CLINICAL INVESTIGATION PLAN

A prospective, open-label, multicenter clinical follow-up investigation of the ARGOS-01 and ARGOS-02 patients to assess the long-term safety and performance of the ARGOS-IO intraocular pressure sensor system in subjects with Primary Open Angle Glaucoma (POAG)

Reference Number: ARGOS-03

Revision:	Rev. C
Release Date:	April 25th, 2018
Sponsor:	Implandata Ophthalmic Products GmbH Kokenstrasse 5 30169 Hannover Germany

Sponsor Signature Page

ARGOS-03

A prospective open-label, multicenter clinical follow-up investigation of the ARGOS-01 and ARGOS-02 patients to assess the long-term safety and performance of the ARGOS-IO intraocular pressure sensor system in subjects with Primary Open Angle Glaucoma (POAG)

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Coordinating Investigator Signature Page

ARGOS-03

A prospective open-label, multicenter clinical follow-up investigation of the ARGOS-01 and ARGOS-02 patients to assess the long-term safety and performance of the ARGOS-IO intraocular pressure sensor system in subjects with Primary Open Angle Glaucoma (POAG)

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ARGOS-03

A prospective open-label, multicenter clinical follow-up investigation of the ARGOS-01 and ARGOS-02 patients to assess the long-term safety and performance of the ARGOS-IO intraocular pressure sensor system in subjects with Primary Open Angle Glaucoma (POAG)

Investigator Statement

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

<Investigator Name>

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SYNOPSIS

Title	A prospective open-label, multicenter clinical follow-up investigation of the ARGOS-01 and ARGOS-02 patients to assess the long-term safety and performance of the ARGOS-IO intraocular pressure sensor system in subjects with Primary Open Angle Glaucoma (POAG)
Study Number	ARGOS-03
Sponsor	Implandata Ophthalmic Products GmbH
Name of MD	**ARGOS-IO System** The ARGOS-IO system is composed of the implant and its accessories: **Implant**: ARGOS-IO pressure sensor implant for sulcus placement **Accessories:** MESOGRAPH reading device, the MESOGRAPH antenna patch and the telemetric Multiline Connector
Study Design	This study is a prospective open-label, multicenter study for clinical follow-up of the ARGOS-01 and ARGOS-02 patients
Patient Population	Subjects of the ARGOS-01 and ARGOS-02 study with an implanted ARGOS-IO pressure sensor. From the ARGOS-01 to the ARGOS-02 study, some modifications were made to the form of the ARGOS-IO implant in consequence of the outcomes of the ARGOS-01 study. Maximal 5 patients of the ARGOS-01 study and maximal 21 patients of the ARGOS-02 study will take part in this study. The sensor was always implanted in one eye only which will be the study eye.
Study Purpose	The purpose of this study is to evaluate the long-term safety and performance of the ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG)
Study Objectives/ Evaluation Criteria	**Primary Objectives** **Safety** - To evaluate the long-term safety and tolerability of the ARGOS-IO pressure sensor under consideration of incidence, nature, severity and seriousness of observed medical device related adverse and serious adverse events.

	Performance - To evaluate the limits of agreement between measurements with Goldmann Applanation Tonometry (GAT), Pascal Dynamic Contour tonometry (DCT) and the ARGOS-IO system - Incidence and nature of observed device malfunctions of the ARGOS-IO system **Secondary Objectives** - Evaluating the patient's compliance in IOP self-monitoring - Evaluating the impact of IOP self-monitoring on glaucoma progression - Evaluation of incidence in glaucoma medication change - Evaluation of number of unscheduled visits due to self-measured increased intraocular pressure
Data Collection Procedures	**Baseline (V01)** Consenting subjects will be enrolled. Baseline visit will include: • Demographics • Medical history and planned surgeries • Comparative measurements ARGOS-IO and GAT between the end of ARGOS-01/ARGOS-02 and study start of ARGOS-03 • Check of the functionality of the Mesograph and Multiline Connector (exchange if necessary) • Confirmation of the correct function of the ARGOS-IO sensor (adjustment if necessary) • Handout of patient diary General • Best-corrected visual acuity (BCVA) using ETDRS • Perimetry • Concomitant medication • Glaucoma medication • National Eye Institute Vision-related Quality of Life Questionnaire – VFQ-25 Anterior segment • External eye photography (Slit-lamp), including iris retroillumination • Slit-lamp biomicroscopy

	• Optical coherence tomography (OCT) of cornea and anterior chamber • Corneal endothelial cell density measurement • Gonioscopy <u>Posterior segment</u> • Funduscopy • Optical coherence tomography (OCT) of macula and optic nerve • Fundus photography <u>IOP measurement</u> • Goldmann Applanation Tonometry (GAT) • Pascal DCT tonometry • ARGOS-IO measurements **<u>Semiannual Follow-up (V02-V07)</u>** The examinations performed at each visit are listed without mentioning the single visit in parentheses. Examinations that are carried out only at distinct visits are indicated in parentheses. The follow-up visits will include: <u>General</u> • ADE/SAE/SADE • Device deficiency • Concomitant medication • Glaucoma medication • BCVA (EDTRS) • Perimetry • National Eye Institute Questionnaire – VFQ-25 (V03, V05 and V07) • Check patient diary for completeness <u>Anterior Segment</u> • External eye photography (slit-lamp), including iris retroillumination • Slit-lamp biomicroscopy • Optical coherence tomography (OCT) of cornea and anterior chamber • Corneal endothelial cell density measurement • Gonioscopy <u>Posterior segment measurement</u> • Funduscopy • Optical coherence tomography (OCT) of macula and optic nerve

	• Fundus photography (V03, V05 and V07) IOP measurement • Goldmann Applanation Tonometry (GAT) • Pascal DCT tonometry • ARGOS-IO measurements • ARGOS-IO self-measurements
Data Collection	Data will be collected using an electronic based Case Report Form (eCRF).
Study Duration	3 years

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2. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACA	Anterior Chamber Angle
ACD	Anterior Chamber Depth
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated serious adverse device effect
ASIC	Application specific integrated circuit
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CA	Competent Authority
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
D	Day
DCT	Dynamic contour tonometry
EC	Ethics Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
GAT	Goldmann Applanation Tonometry
GCP	Good Clinical Practice
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
MD	Medical Device
MHz	Megahertz
Mm	Millimeter
mmHg	millimeter(s) of mercury (a unit of pressure equal to the pressure that can support a column of mercury 1 millimeter high)
MPG	Medizinproduktegesetz
MRI	Magnetic resonance imaging
N	Sample number

