STATISTICAL ANALYSIS PLAN

ARGOS-02

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG)

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Draft 1.0	02-10-2014	Dr. Joanna Wengrzik	First release
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Signatures

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind/database close.

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Table of Contents

List of Abbreviations and Key Terms

α	Type I error
ADE	Adverse Device Effect
AE	Adverse Event
ASIC	Application specific integrated circuit
ATC	Anatomical Therapeutic Chemical Classification
β	Type II error
CIP	Clinical Investigation Plan
DSMB	Data Safety Monitoring Board
FAS	Full-analysis-set
GAT	Goldmann Applanation Tonometry
HLT	High level term
HLGT	High level group term
IO	Intraocular
IOL	Intraocular lens
IOP	Intraocular Pressure
ITT	Intention to treat
LLT	Lowest level term
N	Sample number
OCT	Ophtalmic Coherence Tomography
p0	Proportion of patients in stage 1 with positive outcome
p1	Proportion of patients overall with positive outcome
POAG	Primary apen angle glaucoma
PT	Preferred term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SES	Safety evaluation set
SOC	System organ class
V	Visit

1. Introduction

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses described in the Clinical Investigation Plan Rev. G, date 05th January 2016, and includes planned detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is finalised and signed prior to hard lock of the database.

2. Study Design and Objectives

2.1 Study Design

The trial will be conducted as an open, prospective, multicenter single-arm clinical trial following the principle of the two-stage design described by Simon (Simon, 1989) in patients with Primary Open Angles Glaucoma (POAG) and indicated cataract surgery. The purpose is to evaluate the safety of the ARGOS-IO system and to compare its performance to the Goldmann Applanation Tonometry (GAT).

All 22 patients will be enrolled consecutively, until a serious adverse device effect (SADE) occurs. In that case, the DSMB will be called, and decides whether the enrollment can be continued or not.

An interim analysis will be performed after half of the study population (11-14 subjects) is enrolled with a minimum follow-up of 1 month. Another interim analysis to assess Safety and Performance will be performed, when all patients have completed the 3 month follow-up visit, the 6 month follow-up visit and every time an SADE occurs.

In order to take the two-stage design described by Simon into account, the trial will be terminated, if more than 1 patient out of the first 11 patients enrolled experiences SADEs during the first 3 months of the post-surgical follow-up period.

A conclusion for safety will be made at the 5% significance level, if two or fewer of the total 22 patients experience an SADE. A corresponding 95% confidence interval for the SADE rate will be calculated according to the procedure of Koyoma (2008).

2.2 Treatments

2.2.1 Investigational Device

The ARGOS-IO system was developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor (intraocular pressure (IOP)) in patients with diagnosed glaucoma, or elevated or instable IOP that places them at a risk of ocular damage and loss of visual acuity. It enables numerous IOP measurements daily, providing a complete IOP profile for the entire interval between office visits, and allowing timely detection of both peaks due to patient activities and circadian rhythms and trends due to disease progression.

It is made up of four components:

- the ARGOS-IO implant, which is introduced into the area between the intraocular lens and the iris (ciliary sulcus) using standard procedures that employ an implant injector similar to those commonly used to insert intraocular lenses (IOLs),
- the external hand-held Mesograph reading device, which in the near vicinity of the eye establishes an inductive current between it and the micro-coil, thereby supplying the Application Specific Integrated Circuit (ASIC) with power and permitting data transmission,
- the implant injector and
- the Multiline Connector, which uploads the data recorded by the reader to a secure dedicated data base that can be accessed remotely by the Investigator.

2.2.2 Comparator

The ARGOS-IO system will be directly compared to the non-invasive Goldmann Applanation tonometry (GAT). Therefore, patients will not be exposed to any other active implantable comparators. GAT is the standard tonometry method to which all other tonometers have traditionally been compared.

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

2.3 Trial Schedule

The estimated total duration of the study from first patient screened to last patient last visit is 21 months. The maximum duration of each patient's participation in this clinical intervention is 13

months. The point of enrolment is considered to be the time point at which potentially eligible patients sign the informed consent form. Surgery will be performed within 28 days of this time point. The patient will be followed-up for 12 months post-surgery to obtain data on safety and performance. All patients who receive an ARGOS-IO implant will return for 10 follow-up visits (V02 - V11) to the clinic (day 1, 3, 10, 30, 60, 90, 120, 180, 240, 360) during the 12-month post-surgical period. Table 1 shows the assessment schedule.

