STATISTICAL ANALYSIS PLAN

ARGOS-03

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

Sponsor: Implandata Ophthalmic Products GmbH
Kokenstrasse 5
30169 Hannover
Germany

Author: Dr. Andreas Beust
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen, Germany

Date of document: 05/MAY/2022

Document version: 1.0

Document History

Version	Date	Author(s)	Description
0.1	18/DEC/2020	Andreas Beust	First draft version
0.2	17/MAR/2022	Andreas Beust	Final draft Besides minor editorial changes, the following sections were adapted: • Section 4.2: Subgroups were further specified. • Section 6.2: Derivation of time since implantation added. • Section 7.3.3: Time to onset is calculated based on date of implantation. • Section 7.4.2: Time since implantation added to other patient characteristics. • Section 7.5: Clarification that device malfunctions will be identified among device deficiencies by a medical expert. • Section 7.7: AEs of special interest and eye-related AEs will be identified by a medical expert. Analysis by eye was added. • Section 7.8 Clarifications that external eye photography is not part of this SAP. • Appendix: Tables for subgroup analysis added.
1.0	04/MAY/2022	Andreas Beust	Final version (Only minor editorial changes)

Signatures

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

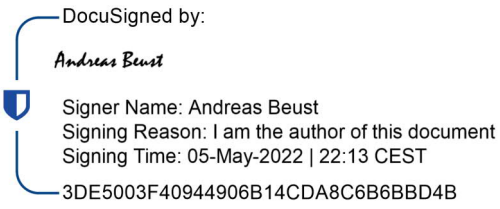
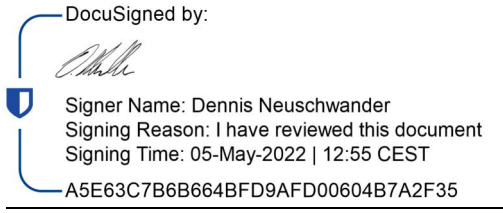
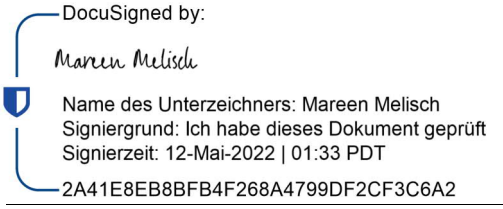
Author:	Andreas Beust, PhD Head of Biostatistics GCP-Service Int. Ltd & Co. KG Anne-Conway-Straße 2 28359 Bremen, Germany	 Signature
Reviewer:	Dennis Neuschwander, MSc Senior Biostatistician GCP-Service Int. Ltd & Co. KG Anne-Conway-Straße 2 28359 Bremen, Germany	 Signature
Approved:	Mareen Melisch Clinical Study Manager Implandata Ophthalmic Products GmbH Kokenstraße 5 30169 Hannover, Germany	 Signature

Table of Contents

List of AbbreATCviations and Key Terms

ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BMO-MRW	Bruch's Membrane Opening Minimum Rim Width
CIP	Clinical Investigation Plan
CYL	Cylindrical Component
D	Diopter
DCT	PASCAL Dynamic Contour Tonometry
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
GAT	Goldmann Applanation Tonometry
IOP	Intraocular Pressure
logMAR	Logarithm of the minimum angle of resolution
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
miss	missing
MRSE	Manifest refraction spherical equivalent
N	Number of subjects
n	Number of non-missing observations
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
OCT	Optical Coherence Tomography
PDF	Portable Document Format
POAG	Primary Open Angle Glaucoma
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RNFLT	Retinal Nerve Fiber Layer Thickness
RTF	Rich Text Format
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SE	Spherical Equivalent

SOC	System Organ Class
SPH	Spherical Component
WHO-CC	World Health Organisation Collaborating Centre for Drug Statistics Methodology

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 Clinial Investigation Plan ARGOS-03, revision B, dated 11/JAN/2018. The purpose of the SAP is to serve as a guideline for statistical programming and creation of the analysis tables, figures and listings for the clinical investigation plan. The SAP is finalised and signed prior to hard lock of the database and start of the statistical analysis.

2. Study Design and Objectives

2.1 Study Design

This is a prospective, open-labeled, multicenter clinical follow-up investigation of the ARGOS-IO pressure sensor to evaluate the long-term safety and performance of the ARGOS-IO system in patients with primary open angle glaucoma (POAG).

The ARGOS-IO system was developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor (intraocular pressure, IOP) patients with diagnosed glaucoma, or elevated or instable IOP that places them at a risk of ocular damage and loss of visual acuity. It is intended to be implanted during cataract surgery, and to remain in place indefinitely. Because the sensors are implanted in the eye, the ARGOS-IO pressure sensor measures IOP directly, without interference from corneal properties or due to operator skill.

