CLINICAL INVESTIGATION PLAN

Follow-up of the first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the long-term safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma underwent non-penetrating glaucoma surgery (Follow-up Month 12 – Month 36)

Reference Number: ARGOS-SC01_Follow-up

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Release Date:	May 27, 2021
Sponsor:	Implandata Ophthalmic Products GmbH Kokensstrasse 5 30159 Hannover Germany

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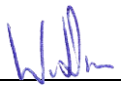
Wouter van Drunen		28.05.2021
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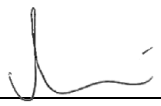
Dr. Kaweh Mansouri		28.05.2021
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Coordinating Investigator Signature Page

ARGOS-SC01__Follow-up

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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.

Name	Signature	Date
		31.5.2021

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SYNOPSIS

Title	Follow-up of the first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the long-term safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma underwent non-penetrating glaucoma surgery (Follow-up Month 12 – Month 36)
Study Number	ARGOS-SC01_Follow-up
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.
Patient Population	Subjects of the ARGOS-SC01 clinical trial with an implanted ARGOS-SC pressure sensor.
Study Purpose	The purpose of this study is to evaluate the long-term safety and performance of the ARGOS-SC system.
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 2 years (Month 12 – Month 36) after the ARGOS-SC implantation to collect safety and performance information.
Study Objectives	**Primary Objective** **Performance** To evaluate the limits of agreement between measurements with Goldmann Applanation Tonometry (GAT), Pascal Dynamic Contour Tonometry (DCT, if available) and the ARGOS-SC system from month 12 throughout month 36 following implantation

	Secondary Objectives **Safety** To evaluate the safety and tolerability the ARGOS-SC pressure sensor throughout a follow-up period from month 12 throughout month 36. **Performance** To evaluate the performance of the ARGOS-SC system from month 12 throughout month 36 after implantation.

Study Procedures	**V09 (Month 12/Day 365)** is the last Visit of ARGOS-SC01 and the Baseline Visit of ARGOS-SC01_Follow-up **Semiannual Follow-up Month 13 (V10) – Month 36 (V13)** The examinations performed for each visit are listed without mentioning the single visit in parentheses. The follow-up visits will include: General • ADE/SAE/SADE • Device Deficiency • Concomitant Medication • Visual acuity (ETDRS) (OU) • Perimetry (OU) • External eye photography • Heidelberg Engineering ANTERION® (location of ARGOS-SC), if available • National Eye Institute Questionnaire – VFQ-25 (V11, V13) Anterior segment (OU) • Optical coherence tomography (OCT) of cornea and anterior chamber • Slit lamp biomicroscopy • Gonioscopy Posterior segment (OU) • Funduscopy • Optical coherence tomography (OCT) of macula and optic nerve • Fundus photography (V11, V13)

	IOP measurements • Goldmann Applanation tonometry (GAT) (OU) • Pascal Dynamic Contour Tonometry (DCT) (if available) (OU) • ARGOS-SC measurements • ARGOS-SC self-measurements
Data Analysis and Statistics	**Primary Endpoint** **Performance** - Level of Agreement between measurements made using GAT, Pascal DCT and the ARGOS-SC system from V09 (month 12) through V13 (month 36). **Secondary Endpoints** **Safety** - Number of patients experiencing a device-related SAE (SADE) from V09 (month 12) to V13 (month 36) - Incidence, nature, severity and seriousness of observed adverse events and adverse device events at any time from month 12 (V09) through month 36 (V13). **Performance** - Repeatability of the ARGOS-SC measurement - Incidence, nature and seriousness of observed device malfunctions from month 12 (V09) throughout month 36 (V13) months follow-up period. **Utility** - User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of physician 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)

	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 65% of the measurements to agree between +/- 5 mmHg for > 60 measurements pairs.[1] **Follow-up Analysis** A safety and performance summary will be provided after V10, V11, V12 and V13 when all included patients have undergone the appropriate visit.
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 24 months.

[1] In the unprobeable case this number of measurement pairs is not reached, the primary objective is to be adjusted according to the actual number of measurement pairs.

TABLE OF CONTENTS

LISTINGS OF FIGURES AND TABLES

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
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
MEMS	micro-electromechanical system

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 [1–3]. 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 for Glaucoma

Glaucoma often remains asymptomatic until late in the disease, when irreversible vision problems and visual field restriction become evident. Although it may be present with intraocular pressure (IOP) considered to be in the normal range, the higher the IOP the more rapidly the damage progresses [1]. Reduction of IOP is the only known treatment to prevent visual disability in the patient's lifetime [3]. Lowering the IOP of patients with OAG by 20 to 40% can halve the rate of progressive nerve fibres damage [1]. 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 an escalation 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 [4].

3.3 Measurement of IOP

Ensuring whether maintenance of target IOP is adequate requires frequent monitoring using an IOP measuring device. There are several tonometric devices on the market, which can be categorized based on whether or not they involve direct corneal contact.

Weighing all limitations of currently available methods for estimating/measuring IOP, the Goldmann Applanation Tonometer (GAT), even though it's development dates back into the 1950's, still represents the gold standard technique for measuring the IOP, necessitating for the treating

ophthalmologist to weigh all influencing factors. During the last couple of years, there has been an effort to establish the Pascal Dynamic Contour Tonometer as an alternative to GAT. Both methods are regulatory approved methods:

Goldmann Applanation Tonometer

Goldmann Applanation Tonometry was first described in the 1950's [5, 6]. Like all applanation tonometers, it is based on the Imbert-Fick principle that the external force needed to flatten a portion of a sphere is proportional to the pressure within the sphere resisting the deformation [7]. Although it is considered to be the gold standard method to which all others IOP-Measurements are compared, GAT is limited by several factors. Corneal anaesthesia is required because the probe touches the cornea, which likewise raises the risk of infection and corneal abrasion [8]. The force needed to applanate the eye is also influenced by biomechanical properties of the cornea (thickness, rigidity, deformation), sclera and surface tear film, all of which can vary and are not fully characterized, making it difficult to correct for differences seen when these properties are outside normal ranges [2] [9–11]. For example, GAT is likely to under- or overestimate IOP in patients with thinner or thicker that average corneas [8].

Repetition of readings in short intervals, or other application of other pressure to the eye, such as pulling the eyelid up, can create artifacts. A skilled operator is required to perform the measurement, which is still prone to operator biases such as digit bias and bias towards the norm.

The greatest limitation however is, because a slit-lamp based, GAT readings have to be performed in a clinic or office setting with the patient in a seated position, limiting the frequency and ease with which readings can be made [7].

Pascal Dynamic Contour Tonometry

In Pascal Dynamic Contour Tonometry (DCT), IOP is measured by determining the force required to mould the cornea to the shape of the concave probe [8]. While it is far less influenced by corneal parameters than GAT, this method is still dependent on the assumption that the corneal properties, including rigidity, curvature and elasticity are within the normal range. As with GAT, the use of a slit-lamp is required, necessitating a clinic visit and limiting the frequency and ease with which it can be used. Direct corneal contact is also required, with its associated need for anaesthesia and risk of corneal damage and infection.