Table 1: Assessment Schedule

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11
Indicative Days (D)	**Up to 28 days before surgery**	**D0**	**D1**	**D3**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D60 +/- 5 Days**	**D90 +/- 10 Days**	**D120 +/- 10 Days**	**D180 +/- 10 Days**	**D240 +/- 10 Days**	**D360 +/- 10 Days**
GENERAL												
Informed consent signed	X											
Allocation of patient number	X											
Inclusion & exclusion criteria	X	X[1]										
Demography	X											
Past and current significant medical history	X											
Pregnancy test (urine beta-hCG)	X	X[2]										
Optical Biometry (IOL Master)	X[3]											
Cataract surgery and ARGOS-IO pressure sensor implantation		X										
Visual acuity (ETDRS)[4]	X		X	X	X	X	X	X	X	X	X	X
Perimetry[5]	X							X		X		X
External eye photography[6]	X	X	X	X	X	X	X	X	X	X	X	X
User acceptance questionnaire (patient)												X
Implantation procedure questionnaire (surgeon)		X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE/ADE/SAE/SADE		X	X	X	X	X	X	X	X	X	X	X
Device malfunction		X	X	X	X	X	X	X	X	X	X	X
ANTERIOR SEGMENT												
Slit-lamp biomicroscopy[7]	X		X	X	X	X	X	X	X	X	X	X
Ultrasound biomicroscopy (UBM)	X											
Optical coherence tomography (OCT)[8]	X							X		X		X
Gonioscopy[9]	X							X		X		X
Confocal Microscopy[10]	X							X		X		X

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11
Indicative Days (D)	**Up to 28 days before surgery**	**D0**	**D1**	**D3**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D60 +/- 5 Days**	**D90 +/- 10 Days**	**D120 +/- 10 Days**	**D180 +/- 10 Days**	**D240 +/- 10 Days**	**D360 +/- 10 Days**
POSTERIOR SEGMENT												
Biomicroscopy[11]	X		X	X	X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)[12]	X							X		X		X
Fundus photography	X							X		X		X
IOP Measurement												
Goldmann Applanation tonometry[13]	X		X	X	X	X	X	X	X	X	X	X
ARGOS-IO pressure sensor measurement[13]						X[14]	X	X[14]	X	X[14]	X	X[14]
ARGOS-IO pressure sensor self-measurement[15]						X	X	X	X	X	X	X

[1] Eligibility must be reassessed at V01 prior to surgery.

[2] For females of childbearing potential, a pregnancy test performed within 24 hours preceding surgery must be negative to confirm eligibility.

[3] The Optical Biometry measurement using the IOL Master made at screening (SC) will be used to determine the implant sizes (IOL and ARGOS-IO implant).

[4] The best corrected visual acuity will be determined after objective and subjective determination of refraction with the ETDRS chart in accordance with the EDTRS protocol.

[5] Perimetry is performed to obtain an accurate examination of the peripheral extent of the visual field. Automated perimeters will be used either with standard glaucoma field, field 30-2 or equivalent.

[6] External eye photography is performed through a slit lamp camera or equivalent. The outer eye shall be photographed in order to document potential changes to the iris or pupil structure.

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

[8] Anterior segment OCT is performed to evaluate effects on change in chamber angle after surgery and to assess the central corneal thickness.

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

[10] Standard confocal microscopy is used to determine the corneal endothelial cell density.

[11] Posterior segment biomicroscopy is performed though a dilated pupil using mydriatic agents by means of indirect ophthalmoscopy on a slit lamp with the aid of a 90D or "Superfield" or comparable lenses. This method is used to evaluate the following parameters: optic nerve lesions, other posterior pole lesions, vitreous opacities, optic nerve head, fundus lesions, retinal arteries and veins (AV), macular area, fundus periphery, normal and abnormal variations of the fundus.

[12] Posterior segment OCT is used to assess macular structures and the peripapillary nerve fiber layer.

[13] IOP measurements will be made in series of 1 Goldmann Applanation tonometry (GAT) standard measurements followed by 3 ARGOS-IO system measurements, the first of which must occur within 10 minutes of the GAT. A series of measurements will be made at both the beginning and end of each visit. An interval of at least 60 minutes should lie between the last measurement of one series and the first measurement in the next.

[14] At visits 5, 7, 9 and 11 at least 4 series of IOP measurements will be performed, with at least 60 minutes between the last measurement in one series and the first measurement in the next.