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

As a result of these tests and the ARGOS-01 study, modifications were made to the form of the device and the implantation procedure to improve the device's safety profile. The ARGOS-02 study investigated the safety and performance of the ARGOS-IO system (second generation) in patients with primary open angle glaucoma. Over a one-year period, 22 patients undergoing phacoemulsification and IOL implantation for cataract received ARGOS-IO implants in an add-on procedure. Their eye condition and IOP were followed over the course of 12 months. The reported results indicate that the modifications to the sensor design implemented after the ARGOS-01 trial as well as the introduction of an injector device for the implantation of the ARGOS-IO pressure sensor

have led to a significant improvement of the safety and performance profile of the investigational device.

This trial is designed to obtain additional data on the long-term safety and performance of the ARGOS-IO system through the observation of patients previously implanted with the ARGOS-IO system as part of the ARGOS-01 and ARGOS-02 clinical trials. Up to five (5) patients of the ARGOS-01 and up to 21 patients of the ARGOS-02 study will take part in the study. All patients were implanted in their respective study with the ARGOS-IO implant in one eye only, which will be considered the study eye. All patients will be followed for 36 months.

2.2 Treatments

Only patients that participated in the ARGOS-01 or ARGOS-02 study may be enrolled in this study. All potential patients have therefore already been implanted with the ARGOS-IO implant as part of their previous study participation. No additional treatment is envisaged for the ARGOS-03 trial.

2.3 Trial Schedule

All enrolled patients are seen according to the following schedule.

Visit 01	Day 0
Visit 02	Day 180 (± 3 weeks)
Visit 03	Day 360 (± 3 weeks)
Visit 04	Day 540 (± 3 weeks)
Visit 05	Day 720 (± 3 weeks)
Visit 06	Day 900 (± 3 weeks)
Visit 07	Day 1080 (± 3 weeks)

Table 1, shown below, lists all assessments to be done at the respective study visits for patient or study eye.

Table 1: Visit Schedule

Visits	V01	V02	V03	V04	V05	V06	V07
Indicative Days (D)	D0	D180 +/- 3 wks	D360 +/- 3wks	D540 +/- 3wks	D720 +/- 3wks	D900 +/- 3wks	D1080 +/- 3wks
General							
Informed Consent	X						
Handout of the patient diary	X						
Demographics	X						
Past and current significant medical history	X						
Comparative measurements	X						
Check of the functionality of the Mesograph and Multiline Connector	X						
Confirmation of the correct function of the ARGOS-IO sensor	X						
Visual acuity (EDTRS)[1] *(both eyes)*	X	X	X	X	X	X	X
Perimetry *(both eyes)*	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Eye related AEs/ADE/SAE/SADE	X	X	X	X	X	X	X
NEI VFQ-25	X		X		X		X
Device deficiency		X	X	X	X	X	X
Check patient diary for completeness		X	X	X	X	X	X
Anterior Segment (both eyes)							
External eye photography (Slit lamp)	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X
Optical coherence tomography[2]	X	X	X	X	X	X	X
Corneal endothelial cell density	X	X	X	X	X	X	X
Gonioscopy	X	X	X	X	X	X	X
Posterior Segment (both eyes)							
Funduscopy	X	X	X	X	X	X	X
Optical coherence tomography[3]	X	X	X	X	X	X	X
Fundus photography[4]	X		X		X		X
IOP measurement[5]							
Goldmann Applanation *(both eyes)*	X	X	X	X	X	X	X
Pascal DCT *(both eyes)*	X	X	X	X	X	X	X
ARGOS-IO clinic	X	X	X	X	X	X	X
ARGOS-IO home[6]	X	X	X	X	X	X	X

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

[2] Anterior segment OCT is performed to assess the central cornea thickness and to evaluate effects on change in chamber angle after implantation.
[3] Posterior segment OCT is used to assess macular structures and the peripapillary nerve fibre layer thickness (RNFLT) and (if possible) BMO-MRW
[4] The fundus should be photographed in order to document potential changes to the optic nerve (cup/disc ration) and nerve fibre layer (red-free illumination).
[5] IOP-measurements will be performed in series of 2 GAT measurement (with difference more than 2mmHg, a third GAT-measurement is required) and 3 directly consecutive measurements with the ARGOS-IO system followed by 2 Pascal tonometry (with difference more than 2mmHg, a third DCT-measurement is required) and 3 directly consecutive measurements with the ARGOS-IO system.
For the non-study eye, only GAT and DCT measurements will be performed as described above.
All measurements should be performed directly one after another.
[6] Measurements at home shall be taken at least 4 times per day (morning, noon, afternoon, evening). Once a month, an "IOP day" will be scheduled with measurements every hour and additionally one-hour pre and post drug administration. The activities on that day will be documented in a patient dairy.
Optional: Quarterly additional night measurements on one of the "IOP days". Patients will be supplied therefore with the MESOGRAPH antenna patch which will do the measurements automatically.

2.4 Study Objectives

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

2.4.1 Primary Performance Objective

The primary performance objective of this trial is to evaluate the performance of the ARGOS-IO system compared to Goldmann Applanation Tonometry (GAT) and Pascal Dynamic Contour tonometry (DCT) by means of their limits of agreement.
Additionally, incidences and nature of observed device malfunctions of the ARGOS-IO system will be evaluated.

