Statistical Analysis Plan

Reference No.	**ARGOS-KP01**
Short Name	ARGOS-KP01
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)
EudraCT No.	N/A
Protocol Version	Revision E, 29-Jan-2016
Protocol Amendment(s)	None
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Dates & Signatures

By signature we declare our approval to the statistical analyses described in this SAP.
No additional changes will be made prior to Database Lock

09-Jan-2018
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0. List of Abbreviations

ADE	Adverse device effect
AE	Adverse event
ATC	Anatomic Therapeutic Chemical
CI	Confidence interval
CIP	Clinical investigation plan
CIR	Clinical investigation report
CRF	Case report form
CRO	Contract research organization
eCRF	Electronic case report form
FSI	First patient in
ICH	International Conference on Harmonization
IMD	Investigational medical device
IOP	Intra-ocular pressure
LSO	Last patient out
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
PPS	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SFS	Safety Set
SOC	System Organ Class
TFLs	Tables, Figures and Listings
WHO	World Health Organization
WHO-DDE	WHO-Drug dictionary enhanced

1. Introduction

This Statistical Analysis Plan (SAP) is based on the final Protocol for the clinical investigation ARGOS-KP01 and its final eCRF.

Aim of this SAP is to determine prospectively the analysis strategy of this clinical investigation and to describe the methods used for the final analysis. The statistical evaluation of all eCRF parameters as well as other data sources will be performed by the CRO X-act Cologne Clinical Research GmbH (X-ACT) according to this SAP.

This SAP is developed in one step and will be agreed on as final version before the Database Lock.

2. Changes from Protocol including Amendments

- Analysis of Questionnaires and daily IOP self-measurement profiles (patients) will not be performed (not databased)
- Performance analysis will also be done on the Safety Population
- No subgroup analyses will be performed

There are no other changes in the statistical evaluation as compared to the final Clinical Investigation Protocol.

3. Study Overview

3.1. Trial Objective(s)

The primary objectives of this clinical investigation are:

- 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

The secondary objectives of this clinical investigation are:

- Safety: To evaluate the safety and tolerability of the 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 weeks 4, 16 and 28 after implantation.

3.2. Trial Design

The investigation is designed as a prospective, open-label, single-arm, early feasibility study.

The ARGOS-IO system is a non-CE marked investigational medical device composed of the implant and its accessories:

- Implant: ARGOS-IO pressure sensor implant for sulcus placement or trans-scleral fixation
- Accessories: MESOGRAPH reading device, Implant Injector

Concerning patients undergoing implantation of a Boston Keratoprosthesis (BKPro), the ARGOS-IO pressure sensor is intended to be implanted in the human eye in combination with BKPro surgery and to remain in place indefinitely. The ARGOS-IO pressure sensor is intended to be used together with the hand-held MESOGRAPH reading device to telemetrically measure the intraocular pressure (IOP) of patients with a BKPro.

The investigation will consist of 15 visits: the Screening visit, the Surgery visit (Day 0), four early follow-up visits 1, 5, 10, and 15 days after surgery and further nine follow-up visits at weeks 4, 10, 16, 22, 28, 34, 40, 46 and 52.

The Screening visit will be performed within 60 days prior to surgery.

3.2.1. Target Population

Patients undergoing implantation of a keratoprosthetic device to salvage remaining vision

3.2.2. Blinding

This is an open label, non-comparative study with one treatment group. No blinding is requested.

3.2.3. Randomization

This is an open label, non-comparative study with one treatment group. No randomization is performed.

3.3. Trial Conduct

Duration of study:

- Per patient: up to 14.5 months consisting of a Screening period up to 60 days, the implantation of the ARGOS-IO pressure sensor in combination with the BKPro surgery and a follow-up period of 52 weeks
- Scheduled for 25 months from first patient screened to last patient last visit

The trial is conducted at 3 sites located in Germany.

3.4. Trial Variables

3.4.1. Primary Endpoints

Safety:

- Number of patients experiencing a device related SAE at any time during the first 12 months following implantation of the IMD [a]. 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 leads to any of the following:
        - Death

- A serious deterioration in the health of the patient 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.

Note: [a] should be read as "following implantation surgery" (in order to allow for situations where implantation was only attempted, see the definition of the Safety Population)

Performance:

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

3.4.2. Secondary Endpoints

Safety:

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

Note: [a] should be read as "following implantation surgery" (in order to allow for situations where implantation was only attempted, see the definition of the Safety Population)

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).

3.4.3. Safety Variables

Safety variables are:

- Occurrence and frequency of adverse events and adverse device effects

3.4.4. Performance Variables

Performance variables are:

- IOP measurements by ARGOS-IO system (at clinic. at home), surgical manometry and finger palpation
- Device deficiencies
- Implantation Procedure Questionnaire (Investigators)
- Investigator Acceptance Questionnaire (Investigators)

3.4.5. Other Variables

Other variables are:

- Informed Consent
- Eligibility assessment
- Demographics (age, sex, ethnicity)
- Medical history (including previous diseases/surgeries) and concomitant diseases
- Prior and concomitant medications and non-drug therapies
- Examination of anterior segment and posterior segment
- Implantation surgery (BKPro, ARGOS-IO)
- IOP measurement by means of Goldmann Applanation Tonometry and pneumotonometry
- Urine pregnancy testing
- Visual acuity
- Perimetry
- End of Clinical Investigation and main reason for early termination.