The accuracy of all devices that use secondary dimensions to estimate IOP 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 [12]. The majority of contact tonometers require use of corneal anaesthetics. 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 [13]. 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 [2, 14].

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

3.4 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, 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 through the forces the vitreous humour applies to the very thin 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 accurately measure IOP themselves in a home setting several times per day.

The IOP measurements obtained are stored in the Mesograph non-volatile 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. Within the study described herein, the patients have already received the implant when participating in the prior ARGOS-SC01 study.

The ARGOS-SC system has been derived from the directly related eyemate-IO system, which implantable part has been designed to be implanted into the ciliary sulcus of the human eye, which received CE-mark approval in 2017, after having demonstrated that to safely and accurately measure IOP in glaucoma patients who underwent cataract surgery [15], with an accuracy comparable to that of GAT.

The purpose of this clinical investigation, which is a follow up study that offers all patients who already participated in the ARGOS-SC01 study to further follow up device safety and performance from month 12 through month 36 after implantation. Follow-up does not require examinations or treatments that are not standard in the follow-up of patients that have received non-penetrating glaucoma surgery. The non-standard methods applied are taking benefit from the advantages the ARGOS-SC system offers in close monitoring of IOP.

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). 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 is 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 [16]. 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 [17].

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 implants 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 [18].

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 can 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 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 was 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

Site personnel responsible for device handling including accountability, storage and shipment procedures was 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.

<u>Intraocular pressure measurement using the Mesograph Reading Device</u>

- 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 are trained by sponsor representatives or their delegates. Subjects were 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 Pre-clinical testing/assessment

4.7.1 In vitro/Bench/Lab testing

4.7.1.1 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 [19]. 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 serrata. 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 [20] 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.

4.7.1.2 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 [21].

4.7.1.3 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 4.5 mm 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.

4.7.1.4 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.

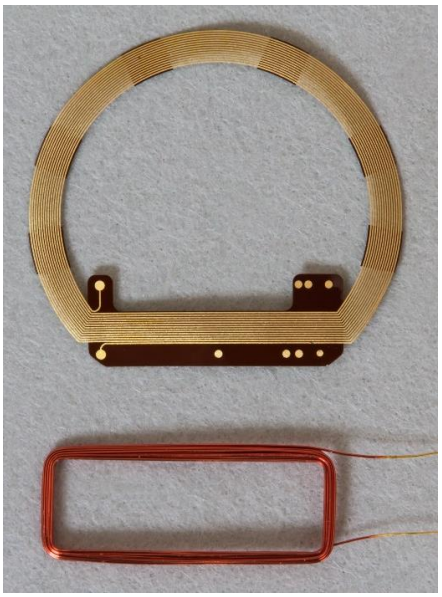
Both systems have a specified 3-sigma accuracy of 2 mmHg, and an annual drift rate not to exceed 2.5 mmHg. The output value of both systems is a pressure reading in mmHg. ISO 8612:2009 -- Ophthalmic instruments – Tonometers, the international standard that is specifying the requirements for conventional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

4.7.1.5 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

4.7.1.6 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) [22]. 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.

4.7.1.7 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 [23]. 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.

4.7.2 In vivo Studies

4.7.2.1 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 [24], 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 [25] 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).

4.7.2.2 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 [26].

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 [27].

4.8 Clinical experience with ARGOS SC Sensor in ARGOS-SC01 Study

4.8.1 Preliminary results of the comparison measurements between GAT and the ARGOS SC Sensor

Based on the concordance data available to date (see Figure 2 and Figure 3), we assess the performance of the test product as very good, since the intraocular pressures measured by the ARGOS SC sensor system compared to gold standard measurements (GAT) are well within the range expected based on pre-clinical experience.

Figure 2: Bland Altman: ARGOS-SC01 vs GAT (values in mmHg), total of 224 Comparisons as of December 04, 2019

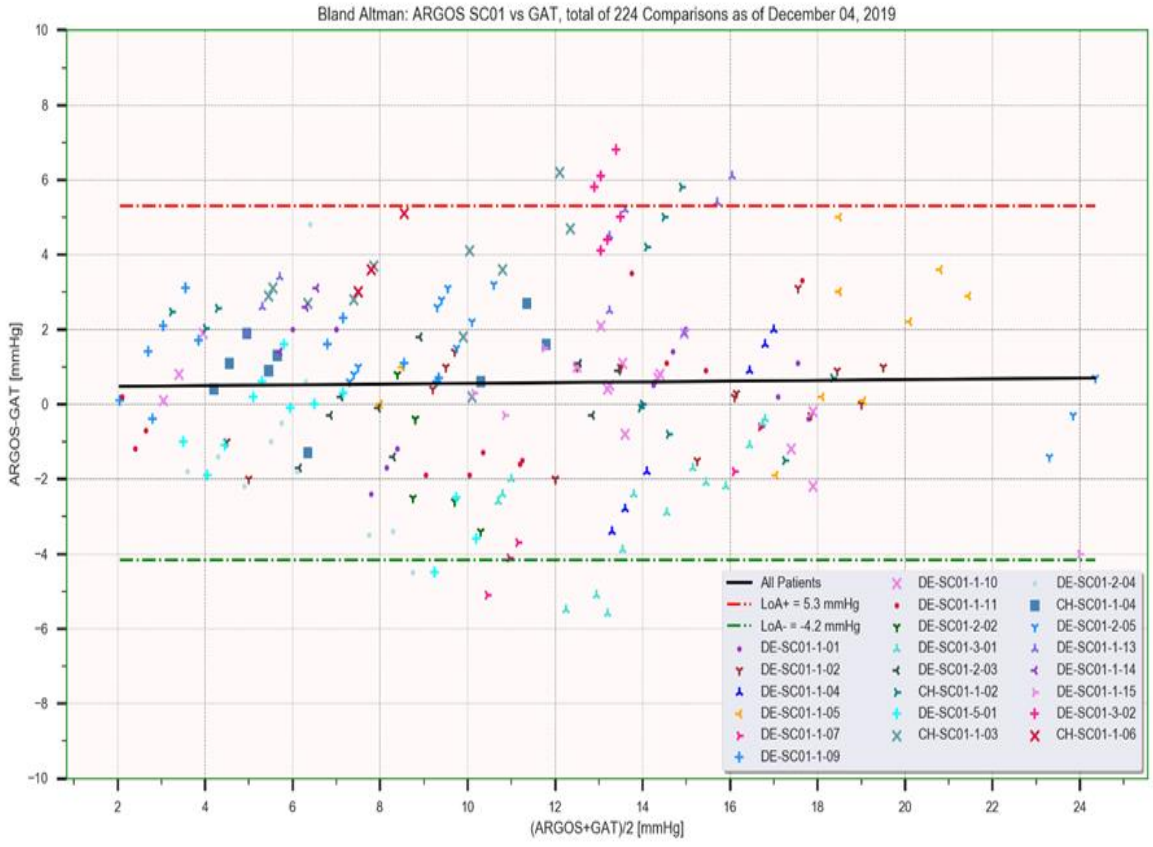
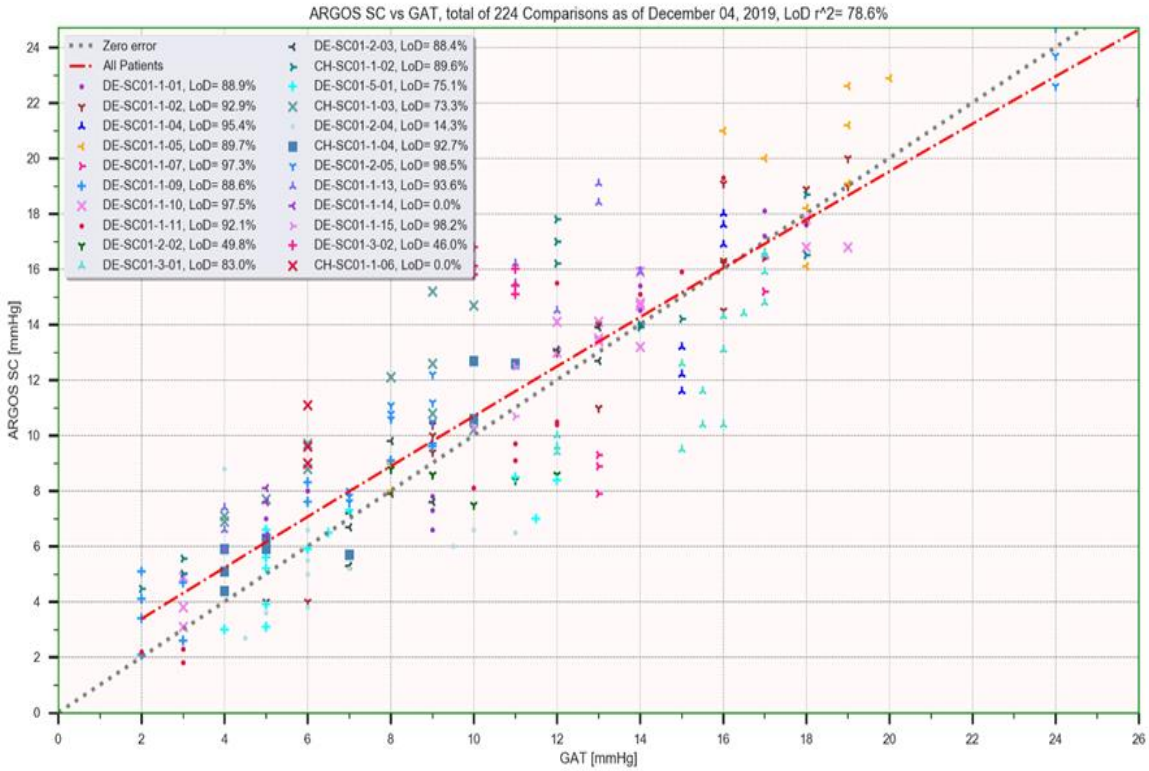