[15] All patients will receive a MESOGRAPH reading device at Visit 05 in order to measure the IOP daily at home. Measurements shall be taken at least 4 times per day (morning, noon, afternoon, evening). The MESOGRAPH reading device will be connected to an external GSM module, which will transfer the measured value directly to a secure database. Investigators can log into the database in order to track the pressure levels of their patients as required.

2.4 Study Objectives

The aim of this trial is to verify the safety and performance of the ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG) and indicated cataract surgery. The measurements of intraocular pressure through the pressure sensor shall be compared with Goldmann Applanation Tonometry (GAT), which is generally accepted as the clinical gold standard. The ARGOS-IO pressure sensor will be implanted during cataract surgery and is to remain permanently in the eye.

2.4.1 Primary Objectives

The primary objectives of this clinical investigation are

- **Safety:** To evaluate the safety and tolerability of the ARGOS-IO pressure sensor in the first 3 months following implantation.
- **Performance:** To evaluate the performance of the ARGOS-IO system compared to GAT from day 30 through day 180.

2.4.2 Secondary Objectives

The secondary objectives of this clinical investigation are

- **Safety:** To evaluate the safety and tolerability of ARGOS-IO pressure sensor implantation between 3 and 12 months.
- **Performance**: To evaluate the performance of the ARGOS-IO system compared to GAT up to 12 months after implantation.

2.5 Study Hypothesis

The specific hypothesis to be tested in this single arm two-stage design study is that the SADE rate is lower than 25%. It is expected that the observed SADE rate will be at most 6%. More precisely, let p be the true proportion of subjects with no SADEs, p_0 the proportion of subjects no SADE to be rejected and p_1 the expected proportion of patients overall without SADE. Then, the null hypothesis H_0 and the alternative hypothesis H_1 are:

$$H_0 = p \leq p_0 = 0.75 \quad \text{vs.} \quad H_1 = p \geq p_1 = 0.94.$$

If at most 2 SADE's occur in the 22 patients enrolled, a SADE rate lower than 25% can be concluded. This will be illustrated by the 95% confidence interval for the SADE rate which will be calculated using the method proposed by Koyama (Koyama & Chen, 2008). If the obtained

confidence interval does not include any value lower than 0.94, it can be concluded that the SADE rate is at most 6%.

2.6 Handling of Screening Failures and Drop-outs

Screen failures are patients who have signed the informed consent form but fail to meet eligibility criteria for enrolment, e.g., they do not meet one or more of the inclusion criteria or do meet one or more of the exclusion criteria. Such patients will be replaced.

Patients will be informed that they have the right to withdraw from the study at any time. The investigator must determine whether voluntary withdrawal is due to safety concerns. All patients who withdraw from the study after implantation and before completing the follow-up visits per protocol will be considered as drop-outs. Patients who drop out or are withdrawn after implantation will not be replaced.

Reasons for withdrawal are:

- The patient withdraws informed consent,
- it is determined during surgery that the patient is not feasible for ARGOS-IO pressure sensor implantation,
- the ARGOS-IO pressure sensor must be removed or replaced for any reason,
- patient becomes pregnant between screening and surgery.

Unless the patient revokes his/her permission to use it, any data collected up to the point of the patient's withdrawal will be included in the safety analysis. The data of all patients who undergo implantation of the ARGOS-IO pressure sensor will be included in the efficacy analysis under the Full Analysis Set.

2.7 Randomization

No randomization will be performed.

2.8 Blinding

No blinding/masking procedures will be performed.

To avoid bias resulting from prior knowledge of the IOP value from the ARGOS-IO system on the measurement obtained with GAT, GAT will be used first.

2.9 Sample Size Calculation

The primary aim of this study is to show "safety", which will be evaluated based on the percentage of subjects who experience an SADE (= "non-safety), as defined in the primary endpoints.. To minimize the required sample size and consequently the number of patients exposed to risk while at the same time maximizing the chances of detecting safety events, the sample size calculation follows the principle of a two-stage design as proposed by Simon (Simon, 1989). The event of interest was defined as patients with at least one serious device related adverse event (SADE) in the 3 month period immediately following implantation. Based on a probability of non-events of p_0=0.75 for the first stage and an overall acceptable probability of p_1=0.94, a sample size of at least 11 evaluable patients in the first stage and additional 11 patients in the second stage are required. This maintains a type 1 error probability of 5% and the power of 80% based on minimizing the maximal sample size. Table 2 summarizes the consequences of the sample size calculation on the study design.