2.4.2 Primary Safety Objective

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

2.4.3 Secondary Objectives

The following secondary objective have been defined for this trial:

- Evaluation of patient compliance in intraocular pressure (IOP) self-monitoring
    - Daily self-measurements with the ARGOS-IO sensor should be done at least 4 times daily (morning, noon, afternoon, evening)

- Evaluation of the impact of IOP self-monitoring on glaucoma progression
    - Parameters to evaluate the glaucoma progression are visual field, cup/disc ratio, OCT of the optic nerve and the IOP
- Evaluation of incidences in glaucoma medication change
- Evaluation of the number of unscheduled visits due to self-measured increased IOP
    - The patients decide to come for a visit by their own due to any reason. This will be documented

2.5 Study Hypothesis

All analyses will be performed in an exploratory and descriptive manner. Therefore, no study hypothesis was defined for this trial.

2.6 Handling of Screen Failures and Drop-outs

All patients having participated in the ARGOS-01 or ARGOS-02 are eligible for this study. Any of these patients not willing to participate in this study will not be replaced. Any patient willing to participate in this study will be considered enrolled.

If an enrolled patient discontinues the study prematurely or is lost to follow-up, the patient is considered a drop-out. Patients who drop out before completion of the study at Visit 07 (day 1080) will not be replaced.

2.7 Randomization and Stratification

No randomisation or stratification is applied.

2.8 Blinding

No blinding procedures are applied.

2.9 Sample Size Calculation

Given the exploratory nature of this study, the sample size is not driven by the need for a formal statistical hypothesis test with a certain degree of power and no formal sample size calculation had been performed. Instead, this study is driven by the desire to obtain a clinically meaningful amount of data to evaluate the long-term safety and performance of the ARGOS-IO system in patients who have already been implanted with the study device. Therefore, the maximum sample size is 26. This maximum sample size is composed of maximal 5 available subjects from the ARGOS-01 study and

maximal 21 available subjects from the ARGOS-02 study. It is envisaged to enroll all of these subjects.

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

2.10 Planned Interim or Sequential Analysis

No interim analyses will be performed.

2.11 Handling of Changes to Study Protocol

Any change which is not only editorial but indicates a change in the statistical analyses planned in the clinical investigation plan (CIP) will be justified and documented at least in the SAP text part if it was decided before database close.

Any change made to the statistical analysis after database close might be described in a new version of the SAP but has to be justified and documented at least in the final clinical investigation report. It has to be specified that these changes occurred after database close and whether they were data-driven or not.

3. Technical Aspects and Coding Conventions

All programs will be written using SAS® version 9.4 or higher. There will be an individual SAS® program written for each table, figure and listing. Each analysis program will be validated by a second qualified SAS® programmer to ensure a correct output and a correct presentation of the data. The validation process is documented and filed in the Trial Master File.

All relevant outputs of the SAS® programs will be transferred into RTF documents with DIN A4 format and saved as write-protected PDF documents with a table of content preceding the content of the file. There will be one RTF/PDF document for tables, one for figures and one for listings. The font size should be consistent within each document and reasonable, i.e., there should be as much required information as possible on one page, but the text should be still easy to read.

In headings, titles and listings only the first word will be capitalised. Whenever data are derived, and the derivation method is not obvious from the information given in the header, a footnote should be added to clarify the derivation method. A footnote should also be considered if additional information facilitates the interpretation of the data.

Patient listings will be sorted by site and patient ID unless specified otherwise. Furthermore, derived data will be marked by "#" in patient listings, while missing data will be represented as blank field. If data from a patient is presented by visit, only attended visits will be listed.

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.

Missing or incomplete dates will not be completed. For additional considerations towards the time allocation of diseases and therapies, refer to Sections 3.2.2 and 3.2.4.

3.2 Coding Systems and Conventions

3.2.1 Coding of Adverse Events and Medical History

All medical terms reported as adverse events (AE) or as medical history/concomitant disease are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed for the final analysis. At least the primary system organ class (SOC) as well as the preferred term (PT) should be available for the statistical analysis.

3.2.2 Separation of Medical History from Concomitant Diseases

Separation of past and current medical conditions will be done by comparison of the stop date of the medical condition with the date of study start (Visit 01). Each medical condition will be allocated unambiguously either to medical history or concomitant diseases.

- **Medical history:** If the stop date is before the date of study start (Visit 01), the medical condition will be allocated to medical history. If the stop date is partially given and unambiguously before study start, the medical condition will also be allocated to medical history. Furthermore, if the stop date is missing and the medical condition is not known to be active at start of study participation, findings coded as "Surgical and medical procedures" will also be allocated to medical history.
- **Concomitant diseases:** If the stop date is at or after the date of study start or the medical condition is active at start of study participation, the medical condition will be allocated to concomitant diseases. Furthermore, if the stop date is missing and the medical condition is not known to be active at the start of study participation, findings **not** coded as "Surgical and medical procedures" will be allocated to concomitant diseases.