Figure 3: ARGOS-SC01 vs GAT (values in mmHg), total of 224 Comparisons as of December 03, 2019



4.8.2 Preliminary results of Adverse Events (AE) and Serious Adverse Events (SAE)

Table 1 provides an overview of the AEs that have occurred so far. A total of 43 AEs have occurred. ADEs and SADEs were not reported. Of the 43 AEs, 32 AEs were assigned to frequent eye pathologies (e.g. dry eye) and scheduled non-penetrating glaucoma surgery and were classified as expected events. In 63% (20) of 32 AEs no further treatment was necessary, 28% of the AEs could be resolved by administration of medication or non-pharmaceutical preparations (e.g. tear substitutes).

Ten percent, i.e. three patients, are currently still under treatment. In eleven of the remaining 11 AEs there is no causal relationship with the surgical intervention or the implant and includes, among other things, increased intraocular pressure in the partner eye or redness of the conjunctiva. For the AE "conjunctival folds", the causal relationship with keratoconjunctivitis sicca is considered probable and unlikely to be related to surgery or implantation of the pressure sensor. Only AEs that are also known to occur in a "standalone" procedure of non-penetrating glaucoma surgery have been reported (see Clinical Evaluation Report ARGOS-SC_RevB Section 2.2.4)

Table 1: Overview of all AEs for the ARGOS-SC01-Study, status 13.01.2020

Patient	AE_No	AE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical Procedure	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-1-01	1	**Keratoconjunktivitis (OU)**	No	No	Mild	**None**	None	None	None	Medication	**Recovered**	29.11.2018	13.12.2018	26.11.2018
	2	**Mild active bleeding**	Yes	No	Mild	**None**	Definite	None	None	None	**Recovered**	27.11.2018	28.11.2018	
	3	**Mild Seidel phenomenom**	Yes	No	Mild	**None**	Definite	None	None	None	**Recovered**	27.11.2018	06.12.2018	
	4	**Hyphema**	Yes	No	Mild	**None**	Definite	None	None	None	**Recovered**	03.12.2018	03.12.2018	
DE-SC01-1-02	1	**Pain in study eye after surgery**	Yes	No	Mild	**None**	Probable	Unlikely	None	Medication	**Recovered**	16.01.2019	16.01.2019	16.01.2019
	2	**Increased IOP**	Yes	No	Mild	**None**	Probable	None	None	Medication	**Recovered**	27.01.2019	05.02.2019	
	3	**Keratitis punctata superficialis**	Yes	No	Mild	**None**	Probable	None	None	None	**Recovered**	14.02.2019	17.04.2019	
	4	**Secundary cataract**	Yes	No	Mild	**None**	None	None	None	None	**Not recovered**	16.07.2019		
DE-SC01-1-04	1	**Catatact surgery combined with canaloplasty** (non-study eye)	Yes	No	Moderate	**None**	None	None	None	Non-pharmaceutical	**Recovered**	03.04.2019	03.04.2019	04.02.2019
	2	**Increased IOP non-study eye**	Yes	No	Mild	**None**	None	to the underlying disease: bilateral glaucoma	None	Medication	**Recovered**	17.04.2019	18.04.2019	

Patient	AE_No	AE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical Procedure	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-1-05	1	**IOP right eye 30 mmHg**	Yes	No	Mild	None	Possible	None	None	Medication	Recovered	06.04.2019	04.06.2019	06.03.2019
	2	**Conjunctival redness**	Yes	No	Mild	None	None	Probable: chronical Blepharitis	None	Medication	Recovered	08.05.2019	04.06.2019	
	3	**Hyphema**	Yes	No	Mild	None	Definite	None	None	None	Recovered	07.03.2019	09.03.2019	
	4	**Keratitis punctata superficialis**	Yes	No	Mild	None	Probable	None	None	Medication	Recovered	14.03.2019	05.04.2019	
DE-SC01-1-07	1	**Erythrocytes at the endothelium**	Yes	No	Mild	None	Definite	None	None	None	Recovered	25.06.2019	03.07.2019	24.06.2019
	2	**Hyphema**	Yes	No	Mild	None	Definite	None	None	None	Recovered	25.06.2019	03.07.2019	
	3	**Corneal edema**	Yes	No	Mild	None	None	None	None	None	Recovered	03.07.2019	04.07.2019	
	4	**Visual field loss** non-study eye	No	No	Moderate	None	None	None	None	None	**Not recovered**	13.09.2019		
DE-SC01-1-09	1	**Hyphema**	Yes	No	Mild	None	Definite	None	None	None	Recovered	26.06.2019	05.07.2019	25.06.2019
	2	**Erythrocytes at the endothelium**	Yes	No	Mild	None	Definite	None	None	None	Recovered	28.06.2019	05.07.2019	

