CLINICAL INVESTIGATION REPORT

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

Reference Number: ARGOS-KP01

Investigational Medical Device:	ARGOS-IO Intraocular Pressure Sensor Implant
Study Design:	Open-label, multicenter, single-arm, safety and performance study
EudaMed No.:	CIV-14-09-012725
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Report Date:	25-JUL-2018

Statement of Compliance

This investigation was conducted in compliance with the protocol, ISO 14155:2011, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines and applicable local and regional laws and regulations.

Signature Page

ARGOS-KP01

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

CIR reviewed and approved by:

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ARGOS-KP01

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

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Summary

SPONSOR Implandata Ophthalmic Products GmbH	**INVESTIGATIONAL DEVICE** ARGOS-IO Intraocular Pressure Sensor Implant and Reader	
STUDY TITLE A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston-Keratoprosthesis (BKPro)		
EudaMed No.: CIV-14-09-012725	**STUDY PERIOD** *Date of First Enrollment: 12 February 2015* *Date of Last Patient Last Visit: 14 June 2017*	**DATE OF REPORT:** *25-JUL-2018*

INTRODUCTION

The ARGOS-IO system combines an implantable intraocular pressure sensor ring (4 haptics at the outer edges of the implant; diameter is available in three sizes 11.3, 11.7 and 12.1 mm; inner diameter 7 mm, thickness 0.5 mm on the edges of the device, tapering to a 0.1 mm rounded outer haptics) with a hand-held reading device (MESOGRAPH) to measure intraocular pressure (IOP). The ring, consisting of microelectromechanical system application specific integrated circuit (MEMS-ASIC) bonded to a gold micro-coil and encapsulated in silicone-rubber, is implanted during Boston-Keratoprosthesis surgery. The implant is introduced into the ciliary sulcus using an open sky approach (through trepanation). In case of inadequate or missing capsular or iris support, the implant may be sutured transsclerally. An electromagnetic inductive connection between the coil of the sensor and the activated reader powers the ASIC, thereby initiating a pressure reading and enabling telemetric data transfer.

Even though the implant contains a complex application-specific integrated circuit (ASIC), from a risk management view-point this implant is a simple product with a potential for mainly mechanical risks to the patients. ARGOS-IO is a diagnostic device for measuring intraocular pressure in Boston-Keratoprosthesis patients. It is not a life-supporting or life-sustaining implant and its malfunction in the worst case scenario will merely result in a wrong pressure measurement value. The IOP measurements obtained by this device is intended as only one of the inputs used for IOP monitoring in Boston-Keratoprosthesis patients. The ARGOS-IO implant is intended for permanent implantation but can be explanted. The implant does not contain a software.

12 patients received ARGOS-IO implants in this open-label clinical investigation. During the 12 months following surgery, the patients returned for 13 follow-up visits consisting of comprehensive ophthalmic examinations as well as IOP measurements with the ARGOS-IO system, finger palpation and surgical manometry at Visit 7, 9, 11 and 15.

OBJECTIVES

PRIMARY:

Safety

To evaluate the safety and tolerability of the ARGOS-IO pressure sensor in the 12 months following implantation.

Performance

To evaluate the performance of the ARGOS-IO system compared to manometry in the 12 months following implantation.

SECONDARY:

Safety

- To evaluate the safety and tolerability of ARGOS-IO pressure sensor use in the first 4, 16 and 28 weeks after implantation.

Performance

- To compare the IOP measured with the ARGOS-IO system to that obtained with manometry at week 4, 16 and 28 after implantation.

ENDPOINTS

PRIMARY:

Safety

- Number of subjects experiencing at any time during the first 12 months a device related SAE defined as any adverse event that both
  - Is considered by the Investigator to have a possible, probable or definite relationship to the device and
  - That leads to any of the following:
    - Death
    - A serious deterioration in the health of the subject that results in a life-threatening illness or injury or a permanent impairment of a body structure or function, or that requires medical/surgical intervention to prevent such
    - Hospitalization or prolongation of existing hospitalization
    - Fetal distress or death or a congenital abnormality or birth defect.

Performance

- Level of agreement between IOP measurements made using manometry and the ARGOS-IO system over the first 12 months following implantation

SECONDARY:

Safety

- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the first 4, 16 and 28 weeks and 12 months following implantation of the ARGOS-IO pressure sensor.

Performance

- Level of agreement between IOP measurements made using surgical manometry and the ARGOS-IO system at 4, 16, 28 and 52 weeks following implantation
- Incidence of device deficiencies in the first 4, 16, 28 and 52 weeks following implantation
- User acceptance of the implantation procedure by means of evaluation of the Implantation Procedure Questionnaire (Investigators)
- User acceptance of the ARGOS-IO system at the investigational site by means of evaluation of the Investigator Acceptance Questionnaires (investigators).
- Daily IOP self-measurement profiles (patients).

STUDY DESIGN AND METHODOLOGY

DESIGN: Prospective, open-label, multicenter, single-arm, safety and performance study.

TREATMENT ALLOCATION: non-randomized, open-label.

TREATMENT: Implantation of an ARGOS-IO pressure sensor in the ciliary sulcus concomitantly to Boston Keratoprosthesis implantation.

CONTROL: Comparison of IOP values obtained with the ARGOS-IO system to those with surgical manometry (V7, V9, V11, V15) at the same time point.

FOLLOW-UP: 13 post-surgical visits over a 12-month period with comprehensive ophthalmic examinations and

IOP measurements with finger palpation, surgical manometry (V 7, 9, 11, 15) and ARGOS-IO system.

STATISTICAL METHODS:

Definition of the analysis populations

The safety population comprises all subjects for whom ARGOS-IO pressure sensor implantation was attempted, whether or not the implantation was successful. The Per Protocol Set (PPS) will comprise all subjects in whom an ARGOS-IO pressure sensor was successfully implanted and for whom the full data set including IOP measurements made in the clinic and safety data according to protocol are available until 28 weeks (Visit 11) after surgery

Statistical analysis

Safety analysis

AEs, SAEs, ADEs and SADEs will be listed. Incidence will be estimated with a 95% confidence interval (Pearson-Clopper, two-sided).

Performance analysis

The Bland-Altman method will be used to assess the limits of agreement between the IOP measurements ARGOS-IO and surgical manometry. When appropriate, two-sided 95% CIs, for these limits will be calculated accounting for repeated measurements based on the method proposed by Zou (2011).

Other secondary performance endpoints will be analyzed by descriptive and explorative statistical methods.

STUDY POPULATION

INCLUSION CRITERIA

Eligible subjects must meet all the following inclusion criteria:

1. Male or female aged ≥ 18 and ≤ 80 years on the day of screening
2. Keratoprosthesis surgery indicated, defined as having a severely opaque and vascularized cornea AND either a verifiable history of two or more prior failed corneal transplant procedures or a medical condition such as alkali burns or autoimmune disease that makes the success of a traditional corneal transplant procedure unlikely. Potential study subjects will be solicited for participation in the clinical trial only after they have consented to the keratoprosthesis operation.
3. Axial length > 21 mm
4. Ability and willingness to attend all scheduled visits and comply with all study procedures

EXCLUSION CRITERIA:

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

1. Reasonable chance of success with traditional keratoplasty
2. Current retinal detachment
3. Connective tissue diseases
4. History or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-IO implantation

5. History of ocular or periocular malignancy
6. History of extensive keloid formation
7. Any known intolerance or hypersensitivity to topical anesthetics, mydriatics, or silicone (component of the device)
8. Presence of another active medical eye implant and/or other active medical implants in the head/neck region
9. Signs of current infection, including fever and current treatment with antibiotics
10. Severe generalized disease that results in a life expectancy shorter than a year
11. Any clinical evidence that the investigator feels would place the subject at increased risk with the placement of the device
12. Currently pregnant or breastfeeding
13. Participation in any study involving an investigational drug or device within the past 30 days or ongoing participation in a study with an investigational drug or device
14. Intraoperative complication that would preclude implantation of the study device
15. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization.
16. Previous or concurrent enrollment of the contralateral eye in this clinical study.

NUMBER OF PATIENTS (PLANNED AND ANALYSED): This exploratory study was planned to enroll a minimum of 10 and a maximum of 15 patients. The sample size was chosen pragmatically based on the number of patients expected to undergo BKPro implantation at the study sites during a 12 months period. It is anticipated to be large enough to provide an initial estimate of common safety events and assessment of performance.

In this clinical trial a total of 14 patients with an indication for Boston-Keratoprosthesis implantation were screened and 13 patients initially enrolled, 12 of whom successfully received the ARGOS-IO implant.

One of the screened patients (DE-3-01) was excluded due to a screening failure. Due to a detected capsular bag instability during surgery, an implantation of the ARGOS-IO pressure sensor was not attempted in a second patient (DE-2-03).

Nine out of 12 patients completed the study with the sensor implanted. One patient voluntary withdrew with sensor left in place. In two patients, the ARGOS-IO sensor was explanted, either after dislocation of the sclera-fixed implant (DE-1-07) or in the course of multiple additional surgeries (DE-1-05, corneal graft melt twice).

<u>RESULTS</u>

PERFORMANCE RESULTS:

IOP estimation by finger palpation was grouped in four categories: normal (A), soft/hypotonic (B), borderline (C) and hypertonic (D). Mean telemetric IOP was 18.2±6.1 mmHg in category A, 8.9±2.8 mmHg in B, 22.4±4.9 mmHg in C, 34.3±11.0 mmHg in D. In visits with manometry, mean manometric IOP was 19.0±8.4 mmHg, mean telemetric IOP was 22.8±11.7 mmHg. Excluding three presumed measuring errors, the two modalities had a correlation of $r=0.874$ ($P<0.001$).

SAFETY RESULTS:

Overall 168 AEs in 13 patients were reported during the ARGOS-KP01 study including 23 SAEs in 9 patients. Only 15 AEs in four patients were possible related to the medical device: anterior chamber cell, cystoid macular edema, hypotony of the eye, iris adhesion, pigment dispersion, vitritis, increased intraocular pressure and retroprosthetic membrane, six thereof serious.

However, all potential ADE's can be caused by the stand-alone procedure and they are not of a higher percentage in this study than in other known publications.

CONCLUSIONS:

The implantable ARGOS-IO pressure sensor in Boston-Keratoprosthesis patients was well tolerated. The observed adverse events constitute known complications of keratoprosthesis surgery. The implant does not appear to be associated with additional or more severe complications. The system showed a good and reliable performance in comparison to other IOP measuring modalities.

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Abbreviations and Definitions

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ASIC	Application specific integrated circuit
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CIP	Clinical Investigation Plan
CRF	Case Report Form
dB	Decibel
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EEPROM	Electrically erasable programmable read-only memory
ETDRS	Early Treatment Diabetic Retinopathy Study
GAT	Goldmann Applanation Tonometry
GCP	Good Clinical Practice
GDD	Glaucoma Drainage Device
IB	Investigator's Brochure
IEC	Independent Ethic Committee
IO	Intraocular
IOL	Intraocular lens
IOP	Intraocular Pressure
ISF	Investigator Site File
Max	Maximum (highest observation)
MD	Macular degeneration
MDN	Median
Min	Minimum (smallest observation)
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)
MRI	Magnetic resonance imaging
N	Sample number
NCT	Non-contact tonometry
ND:YAG	Neodymium doped yttrium aluminum garnet
P	Pressure
P25%	25% quartile
P75%	75% quartile
PIC	Patient informed consent

POAG	Primary open angle glaucoma
PP	Per Protocol
ppV	Pars plana vitrectomy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source Data Verification
T	Temperature (in °C)
TMF	Trial Master File
WTW	White-to-white

1 INTRODUCTION

1.1 Keratoprosthesis Devices

Approximately 8 million people are bilaterally blind (defined as visual acuity < 19/180) because of corneal disease or injury (Ament, et al., 2010). Corneal transplantation, otherwise known as penetrating keratoplasty (PKP), which involves removing a disc comprising the majority of the patient's cornea and replacing it with a corresponding disc from a donor eye, can restore sight to many of these patients. In 2008, 41,652 corneal transplants were performed in the United States alone (Eye Bank Association of America, 2014).

Although the procedure usually leads to positive results over the long-term, certain high-risk groups, such as patients with cicatrizing diseases like Stevens-Johnson syndrome, ocular cicatricial pemphigoid and other autoimmune diseases; alkali burns; herpetic neurotrophic keratopathy; and some pediatric corneal opacities have a low success rate and often experience repeat graft failures (Klufas & Starr, 2009). Artificial corneas, otherwise known as keratoprostheses, are a final alternative treatment to salvage the vision of these patients.

There are presently many keratoprostheses in development, but only three are generally used in the normal clinical setting (Lam & Liu, 2011):

- Boston Keratoprosthesis (KPro) (Massachusetts Eye and Ear Infirmary, Boston, MA),
- AlphaCor artificial cornea (Addition Technology Inc., Des Plaines, IL), and
- Osteo-odonto keratoprosthesis (originally described by Strampelli, modified by Falcinelli, optic available from Osteo-Odonto Keratoprosthesis Optics [Sussex Eye Hospital, Brighton, United Kingdom])

The Boston type 1 KPro used in this study is the most widely used keratoprosthesis. It consists of a polymethylmethacrylate (PMMA) collar-button-like front plate that houses a periscope-like central optical cylinder (aphakic and pseudophakic powers available) and a threadless, titanium back plate. Prior to implantation, the two plates are snapped together sandwiching a ring of donor corneal tissue between them, which is then used to suture the device to the eye. With the exception of the assembly of the device, the implantation of a BKPro, which employs 12 interrupted sutures, is quite similar to that used for PKP (Santaella & Afshari, 2011).

Use of the BKPro has risen from 50 implantations in 2002 to 1188 in 2010 (Klufas & Starr, 2009). Various retrospective studies reported improvements in vision from preoperative best corrected visual acuity (BCVA) of ≤20/400 in 86-95% of the eyes to BCVAs ≥ 20/200 in 57 – 89% at various time points following surgery (Greiner, Li, & Mannis, 2011), with some studies reporting BCVAs of better than 20/40 in 25% of the patients included (Klufas & Starr, 2009). Continued advances in the design of the BKPro and the post-operative care given its recipients have resulted in improved outcomes. However, a significant number of BKPro patients lose their initial visual gains permanently over the longer term as a result of glaucoma, which may affect up to 75% of patients awaiting BKPro implantation and up to 100% of patients post-operatively (Nguyen & Chopra, 2014), (Greiner, Li, & Mannis, 2011) .

1.2 Limitations of Existing Treatments

Glaucoma treatment generally aims to reduce damage to the optic nerve by reducing the elevated intraocular pressure (IOP) believed to cause it. IOP management in patients with a keratoprosthesis is challenging. Conventional tonometry methods typically used to measure IOP deduce it indirectly by measuring the pressure required to applanate the cornea or the response to pressure applied to the sclera. The rigid PMMA cylinder that replaces the central part of the donor corneal graft in BKPro recipients makes corneal applanation methods of IOP measurement such as Goldmann Applanation Tonometry impossible to use, while changes in the sclera caused by BKPro implantation also make alternatives that assess scleral pressure infeasible. In current clinical practice, finger palpation by a highly experienced specialist is seen as the only feasible option for routine monitoring of IOP in BKPro patients, but the values obtained are at best highly subjective estimations (Santaella & Afshari, 2011). The only available method to accurately measure IOP in these patients is surgical manometry, which carries significant risks and should not be performed frequently. To further compound the situation, the rapid progression to end-stage glaucoma that is frequently observed in BKPro patients with apparently normal IOP has raised the hypothesis that these patients experience undetected transient IOP spikes (Greiner, Li, & Mannis, 2011).

1.3 State of Device Development

The ARGOS-IO implant is an innovative ring-shaped intraocular pressure sensor consisting of a miniature application specific integrated circuit (ASIC) with integrated electromechanical pressure sensors that is bonded to a gold micro-coil and encased in silicon rubber material. The ARGOS-IO pressure sensor is intended to be permanently implanted in the eyes of glaucoma patients in conjunction with surgery for cataract removal and concurrent intraocular lens implantation, and is anticipated to enable patients to make direct accurate IOP measurements by themselves, and quasi-continuous IOP diurnal curves. This in turn will permit more frequent measurement of IOP, providing a more detailed and accurate basis for treatment decisions. Power for pressure measurement and data transmission is provided during the measurement process via magnetic coupling with a portable hand-held device, which also receives and stores the data.

The accuracy of the device was initially demonstrated in direct comparison with manometry in enucleated porcine eyes. Long term implantation testing in rabbits confirmed biocompatibility and permitted comparison of measurements obtained in vivo with the ARGOS-IO pressure sensor to those of other tonometers in vivo over a period lasting up to 2.5 years.

In 2012 in an initial first-in-human case study, a sensor was implanted in the ciliary sulcus of a 66 year old female glaucoma patient in Beirut Lebanon and her condition followed over 18 month period. No significant adverse events were noted (Melki, Todani, & Cherfan, An Implantable Intraocular Pressure Transducer: Initial Safety Outcomes, 2014).

Two patients who received an earlier ARGOS-IO implant in conjunction with a Boston Keratoprosthesis Type 1 in a carrier corneal graft, showed no significant AEs. IOP measurements obtained with the ARGOS-IO system demonstrated reasonable IOP comparability when compared to finger palpation in these patients in whom use of alternative tonometry methods were not possible. Peaks in IOP could be detected timely, permitting medical treatments and procedures to be adjusted or initiated.

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

Analysis of an extensive databank of eye MRIs, obtained from MRI Research Inc., a company supported by the American National Institute of Health National Eye Institute, demonstrated that the ciliary sulcus undergoes a distortion in the first months following cataract extraction. This distortion, which is extenuated by the use of single piece IOLs such as those received by all patients in the

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

In May 2017, the ARGOS-IO system got the CE approval as intraocular pressure sensor for measurement of intraocular pressure in patients with primary open angle glaucoma due to the ARGOS-02 study. This clinical trial investigated the safety and performance of the ARGOS-IO systems in patients with primary open angle glaucoma undergoing phacoemulsification and IOL implantation for cataract and received ARGOS-IO implants in an add-on procedure. 22 patients were enrolled and their eye condition and IOP were followed over a course of 12 months. The ARGOS-IO measurements showed an excellent level of concordance to the conventional Goldmann Applanation tonometry and no device related serious adverse events were recorded (Implandata, 2017).

The ARGOS-KP01 study described in this report investigated the safety and performance of implantation of the ARGOS-IO in conjunction with keratoprosthesis implantation in a larger patient population. Over a one year period 12 patients underwent Boston-Keratoprosthesis implantation and received ARGOS-IO implants. Their eye condition and IOP were followed over the course of 12 months.

This investigation was designed and conducted in accordance with ISO 14155:2011, European Medical Device Directive and German Medical Device Act and Medical Device Ordinance.

2 INVESTIGATIONAL DEVICE AND METHODS

2.1 IMD Classification and Intended Use

The ARGOS-IO system is an investigational medical device developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor (IOP, intraocular pressure) in patients with Boston Keratoprosthesis (BKPRO). It is composed of the ARGOS-IO pressure sensor implant and the separate hand-held MESOGRAPH reading device.

The ARGOS-IO implant is classified as active implantable medical device under the consolidated Active Implantable Medical Device Directive 90/385/EEC Annex IX and AIMDD as amended by directive 2007/47/EC.

2.1.1 Accessoiries

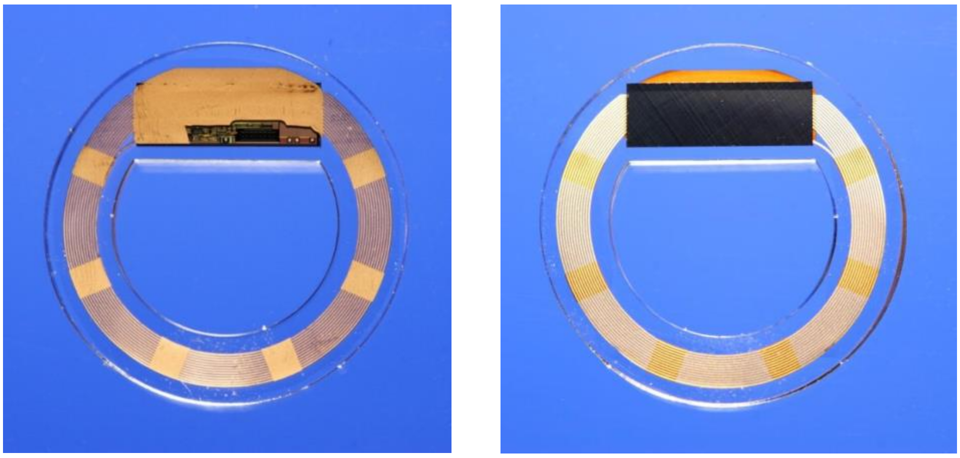
Both, the Injector with its constituent parts (hand-piece, cartridge and plunger tip) and the MESOGRAPH reader device are classified as accessories to an active implantable medical device under the consolidated Active Implantable Medical Device Directive 90/385/EEC Annex IX and AIMDD as amended by directive 2007/47/EC.

2.2 IMD Description

The ARGOS-IO pressure sensor, which is intended for permanent implantation in the posterior chamber of the eye and implanted in conjunction with a Boston Keratoprosthesis, bears a microelectromechanical system-application specific integrated circuit (MEMS-ASIC) that integrates pressure and temperature sensors, identification and analog-to-digital encoders and a telemetry unit. The ASIC is bonded to a gold micro-coil and hermetically encapsulated in a ring of silicone rubber material. When the external reading device (Mesograph) is activated in the close proximity of the eye, an electromagnetic inductive connection is formed between it and the microcoil that provides the ASIC with power and enables the measurement and telemetric data transfer between the sensor and the reader.

An earlier version of the ARGOS-IO implant was used in the two described case studies and the ARGOS-01 study. This early ARGOS-IO implant prototype, shown in Figure 1, had an outer diameter size of 11.3 mm, an inner diameter size of 7 mm and an overall thickness of 0.9 mm.

Figure 1. ARGOS-IO implant (previous prototype)



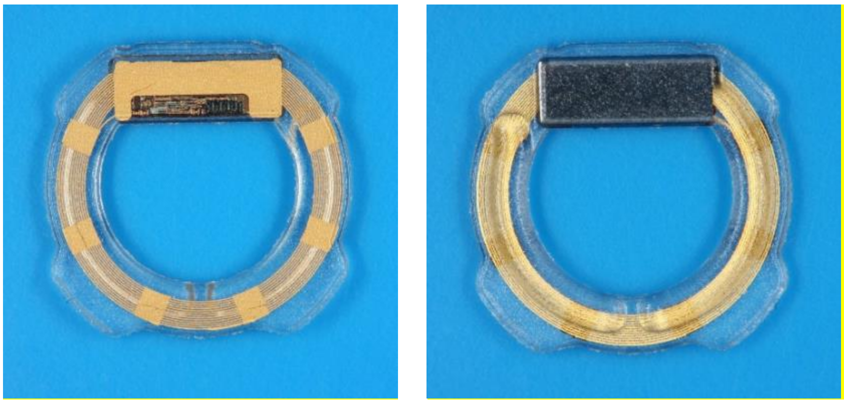
a) Anterior view (side towards the iris)

b) Posterior view (side toward the lens).