3.2.3 Coding of Medications

Concomitant medications will be coded using the Anatomical Therapeutic Chemical classification system provided by the WHO Collaborating Centre for Drug Statistics Methodology (WHO-CC). At least the ATC level 2 and 3 should be available for the statistical analysis.

3.2.4 Separation of Past from Concomitant Medications

Separation of past and concomitant medication will not be performed as only concomitant medication will be recorded for this study.

4. Analysis Populations and Subgroups

4.1 Analysis Populations

All patients enrolled in this study will be included in the analysis. No additional analysis sets are defined.

4.2 Subgroups

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

- Size of ARGOS-IO implant (outer diameter of: 11.3 mm, 11.7 mm or 12.1 mm)
- Gender (male, female)
- Age groups (≤70 years at Visit 01, >70 years at Visit 01)
- Educational level (A-Level, Intermediate, Primary, University, Vocational, Other)

A subgroup analysis for the respective subgroups will only be performed if at least two of the features contain five (5) or more patients.

4.3 Stratification

No general stratification will be applied. Only subgroup analyses will be performed for subgroups described in Section 4.2.

5. Data Handling

5.1 Handling of Missing Data and Outliers

Missing data will not be imputed, and data will only be analysed as available.

During data recording and manual data checks, queries may be raised regarding implausible data. All queries will be closed prior to the hard lock of the database. The investigator will either confirm or correct the value. Subsequently, the corrected or confirmed value will be used for the analysis.

5.2 Handling of Data from Withdrawals and Drop-outs

Data of withdrawals and drop-outs will be used as available.

5.3 Handling of Multiple Comparisons and Multiple Primary Variables

Given the exploratory nature of this study, no confirmatory statistical tests are done, and no multiple comparisons will be performed.

5.4 Data Review

There will be no data review meeting. All open queries and issues will be resolved prior to the hard lock of the database. All open questions/discrepancies for a patient that cannot be solved (even after consultation of the corresponding investigator (if applicable)), will be provided in a list to the sponsor for a case-by-case evaluation before hardlock.

Protocol deviations will be identified in a joined effort by the Sponsor, Project Management, Data Management, Clinical Monitors and Statisticians and provided in a protocol deviation listing.

6. Variables for Analysis

6.1 Disposition

- Number of subjects enrolled
- Number of subjects who completed the study (according to protocol)
- Number of subjects who discontinued the study including the reason for discontinuation
- Number of subjects who discontinued the study for reasons associated with COVID-19
- Number of subjects per visit
- Time to discontinuation / study completion

6.2 Demographics and Other Patient Characteristics

The following demographic and other patient characteristics will be evaluated:

- Demographic information (race, sex, age, weight, height, BMI, educational level)

  Since only the year of birth is recorded in the eCRF, the age of subjects will be calculated as follows:

  Age = Year of Visit 01 – Year of birth.

The BMI is automatically calculated in the eCRF as follows:

$$BMI = \text{Weight [kg]} / (\text{Height [m]})^2$$

- Time since implantation in months

  Time since implantation = (Date of Visit 01 – Date of implantation + 1) ÷ 30.4375

  with 1 month counted as 30.4375 days (=360.25 days / 12 months)

- Medical history, concomitant diseases and concomitant medications
- Glaucoma medication

6.3 Primary Performance Variables

The following primary performance variables are planned to be evaluated:

- Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system at each study visit
- Limits of agreement between IOP measurements made using DCT and the ARGOS-IO system at each study visit
- Incidences of observed device malfunctions and nature of device malfunction

6.4 Secondary Performance Variables

The following secondary variables are planned to be evaluated:

- Glaucoma progression over the course of the study evaluated by change in
  - visual field
  - cup/disc ratio (horizontal and vertical)
  - OCT results for the optic nerve
  - IOP
- Number of changes in glaucoma medication
- Number of unscheduled visits due to self-measured increased IOP

6.5 Primary Safety Variables

The following safety variables are planned to be evaluated:

- Incidences of medical device related adverse events
- Incidences of medical device related serious adverse events

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

6.6 Other Variables

The following additional variables are planned to be evaluated:

- Visual acuity (BCVA, sphere, cylinder, axis) at each visit
- Score for the National Eye Institute Vision-related Quality of Life Questionnaire – VFQ-25 at the respective visit
- Device deficiencies
- External eye photography results at each visit
- Slit-lamp biomicroscopy results at each visit
- Funduscopy results at each visit
- Gonioscopy results at each visit
- Corneal endothelial cell density at each visit
- Central corneal thickness at each visit
- Comparative measurements performed in the clinic between study end of ARGOS-01/ARGOS-02 and Visit 01 (GAT vs. ARGOS-IO)
- Position of IOL and ARGOS-IO pressure sensor
- IOP self-measurements (Analysis is not part of this SAP but will be done by the Sponsor)

7. Statistical Analysis Methods

7.1 Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n), number of missing observations (miss), arithmetic mean, standard deviation (SD), lower quartile (Q1), upper quartile (Q3), minimum (min), median, and maximum (max) for those patients with data available.