Patient	AE_No	AE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical Procedure	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-1-10	1	**Seidel**	Yes	No	Mild	**None**	Definite	None	None	Non-pharmaceutical	**Recovered**	23.07.2019	01.08.2019	22.07.2019
	2	**Hyphema**	Yes	No	Mild	**None**	Definite	None	None	None	**Recovered**	23.07.2019	25.07.2019	
DE-SC01-1-11	1	**Hyphema**	Yes	No	Mild	**None**	Definite	None	None	None	**Recovered**	24.07.2019	26.07.2019	23.07.2019
DE-SC01-2-02	1	**Reduced visual acuity OS**	Yes	No	Moderate	**Unlikely**	Probable	None	None	None	**Recovered**	01.04.2019	03.04.2019	29.03.2019
	2	**Hypersensitivity if contact with upper lid and temporal forehead**	Yes	No	Moderate	**Unlikely**	Possible	Possible: Deep sclerectomy plus bleb plus sutures	None	None	**Recovering**	30.04.2019		
	3	**Upper lid sensations**	Yes	No	Mild	**Unlikely**	Possible	Possible: After deep sclerectomy procedure and bleb formation and sutures	None	Tear film lubrication	**Recovered**	22.05.2019	03.07.2019	
	4	**Keratoconjunktivitis sicca symptoms**	Yes	No	Mild	**Unlikely**	Possible	None	None	Tear film lubrication	**Recovered**	22.05.2019	03.07.2019	

Patient	AE_No	AE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical Procedure	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-2-03	1	**Hyphema**	Yes	No	Mild	**Unlikely**	Possible	Probable: After deep sclerectomy procedure	None	None	**Recovered**	27.08.2019	05.09.2019	26.08.2019
	2	**Choroidal detachment**	Yes	No	Mild	**Unlikely**	Probable	Probable: Hypotonic shift from 25 mmHg to 5-10 mmHg after deep sclerectomy	None	None	**Recovered**	05.09.2019	26.09.2019	
DE-SC01-2-05	1	**Hyphema**	Yes	No	Severe	**None**	Probable	None	None	None	**Recovering**	17.10.2010		16.10.2019
	2	**Visual acuity loss due to hyphema (AE 1)**	Yes	No	Severe	**None**	None	None	None	None	**Recovering**			
	3	**Conjunctivitis**	No	No	Mild	**None**	None	None	None	Medication	**Recovering**	01.11.2019		
DE-SC01-5-01	1	**Irritation because of conjunctival suture**	Yes	No	Moderate	**None**	Definite	None	None	Medication, Non-pharmaceutical	**Recovered**	09.10.2019	18.10.2019	18.09.2019
CH-SC01-1-05	1	**Perforation of the TDM**	Yes	No	Moderate	**None**	Definite	Unlikely	Implantation of ARGOS-SC sensor not possible	Surgery converted to trabeculectomy	**Recovering**	22.10.2019		

Patient	AE_No	AE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical Procedure	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-3-01	1	**Subconjunctival bleeding**	Yes	No	Moderate	**None**	Definite	None	None	Bleeding stopped with sponges	**Recovered**	27.08.2019	27.08.2019	27.08.2019
	2	**Vomiting**	Yes	No	Mild	**None**	Possible	Probable: Anaesthesia	None	Medication	**Recovered**	27.08.2019	27.08.2019	
	3	**Headache**	Yes	No	Mild	**None**	Possible	None	None	Medication	**Recovered**	27.08.2019	27.08.2019	
	4	**Hyposphagma**	Yes	No	Severe	**None**	Definite	None	None	None		27.08.2019		
	5	**Headache (intermittend)**	No	No	Moderate	**None**	Possible	None	None	Medication		01.09.2019		
	6	**Touch sensitivity of the eye at 12h**	Yes	No	Mild	**Possible**	Definite	None	None	None	**Recovered**	27.08.2018	27.11.2019	
	7	**Conjunctival folds**	No	No	Mild	**Unlikely**	Unlikely	Possible: sicca	None	Medication	**Not recovered**	26.09.2019		
	8	**Incision right arm**	No	No	Moderate	**None**	None	None	None	Medication, Wound suture, Tetanus vaccination	**Recovering**	13.11.2019		
	9	**Irritation surgical areal**	No	No	Moderate	**Possible**	Probable	None	None	Medication	**Recovered**	31.10.2019	27.11.2019	

Table 2: Overview of all SAEs for the ARGOS-SC01-Study, status 27.12.2020

Patient	SAE_No	SAE	Expected event	Serious	Severity	Causal Relationship with Medical Device	Causal Relationship with Medical	Causal Relationship with other	Action taken with regard to IMP	AE Treatment	Outcome	Start Date	Stop Date	Surgery Date
DE-SC01-1-02	**1**	**Undefinded Stomach Ache**	No	Yes	Moderate	**None**	None	None	None	Hospitalisation/Unkown	**Recovered**	21.10.2019	24.10.2019	16.01.2019
DE-SC01-1-13	**1**	**Syncope and retrograd amnesie, fracture of vertebrae**	No	Yes		**None**	None	None	None	Hospitalisation	**Ongoing**	18.11.2019		
DE-SC01-2-02	**1**	**Acute Dyspnoe**	No	Yes	Severe	**None**	None	None	None	Medication	**Recovering**	12.09.2019		29.03.2019

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 [28, 29].

5. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION FOR THE ARGOS-SC01_FOLLOW-UP STUDY

The planned ARGOS-SC01 follow-up study is an anticipated pre-market clinical follow-up study to systematically collect long-term data in patients who have completed the ongoing ARGOS-SC01 study after 12 months and are willing to participate in the study. Due to the fact that not all patients in the ARGOS-SC01 study are expected to be willing to participate in the clinical trial for another two years for personal or age-related reasons, we have designed this study in such a way that the patients are not exposed to any significant additional burden or risk beyond the clinical examination that is already regularly required in standard of care.

6. RISK EVALUATION

6.1 Anticipated clinical benefits

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 [30, 31]. Despite the emergence of newer technology [32, 33], the GAT is currently the most common method to routinely measure IOP [30]. The accuracy of GAT is dependent on corneal biomechanics, curvature, and thickness [34, 35]. In some situations, Applanation Tonometry is not possible such as in eyes implanted with keratoprosthesis [36].