NCT	Non-contact tonometry
NPG	Normal Pressure Glaucoma
OCT	Optical coherence tomography
PCB	Printed circuit board
PIC	Patient informed consent
POAG	Primary open angle glaucoma
Rev.	Revision
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMD	Surface mounted
SDV	Source Data Verification
TMF	Trial Master File
UBM	Ultrasound Biomicroscopy
V	Visit
VA	Visual acuity
USADE	Unanticipated serious adverse device effect

3. BACKGROUND INFORMATION

3.1 Glaucoma

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

3.2 Glaucoma Treatment

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

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

3.3 Measurement of IOP

3.3.1 Principle and Gold Standard

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

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

3.3.2 Available Devices

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

3.3.2.1 Direct Tonometer

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

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

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

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

3.3.2.2 Non-Contact Tonometer

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

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

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

3.3.3 Limitations

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

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

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

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

4. IDENTIFICATION AND DESCRIPTION OF THE ARGOS-IO SYSTEM

4.1 Summary Description of the ARGOS-IO System and its intended Purpose

The ARGOS-IO system was developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor (IOP, intraocular pressure) in patients with diagnosed glaucoma, or elevated or instable IOP that places them at a risk of ocular damage and loss of visual acuity. It is made up of four components: the ARGOS-IO implant, the external hand-held Mesograph reading device, the implant injector and the Multiline Connector.

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

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

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

A Mesograph antenna patch allows continuous 24h-measurements which are triggered automatically at regular intervals (e.g. every hour). This makes night measurements possible without the need of waking up the patient which can also influence the IOP. designed as follows: A flexible printed circuit board (PCB) representing a coil/antenna structure and tuned miniature surface mounted (SMD)

capacitors soldered onto the PCB result in the coil/antenna structure to resonate and induce an electromagnetic field when excited with a 13.56 MHz RF voltage. A low loss connector cable (coaxial) is connected to the PCB in a ruggedized fashion. The cable is terminated by a cable connector matching the Mesograph reader device RF connector. The PCB is protected from moisture ingress, and insulating the voltages induced within the resonating coil.

The PCB/cable assembly is laminated into a custom skin fixation system designed as an oval patch that is surrounding the eye, avoiding obstruction of the optical axis, minimizing patient discomfort, and securely fixating the coil/antenna in close proximity to the EYEMATE implantable device for >24h. All materials having skin contact are medical grade with an appropriate level of documentation.

The skin fixation system is a complex, multi-layer construction of highly breathable materials, conforming facial features surrounding the orbit. The adhesive layer design is emphasizing on sparing out facial hair, avoiding cosmetic issues and patient discomfort upon patch removal.

4.2 State of Device Development

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

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

As a result of these tests and the ARGOS-01 study, modifications were made to the form of the device and the implantation procedure to improve the device's safety profile. The implant thickness was reduced from 0.9 mm to 0.5 mm overall, tapering to a rounded outer edge of only 0.1 mm, and haptics were added to the device to better maintain its positional stability and to reduce mechanical stresses of the sensor on the eye. In addition, four haptic arms and two allantoid protrusions on the posterior surface of the ring were added to the ring to improve its positional stability, facilitate unfolding and better distribute pressure on the ring. When subjected to radial force, the redesigned sensor ring did not show the abnormalities in pressure readings or the plane distortions seen in the earlier version. The implant is also now available in three different diameters to allow selection of the implant size that best fits the individual participant. Related procedural changes, including the use of a cartridge injector similar to those used to insert foldable IOLs to insert the implant and first use of the sensor at 30 days post-surgery instead of at day 1 to 3 as in the previous study, are expected to reduce potential stress to the patients' anterior chambers during surgery and the initial post-surgical period. Together, these changes are expected to reduce irritation of the iris and pressure drifting observed in the ARGOS-01 study.
Due to the unique form of the human eye, and the exacting nature of the fit, it is not possible to assess the effects of the design modification in animals.

The **ARGOS-02 study** investigated the safety and performance of the ARGOS-IO system (second generation) in patients with primary open angle glaucoma. Over a one year period, 22 patients undergoing phacoemulsification and IOL implantation for cataract received ARGOS-IO implants in an add-on procedure. Their eye condition and IOP were followed over the course of 12 months.

The reported results indicate, that the modifications to the sensor design implemented after the ARGOS-01 trial as well as the introduction of an injector device for the implantation of the ARGOS-IO pressure sensor have led to a significant improvement of the safety and performance profile of the investigational device. The most notable clinical differences compared to the first generation of the device are as follows:

- Less inflammation: while all patients in the ARGOS-02 trial experienced at least some degree of postsurgical inflammation, in most cases this inflammatory response was similar in intensity and duration to that observed after standard cataract surgery. Most notably, not a single case of hypopyon occurred during the ARGOS-02 trial compared to two cases (33.3%) in the ARGOS-01 trial. There were still five patients (21,7%) who experienced fibrin exudation after surgery

(compared to 66.7% in the ARGOS-01 trial), two of which were briefly hospitalized and treated accordingly. All instances of anterior chamber inflammation resolved quickly however and the number of other inflammation related adverse events (corneal edema, cystoid macular edema) was low and comparable to rates reported in literature for cataract surgery alone.

- Less pigment dispersion: pigment dispersion, which may lead to increased intraocular pressure, was reported as adverse event for five out of six patients in the ARGOS-01 and eight out of 22 patients in the ARGOS-02 trial, thus constituting a significant reduction of pigment release to a rate similar to that seen in cataract surgery with sulcus fixed intraocular lenses. Further improvements can be expected, when the level of experience with the redesigned device increases.
- Better performance: concordance between ARGOS-IO measurements and GAT IOP was significantly better than in the ARGOS-01 trial. The mean difference between IOP obtained through ARGOS-IO and GAT was 10.2 mmHg in the ARGOS-01 trial and 2.8 mmHg in the ARGOS-02 trial. The 95% limits of agreement changed from -7.58 mmHg and 30.01 mmHg in the ARGOS-01 trial to -1.7 mmHg and 7.4 mmHg in the ARGOS-02 trial.
- Better fit in the ciliary sulcus: while in the ARGOS-01 trial the thickness and rigidity of the implant led to the flattening of the anterior chamber and some patients, no AC flattening was seen in the ARGOS-02 trial. At least one serious adverse event was related to the implant size in the ARGOS-02 trial (see SAE DE-07-001). This was due to the outer diameter of the implant, rather than its thickness, and led to the revision of the clinical investigation plan: in order to better estimate the diameter of the ciliary sulcus UBM is preferable to determination of the white to white distance (corneal diameter).
- In the ARGOS-01 trial, a sudden and unexpected offsets in IOP measurements occurred in one patient without discernible external cause. Two similar offsets in ARGOS-02 trial where the direct result of external manipulation of the eye: one patient experienced an offset after ultrasound biomicroscopy (UBM), one of the patient had an offset after YAG capsulotomy during follow-up. In both cases, the sensor could be successfully recalibrated.