For categorical variables, the number (n) and percentage (%) of patients per category will be the default summary presentation, and, if applicable, the number of missing values is provided in a "Missing" category. For the number of missing values, only patients that attended the respective visit will be counted. Percentages will be calculated using a denominator of all patients with non-missing data. If necessary, the denominator will be specified in a footnote to the tables for clarification.

All tables including calculation of change over time (Visit 01 vs Visit 02 – Visit 07) will also include summary tabulations for the raw values of the respective variable analysed.

In case of analyses per eye, results will be grouped by study eye / fellow eye instead of right eye / left eye.

7.2 Rounding Rules

7.2.1 Estimates of the Mean and Standard Deviation

When using actual data, the mean and standard deviation will both be calculated to at least 2 extra places than the actual data and the result will be rounded to one more decimal place than the original data.

When using derived data, i.e., data already derived from actual data, results are calculated to at least one more decimal place than these derived data and subsequently rounded to the same number of decimal places as the used values.

7.2.2 Other Data

Quartiles as well as the confidence interval and median will be presented with the same number of decimal places as the mean. Minimum and maximum will be presented with the same number of decimal places as the data used. For estimates of proportions, the result will be rounded to 3 decimal places. If proportions are displayed as percentage, 1 decimal place will be displayed. For example, a proportion of 0.655 will be presented in percentage as 65.5%.

7.3 Data Derivation

7.3.1 Change Over Time

Whenever the change over time is analyzed, the result at the start of the time period of interest (usually Visit 01) is subtracted from the result at the end of the time period of interest (usually Visit 02 – Visit 07)

7.3.2 Study Days and Durations

Study days and, if applicable and meaningful, durations will be determined by comparing the respective date to the date of the first study visit (Visit 01).

- If the respective date is on or after the date of the first study visit:

  Study day/Duration = date (e.g. date of visit) - date of first study visit + 1
- If the respective date precedes the date of the first study visit:

  Study day/Duration = date (e.g. date of medical history event) – date of first study visit

7.3.3 Time to Onset and Duration of Adverse Events

Time to onset and duration of adverse events will be calculated as follows:

- Time to onset = start date of AE - date of implantation of ARGOS-IO pressure sensor +1
- Duration of adverse event = stop date – onset/worsening date + 1

7.3.4 Time to Discontinuation / Study Completion

Time to discontinuation / study completion will be calculated as follows:

- Time to discontionuation / study completion = date of Visit 07 / discontinuation - date of first study visit + 1

7.3.5 Derivation of Other Variables

Manifest refraction spherical equivalents will be derived from their cylindrical and spherical components according to the following formula:

MRSE = Spherical component [D] + 0.5 cylindrical component [D]

Cylindrical component (CYL) of manifest refraction can be indicated as plus CYL diopter using plus cylinder notation or alternatively, as minus CYL value at axis rotated through 90° using minus cylinder notation. Both notations are equivalent, but including both notations in the same analysis leads to incorrect estimate of mean of spherical (SPH) and of CYL variables. The conversion from one notation to the other influences also the spherical component of spherocylindrical correction. Therefore, a conversion of cylindrical compotent, sphere and axis are required in case data was recorded in minus notation. To convert minus into plus notation, the following formula is used:

SPH' = SPH + CYL

CYL' = -CYL

Axis' = Axis + 90°

In case the resulting axis value (Axis') is greater or equal to 180°, 180° will be subtracted to determine the final axis value. No changes will be made to positive notations.

Best corrected visual acuity (BCVA) will be provided in Snellen. For preparation of summary statistics, these will be converted to logMAR according to Holladay[a] as follows:

1) Convert Snellen visual acuity to equivalent decimal acuity (e.g. 20/40 = 0.50)
2) LogMAR = -log(Decimal acuity)

[a] Holladay, J.T. (1997): Proper Method for Calculating Average Visual Acuity. J Refract Surg 13:388-91.

7.4 Evaluation of Demographics and Other Patient Characteristics

7.4.1 Disposition of Patients

Subject disposition will be tabulated including the numbers of subjects enrolled, number of subjects completing the study (according to protocol), number of subjects who discontinued the study (including the reason for discontinuation) and the number of subjects who discontinued the study early due to COVID-19. Percentages will be calcuted based on the number of subjects enrolled in the trial, except for the tabulation of reasons for discontinuation and number of subjects discontinuing due to COVID-19, where the percentages will be based on the number of subjects who discontinued the study early.

The number of subjects attending the respective visit as well as the time to discontinuation / study completion calculated as described in Section 7.3.2 will further be tabulated. A flow-chart detailing the number of subjects at the different visits and the reason for discontinuation will be prepared.

7.4.2 Demographics and Other Patient Characteristics

Demographic information and other patient characteristics (i.e. age (year of birth), gender at birth, race, weight, height, BMI and educational level) will be summarized using summary statistics (N, mean, SD, median, minimum, maximum, upper and lower quartile) for continuous variables (i.e. age, weight, height, BMI, time since implantation) or absolute and relative frequencies (n, %) for categorical variables (i.e. gender at birth, race, educational level).