3.5. Determination of Sample Size

The sample size of 10 to 15 was chosen based on the number of patients undergoing BKPro implantation at the study site in a 12 month period. Although no formal sample size calculation was conducted, this sample size is considered large enough to allow a relatively high probability that common adverse events will be detected and enough data to be collected to estimate the level of agreement of IOP values obtained with ARGOS-IO and surgical manometry.

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

Patients who drop-out or are withdrawn after implantation will not be replaced.

4. Data Analysis Considerations

4.1. Analysis Populations

All patients screened will be considered for analysis.

The CIP provides the following definitions of analysis populations that will be used for statistical evaluation:

- Safety Population: It comprises all patients for whom ARGOS-IO pressure sensor implantation was attempted, whether or not the implantation was successful.
- Per Protocol Population: It comprises all patients 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.

Safety analysis will be performed on the safety population. Performance endpoints will be analyzed on the Per-protocol population (primary analysis) and on the safety population.

A definite allocation of patients to the analysis populations is listed in Section 13.2. These patients constitute then the Safety Set (SFS) and the Per Protocol Set (PPS).

4.2. Definition of Subgroups

Subgroups are addressed in the CIP but will not be considered for analysis.

4.3. Analysis Time Points

A schedule of assessments is given in section 8.5 of the CIP.

4.4. Definition of Derived Variables

In case a proportion for a specified criterion is computed, all patients meeting the criterion will be divided by the number of all patients within a population.

In this study, Baseline is the value recorded at Screening visit. If no value at Screening visit is available, the pre-surgical value will be used as Baseline assessment (if applicable).

Changes from Baseline (if applicable) will be computed as follows:

- Absolute change (original unit): post-Baseline value – Baseline value
- Relative change (%): 100 × (post-Baseline value – Baseline value) / Baseline value
  If the Baseline value is 0, no relative change will be computed.

Adverse events should be documented from the point of surgery until the patient is discharged from the clinical investigation..

A flag variable will be defined indicating for each adverse event the period of the onset:

- up to 4 weeks (Day 0 – Day 28) after surgery
- after 4 weeks up to 16 weeks (Day 29 – Day 112)
- after 16 weeks up to 28 weeks (Day 113 – Day 196)
- after 28 weeks up to 12 months (Day 197 – max(Day 365, Day of study termination))

4.5. Coding Dictionaries

Coding of medical data is performed by the Data Management department of X-ACT. Internationally recognized and accepted dictionaries are used for the coding of medical terms.

- The coding of the previous and concomitant diseases and adverse events is performed using MedDRA version 20.0.
- Prior and concomitant medication and non-drug therapies is coded using the WHO-Drug Dictionary Enhanced (WHO-DDE, version 2012/Q4).

The version of the used dictionary will be indicated in the tables and listings.

4.6. Protocol Deviations

Protocol deviations are identified during monitoring and classified according to the category affected:

- Patient rights/ welfare
- Patient safety
- Integrity of research
- other

Protocol deviations are specified regarding the involvement of deviation.

- Consent process
- Patient eligibility
- AE/ SAE reporting
- Assessments
- Device implantation
- Visit window / missed visit
- Audit finding that requires corrective action
- Other

4.7. General Presentation of Summaries and Analysis

All data as documented will be presented in individual patient data listings (depicting all data obtained in the eCRFs as well as additional external data). Data will be sorted by patient number and visit. Treated patients will be listed first, followed by Screening failures. Where appropriate, the listings will include changes from Baseline.

Descriptive statistics will be computed as follows:

- Continuous variables will be presented using the number of valid cases, arithmetic mean, standard deviation, minimum value, median, maximum value (summary statistics)
- Categorical variables will be presented by the absolute frequency (n) and the relative frequency (%) for each observed modality including missing values as own category if not otherwise specified (frequency tables).

Further specifications regarding the layout of end-of-text tables and listings are given in Appendix 13.5 of this SAP. A list of all statistical tables, figures and listings to be produced can be found in Appendices 13.3 and 13.4. These overviews also indicate the analysis population(s) for which a respective parameter will be evaluated. Any figures/graphics produced must be legible after been copied in black even if the original version is colored.

Raw SAS procedural outputs will not be presented as statistical evaluation is descriptive only.

4.8. Statistical Software

All statistical analyses will be performed by programming using the software SAS® Version 9.3 or higher (STATISTICAL ANALYSIS SYSTEM, SAS Institute, Cary, NC, USA).

5. Statistical/Analytical Issues

5.1. General Considerations

Analysis data sets following internal standards will be programmed which will be used for the generation of tables, figures and listings (TFLs). To meet common quality control requirements, the analysis of the following variables will be double-programmed by a second biostatistician:

- Overview about the frequency and percentage of patients with device related serious adverse events during the first 12 months (primary safety endpoint)
- Level of agreement between IOP measurements made using manometry and the ARGOS-IO system over the first 12 months following implantation (primary performance endpoint)
- Summary of adverse events by system organ class and preferred term during the first 12 months.

The SAS program codes for all other summary tables, listings or graphics will be reviewed by a second biostatistician and the results checked for consistency at least visually. All SAS programs used for the evaluation will be stored in a study-specific directory on the X-ACT file server together with the corresponding 'list' and 'log' files.