Suboptimal safety and performance outcomes in the ARGOS-01 study made it apparent that modifications to the form of the ARGOS-IO implant were necessary before clinical investigation of the ARGOS-IO system could be continued. The design modifications made included:

- Addition of 4 haptics at the outer edges 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 running on either side of the posterior surface from the middle of the ring to the ASIC.

Figure 2. ARGOS-IO Implant (second generation)



a) Anterior view (side towards the iris) **b) Posterior view (side toward the lens)**

In this clinical investigation, three ARGOS-IO implant sizes will be tested:

∅ 11.3 mm; 0.5 mm thickness

∅ 11.7 mm; 0.5 mm thickness

∅ 12.1 mm; 0.5 mm thickness.

The implant contains four haptics to maintain positional and rotational stability. In addition, the two haptics on either side of the ASIC act as a spacer to prevent the ASIC from being pressed into the surrounding tissue. Two flattened allantoid protrusions running from the bottom middle to the ASIC on the posterior surface of the ring serve to facilitate unfolding of the implant after insertion into the eye, as well as to decrease force exerted on the ASIC by the ocular structures. All three implant sizes have an inner diameter size of 7 mm.

2.2.1 ARGOS-IO pressure sensor ring

2.2.1.1 ASIC

The ASIC comprises functional blocks dedicated to pressure and temperature sensing, sensor readout and analog-to-digital conversion, a digital state machine to control the sequence of operation such as computation of checksum for data transmission and timing of the ASIC operation, EEPROM memory to store unique serial number for implant identification, and a radio frequency front end for power supply and filtering, and data transmission.

The miniature, highly reliable, and stable pressure sensor systems manufactured by surface micromachining techniques are similar to those used in automotive and other technical and

consumer applications. The ASIC incorporates an array of 8 capacitive pressure sensors, each comprised of a rigid base plate and a parallel flexible membrane (Figure 3 and
Figure **4**).

When the membrane is deflected by pressure changes, its distance to the base plate changes, generating a change in the capacity of the sensor cell that is directly proportional to the pressure within the eye. The capacity change is digitalized by the integrated power-saving analog/digital converter circuit, which converts it to a numerical value and transmits it to the MESOGRAPH reader. The sensors are referenced internally to a vacuum to compensate for their pneumatic isolation from the ambient pressure when implanted. Computation of the actual IOP is made by comparing the pressure detected by the sensor in the eye to the atmospheric pressure read by the MESOGRAPH. The sensors have an absolute accuracy of 3σ at 2 mmHg over a range of 800 to 1.150 hPa (absolute). Extrapolations from long-term stability testing have estimated their lifespan to be > 35 years at room temperature.

Figure 3. Pressure sensor cell in profile

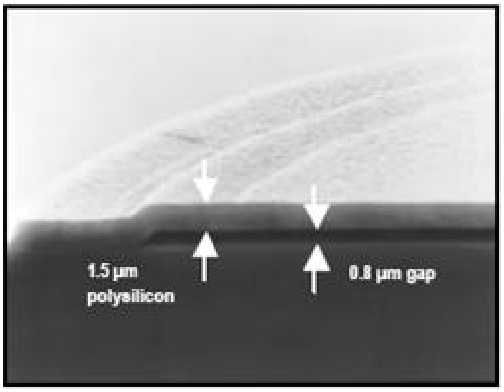
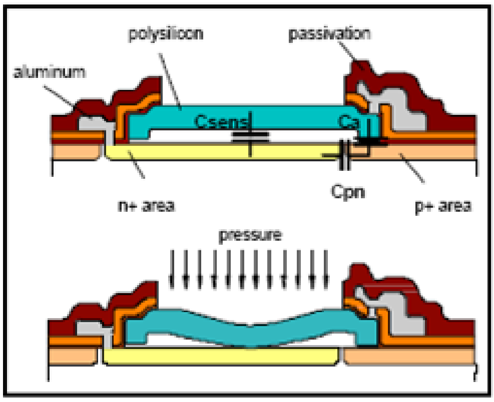


Figure 4. Depiction of a micro-plate capacitor for pressure measurement



The pressure sensing ASIC transfers data by means of absorption modulation via a passive transponder system that uses a pair of coupled coils to establish a radio frequency link between the reader and the transducer (implant). The RF field emitted by the Mesograph at a frequency of 13.56 MHz, which is reserved for medical devices and similar applications, both provides power to the ASIC and enables it to transmit the digitalized data from the implant to the reader via absorption modulation.

The implant contains no energy storage device and is electrically passive if not coupled to the external magnetic field. The ASIC acquires the external power below 250µA with a voltage of 3 V needed for the entire duration of a measurement from an electrical current induced in the micro-coil by exposure to the RF field generated by the activated MESOGRAPH.

2.2.1.2 Micro-coil and Bonding Process

The The micro-coil is manufactured using photolithographic technics in a gold micro-galvanic thin film process to create gold structures of approximately 20µm thickness on a PI layer of approx. 7 – 10 µm. It is bound to the ASIC in a thermocompression flip-chip process that requires no adhesives or other agents. All silicone-aluminum interfaces and metal surfaces of the ASIC are hermetically sealed with gold bumps, which are also required for the bonding process. The very thin structure of the coil facilitates a high flexibility and foldability, which is a prerequisite for a foldable implant for safe implantation process.

2.2.1.3 Encapsulation

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

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

Because the encapsulation material is soft and transfers pressure to the pressure sensors, the ASIC's measurement function remains preserved without restrictions.

The encapsulation is intended to permanently protect the electronic module against electrolytes dissolved in the aqueous humor. In the event that the silicone coating was to become breached, the patient may indirectly come into contact with the materials of the ASIC and the micro-coil as well. Detailed risk assessments determined that the materials used to manufacture the ARGOS-IO implant, which consists of silicon, and traces of silicon dioxide, silicon nitride, gold, aluminum, titanium, phosphorus, arsenic, borium, polyimide and tungsten-titanium, pose no risk of an adverse biological effect to the patient (Cao, M, 2010). The silicone encapsulation, which is composed of polydimethylsiloxanes and diphenylsiloxane-dimethylsiloxane copolymers, has recognized inert and biostable properties under physiological conditions and is a commonly used component of medical devices such as IOLs. Cytotoxicity and chemical analyses of extracts obtained from final sensors detected no organic or inorganic leachables above the lower limit of quantification and no evidence that the sensors contained or would release any residues/contaminants in toxicologically relevant concentrations during clinical application (Timme, 2015).

See IFU ARGOS-IO Implant for further details about implantation and use.

2.2.2 MESOGRAPH reading device

The Mesograph reading device (Figure 5) is a handheld device powered by a 2CR5 lithium battery. When activated approximately 5 cm from the eye, it provides the power required by the ASIC for the duration of a measurement by generating a high-frequency electromagnetic field that produces a current in the microcoil.

Figure 5: Mesograph Reading Device

Dimensions: width x length x height ca. 65 mm x 180 mm x 26 mm

The implant measures IOP within the eye, isolated from the ambient atmospheric pressure. When a reading is made, the Mesograph measures the atmospheric pressure and uses it to automatically compute the relative IOP (which is the metric comparable to commonly measured IOP values).

Detailed reading device technical data for pressure measurement:

- Storage capacity: ca. 3,000 measurements
- Battery: type 2CR5 (lithium photo battery)
- Battery capacity: ca. 3,000 measurements
- Reading device dimensions: 180 mm x 65 mm x 25 mm
- Reading device weight (incl. battery). ca. 160 g
- Connection to PC: galvanically separated data transmission adapter

The maximum range for the wireless operation of the pressure transponder is up to 50 mm or more (distance between micro-coil and reading device coil).

Data Transmission

In the normal operating mode, the site personnel or patient can take several measurements per day simply by holding the activated Mesograph up to his/her eye for a short moment. Measurements can be transmitted through the connected Multiline Connector to a secure database and are recorded in parallel by the Mesograph as back-up. The measurements taken from the patient at home can be read by the physician, whenever needed.

3 CLINICAL INVESTIGATION PLAN

3.1 Study Design and Objectives

The purpose of the ARGOS-KP01 study is to evaluate the safety and performance of the ARGOS-IO system in patients with indicated Boston Keratoprosthesis surgery.

3.1.1 Type of Investigation

The trial was conducted as an open, prospective, multicenter single-arm clinical trial.

3.1.2 Objectives

The aim of this trial is to verify the safety and performance of the ARGOS-IO system in patients with indicated Boston Keratoprosthesis surgery over 12 months' period following implantation. The measurements of intraocular pressure through the pressure sensor were compared with surgical manometry (V7, V9, V11, V15) at the same time point. The ARGOS-IO pressure sensor was implanted during Boston Keratoprosthesis implantation and is to remain permanently in the eye.

3.1.3 Endpoints

3.1.3.1 Primary Endpoint

<u>Safety</u>

- Number of patients experiencing a device related SAE at any time during the first 12 months following implantation of the IMD. For the purpose of this analysis, a device-related SAE is defined as any adverse event that both:
  - Is considered by the Investigator to have a possible, probable or definite relationship to the device and
  - That meets any of the following criteria of a serious adverse event:
    1. Led to death
    2. Led to a serious deterioration in the health of a subject that:
       a. Resulted in a life-threatening illness or injury
       b. Resulted in a permanent impairment of a body structure or body function
       c. Required in-patient hospitalization or prolongation of existing hospitalization
       d. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
    3. Led to fetal distress, fetal death or congenital abnormality or birth defect.

<u>Performance</u>

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

3.1.3.2 Secondary Endpoints

<u>Safety</u>

- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the 4 weeks immediately following implantation of the ARGOS-IO pressure sensor.
- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the first 16 weeks following implantation of the ARGOS-IO pressure sensor.
- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the 28 weeks following implantation of the ARGOS-IO pressure sensor.

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

Performance

- Level of agreement between IOP measurements made using surgical manometry and the ARGOS-IO system at 4, 16, 28 and 52 weeks following implantation
- Incidence of device deficiencies in the first 4, 16, 28 and 52 weeks following implantation
- User acceptance of the implantation procedure by means of evaluation of the Implantation Procedure Questionnaire (Investigators)
- User acceptance of the ARGOS-IO system at the investigational site by means of evaluation of the Investigator Acceptance Questionnaire (Investigators)
- Daily IOP self-measurement profiles (patients).

3.2 Study Population / Patient Selection

3.2.1 Eligibility Criteria

3.2.1.1 Inclusion Criteria

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

1. Male or female aged ≥ 18 and ≤ 80 years on the day of screening
2. Keratoprosthesis surgery indicated, defined as having a severely opaque and vascularized cornea AND either a verifiable history of two or more prior failed corneal transplant procedures or a medical condition such as alkali burns or autoimmune disease that makes the success of a traditional corneal transplant procedure unlikely. Potential study patients will be solicited for participation in the clinical trial only after they have consented to the keratoprosthesis operation.
3. Axial length > 21 mm
4. Ability and willingness to attend all scheduled visits and comply with all study procedures

3.2.1.2 Exclusion Criteria

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

1. Reasonable chance of success with traditional keratoplasty
2. Current retinal detachment
3. Connective tissue diseases
4. History or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-IO implantation
5. History of ocular or periocular malignancy
6. History of extensive keloid formation
7. Any known intolerance or hypersensitivity to topical anesthetics, mydriatics, or silicone (component of the device)
8. Presence of another active medical eye implant and/or other active medical implants in the head/neck region
9. Signs of current infection, including fever and current treatment with antibiotics
10. Severe generalized disease that results in a life expectancy shorter than a year
11. Any clinical evidence that the investigator feels would place the subject at increased risk with the placement of the device
12. Currently pregnant or breastfeeding
13. Participation in any study involving an investigational drug or device within the past 30 days or ongoing participation in a study with an investigational drug or device
14. Intraoperative complication that would preclude implantation of the study device
15. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization.
16. Previous or concurrent enrollment of the contralateral eye in this clinical study.

3.2.2 Setting and Location

The trial was conducted as an open, prospective, multicenter single-arm clinical trial at 3 sites in Germany.

3.2.3 Sample Size and Enrollment

This prospective, open-label, multicenter, single-arm clinical investigation enrolled 12 consecutive patients.

The primary aim of this study is to show “safety”, which is evaluated based on the number of subjects who experience an SADE (= “non-safety), as defined in the primary endpoints.
AEs, SAEs, ADEs and SADEs are listed. Incidence is estimated with a 95% confidence interval (Pearson-Clopper, two-sided).

A data safety monitoring board (DSMB) was established prior to enrollment of the first patient. The DSMB reviewed the safety data on a regular basis and advised on any changes required in the conduct of this clinical investigation.

3.3 Study Procedures

3.3.1 Study Intervention and Control

The ARGOS-IO pressure sensor is intended to be permanently implanted in the subject’s eye concomitantly with implantation of the BKPro. Once its safety and performance have been demonstrated through comparison to an established method of IOP measurement in a patient population, the frequency of measurements possible with the ARGOS-IO system is expected to provide a more accurate basis for physicians to use to make treatment decisions. The system consists of an IOP sensor that is implanted in the eye and a hand-held Mesograph reader that powers the sensor and downloads the data from it, simultaneously correcting the pressure reading for ambient air pressure and converting it to the format obtained with standard tonometers in clinical use. Conventional methods of measuring IOP typically used in the clinical setting all involve manipulation of the (preferably intact) cornea and cannot be used in eyes with keratoprostheses (Santaella & Afshari, 2011)(Sentinels et al 2011). Finger palpation remains the only method available for frequent assessment of IOP in these eyes. It is however not very precise or reproducible and its use is reserved to a few experts (Lin et al. 2014, Banat 2011).

All consenting patients who met all inclusion criteria and no exclusion criteria had an ARGOS-IO sensor implanted in combination with a Boston-Keratoprosthesis implantation. The condition of patients was followed up for 12 months after surgery. To assess the accuracy of IOP measurements obtained with the ARGOS-IO system in BKPro recipients, IOP values obtained with ARGOS were compared to the exact and reliable direct measurements obtained using surgical ocular manometry, in which a cannula was temporarily inserted into the eye, at visits 7, 9, 11, and 15. However, even though the IOP measured with this procedure is very exact, the surface of the eye was penetrated, which may cause the leak of small amounts of aqueous humor, leading to a pressure that differs from the true physiologic pressure. The actual physiologic pressure is of less importance in this investigation because the measurement were used to verify or calibrate the measurement taken with the intraocular ARGOS sensor at the same time under the same conditions.

The Bland-Altman method was used to assess the limits of agreement between the IOP measurements ARGOS-IO and surgical manometry. When appropriate, two-sided 95% Cis, for these limits were calculated accounting for repeated measurements based on the method proposed by Zou (2012).

AEs, SAEs, ADEs and SADEs are listed. Incidence is estimated with a 95% confidence interval (Pearson-Clopper, two-sided).

This exploratory study aims to estimate the agreement of IOP measurements obtained surgical manometry and the ARGOS-IO system at the same time point to allow assessment of the accuracy of the ARGOS-IO system and to collect further information on the occurrence of AEs and ADEs and about the reliability of the device in humans.

3.3.2 Treatment Schedule

During the study, subjects attended 15 clinic visits, including 1 screening visit (up to 60 days prior to surgery), 1 surgery visit (day 0 = V2 surgery), and 13 follow-up visits (day 1, 5, 10, 15, week 4, 10, 16, 22, 28, 34, 40, 46 and 52). The assessment schedule in Table 1 summarizes all visits and the assessments which were performed at each. The visit window given in the table should be adhered to as closely as possible.

Table 1: Assessment Schedule

	Screening	*Surgery*	*Follow-up*												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	Day -60 to -0	**Day 0**	**Day 1**	**Day 5**	**Day 10**	**Day 15**	**Wk4**	**Wk10**	**Wk16**	**Wk 22**	**Wk 28**	**Wk 34**	**Wk 40**	**Wk 46**	**Wk 52**
Visit Window (in days)			**+/- 0**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**
Procedure															
Informed Consent [a]	X														
Demographics	X														
Eligibility	X	X													
Enrollment	X														
Medical History [b]	X	X													
AE/ADE/SAE/SADE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior treatments	X														
Urine pregnancy test	X	X													
Device deficiency		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Implantation Surgery															
BKPro		X													
ARGOS-IO		X													
Anterior Segment															
Slit-lamp biomicroscopy			X	X	X	X	X	X	X	X	X	X	X	X	X
Biometry (axial length)	X														
White-to-white	X														
External eye photography – slit lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	***Surgery***	***Follow-up***												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Posterior Segment															
Biomicroscopy	X						X		X		X				X
Macula and Optic nerve OCT [c]	X						X		X		X				X
Fundus photography [c]							X		X		X				X
IOP measurement															
Goldmann Applanation	X														
Pneumotonometry	X														
ARGOS-IO clinic			X	X	X	X	X	X	X	X	X	X	X	X	X
ARGOS-IO home							X	X	X	X	X	X	X	X	X [e]
Surgical manometry							X		X		X				X
Finger palpation [d]			X	X	X	X	X	X	X	X	X	X	X	X	X
Miscellaneous															
Questionnaire surgeon		X													
Questionnaire site staff															X
Questionnaire patient															X
BCVA							X								X
Perimetry										X					X

[a] Potential participants must have consented to BKPro surgery before undergoing informed consent process for ARGOS-IO study.
[b] Medical history includes conditions and events up to ARGOS-IO implantation, and will include ophthalmic history, condition and pretreatments, as well as any ongoing or significant general conditions.
[c] If feasible
[d] Finger palpation will be used to estimate IOP according to the categories: soft/ hypotonic, definitely normal, borderline, definitely hypertonic.
[e] Collection of the Mesograph reader and Multiline Connector.

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3.3.3 Assessments

Individual assessments, described in the following sections, were repeated regularly throughout the study period. A list of the assessments and procedures conducted at each visit is contained in the Assessment Schedule, Table 1. The assessments and procedures are described in more detail in the following sections.

3.3.3.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: year of birth, age, sex, race, pre-treatments and source of subject referral. This information was collected at V01.

3.3.3.2 Medical history

Relevant medical history/current medical condition data includes data regarding ongoing or significant previous ophthalmic and general medical conditions and procedures until start of ARGOS-IO pressure sensor implantation. Relevant medical history should be supplemented by review of the subject's medical chart and/or by documented dialog with the subject's referring physician. If possible, diagnoses and not symptoms were recorded.

3.3.3.3 Pregnancy test

Urine dip stick test at screening (SC) and before surgery (V01) was performed in female subjects of childbearing potential. The test type and results were recorded in the subject's source documents. A positive result necessitated the exclusion of the subject from the study.

3.3.3.4 Concomitant medication, treatments and devices

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

Concomitant medication and devices during surgical procedure

Medication administered during surgery was recorded in the eCRF. Data were collected about the surgical techniques used to implant the ARGOS-IO and the keratoprosthesis as well as about any clinically significant differences from the expected course of the procedure.

Concomitant medication after implantation

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

Concomitant therapy in case of inflammatory events after implantation

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

3.3.3.5 AEs/ADEs/SAEs/SADEs

All AEs/ADEs/SAEs/SADEs were recorded starting with the implantation of the ARGOS-IO pressure sensor.

3.3.3.6 Device Malfunctions

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

3.3.3.7 Questionnaires

In the study, three types of questionnaires were used to assess potential strength and weaknesses of the ARGOS-IO system. Surgeons were asked to complete an implantation procedure questionnaire after each implantation at V02 (D0). At V15 (Wk52), the site staff responsible for IOP measurement as well as the subjects were asked to complete a user acceptance questionnaires for the MESOGRAPH reading device and the general measurement procedure.

The aim of these questionnaires was to gain more information about the level of user-acceptance of the ARGOS-IO system during implantation and during IOP measurement. The data collected with these questionnaires is only of exploratory nature and is included in the analysis. Results provided the sponsor with data that could influence future device system improvements.

3.3.3.8 External Eye Photography

Standard external eye photography was performed in conjunction with a slit-lamp in order to document changes to the outer eye.

3.3.3.9 Anterior eye segment measurement

Slit-lamp biomicroscopy (undilated, anterior segment)

The external ocular structures and the front of the eye were assessed at every visit using the slit-lamp biomicroscopy according to standard site procedures and following removal of the bandage contact lens (BCL), if present. Particular attention was paid to the ocular surface and, during follow-up, the posterior portion of the PMMA cylinder. Following structures were assessed:

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

Optical Biometry

When permitted by the subject's condition, the IOL Master (Carl Zeiss Meditec, Germany) was used during screening to measure the axial length of the globe and the horizontal white-to-white diameter.

To determine the implant size, at least three WTW measurements were taken and the average calculated. The average in mm was then determine the right ARGOS-IO implant size (see Table 5).

Table 2: Recommended ARGOS-IO Implant Sizes

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

If optical biometry was not possible, for example due to opacity of the subject's cornea, ultrasound biomicroscopy or corneal diameter measurement using an ophthalmosurgical caliper was used to assess the dimensions of the subject's anterior chamber.

3.3.3.10 Posterior eye segment measurement

All posterior eye segment examinations were done as permitted by the condition of the subject's cornea.

Biomicroscopy (dilated, fundus)

The posterior eye segment was examined using a slit lamp in combination with a 90D or "Superfield" or comparable lenses. The following parameters were assessed:

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

Optical coherence tomography (OCT)

Posterior segment OCT (PS-OCT) was used to assess macular structures and the peripapillary nerve fiber layer.

Fundus photography

Standard fundus photography was performed at visits 7, 9, 11 and 15 to document potential changes to the interior surface of the eye, including the retina.

3.3.3.11 Intraocular pressure (IOP) measurement

Intraocular pressure (IOP) was measured using four techniques. To provide a baseline IOP measurement, both Goldmann Applanation Tonometry (GAT) and pneumotonometry were performed at V01 (screening) if possible. Beginning at V03 (first follow-up visit), IOP measurement was performed with the ARGOS-IO system, both by site personnel at clinic visits and after discharge from hospital by the subject at home between visits. Direct manometry was performed at visits 07, 09, 11 and 15 to allow assessment of the accuracy of the ARGOS-IO system.