Table 2: Two-stage study design

	First Stage	Overall
SADE-free Patients		
Proportion	$p_0 = 0.75$	$p_1 = 0.94$
Minimum number required	10	20
Patients with SADE		
Proportion	$1 - p_0 = 0.25$	$1 - p_1 = 0.06$
Maximum number allowed	1	2
Total Number of Patients	11	22

2.10 Planned Interim Analysis

All 22 patients will be enrolled consecutively, until a serious adverse device effect (SADE) occurs. In that case, the DSMB will be called, and decides whether the enrollment can be continued or not.

An interim analysis will be performed after half of the study population (11-14 subjects) is enrolled with a minimum follow-up of 1 month (Visit 5). Another interim analysis to assess Safety and Performance will be performed, when all patients have completed the 3 month follow-up visit, the 6 month follow-up visit and every time an SADE occurs.

In order to take the principle of the two-stage design described by Simon into account, the trial will be terminated for futility if more than 1 patient out of the first 11 patients enrolled experience at least one SADE during the first 3 months of the post-surgical follow-up period.

The study will also be stopped if the DSMB otherwise determines that severe safety risks to the patients exist.

2.11 Handling of Changes to Study Protocol

All changes of study protocol will be documented by amendments. If an amendment implies changes in the SAP, the SAP will be adapted and the adaptation will be documented in the document history.

3. Technical Aspects and Coding Conventions

All programmes will be written using SAS version 9.3 or higher. For the final analysis, tables, figures and listings will be provided in separate documents with own table of contents. For the interim analyses the separation is not mandatory. A minimum font size of 8 points will be used for the tables and figures, corresponding to a linesize of 140 digits and a pagesize of 52 lines for an output in DIN A4 format. For listings, a standard font size of 8 points with the linesize and pagesize as defined above will be used to produce the output in DIN A4 format.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) for those patients with data available. Additionally, the 1st and the 3rd quartiles (Q1 and Q3, respectively) may be calculated in some cases.

All summary statistics will be presented to one decimal place more than the raw value, except for the minimum and maximum values that will be presented with the same decimal precision as the raw value. Percentage values are to be presented to one decimal place.

Percentages will be presented with two decimal places. For the calculation, The number of all patients in a specified population or treatment group is used as denominator. The denominator will be specified in a footnote to the tables for clarification if necessary.

For qualitative variables (i.e. categorical data), the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a “Missing” category.

Content of free-text fields will only be provided in listings but not in tables.

If the eCRF is changed by deletion of existing items, by addition of new items or by change of the response options for an item, this information will be given in the footer of the table along with the number of subjects affected by the change of the eCRF.

Courier New will be used as font for all tables, figures and listings. In headings and titles only the first word will be capitalised. Missing data will be represented on patient listings as blank field or ".". Listings will be sorted by subject number unless specified otherwise.

3.1 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh.mm.

If dates are partially given, they will be completed, if necessary for the calculation of durations, according to a worst-case imputation. Deviations will be documented and explained.

All assessment dates will be related to the surgery visit. The surgery day is defined as day 0 (D0) and denoted by V01. The screening visit, which may be up to 28 days prior to surgery (Day -28 to 0) is abbreviated as SC. The 10 follow-up visits (V02-V11) are denoted as follows in Table 3:

Table 3: Time Windows

Visit name:	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11
Indicative Days:	Up to 28 days before surgery	D0	D1	D3	D10 +/- 1 Day	D30 +/- 5 Days	D60 +/- 5 Days	D90 +/- 10 Days	D120 +/- 10 Days	D180 +/- 10 Days	D240 +/- 10 Days	D360 +/- 10 Days

3.2 Coding Systems and Conventions

3.2.1 Separation of Medical History from Concomitant Diseases

Separation of medical history from concomitant diseases will be done according to the stop date of the finding in comparison to implantation date. Each finding will be allocated unambiguously either to medical history or to concomitant diseases.

- **Medical history:** If the stop date is before implantation of the ARGOS-IO pressure sensor, the medical condition is allocated to medical history.
- **Concomitant diseases:** If the stop date is at or after implantation of the ARGOS-IO pressure sensor, the medical condition is allocated to concomitant diseases. Furthermore, if the stop date is missing or partially given and not unambiguously before start of

treatment, the worst case is assumed. Consequently, the medical condition is allocated to concomitant diseases.