7.4.3 Medical History, Concomitant Diseases and Concomitant Medications

Absolute and relative frequencies (n, %) of medical history and concomitant diseases will be described based on MedDRA system organ class (SOC) and preferred term (PT) levels by related body system. Results will be prepared by frequency of occurrence.

Absolute and relative frequencies (n, %) of concomitant medication will be provided based on Anatomical Therapeutic Chemical (ATC) Classification code levels 2 and 3 separately for glaucoma medication and other medications. Only medications ongoing at screening or with start date during the study will be considered, all other medications will be listed only.

7.5 Evaluation of Primary Performance Variables

Limits of agreement

The Bland-Altman method, which compares the mean of paired measurements to their difference, will be used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with the ARGOS-IO system and GAT. The agreement evaluation will follow

the publication of Zou (2011)[b]. Zou describes two cases, namely Case I for the assumption that the true value varies over time and Case II for the assumption that the true value is constant over time. Case I requires a pairing of measurements between devices while Case II requires no pairing. Since within each visit only one series of GAT measurements is done and GAT measurements are done consecutively followed directly by the measurements with the ARGOS-IO system, no pairing is possible, and Case II is assumed for the evaluation for data within a visit. By assumption of Case II, it is not necessary to calculate the mean of each series with the respective device, but data can be used as available for the analysis per visit. Please note that this procedure differs from the CIP since it was originally assumed that several series of measurements per visit would be available. The two-sided 95% confidence intervals for each of the agreement limits will be calculated using the Mover method to account for repeated observations. In case of the overall analysis, available data of all visits are included under assumption of Case I since it can not be assumed that the IOP is constant between visits. For this purpose, the mean of each measurement series will be calculated and used for evaluation of limits of agreement as described in the CIP. IOP values will be displayed as Bland-Altman plots of individual measurement pairs by measurement technique for each visit and overall. The limits of agreement between the ARGOS-IO system and DTC measurements will be also calculated by the described procedure.

The difference of measurements between the ARGOS-IO measurements and GAT / DTC will further be summarized per visit using descriptive statistics. The difference per subject will be calculated as the difference between mean of ARGOS-IO values and mean of GAT / DTC values of the same series (Difference = mean of ARGOS-IO values – mean of GAT/DTC values).

Device malfunctions

Device malfunctions will be identified among device deficiencies by a medical expert before start of the statistical analysis.

Incidence of observed device malfunctions and the nature of device malfunctions (based on components involved) will be summarized for subjects using the descriptive statistics defined in Section 7.1. The number of subjects with malfunction including percentage based on all subjects enrolled, and the number of events will be provided. In addition, the rate of device malfunctions per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that

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

the number of such device malfunctions is Poisson distributed. The procedure will be analogous to the procedure for incidence rates of AEs (see Section 7.7).

7.6 Evaluation of Secondary Variables

Progression analysis

Summary statistics for raw values and change over time will be provided for visual field, cup/disc ratio and IOP (for all types of measurements) by eye and visit. Frequency tabulations (absolute and relative) will be prepared for OCT results for the optic nerve over the course of the study, by eye and visit. The denominator for the calculation of relative frequencies will be the number of subjects attending the respective visit.

Changes in glaucoma medication

Any glaucoma medication with a start date at or after first visit (V01) will be regarded as new and/or changed glaucoma medication. Analysis for incidence rates of changes in glaucoma medication will be performed analogue to the analysis for incidence rates of AEs (see Section 7.7). The rate of changes in medication per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that the number of such events is Poisson distributed.

Unscheduled visits due to self-measured increase of IOP

Analysis of number of unscheduled visits due to self-measured increased IOP will be performed analogue to the analysis for incidence rates of AEs (see Section 7.7). The rate of unscheduled visits due to self-measured increase of IOP per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that the number of such events is Poisson distributed.

7.7 Evaluation of Primary Safety Variables

All recorded AEs will be coded using the MedDRA version in effect at the time the database is closed. Events that undergo worsening or improvement (i.e., changes in severity) prior to resolution will be evaluated as single events using the worst severity reported during its course. Only eye-related AEs will be included in the analysis while remaining AEs will be listed only. The categorization of AEs into eye-related / not eye-related will be done by a medical expert before start of the statistical analysis. In addition, it will be determined whether the eye-related AE occurred in the study eye or fellow eye under consideration of all information recorded for the AE in the eCRF. If an eye-related AE can not unequivocally be assigned to an eye, it will be assigned to the study eye.

Incidences will be calculated for eye-related AEs, medical device related AEs and, in case there are more than five (5) events, also for medical device related SAEs on the system organ class level and on the preferred term level, in total (i.e., number and percentage of subjects with any/respective AE and number of any/respective AE) and by worst severity and seriousness (i.e., number and

percentage of subjects with any/respective AE). In case of the analysis of all eye-related AEs, the analysis will be done by eye (study eye / fellow eye) and overall.