After surgery, treatment decisions was based on direct manometry, supplemented by finger palpation.

IOP measurement in the clinic

On the occasions when IOP was measured with both ARGOS-IO and manometry, it was measured as a series consisting of first with ARGOS-IO prior to positioning of the operating microscope, then manometry and followed again by ARGOS-IO. At the other follow-up visits IOP was measured with ARGOS-IO at least two times at every visit preferably at the beginning and end of the visit.

The surgical manometry measurements was conducted in the surgical suite under an operating microscope. A manometry system utilizing sterile saline solution was implemented via a 21-gauge needle cannulated to the anterior chamber. A standard procedure was followed both during the preparation of the system and the measurement in order to minimize the possibility of leaks or trapped air in the system.

At follow-up visits where manometry was not performed, the physician also estimated IOP using finger palpation, categorizing pressure as soft/hypotonic, definitely normal, borderline or definitely hypertonic.

ARGOS-IO system measurement by the subject at home

While in the clinic following surgery, subjects received detailed instruction in the use of the Mesograph reading device. Upon discharge from the clinic, they received an individual Mesograph reading device, a copy of the instructions for use and the Multiline Connector to perform self-tonometry at home. Subjects were requested to perform at least 4 IOP measurements with the Mesograph daily, evenly spread throughout the day.

No manual recording of data by the subject was required. The MESOGRAPH is capable of storing up to 3,000 measurements. Subjects were instructed to bring the Mesograph reading device to every visit, at which time site staff checked its functionality, access and downloaded the recorded readings and then deleted the measured IOP data from the device.

3.3.4 Study Visits

3.3.4.1 Screening

Only patients who had already independently agreed to undergo BKPro surgery were approached by the trial team about participation in the study.

At V01, the Investigator conducted the informed consent process (Section 12.1), ensuring that the subject's signature had been obtained on the patient informed consent (PIC) form and that the subject had received a copy before any study specific procedures are conducted. Once the PIC was signed, the subject was assigned a patient number (Section 8.2) and the Investigator determined if the subject met the eligibility criteria, surgery (V02) was scheduled and the screening fax form completed and faxed to the sponsor.

In addition, the following procedures were performed at the screening visit:

- Collection of background information about the subject including: demographics, medical history with prior treatments and current medications.
- Pregnancy test, when applicable
- External eye photography
- Anterior Segment assessments (slit-lamp biomicroscopy)
- Optical biometry, including ARGOS-IO implant size assessment
- Posterior Segment assessments (biomicroscopy, PS-OCT if feasible)
- IOP measurement with GAT and pneumotonometry
- Instruction of subjects on the need to report as soon as possible any SAEs occurring at any time during the study (starting from Visit 02 surgery)
- Completion the screening fax form and send to sponsor
- Completion of the eCRF.

3.3.4.2 Surgery

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

- Verification that the subject continues to meet eligibility criteria

- For female subjects of childbearing potential: collection of urine for pregnancy test. A test done within 24 hours prior to surgery had to be negative
- Performance of external eye photography prior to surgery.

The following procedures were performed on the day of the surgery:

- BKPro and ARGOS-IO pressure sensor implantations, including the updating medical history (up to surgery) and recording of concomitant medications, device deficiencies or malfunctions (including those detected during device preparation) and any AEs (starting from implantation of the ARGOS-IO pressure sensor)
- Completion of the implantation procedure questionnaire (surgeon) and the eCRF
- Completion of the patient inclusion form and fax it to the sponsor
- Instruction of subjects on the need to promptly report any SAE that may occur at any time during the study.
- Schedule Visit 2 (V02).

The duration of the subject's hospitalization was at the discretion of the Investigator. Durations of up to 7 days were not considered in themselves to be SAEs.

3.3.4.3 Follow-up, including duration

Following surgery, patients attended a total of 13 follow-up visits (Day 1 until Week 52). The main purpose of the follow-up visits was to assess eye condition and to determine if the patients had experienced any AEs. In addition, IOP was measured with the ARGOS-IO system beginning on Day 1 (V2) at the clinic to permit assessment of the performance of the ARGOS-IO pressure sensor and from week 4 (V7) ARGOS-IO home measurements were performed as well. V7, V9, V11 and V15 surgical manometry and ARGOS-IO measurements were performed at the same time point.

A detailed listing of the visit schedule and main activities conducted at each can be found in the assessment schedule in Table 1.

3.4 Treatment Allocation

This was a single-arm open-label study. No randomization and blinding/masking procedures were used in this study. To avoid bias resulting from patient selection, all consecutive patients potentially meeting the eligibility requirements were informed of the study and asked to participate. Those agreeing underwent the informed consent procedure and if they consented, was screened. All eligible patients were enrolled.

Measurements of IOP with the ARGOS-IO sensor was compared to IOP measured with surgical manometry in the same subject at the same time point to allow assessment of performance.

3.5 Data Quality Assurance

The study was 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 were conducted by trained and qualified monitors, who documented each individual monitoring visit. In general, during monitoring visits the monitor ensured 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 compared the CRF entries to original source data. He/she also made sure the informed consent procedure had been appropriately carried out and ensured that all SAEs had been reported within applicable timeframes. He/she also ensured that investigational device accountability had been maintained and, after completion of the study, performed final accountability and arranged return or destruction of investigational products. Detailed monitoring procedures are described in a separate monitoring plan.

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

The investigator was 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 had to be maintained. The sites maintained a list of the subjects´ names and the Patient ID assigned to each individual patient. Documents that identifed the subject beyond the Patient ID were not submitted to the sponsor (e.g. the signed informed consent document) and had to 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 had promptly reviewed the completed eCRFs for each subject promptly and had to confirm the accuracy of all data entered with his/her signature at the end of each documented subject's visit in the eCRF. Any corrections made to data entries were GCP conform.

During data review, data management generated queries for any missing, out of range or questionable data and sent these to the investigator for resolution. The physician answered the query and this answer was documented. All queries had to be answered and the database locked before any (interim) analysis of the data.

It had been verified by the sponsor that only validated and secure electronic data systems were used in this clinical investigation. Electronic data systems included the clinical data management database and the ARGOS-IO system measurement database. Database validation and security followed the respective national and international requirements.

3.6 Statistics

Statistical design, method and analytical procedures

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

Demographic and baseline characteristics

Demographic characteristics (age, sex, educational level), pre-existing glaucoma, secondary glaucoma to BKPro, pressure lowering surgeries incl. GDD prior to BKPro, GDD post BKPro, anti-glaucoma medication, and other previous and concurrent treatments are tabulated for the safety set.

Patient Disposition

The number and percentage of screened, enrolled and implanted subjects, as well as those who completed the follow-up are tabulated for the safety set. The number and percentage of screen failures and early withdrawals is also tabulated, along with the reason for the screen failure or drop-out.

Safety Analysis

The incidence within the safety population was estimated with a 95% confidence interval (Pearson-Clopper, two-sided).

Performance Analysis

The Bland-Altman method, which compares the mean of paired measurements to their difference, was used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with ARGOS-IO and surgical manometry. The two-sided 95% confidence intervals for each of these limits were calculated using the Mover method (Zou, Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual, 2011) to account for repeated observations of a changing value in individuals. IOP values were plotted both as Bland-Altman plots of individual measurement pairs, and by measurement technique as time plots of both population means and individual participant values.

The level of agreement was calculated to provide an estimate of the agreement, and eventually a correction factor to allow direct comparison of values obtained with different methods.

4 RESULTS

4.1 Critical Study Dates, Disposition of Subjects and Investigational Devices

Patients were recruited from prior patients and referrals from other physicians requiring and consenting to surgery for Boston-Keratoprosthesis implantation at 3 sites in Germany between December 2014 and June 2016. In this clinical trial a total of 14 patients with indication for a Boston-Keratoprosthesis implantation were screened and 13 patients initially enrolled, 12 of whom successfully received the ARGOS-IO implant.

One of the 14 screened patients (DE-3-01) was excluded due to a screening failure based on inclusion criterion 1 (Male or female aged ≥ 18 and ≤ 80 years on the day of screening). The patient was 83 years old. Due to a capsular bag instability detected during surgery, an implantation of the ARGOS-IO pressure sensor was not attempted in the second patient (DE-02-03). Thus, exclusion of this patient was unrelated to the ARGOS-IO device or procedures.
The capsular bag instability for DE-02-03 is, however, included in the overall safety data for the trial. All patients underwent Boston-Keratoprosthesis and ARGOS-IO pressure sensor implantation between 15-FEB-2015 and 15-JUN-2016 and were followed up for approximately 12 months. The last patient visit took place on 14-JUN-2017.

A total of 12 sensors were used for this study. 9 patients completed the study with the implanted sensors. One patient (DE-1-02) voluntary withdrew from the study after visit 10. In patient DE-1-05 the ARGOS-IO sensor was explanted on 13-JUN-16 (last Visit V10) after two SAEs of corneal graft melt which had, however, no causal relationship with the ARGOS-IO sensor. And in patient DE-1-07 sensor explantation was done on 31-MAY-16 (last Visit V7) after a dislocation of the ARGOS-IO implant (SAE).

4.2 Protocol changes during the study

The trial started out with revision B (Approval December 9th, 2014) of the clinical investigation plan. On March 30th, 2015 CIP Rev. C was approved with change from a paper-based Case Report Form to an electronic CRF. Rev. D resulted from an additional study center (change from monocenter to multicenter study) and from previous experiences within the trial (Approval August 5th, 2015). This clinical trial was finished with CIP Rev. E approved on April 13th, 2016. The most important changes to the protocol where as follows:

CIP Rev. D: Changes in **Determination of ARGOS-IO Implant Size**

CIP 8.4.4.9, p. 68 "Anterior eye segment measurement, **Optical Biometry"**

- "If optical biometry is not possible, for example due to opacity of the subject's cornea, ultrasound biomicroscopy **or corneal diameter measurement using an ophthalmosurgical caliper** will be used to assess the dimension of the subject's anterior chamber."

  This method has been shown to be a feasible approach during the first implantation by Professor Neuhann.

CIP Rev. E: Changes in **Sample Size Considerations** and **Usage of the ARGOS-IO injector during implantation (optional)**

CIP Synopsis, p. 6 "Sample Size Considerations", **CIP 8.3.7, p. 68** "Number of subjects required", **CIP 8.38, p. 68** "Estimated time needed to select the planned number of subjects" **and CIP 9.2, p. 83** "Sample Size Calculation"

- The enrollment from a minimum of 6 and a maximum of 10 patients was increased to a minimum of **10** and a maximum of **15** patients. Due to very different baseline parameters of the patients and a good tolerance of the ARGOS-IO implant until then, the enrollment number was increased to gain more experience.

CIP 4.7, p. 35 "Description of any specific medical or surgical procedures involved in the use of the investigational device", **CIP 5.1.1.3, p. 38** "Sterilization Verification", **CIP 6.5, p. 54** "Possible Interactions with concomitant Medical Treatments" **and CIP 8.4.5.2, p. 75** "ARGOS-IO pressure sensor implantation"

- The surgeons was given the option to use the ARGOS-IO Implant Injector as in the ARGOS-02 study for an easier access to the posterior chamber by an intact narrow pupil.

In the following table is listed which Revision of the Clinical Investigation Plan was valid for.

Table 3: Protocol changes during the study

Patient	Date of Screening	Date of Implantation	Relevant CIP Version
DE-1-01	12-Feb-15	12-Feb-15	Rev. B
DE-1-02	29-Jul-15	30-Jul-15	Rev. C
DE-1-03	10-Sep-15	10-Sep-15	Rev. D
DE-1-04	29-Oct-15	29-Oct-15	Rev. D
DE-1-05	10-Dec-15	10-Dec-15	Rev. D
DE-1-06	14-Dec-15	21-Jan-16	Rev. D
DE-1-07	28-Apr-16	28-Apr-16	Rev. E
DE-1-08	02-Jun-16	02-Jun-16	Rev. E
DE-2-01	21-Oct-15	22-Oct-15	Rev. D
DE-2-02	10-Mar-16	11-Mar-16	Rev. D
DE-2-03	18-Apr-16	(19-Apr-16, ARGOS-IO Implantation not done)	Rev. E
DE-2-04	23-May-16	24-May-16	Rev. E
DE-2-05	15-Jun-16	16-Jun-16	Rev. E
DE-3-01	06-Jun-16	n. a.	Rev. E

4.3 Subject Demographics and Other Baseline Characteristics

At enrollment, the patients (6 women and 7 men) were between 18 and 62 years of age (mean 39.4 years, SD 15.4 years). All patients had a verifiable history of two or more prior failed corneal transplant procedures or a medical condition such as alkali burns or autoimmune disease that makes the success of a traditional corneal transplant procedure unlikely (Table 4 and Table 5). Seven subjects were already treated for elevated IOP or glaucoma.
The patients had a mean axis length of 23.46 (SD 1.54) mm.

Previous general illnesses of interest included myocardial infarction in one patient. All other reported Medical History are related to the eyes. Concomitant diseases besides eye disorders are related to endocrine disorders (5 patients), nervous system disorders (5 patients), metabolism and nutrition disorder (2 patients), vascular disorders (2 patients), the blood and lymphatic system (1 patient), gastrointestinal disorder (1 patient), and asthma, renal failure and leukemia (1 patient).

Medical History and Baseline medical conditions related to the study eye are summarized in Table 4 and Table 5.

Concomitant diseases are listed in Table 6.

Table 4: Ophthalmic primary underlying condition/disease/event leading to need for KPro

Patient	Need for keratoprosthesis	Date of Onset	Result of	Current or previous treated for elevated IOP or glaucoma?
DE-1-01	Aniridia syndrome, Limbal stem cell insufficiency, Failed keratoplasty, Secundary glaucoma	26-May-1996	Aniridia syndrome (genetic)	Yes
DE-1-02	Corneal decompensation	22-Aug-2014	Congenital glaucoma	Yes
DE-1-03	Limbal stem cell insufficiency, Aniridia	23-Apr-1983	Genetic condition	No
DE-1-04	Graft versus Host Disease	2005	Autoimmune disease	No
DE-1-05	Explosion injury	2005	Injury, mechanical	No
DE-1-06	Chemical burn	28-Jul-1995	Injury, chemical	Yes
DE-1-07	Congenital aniridia syndrome	05-Jan-1975	Congenital disease	Yes
DE-1-08	Congenital aniridia syndrome	23-May-1995	Congenital disease	Yes
DE-2-01	Corneal opacity with vascularization	22-May-2006	Injury, chemical	No
DE-2-02	Corneal decompensation after keratoplasty in complicated secondary glaucoma	06-Jan-2016	Aniridia	Yes
DE-2-03	Corneal transplant failure, Chronic keratocinjunctivitis	18-Jun-2015	Atopic dermatitis	No
DE-2-04	Aniridia, Corneal graft failure	16-Dec-2015	Hereditary disease	Yes
DE-2-05	Corneal decompensation after corneal ulcer	09-Dec-2011	Autoimmune disease	No

Table 5: Summary of Disease Characteristics concerning the study eye

Parameter	**Total (N=13)**	
Disease Characteristics concerning Study Eye		
Study Eye	**n**	**%**
OD	4	30.8
OS	9	69.2
Ophthalmic primary underlying condition	**n**	**%**
Autoimmune disease	2	15.4
Chemical injury	2	15.4
Mechanical injury	1	7.7

Other	8	61.5
Time since onset at surgery (in years)	**Mean**	14.2
	SD	12.9
	Min	1
	Max	42
Treated for elevated IOP or glaucoma*	**n**	**%**
No	6	46.2
Yes	7	53.8
Axial length (mm)	**Mean**	23
	SD	1.54
	Min	21.23
	Max	27

IOP Measurements at Screening Visit		***GAT (mmHg)***	***Pneumotonometry (mmHg)***
Beginning of Visit	**n**	8	4
	Mean	12.9	12.3
	SD	5	6.2
	Min	7	7
	Max	22	12
End of Visit	**n**	5	4
	Mean	15	14.5
	SD	4.6	5.6
	Min	8	7
	Max	20	20

Medical History Related to Study Eye	**n[1]**	**%**
Any System Organ Class	**11**	**84.6**
Congenital, Familial and Genetic Disorders	**1**	**7.7**
Cataract congenital	1	7.7
Eye Disorders	**6**	**46.2**
Conjunctivalisation	2	15.4
Corneal disorder	1	7.7
Corneal erosion	1	7.7
Retinal detachment	1	7.7
Symblepharon	1	7.7
Trichiasis	1	7.7
Injury, Poisoning and Procedural Complications	**2**	**15.4**
Blast injury	1	7.7
Chemical burns of eye	1	7.7
Surgical and Medical Procedures	**9**	**69.2**
Keratoplasty	4	30.8
Cataract operation	3	23.1
Photocoagulation	3	23.1
Amniotic membrane graft	2	15.4

Eye operation	2	15.4
Stem cell transplant	2	15.4
Corneal sutures removal	1	7.7
Cryotherapy	1	7.7
Depilation	1	7.7
Eye prosthesis insertion	1	7.7
Eyelid operation	1	7.7
Intraocular lens implant	1	7.7
Vitrectomy	1	7.7
Concomitant Diseases Related to Study Eye	**n[1]**	**%**
Any System Organ Class	**11**	**84.6**
Congenital, Familial and Genetic Disorders	**6**	**46.2**
Aniridia	5	38.5
Developmental glaucoma	1	7.7
Eye Disorders	**8**	**61.5**
Glaucoma	4	30.8
Limbal stem cell deficiency	4	30.8
Amblyopia	3	23.1
Ulcerative keratitis	2	15.4
Aphakia	1	7.7
Corneal neovascularisation	1	7.7
Corneal edema	1	7.7
Keratitis	1	7.7
Keratoconus	1	7.7
Symblepahron	1	7.7
Xerophthalmia	1	7.7
Immune System Disorders	**1**	**7.7**
Graft versus Host Disease	1	7.7
Nervous System Disorders	**4**	**30.8**
Nystagmus	4	30.8
Skin and Subcutaneous Tissue Disorders	**1**	**7.7**
Toxic epidermal necrolysis	1	7.7
Surgical and Medical Procedures	**7**	**53.8**
Eye operation	3	23.1
Keratoplasty	3	23.1
Photocoagulation	2	15.4
Trabeculectomy	2	15.4
Amniotic membrane graft	1	7.7
Cataract operation	1	7.7
Corneal transplant	1	7.7
Phacocystectomy	1	7.7

Source: Final Statistical Output – Tables
Table 14.1.4.2.1 – Disease Characteristics concerning Study Eye
Table 14.1.4.7.1 – IOP Measurements at Screening Visit

Table 14.1.5.2.1 – Medical History Related to Study Eye by SOC and PT *Table 14.1.5.4.1 – Concomitant Diseases Related to Study Eye by SOC and PT*
%: Percentage based on N n: Number of subjects with data available N: Number of subjects in total (Safety Set) (*): Previously or currently treated n[1]: Number of patients reporting at least one past diagnosis/procedure

Table 6: Summary of Concomitant Diseases without any Relation to Study Eye

Concomitant diseases	**Total (N=13)**	
	n[1]	**%**
Any System Organ Class	**12**	**92.3**
Blood and Lymphatic System Disorders	**1**	**7.7**
Anaemia	1	7.7
Congenital, Familial and Genetic Disorders	**1**	**7.7**
Cataract congenital	1	7.7
Endocrine Disorders	**5**	**38.5**
Hypothyroidism	4	30.8
Cushing’s syndrome	1	7.7
Eye Disorders	**2**	**15.4**
Atrophy of globe	2	15.4
Conjunctivalisationl	1	7.7
Macular edema	1	7.7
Retinal detachment	1	7.7
Gastrointestinal Disorders	**1**	**7.7**
Hyperchlorhydria	1	7.7
Pancreatic failure	1	7.7
General Disorders and Administration Site Conditions	**1**	**7.7**
Pain	1	7.7
Metabolism and Nutrition Disorders	**2**	**15.4**
Diabetes Mellitus	2	15.4
Vitamin B12 Deficiency	1	7.7
Neoplasms Benign, Malignant and Unspecified	**1**	**7.7**
Leukaemia	1	7.7
Nervous System Disorders	**1**	**7.7**
Epilepsy	1	7.7
Psychiatric Disorders	1	7.7
Psychotic disorder	1	7.7
Renal Failure and Urinary Disorders	**1**	**7.7**
Renal failure	1	7.7

Respiratory, Thoracic and Mediastinal Disorders	**1**	**7.7**
Asthma	1	7.7
Skin and Subcutaneous Tissue Disorders	**1**	**7.7**
Dermatitis atopic	1	7.7
Surgical and Medical Procedures	**1**	**7.7**
Intraocular lens implant	1	7.7
Vascular Disorders	**2**	**15.4**
Hypertension	2	15.4

Source: Final Statistical Output – Tables
Table 14.1.5.3.1 – Concomitant Diseases by SOC and PT

%: Percentage based on N
N: Number of subjects in total (Safety Set)
n[1]: Number of patients reporting at least one past diagnosis/procedure

4.4 Implantation Characteristics

The surgical approach involved a typical trephination of adequate size of the central cornea of the recipient. Phakic subjects underwent cataract extraction by an open sky approach. If the subject was pseudophakic, the IOl was dealt with according to the site's customary keratoprosthesis implantation procedure. A posterior chamber IOL implanted in the capsular bag could remain in the eye.

Table 7: Summary of Surgical Approach

Patient	Was the patient pseudophacik? Location/Disposition	Iridectomy	Glaucoma Drainage Device	Fixation of ARGOS-IO sensor
DE-1-01	Yes Posterior chamber, sulcus ciliaris/remained in eye	No	Yes, already at start of KPro surgery/left in place	ukn
DE-1-02	Yes Posterior chamber, capsular bag/removed	Yes	Yes, already at start of KPro surgery/left in place	Supported by sulcus Sutured to sclera
DE-1-03	No	No	No	Sutured to sclera
DE-1-04	Yes Posterior chamber, capsular bag/remained in eye	Yes	No	Supported by sulcus
DE-1-05	No	No	No	Supported by sulcus
DE-1-06	Yes	Yes	No	Supported by sulcus

	Posterior chamber, capsular bag/remained in eye			
DE-1-07	No	No	No	Sutured to sclera
DE-1-08	Yes Posterior chamber, capsular bag/removed	No	No	Supported by sulcus
DE-2-01	Yes Posterior chamber, sulcus ciliaris/remained in eye	Yes	No	Supported by sulcus
DE-2-02	Yes Posterior chamber, capsular bag/remained in eye	No	Yes, already at start of KPro surgery/left in place	Sutured to sclera
DE-2-03	Yes Posterior chamber, capsular bag/remained in eye	No	No	No Implantation of ARGOS-IO sensor
DE-2-04	No	No	No	Sutured to sclera
DE-2-05	Yes Posterior chamber, capsular bag/remained in eye	Yes	No	Supported by sulcus

Source: Final Statistical Output – Listings
Listing 16.2.5.1 – Implantation Surgery Data
Listing 16.2.5.2 – ARGOS-IO Implantation

Most frequently the ARGOS-IO sensor with a diameter of 11.7 mm was implanted (58.3%). In three patients (25.0%) was the smallest sensor implanted (11.3 mm) and two patients got (16.7%) got the ARGOS-IO sensor with a diameter of 12.1 mm. The implant was fixated in the ciliary sulcus in seven patients (58.3%), in four patients it was sutured to the sclera (33.3%) and in one case the fixation of the ARGOS-IO sensor was not documented.