Overall, the second generation ARGOS-IO pressure sensor and the use of an implant injector significantly improve the outcome of implantation and got a CE-Certificate on May 24th, 2017.

4.3 Anticipated clinical Benefits

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

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

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

will receive from the device is expected to motivate better compliance with the treatment regimen, thereby facilitating improved IOP control and optimizing long-term patient outcome.

5. STUDY OBJECTIVES

5.1 Objectives

The aim of this trial is to verify the long-term safety and performance of the ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG). The measurements of intraocular pressure through the pressure sensor shall be compared with Goldmann Applanation Tonometry (GAT), which is generally accepted as the clinical gold standard and the Pascal Dynamic Contour Tonometer (DCT).

5.1.1 Primary Objectives

5.1.1.1 Safety

- The primary objective of this clinical trial is to evaluate the long-term safety and tolerability of the ARGOS-IO pressure sensor under consideration of incidence, nature, severity and seriousness of observed medical device related adverse and serious adverse events.

5.1.1.2 Performance

- To evaluate the performance of the ARGOS-IO system compared to Goldmann Applanation Tonometry (GAT) and Pascal Dynamic Contour tonometry (DCT)
- Incidence and nature of observed device malfunctions of the ARGOS-IO system

5.1.2 Secondary Objectives

- Evaluating the patient's compliance in IOP self-monitoring
  - Daily self-measurements with the ARGOS-IO sensor should be done at least 4 times daily (morning, noon, afternoon, evening)
- Evaluating the impact of IOP self-monitoring on glaucoma progression
  - Parameters to evaluate the glaucoma progression are visual field, cup/disc ratio, OCT of the optic nerve and the IOP.
- Evaluation of incidence in glaucoma medication change
- Evaluation of number of unscheduled visits due to self-measured increased intraocular pressure
  - The patients decide to come for a visit by their own due to any reason. This will be documented.

5.2 Claims and intended Performance of the ARGOS-IO System to be verified

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

5.3 Risks and anticipated Adverse Device Effects to be assessed

Information will be collected on all ADEs. Particular attention will be paid to the following AEs (AEs of special interest):

- Signs of toxicity of the implant
- Uncontrolled increase in IOP
- Changes in anterior chamber structures including ACD and ACA
- Anterior chamber inflammation (Tyndall/flare/anterior chamber cells)
- Fibrin reaction (e.g. anterior chamber fibrin, fibrin deposition on lens)
- Corneal endothelial cell loss
- Pigment dispersion
- Iris transillumination defect

6. DESIGN OF THE CLINICAL OBSERVATIONAL STUDY

6.1 General Aspects

6.1.1 Description of the Type of Clinical Trial

The trial will be conducted as a prospective, open-label, multicenter clinical follow-up trial.

The trial will include the ARGOS-01 patients (max. 5 patients) and the ARGOS-02 patients (max. 21 patients). From the ARGOS-01 study to the ARGOS-02 study, some modifications to the form of the ARGOS-IO implant were made in consequence of the outcomes of the ARGOS-01 study.

The design modifications made included:

- Addition of 4 haptics at the outer edge of the implant
- Reduction in device thickness from a uniform 0.9 mm to 0.5 mm overall, tapering to a 0.1 mm rounded outer edge

- Addition of two allantoid protrusions runnine on either side of the posterior surface from the middle of the ring to the ASIC.

The ARGOS-IO implant used in the ARGOS-01 study had an outer diameter size of 11.3 mm, an inner diameter size of 7 mm and an overall thickness of 0.9 mm. In the ARGOS-02 study three different sizes were used: Ø 11.3 mm, Ø 11.7 mm and Ø 12.1 mm; all with an inner diameter of 7 mm and thickness of 0.5 mm.

All consenting ARGOS-IO patients are eligible for enrolment into the study.

6.1.2 Equipment to be used to assess the clinical trial variables and arrangements for monitoring maintenance and calibration

Sites will use their own ophthalmology diagnostic devices. The requested calibration intervals have to be followed.

Following any ocular procedure and at least once a year the correct function of the ARGOS-IO implant must be confirmed by an experienced and qualified specialist using GAT (the average of 3 ARGOS-IO measurements are compared to one GAT measurement), and adjusted if necessary (please refer to the *Mesograph IFU* for details).

6.2 ARGOS-IO and comparator(s)

6.2.1 Justification of the choice of comparator

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

6.2.2 Other medical devices or medication to be used

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

6.3 Subjects

6.3.1 Inclusion Criteria

ARGOS-01 and ARGOS-02 patients who are willing to provide written informed consent.

6.3.2 Discontinuation or Withdrawal Criteria

6.3.2.1 Premature subject withdrawal

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

All subjects who withdraw from the study before completing the last follow-up visit (V7) will be considered to be drop-outs. Unless the patient revokes his/her permission to use it, any data collected up to the point of the patient's withdrawal will be included in the safety analysis. The data of all subjects will be included in the efficacy analysis under the Full Analysis Set.

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

- The patient withdraws informed consent.
- The ARGOS-IO pressure sensor must be removed or replaced for any reason (e.g. in consequence of an AE related to a study device or procedure).

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

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

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

- Removal of the ARGOS-IO sensor
- Other reason.

6.3.2.2 Completed Subjects

A completed subject is considered to be a subject that completed the last follow-up visit (V7). In addition, a subject who completed the study according to the clinical investigation plan is defined as a subject who attended all study visits.

6.3.2.3 Subjects lost to Follow-up

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

6.3.3 Point of Enrolment

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

6.3.4 Expected Duration of each Subject's Participation

The maximum duration of each patient's participation in this clinical intervention is 3 years. The point of enrolment is considered to be the time point at which potentially eligible subjects sign the informed consent form. The patient will be followed-up for 3 years to obtain data on safety and performance.