All statistical analyses will be performed in a descriptive way. Two-sided 95% confidence intervals (Pearson-Clopper, e.g. Hartung [4]) will be calculated for overall AE rates. Two-sided 95% confidence intervals will be determined for the lower and for the upper limit of agreement regarding the level of agreement between IOP measurements using manometry and the ARGOS-IO system (Zou [5]).

Usually, all patients within a given analysis population will be considered for analysis.

By-visit tabulations will be based on scheduled visits. If data are described by scheduled visit, the analysis will be based upon only those patients who were on study at a given visit.

Correspondingly, the AE rates will be calculated for those patients who enter the period considered.

5.2. Adjustments for Covariates

N/A – Covariates will not be included in the statistical analyses.

5.3. Handling of Dropouts and Missing Data

Patients terminating the trial prematurely due to whatever reason will be evaluated like any patient completing the trial as per protocol, within the analysis sets they qualify for.

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Missing data will not be imputed in any way. In general, missing values will be displayed as own category in frequency tables.

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

5.4. Interim Analysis and Data Monitoring

N/A

5.5. Multicenter Studies

This study is conducted as a multicenter clinical investigation. The data of all sites will be pooled for statistical analysis.

5.6. Multiple Comparisons/Multiplicity

No statistical tests will be performed. Only descriptive analyses including 95% confidence intervals are planned.

5.7. Examination of Subgroups

Subgroups will not be considered for analysis.

6. Study Population Characteristics

In general, statistical tables described in this chapter will show data separated by analysis population (safety set, per-protocol set) and for the total analysis population.

6.1. Population Overview

A frequency table will be prepared describing the number of patients screened, not eligible (i.e. screen failure), treated, and implanted (ARGOS-IO sensor). This table will present the frequencies by site and in total. The reason for screen failure will be shown in a patient data listing.

Furthermore, the date of the first patient in (FSI) (date of informed consent) and the date of last patient out (LSO) will be presented for the treated patients. FSI will be derived using the date of the Screening visit. LSO will be derived using the date of study termination

Inclusion and exclusion criteria will be listed per patient in a patient data listing.

The number and percentage of patients included in the SFS and PPS will be tabulated in total. Percentages are based on the number of treated patients.

A frequency table will be prepared describing for the treated patients the patient disposition at the end of the clinical investigation (categories: completed, early termination) for each analysis population. The treated patients with premature termination of the clinical investigation will be summarized by the pre-specified primary reason for premature termination. Further specifications given for the reasons of premature termination will be shown in a patient data listing.

All patient summary data will be listed.

6.2. Protocol Deviations

A frequency table will be prepared presenting the number and percentage of all treated patients with at least one deviation from the CIP.

In addition, the number and percentage of all treated patients with deviations will be summarized by category affected. Correspondingly, the number and percentage of all treated patients with deviations will be summarized by involvement of deviation.

A patient data listing will be prepared displaying for each patient the protocol deviations.

6.3. Patients Excluded from Analysis Populations

Appendix 13.2 lists all patients excluded from any analysis population. A patient data listing will be prepared displaying excluded patients and the reason(s) for exclusion.

7. Demographics and Other Baseline Characteristics

Demographics and baseline characteristics (e.g. sex, age, educational level, disease characteristics, prior and concomitant treatments, medical history) will be evaluated for the SFS, and PPS.

7.1. Demographics

Age, weight and height at screening will be described by summary statistics. The age of the patient (in years) is exported from the database and will be used.

The distribution of the demographic characteristics sex, ethnicity and educational level will be tabulated for the pre-specified categories by frequencies and percentages.

7.2. Disease Characteristics concerning Study Eye

The number and percentage of patients will be presented by category for

- Study eye (categories: OS, OD)
- Ophthalmic primary underlying condition (autoimmune disease, chemical injury, mechanical injury, other)
- Previously/currently treated for elevated IOP or glaucoma (no, yes)

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Summary statistics will be tabulated for

- the time since the onset of the ophthalmic primary underlying condition and the date of surgery (in years)
- the axial length (in mm)

7.3. External Eye Photography

External eye photographies performed at the screening examination will be displayed by patient in a patient data listing. In addition, the reason will be listed when no photography was performed.

7.4. Anterior Eye Segment Assessments

Findings of the slip-lamp biomicroscopy will be summarized overall (‘any finding’) and by segment (lids, conjunctiva, cornea, anterior chamber, iris, pupil, lens, aqueous humor, other) and will include the number and percentage of patients with at least one finding reported. A summary table will be

generated on a patient level: Patients are counted only once for each segment when they have more than one finding within the segment of the anterior eye.

In addition, clinically significant findings will be summarized overall ('any finding') and by segment and will include the number and percentage of patients with at least one clinically significant finding reported. A summary table will be generated on a patient level: Patients are counted only once for each segment when they have more than one clinically significant finding within the segment of the anterior eye.

Further description of the anterior segment findings including severity will be presented in corresponding patient data listings only.

Measurements regarding the cup disc ratio, central retinal thickness and white-to-white diameters will be listed in a patient data listing.

7.5. Posterior Eye Segment Assessments

Findings will be summarized overall ('any finding') and by segment (fundus, macula, retina, vitreous body, other) and will include the number and percentage of patients with at least one finding reported. A summary table will be generated on a patient level: Patients are counted only once for each segment when they have more than one finding within the segment of the posterior eye.