Intraoperative complications were reported in 3 patients (23.1%). In patient DE-1-02, a retinal hole occurred prior to the ARGOS-IO implantation. The other two complications occurred during the placement of the ARGOS-IO sensor, in patient DE-1-04 pigment dispersion and in patient DE-2-03 a posterior capsular tear so that the investigator decided to do no further attempts to implant the ARGOS-IO sensor in this patient. All these AEs have a causal relationship to the medical procedure and can also occur in a stand-alone implantation of a Boston-Keratoprosthesis. Pigment dispersion was rated as possible related to the medical device as well as to the medical procedure. It is known possible risk and is described in the CIP (7.4 Risks and anticipated adverse device effects to be assessed). All intraoperative complications were documented as AE (see *4.8 Safety*).

4.5 CIP Compliance

A summary of the protocol deviations is given by Table 8.

Table 8: Summary of Protocol Deviations

Parameter	**Total (N=13)**	
	n	**%**
At least one deviation	**12**	**92.3**
Deviation related to		
Patient rights/welfare	0	0.0
Patient safety	1	7.7
Integrity of research data	0	0.0
Other	11	84.6
Involvement of deviation		
Consent process	1	7.7
Patient eligibility	0	0.0
AE/SAE reporting	0	0.0
Assessments	10	76.9
Device implantation	0	0.0
Visit window/missed visit	12	92.3
Audit finding that require corrective action	0	0.0
Other	4	30.8

Source: Final Statistical Output – Tables
Table 14.1.3 – Summary of Protocol Deviations

%: Percentage based on N
N: Number of subjects in total (Treated patients)

Patient rights and welfare were not affected by the protocol deviations. The deviation related to the patient safety was a missed signature on the Informed Consent Form by the investigator. For this issue, the investigator stated with actual date that the patient was informed about the study, agreed to participate, signed and got a copy of the patient information and Informed Consent Form.

Most protocol deviations include visits out of the time window and assessments which were not completed as described in the CIP. The most frequent violation of the assessments was missing the external eye photography. This was only a minor deviation because these photos were not included in the evaluation. Missed surgical manometries were not performed due to medical reasons (hypotony of eye, Site DE-02 did no further surgical manometry in aniridia patients after SAEs (see *4.8.1.1 Serious Adverse Events in the follow-up period*)).

4.6 Data Sets Analyzed

Safety Population

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

The Per-Protocol-Set (PPS) population

The Per Protocol Set (PPS) will comprise all subjects in whom ARGOS-IO pressure sensor was successfully implanted and for whom the full data set including IOP measurements made in the clinic and safety data according to protocol are available until 28 weeks (Visit 11) after surgery. Because IOP measurements conducted outside the clinic will made at varying times under varying conditions, they are not anticipated to be comparable to those made in the clinic and will not be included in the Per-Protocol evaluation of agreement.

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

4.7 Performance

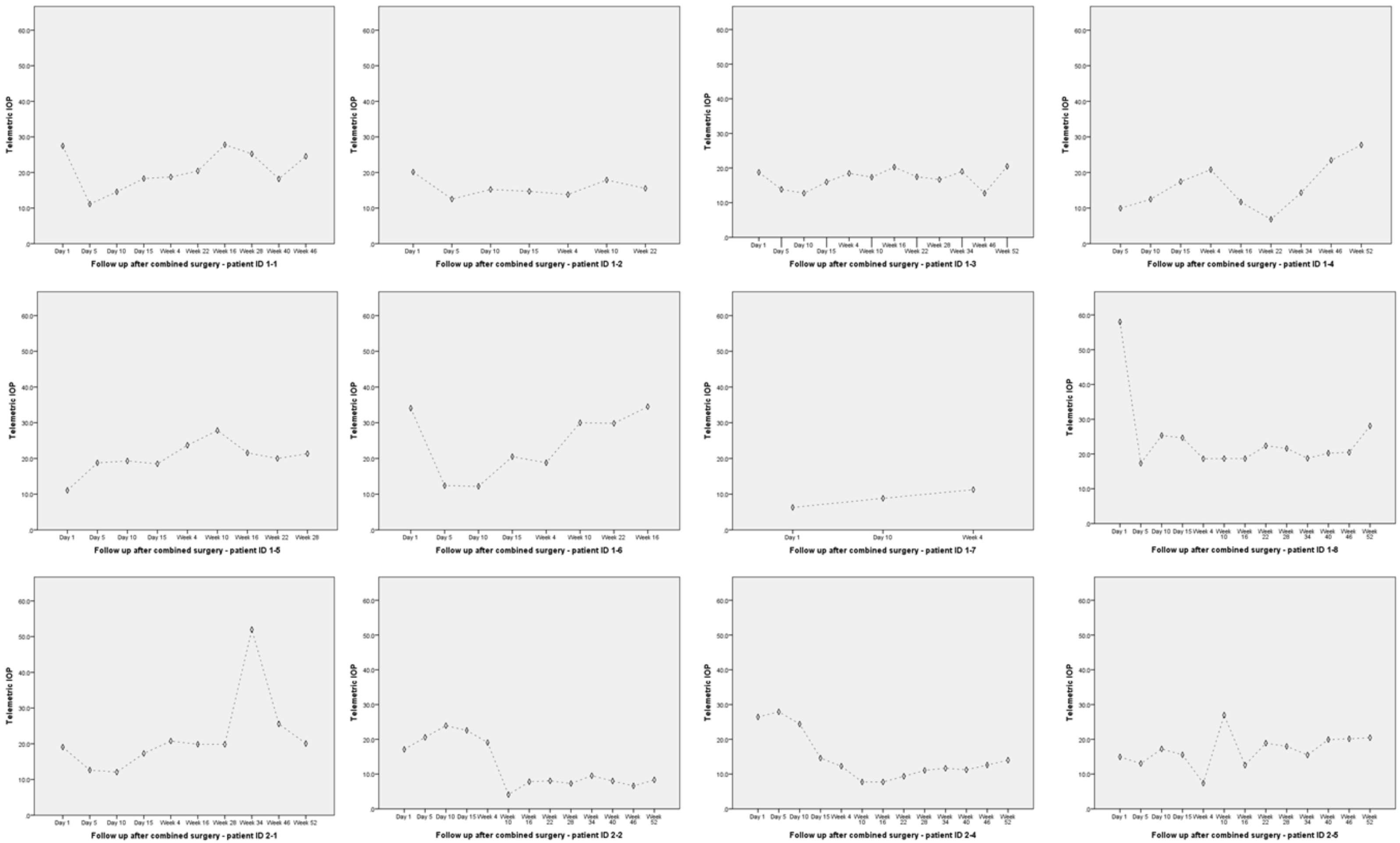
4.7.1 Tonometry

4.7.1.1 ARGOS-IO System

Telemetric IOP assessments by the ARGOS-IO implant was conducted at every study visit of every patient.

In the following line graphs (Figure 6) display the individual ARGOS-IO measurements over per patient at scheduled visits. Post-operative study visits were at Day 1, 5, 10, 15 and week 4, 10, 16, 22, 28, 34, 40, 46 and 52.

Figure 6. Individual IOP follow-up during study period per patient measured with the ARGOS-IO system



4.7.1.2 Comparison of ARGOS-IO system compared to finger palpation and surgical manometry

<u>Comparison to finger palpation</u>

IOP by finger palpation was assessed at every study visit. Figure 7 shows the average of the within subjects ARGOS-IO measurements at the beginning of the visit. Concerning Visit V07, V09, V11 and V15, ARGOS-IO measurements were taken before surgical manometry. Categories for the outcome of the finger palpation were normal, soft hypotonic, borderline and hypertonic. Measurements were not always performed.

Figure 7. ARGOS-IO Measurements versus Finger Palpation – Scatter Plot for each Post-Surgery Visit

Population: Safety Set

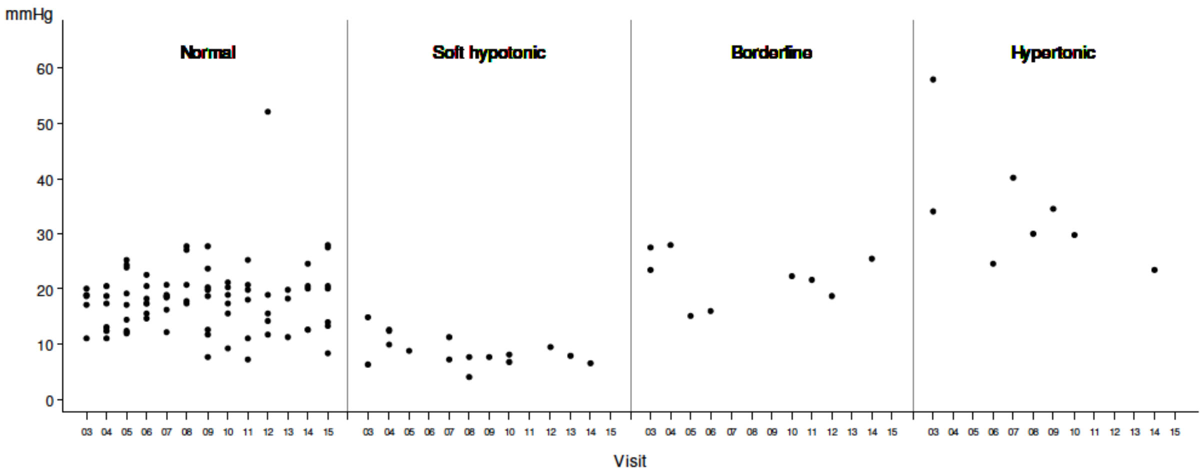


Figure 14.2.6.1; *Reference Table 14.2.6.1*

IOP by finger palpation was assessed at every study visit. In 82 visits IOP by finger palpation was seen "normal", mean telemetric IOP in these visits was 18.2 ± 6.1 mmHg, ranging from 7.3 to 52.0 mmHg. In 16 visits, patients' eyes were rated soft/hypotonic in finger palpation, while mean ARGOS-IO measurement was 8.9 ± 2.8 mmHg (range, 4.1 – 14.9 mmHg). In 9 visits, palpated IOP was classified as borderline, mean IOP assessed by the ARGOS-IO system was 22.4 ± 4.9 mmHg (range, 15.2 – 27.9 mmHg). In 8 visits, eyes were seen hypertonic in palpation. In these cases, mean telemetric IOP was 34.3 ± 11.0 mmHg, ranging from 23.4 to 58.0 mmHg. Kruskal Wallis test showed a statistically significant difference of telemetric IOP measurements between finger palpation categories with P < 0.001.

Comparison to surgical manometry

The following figures show the ARGOS-IO measurements within subject average of ARGOS-IO measurements during surgical manometry of the visit. The difference between surgical manometry and ARGOS-IO measurements is plotted as well. The difference was only derived when the time points of measurements differed for at most 2 min. Measurements were not always performed (Surgical Manometry in patients DE-1-02, DE-1-07 and DE-2-05 was never done).

Figure 8. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-01

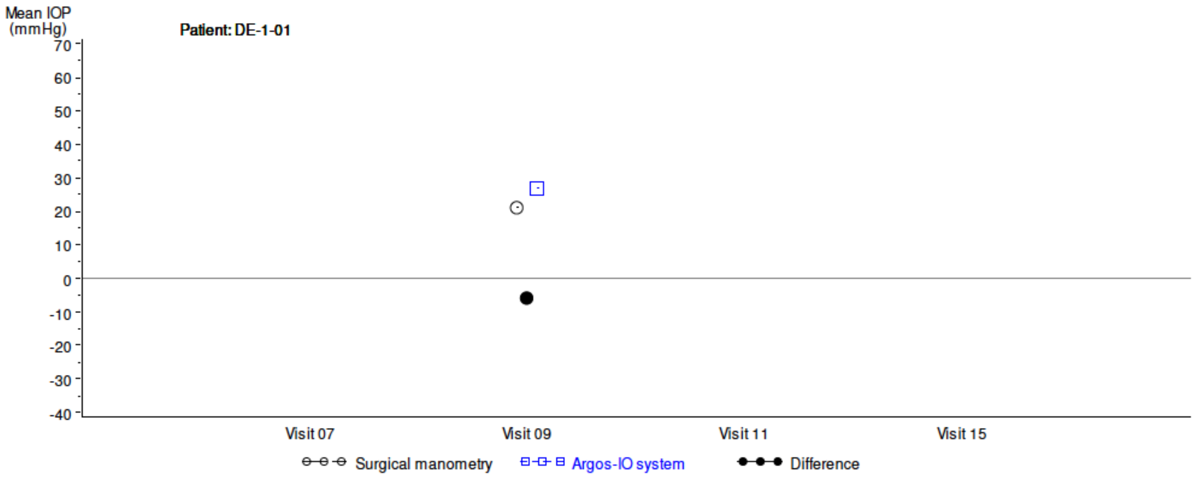


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	12:40	**17.0**	12:30	**18.7**	Not done		14:18	**16.9**
V09	14:30	**21.0**	08:34	**27.8**	14:30	**27.0**	Not done	
V11	Not done		17:04	**25.2**	Not done		Not done	
V15	Not done		Not done		Not done		Not done	

Figure 9. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-03

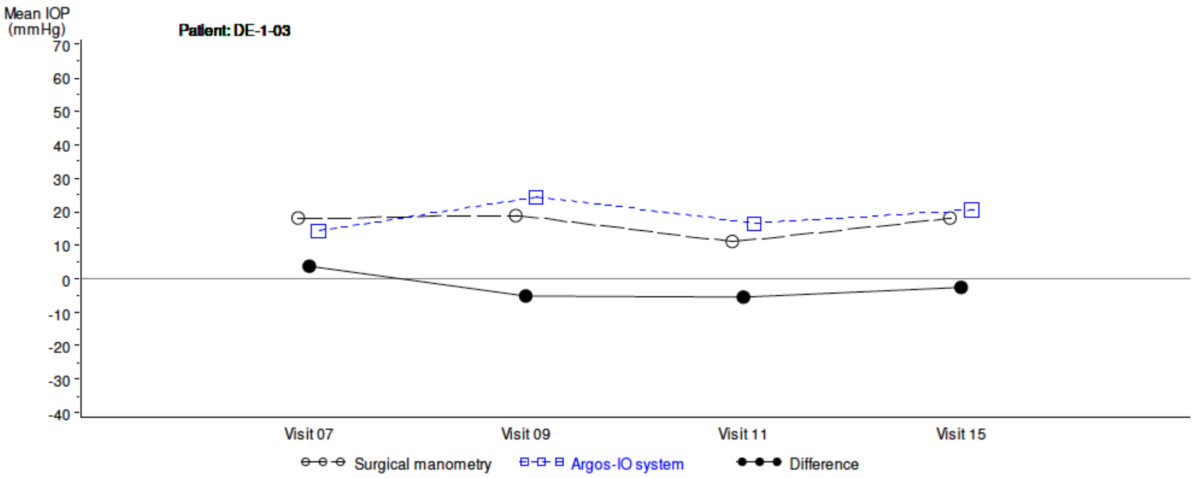


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	09:40	**18.0**	Not done		09:40	**14.4**	10:40	**18.5**
V09	11:45	**19.0**	09:41	**20.3**	11:45	**24.3**	13:25	**11.8**
V11	12:05	**11**	11:33	**20.7**	12:05	**16.7**	13:31	**14.9**
V15	13:16	**18**	12:45	**11.7**	12:48	**13.9**	Not done	

Figure 10. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-04

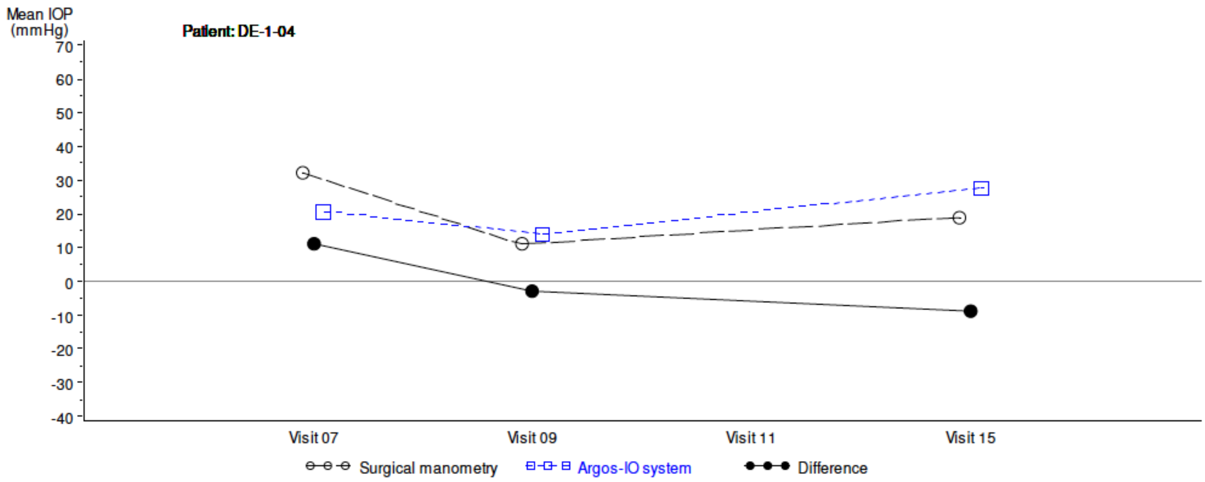


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	11:03	**32.0**	09:02	**16.4**	11:04	**20.8**	12:57	**30.3**
V09	12:48	**11**	12:45	**11.7**	12:48	**13.9**	Not done	
V11	Not done		Not done		Not done		Not done	
V15	13:25	**19**	10:44	**27.6**	13:25	**27.7**	Not done	

There is no explanation for the discrepancy of more than 10 mmHg between ARGOS-IO and surgical manometry in V07.

Figure 11. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-05

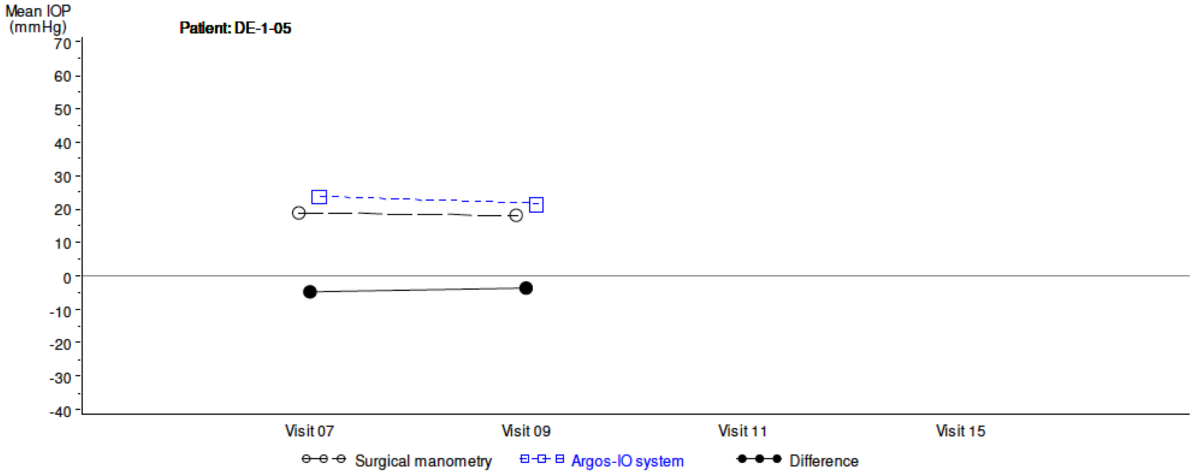


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	12:30	**19.0**	10:48	**40.1**	12:30	**23.7**	Not done	
V09	10:50	**18.0**	08:40	**23.7**	10:50	**21.6**	12:36	**21.9**

Figure 12. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-06

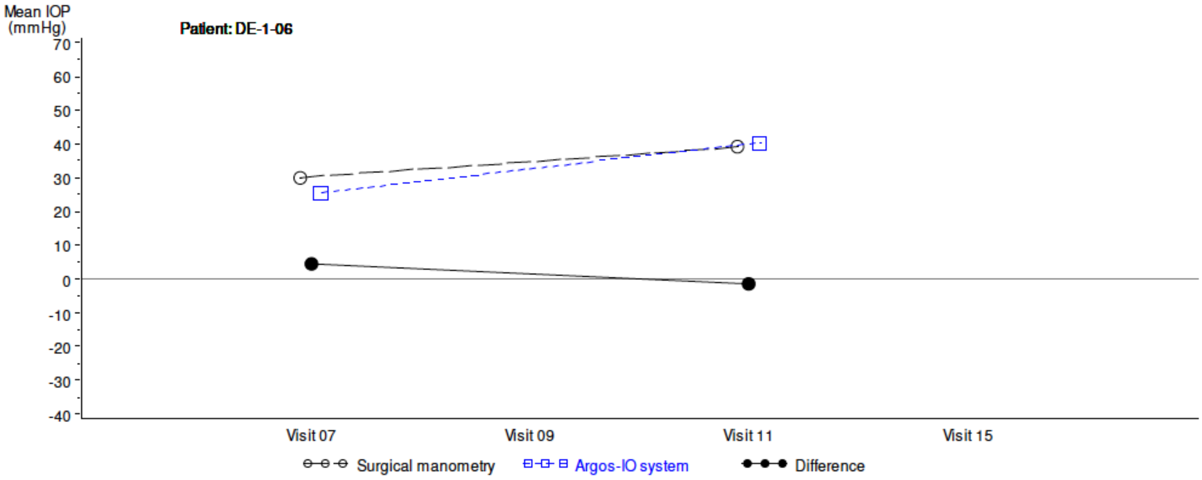


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	14:45	**30.0**	12:08	**18.8**	14:45	**25.6**	14:48	**20.4**
V09	Not done		12:42	**34.5**	Not done		Not done	
V11	18:09	**39.0**	Not done		18:09	**40.3**	18:26	**17.5**
V15	Not done		Not done		Not done		Not done	

Figure 13. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-1-08

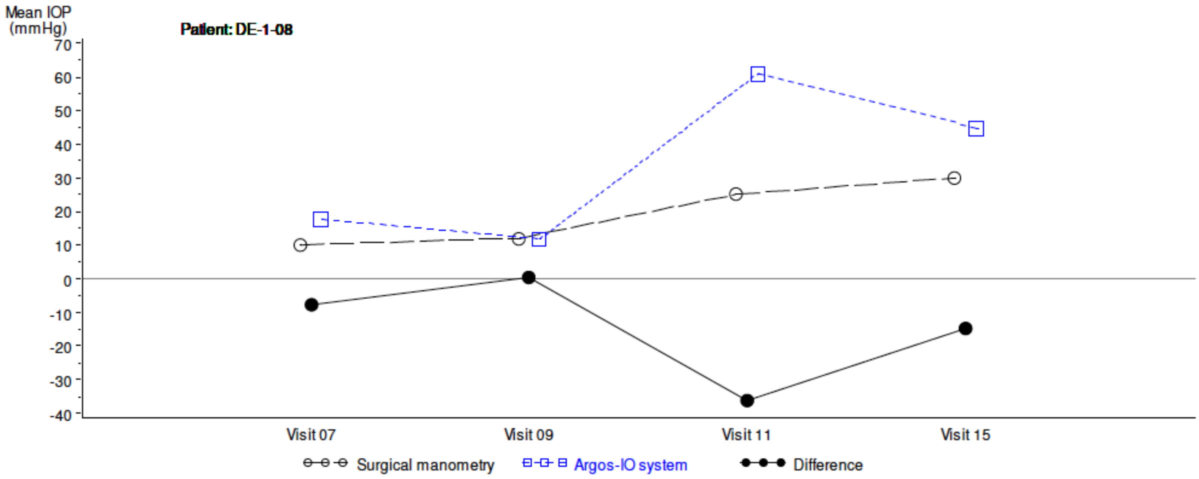


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	10:09	**10.0**	Not done		10:09	**17.7**	15:33	**18.6**
V09	14:59	**12.0**	09:38	**18.7**	14:59	**11.8**	15:16	**2.4**
V11	11:00	**25.0**	08:29	**21.6**	11:00	**61.0**	11:01	**1.4**
V15	11:05	**30.0**	09:52	**28.1**	11:05	**44.8**	Not done	

Almost certainly, a measurement error is existent for the ARGOS-IO measurements during surgical manometry at V11 and V15 in this patient. ARGOS-IO measurements which were obtained before surgical manometry correspond well with the manometric values. Patient DE-1-08 has a congenital aniridia syndrome. The IOL was removed during the BkPro and ARGOS-IO implantation. The ARGOS-IO sensor is supported by the sulcus. It cannot be excluded that the sensor was touched during the manometry which could explain this high values.