6.4 Study Procedures

6.4.1 Informed Consent

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

6.4.2 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-01 or ARGOS-02 study.

6.4.3 Methods and Timing for assessing, recording, and analyzing Parameters

During the study, subjects will attend 7 clinic visits V01-V07 (days 0, 180, 360, 540, 720, 900 and 1080). The assessment schedule in Table 2 summarizes all visits and the assessments to be performed at each visit. The study protocol does not define exact referral dates for follow-up visits. However, follow-up visits should be scheduled +/- 3 weeks around the respective date.

6.4.3.1 Safety

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

6.4.3.2 Performance

IOP level will be assessed at every visit with GAT, Pascal DCT and the ARGOS-IO system. Measurements will be performed in series of 2 GAT measurement followed by 3 consecutive measurements with the ARGOS-IO system and 2 DCT measurements followed by 3 consecutive measurements with the ARGOS-IO system.

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

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

6.4.4 Assessments

6.4.4.1 Patient Demographics/other Baseline Characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: year of birth, sex, race, weight, height and educational level

6.4.4.2 Comparative Measurements

All ARGOS-IO measurements which were performed in the clinic between study end of the ARGOS-01/ARGOS-02 trial and which have a comparative GAT measurement should be entered in the eCRF.

6.4.4.3 Medical History

Relevant medical history/current medical condition data includes data five years back until start of the study and everything what is important of the investigator's point of view. 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.

6.4.4.4 Concomitant Medication, Treatments and Devices

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

6.4.4.5 ADEs/SAEs/SADEs

All ADEs/SAE/SADEs will be recorded.

6.4.4.6 Check of functionality of the Mesograph and Multiline Connector

At V01, the Mesograph will be tested for no error messages, enough storage and filled charged battery. The Multiline Connector will be tested for proper data transmission. If necessary, the devices will be changed.

6.4.4.7 Confirmation of the correct function of the ARGOS-IO sensor

The correct function of the ARGOS-IO implant must be confirmed using GAT (the average of 3 EYEMATE-IO measurements are compared to one GAT measurement), and adjusted if necessary (please refer to the *Mesograph IFU* for details).

6.4.4.8 Device Malfunctions

All observed device malfunctions will be recorded.

6.4.4.9 Patient diary

At V01, the investigator hand out a patient diary to the patient in order to document their medication administration and activities at the "IOP day" once a month.

At the follow-up visits, the investigator should check it for completeness and if the diary is not kept regularly, the investigator should brief the patient again.

6.4.4.10 Visual Acuity (VA)

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

6.4.4.11 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 eyes.

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

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

The VFQ-25 is a standardized questionnaire about quality of life relating the patient's vision. It should be completed by the patient at V01, V03, V05 and V07.

6.4.4.13 Anterior Segment Evaluation

External Eye Photography (Slit-lamp)

External eye photography will be performed in order to document potential changes to the anterior segment of the eye involving the conjunctiva, cornea, iris (e.g. iris transillumination) or pupil structure.

Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy involves the examination of the external eye and anterior segment structures. The following anatomic parameters will be assessed by using the slit-lamp biomicroscopy:

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

Optical Coherence Tomography (OCT)

Standard anterior segment OCT will be used to evaluate effects on change in chamber angle and to assess the central corneal thickness. A change of the OCT device should be avoided during the study.

Confocal Microscopy

tandard confocal microscop will be to determine corneal endothelial cell density.
A change of the should be avoided during the study.

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.

6.4.4.14 Posterior Segment

Funduscopy (dilated)

The posterior segment will be examined using a slit lamp in combination with a 90D or “Superfield” or comparable lenses. The entire fundus should be assessed including optic disc, posterior pole including macula and peripheral retina. Any variations of the norm, defects or lesions should be documented.

Optical Coherence Tomography (OCT)

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

If available, it should be used the Heidelberg Engineering Spectralis Glaucoma-Module Premium Edition (Minimum rim width at Bruch membrane opening (BMO-MRW), RNFLT and macula). This should always be done on both eyes in order to compare study and fellow eyes.

Fundus Photography

Standard fundus photography will be performed at baseline D180 and then once a year 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.

6.4.4.15 Intraocular Pressure (IOP) Measurement

Intraocular pressure (IOP) will be measured using three techniques. Goldmann Applanation Tonometry (GAT) and Pascal Dynamic Contour Tonometer (DCT) will be performed in the clinic at every visit. ARGOS-IO will be performed in the clinic at every visit and by the patient at home between 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

Each IOP measurement will be conducted as a series of 2x GAT (with difference more than 2mmHg, a third GAT-measurement is required) followed by 3x ARGOS-IO system. When series of measurements are made, GAT must always be used first to avoid potential operator bias. For the ARGOS-IO measurements the patient has to stay in the same position as for the GAT-measurements (chin on chin rest, forehead installed). Then a series of 2x DCT (with difference more than 2mmHg, a third DCT-measurement is required) followed by 3x ARGOS-IO will be performed after the series of GAT and ARGOS-IO measurements. For the ARGOS-IO measurements, the patient has to stay in the same position as for the DCT-measurements (chin on chin rest, forehead installed).

ARGOS-IO System Measurement by the Patient at Home

The patients will be requested to perform IOP measurements with the Mesograph 4 times daily at home. The measurements should be done in the morning (7-9 o'clock), about noon (11.30-13.30 o'clock), in the afternoon (15-17 o'clock) and in the evening (19-24 o'clock).

Once a month, a fixed "IOP-day" will be scheduled where the patients are asked to measure their IOP every hour and additionally 1 hour pre and post drug administration. For these days, patients are requested to document their activities in the delivered patient dairy. The day will be scheduled at the convenience of the patient and investigator and should remain the same for every month and the study duration (e.g. first day of the month, first Saturday of the month etc.).

Quarterly and optional for the patients, one of the "IOP-days" will be scheduled for night measurements (22-6 o'clock) in addition to the day measurements every hour. The patient will be supplied therefore with the MESOGRAPH antenna patch which will do the measurements automatically.

Patients will also be requested to connect the reader to the Multiline Connector on a regular basis to transfer the recorded IOP data directly into the secure database. No manual recording of data by the patient will be required.