In order to evaluate the long-term safety, the incidence rate of medical device related adverse events per 10 patient years and accompanying exact 95% confidence intervals will be calculated, assuming that the number of such adverse events is Poisson distributed. The incidence rate per 10 patient years will be calculated as 10 times the number of medical device related AEs divided by the number of patient years. Patient years will be defined as the sum of the individual on-study times from first visit (V01) until date of study completion/last attended study visit / last medical device related adverse event (whichever is later).

This calculation will also be done for AEs of special interest and medical device related SAEs. The definition of AEs of special interest will be done by a medical expert prior to start of the statistical analysis.

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

7.8 Evaluation of Other Variables

Visual acuity

Summary statistics for raw values and change over time will be provided for best corrected visual acuity (BCVA). Results will be presented by eye and visit.

Additionally, summary statistics for raw values and change over time will be provided for subjective and objective refraction (spherical and cylindrical component, axis) and for visual field deviation. Results will be presented by eye and visit.

National Eye Institute Vision-related Quality of Life Questionnaire

Evaluation of the NEI-VFQ-25 questionnaire will follow the description provided by Mangione[c]. First, response categories for each provided answer will be converted into scores ranging from 0 to 100 according to the official scoring key. These scores will then be averaged among all items belonging to the same subscale. Subscale scores will only be calculated if at least one of the contributing items was answered. A total of 12 subscale scores may be calculated, with missing items not being considered during averaging. Furthermore, the composite score which is defined as average of all vision-targeted subscale scores, excluding the general health rating, will be calculated.

[c] Mangione, C.M. (2000): National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25), Version 2000: NEI VFQ-25 Scoring Algorithm

Subscale scores and composite score as well as their change over time will be summarized by visit using summary statistics.

Device deficiencies

The analysis of device malfunctions is already described in Section 7.5. All other device deficiencies will be listed only.

External eye photography

The analysis of external eye photography is not part of this SAP but will be done by the Sponsor.

Slit-lamp biomicroscopy

All assessments will be listed only. Noteworthy abnormal findings will be reported as adverse events and will be analyzed as part thereof.

Funduscopy

Frequency (absolute and relative) of funduscopy abnormalities as well as abnormality details will be displayed for each examined area (macula, retina, optic nerve, other) by visit and eye. The denominator for the relative frequency will be the number of subjects attending the respective visit.

Gonioscopy

Frequency (absolute and relative) of Gonioscopy results will be displayed by visit and eye.

Corneal endothelial cell density

Summary statistics (raw values and change over time) for corneal endothelial cell density will be provided by visit and eye.

Central corneal thickness

Summary statistics (raw values and change over time) for central corneal thickness will be provided by visit and eye.

Comparative measurements performed in the clinic between study end of ARGOS-01/ARGOS-02 and Visit 01 (GAT vs. ARGOS-IO)

Values for comparative measurements performed in the clinic between study end of ARGOS-01/ARGOS-02 and Visit 01 (GAT vs. ARGOS-IO) will be listed since only a few data are expected.

Position of IOL and ARGOS-IO pressure sensor

Frequency (absolute and relative) of whether the IOL/ARGOS-IO pressure sensor were still in situ will be provided by visit.

IOP self-measurements

Analysis of IOP self-measurements is not within scope of this SAP and will be described at least in the clinical investigation report if results are included.

7.9 Special Analytical Issues

Unscheduled visits

Unscheduled visits may be performed, as necessary, to ensure the safety and well-being of subjects. Data from these visits will only be included in the patient listings but not in the statistical analysis tables and figures with the following exceptions:

- AEs
- Device deficiencies
- Concomitant medications
- Number of unscheduled visits due to increased self-measured IOP

8. Changes in the Planned Analysis

As only one series of measurements of IOP per type of IOP measurement and visit is available, the descsription of the analysis of the primary endpoint has been adapted to cover this case, in line with the guidance provided by Zhou et al., 2011.