Figure 14. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-2-01

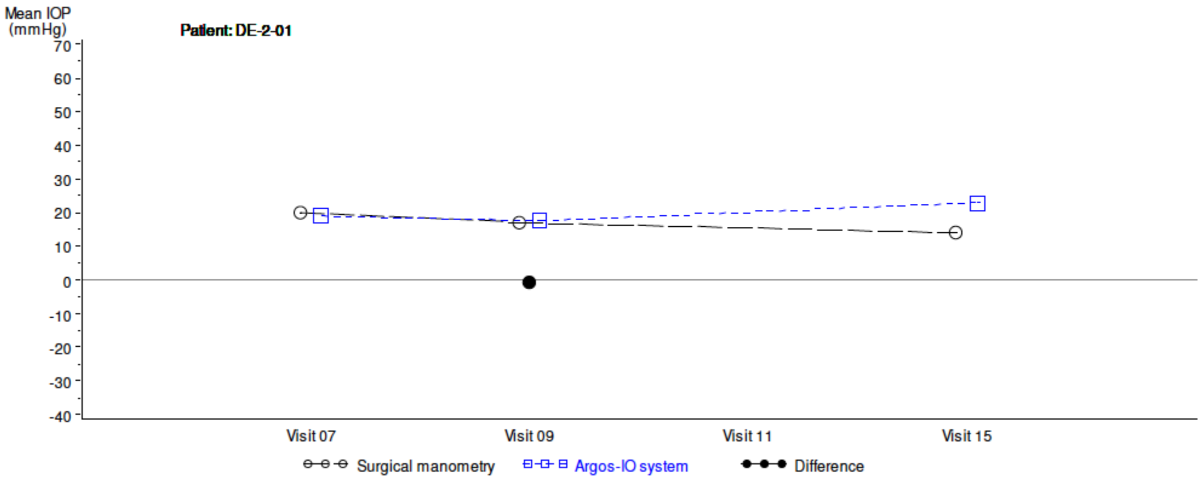


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	16:01	**20.0**	11:14	**20.8**	16:20	**19.0**	16:45	**16.3**
V09	15:55	**17.0**	15:00	**19.9**	15:56	**17.6**	16:30	**17.1**
V11	17:15	**24**	12:30	**19.8**	Not done		17:30	**23.8**
V15	15:36	**14**	12:00	**20.1**	15:32	**22.8**	Not done	

Figure 15. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-2-02

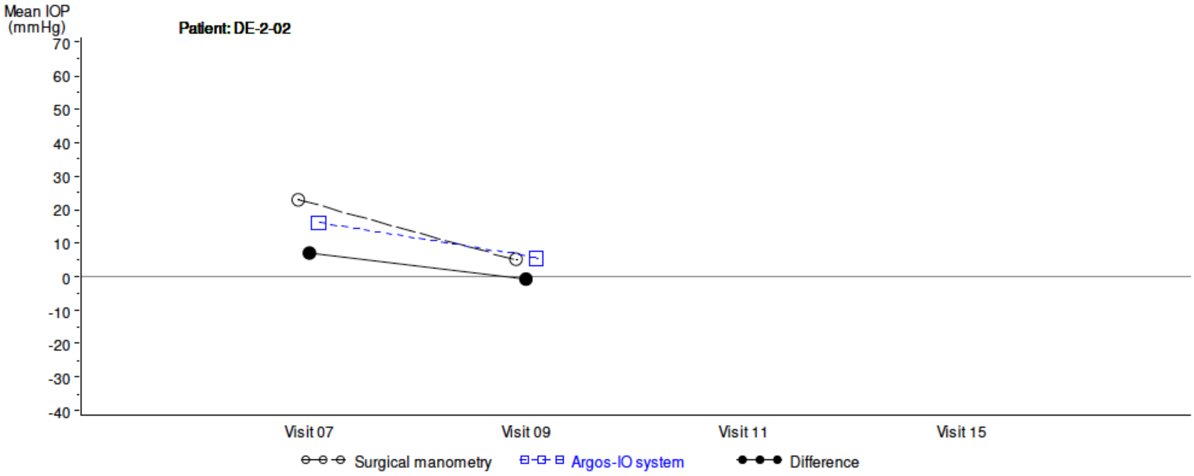


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurements					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	15:46	**23.0**	15:40	**19.1**	15:46	**16.1**	15:52	**16.0**
V09	14:05	**5.0**	12:16	**7.8**	14:05	**5.7**	Not done	
V11	Not done		11:15	**7.3**	Not done		Not done	
V15	Not done		12:00	**8.3**	Not done		13:00	8.5

In this patient with aniridia, PVR with consecutive tractive retinal detachment developed in timely connection to surgical manometry (*see 4.8.1.1 Serious adverse events in the follow-up period; DE-2-02: Proliferative vitreoretinopathy (PVR) with retinal detachment)*. Therefore, the investigator decided against assessing a manometry in this patient at V11 and V15.

Figure 16. Difference between Manometry and ARGOS-IO over the time – mean value plot; DE-2-02

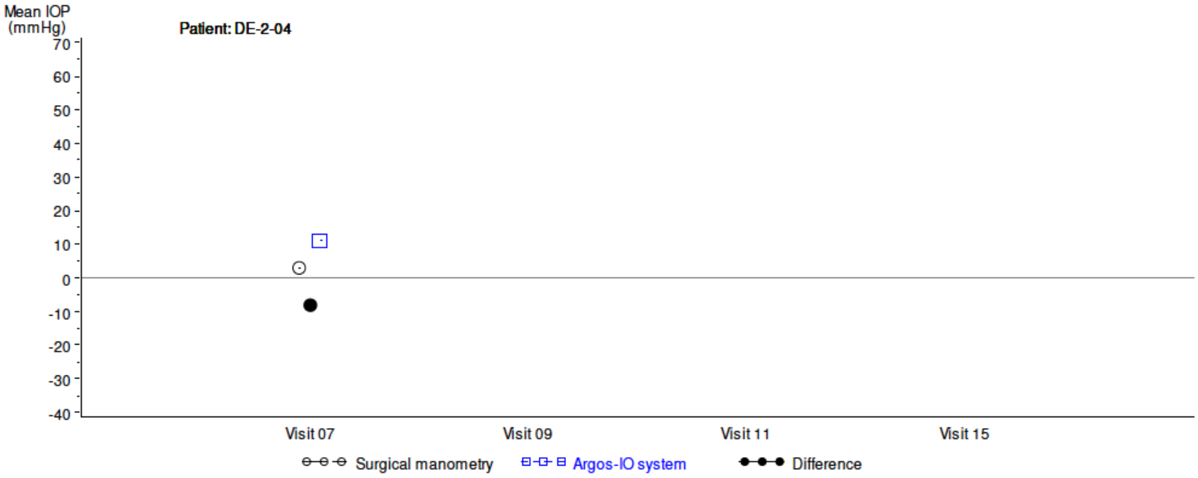


Figure 14.2.1.3; *Reference: Subject Data Listing 16.2.6.1*

Visit	Surgical Manometry		Average of 3 consecutive ARGOS-IO measurments					
			Before Manometry		During Manometry		Following Manometry	
	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)	Time	IOP (mmHg)
V07	14:30	**03**	12:17	**12.3**	14:30	**11.1**	Not done	
V09	Not done		11:00	**7.7**	Not done		Not done	
V11	Not done		14:25	**11.1**	Not done		Not done	
V15	Not done		09:31	**14.0**	Not done		Not done	

In this patient with aniridia, PVR with consecutive tractive retinal detachment developed in timely connection to surgical manometry (*see 4.8.1.1 Serious adverse events in the follow-up period; DE-2-04: Proliferative vitreoretinopath)*. Therefore, the investigator decided against assessing a manometry in this patient at V09, V11 and V15.

Figure 17. Difference between Manometry and ARGOS-IO over the time – mean value plot (all patients)

Population: Safety Set

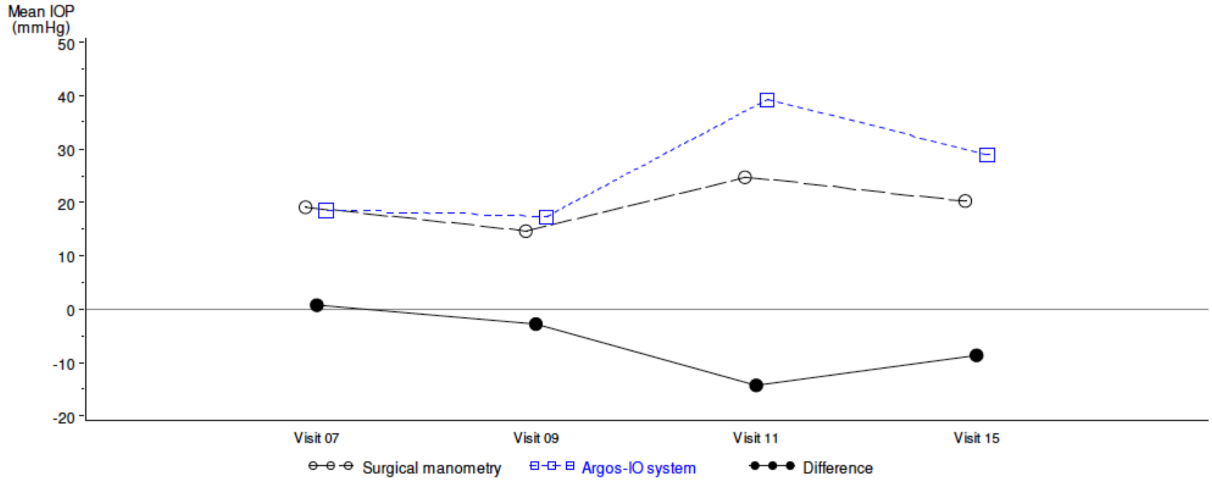


Figure 14.2.1.2; *Reference Table 14.2.1.2*

Surgical intracameral manometry was performed in a total of 24 visits in nine patients. The study protocol entailed manometry in four visits in every patient, when the investigators rated the study eye sufficiently stable to undergo surgical manometry. In these visits, the mean telemetric IOP, representing the averaged value of three repeated measurements, was 22.8 ± 11.7 mmHg. The mean invasive IOP by manometry was 19.0 ± 8.4 mmHg. In nine of 24 events (37.5%), both IOP measurements deviated by less than 10%, and in 14 of 24 by less than 20% (58.3%). In three visits, telemetric and manometric IOP measurements showed a discrepancy of more than 10 mmHg, suggesting measurement errors. In these cases, a major discrepancy was noted between preoperative and intraoperative telemetric IOP measurements. Two of the three outliers occurred in the same patient (DE-1-08). While intraoperative telemetric measurements obtained by the ARGOS-IO system showed high values of 45 mmHg and 60 mmHg respectively, manometric values corresponded well with telemetric values obtained one hour preoperatively. In the first visit, the preoperative mean telemetric IOP was 28.1 mmHg with a manometric measurement of 30 mmHg. In the second visit, a manometric IOP of 25 mmHg compared to a preoperative mean telemetric IOP of 21.6 mmHg. In the third outlier (DE-1-04), preoperative telemetric IOP measurements showed a consistent discrepancy. When these three cases of outliers were excluded, IOP measurements by both modalities had a correlation of r = 0.874 (P < 0.001).

Figure 18 and 19 are a Bland-Altman plot of all acquired events in this study for graphical display of the congruence between both modalities to measure IOP.

Figure 18. Bland-Altman Plot: Level of Agreement between Manometry and ARGOS-IO by Visit

Population: Safety Set

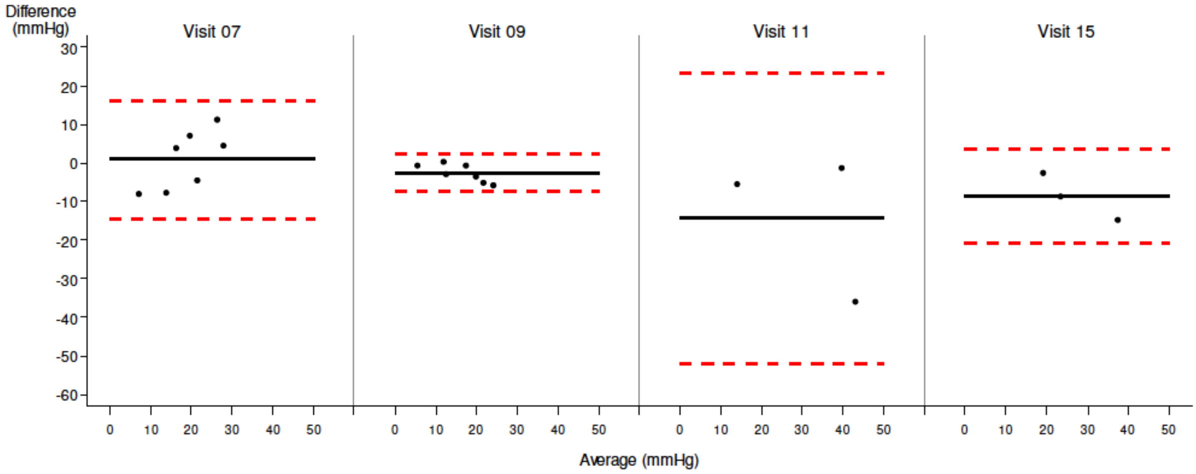
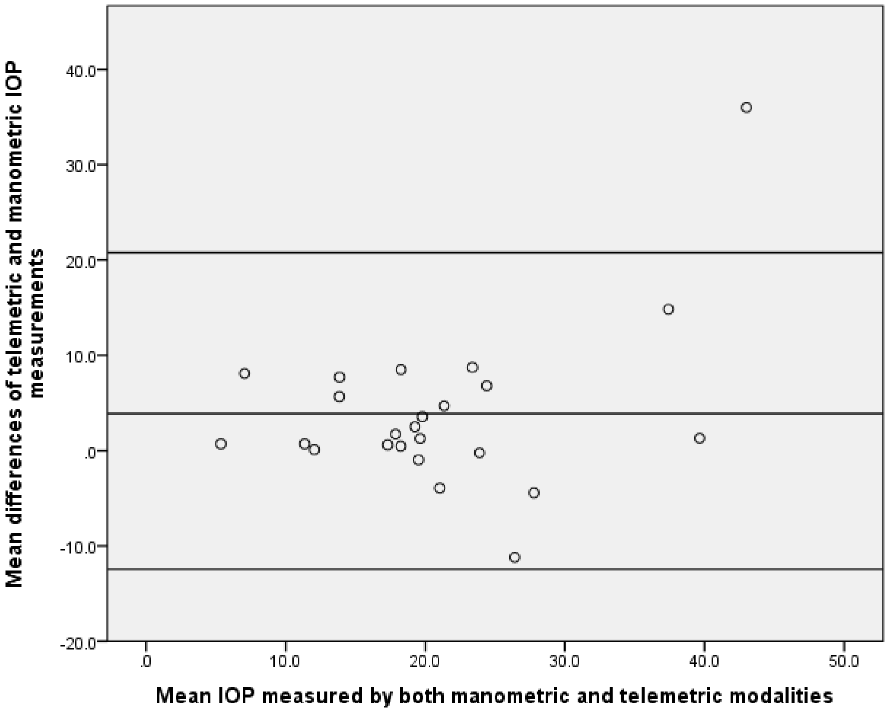


Figure 14.2.3.1; *Reference: Table 14.2.3.1*

ARGOS-IO measurements: within subject average of ARGOS-IO measurements during surgical manometry of the visit.
NOTE: Measurements were not always performed. The difference between surgical manometry and ARGOS-IO measurements is plotted against the average of the two values by visit. The solid line represents the level of agreements the broken lines display the lower 95% and the upper 95% bound for the level of agreement.

Figure 19. Bland-Altman Plot: Overall Level of Agreement between Manometry and ARGOS-IO
Population: Safety Set



4.7.2 User acceptance of the ARGOS-IO system at home by evaluation of patient acceptance questionnaire

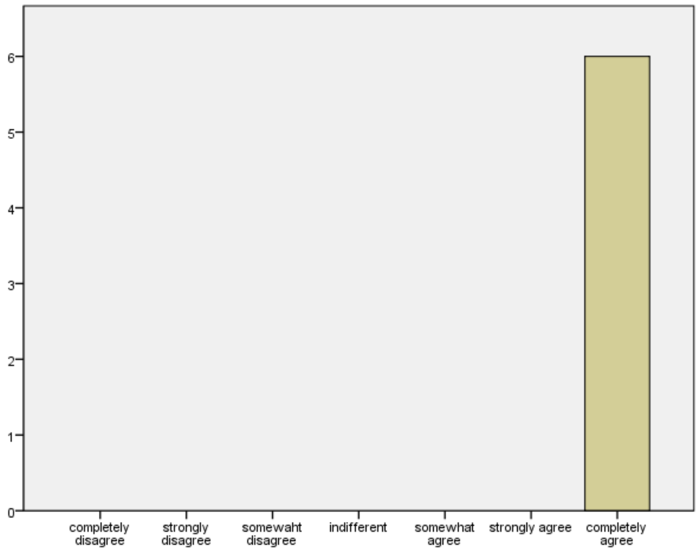
In all patients who completed the patient acceptance questionnaire was a very high overall acceptance in using the ARGOS-IO system in their daily routine. The instruction for use for the Mesograph reader device was easily to understand, the implant did not cause them any problems and the patients were less concerned about unidentified high IOP.

Patients could give an estimate on a scale of 1 to 7 how strongly they agree with the following questions. 1 means totally disagree and 7 stands for totally agree.

Q2 - ***To what extend do you agree with the following statements:***

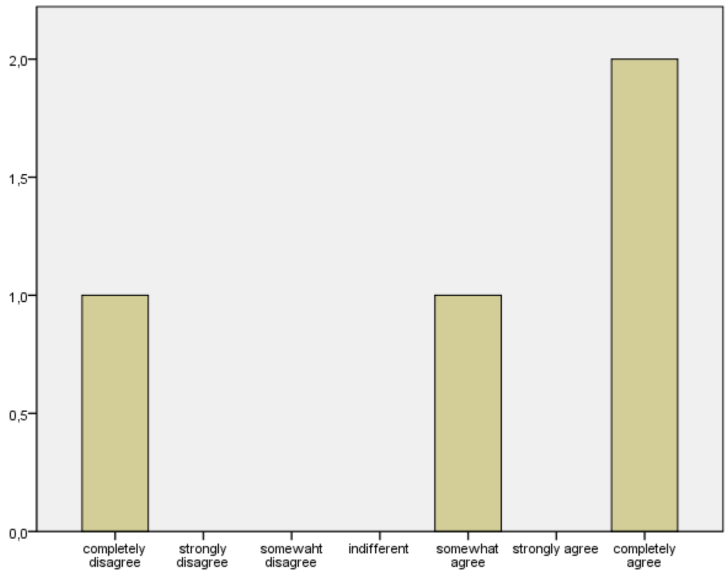
Based on my experience with the ARGOS-IO system in this study, I would seriously consider

…permanently using ARGOS-IO system at home.



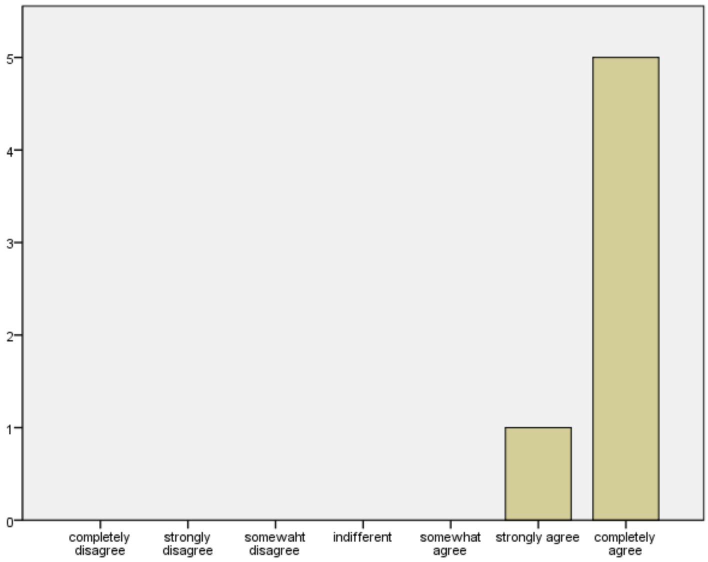
Answer	Frequency (N=6)	
	n	%
Completely agree	6	100.0

…using ARGOS-IO system at workplace.