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 [37–39].

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 [40, 41].

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, DCT. IOP values derived from the ARGOS-SC implant will in no case be used for therapy decisions as long as not validated.

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

No new ARGOS-SC implants will be implanted as part of this clinical trial. The regular glaucoma follow-up of the ARGOS-SC01 patients will be documented in this study. In addition to the clinical routine, the patients will measure their own IOP with the already implanted sensor device; patients gave their consent for implantation already in the ARGOS-SC01 study. The measured intraocular pressure is compared to the GAT-measurement. The measurement with the GAT with the associated anaesthesia of the ocular surface is part of the clinical standard of care routine for glaucoma patients, which is performed anyhow.

GAT, despite its minor risk factors (section 3.3), represents the current Gold-Standard in intraocular pressure measurement. Pascal Dynamic Contour Tonometry (DCT), when applied within the same examination, does not pose additional risk. The measurement of their own IOP with the already implanted sensor device does not pose a risk or burden on the patient. Home measurements with the ARGOS-SC should be performed by the patient four times a day, as already known from the ARGOS-SC01 study and recommended by physicians.

Table 3: Comparison IOP Measurements in Clinical routine and ARGOS-SC01_Follow-up study

Ophthalmological recommendation for appropriate patient care of glaucoma / glaucoma suspected patients (Leitlinie Nr. 15a[2])	Measurements in the ARGOS-SC01_Follow-up study
• Tonometry approximately 4 times a year and in case of e.g. deterioration of findings or doubts about compliance, at different times of day	• Tonometry with GAT and DCT semi-annual. ARGOS-SC measurements 4 times Daily (as recommended by physicians: morning, noon, afternoon and in the evening)
• Assessment of the optic nerve and nerve fibrous layer at least once annually	• Fundoscopy semi-annual
• Perimetry at least once a year	• Perimetry semi-annual
• Gonioscopy at least at the time of initial diagnosis	• Gonioscopy semi-annual

[2] Leitlinie Nr. 15a: Primary chronic open angle glaucoma, normal pressure glaucoma and ocular hypertension; Berufsverband der Augenärzte Deutschlands e.V., Deutsche Opthalmologische Gesellschaft e.V., October 2006

Patients are therefore not exposed to any significant additional burden or risk beyond the clinical examination that is already regularly required.

Data Privacy Risks – Health data about study patients will be collected and transferred to a state of the art electronic database. The data is stored pseudonymized. The sponsor has no access to personal data.

Patients will be requested to attend visits on a regular basis. Patients will be reminded that their continued participation is voluntary and in their best interest.

6.3 Possible Interactions with Concomitant Medical Treatments

The 12 o'clock quadrant of the eye is occupied because of the pressure-lowering surgical intervention in these patients.

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

- **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.
- **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).
- **X-ray:** High energy gamma radiation muss not be targeted towards the ARGOS-SC implant.
- **Other devices generating high-frequency electromagnetic fields:** The device meets the current requirements for EC and electronic radiation immunity.

Interactions with other active implanted medical devices:

- **Pacemakers:** the ARGOS-SC reader device 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

6.4 Risk/Benefit Assessment

The regular follow-up of the ARGOS-SC01 patients represents a low risk compared to the clinical standard of care routine of these glaucoma patients. The benefit to a patient of participating in the ARGOS-SC01_Follow-up study outweighs the low risks described above. 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. Additionally, it gives the treating ophthalmologists valuable information about the individual disease of a patient and the effectiveness of the medication regimen.

Consequently, the medical benefits of direct IOP measurement and frequent self-tonometry by patients at home clearly outweigh the identified risks of the regular follow-up of these ARGOS-SC patients and the ophthalmological measurements that are already necessary and that have to be performed during routine ophthalmological visits.

7. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

7.1 Objectives

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

7.1.1 Primary Objectives

Performance

- To evaluate the limits of agreement between measurements with the GAT, DCT and the ARGOS-SC system from month 12 throughout month 36 following implantation.

7.1.2 Secondary Objectives

Safety

- To evaluate the safety and tolerability of the ARGOS-SC pressure sensor throughout a follow-up period from month 12 throughout month 36.

Performance

- To evaluate the performance of the ARGOS-SC system from month 12 throughout month 36.

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 long-term assessment of the implanted ARGOS-SC sensor.

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 long-term safety of implantation and use of the ARGOS-SC sensor in humans who underwent 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 follow-up multicenter clinical investigation will enroll only subjects of the ARGOS-SC01 study with an implanted ARGOS-SC pressure sensor.

Subjects will be followed-up at regular intervals for 2 years (Month 12 – Month 36 following implantation).

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

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

<u>Performance</u>

- Level of Agreement between measurements made using GAT, Pascal DCT and the ARGOS-SC system from V09 (month 12) throughout V13 (month 36).

8.1.3.2 Secondary endpoints

Safety

- Number of patients experiencing a device-related SAE (SADE) at any from V09 (month 12) throughout V13 (month 36).
- Incidence, nature, severity and seriousness of observed adverse events and adverse device events at any time from month 12 (V09) throughout month 36 (V13).

Performance

- Incidence, nature and seriousness of observed device malfunctions during from month 12 (V09) throughout month 36 (V13).

Utility

- User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of physician 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.

8.2 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 09 through Visit 13 will be compared to those obtained using 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.

8.3 Subjects

8.3.1 Inclusion Criteria

Subjects of the ARGOS-SC01 clinical investigation with an implanted ARGOS-SC pressure sensor.

8.3.2 Discontinuation or Withdrawal Criteria

8.3.2.1 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.

8.3.2.2 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 inclusion in the study 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.
- 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.

8.3.2.3 Completed Subjects

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

8.3.2.4 Subjects lost to follow-up

If a subject fails to appear for a follow-up examination, reasonable effort should be made to locate or contact them to at least to determine their health status while fully respecting the subject's rights, 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 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.

8.3.4 Total expected duration of the clinical investigation

The estimated total duration of the study from first patient screened to last patient last visit is 36[3] months.

[3] The study duration of the ARGOS-SC01_Follow-up study is expected to be 36 months, as the overall recruitment for the ARGOS-SC01 study is expected to be finished by the end of February 2020, therefore the last patient will not be completed until February 2021 with V09, which is the V01 of the ARGOS-SC01_Follow-up study.

8.3.5 Expected duration of each subject's participation

The maximum duration of each subject's participation in this clinical intervention is 24 months. The point of enrollment is considered to be the last Visit 09 of the ARGOS-SC01 clinical trial.

8.3.6 Number of subjects required

This exploratory investigation will enroll maximal 24 patients.

8.3.7 Informed Consent

Eligible patients may only be included in the study after providing written informed consent as described in Section 11.1. Failure to obtain signed informed consent renders the patient ineligible for the study.

8.3.8 Allocation of Patient Number

Each subject is uniquely identified in the study by a combination of his/her country identifier, site number and patient number. The number will be the same number as in the ARGOS-SC01 clinical trial.