3.2.2 Separation of Previous from Concomitant Medication

Separation of previous from concomitant medication will be done according to the start and stop date of medication in comparison to implantation date. Each medication will be allocated unambiguously either to previous or to concomitant medication.

- **Previous medication**: If the stop date is before implantation of the ARGOS-IO pressure sensor, the medication is allocated to previous medication.

- **Concomitant medication:** If the stop date is at or after implantation of the ARGOS-IO pressure sensor, the medication is allocated to concomitant medication. Furthermore, if the stop date is missing or partially given and not unambiguously before start of treatment, the worst case is assumed. Consequently, the therapy is allocated to concomitant medication.

3.2.3 Coding of Adverse Events and Medical History

Adverse event and medical history terms are assigned to a lowest level term (LLT) and a preferred term (PT). Furthermore, they will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities version in effect at the time the database is closed.

3.2.4 Coding of Medications

Previous and concomitant medications will be given based on different Anatomical Therapeutic Chemical Classification [ATC] code levels as well as by generic name.

4. Analysis Populations and Subgroups

4.1 Analysis Populations

Within the framework of this study, the following two main populations are analysed:

- **Safety Population:** consists of all patients with attempted implantation of the ARGOS-IO implant, whether or not successful.

- **Full Analysis Set (FAS):** The FAS population comprises all subjects in whom an ARGOS-IO pressure sensor was successfully implanted. Measurements recorded by the patient will not

be included into the evaluation of the FAS population. Additional information about the drop-outs: all patients who revoke their consent and agreement preoperatively will be regarded as screen failures and will not be included in the statistical evaluation. All patients who revoke their consent and agreement postoperatively will be considered withdrawals and their data will be evaluated in the safety analysis.

4.2 Subgroups

In order to investigate the impact of certain characteristics on performance, the co-primary endpoints will also be examined by the following variables in the final analysis if meaningful:

- Gender (Male/Female)
- Post-surgery complications (Yes/no)
- Successful implantation (Yes/No)
- Age groups (<67 years/≥67 years)
- Concomitant medication (Yes/No)
- Pre-treatment (Yes/No)
- Size of ARGOS-IO implant (11.3 mm/11.7 mm/12.1 mm)
- Country of investigational site
- Educational level (Primary/Intermediate/A-Level/University/Vocational/Other).

A subgroup analysis will not be performed for a subgroup, if the subgroup is too small to provide meaningful results. For example, this is the case if all subjects are in the same subgroup.

5. Data Handling

5.1 Handling of Missing Data

All data of the patients will be used as available. All analyses will be performed on observed cases only. Missing data will not be replaced. Implausible values will be only excluded from the analysis if reasonable. The reason for exclusion will be given in the footer of the table or description of the figure.

5.2 Handling of Withdrawals and Drop-outs

For the analysis of the primary safety endpoint, 22 patients are required. If withdrawals and drop-outs occur after the implantation of the ARGOS-IO, a recalculation of the critical value for the decision rule of Simon's Design is necessary. The recalculation will be performed based on the method described by Simon (Simon, 1989).

5.3 Handling of Multiple Comparisons and Multiple Primary Variables

A statistical test will be only performed for the primary safety variable. The primary performance variable is not evaluated by using a statistical test but analysed by descriptive and explorative statistical methods. None of the other variables will be tested in a deductive sense. Thus, no multiple testing problems may evolve.

5.4 Data Review

A data safety monitoring board (DSMB) will be established prior to enrolment of the first patient. The DSMB is to review the safety data, including SAEs/SADEs, on a regular basis or if a SADE occurs, and will advise on any changes required in the conduct this clinical investigation. The DSMB will also review the data of the interim analysis and give recommendations to the Sponsor to either continue the clinical investigation (with or without an amendment of the clinical investigation plan) or to stop enrolment into the clinical investigation based on safety concerns.

The first meeting is planned when the 11 patients in the first stage have completed their 3 month follow-up visits. Enrollment will be halted to allow the DSMB to review their data and for changes to be made to the clinical investigation plan, if recommended. The DSMB may hold additional meetings whenever deemed appropriate.