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

6.4.5 Concomitant Medication

The use of concomitant medication is at the discretion of the investigator.

6.5 Study Visits

6.5.1 Baseline Visit, V01 (Day 0)

At the Baseline visit, the investigator will conduct the informed consent process (section 12.1), ensuring that the subject's signature has been obtained on the patient informed consent (PIC) form and that the subject has received a copy before any study specific procedures are conducted. Once the PIC is signed, the subject will be assigned a patient number (section 6.4.2).

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

- Collection of background information about the subject including: demographics, medical history with prior treatments and current medications and comparative measurements (see 6.4.4.2)
- Check of the functionality of the Mesograph and Multiline Connector (exchange if necessary)
- Confirmation of the correct function of the ARGOS-IO sensor (adjustment if necessary)
- Handout of patient diary
- Best corrected visual acuity (BCVA) using ETDRS
- Visual field (standard automated static perimetry, see section 6.4.4.8)
- National Eye Institute – Vision-related Quality of Life Questionnaire-25 (VFQ-25)
- Anterior Segment
    - External eye photography (Slit-lamp), including iris retro illumination
    - Slit-lamp biomicroscopy
    - OCT of cornea and anterior chamber
    - Corneal endothelial cell density measurement
    - Gonioscopy
- Posterior Segment Measurement
    - Funduscopy
    - OCT of macula and optic nerve
    - Fundus photography
- IOP Measurement:
    - GAT and ARGOS-IO system
        - 2x GAT, 3x ARGOS-IO (Measurement by investigator with the patient's head still in the headrest from GAT, see 6.4.4.12)
    - DCT and ARGOS-IO system
        - 2x DCT, 3x ARGOS-IO (Measurement by investigator with the patient's head still in the headrest from DCT, see 6.4.4.12)
    - ARGOS-IO self-measurements at home (4 measurements daily, "IOP-day" once a month see 6.4.4.12)
- Instruct subjects on the need to report as soon as possible any SAEs occurring at any time during the study

- Complete the CRF and arrange the next visit

6.5.2 Follow-up Visits V02-V07 (D180, D360, D540, D720, D900, Day 1080)

Procedures to be conducted at the visits include:

- Recording of eye related AEs, ADEs, AEs and SADEs
- Device deficiencies
- Concomitant medications
- Check patient diary for completeness
- BCVA (EDTRS)
- Perimetry
- National Eye Institute – Vision-related Quality of Life Questionnaire-25 (VFQ-25) (V03, V05, V07)
- Anterior Segment Measurements:
    - External eye photography, including iris retroillumination
    - Slit-lamp microscopy
    - OCT of cornea and anterior chamber
    - Corneal endothelial cell density measurement
    - Gonioscopy
- Posterior Segment Measurements:
    - Funduscopy
    - OCT of macula and optic nerve
    - Fundus photography (V03, V05, V07)
- IOP Measurement:
    - GAT and ARGOS-IO system
        - 2x GAT, 3x ARGOS-IO (Measurement by investigator with the patient's head still in the headrest from GAT, see 6.4.4.11)
    - DCT and ARGOS-IO system

- 2x DCT, 3x ARGOS-IO (Measurement by investigator with the patient's head still in the headrest from DCT, see 6.4.4.11)

- ARGOS-IO self-measurements at home (4 measurements daily, "IOP-day" once a month see 6.4.4.12)

- Complete the CRF and arrange the next visit

6.6 Visit Schedule and Assessments

Table 1 lists all assessments and indicates with an "X" the visits at which they and related assessments are to be performed. The visit window given in the table should be adhered to as closely as possible.

Table 1 Assessment Schedule

Visits	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**
Indicative Days (D)	**D0**	**D180 +/- 3 wks**	**D360 +/- 3wks**	**D540 +/- 3wks**	**D720 +/- 3wks**	**D900 +/- 3wks**	**D1080 +/- 3wks**
General							
Informed Consent	X						
Handout of the patient diary	X						
Demographics	X						
Past and current significant medical history	X						
Comparative measurements	X						
Check of the functionality of the Mesograph and Multiline Connector	X						
Confirmation of the correct function of the ARGOS-IO sensor	X						
Visual acuity (EDTRS)[1] *(both eyes)*	X	X	X	X	X	X	X
Perimetry *(both eyes)*	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Eye related AEs/ADE/SAE/SADE	X	X	X	X	X	X	X
NEI VFQ-25	X		X		X		X
Device deficiency		X	X	X	X	X	X
Check patient diary for completeness		X	X	X	X	X	X

Visits	V01	V02	V03	V04	V05	V06	V07
Indicative Days (D)	**D0**	**D180 +/- 3 wks**	**D360 +/- 3wks**	**D540 +/- 3wks**	**D720 +/- 3wks**	**D900 +/- 3wks**	**D1080 +/- 3wks**
Anterior Segment (both eyes)							
External eye photography (Slit lamp)	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X
Optical coherence tomography[2]	X	X	X	X	X	X	X
Corneal endothelial cell density	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X
Posterior Segment (both eyes)							
Funduscopy	X	X	X	X	X	X	X
Optical coherence tomography[3]	X	X	X	X	X	X	X
Fundus photography[4]	X		X		X		X
IOP measurement[5]							
Goldmann Applanation *(both eyes)*	X	X	X	X	X	X	X
Pascal DCT *(both eyes)*	X	X	X	X	X	X	X
ARGOS-IO clinic	X	X	X	X	X	X	X
ARGOS-IO home[6]	X	X	X	X	X	X	X

[1]The best corrected visual acuity will be determined after objective and subjective determination of refraction with the EDTRS chart.

[2] Anterior segment OCT is performed to assess the central cornea thickness and to evaluate effects on change in chamber angle after implantation.

[3] Posterior segment OCT is used to assess macular structures and the peripapillary nerve fiber layer thickness (RNFLT) and (if possible) BMO-MRW

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

[5] IOP-measurements will be performed in series of 2 GAT measurement (with difference more than 2mmHg, a third GAT-measurement is required) and 3 directly consecutive measurements with the ARGOS-IO system followed by 2 Pascal tonometry (with difference more than 2mmHg, a third DCT-measurement is required) and 3 directly consecutive measurements with the ARGOS-IO system.
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.