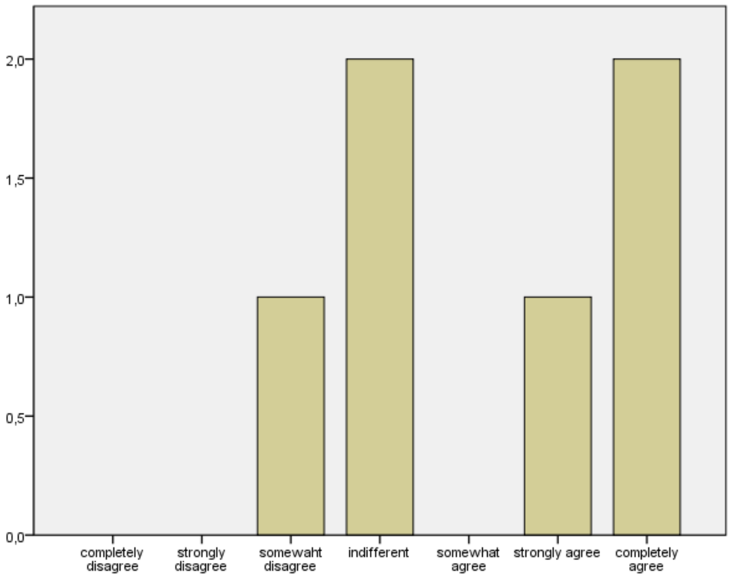
Answer	Frequency (N=6)	
	n	%
Completely disagree	1	16.7
Somewhat agree	1	16.7
Completely agree	2	33.3
Missing	2	33.3

…using the ARGOS-IO system while travelling.



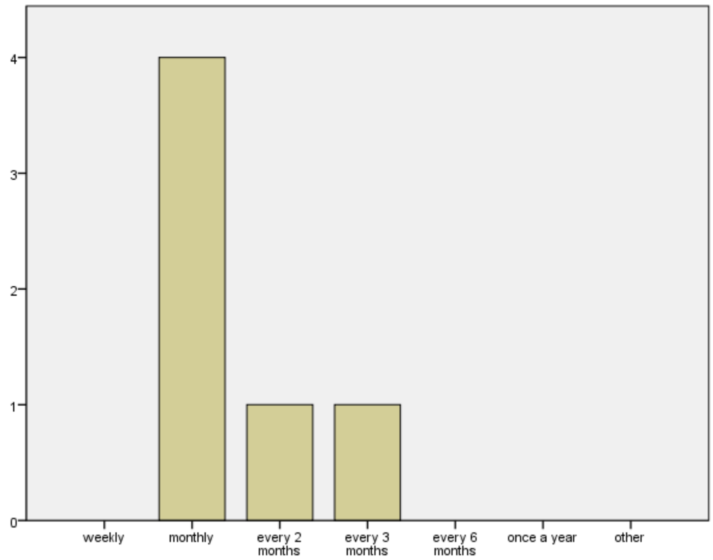
Answer	Frequency (N=6)	
	n	%
Strongly agree	1	16.7
Completely agree	5	83.3

…recommending the ARGOS-IO system to other glaucoma patients.



Answer	Frequency (N=6)	
	n	%
Somewhat disagree	1	16.7
Indifferent	2	33.3
Strongly agree	1	16.7
Completely agree	2	33.3

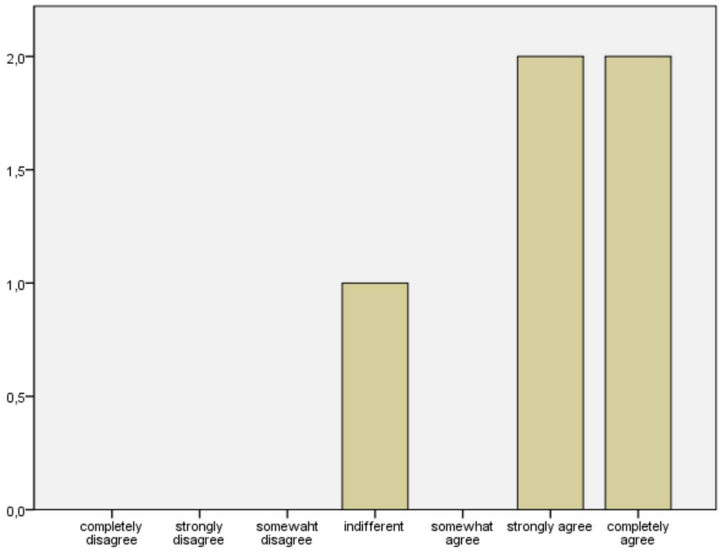
Q3 – How do you normally have your IOP measured (outside of the study)?



Answer	Frequency (N=6)	
	n	%
Monthly	4	66.7
Every 2 months	1	16.7
Every 3 months	1	16.7

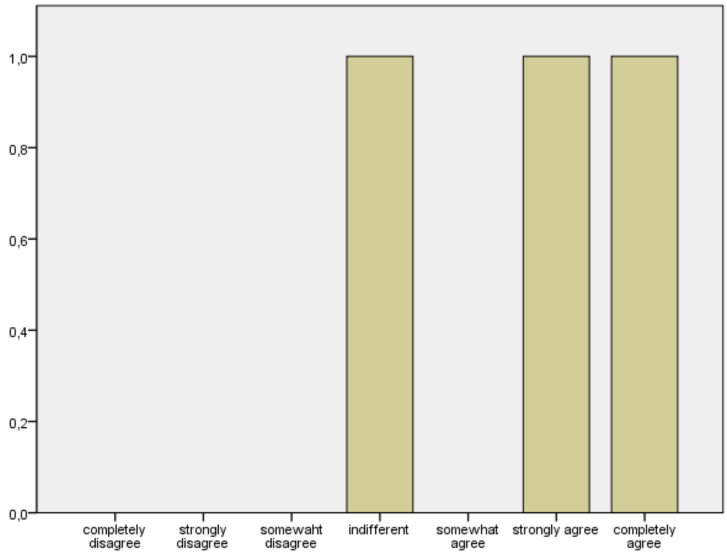
Q4 – To what extend do you agree with the following statements regarding the user instructions

…user instructions for the Mesograph reader device can easily be understood.



Answer	Frequency (N=6)	
	n	%
Indifferent	1	16.7
Strongly agree	2	33.3
Completely agree	2	33.3
Missing	1	16.7

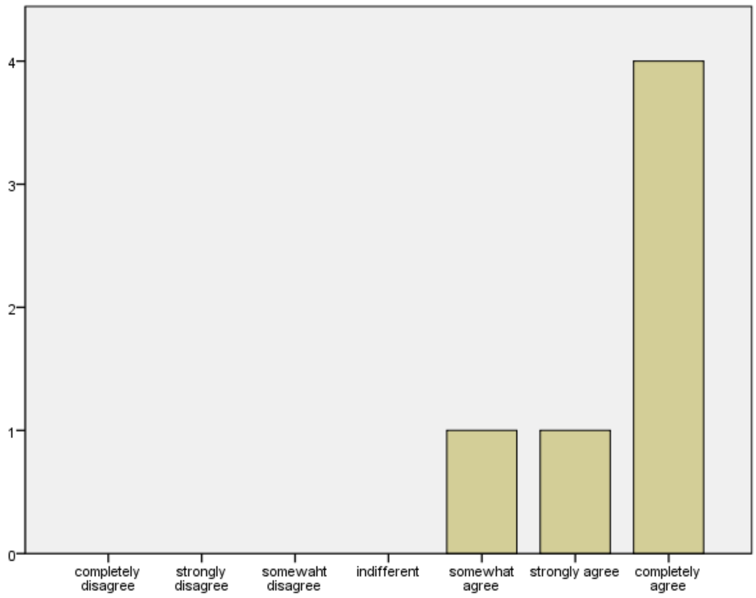
…user instructions for the Multiline connector can easily be understood.



Answer	Frequency (N=6)	
	n	%
Indifferent	1	16.7
Strongly agree	1	16.7
Completely agree	1	16.7
Missing	3	50.0

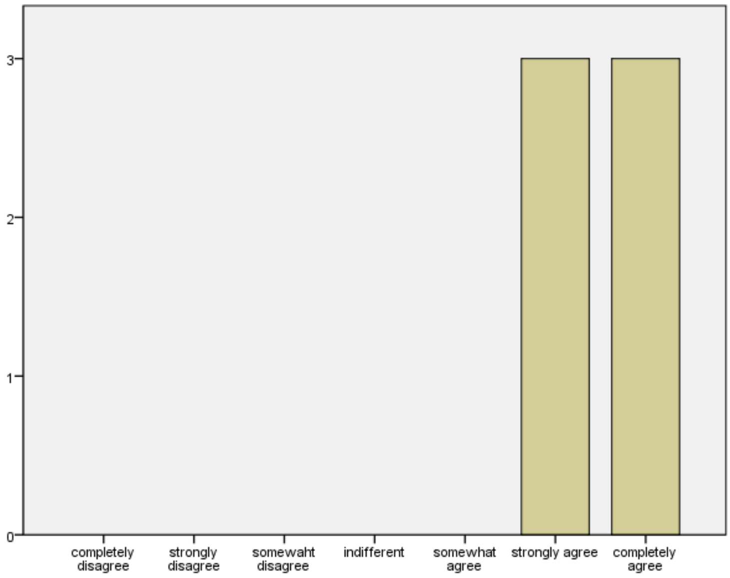
Q5 – To what extend do you agree with the following statements about the Mesograph reader device?

The Mesograph reader device fits well in the hand…



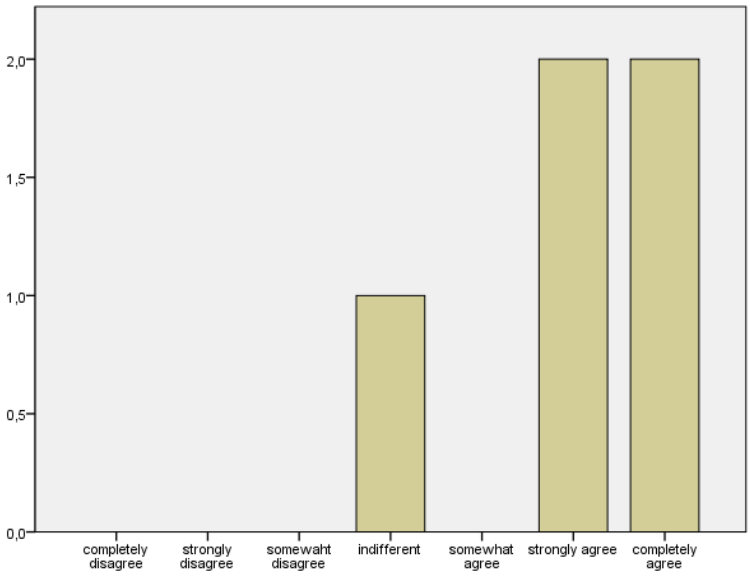
Answer	Frequency (N=6)	
	n	%
Somewhat agree	1	16.7
Strongly agree	1	16.7
Completely agree	4	66.7

The display of the Mesograph reader is large enough…



Answer	Frequency (N=6)	
	n	%
Strongly agree	3	50.0
Completely agree	3	50.0

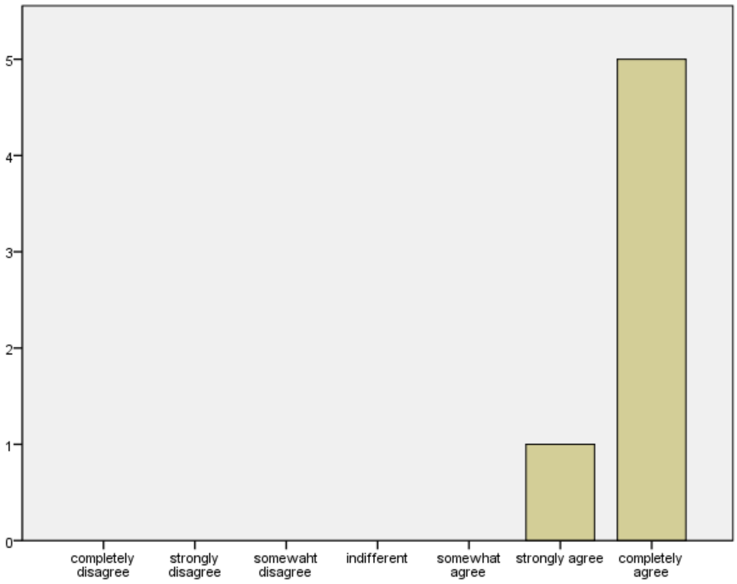
The battery of the MESOGRAPH reader lasts long and can be easily exchanged…



Answer	Frequency (N=6)	
	n	%
Indifferent	1	16.7
Strongly agree	2	33.3
Completely agree	2	33.3
Missing	1	16.7

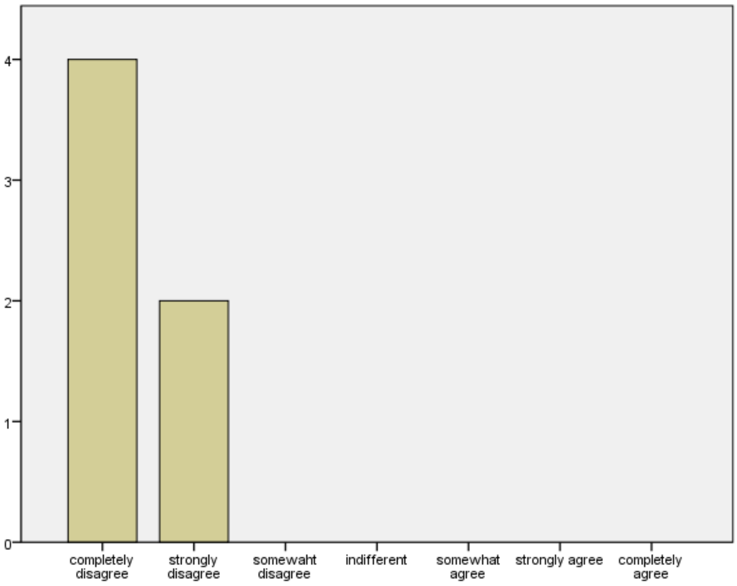
Q6 – To what extend do you agree with the following statements about the implant:

The implant does not cause me any problems…



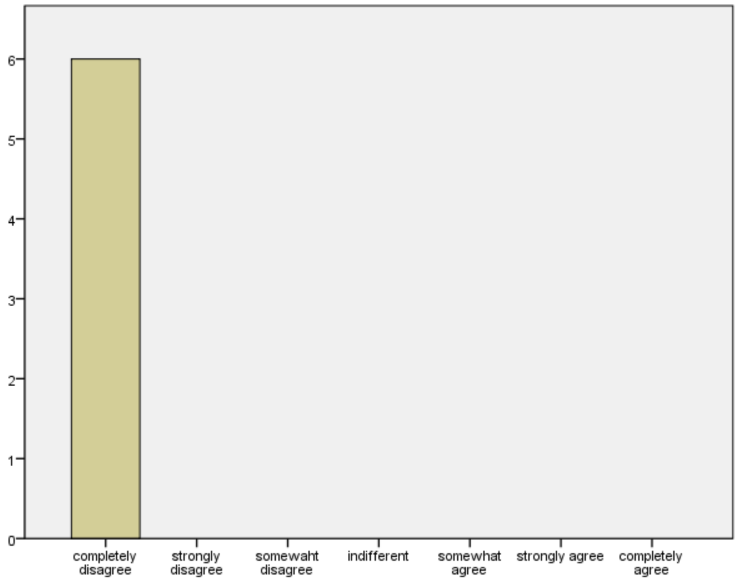
Answer	Frequency (N=6)	
	n	%
Strongly agree	1	16.7
Completely agree	5	83.3

I feel the implant as a foreign body…



Answer	Frequency (N=6)	
	n	%
Completely disagree	4	66.7
Strongly disagree	2	33.3

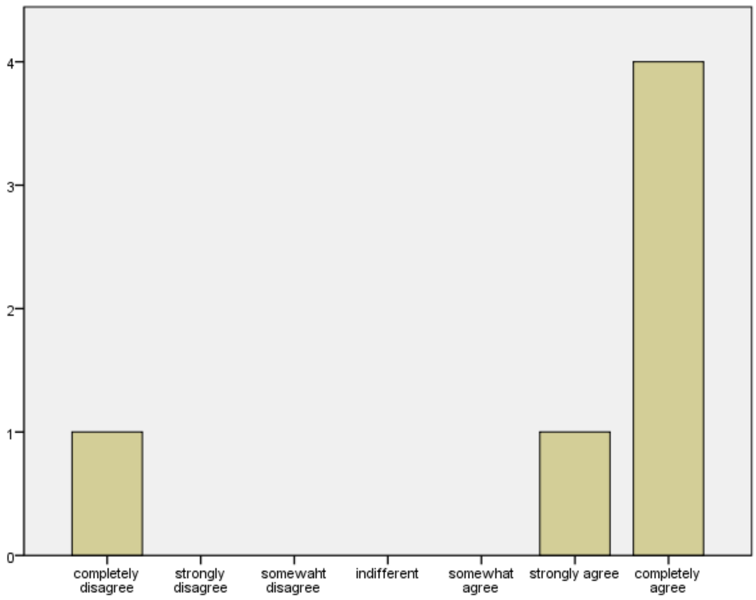
The implant affects my visual field…



Answer	Frequency (N=6)	
	n	%
Completely disagree	6	100.0

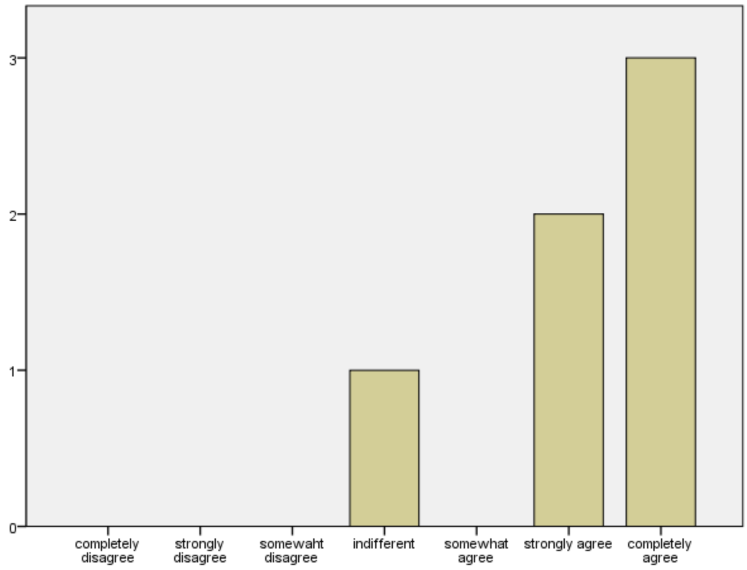
Q7 – To what extend do you agree the following statements:

Pressure measurements at home do not disturb my daily routine…



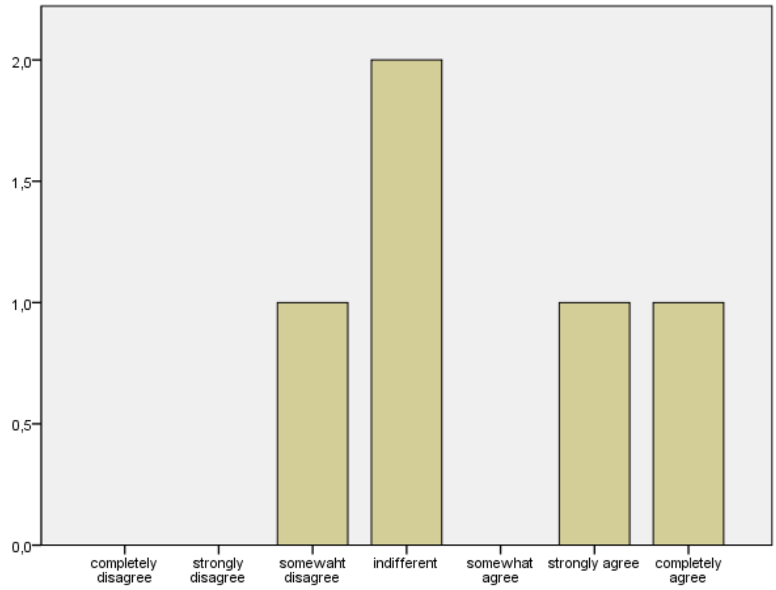
Answer	Frequency (N=6)	
	n	%
Completely disagree	1	16.7
Strongly agree	1	16.7
Completely agree	4	66.7

Pressure measurements at home reduced my worries about unidentified high ocular pressure…



Answer	Frequency (N=6)	
	n	%
Indifferent	1	16.7
Strongly agree	2	33.3
Completely agree	3	50.0

Pressure measurements at home increased my motivation to regularly take my pressure lowering medication…



Answer	Frequency (N=6)	
	n	%
Somewhat disagree	1	16.7
Indifferent	2	33.3
Strongly agree	1	16.7
Completely agree	1	16.7
Missing	1	16.7

4.8 Safety

4.8.1 Adverse Events

Information about all untoward medical occurrences occurring during a subject's study participation was collected at study visits through examination by the Investigator. Information about events occurring between visits was obtained by asking the patient non-leading questions.

Particular attention was paid to ophthalmic AEs, for which increased risks are considered possible (CIP 7.4 Risks and anticipated adverse device effects to be assed):

- Retroprosthetic membrane formation
- Increased intraocular pressure
- Glaucoma progression
- Endophthalmitis
- Angle narrowing or angle closure
- Sterile keratolysis
- Fungal infections
- Choroidal effusions/hemorrhage
- Vitritis
- Vitreous hemorrhage
- Retina detachments
- Corneal melt/necrosis
- Loss of implant, disintegration of implant, implant dislocation or extrusion
- Need for GDD implantation (pars plana vitrectomy)
- Cystoid macular edema
- Fibrin reactions
- Hypopyons
- Pigment dispersion during surgery
- Postsurgical pigment dispersion

Overall 168 AEs were reported during the ARGOS-KP01 study. 12 months after implantation were reported 168 AEs in 13 patients, including 23 SAEs in 9 patients. 92 AEs in 5 patients were rated as unlikely to the medical device and 61 AEs in patients have no relationship to the ARGOS-IO sensor. Only 15 AEs in four patients were possible related to the medical device: anterior chamber cell, cystoid macular edema, hypotony of the eye, iris adhesion, pigment dispersion, vitritis, increased intraocular pressure and retroprosthetic membrane.