APPENDIX

Tables

8.1 Study subjects

8.1.1 Disposition of subjects

8.1.1.1 Number of subjects enrolled

8.1.1.2 Number of subjects per visit

8.1.1.3 Duration of study participation

8.1.2 Demographics and other patient characteristics

8.1.3 Medical history and concomitant medication

8.1.3.1 Medical history by SOC and PT

8.1.3.2 Concomitant diseases by SOC and PT

8.1.3.3 Concomitant medications by ATC level

8.2 Performance

8.2.1 Comparison of intraocular pressure measurements (IOP)

8.2.1.1 IOP measurements with ARGOS-IO and comparators by visit

8.2.1.2 Limits of agreement between IOP measurements with ARGOS-IO and comparators by visit

8.2.1.3 Limits of agreement between IOP measurements with ARGOS-IO and comparators by subgroup and visit

8.2.2 Device malfunctions

8.2.2.1 Summary of device malfunctions

8.2.2.2 Summary of device malfunctions by subgroup

8.2.2.3 Device malfunctions per 10 patient years

8.2.3 Glaucoma progression by visit

8.2.4 Change in glaucoma medication

8.2.4.1 Summary of changes in glaucoma medication

8.2.4.2 Changes in glaucoma medication per 10 patient years

8.2.5 Unscheduled visits due to self-measured increased IOP

8.3 Safety data

8.3.1 Adverse Events (AEs) and device related adverse events (ADEs)

8.3.1.1 Overall summary of AEs

8.3.1.2 Overall summary of ADEs

8.3.1.3 Subjects with eye-related AEs and number of eye-related AEs by SOC and PT

8.3.1.4 Subjects with eye-related ADEs and number of eye-related ADEs by SOC and PT

8.3.1.5 Subjects with eye-related AEs by worst severity, SOC and PT

8.3.1.6 Subjects with eye-related ADEs by worst severity, SOC and PT

8.3.1.7 Subjects with eye-related AEs by seriousness, SOC and PT

8.3.1.8 Subjects with eye-related ADEs by seriousness, SOC and PT
8.3.1.9 Eye related ADEs per 10 patient years
8.3.2 Deaths and other serious / significant adverse events
8.3.2.1 Serious AEs, listing of subjects
8.3.2.2 Deaths, listing of all serious AEs of subjects who died
8.3.2.3 AEs leading to discontinuation, listing of subjects

8.4 Other data
8.4.1 Visual acuity assessments by eye and visit
8.4.2 Results of the National Eye Institute Vision-related Quality of Life Questionnaire (NEI VFQ-25) by visit
8.4.3 Ophthalmic examinations
8.4.3.1 Abnormalities detected by funduscopy by eye and visit
8.4.3.2 Gonioscopy results by eye and visit
8.4.3.3 Central corneal thickness and corneal endothelial cell density by eye and visit
8.4.4 Position of IOL and ARGOS-IO pressure sensor

The selection, naming and numeration of the tables is not mandatory but might be adapted in accordance with the described analyses in this SAP.

Figures

8.1 Study subjects
8.1.1 Flow chart of study disposition
8.2.1 Comparison of intraocular pressure measurements (IOP)
8.2.1.1 Limits of agreements between ARGOS-IO and Goldmann applanation tonometry (GAT)
8.2.1.1.1 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 01
8.2.1.1.2 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 02
8.2.1.1.3 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 03
8.2.1.1.4 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 04
8.2.1.1.5 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 05
8.2.1.1.6 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 06
8.2.1.1.7 Bland-Altman Plot (ARGOS-IO vs. GAT), Visit 07
8.2.1.1.8 Bland-Altman Plot (ARGOS-IO vs. GAT), overall
8.2.1.2 Limits of agreements between ARGOS-IO and PASCAL dynamic contour tonometer (DCT)
8.2.1.2.1 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 01
8.2.1.2.2 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 02

8.2.1.2.3 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 03
8.2.1.2.4 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 04
8.2.1.2.5 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 05
8.2.1.2.6 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 06
8.2.1.2.7 Bland-Altman Plot (ARGOS-IO vs. DCT), Visit 07
8.2.1.2.8 Bland-Altman Plot (ARGOS-IO vs. DCT), overall

The selection, naming and numeration of the figures are not mandatory but might be adapted in accordance with the described analyses in this SAP.

Listings

12.2 Subject data listings
12.2.1 Disposition of subjects
12.2.1.1 Site numbers and principal investigators
12.2.1.2 Informed consent
12.2.1.3 Visit dates and discontinuation
12.2.2 Protocol deviations
12.2.3 Demographics and other patient characteristics
12.2.4 Medical history and concomitant diseases
12.2.4.1 Medical history
12.2.4.2 Concomitant diseases
12.2.5 Concomitant medications
12.2.5.1 Glaucoma medication
12.2.5.2 Other concomitant medications
12.2.6 Performance
12.2.6.1 IOP measurements by visit
12.2.6.2 Device malfunctions
12.2.6.3 Glaucoma progression by visit
12.2.6.4 Unscheduled visits
12.2.7 Safety data
12.2.7.1 Adverse events listing
12.2.8 Other data
12.2.8.1 Best corrected visual acuity by eye and visit
12.2.8.2 National Eye Institute Vision-related Quality of Life Questionnaire (NEI VFQ-25) by visit
12.2.8.3 Device deficiencies
12.2.8.4 Ophthalmic examinations
12.2.8.4.1 Abnormalities detected by slit-lamp microscopy by eye and visit

12.2.8.4.2	Abnormalities detected by funduscopy by eye and visit
12.2.8.4.3	Gonioscopy results by eye and visit
12.2.8.4.4	Other examinations
12.2.8.5	Position of IOL and ARGOS-IO pressure sensor by visit
12.2.8.6	Comparative measurements performed in the clinic between study end of ARGOS-01/ARGOS-02 and Visit 01 (GAT vs. ARGOS-IO)

The selection, naming and numeration of the listings is not mandatory but might be adapted in accordance with the described analyses in this SAP.