6. Variables for Analysis

6.1 Demographics and Baseline Characteristics

The following assessments shall be performed at Visit 0 and analysed as baseline values:

- Demographic and baseline characteristics including year of birth, sex, race, weight, height, child-bearing potential, educational level,, and source of patient referral
- Previous and concomitant medications
- Medical history and glaucoma medical history including length of time since diagnosis of glaucoma and anti-glaucoma medication
- Ophtalmic examinations including
    - visual acuity measurments
    - anterior segment measurements
    - posterior segment measurements

- anterior segment abnormalities
- posterior segment abnormalities
- intraocular pressure using Goldmann Applanation Tonometry (GAT)
- other examinations (e.g optical biometry)

6.2 Primary Safety Variables

For the assessment of the primary safety endpoint, the number of patients who experienced a SADE within the 3 months following implantation is examined. A SADE 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:
  - resulted in death, permanent damage or disability or a congenital anomaly,
  - was life threatening,
  - required hospitalization or intervention to prevent permanent impairment or damage.

6.3 Primary Performance Variables

To evaluate the performance of the ARGOS-IO system compared to GAT from day 30 through day 180, limits of agreement between IOP measurements made using GAT and measurements made using the ARGOS-IO system will be examined from V05 (day 30) through V09 (day 180).

6.4 Secondary Safety Variables

Evaluation of the secondary safety objectives include the assessment of the incidence, nature, seriousness, severity and duration of both adverse events and adverse device effects in the 3, 6 and 12 months immediately following implantation of the ARGOS-IO pressure sensor.

6.5 Secondary Performance Variables

Assessment of the secondary performance variables include

- Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system from Visit 10 through Visit 11
- Incidence of observed of device malfunctions in the 3, 6 and 12 months following implantation
- User acceptance of the implantation procedure by means of evaluation of the implantation procedure questionnaires (investigators)
- User acceptance of the ARGOS-IO system at the investigational site by means of evaluation of the investigator acceptance questionnaires (investigators)
- User acceptance of the ARGOS-IO system at home by means of evaluation of patient acceptance questionnaires (patients) at Visit 11
- Daily IOP self-measurement profiles (patients).

6.6 Other Variables

Other assessed variables are:

- Surgery and lens transplantation variables
- Variables regarding complications during surgery
- Ophtalmic examinations at the follow-up visits including
    - visual acuity and visual field measurements
    - anterior segment measurements
    - posterior segment measurements
    - anterior segment abnormalities
    - posterior segment abnormalities

7. Statistical Analysis Methods

7.1 Evaluation of Demographics and Baseline Characteristics

7.1.1 Disposition of Patients

The number and percentage of screened, enrolled and implanted patients, as well as those who complete the follow-up will be tabulated for the safety population and FAS. The number and percentage of screen failures and early withdrawals will also be tabulated, along with the reason for the screen failure or drop-out.

7.1.2 Demographics

Demographic data and baseline characteristics listed in section 6.1 will be presented using standard descriptive statistics, i.e. summaries (n, mean, standard deviation, median, minimum and maximum) for quantitative variables and absolute as well as percent frequencies (n, %) for qualitative (i.e categorical data). The analysis is based on the FAS.

7.1.3 Medical History, Concomitant Diseases, Previous and Concomitant Medication

Glaucoma related medical history will be assessed separated from medical history. The time since diagnosis of glaucoma will be displayed in days using statistical summaries (n, mean, standard deviation, median, minimum and maximum). The duration will be calculated as follows:

Time since diagnosis = Date of surgery (V01) – Date of diagnosis + 1

Absolute and relative frequencies (n, %) of subjects will be used for presenting the type of glaucoma and other related questions with categorical response options.

Medical history and concomitant diseases not related to glaucoma will be described based on MedDRA system organ class and preferred term levels. Absolute and relative frequencies (n, %) of subjects will be provided.

Absolute and relative frequencies (n %) of subjects with previous and concomitant medications will be given based on different Anatomical Therapeutic Chemical Classification [ATC] code levels. Absolute and relative frequencies (n %) will be given. Medical history, concomitant diseases as well as previous and concomitant medication will be presented based on the FAS.

7.2 Evaluation of Primary Safety Variables

Incidence of SADEs in the 3 month period immediately following implantation will be assessed. The decision on safety follows the rule of Simon's optimal two-stage design (parameters: α=0.05, β=0.20, p_0 = 0.75, p_1 = 0.94). A corresponding 95% confidence interval will be given for the portion of SADEs within the safety population. The confidence interval for the SADE rate will be calculated using the method proposed by Koyama (Koyama & Chen, 2008). These calculations will be based on the number of patients experiencing a SADE based on the safety population. If the obtained confidence interval does not include any value lower than 0.94, it can be concluded that the SADE rate is at most 6%.

