman - Vorversuche Dummies - Humanaugen_20130719.

19 Implandata Ophthalmic Products GmbH. Hartschliffpräparate ARGOS-SC.

20 Implandata Ophthalmic Products GmbH. 2013_04_26_ARGOS-SC.

21 Implandata Ophthalmic Products GmbH. 01-RE-01B Temperature Elevation ARGOS-IO (worst-case-estimation).

22 Shellock R&D Services Inc. 01-RE-18A Evaluation of Magnetic Field Interactions, Heating, and Artifacts at 3-Tesla for the ARGOS-IO.

23 Werner L, Chew J, Mamalis N. (2006) Experimental evaluation of ophthalmic devices and solutions using rabbit models. *Vet. Ophthalmol.*, 9(5), 281–291.

24 AnaPath GmbH. (2016) Histological Processing and Histopathology Evaluation of 6 Months Ocular Implantation Study of ARGOS-SC Device in Rabbits.

25 Implandata Ophthalmic Products GmbH. 20171217_Mariacher_ARGOS-SC implantation in human donor eye.

26 McCafferty S, Levine J, Schwiegerling J, Enikov ET. (2017) Goldmann applanation tonometry error relative to true intracameral intraocular pressure in vitro and in vivo. *BMC Ophthalmol.*, 17(1), 1–9.

27 Kniestedt C, Nee M, Stamper RL. (2004) Dynamic contour tonometry: a comparative study on human cadaver eyes. *Arch. Ophthalmol.*, 122(9), 1287–1293.

28 Szurman P, Januschowski K, Boden KT, Seuthe AM. (2018) Suprachoroidal drainage with collagen sheet implant- a novel technique for non-penetrating glaucoma surgery. *Graefe's Arch. Clin. Exp. Ophthalmol.*, 256(2), 381–385.

29 Nduaguba C, Lee RK. (2006) Glaucoma screening: current trends, economic issues, technology, and challenges. *Curr. Opin. Ophthalmol.*, 17(2), 142–152.

30 Konstas AGP, Irkec MT, Teus M a, Cvenkel B, Astakhov YS, Sharpe ED, et al. (2009) Mean intraocular pressure and progression based on corneal thickness in patients with ocular hypertension. *Eye (Lond).*, 23(1), 73–8.

31 Pourjavan S, Boghossian P, Detry-Morel M. (2010) Comparison of the quality score of intraocular pressure and ocular pulse amplitude values measured by the Pascal dynamic contour tonometer. *Int. Ophthalmol.*, 30(1), 1–5.

32 Mollan SP, Wolffsohn JS, Nessim M, Laiquzzaman M, Sivakumar S, Hartley S, et al. (2008) Accuracy of Goldmann, ocular response analyser, Pascal and TonoPen XL tonometry in keratoconic and normal eyes. *Br. J. Ophthalmol.*, 92(12), 1661–1665.

33 Salvetat ML, Zeppieri M, Tosoni C, Brusini P. (2007) Comparisons between Pascal dynamic contour tonometry, the TonoPen, and Goldmann applanation tonometry in patients with glaucoma. *Acta Ophthalmol. Scand.*, 85(3), 272–279.

34 Elsheikh A, Alhasso D, Pye D. (2009) Goldmann Tonometry Correction Factors Based on Numerical Analysis. *J. Biomech. Eng.*, 131(11), 111013.

35 Ilhan-Sarac O, Akpek EK. (2005) Current concepts and techniques in keratoprosthesis. *Curr. Opin. Ophthalmol.*, 16(4), 246–250.

36 Sit AJ. (2009) Continuous monitoring of intraocular pressure: Rationale and progress toward a clinical device. *J. Glaucoma*, 18(4), 272–279.

37 Sit AJ, Liu JH. (2009) Pathophysiology of glaucoma and continuous measurements of intraocular pressure. *Mol. Cell. Biomech.*, 6(1), 57–69.

38 Jürgens C, Antal S, Henrici K, Großjohann R, Tost FH. (2009) Fluctuation of Intraocular Pressure in 24-Hour Telemonitoring Compared to Tonometry during Normal Office Hours. *Klin. Monbl. Augenheilkd.*, 226(1), 54–59.

39 Gurwitz JH, Glynn RJ, Monane M, Everitt DE, Gilden D, Smith N, et al. (1993) Treatment for glaucoma: Adherence by the elderly. *Am. J. Public Health*, 83(5), 711–716.

40 Hermann MM, Bron AM, Creuzot-Garcher CP, Diestelhorst M. (2011) Measurement of adherence to brimonidine therapy for glaucoma using electronic monitoring. *J. Glaucoma*, 20(8), 502–508.

41 Implandata Ophthalmic Products GmbH. Risk Management Report ARGOS-SC Rev. A.

42 Paschalis E, Cade F, Melki S, Pasquale L, Dohlman C, Ciolino J. (2014) Reliable intraocular pressure measurement using automated radio-wave telemetry. *Clin. Ophthalmol.*, 8, 177–185.