Table 9 lists all adverse events including SAEs.

Table 9: Summary of all AEs

Adverse Events	Total (N=13)		
	n	**%**	**AE**
Any System Organ Class	**13**	**100**	**168**
Ear and Labyrinth Disorders	**1**	**7.7**	
Tinnitus	1	7.7	
Eye Disorders	**11**	**84.6**	**79**
Eye pain	6	46.2	7
Hypotony of eye	6	46.2	8
Vitritis	4	30.8	5
Cystoid macular edema	3	23.1	7
Retinal detachment	3	23.1	3
Choroidal detachment	2	15.4	2
Corneal infiltrates	2	15.4	2
Iris adhesion	2	15.4	4
Keratitis	2	15.4	3
Retinopathy proliferative	2	15.4	4
Visual acuity reduced	2	15.4	2
Anterior chamber cell	1	7.7	1
Anterior chamber fibrin	1	7.7	1
Blepharitis	1	7.7	1
Choroidal haemorrhage	1	7.7	1
Conjunctival disorder	1	7.7	1
Conjunctival haemorrhage	1	7.7	1
Conjunctival hyperaemia	1	7.7	1
Corneal epithelium defect	1	7.7	3
Corneal neovascualrisation	1	7.7	1
Corneal perforation	1	7.7	1
Erythema of eyelid	1	7.7	1
Eye inflammation	1	7.7	1
Eye pruritus	1	7.7	1
Keratic precipitates	1	7.7	1
Lacrimation increased	1	7.7	1
Lens disorder	1	7.7	1
Ocular discomfort	1	7.7	2
Pigment dispersion	1	7.7	1
Retinal disorder	1	7.7	1
Retinal haemorrhage	1	7.7	1
Retinal scar	1	7.7	1
Retinal tear	1	7.7	1

Retinal thickening	1	7.7	1
Subretinal fibrosis	1	7.7	1
Trichiasis	1	7.7	2
Visual impairment	1	7.7	1
Vitreous haemorrhage	1	7.7	1
Vitreous opacities	1	7.7	1
<u>Gastrointestinal Disorders</u>	**2**	**15.4**	**2**
Constipation	1	7.7	1
Nausea	1	7.7	1
<u>General Disorders and Administration Site Conditions</u>	**3**	**23.1**	**4**
Atrophy of the donor cornea	1	7.7	1
Leakage between keratoprosthesis and keratoplasty	1	7.7	1
Subjectively worse impression	1	7.7	1
Drug intolerance	1	7.7	1
<u>Infections and Infestations</u>	**3**	**23.1**	**3**
Bacterial disease carrier	1	7.7	1
Gastroenteritis	1	7.7	1
Urinary tract infection	1	7.7	1
<u>Injury, Poisoning and Procedural Complications</u>	**4**	**30.8**	**8**
Procedural Pain	3	23.1	3
Hyphaema	1	7.7	1
Post procedural complication	1	7.7	1
Post procedural haemorrhage	1	7.7	1
Suture related complication	1	7.7	1
Corneal graft melt	1	7.7	1
<u>Investigations</u>	**8**	**61.5**	**35**
Intraocular pressure increased	8	61.5	30
Intraocular pressure decreased	3	23.1	4
Seidel Test positive	1	7.7	1
<u>Musculoskeletal and Connective Tissue Disorders</u>	**1**	**7.7**	**3**
Back pain	1	7.7	1
Bone pain	1	7.7	1
Fibromyalgia	1	7.7	1
<u>Nervous System Disorders</u>	**3**	**23.1**	**4**
Dizziness	1	7.7	1
Headache	1	7.7	1
Paraesthesia	1	7.7	1
Syncope	1	7.7	1
<u>Product Issues</u>	**8**	**61.5**	**13**
Retroprosthetic membrane	6	46.2	7
Device material opacification (BkPro and IOL)*	3	23.1	5
Dislocation of ARGOS-IO sensor	1	7.7	1

Psychiatric Disorders	**1**	**7.7**	**1**
Panic attack	1	7.7	1
Renal and Urinary Disorders	**1**	**7.7**	**2**
Renal failure	1	7.7	2
Surgical and Medical Procedures	**6**	**46.2**	**12**
Corneal sutures removal	5	38.5	8
Corneal transplant	2	15.4	4
Vascular Disorders	**1**	**7.7**	**1**
Hypertension	1	7.7	1

Source: Final Statistical Output – Tables
Table 14.3.1.3 – Adverse Events by SOC and PT: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery

%: Percentage based on N
N: Number of subjects in total (Safety Set)
n: Number of patients reporting at least one adverse event with the specification
*: 3x opacification of BkPro's rear surface/1x milky optic of KPro/1x hazy IOL

The majority of the AEs (116 of 168) has a relationship to the medical procedure which implements both the implantation of the ARGOS-IO sensor and the Boston-Keratoprosthesis surgery (Table 10). Often, an AE cannot be assigned definitely to one procedure as the two implantations were performed in one surgery and many of the AEs are already known as complications for a stand-alone BkPro procedure.

Table 10: AEs related to the Medical Procedure – Time of Occurrence and Outcome

Adverse Event	Total (N=13)												Outcome
	First 4 weeks			First 16 weeks			First 28 weeks			First 12 months			
	n	%	AE	n	%	AE	n	%	AE	n	%	AE	
Any System Organ Class	**5**	**38.5**	**32**	**10**	**76.9**	**62**	**13**	**100**	**80**	**13**	**100**	**116**	
Eye Disorders	**9**	**69.2**	**16**	**11**	**84.6**	**36**	**11**	**84.6**	**44**	**11**	**84.6**	**61**	
Hypotony of eye	1	7.7	2	4	30.8	5	5	38.5	6	6	46.2	7	6 recovered 1 recovering
Eye Pain	2	15.4	2	3	23.1	3	3	23.1	4	4	30.8	5	recovered
Cystoid macular edema	0	0.0	0	2	15.4	3	3	23.1	4	3	23.1	6	4 recovered 1 recovering 1 recurrent
Vitritis	0	0.0	0	1	7.7	1	1	7.7	1	3	23.1	4	recovered
Choroidal detachment	0	0.0	0	2	15.4	2	2	15.4	2	2	15.4	2	recovered
Corneal infiltrates	0	0.0	0	0	0.0	0	1	7.7	1	2	15.4	2	1 recovered 1 recovered with sequelae
Retinal detachment	0	0.0	0	1	7.7	1	1	7.7	1	2	15.4	2	1 recovered 1 recovered with sequelae
Retinopathy proliferative	0	0.0	0	1	7.7	2	1	7.7	2	2	15.4	4	recovered
Visual acuity reduced	0	0.0	0	2	15.4	2	2	15.4	2	2	15.4	2	1 recovered 1 recovering
Anterior chamber cell	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Anterior chamber fibrin	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Blepharitis	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovering

Choroidal haemorrhage	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	not recovered
Conjunctival disorder	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Conjunctival haemorrhage	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Conjunctival hyperaemia	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovering
Corneal epithelium defect	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Corneal neovascularisation	0	0.0	0	0	0.0	0	1	7.7	1	1	7.7	1	not recovered
Eye inflammation	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Eye pruritus	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Iris adhesion	0	0.0	0	1	7.7	1	1	7.7	2	1	7.7	2	recovered
Keratic precipitates	0	0.0		0	0.0	0	0	0.0	0	1	7.7	1	recovered
Keratitis	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Lacrimation increased	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Capsular bag instability	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	unknown
Ocular discomfort	1	7.7	1	1	7.7	1	1	7.7	2	1	7.7	2	recovered
Pigment dispersion	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Retinal disorder	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Retinal haemorrhage	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Retinal scar	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Retinal tear	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Retinal thickening	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	not recovered
Vitreous haemorrhage	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Vitreous opacities	0	0.0	0	0	0.0	0	1	7.7	1	1	7.7	1	recovered
General Disorder and Administration Site Conditions	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**7.7**	**1**	**2**	**15.4**	**2**	
Atrophy of the donor cornea	0	0.0	0	0	0.0	0	1	7.7	1	1	7.7	1	not recovered
Subjectively worse impression	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Injury, Poisoning and Procedural Complications	**4**	**30.8**	**6**	**4**	**30.8**	**7**	**4**	**30.8**	**7**	**4**	**30.8**	**7**	
Procedural pain	3	23.1	3	3	23.1	3	3	23.1	3	3	23.1	3	recovered
Hyphaema	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Post procedural complication	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Post procedural haemorrhage	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered

Suture related complication	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Investigations	**6**	**46.2**	**7**	**6**	**46.2**	**10**	**7**	**53.8**	**16**	**7**	**53.8**	**25**	
Intraocular pressure increased	6	46.2	7	6	46.2	10	7	53.8	16	7	53.8	24	recovered
Intraocular pressure decreased	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	not recovered
Nervous System Disorders	**1**	**7.7**	**1**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	
Headache	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Product Issue	**1**	**7.7**	**1**	**5**	**38.5**	**6**	**6**	**46.2**	**7**	**7**	**53.8**	**11**	
Retroprosthetic membrane	1	7.7	1	4	30.8	4	4	30.8	4	5	38.5	5	3 recovered 2 not recovered
Device material opacification (BKPro and IOL)*	0	0.0	0	2	15.4	2	2	15.4	2	3	23.1	5	recovered
Dislocation of ARGOS-IO sensor	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Surgical and Medical Procedures	**1**	**7.7**	**1**	**2**	**15.4**	**2**	**3**	**23.1**	**4**	**6**	**46.2**	**9**	
Corneal suture removal	1	7.7	1	1	7.7	1	2	15.4	2	5	38.5	7	recovered
Corneal graft melt	0	0.0	0	1	7.7	1	1	7.7	2	1	7.7	2	recovered

Source: Final Statistical Output – Tables
Table 14.3.1.7 – Adverse Events Related to Procedure by SOC and PT – periods first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery

%: Percentage based on N
N: Number of subjects in total (Safety Set)
n: Number of patients reporting at least one adverse event with the specification
AE: Number of individual adverse events which occurred among the n patients

*: 3x opacification of BKPro's rear surface/1x milky optic of KPro/1x hazy IOL

The most common adverse event was an increased intraocular pressure (30 AEs in eight patients) which was related to the medical procedure 24 times in seven patients. It is a common complication in patients with Boston-Keratoprothesis and an expected event. Seven patients were already treated for glaucoma previous and/or in the study for glaucoma. Retroprostethic membrane was seen in five study eyes and hypotony in six patients. All of these AEs are also well known to occur in a standalone Boston-Keratoprosthesis implantation procedure and were in line with the expected prevalence of complications after BkPro surgery (Lee WB, 2015) (Ahmad S, 2016).

Visual acuity reduced was seen in two patients (DE-2-02 and DE-2-04) and was caused by a retroprosthetic membrane and other AEs of these patients.

The choroidal hemorrhage in patient DE-2-02 occurred after a complicated retina surgery due to an amotio (retinopathy proliferative (PVR)). The resorption of this bleeding takes a long time why it was not recovered to the end of the study.
PVR with consecutive tractive retinal detachment developed in two patients (DE-2-02 and DE-2-04) with congenital aniridia in timely connection to surgical manometry. As a causal relationship – while unlikely – could not be excluded by the investigators with certainty, a decision to undergo manomety was weighted carefully by the investigators. A causal relationship between PVR formation and the sensor implant was not obsereved.

In the following Table are listed the adverse device effects. All these ADEs were documented with a possible causal relationship to the ARGOS-IO sensor by the investigators.

Table 11: ADEs – Time of Occurrence and Outcome

Adverse Device Defect	Total (N=13) First 4 weeks			First 16 weeks			First 28 weeks			First 12 months			Outcome
	n	%	AE	n	%	AE	n	%	AE	n	%	AE	
Any System Organ Class	**1**	**7.7**	**3**	**3**	**23.1**	**8**	**4**	**30.8**	**11**	**4**	**30.8**	**15**	
Eye Disorders	**2**	**15.4**	**2**	**4**	**30.8**	**6**	**4**	**30.8**	**9**	**4**	**30.8**	**13**	
Cystoid macular edema	0	0.0	0	2	15.4	3	3	23.1	4	3	23.1	6	4 recovered 1 recovering 1 recurrent
Hypotony of eye	0	0.0	0	0	0.0	0	1	7.7	1	2	15.4	2	recovered
Anterior chamber cell	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Iris adhesion	0	0.0	0	1	7.7	1	1	7.7	2	1	7.7	2	recovered
Pigment dispersion	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Vitritis	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Investigations	**1**	**7.7**	**1**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	
Intraocular pressure increased	1	7.7	1	1	7.7	1	1	7.7	1	1	7.7	1	recovered
Product Issue	**0**	**0.0**	**0**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	**1**	**7.7**	**1**	
Retroprosthetic membrane	0	0.0	0	1	7.7	1	1	7.7	1	1	7.7	1	not recovered

Source: Final Statistical Output – Tables
Table 14.3.1.6 – Adverse Device Effects by SOC and PT – periods first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery

%: Percentage based on N
N: Number of subjects in total (Safety Set)
n: Number of patients reporting at least one adverse event with the specification
AE: Number of individual adverse events which occurred among the n patients

Of the 15 ADEs, three were classified as mild, six as moderate and six as severe.

- <u>Anterior chamber cell:</u> *moderate*
  - Inflammation is a normal and common response to any trauma of the eye, including intraocular surgery. A moderate intraocular inflammation after surgery is expected and can be caused by the implantation of the Boston keratoprothesis as well as by the manipulation of the iris caused by the implantation of the ARGOS-IO sensor. A self-resolving, sterile anterior chamber inflammation after surgery is not expected to negatively impact device functioning, healing or functional recovery.

- <u>Cystoid macular edema:</u> *3 moderate, 3 severe*
  - A cystoid macular edema is a known complication of all intraocular surgeries and has in most times a self-limiting nature. In stand-alone BK-Pro surgery, CME is with up to 27% also a frequent complication (Moshin H. Ali, 2018). However, a causal relationship with the ARGOS-IO sensor can never be excluded.

- <u>Hypotony of eye:</u> *1 moderate, 1 severe*
  - Boston keratoprothesis represents a second line surgical treatment in eyes, where primary keratoplasty has a low chance of success. In many cases, eyes scheduled for keratoprothesis surgery experienced ocular trauma or condition after multiple surgical interventions. Due to a lack of aqueous humor production and/or leckage because of insufficient corneal sutures, hypotony of the eye is an expected event after surgery. Therefore it is unlikely, that the device itself caused hypotony of the eye.

- <u>Iris adhesion:</u> *severe*
  - Iris adhesions can occur between the iris and the sensor and as anterior synechiae between iris and cornea. Both phenomena can be caused as a consequence of Boston keratoprothesis surgery. The additional volume in the posterior chamber related to the ARGOS sensor might have an impact on formation of adhesions. However, as this ADE only occurred in one case, the significance may be questioned.

- <u>Pigment dispersion:</u> *mild*
    - ➢ Manipulation of the iris may lead to disruption of cells of the pigmented layer of the iris and dispersion of pigment granula into the anterior chamber. The pigment can settle anywhere in the anterior chamber, frequently showing as non-symptomatic small deposits on the posterior surface of the cornea or anterior surface of the IOL. This is not limited to the implantation of the ARGOS-IO sensor but to any anterior chamber surgery during which there is accidental or initial manipulation the iris. A second potential cause of pigment release after initial surgery can be posterior iris chafing on the sensor placed in the ciliary sulcus.

- <u>Vitritis:</u> *moderate*
    - ➢ Vitritis in the posterior chamber is the equivalent intraocular inflammation in the anterior chamber. A moderate vitritis after surgery is expected with a frequency of up to 23% in stand-alone BK-Pro of aniridia patients (Salima I. Hassanaly, 2014) and can be caused by the implantation of the Boston keratoprothesis as well as by manipulation of caused by the implantation of the ARGOS-IO sensor. A self-resolving, sterile posterior chamber inflammation after surgery is not expected to negatively impact device functioning, healing or functional recovery.

- <u>Intraocular pressure increased:</u> *mild*
    - ➢ A postoperative increase in intraocular pressure can be considered as an expected event, not only in this study, but highly frequently after intraocular surgery.

- <u>Retroprosthetic membrane:</u> *moderate*
    - ➢ Formation of a retroprosthetic membrane is a key adverse event after stand-alone Boston keratoprothesis surgery and represents with >50% the most frequent complication after BKPro surgery (Lee WB, 2015). Therefore, the occurrence in this study is not surprising. An additional impact of the ARGOS sensor on formation of the membrane cannot be fully ruled out excluded. But giving the extent and the frequency of membrane formation after stand-alone keratoprothesis surgery, it seems more likely to be caused by the procedure itself.

To summarize, all potential ADE's can be caused by the stand-alone procedure and they are not of a higher percentage in this study than in other known publications. The overall benefit to offer IOP measurement in a situation where - without implantable device - only palpatory IOP would be possible outweighs a possibly increased likelihood of occurrence of theses ADE's.

4.8.1.1 Serious adverse events in the follow-up period

23 out of 168 AEs in 9 Patients fulfilled at least one criterion for "serious adverse event" (SAE) and were reported as such.

10 of these SAEs were unrelated to the IMD or implantation procedure of which seven occurred in the non-study eye:

- Corneal melting non-study eye (twice)
- Corneal perforation non-study eye
- High intraocular pressure study eye
- High intraocular pressure non-study eye
- Leakage between keratoprosthesis and keratoplasty non-study eye
- Renal failure
- Sterile vitritis non-study eye
- Surface defect of graft (non-study eye)
- Tractive retinal detachment study eye

13 SAEs were at least possibly related to the implant (6 initial SADEs) and/or the implantation procedure in the initial SAE report. Table 12 shows an overview of time, occurrence and outcome of the SADEs.

Table 12: SADEs – Time of Occurrence and Outcome

Adverse Device Defect	Total (N=13) First 4 weeks			First 16 weeks			First 28 weeks			First 12 months			Outcome
	n	%	AE	n	%	AE	n	%	AE	n	%	AE	
Any System Organ Class	**0**	**0.0**	**0**	**1**	**7.7**	**2**	**2**	**15.4**	**4**	**3**	**23.1**	**6**	
Eye Disorders	**0**	**0.0**	**0**	**1**	**7.7**	**2**	**2**	**15.4**	**4**	**3**	**23.1**	**6**	
Cystoid macular edema	0	0.0	0	1	7.7	1	2	15.4	2	2	15.4	3	2 recovered 1 recovering
Hypotony of eye	0	0.0	0	0	0.0	0	0	0.0	0	1	7.7	1	recovered
Iris adhesion	0	0.0	0	1	7.7	1	1	7.7	2	1	7.7	2	recovered

Source: Final Statistical Output – Tables
Table 14.3.6 – Serious Adverse Device Effects by SOC and PT – periods first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery

%: Percentage based on N
N: Number of subjects in total (Safety Set)
n: Number of patients reporting at least one adverse event with the specification
AE: Number of individual adverse events which occurred among the n patients

The investigations of the SAEs with a causal relationship to the medical device and/or medical procedure resulted in the following:

DE-1-01

Hypotony of eye:

Description of the event: Patient DE-1-01 was hospitalized for a bulbus hypotony and sterile vitritis.

Remedial action taken by the investigation site: The first remedial action was a bulbus tonification with BSS on January 26th, 2016. A tonification was repeated with Healon on February 2nd, 2016. On March 6th, 2016 the patient was hospitalized again for pars-plana-vitrectomy and silicone oil tamponade (07-MAR-2016).

Rationale for the classification as expected or unexpected: The sterile vitritis was rated as expected by the site. The bulbus hyptony was unexpected in this case.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: Both events were classified as possibly related to the medical device and to the medical procedure. The cause of the bulbus hypotony could not be determined. Sterile vitritis is a known complication in patients with Boston-Keratoprosthesis implantation (Dokey, et al., 2012) and has no relationship to the ARGOS-IO implant. This adverse event therefore is concluded to be unrelated to the ARGOS-IO Implant.

Corneal infiltrates:

Description of the event: The site became aware of corneal infiltrates on January 26th, 2016. The severity was rated as "severe".

Remedial action taken by the investigation site: The patient was treated with medication and the infiltrates regressed to February 17th, 2016.

Rationale for the classification as expected or unexpected: This adverse event was rated as definite related to the medical procedure. It is a known complication and therefore an expected event.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: No causal relationship with the implant could be established. Corneal infiltrates occur in 10-20% of patients with Boston-Keratoprosthesis (Aravena, Bozkurt, Yu, & Aldave, 2016).

DE-1-04:

Cystoid macular edema (two events):

Description of the event: A severe cystoid macular edema was detected on April 8th, 2016.

Remedial action taken by the investigation site: The patient was treated with an intravitreal Ozurdex-Injection on April 21st,2016.

Rationale for the classification as expected or unexpected: It is an expected adverse event described in section 7.4 "Risks and anticipated adverse device effects to be assessed" in the Clinical Investigation Plan.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: The cystoid macular edema was recovered on May 24th, 2016. It cannot definitely excluded that there is no relationship to the medical device. Most likely, the cystoid macular edema is due to the underlying autoimmune disease. Furthermore, cystoid macular edemas are one of the most common complications in intraocular surgeries.

On August 17th, 2016, the site became aware of a further cystoid macular edema, treated with an additional intravitreal Ozurdex-Injection.

DE-1-05

Corneal graft melt (two events):

Description of the event: On March 19th, 2016, three months after Boston-Keratoprosthesis and ARGOS-IO implantation, the site became aware of corneal graft melt in patient DE-1-05.

Remedial action taken by the investigation site: The patient was hospitalized with following surgical intervention in peribulbar anaesthesia: renewal of the corneal graft and bulbus tonification. Discharge was on March 24th, 2016.

Rationale for the classification as expected or unexpected: It is an expected adverse event described in section 7.4 "Risks and anticipated adverse device effects to be assessed" in the Clinical Investigation Plan.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: No causal relationship to the medical device could be established. It is a known "classic" complication in Boston-Keratoprosthesis implantation and occurs in 10% of these patients by experience of the site. Another three months later (June 11th, 2016), corneal graft melt occurred again with hospitalization and renewal of the corneal graft in combination with explantation of the ARGOS-IO sensor (June 13th, 2016).

DE-1-06

Cystoid macular edema:

Description of the event: Patient DE-1-06 experienced a macular edema in the first three months after implantation (April 5th, 2016).