In addition, clinically significant findings will be summarized overall ('any finding') and by segment and will include the number and percentage of patients with at least one clinically significant finding reported. A summary table will be generated on a patient level: Patients are counted only once for each segment when they have more than one clinically significant finding within the segment of the posterior eye.

Further description of the posterior segment findings including severity will be presented in corresponding patient data listings only.

7.6. IOP measurements

Measurements of the intra-ocular pressure (IOP) are performed at the beginning and at the end of the screening visit using Goldmann Applanation Tonometry and/ or pneumotonometry.

Summary statistics will be tabulated for IOP measurements (in mmHg) by measurement procedure (Goldmann Applanation Tonometry, pneumotonometry) and time point (beginning, end of the visit).

Further details (time of measurements) will be presented in a corresponding patient data listing.

7.7. Medical History and Concomitant Diseases

Medical history are all diagnoses/procedures where the stop date is on the date of the surgery (Day 0) or before, and *concomitant diseases* are all diagnoses/procedures with either a ticked 'Ongoing?' box or a stop date after the date of surgery (Day 0). If start date and stop date are identical and the date of surgery, the disease will only be evaluated as concomitant disease.

Medical history and concomitant diseases are coded according to the MedDRA terminology (version 20.0).

Medical history findings and concomitant diseases will be summarized separately by System Organ Class and Preferred Term and will include the number and percentage of patients with at least one disease reported. Summary tables will be generated on a patient level: Patients are counted only once for each preferred term when they have more than one disease with the same preferred term. Patients with more than one disease within a SOC will be counted for each corresponding preferred term within the SOC, but are counted only once for the SOC. All tabulations will be sorted alphabetically by SOC and by frequency of preferred terms within each SOC.

Corresponding tables will be presented for the medical history findings and concomitant diseases regarding the study eye.

Specific previous/concomitant disease findings will be presented in a corresponding patient data listing.

7.8. Prior and Concomitant Medications and Non-drug Therapies

Prior medications or prior non-drug therapies are all medications or non-drug therapies where the stop date is before the date of surgery (Day 0). *Concomitant medications or concomitant non-drug therapies* are all medications or non-drug therapies with either a ticked 'Ongoing?' box or a stop date on or after the date of surgery (Day 0). If start date and stop date are identical and the date of surgery, the medication or non-drug therapy will only be evaluated as concomitant medication or concomitant non-drug therapy.

Recorded medications are coded according to WHO-DDE (version 2012/Q4). The allocation of reported terms to higher-level classifications is made using the preferred ATC code.

Prior and concomitant medications will be summarized separately using Level 2 (3-digit) and Level 3 (4-digit) of the ATC code. Summary tables will be generated on a patient basis: Patients are counted only once for each ATC class when they have more than one medication within the same ATC class. Patients with more than one medication within a level 2 ATC class will be counted for each corresponding level 3 term, but only once for the level 2 class. The number and percentage of patients with at least one medication reported will also be displayed. All tabulations will be sorted alphabetically by level 2 ATC decode and by frequency of level 3 decodes within level 2 class.

Specific details of prior or concomitant medication findings (e.g. dose, route and frequency of administration) will be presented in corresponding patient data listings only.

Note: Reported medications or non-drug therapies which a start date after the date of study termination will only be presented and flagged in the patient data listing but not tabulated in summary tables.

7.9. Other Baseline Characteristics

Regarding female patients, childbearing potential and the result of a urine pregnancy test before investigational device implantation will be listed in a patient data listing.

8. Clinical Investigation Treatments

8.1. Findings Associated with Surgery

The following descriptive statistics will be presented for each analysis population:

- A frequency table regarding intraocular lens (IOL): patient pseudophakic (yes, no), IOL location (posterior, other location), disposition of IOL (removed, remained in eye)
- A frequency table regarding iridectomy: iridectomy performed (yes, no), method (manual, laser), location
- A frequency table regarding glaucoma drainage device (GDD): GDD in situ at start of surgery (yes, no), GDD left in place (yes, no), GDD implanted during surgery (yes, no), GDD now (yes, no), location of GDD (superior 12 o'clock, nasal, inferior 6 o'clock, temporal)
- A frequency table regarding keratoprothesis device: implanted (yes, no)

8.2. Investigational Device

The details for the implantation of the ARGOS-IO will be tabulated in a frequency table for

- Implantation performed (yes, no)
- Size of the sensor (11.3 mm, 11.7 mm, 12.1 mm)
- Placement of the ARGOS-IO sensor: sulcus support adequate (yes, no, not assessed), fixation of the sensor
- Orientation of application specific integrated circuit (ASIC) (superior 12 o'clock, nasal, inferior 6 o'clock, temporal)

In addition, the number and percentage of patients with intraoperative complications will be presented in a table. The specification of the intraoperative complications and any difficulties with the placement of the ARGOS-IO sensor will be presented in the corresponding patient data listing.

Further information including data regarding keratoprothesis and discharge date will be given in patient data listings.

8.3. Rescue Medication

N/A

9. Performance Analyses

All statistical tables will show the results for all patients of the PPS (primary analyses) and the SFS.

Concerning IOP, a summary of all manometry and ARGOS-IO system measurements will be displayed in a table by visit (Week 4, 16, 28, 52 visit): For each patient the mean value of the ARGOS-IO system measurements (mean within subject value) at the visit will be derived and the difference to the manometry value calculated.

The difference between manometry and ARGOS-IOP measurements will be displayed over time in a mean value plot.