[6] Measurements at home shall be taken at least 4 times per day (morning, noon, afternoon, evening). Once a month, an "IOP day" will be scheduled with measurements every hour and additionally one hour pre and post drug administration. The activities on that day will be documented in a patient dairy.
Optional: Quarterly additional night measurements on one of the "IOP days". Patients will be supplied therefore with the MESOGRAPH antenna patch which will do the measurements automatically.

7. STATISTICS

This section describes the most important aspects of the statistical analyses intended at the time of investigation planning. Further details on the statistical and analytical aspects will be presented in the Statistical Analysis Plan (SAP). The Statistical Analysis Plan will be finalized before study database lock.

7.1 Variables for Analysis

7.1.1 Disposition

- Number of subjects enrolled
- Number of subjects who completed the study (according to protocol),
- Number of subjects who discontinued the study including the reason for discontinuation
- Number of subjects per visit
- Time to discontinuation / study completion

7.1.2 Demographics

- Age calculated by: Year fraction of date of V01 - Year of birth
- Sex
- Race
- Weight
- Height
- BMI calculated from weight and height by: Weight [kg] / Height [m]^2
- Educational level

7.1.3 Medications and Medical History

- Past and current medical history
- Concomitant medication
- Glaucoma medication

7.1.4 Primary Outcome Variables

Safety:

- Incidence of medical-device related adverse events

- Incidence of medical-device related serious adverse event.
    - An AE is considered to be device-related if there is at least a possible relationship to the medical device according to the rating of the investigator
    - An AE is considered to be serious if it meets any of the criteria defined in Section 9.1.1.2

The analysis will be split by nature, severity and seriousness of medical device related adverse and serious adverse events.

Performance:

- Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system at each study visit.
- Limits of agreement between IOP measurements made using DCT and the ARGOS-IO system at each study visit.
- Incidence of observed device malfunctions and nature of device malfunction (e.g. difference of more than 5 mmHg between ARGOS-IO and GAT, readout error of the Mesograph because of measurements outside -2 and +70mmHG).

7.1.5 Secondary Outcome Variables

- Progression of visual field, cup/disc ratio, OCT results for the optic nerve and IOP over the course of the study.
- Number of changes in glaucoma medication.
- Number of unscheduled visits due to self-measured increased IOP.

7.1.6 Additional Outcome Variables

- Best corrected visual acuity at each visit (both eyes).
- Scores for the National Eye Institute Vision-related Quality of Life Questionnaire – VFQ-25 at the respective visit.
- Device deficiencies.
- External eye photography results at each visit (both eyes)
- Slit-lamp biomicroscopy results at each visit (both eyes)
- Corneal endothelial cell density results at each visit (both eyes)
- Gonioscopy results at each visit (both eyes)
- Funduscopy results at each visit (both eyes)

- IOP self-measurements

7.2 Statistical Design, Method and analytical Procedures

The statistical analysis of this study will include an explorative and descriptive analysis of the outcome variables described above. 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-IO sensor, and the fellow eye, i.e. the eye without ARGOS-IO sensor, will be also analyzed separately to allow comparisons between the study and fellow eyes.

All details regarding calculated variables and proposed format and content of tables will be described in the SAP.

7.2.1 Subject Disposition

The variables describing the subject disposition will be tabulated using the descriptive statistics defined at the beginning of Section 7.2.

7.2.2 Demographic and Baseline Characteristics

Demographic characteristics (year of birth, sex, race, weight, height, BMI, educational level) and all other outcome variables including medications and medical history assessed at V01 will be tabulated using the descriptive statistics defined at the beginning of Section 7.2.

Frequencies of previous and concomitant medications will be given based on different ATC code levels. Medical history and concomitant diseases will be described based on MedDRA system organ class and preferred term levels.

7.2.3 Analysis of Primary Safety Outcome Variables

All recorded AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time the database is closed. Only eye-related AEs will be included in the analysis.

Incidences will be calculated for eye-related AEs, medical-device related AEs and, in case there are more than 5 events, also for medical-device related SAEs on the system organ class level and on the preferred term level.

In addition to incidences in total, incidences of will be given by severity and seriousness.

In order to evaluate the long-term safety, the incidence rate of medical-device related adverse events per 10 patient years and accompanying exact 95% confidence intervals will be calculated for the safety population, assuming that the number of such adverse events is Poisson distributed. The incidence rate per 10 patient years will be calculated as the number of medical-device related AEs divided by patient years covered in the study multiplied by 10 patient years. Patient years covered in the study will be defined as the sum of the individual on-study times from Baseline Visit (V01) until date of study completion.

This calculation will be also done for AEs of special interest and medical-device related SAEs.

Since reliability of the incidence rates strongly depends on the number of patient years covered by the single patients in the study, the on study time of each patient will be analyzed additionally.

Listings for eye-related AEs leading to discontinuation, serious AEs, and deaths will also be provided.

7.2.4 Analysis of Primary Performance Outcome Variables

Limits of Agreement

The Bland-Altman method, which compares the mean of paired measurements to their difference will be used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with the ARGOS-IO system and GAT. For this purpose, the mean of each series with the respective device will be calculated and used for comparison. The agreement evaluation will be based on the assumption that the measurements are constant within the measurement series but not between measurement series with the same device. The two-sided 95% confidence intervals for each of the agreement limits will be calculated using the Mover method (Zou, 2011) to account for repeated observations. IOP values will be displayed as Bland-Altman plots of individual measurement pairs by measurement technique for each visit and overall as well as mean plots over time.

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

Consequently, the absolute IOP values obtained with the ARGOS-IO system are expected to show a systematic shift in measurements compared to those obtained from indirect methods. The Pascal

Dynamic Contour Tonometer (DCT) is constructed to alleviate some of the operator bias of GAT measurements as well as eliminate most of the corneal biomechanical influence on IOP readings. Therefore the limits of agreement between the ARGOS-IO system and DTC measurements will be also calculated by the described procedure.

Device Malfunctions

Incidence of observed device malfunctions and nature of device malfunction will be summarized for subjects using the descriptive statistics defined at the beginning of Section 7.2. In addition, the rate of device malfunctions per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that the number of such device malfunctions is Poisson distributed. The procedure will be analogous to the procedure for incidence rates of AEs.

7.2.5 Analysis of Secondary Outcome Variables

Progression of visual field, cup/disc ratio, OCT results for the optic nerve and IOP over the course of the study will be summarized for the subjects by eye and visit using the descriptive statistics defined at the beginning of Section 7.2. The Change from baseline will be calculated for continuous outcome variables and, where meaningful, shift-tables for categorical variables.