***Remedial action taken by the investigation site*:** The patient was treated with an intravitreal injection of 10 mg Triamcinolone.

***Rationale for the classification as expected or unexpected*:** This event was expected as described in section 7.4 of the clinical investigation plan. It was documented as possible related to the medical device and has a probable relationship to the medical procedure.

***Investigation results and rationale for the above root cause classification taking all SAEs into consideration*:** A cystoid macular edema is a known complication of all intraocular surgeries. In this case, it is almost certainly due to the underlying disease. However, a causal relationship with the ARGOS-IO sensor can never be excluded.

The cystoid macular edema was recovered on May 9th, 2016.

Anterior synechiae (two events):

Description of the event: Patient DE-1-06 experienced anterior synechiae in the first three months after implantation (April 5th, 2016).

***Remedial action taken by the investigation site*:** The anterior synechiae were resolved by surgical lysis.

***Rationale for the classification as expected or unexpected*:** This event was rated as possible related to the medical device and as probable related to the medical procedure. It is a known complication and therefore an expected event.

***Investigation results and rationale for the above root cause classification taking all SAEs into consideration*:** Anterior synechiaes are a known complication in Boston-Keratoprosthesis patient. However, a causal relationship with the ARGOS-IO sensor can never be definitely excluded.

Anterior synechiae reoccurred on July 21st, 2016 and the patient got a surgical lysis again.

Detachment of retina and choroid membrane:

Description of the event: A retinal and choroidal detachment was detected by during ultrasound examination one year after surgery (January 13th, 2017).

***Remedial action taken by the investigation site*:** The remedial action taken by the site was the exchange of the Boston-Keratoprosthesis, explantation of the IOL and of the ARGOS-IO sensor and a pars-plana vitrectomy (January 23rd, 2017 at site). Additional, a membrane peeling, retinotomy, endolaser and endotamponade was done on January 26th, 2017, extern.

***Rationale for the classification as expected or unexpected*:** It is an expected adverse event described in section 7.4 “Risks and anticipated adverse device effects to be assessed” in the Clinical Investigation Plan.

***Investigation results and rationale for the above root cause classification taking all SAEs into consideration*:** Retinal detachment is a known complication in patients with Boston-Keratoprosthesis. It occurs in 7,69% of Boston-Keratoprosthesis patients up to 42% in patients with an additional autoimmune disease (Schaub, et al., 2016) (Neuhann, Koller, & Neuhann, 2015) (Jardeleza, Rheaume, Chodosh, Lane, & Dohlman, 2015). This adverse event is concluded therefore to be unrelated to the ARGOS-IO implant.

DE-1-07

Dislocation of ARGOS-IO sensor:

Description of the event: At visit 5 (May 30th, 2016), a dislocation of the ARGOS-IO sensor was noticed in patient DE-1-07.

***Remedial action taken by the investigation site*:** The site immediately hospitalized the patient and explanted the sensor the next day.

***Rationale for the classification as expected or unexpected*:** It is an expected potential risk of implantation of the ARGOS-IO sensor described in section 6.3 “Anticipated Adverse Device Effects associated with the ARGOS-IO sensor device and their control”.

***Investigation results and rationale for the above root cause classification taking all SAEs into consideration*:** Because of a congenital aniridia syndrome, the sensor was sutured to the sclera. The temporal suture dissolved. Due to the underlying conditions as aphakia, no intact iris and a severe hypotony during the surgery, the implantation of the Boston-Keratoprosthesis after ARGOS-IO implantation was a challenge. After implantation of the Boston-Keratoprosthesis a slightly rotation of the sensor was already recognized. The implantation of the ARGOS-IO sensor harbors not a huge risk per se and is easy to handle. However, the condition of these eyes is really difficult to evaluate. Mostly, no examination to look insight the eye is possible.

DE-2-02

Proliferative vitreoretinopathy (PVR) with retinal detachment

Description of the event: On August 22th, 2016 the patient was hospitalized with the diagnosis of proliferative vitreoretinopathy and suspicion of PVR-related retinal detachment in the study eye.

Remedial action taken by the investigation site: A diagnostic pars plana vitrectomy was performed and following interventions were done: an intraoperative retinonotomy, retinopexy by photo and kryocoagulation, membrane peeling and endotamponade of the eye with silicone oil.

Rationale for the classification as expected or unexpected: It was an unexpected event for the site.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: After implantation of the Boston-Keratoprosthesis and ARGOS-IO implantation, the patient with genetic aniridia had a normal postoperative healing process and increase of visual acuity. On June 27th, 2016 the second surgical manometry was performed according to CIP. Due to a loss of visual acuity in the study eye from 0.02 to hand movements, the patient has consulted the hospital twice per month in unscheduled visits. The formation of a retroprosthethic membrane was diagnosed and the patient was treated with YAG-membranotomy on Aug 18th, 2016. One week after this treatment, the patient experienced progressive loss of visual acuity and increased formation of retroprosthetic membranes. Therefore the decision for diagnostic vitrectomy was made. Intraoperatively, a PVR retinal detachment required surgical treatment. Several factors could have contributed to the development of this PVR retinal detachment. First the congenital anridia of the patient is followed by an increased risk for retinal detachment. Second, both the intraocular manometry and the YAG capsulotomy could be responsible for the occurrence of a retinal detachment. Also it cannot be fully ruled out, that the PVR detachment is associated with the BKPro implant or the ARGOS sensor.

PVR-Amotio under oil tamponade

Description of the event: On November 20th, 2016 the patient was hospitalized again due to a recurring PVR related retinal detachment under oil tamponade.

Remedial action taken by the investigation site: A pars plana vitrectomy was performed and following interventions were done: an intraoperative cerclage and retinotomy, closure of the Baerveldt implant, silicone oil change.

Rationale for the classification as expected or unexpected: It was an unexpected event for the site.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: The recurring retinal detachment is most likely due to the primary retinal detachment and the proliferative vitreoretinopathy. As it is well documented in literature, occurrence of PVR increases the risk for recurring detachment significantly (Enders et al, Retina 2017). Therefore it is highly unlikely, that the ARGOS IO implant has a causal relationship with this serious adverse event.

DE-2-04

Proliferative vitreoretinopathy

Description of the event: Patient DE-2-04 was hospitalized because of a decreased visual acuity, retroprosthetic membrane and vitritis on August 18th, 2016.

Remedial action taken by the investigation site: A diagnostic ppV (pars plana vitrectomy) was performed. Intraooperative appeared an older tractive retinal detachment which was treated surgical with retinotomy, oil-tamponade, kryopexy and laser retinopexy.

Rationale for the classification as expected or unexpected: The site rated this event as unexpected.

Investigation results and rationale for the above root cause classification taking all SAEs into consideration: After implantation of the Boston-Keratoprosthesis and ARGOS-IO implantation, the patient had a normal postoperative healing process. The visual acuity increased from finger counting to 0.05 (distance 1m). On June 30th, 2016 the first surgical manometry was performed according to CIP. On July 20th, 2016 the patient was scheduled for an unscheduled visit because of loss of her therapeutic contact lens. At this visit, the decreased visual acuity, retroprosthetic membrane and vitritis were observed. According to the subjective description of the patient, the decrease of visual acuity decreased followed after manometry. A leakage could not be detected. The IOP was normoton according to palpation and ARGOS-IO sensor. After no improvement, the diagnostic ppV was performed on August 17th, 2016. Due to the time context of this serious adverse event and the surgical manometries, a causality by the surgical manometry could not be excluded (see also DE-2-02 “Proliferative vitreoretinopathy (PVR) with retinal detachment”). However, a direct relationship between the ARGOS sensor and this SAE is unlikely.

4.8.2 Concomitant Medications

No restrictions were placed on patients’ use of concomitant medications during study participation.

Antiglaucoma preparations and miotics were used in 12 patients.

4.8.3 Device Deficiencies

In the ARGOS-KP01 trial did not occur any device deficiency which affected (potentially) the safety and well-being of a patient.

ARGOS-IO sensor:

During the trial two sensors had to be recalibrated after an offset occurred. In patient DE-1-01, the ARGOS-IO sensor was adjusted to surgical manometry after a minimal offset was detected at Visit 9. The IOP measured by surgical manometry was 21 mmHg, the ARGOS-IO sensor measured 27.3 mmHg. The ARGOS-IO sensor was recalibrated to the value of 21 mmHg of the surgical manometry. The recalibration was requested by the site. In patient DE-1-02, measurements were outside limits caused by external manipulation/application of high energy densities to the eye (YAG-capsulotomy). This was necessary due to retroprosthetic opacification (a common occurrence in patients with Boston-Keratoprosthesis).
No safety issues arose from these two incidences, the devices remained in place and no surgery was necessary.

Mesograph reader device:

There were several device deficiencies of the Mesograph reader device, all of which could be fixed by replacing the device itself. The deficiencies were limited to storage space due to a software failure, no data transfer possible and a defect button.

4.8.4 Examination Results over Time

All relevant and clinical significant findings of the anterior and posterior segment following surgery were documented as adverse events.

4.8.4.1 Visual Acuity

Visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. There was no measurement scheduled for the baseline visit but for Visit 07 (4 weeks post surgery) and V15 (52 weeks post surgery). The mean number of letters correctly read by 12 patients at V07 was 1.7 (SD 2.7) (range 0-9). For V15, the visual acuity was measured in 7 patients. The mean number of letters correctly read was 7.7 (SD 13.8) (range 0-34).

5 DISCUSSION

5.1 Limitations of the Study

Several aspects of the study limited its conclusiveness.

1. Only 12 patients were included and only 9 patients finished the study, which is sufficient to detect problematic design features that lead to common adverse events and still limits the number of patients that could potentially be harmed due to unforeseen events. However, with this low number of patients it is unlikely to detect rare negative effects particularly with regard to the different underlying diseases of these patients and different indications for the Boston-Keratoprosthesis implantation.
2. 12 months follow-up for a device intended for permanent implantation are too short to detect any long-term complications or late device deficiencies in patients with Boston Keraprosthesis. Since the device itself is technical identical to the CE approved EYEMATE-IO device, to be placed into the posterior chamber/ciliary sulcus of the eye during cataract surgery and this device performs well for more than several years, no main device related issues are to be expected.
3. Although surgical manometry is the only available method to accurately measure IOP in BKPro patients, it carries problems in the performance and therefore some limitations for the comparability with ARGOS-IO measurements:
    a. Due to the puncture of the bulbus and following removal of the needle, aqueous humor can be lost which lead to a decrease of the intraocular pressure.
    b. The quality of the measurements can be strongly influenced by experience of the investigator.

5.2 Safety and Tolerability

The overall outcome of the ARGOS-KP01 clinical trial provide sufficient evidence that the ARGOS-IO system is safe and well tolerated in to support its implantation in patients with an indication for a BKPro. Adverse events and serious adverse events in this study were in line with the expected complications after BKPro surgery (Lee WB S. R., 2015) (Ahmad S M. P., 2016). Most frequent complications were formation of a retroprosthetic membrane and hypertonic or hypotonic IOP. The study investigators saw the causality of most adverse events linked to the implantation of both the BKPro and the ARGOS-IO sensor. While it is not possible to clearly differentiate causality between those two potential causes, all observed complications are also well known to occur in stand-alone BKPro implantation.

5.3 Performance

Performance data acquired in this study showed overall good consistency between manometric and telemetric IOP results and between ARGOS-IO and finger palpation. There was not seen a trend for increasing discrepancies between modalities during the follow-up.

The technical performance of the components of the ARGOS-IO system during the ARGOS-KP01 trial was good. There were no major device deficiencies of any of its components that compromised the safety of the patients in the trial. None of the adverse events reported for the trial where a direct or indirect result of a device deficiency.

5.4 Relevance of the Results in the Light of Previous / External Data

The ARGOS-IO device performed well in patients with a Boston Keraprosthesis and showed an overall good consistency between the telemetric IOP and finder palpation/manometry. Though the implantation of the ARGOS-IO device in conjunction with the BKPro might pose additional risks compared to stand-alone BKPro implantation, the complications observed where found to be in the range of the occurrences reported in the literature. Considering the high prevalence of preexisting glaucoma in patients undergoing the Boston Keratoprosthesis surgery (Ahmad S. M. P., 2016) and the Glaucoma progression after implantation of the BKPro (de Oliveira L. A., 2014) (Samarawickrama C., 2018), the implantation of a monitoring device (ARGOS-IO) clearly outweighs the risks induced by implantation of an additional device within the same surgical procedure.

5.5 Risk / Benefit Assessment

Glaucoma is the most significant cause of the loss of regained vision in keratoprosthesis recipients. 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, Glaucoma, 2013).

The presence of BI-KPro does not allow conventional tonometric IOP measurement, as this requires a normal cornea. Patient self-monitoring or home measurement is also not possible, as available devices are also using tonometric IOP measurement methods. Currently, surgical manometry – if properly performed - is the only accurate means of measuring IOP in BKPro recipients. But due to its invasiveness and risk for complications, most ophthalmologists don't perform surgical manometry at BI-KPro patients. Equipment for surgical manometry is in general not available either, which is another reason why invasive IOP measurements are performed only in very rare cases. Usually finger palpation is applied to estimate IOP, but is highly dependent on the skill of the individual examiner, provides highly subjective values and thus prone to error.

IOP in BI-KPro patients can be extremely high, potentially causing severe glaucomatous damage in unusually short periods of time. Even a comprehensive follow-up schedule may not be appropriate. This problem is compounded if no physician experienced in the finger palpation technique is available to perform IOP estimation.

The ARGOS-IO device allows frequent, reproducible IOP monitoring in both the clinical and home setting, facilitating the management of IOP in this vulnerable patient group. In addition, because of the ease of its use, it will also permit detection of fluctuations in IOP resulting from the patient's daily activities and circadian rhythm.

One objective of this study was to verify the device's accuracy in the patient population. Patients will benefit from a continual long-term monitoring of IOP independent from visits to the ophthalmologist. 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 by the treating physician between office visits. This will permit a more rapid response to changes in IOP and a better fine-tuning of treatment protocols.

Because of the high risk of critically IOP values possible in BKPro patients, glaucoma may progress more rapidly as at open angle glaucoma patients, which requires an even closer monitoring regimen. An additional effect may be improved adherence to prescribed treatment regimens. The potential consequences of poor IOP control are serious and can lead to irreversible loss of vision and accompanying handicap. Patient self-measurement is expected to motivate better compliance with the treatment regimen, thereby facilitating improved IOP control and optimizing long-term outcome.

The ARGOS-KP01 clinical trial was conducted to address these questions:

Compatibility with Boston-Keratoprosthesis

The ARGOS-KP01 study confirmed that it possible to implant a BKPro and ARGOS-IO sensor without mutual interference.

Irritation, Inflammation of Eye, Iris Pigment Abrasion

Does the implant cause irritation, inflammation and pigment abrasion?

- Implant surface material has history as IOL material for ocular implantation, with well-known biocompatibility properties; material surface is soft, edges are rounded and smooth, possible small material flashes are soft and atraumatic
- In ARGOS-KP01 trial, the ARGOS-IO device was found to be safe and well tolerated within the eye. No higher levels of irritation, inflammation and pigment abrasion were observed compared to standard Boston Keratoprosthesis implantation and were manageable under standard of care.

Accuracy, precision and sensor drift

Does the ARGOS-IO device exhibit acceptable levels of accuracy and precision?

- Accuracy, precision and sensor drift have been tested and validated in bench tests and in animal trials
- The ARGOS-IO device was compared to finger palpation (the current gold standard in BI-KPro patients) within this clinical trial and showed a positive statistically significant difference of telemetric IOP measurements between the finger palpation categories (soft hypertonic, normal, borderline, hypertonic).
- ARGOS-KP01 trial has shown that the human anatomy does not have an impact on the accuracy of the device. It is recommended to re-calibrate the device once a year and following ocular surgery.

Usability

The patient acceptance of the ARGOS-IO system at home was very good, showing a very high overall acceptance in using the ARGOS-IO system in their daily routine. The instruction for use for the Mesograph reader device was easily to understand, the implant did not cause them any problems and the patients were less concerned about unidentified high IOP.

Compatibility of the ARGOS-IO implant with Glaucoma drainage devices (GDD)

Compatibility of the ARGOS-IO implant with Glaucoma drainage devices (GDD) was an issue that was long discussed within the risk analysis team. This clinical trial showed if the GDD is placed in the anterior chamber, there is no physical contact with the ARGOS-IO implant, which is located in the ciliary sulcus, and consequently no interference occurs between the two devices.

<u>**Overall Summary:**</u> Based on the clinical study results, risk management effort and user information, it is concluded that the benefits for a patient from the implantation of an ARGOS-IO implant device outweighs the risk. Predicate implantable ophthalmic medical devices, like Boston-Keratoprosthesis, show that there is also residual risk with regard to the surgical procedure in general. The adverse event rate by combining BKPro implantation with EYEMATE-IO/KP insertion is similar to BKPro implantation alone and adverse events were in general manageable under standard of care. **The medical benefit of the implantation of the device, and resulting possibility of direct IOP measurement and frequent self-tonometry by the patients at home clearly outweighs the identified residual risks of the device. The residual risks and their probability of occurrence are within the acceptable range, compared to similar marketed devices in the ophthalmic field.**

Being able to monitor IOP quasi-continuously over extended periods of time will give the treating ophthalmologists valuable information about the individual disease of a patient and the effectiveness of the medication regimen. Most importantly, it will alert the ophthalmologist early on in case of a critically elevated IOP. Patients treated with BKPro for corneal blindness face a significant risk to consecutively loose vision due to progressive glaucomatous damage. Continual and reliable IOP monitoring, as only possible with a telemetric sensor system, is an indispensable prerequisite for adequate glaucoma management at BKPro patients to reduce post-surgical BKPro complications and to improve chances of these patients to maintain vision.

6 ETHICS AND REGULATORY COMPLIANCE

6.1 Independent Ethics Committee (IEC) and Competent Authority

In compliance with ICH-GCP, the European Medical Device Directives, the German Medical Device Act and its Ordinance on Clinical Trials with Medical Devices (MPKPV), the study approved by the responsible Ethics Committee in Munich (Ethik-Kommission der Medizinischen Fakultät der Technischen Unversität München) on November 14th, 2014, and by the German Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)] on December 09th, 2014, and before any potential patient underwent any study-specific procedures.

6.2 Ethical and Legal Conduct of the Study

This investigation was conducted in compliance with the ethical standards having their origin in the Declaration of Helsinki, with ICH-GCP, ISO 14155:2011 and with all relevant German and European laws and regulations governing medical devices and clinical trials on humans.

6.3 Patient Information and Consent

To avoid any possible effect of the study on a patient's decision to undergo necessary Boston keratoprosthesis surgery, only patients who had already been scheduled for surgery with Boston keratoprosthesis implantation were approached about the possibility of participating in the ARGOS-KP01 clinical investigation.

Each potential patient was thoroughly informed about the device and the aims and procedures of the investigation through appropriate EC approved written patient information material and in an individual discussion with an investigator. Information given included the potential risks and benefits associated with the implantation and use of the ARGOS-IO pressure sensor and study participation, as well as the explicit statement that the patient's participation was voluntary and could be ended by the patient at any time. The investigator answered any study-related questions the potential patient may have had. Prior to undergoing any study related procedure all patients signed and dated Patient Informed Consent forms, which were then countersigned and dated by the informing investigator. Patients were given one copy for their own records. The second copy was filed in the Investigational Site File.

Copies of the informed consent form and patient information are included in Annex D.

7 STUDY ADMINISTRATIVE STRUCTURE

The study was financed and managed by the Sponsor Implandata Ophthalmic Products GmbH, which is the developer and manufacturer of the ARGOS-IO system.

The study was conducted at 3 sites in Germany with Prof. Dr. med. Thomas Neuhann, MVZ Prof. Neuhann, Helene-Weber-Allee 19, 80637 Munich, Germany as Coordinating Investigator.

The additional sites included:

Prof. Dr. med. Claus Cursiefen	Universität zu Köln, Zentrum für Augenheilkunde Kerpenerstr. 62, 50924 Cologne, Germany
Prof. Dr. med. Gerd Geerling	Universitäts-Augenklinik Düsseldorf Moorenstr. 5, 40225 Dusseldorf, Germany

The following functional areas were outsourced to third parties:

Safety Reporting	MDSS GmbH Schiffgraben 41 30175 Hanover, Germany
Data Management	X-act Cologne, Clinical Research GmbH Hansaring 97 50670 Cologne, Germany
Statistics	X-act Cologne, Clinical Research GmbH Hansaring 97 50670 Cologne, Germany
Clinical Monitoring	Dr. Gerlinde Lang Dienstleistungen für klinische Prüfungen Blumenstr. 3 91094 Langensendelbach

The Data Safety Monitoring Board was composed of the following member:

Member	PD Dr. med. Konrad Hille Wolgang Dachstein Str. 28 77654 Offenburg, Germany

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9 ANNEXES TO THE REPORT

Annexes to the report are provided separately. They include:

Annex A: Clinical Investigation Plan ARGOS-KP01

Reference Number: ARGOS-KP01

Revision B, 03-OCT-2014

A prospective, open-label, monocenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

Clinical Investigation Plan ARGOS-KP01

Reference Number: ARGOS-KP01

Revision C, 17-MAR-2015

A prospective, open-label, monocenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

Clinical Investigation Plan ARGOS-KP01

Reference Number: ARGOS-KP01

Revision D, 05-MAY-2015

A prospective, open-label, mullticenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

Clinical Investigation Plan ARGOS-KP01

Reference Number: ARGOS-KP01

Revision E, 29-JAN-2016

A prospective, open-label, mullticenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis (BKPro)

Annex B: Investigator's Brochure

Reference Number: ARGOS-KP01

Rev. A, 15-SEP-2014

Investigator's Brochure

Reference Number: ARGOS-KP01

Rev. B, 29-JAN-2016

Annex C: Instructions for Use

Annex D: Patient Informed Consents

Patienten-Information und –Einwilligung, Version 2.1, 24-FEB-2015

Patienten-Information und –Einwilligung, Version 3.0, 18-SEP-2015

Patienten-Information und –Einwilligung, Version 4.0, 02-FEB-2016

Annex E: Statistical Analysis Plan (SAP)

Statistical Analysis Plan

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients undergoing implantation of a Boston Keratoprosthesis

Reference Number: ARGOS-KP01

Version 1.0, 09-JAN-2018

Annex F: Relevant Data Sets

Final Statistical Output – Listings

Version 2.0 (21FEB2018)

Reference Number: ARGOS-KP01

Final Statistical Output – Tables

Version 2.0 (21FEB2018)

Reference Number: ARGOS-KP01