7.3 Evaluation of Primary Performance Variables

The primary performance objective is the assessment of the agreement between measurements made using GAT and the ARGOS-IO system from V05 (day 30) through V09 (day 180). If multiple ARGOS-IO system measurements have been made at time points for which paired GAT/ARGOS-IO system measurements are to be compared, the mean of the replicate ARGOS-IO system measurements will be used for agreement evaluation. The agreement evaluation is based on the assumption, that the measurements are constant over the measurement period.

The Bland-Altman method, which compares the mean of paired measurements to their difference will be used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with the ARGOS-IO system and GAT. The two-sided 95% confidence intervals for each of these limits will be calculated using the Mover method (Zou, 2011) to account for repeated measurements. IOP values will be displayed as Bland-Altman plots of individual measurement pairs by measurement technique for each individual participant as well as mean plots over time (per visit and overall).This analysis is based on the FAS and is repeated for each subgroup as described in section 4.2.

7.4 Evaluation of Secondary Safety Variables

Safety will be described in detail by frequency, seriousness, severity, nature and duration of adverse events based on the safety evaluation set. Number of adverse events as well as the number and relative frequency of patients reporting adverse events will be tabulated by system organ class and preferred terms. The same table will be prepared for serious adverse events. In addition, the number and relative frequency of patients reporting adverse events will be tabulated by system organ class and preferred terms in dependence on the worst severity and worst causal relationship. Furthermore, number of adverse device effects as well as the number and frequency of patients reporting adverse device effects will be tabulated by system organ class and preferred

terms and not by event description as stated in the protocol Separate tables will be provided for events occurring 3, 6 and 12 month following implantation.

SADEs. SAEs leading to discontinuation as well as the nature and duration of AEs will be provided in listings only. The duration of adverse events will be calculated as follows:

Duration of AE = Stop date of AE – Start of AE + 1.

7.5 Evaluation of Secondary Performance Variables

All secondary performance variables will be analysed on the basis of the FAS population.

7.5.1 Limits of Agreement

Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system from V10 (day 240) through V11 (day 360) will be assessed. If multiple ARGOS-IO system measurements have been made at time points for which paired GAT/ARGOS-IO system measurements are to be compared, the mean of the replicate ARGOS-IO system measurements will be used for agreement evaluation. The agreement evaluation is based on the assumption, that the measurements are constant over the measurement period.

The Bland-Altman method will be used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with the ARGOS-IO system and GAT. The two-sided 95% confidence intervals for each of these limits will be calculated using the Mover method (Zou, 2011) to account for repeated observations. IOP values will be displayed as Bland-Altman plots of individual measurement pairs by measurement technique for each individual participant as well as mean plots over time (per visit and overall).

7.5.2 Device Malfunctions

Performance of the ARGOS-IO system after 3, 6 and 12 months will be assessed by means of incidence of observed device malfunctions. Number of device deficiencies as well as the number and relative frequency of patients reporting device deficiencies will be tabulated by event description.

7.5.3 Implantation Procedure Questionnaire

The acceptance of the implantation procedure will be assessed by the implantation procedure questionnaire, which is completed after surgery. Non free-text fields of the questionnaire will be summarised by absolute and percent frequencies (n, %). Free-text fields will be only displayed in listings.

7.5.4 Investigator Acceptance Questionnaire

The acceptance of the ARGOS-IO system by the investigator will be assessed by the user acceptance questionnaire, which is completed by the investigator at Visit 11. Non free-text fields of the questionnaire will be summarised by absolute and percent frequencies (n, %). Free-text fields will be only displayed in the listings.

7.5.5 Patients Acceptence Questionnaire

The acceptance of the ARGOS-IO system by patients at home will be assessed by the patient acceptance questionnaire, which is completed by the patient at Visit 11. Non free-text fields of the questionnaire will be summaries by absolute and percent frequencies (n, %). Free-text fields will be displayed in the listings only.

7.5.6 Self-measurement Patient Profiles

Measurements recorded by the patient will not be included into the evaluation of the FAS population.

7.6 Evaluation of Other Variables

7.6.1 Surgery and Lens Transplantation

Variables related to lens and surgery will be assessed using appropriate descriptive summary statistics for categorical data.

7.6.2 Complications during Surgery

Variables related to complications during surgery will be presented using alsolute and relative frequencies (n, %).