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

During the study, subjects will attend 4 clinic visits (V10 – V13). The Baseline Visit is V09, the last visit of the ARGOS-SC01 clinical investigation. The assessment schedule in summarizes all visits and the assessments to be performed at each. The visit window given in the table should be adhered to as closely as possible.

8.3.10 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.

8.3.11 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 and if available, additional 2 DCT measurements followed by 3 consecutive measurements with the ARGOS-SC system.

Patients were 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 general usability of the ARGOS-SC system, physicians 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 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.

8.3.12 Assessments

8.3.12.1 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.

8.3.12.2 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.

8.3.12.3 AEs/ADEs/SAEs/SADEs

All AEs/ADEs/SAEs/SADEs will be recorded.

8.3.12.4 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. Reasonable deviations from GAT measurements or reasonable intraserial ARGOS-SC measurement variability is not classified as a Device Deficiency.

8.3.12.5 Acceptance Questionnaires ARGOS-SC

In the study, two types of questionnaires will be used to assess potential strengths and weaknesses of the ARGOS-SC system. At V13 (Month 36), the investigator responsible for IOP measurement as well as the patients will be asked to complete a user acceptance questionnaire for the MESOGRAPH reading device and the general measurement procedure.

The aim of these questionnaires is to gain more information about the level of user-acceptance of the ARGOS-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.

8.3.12.6 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 V11 and V13.

8.3.12.7 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 of **both eyes**. The number of character read and the reading distance will be recorded. The standard testing distance is 4 meters.

8.3.12.8 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.

8.3.12.9 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.

8.3.12.10 Heidelberg Engineering ANTERION® (if available)

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

8.3.12.11 Anterior eye segment measurement of both eyes

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.

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.

8.3.12.12 Posterior eye segment measurement of both eye

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).
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 V11 and V13 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.

8.3.12.13 Intraocular pressure (IOP) measurement of both eyes

Intraocular pressure will be measured using three techniques. GAT will be performed in the clinic at every visit and if available,DCT. 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 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).

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-SC measurements, the patient has to stay in the same position as for the DCT-measurements (chin on chin rest, forehead installed).

ARGOS-SC system measurement by the subject at home

Subjects will receive detailed instruction in the use of the MESOGRAPH reading device. 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.

8.3.13 Surgery

No additional surgery is necessary in the ARGOS-SC01_Follow-up study, as the included patients have already received an implantation of the ARGOS-SC sensor in the ARGOS-SC01 study.

8.3.13.1 ARGOS-SC pressure sensor explantation, if medically necessitated

Note:	It is not necessary to explant an ARGOS-SC implant which is either non-functional or is known to function incorrectly. The malfunctioning device may safely remain in the eye.

Explantation of the ARGOS SC sensor can be performed if the implant poses a medical risk and the treating ophthalmologist deems it necessary. The explantation should only take place if the benefits outweigh the risks. The investigator is responsible for notifying the sponsor of such a procedure immediately upon gaining knowledge of it.

In the event that the sensor has to 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 will to be returned to Implandata Ophthalmic Products GmbH for analysis.
For the detailed ARGOS-SC explantation, please see *"IFU ARGOS-SC Implant).*

8.3.14 Study Visits

Assessments and procedures to be performed at each visit are indicated with an X in the assessment schedule in Table 4 (see also Section 8.3.12 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 4).

Table 4: Assessment Schedule ARGOS-SC01_Follow-up

Visit	V09	V10	V11	V12	V13
Indicative Days (D) Visit window	**Last Visit of ARGOS-SC01 (Baseline)**	**Month 18 (Day 540) +/- 3 weeks**	**Month 24 (Day 720) +/- 3 weeks**	**Month 30 (Day 900) +/- 3 weeks**	**Month 36 (Day 1080) +/- 3 weeks**
General					
Informed consent signed	X				
Inclusion & exclusion criteria	X				
Past and current significant medical history	X				
Vision related Quality of Life (VQoL) questionnaire	X		X		X
Visual acuity (ETDRS)[1] (OU)	X	X	X	X	X
Perimetry[2] (OU)	X	X	X	X	X
Heidelberg Engineering ANTERION®	X	X	X	X	X
External eye photography[3]	X	X	X	X	X
User acceptance questionnaire (patient)	X				X
User acceptance questionnaire (investigator)	X				X
Concomitant medication	X	X	X	X	X
AE/ADE/SAE/SADE	X	X	X	X	X
Device malfunction	X	X	X	X	X
Anterior Segment (OU)					
Optical Coherence Tomography[4]	X	X	X	X	X
Slit-lamp biomicroscopy[5]	X	X	X	X	X
Gonioscopy[6]	X	X	X	X	X
Posterior Segment (OU)					
Funduscopy[7]	X	X	X	X	X
Optical coherence tomography (OCT)[8]	X	X	X	X	X
Fundus photography[9]	X		X		X

Visit	V09	V10	V11	V12	V13
Indicative Days (D) Visit window	**Last Visit of ARGOS-SC01 (Baseline)**	**Month 18 (Day 540) +/- 3 weeks**	**Month 24 (Day 720) +/- 3 weeks**	**Month 30 (Day 900) +/- 3 weeks**	**Month 36 (Day 1080) +/- 3 weeks**
IOP Measurements					
Goldmann Applanation Tonometry[10] (OU)	X	X	X	X	X
Pascal Dynamic Contour Tonometry[10] (OU)	X	X	X	X	X
ARGOS-SC pressure sensor measurement[10]	X	X	X	X	X
ARGOS-SC pressure sensor self-measurement[11]	X	X	X	X	X

[1] 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.

[2] 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.

[3] 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.

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

[5] 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.

[6] 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.

[7] Funduscopy 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.

[8] 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).

[9] 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).

[10] 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:* additionally followed by 2 Pascal DCT measurements (in case of a difference of more than 2 mmHg, a third Pascal DCT measurement is required) and 3 directly consecutive ARGOS-SC system measurements.

For the non-study eye, only GAT and DCT measurements will be performed as described above.
All measurements should be performed directly one after another.

[11] 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.

8.3.15 Visit 09 (Month 12/Day 365)

V09 of ARGOS-SC01 is the baseline visit of ARGOS-SC01_Follow-up. At the Baseline visit, the investigator will conduct the informed consent process (section 11.1), ensuring that the subject's signature has been obtained on the patient informed consent (PIC) form and that the subject has received a copy before any study specific procedures are conducted. Once the PIC is signed, the subject will keep his assigned patient number from the ARGOS-SC01 study assigned (section 8.3.8).
In addition, the following procedures will be performed at this visit:

- Past and current significant medical history
- Recording of AEs/SAEs/ADEs/SADEs, concomitant medications and device malfunctions
- VQoL questionnaire
- User acceptance questionnaire (Investigator)
- User acceptance questionnaire (patient)
- Visual acuity (ETDRS) (OU)
- External eye photography
- Heidelberg Engineering ANTERION® (if available)
- Perimetry (OU)
- Anterior Segment assessments: slit-lamp biomicroscopy, AS-OCT), gonioscopy (OU)
- Posterior Segment assessments: funduscopy, PS-OCT, fundus photography (OU)
- IOP Measurement: GAT (OU) and ARGOS-SC. If available: Pascal DCT (OU)
- Patient ARGOS-SC self-measurements
- Remind subjects to promptly report any SAE that may occur at any time during the study.
- Complete the CRF and arrange the next visit.