Analysis of changes in glaucoma medication and number of unscheduled visits due to self-measured increased IOP will be analyzed analogue to the analysis for incidence rates of AEs. The rate of changes in medication / unscheduled visits per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that the number of such events is Poisson distributed.

7.2.6 Analysis of Additional Outcome Variables

For all additional outcome variables, except for the IOP self-measurements and device deficiencies, summaries will be provided per visit and eye or, in case of the VFQ-25, only per visit. Further details about the analysis of additional outcome variables will be provided in the SAP.

7.2.7 Sample Size Calculation

Given 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-IO system in patients who have been already implanted with the study device. Therefore the maximum sample size is 26. This maximum sample size is composed of maximal 5 available subjects from the ARGOS-01 study and maximal 21 available subjects from the ARGOS-02 study. It is envisaged to enroll all of these subjects.

The minimal sample size for this study is at the Sponsor's discretion. This is considered to be appropriate since no experimental treatments are planned and all assessments with exception of IOP measurement using the ARGOS-IO device are established standard methods.

7.3 Level of Significance and the Power of the clinical Investigation

If not specified otherwise, the level of significance for confidence intervals is 5%. A power calculation is not required for this exploratory study since no statistical test is envisaged.

7.4 Interim Analysis

An annual interim analysis for primary and secondary outcome variables is planned. The study status and ongoing safety information will be reported to DEKRA on a regular basis.

7.5 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.

7.6 Specification of Subgroups for Analysis

In order to investigate the impact of certain characteristics on performance, the primary endpoints will also be examined, provided that there are enough subjects in the respective subgroup, by the following variables:

- ARGOS-01 patients
- ARGOS-02 patients
- Gender
- Age groups
- Size of ARGOS-IO implant
- Educational level.

The extent of the subgroup analysis will be described in more detail in the SAP.

7.7 Treatment of missing, unused and spurious Data, including Drop-outs and Withdrawals

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

7.8 Datasets to be analyzed

All subjects enrolled in this study will be included in the analysis since all subjects already have the ARGOS-IO sensor implanted and evaluable data for the primary performance are already recorded at the baseline visit (V01). As described in the previous section, the handling of missing data will be detailed in the statistical analysis plan. Depending on the number of drop-outs during the course of the study, sensitivity analyses with subsets of subjects might be planned in the SAP if deemed necessary for the correct interpretation of the results.

8. DATA MANAGEMENT

All Data Management procedures will be detailed in a separate document known as the Data Management Plan (DMP). The DMP will also describe the Clinical Data Management System (CDMS) that will be used to collect data with an electronic Case Report Form (eCRF) in detail. Relevant study data for statistical analysis and study reports according to this protocol have to be recorded in this web-based electronic data capture system.

8.1 Site Monitoring

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

8.2 Data Collection

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

8.3 Database Management and Quality Control

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

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

Inconsistencies in the data will be queried to the investigators via the electronic data capture system. Answers to queries or changes to the data will also be documented in this system directly by the physician respectively an authorized member of the investigator's staff. The audit trail in the eCRF documents all changes. Edit checks trigger automatically queries during data entry when a field is not populated to specifications defined in the Data Validation Plan (DVP). Manual queries can be issued during medical or safety review and data management review. These processes will be performed on an ongoing basis as outlined in the DMP until all queries are resolved.

All queries must be answered and the database locked before any (interim) analysis of the data may begin.

8.4 Verification, Validation and Security of electronic Data System

It has been verified by the sponsor that only validated and secure electronic data systems will be used in this clinical trial. Electronic data systems include the clinical data management database and the ARGOS-IO system measurement database. Database validation and security follow the respective national and international requirements.

8.5 Data Retention and Retention Period

8.5.1 Investigator Records Retention

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

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

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

8.5.2 Sponsor Records Retention

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

- All correspondence pertaining to the investigation
- Signed and dated Investigator Agreements and signed and dated investigator curriculum vitae that were current at the time of the study
- Copies of all EC approval letters, the EC review and approval procedures, and relevant EC correspondence
- Names and addresses of the institutions where the clinical investigation was conducted, as well as records of approval from site administration
- Correspondence with authorities as required by national legislation
- Insurance certificates
- Adverse Events report forms

- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final and all interim reports of the clinical investigation
- Study training records for site personnel and sponsor/CRO personnel.
- Quality assurance

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

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

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

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

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

The regulatory authorities, both national and foreign, may inspect the study site at any time. The Investigator is responsible for notifying the sponsor of such an inspection immediately upon gaining knowledge of it. During the audit or inspection, the investigator/institution will permit the auditor, and regulatory inspector(s) direct access to all relevant medical records and other source data, study related files and CRFs.

9. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

9.1 Definitions

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

9.1.1 Adverse Event (AE)

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

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

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

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

9.1.1.1 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.

9.1.1.2 Serious Adverse Events

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

- Led to death
- Led to a serious deterioration in the health of a subject that:
    1. Resulted in a life-threatening illness or injury
    2. Resulted in a permanent impairment of a body structure or body function
    3. Required in-patient hospitalization or prolongation of existing hospitalization

4. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

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

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

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

9.1.1.3 Serious Adverse Device Effect (SADE)

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

9.1.1.4 Anticipated Serious Adverse Device Effect (ASADE)

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

9.1.1.5 Unanticipated Serious Adverse Device Effect (USADE)

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

9.1.1.6 Device Deficiency

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

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

9.1.2 Recording of Adverse Device Effects (ADEs)

All Adverse Device Effects (ADEs) will be documented from the V01 until the subject is discharged from the study.

ADEs will be collected with a non-leading question at each visit: "Have you had any new or worsening health problems since the last visit?" as well as by reporting those events directly observed and

spontaneously reported by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome whenever possible. Seriousness, **severity** (mild, moderate or severe), outcome and **relationship to investigational device** as well as expectedness and **action taken** will be recorded in the AE page of the CRF. **Start and end date and time** of the event will also be recorded.

Seriousness

Seriousness will be recorded as described in section 11.1.2.2.