Pairs of measurement will only be used when there was no more than 2 minutes difference between manometry and ARGOS-IO system measurements.

All measurement values including the mean within subject ARGOS IOP value will be displayed in a patient data listing. In addition, the time points of measurements and the difference between the time points will be presented in the listing.

9.1. Primary Performance Endpoint

Primary performance endpoint is the level of agreement between IOP measurements made using manometry and the ARGOS-IO system over the first 12 months following implantation of the IMD.

A Bland-Altman analysis will be done for a point estimation of the level of agreement between the two IOP measurement methods with repeated observations. It is assumed that the true IOP value varies over time for each patient.

Concerning ARGOS-IO, the average of the (three) measurements during surgical manometry will be taken.

All complete measurement pairs (manometry value, average of the ARGOS-IO values during surgical manometry) will be used per patient, to calculate the mean within subject difference between the methods. Pairs of measurement will only be used when there was no more than 2 minutes difference between both measurements.

The average over the mean within subject differences (Δ) is an estimate for the bias between the two IOP measurement methods. The lower and the upper level of agreement will be estimated as

$$LoA_{low} = \Delta - z_{\beta/2} * s$$

$$LoA_{upp} = \Delta + z_{\beta/2} * s$$

($z_{\beta/2}$ is the upper β/2 quantile of the standard normal distribution (=1.96), s is an estimate for the variation of the differences which comprises both between and within individual components, see Zou, section 2.1.1)

95% confidence interval estimation for the lower limit of agreement (LoA_{low}) and for the upper limit of agreement (LoA_{upp}) will be obtained using the MOVER method, see Zou, section 2.2.2.

9.2. Secondary Performance Endpoint: Level of Agreement at Specific Visits

Secondary performance endpoint is the level of agreement between IOP measurements made using surgical manometry and the ARGOS-IO system at visits 4, 16, 28 and 52 weeks following implantation.

For each of the visits mentioned above a Bland-Altman analysis will be done to assess the level of agreement between the two IOP measurement methods. Concerning ARGOS-IO, the average of the (three) measurements during surgical manometry will be taken.

For each of the visits mentioned above, the mean of the within subject differences and 95% limits of agreement between the two methods will be calculated. Pairs of measurement will only be used when there was no more than 2 minutes difference between both measurements.

For each of the visits mentioned above, the within subject differences will be plotted against the within subject means (Bland-Altman plot).

9.3. Secondary Performance Endpoint: Incidence of Device Deficiencies

Secondary performance endpoint is the incidence of device deficiencies in the first 4, 16, 28 and 52 weeks following implantation.

A summary table on device deficiencies will be generated displaying the number and percentage of patients with any device deficiency in the first 4, 16, 28 and 52 weeks following implantation. In addition, the number and percentage of patients with a device deficiency regarding the ARGOS-IO implant, the Mesograph reader, the multiline connector or other will be presented in the table for each of the periods mentioned above.

All device deficiencies and associated collected information will be presented in a corresponding patient data listing.

9.4. Secondary Performance Endpoint: User Acceptance of the Implantation Procedure

Data are not available in the database for the Investigator Implantation Procedure Questionnaire scheduled for the evaluation of the user acceptance.

9.5. Secondary Performance Endpoint: User Acceptance of the ARGOS-IO System

Data are not available in the database for the Investigator Acceptance Questionnaire scheduled for for the evaluation of the user acceptance.

9.6. Unplanned Analysis

Summary statistics will be presented in a table by visit (Week 4, 16, 28, 52 visit) and time point (measurement 1 - prior to manometry, measurement 2 - during manometry, measurement 3 - following manometry) for the within subject mean IOP values. Concerning each patient and time point, the maximal difference between the IOP values will be derived and summarized in the table.

Concerning each post-surgery visit, the within subject mean IOP value will be derived for measurement 1 (at the beginning of the visit). Summary statistics will be tabulated for the within subject mean IOP value by the result of finger palpation assessment of IOP (soft/ hypotonic, borderline, normal, hypertonic). Furthermore, within subject mean IOP value and finger palpation assessment will be presented per patient in a scatter plot.

10. Safety Analyses

All safety parameters will be evaluated on the SFS. Only descriptive statistics will apply.

10.1. Primary Safety Endpoint: Occurrence of Serious Adverse Device Events (SADE)

The number and percentage of patients experiencing a device related SAE at any time during the first 12 months following implantation surgery will be presented in a table. In addition, a 95% confidence interval will be calculated for the percentage of patients with SADE as specified above.

For the purpose of this analysis, a device-related SAE is defined as any serious adverse event that is considered by the Investigator to have a possible, probable or definite relationship to the device.

10.2. Secondary Safety Endpoints: Incidence and Description of Adverse Events

All adverse events (AEs) including all adverse device effects (ADEs) as recorded in the CRF module 'Adverse Events' will be analyzed.

Initially, an overview will be generated tabulating the number and proportion of patients (and the total number of events) with

- AEs
- Adverse device effects (all adverse events that are considered by the Investigator to have a possible, probable or definite relationship to the medical device)
- AEs related to procedure (all adverse events that are considered by the Investigator to have a possible, probable or definite relationship to the procedure)
- AEs leading to withdrawal of patient
- serious AEs

All adverse events at any time during the first 12 months following implantation surgery will be considered. In addition, 95% confidence intervals will be presented for the percentage of patients with AE(s) considered as specified above.