7.6.3 Ophtalmic examinations

will be presented using standard descriptive statistics, i.e. summaries (n, mean, standard deviation, median, minimum and maximum) for quantitative variables and absolute as well as percent frequencies (n, %) for qualitative (i.e categorical data).

8. Special Statistical/Analytical Issues

8.1 Interim Analysis

All 22 patients will be enrolled consecutively, until a serious adverse device effect (SADE) occurs. In that case, the DSMB will be called, and decides whether the enrollment can be continued or not.

An interim analysis will be performed after half of the study population (11-14 subjects) is enrolled with a minimum follow-up of 1 month. Another interim analysis to assess Safety and Performance will be performed, when all patients have completed the 3 month follow-up visit, the 6 month follow-up visit and every time an SADE occurs.

In order to take the principle of the two-stage design described by Simon into account, the trial will be terminated if more than 1 patient out of the first 11 patients enrolled experience at least one SADE during the first 3 months of the post-surgical follow-up period.

For the interim analyses, the report will comprise the following tables and listings specified in the DSMB charter from 3rd June 2014:

- Information on patient screening – number of screening failures
- Patient recruitment by month and by institution
- Eligibility violations
- Summary tables:
    - Baseline characteristics including
        - Date of informed consent signatures
        - Demographics (Age, Gender, Race)
        - Weight, Height
        - Anterior and posterior segment examination results and abnormalities
        - GAT measurement
    - Number of subjects with Adverse events by System Organ Class and Preferred terms
        - Serious adverse events
        - Adverse events
        - Device-related adverse events
    - Medical history (Year of Glaucoma diagnosis, Type of Glaucoma, Study Eye, Previous/concomitant illnesses, conditions and procedures)
    - Concomitant medications
    - Anterior and posterior examination results and abnormalities (follow-up visits)
    - Surgery documentation including
        - Complications

        - Incision location
        - Iridectomy
        - IOL Implantation and location of the IOL haptics
        - ARGOS-IO pressure sensor implantation and location of ASIC
    - In situ position of IOL and ARGOS-IO implant at all relevant follow-up visits
    - GAT measurements (V01, V02, V03, V04)
    - GAT and ARGOS-IO serial measurements (V05, V06, V07)
    - Protocol deviations
    - Device Deficiencies, if any
    - Unscheduled Visits, if any
    - Premature termination of patients including date and reason
    - Pregnancy reports, if any

8.2 Changes in the Planned Analysis

Departing from the planned analysis, the first DSMB meeting was conducted after 6 patients had completed Visit 4. The sponsor of this trial was enlightened that it is necessary to increase the overall sample size if this first DSMB meeting corresponds to a prepond analysis of the first stage of Simon's two stage design in order to maintain the type I and type II error. The report provided for this DSMB meeting comprised the listings and tables in the DSMB charter plus a table summarizing the compliance of subjects.

The second DSMB meeting was conducted after 11 patients completed Visit 5 (one month after implantation of the medical device). The report provided for this DSMB meeting comprised the listings and tables in the DSMB charter minus the summary of anterior segment examination results, posterior examination results, GAT measurements and ARGOS-IO measurements.

The first interim analysis independent from the DSMB was conducted after 21 subjects completed Visit 5 (one month after implantation of the medical device). The report provided comprised the listings and tables in the DSMB charter plus:

- Summaries of visual field and visual acuity results at screening and follow-up visits
- More detailed information about medical history, concomitant illnesses and previous/concomitant medications
- More detailed information about adverse events
- Additional summaries of GAT measurements and ARGOS-IO measurements including limits of agreement per visit and for all visits

The limits of agreemement were provided in a separate document with corresponding table and figures. If multiple ARGOS-IO system measurements have been made at time points for which paired GAT/ARGOS-IO system measurements were to be compared, the mean of the replicate ARGOS-IO system measurements were used for agreement evaluation. Subsequently, this analysis was repeated by using the first replicate ARGOS-IO system measurement instead of the mean of the replicate measurements.

The second interim analysis independent from the DSMB was conducted after all subjects completed Visit 9 (6 months after implantation of the medical device). The report provided comprised the same tables and listings as the report for the interim analysis conducted after 21 subject completed Visit 5.

A. APPENDICES

List of Tables

List of Figures

A detailed list of figures is not provided here. Planned figures are:

- Disposition of patients
- Bland-Altman plots of individual measurement pairs
- Bland-Altman plots over time (Visit 02 to Visit 11 plus overall)
- Bland-Altman plots for subgroups (if meaningful)

List of Listings