Intensity/Severity

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

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

Relationship to Study Device

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

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

- ***None*****:** The time course between use of the device and occurrence or worsening of the AE rules out causal relationship; and/or another cause is confirmed and no indication for involvement of the study device in the occurrence/worsening of the AE exists
- ***Unlikely:*** The time course between use of the device and occurrence/worsening of the AE makes causal relationship unlikely; and/or the known effects of the device provides no indication for involvement of the study device in the occurrence/worsening of the AE; and/or although it is conceivable based on previous knowledge that study device may have causal relationship to occurrence/worsening of the AE, another cause is much more probable;

and/or another cause is confirmed and involvement of the study device in the occurrence/worsening of the AE is unlikely

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

Action taken

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

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

The categories in relation to other treatments are:

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

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

- Recovered
- Recovered with sequelae
- Recovering
- Not recovered
- Death

- Unknown.

All AEs will be recorded on an Adverse Event Form, one for each Adverse Event, which is part of the Case Report Form.

9.1.3 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-IO sensor)
2. An SADE affecting a user or third party (all)
3. A device deficiency that might have led to an SAE involving a subject, user or third party if suitable action or intervention had not been taken or if circumstances had been less fortunate (all)

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

The sponsor will report SAEs to the Competent Authority in accordance with ISO 14155, Annex X of Directive 93/42/EEC, its amendment Directive 2007/47/EC, Annex 7 of Directive 90/385/EEC, MEDDEV 2.7/3 (Dec 2010), the German Ordinance on Medical Device Vigilance (MPSV) (effective 25 July 2014) and applicable local laws and regulations. Reporting modalities defined in the MPSV and MEDDEV 2.7.3 (Dec 2010) will be followed. All SAEs will be documented completely. SAEs for which a relationship to the study device or diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial cannot be excluded will be reported to BfArM immediately using the SAE report form found on the BfArM website. A summary report for all other SAEs will be submitted to BfArM every three months or as requested by BfArM using the SAE summary table from MEDDEV 2.7.4.

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 3.

Table 2. SAE reporting Requirements

Reporting Party	Reports to	Causal Relationship to Study Devices or Procedures	Reporting Timeline	Reporting Method
Investigator	Sponsor	All SAEs, regardless of relationship	Immediately upon learning of the event	Phone, fax or email to MDSS GmbH ***and*** 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 (BfArM website)
		Relatedness can be excluded	Summary report every 3 months or as otherwise requested by BfArM	Submission of MEDDEV 2.7.3 Summary Table

In case of an immediately reportable Adverse Event the investigators can contact **MDSS GmbH** via Phone, Fax or Email.

Please send the completed form to:

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

The sponsor should be informed in a parallel process.

9.1.4 Device Deficiencies

The investigator will record all observed device deficiencies by completing a Device Deficiency Form.
The reporting modalities are defined in ISO 14155:2011 and MEDDEV 2.7/4 in line with the requirements of Annex X of Directive 93/42/EEC and its amendment Directive 2007/47/EC, Annex 7 of 90/385/EEC and local laws and regulations.
All device deficiencies must be reported to the sponsor immediately. Any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate must be reported as described in Table 8.6.3 following the SAE reporting modalities.

9.1.5 Medical Care

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

9.1.6 Sponsor Responsibilities

The Sponsor is responsible for reporting Serious Adverse Events, interim or annual safety reports, premature termination or suspension of the clinical trial, and the final Study Report to Regulatory Authorities, the ECs and investigators. Refer to table 4 for details.

Table 3. Sponsor reporting Responsibilities

Reporting Responsibility	Reports to	Description
Serious Adverse Events (SAEs)	Regulatory Authorities, ECs	See Sections 11.1.2.2 for details
Interim or annual safety reporting	ECs and/or CA per local regulations	An interim or annual safety report may be required by country regulations, or may be specifically requested by the EC/CA
Premature termination or suspension of the clinical investigation	Investigators, ECs, relevant Regulatory Authorities	Provide prompt notification of termination or suspension and reasons. GERMANY: According to MPG §23a, Abs. 1, the Sponsor is required to notify BfArM of the completion of the clinical investigation within 90 days after close-out. GERMANY: According to MPG §23a, Abs. 2, the Sponsor is required to notify BfArM of the premature termination of the clinical investigation within 15 days after termination.
Final Study Report	Investigators, ECs, relevant Regulatory Authorities	The sponsor will notify the investigators of the completion or termination of the study. A Final Study Report will be submitted to the investigators and the ECs following local regulations. Germany: According to MPG §23a, a CIR has to be submitted to BfArM within 12 month completion or premature termination of the clinical investigation.

10. ADMINSTRATIVE PROCEDURES AND RESPONSIBILITIES

10.1 Informed Consent

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

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

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

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

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

10.2 Regulatory and Ethical Compliance

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

10.3 Approval from Ethics Committee or Regulatory Authority

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

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

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

10.4 Investigator Responsibilities for Ethics Committees and Regulatory Authorities

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

10.5 Reporting Responsibilities

10.5.1 Investigator reporting Responsibilities

The investigator or designee is responsible for completing (including review and signature) and submitting to the sponsor all case report forms, as well as reports of any Adverse Events (according to country-specific collection requirements), deaths or deviations from the clinical investigation plan. If any action is taken by the EC with respect to the investigation, the investigator will forward the information to the sponsor as soon as possible. Reports are subject to inspection and to the retention requirements as described in section 10.5. Refer to Table 3 for SAE reporting responsibilities.

10.5.2 Sponsor reporting Responsibilities

The sponsor is responsible for reporting Serious Adverse Events, interim or annual safety reports, premature termination or suspension of the clinical trial, and the Final Study Report. Refer to Table 4 for details.

10.6 Insurance

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

10.7 Subject follow-up Requirements

All pregnancies will be followed to birth. All ongoing ADEs 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.

10.8 Investigator and Site Selection

Site selection will be based on the sites of the ARGOS-01 and ARGOS-02 study. 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
- Patient enrolment and site commitment not expected to be impacted by any competing studies

- Clinical support staff
  - Study nurse/assistant/coordinator or equivalent who are adequately trained and willing to invest time in study administration and electronic data input
- Time investment
  - Investigator has sufficient time to fulfill the study requirements, including reporting, and to attend the study meetings.
- Equipment / Procedures
  - Separate rooms to perform study procedures
  - Sufficient, lockable storage capacities for study materials.

11. PUBLICATION POLICY

11.1 Clinical Investigation Report (CIR)

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

In Germany, according to MPG §23a, a CIR has to be submitted to BfArM within 12 month completion or premature termination of the clinical trial. Also see Table 7 in chapter 11.1.8 for further details.

11.2 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.

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