Corresponding overview tables will be given describing the number and proportion of patients with adverse events as specified above at any time during the first 4 weeks, during the first 16 weeks, and during the first 28 weeks following implantation of the IMD, respectively. In addition, 95% confidence intervals will be presented for the percentage of patients with AE(s) considered as specified above.

All adverse events with onset date during the period will be considered.

- AEs with incomplete onset date will be regarded with an onset date completed by ‘01’ for the day (when the month and the year of the onset date are known)
- AEs with an unknown onset date will be regarded with an onset date identical to the date of awareness of the AE

Note that AEs will be counted for each period since onset. Reported frequencies are cumulative over the time for this reason.

Adverse events are coded according to the MedDRA terminology. The following summaries will be provided for adverse events broken down by System Organ Class (SOC) and Preferred Term within SOC:

- All AEs
- All AEs by severity (categories: mild, moderate, severe)
- All AEs by causal relationship to IMD (categories: none, unlikely, possible, probable or definite)
- All adverse device effects (all adverse events that are considered by the Investigator to have a possible, probable or definite causal relationship to the device)
- All AEs related to procedure (all adverse events that are considered by the Investigator to have a possible, probable or definite causal relationship to the procedure)
- All adverse device effects by severity
- All serious AEs
- All serious adverse device effects

These summaries will generally provide the number and percentage of patients with AEs (and the total number of events) within each preferred term and within each SOC. Patients are counted only once for each preferred term when they have more than one AE with the same preferred term. Patients with more than one AE within a SOC will be counted for each corresponding preferred term within the SOC, but are counted only once for the SOC. The number of patients with at least one AE and the total number of events will also be displayed.

These summaries will be provided for adverse events at any time during the first 4 weeks, during the first 16 weeks, during the first 28 weeks and at any time during the first 12 months following implantation surgery, broken down by System Organ Class (SOC) and Preferred Term within SOC.

All tabulations will be sorted alphabetically by SOC and by frequency of preferred terms within each SOC.

A glossary of adverse events will be presented showing how investigator reported terms were actually coded to preferred terms and body systems.

All adverse events and associated collected information will be presented by patient in a corresponding patient data listing.

10.3. Death and Other Serious Adverse Events

In addition to the general AE listing, a separate patient listing will be generated for serious adverse events and death cases. Summary tables on serious AEs are described in Section 10.2.

10.4. Adverse Events Leading to Withdrawal

In addition to the general AE listing, a separate patient listing will be generated for adverse events leading to withdrawal.

10.5. Anterior Eye Segment Assessments

Anterior eye segment assessments are scheduled for the day of surgery before implantation of the device and at each visit following surgery.

Concerning each segment, frequencies will be displayed for the changes from baseline at each visit (categories by severity: no finding, mild, moderate, severe) depending on the baseline classification (shift tables). Percentages are based on the number of patients who attended the visit considered.

Concerning each anterior eye segment, the baseline value is the last severity category reported before surgery for the patient. In general, this will be the value reported at the Screening visit when there are no new pre.-surgical findings or changes from screening observed at surgery visit.

All data will be presented in a patient data listing.

10.6. Posterior Eye Segment Assessments

Posterior eye segment assessments are scheduled for the day of surgery before implantation of the device and at specific visits following surgery (Week 4 visit, Week 16 visit, Week 28 visit, Week 52 visit).

Concerning each segment, frequencies will be displayed for the changes from baseline at each visit (categories by severity: no finding, mild, moderate, severe) depending on the baseline classification (shift tables). Percentages are based on the number of patients who attended the visit considered.

Concerning each posterior eye segment, the baseline value is the last severity category reported before surgery for the patient. In general, this will be the value reported at the Screening visit when there are no new pre.-surgical findings or changes from screening observed at surgery visit.

All data will be presented in a patient data listing.

10.7. Visual Acuity

Visual acuity data are reported at Week 4 visit (visit 7) and Week 52 visit (visit 15).

All collected information regarding visual acuity (number of correct letters at 4m, CC Snellen measurements, clinically significant findings) will be displayed in a patient data listing.

The number of correct letters at 4m will be tabulated by summary statistics for each visit.

10.8. Perimetry

Data concerning visual field examination are reported at Week 12 visit (visit 10) and Week 52 visit (visit 15). All collected information will be displayed in a patient data listing.

11. Analysis of Other Variables

All flag variables reporting any change for the patient during the course of the study (e.g. concerning adverse events, concomitant medications) will be presented in patient data listings.

12. References

[1] ICH E3, Structure and Content of Clinical Study Reports, 1996

[2] ICH E9, Statistical principles for clinical trials, 1988

[3] SAS, Statistical Analysis System, SAS Institute, Cary, NC, USA

[4] Hartung, J. (1982). Statistik. Oldenbourg, München

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

13. Appendices

13.1. Actually Found Protocol Deviations

Databased, will be listed

13.2. Patients Excluded from Analysis Populations

One patient (DE-3-01) was only screened. All other patients will be included in the SFS, because a surgery for implantation was performed.

According to the definition of the PPS, the PPS comprises all SFS patients 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.