8.3.16 Semiannual Follow-up visits V10 – V13 (Month 18 – Month 36)

Procedures to be conducted at the visits include:

- Recording of AEs/SAEs/ADEs/SADEs, concomitant medications and device malfunctions
- VQoL questionnaire (V11, V13)
- User acceptance questionnaire (Investigator) (V13)

- User acceptance questionnaire (patient) (V13)
- Visual acuity (ETDRS) (OU)
- External eye photography
- Heidelberg Engineering ANTERION® (if available)
- Perimetry (OU)
- Anterior Segment assessments: slit-lamp biomicroscopy, AS-OCT), gonioscopy (OU)
- Posterior Segment assessments: funduscopy, PS-OCT, fundus photography (V11, V13) (OU)
- IOP Measurement: GAT (OU) and ARGOS-SC. If available: Pascal DCT (OU)
- Patient ARGOS-SC self-measurements
- 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 13 is the study discharge/end of study visit. After this visit, subjects will return to standard care. The choice of keeping the implant or letting the implant be retrieved will be offered to the participating patients.

9. STATISTICS

9.1 Statistical design, method and analytical procedures

The primary purpose of this investigation is to assess the long-term performance of the investigational device. In order to investigate the long-term performance of the investigational device, the data obtained from the study will be evaluated with explorative and descriptive analysis of the outcome variables described below. Generally, summary tables will be presented. These are either frequency tables (ordinal or nominal data) or summary statistics with mean, standard deviation, median, minimum, maximum, lower and upper quartile (metric data).

Outcome variables that are recorded separately for the study eye, i.e. the eye with implanted ARGOS-SC sensor, and the fellow eye, i.e. the eye without ARGOS-SC sensor, will be also analyzed separately to allow comparisons between the study and fellow eyes.

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 those who complete the follow-up will be tabulated for the safety set. The number and percentage of 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 65% of the measurements to agree between +/- 5 mmHg for > 60 measurement pairs.[4]

9.2 Sample Size Calculation

Given by the exploratory nature of this study, the sample size is not driven by the need for a formal statistical hypothesis test with a certain degree of power. Instead, this study is driven by the desire to obtain a clinically meaningful amount of data to evaluate the long-term safety and performance of the ARGOS-SC system in patients who have been already implanted with the study device. Therefore the maximum sample size is 24. The minimal sample size for this study is at the Sponsor's direction. This is considered to be appropriate since no experimental treatments are planned and all assessments with exception of IOP measurement using the ARGOS-SC device are established standard methods.

9.3 Level of significance and the power of the clinical investigation

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

9.4 Interim analysis

A safety and performance summary will be provided after V10, V11, V12 and V13 when all included patients have undergone the appropriate visit.

9.5 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 8.3.2 Discontinuation or Withdrawal Criteria Early Patient Withdrawal and Section 11.11 Criteria for Suspension and Premature Termination of Study

[4] In the unprobeable case this number of measurement pairs is not reached, the primary objective is to be adjusted according to the actual number of measurement pairs.

- If, throughout the course of the study, the DSMB comes to the conclusion that the ARGOS-SC pressure sensor would expose the subject study patients to undue risk

All patients 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.

9.6 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.

9.7 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.

9.8 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.

9.9 Datasets to be analyzed

All subjects enrolled in this study will be included in the analysis since all subjects already have the ARGOS-SC sensor implanted and evaluable data for the primary performance are already recorded.

9.10 Site Monitoring

The study will be monitored in compliance with the Declaration of Helsinki, ISO 14155:2011, the Clinical Investigation Plan (CIP) and all applicable national and local regulations. All monitoring activities will be conducted by trained and qualified monitors, who will document each individual monitoring visit. In general, during monitoring visits the monitor will ensure that the study is being conducted according to the CIP, ISO 14155:2011, ICH GCP (International Conference on Harmonisation Good Clinical Practice) and other applicable regulations, and will compare the CRF entries to original source data. He/she will also make sure the informed consent procedure has been appropriately carried out and will ensure that all SAEs have been reported within applicable timeframes. He/she will also ensure that investigational device accountability has been maintained and will, after completion of the study, perform final accountability and arrange return or destruction of investigational products. 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.

9.11 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.

9.12 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 promptly 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. 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.

9.13 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.

9.14 Data retention and Retention period

9.14.1 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.

9.14.2 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.

10. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

10.1 Definitions

The following definitions are based on EU MDR 2017/745 Article 2 (part 57, 58 and 59) and the guidance document MDCG 2020-10/1.

10.2 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 subjects, whether or not related to the investigational medical device and whether anticipated or unanticipated.

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 or the comparator

10.2.1 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.

10.2.2 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, users or other persons, as defined by one or more of the following:
   a) a life-threatening illness or injury, or
   b) a permanent impairment of a body structure or body function including chronic diseases, or
   c) in-patient hospitalization or prolonged hospitalization, or
   d) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function
3. foetal distress, foetal death, a congenital abnormality or birth defect including physical or mental impairment

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

NOTE for Germany: The term SAE is defined according to EU MDR 2017/745 Article 2, (58).

10.2.3 Serious Adverse Device Effect (SADE)

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

10.2.4 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 current risk assessment report is defined as an Anticipated Serious Adverse Device Effect (ASADE).

10.2.5 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 assessment report is defined as an Unanticipated Serious Adverse Device Effect (USADE).

10.2.6 Device Deficiency

In accordance with EU MDR Article 2 (59), inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance is defined as a Device Deficiency. This includes malfunctions, use errors, or inadequacy of information supplied by manufacturer including labelling.

NOTE: Reasonable deviations from GAT measurements or reasonable intraserial ARGOS-SC measurement variability is not classified as a Device Deficiency.

10.3 Recording of Adverse Events (AEs)

All AEs will be documented throughout the clinical trial as per ISO 14155, chap. 7.4.1, 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.

10.3.1 Seriousness

Seriousness will be recorded as described in Section 10.2.2.

10.3.2 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.

10.3.3 Causality assessment (relationship to study device)

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan (this document) or the risk management file shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The following definitions are to be used (MDCG 2020-10/1):

- ***Not Related:*** Relationship to the device or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
  - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;

- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

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

- ***Probable:*** The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

- ***Causal Relationship:*** The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
  - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

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

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.
In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting not be delayed.
Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

10.3.4 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

10.3.5 Outcome

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

- Recovered
- Recovered with sequelae
- Ongoing
- Death

10.4 Reportable events and reporting methods

Based on the definitions above, the following events are considered reportable events in accordance with EU MDR 2017/745, Article 80 (2) and MDCG 2020-10/1:

a) any serious adverse event that **has a causal relationship** with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

All causality assessments should be made (see section 10.3.3). Only causality level 1 (i.e. “not related”) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event shall be reported.