Therefore, all patients who prematurely discontinued the study before Week 11 will be excluded from the PPS:

Patients excluded from the PPS due to premature discontinuation of the study

Patient ID	Last visit	Reason
DE-1-02	Week 22 (Visit 10)	Voluntary withdrawal
DE-1-05	Week 22 (Visit 10)	Other (sensor explantation)
DE-1-07	Week 4 (Visit 7)	SAE
DE-2-03	Screening visit	Other (decision of surgeon. capsular bag instability)

13.3. Table of 'End-of-Text' Tables / Figures

[To be included in Section 14 of CIR]

The numbering of statistical tables follows the ICH E3 guideline. Shown abbreviations denote the analysis populations for which a variable will be evaluated. Please note that some tables may be split into sub-tables covering different aspects of the evaluation. An additional number for analysis population will be attached to the shown table/figure number (if applicable).

Table / Figure	Title	Analysis Population
Table 14.1.1	Patient Disposition	Screened patients
Table 14.1.2	Patient Disposition after Start of Treatment	Treated patients
Table 14.1.3	Summary of Patient Populations and Protocol Deviations	Treated patients
Table 14.1.4.1	Demographic Data	SFS, PPS
Table 14.1.4.2	Disease Characteristics concerning Study Eye	SFS, PPS
Table 14.1.4.3	Anterior Eye Segment Assessments (abnormal findings) at Screening	SFS, PPS
Table 14.1.4.4	Anterior Eye Segment Assessments (clinically significant findings) at Screening	SFS, PPS

Table / Figure	Title	Analysis Population
Table 14.1.4.5	Posterior Eye Segment Assessments (abnormal findings) at Screening	SFS, PPS
Table 14.1.4.6	Posterior Eye Segment Assessments (clinically significant findings) at Screening	SFS, PPS
Table 14.1.4.7	IOP Measurements at Screening Visit	SFS, PPS
Table 14.1.5.1	Medical History by SOC and PT	SFS, PPS
Table 14.1.5.2	Medical History Related to Study Eye by SOC and PT	SFS, PPS
Table 14.1.5.3	Concomitant Diseases by SOC and PT	SFS, PPS
Table 14.1.5.4	Concomitant Diseases Related to Study by SOC and PT Eye	SFS, PPS
Table 14.1.6.1	Prior Medication and Non-Drug Therapies by ATC Level	SFS, PPS
Table 14.1.6.2	Concomitant Medication and Non-Drug Therapies by ATC Level	SFS, PPS
Table 14.1.7.1	Intraocular Lens Implantation	SFS, PPS
Table 14.1.7.2	Iridectomy	SFS, PPS
Table 14.1.7.3	Glaucoma Drainage Device	SFS, PPS
Table 14.1.7.4	Keratoprothesis Device	SFS, PPS
Table 14.1.8.1	ARGOS-IO Sensor Implantation	SFS, PPS
Table 14.1.8.2	Orientation of ASIC	SFS, PPS
Table 14.1.8.3	Intraoperative Complications	SFS, PPS
Table 14.2.1	IOP Measurements by Manometry and ARGOS-IO	SFS, PPS
Figure 14.2.1	Difference between Manometry and ARGOS-IO over the time – mean value plot	SFS, PPS
Table 14.2.2	Level of Agreement (repeated measurements over visits) between Manometry and ARGOS-IO and 95% confidence intervals (primary performance endpoint)	SFS, PPS
Table 14.2.3	Level of Agreement between Manometry and ARGOS-IO by Visit (secondary performance endpoints)	SFS, PPS
Figure 14.2.3	Bland-Altman Plot: Level of Agreement between Manometry and ARGOS-IO by Visit	SFS, PPS
Table 14.2.4	Incidence of Device Deficiencies in the first 4, 16, 28 and 52 weeks following implantation	SFS, PPS
Table 14.2.5	ARGOS-IO Measurements by Post-Surgery Visit and Time Point at Visit	SFS, PPS
Table 14.2.6	ARGOS-IO Measurements by Finger Palpation for each Post-Surgery Visit	SFS, PPS
Figure 14.2.6	ARGOS-IO Measurements versus Finger Palpation – Scatter Plot for each Post-Surgery Visit	SFS, PPS
Table 14.3.1.1	Overview on Incidence of Serious Device Related Adverse Events - periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS

Table / Figure	Title	Analysis Population
Table 14.3.1.2	Overview on Incidence of Adverse Events – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
Table 14.3.1.3	Adverse Events by SOC and PT – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
Table 14.3.1.4	Adverse Events by SOC, PT and Severity – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
Table 14.3.1.5	Adverse Events by SOC, PT and Causal Relationship to IMD – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
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	SFS
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	SFS
Table 14.3.1.8	Adverse Device Effects by SOC and PT and Severity – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	
Table 14.3.1.9	Glossary of all Adverse Events	SFS
Table 14.3.2.1	Serious Adverse Events by SOC and PT – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
Table 14.3.2.2	Serious Adverse Device Effects by SOC and PT – periods: first 4 weeks, 16 weeks, 28 weeks, 12 months following implantation surgery	SFS
Table 14.3.3	Anterior Eye Segment Assessments by Visit – Shift from Baseline	SFS
Table 14.3.4	Posterior Eye Segment Assessments by Visit – Shift from Baseline	SFS
Table 14.3.5	Visual Acuity: Number of Correct Letters at 4m by Visit	SFS

13.4. Table of Patient Data Listings

[To be included in Appendix 16.2 of CIR]

The numbering of data listings follows the ICH E3 guideline.