Transition from MDD/AIMDD to MDR

Due to the transitional provisions in EU MDR Article 120 (11) the MDCG 2020-10/1 also covers clinical investigations which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC (AIMDD) or Article 15 of Directive 93/42/EEC (MDD) prior to 26 May 2021. These investigations may continue to be conducted after date of application of the MDR, but the reporting of serious adverse events and device deficiencies shall be carried out in accordance with the MDR requirements from 26 May 2021 and onwards.

It is acknowledged that the MDR implies changes to the reporting requirements compared to the directives’ requirements where all SAEs should be reported regardless of relatedness. Under MDR sponsors are no longer obliged to report SAEs that are “not related” to the clinical investigation procedures or the investigational device. At the date of application for MDR there will be ongoing events for clinical investigations initiated under directives legislation. As from the 26th of May 2021 sponsors are no longer expected to submit follow-up reports to NCAs for events that have been deemed “not related“. For ongoing events that have a causality assessment other than “not related” follow up reports will still have to be provided.

To facilitate the transition and give time for sponsors to update Clinical Investigation Plans and study procedures in clinical investigations a sponsor may continue to report all SAEs to NCAs until Eudamed reporting is mandatory. This applies only to studies which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC prior to 26 May 2021.

Overview of formats to be used by sponsor when reporting to CA

Table 5: Overview of formats to be used by sponsor when reporting to CA

Until May 25th 2021		**The tabular format from MEDDEV 2.7/3 Appendix I should be used**
Transition period	From May 26th 2021 until EUDAMED is available	The Tabular format of the guidance document (MDCG 2020-10/1, Appendix- Summary Reporting Form) should be used.
	When EUDAMED is available but not yet mandatory (the initial 6 months)	Either the Tabular format of the MDCG 2020-10/1 (Appendix- Summary Reporting Form) or the Eudamed web form can be used. Note: Once the shift to Eudamed reporting has been made for a specific clinical investigation, Eudamed should continue to be used for reporting all new events and updates to those events throughout the remainder of the clinical investigation.
From the timepoint when EUDAMED is mandatory		Web form via Eudamed shall be used for all new events, and updates to those events. The Tabular format of MDCG 2020-10/1 (Appendix- Summary Reporting Form) can be used only to transmit follow-up reports/final reports to the NCAs on events which were initially reported in this format.

The reporting form template provided in Annex of the guidance document MDCG 2020-10/1 shall be completed according to the information provided in section 10 of the guidance document.

Report to whom/when

Table 6: Reporting requirements

Report by	Report to	Timeline and description
Investigator	Sponsor	All "reportable events" to be reported immediately, but not later than three calendar days, after investigation site study personnel's awareness of the event.
Sponsor	All relevant NCAs	- For all "reportable events" which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **Immediately, but not later than 2 calendar days** after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. These concerns may be identified by either the NCA or the manufacturer. - Any other reportable events or a new finding/update to it: **Immediately, but not later than 7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

10.5 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.

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 authorities and ECs will be informed about SAEs according to local regulations as described in Table 6 and 7.

Table 7: SAE and Device Deficiency reporting requirements

Reporting Party	Reports to	Causal Relationship to Study Devices or Procedures	Reporting Timeline	Reporting Method
Investigator	Sponsor	All SAEs, regardless of relationship All Device Deficiencies according to EU MDR 2017/745 Article 2, (59)	Immediately upon learning of the event	Sponsor, monitor or other sponsor representative
Sponsor	BfArM	Relatedness cannot be excluded	Immediately upon learning of the event	Submission of SAE report form for single events within Germany (BfArM website)
		Relatedness can be excluded	Summary report every 3 months or as otherwise requested by BfArM	Submission of MDCG-SAE-Sammeltabelle

10.6 Recording and Reporting of Device Deficiencies

The investigator will record all observed device deficiencies by completing a Device Deficiency Form. The definition of device deficiency is based on EU MDR Article 2 (59) and is described in section 10.2.6 of this CIP.

If the device deficiency had the potential to lead to an SAE in the absence of appropriate measures or intervention, or in less favorable circumstances, then the investigator or principal investigator shall report this to the sponsor of the clinical Investigation without undue delay and the SAE form is to be completed.

10.7 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.

10.8 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 6 and Table 7 for details.

Table 8: Sponsor Reporting Responsibilities

Reporting Responsibility	Reports to	Description
Serious Adverse Events (SAEs) Device Deficiencies	Regulatory Authorities, ECs	See Section 10.2.2, 10.2.6 and 10.4 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	If the sponsor has temporarily suspended a clinical investigation or prematurely terminated a clinical investigation, he shall notify the Member State in which that clinical investigation has been temporarily suspended or prematurely terminated within 15 days by means of the electronic system referred to in Article 73, stating the reasons. If the clinical investigation has been temporarily suspended or prematurely terminated by the sponsor for safety reasons, he shall notify all Member States in which that clinical investigation is being conducted thereof within 24 hours.

Reporting Responsibility	Reports to	Description
Final Study Report	Investigators, ECs, relevant Regulatory Authorities	The sponsor will notify each Member State in which a clinical investigation has been conducted of the end of that clinical investigation in that Member State. That notification shall be made within 15 days of the end of the clinical investigation in that Member State. Furthermore the sponsor will notify the investigators of the completion or termination of the study. Regardless of the outcome of the clinical investigation, the sponsor has to submit a clinical investigation report in accordance with EU MDR 2017/745 Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV to the Member States in which a clinical investigation has been conducted within one year of the end or within three months of the early termination or temporary suspension of the clinical investigation.

11. ADMINISTRATIVE PROCEDURES AND RESPONSIBILITIES

11.1 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 14155:2011 standard and is considered appropriate for this study will be submitted to the Ethics Committees. The PIC will be translated into the local language of each country in which the study will be conducted and will contain language that is non-technical and understandable to the patient. Any changes to the PIC suggested by the investigator must be agreed to by Implandata Ophthalmic Products GmbH before submission to the EC and a copy of the EC approved version must be provided to the monitor after EC approval.

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

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

Subject information and the PIC will be revised if new information becomes available or a CIP amendment is issued regarding patient 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.

11.2 Vulnerable Subjects

Only mentally competent subjects will be enrolled in this study.

11.3 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.

11.4 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.

11.5 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.

11.6 Reporting responsibilities

11.6.1 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 10.3. Refer to Tables Fehler! Verweisquelle konnte nicht gefunden werden. **and Table 8: Sponsor Reporting Responsibilities** for SAE reporting responsibilities.

11.6.2 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 8: Sponsor Reporting Responsibilities
for details.

11.7 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.

11.8 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.

11.9 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.

11.10 Corrective and preventive action and principal investigator disqualification criteria

See section 11.9 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.

11.11 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.

11.12 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.

11.13 Subject follow-up requirements

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

11.14 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
- 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

12. PUBLICATION POLICY

12.1 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 8: Sponsor Reporting Responsibilities

in section 10.8 for further details.

12.2 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.

12.3 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.

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