Listing	Title	Analysis Population
16.2.1.1	Patient Disposition	Screened patients
16.2.1.2	Patient Disposition after Start of Surgery	Treated patients
16.2.1.3	Patient Summary	Treated patients
16.2.2	Protocol Deviations	Treated patients

Listing	Title	Analysis Population
16.2.3.1	Patients Excluded from Analysis Sets	Treated patients
16.2.3.2	Description of Inclusion and Exclusion Criteria	-
16.2.3.3	Fulfilment of Inclusion and Exclusion Criteria	Eligible patients
16.2.4.1	Demographic Data	Eligible patients
16.2.4.2	Disease Characteristics concerning Study Eye	Eligible patients
16.2.4.3	Baseline Ophthalmic Examinations - Anterior Eye Segment	Eligible patients
16.2.4.4	Anterior Eye Segment Findings prior to Surgery	Eligible patients
16.2.4.5	Baseline Ophthalmic Examinations - Posterior Eye Segment	Eligible patients
16.2.4.6	Posterior Eye Segment Findings prior to Surgery	Eligible patients
16.2.4.7	IOP Measurements (Goldmann Applanation Tonometry, pneumotonometry) at Screening Visit	Eligible patients
16.2.4.8	Medical History and Concomitant Diseases	Eligible patients
16.2.4.9	Prior/Concomitant Medication	Eligible patients
16.2.5.1	Implantation Surgery Data	Treated patients
16.2.5.2	ARGOS-IO Implantation	Treated patients
16.2.5.3	Intraoperative Complications	Treated patients
16.2.5.4	Status of KPro Device and ARGOS-IO Sensor after Surgery	Treated patients
16.2.6.1	IOP Measurements by ARGOS-IO and Manometry	Treated patients
16.2.6.2	IOP Measurements by ARGOS-IO and Finger Palpation	Treated patients
16.2.6.3	Device Deficiencies	Treated patients
16.2.7.1	Adverse Events	Treated patients
16.2.7.2	Serious Adverse Events	Treated patients
16.2.7.3	Adverse Device Effects	Treated patients
16.2.7.4	Adverse Events leading to Withdrawal	Treated patients
16.2.8	Pregnancy Tests	Eligible patients
16.2.9.1	Ophthalmic Examinations after Surgery - Anterior Eye Segment	Treated patients
16.2.9.2	Anterior Eye Segment Findings After Surgery	Treated patients
16.2.9.3	Ophthalmic Examinations after Surgery - Posterior Eye Segment	Treated patients
16.2.9.4	Posterior Eye Segment Findings after Surgery	Treated patients
16.2.9.5	Visual Acuity and Perimetry	Treated patients
16.2.9.6	Status Variables concerning Adverse Events and Concomitant Medication Changes	Treated patients

13.5. Layout of End-of-Text Tables and Listings

Issue	Specification

Basic layout of 'End-of-text' tables and listings (header, footnote)	3 horizontal lines per page: one above column headers, one below column headers, one below the body of the table or listing (footnotes below this last line).
	Footnotes for all tables and listings:
	`Program xxx.SAS, executed on DDMONYYYY at HH:MM`
	`PAGE 1 OF X`

Page margins based on DIN-A4 sized page	Landscape format: Top 3 cm, bottom 2 cm, left 2.5 cm, right 2 cm
Font and font size	Courier New 8
Column header	First letter of column capitalized (if applicable)
Patient or Patient as label?	Patient
Patient identification numbers	Use patient number as shown on CRF
Order in patient data listings	Eligible patients by patient number and visit (if applicable) followed by screen failures (if applicable)
Labels and order of sub-groups	Varying
Labels and order of visits	see CIP
Labels for descriptive statistics for continuous variables	Use n, Mean, SD, Min, Median, Max (instead of number of valid cases, arithmetic mean, standard deviation, minimum value, median, maximum value
Display of categorical variables	Display all categories present in the data as shown in the CRF, including missing values
In case a category does not occur	Display absolute frequency 0 (instead of "-") "-" should only be used if the category or table cell (e.g. concerning analysis results) is impossible
Display of absolute frequencies and percentages in tables	Frequencies are presented right aligned, followed by left aligned percentages in brackets, without % sign. Percentages are presented with one decimal place, 0 and 100 percentages without any decimal place: xx (xx.x) x (x.x) 0 (0) xxx (100) Percentages greater than 0 but rounded to 0.0 will be written as '<0.1'; percentages smaller than 100 but rounded to 100.0 will be written as '>99.9'.
P-values	P-values will be quoted with four decimal places; p-values which round to 0 will be reported as '<0.0001', p-values rounding to 1 will be displayed as '>0.9999'.
Display of ranges	xx – yy
Display of 2-sided confidence intervals	[lower limit , upper limit]
Display of units	Presentation case-sensitive and in round brackets, e.g. Age (years)

13.6. Documentation of Statistical Methods

[To be included in Appendix 16.1.9 of CSR]

The statistical analysis of this trial is done in descriptive way as described in the SAP.

13.7. Table of 'In Text' TFLs

N/A

13.8. Shells for TFLs

For the general layout of end-of-text tables and listings, see Section 13.5. For a better visualisation, some sample mock table for summary statistics and frequencies are attached to the SAP.

13.9. Raw Statistical Output

[To be included in Appendix 16.1.9 of CSR]

Raw output of all applied SAS procedures will be stored in study-specific folders. It is currently not planned to hand over SAS raw outputs. Only the agreed end-of-text tables that are based on the raw output will be compiled.