A first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma undergoing non-penetrating glaucoma surgery

Reference Number: ARGOS-SC01

Statistical Analysis Plan (SAP)

Sponsor:	Implandata Ophthalmic Products GmbH Kokensstraße 5 30159 Hannover (Germany)
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Signature Page

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Ahlen, 15.07.2020 .....

Place and date

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Approval: Sponsor's Signature:

Berlin, 17.07.2020 .....

Place and date

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Content

1 Abbreviations

A	
ADE	*Device-related AE*
AE	*Adverse event*
AS	*Anterior Segment*
C	
CCT	*Central corneal thickness*
CIP	*Clinical Investigation Plan*
CRF	*Case report form*
CRO	*Clinical Research Organisation*
D	
DCT	*Pascal Dynamic Contour Tonometry*
E	
eCRF	*electronic case report form*
G	
GAT	*Goldman Applanation Tonometry*
M	
MMRM	*Mixed Model repeated measurement*
N	
NEI-VFQ	*National Eye Institute Visual Function Questionnaire-25*
O	
OCT	*Optical coherence tomography*
OPA	*Ocular Pulse Amplitude*
P	
PS	*Posterior Segment*

S

SADE	D*evice-related SAE*
SAE	*Serious adverse event*
SAP	*Statistical Analysis Plan*

V

V	*Visit*
VFQ-25	*National Eye Institute – Vision related Quality of Life Questionnaire-25*

2 Summary of clinical investigation

2.1 Title

A first in man, prospective, open-label, single arm, multicenter clinical investigation to assess the safety and performance of the ARGOS-SC suprachoroidal pressure sensor system in patients with glaucoma undergoing non-penetrating glaucoma surgery (ARGOS-SC01)

2.2 Study type

Interventional study

2.3 Study design

Single arm, open label, multicenter, prospective, clinical investigation

2.4 Inclusion Criteria

1. Subjects able to understand the informed consent and willing to participate as evidenced by providing informed consent.

2. Male or female aged ≥ 18 years on the day of screening.
   Female subjects of childbearing potential (not surgically sterilized or more than one year post-menopausal) must be willing to use adequate contraception throughout the trial and must have a negative pregnancy test (urine beta-hCG) within 24 hours prior to ARGOS-SC pressure sensor implantation

3. Diagnosis of open angle glaucoma requiring a non-penetrating glaucoma surgery (NPGS). The medical indication for a non-penetrating glaucoma surgery must be given irrespective of the study participation. Potential study patients will be solicited for participation in the clinical trial only after the patient has given consent to the non-penetrating glaucoma operation.

4. Subjects able and willing to attend all scheduled visits and comply with all study procedures.

2.5 Exclusion Criteria

1. Contraindications for a non-penetrating glaucoma surgery
    a. Neovascular glaucoma, primary and secondary angle closure glaucoma
    b. Condition after previous glaucoma incisional surgery
    c. IOP > 40 mmHg
2. Myopia (> -6 dpt) or hypermetropia (> +4 dpt)
3. Axis length < 22 mm or > 26 mm
4. Patient with single eye vision (monovision)
5. Exudative age-related macular degeneration, instable macular degeneration 30 days prior to inclusion, or macular edema
6. Acute retinal detachment
7. Uncontrolled Diabetes Mellitus (DM) with manifestation of moderate to severe non-proliferative diabetic Retinopathy (DR) or proliferative DR.
8. History or evidence of severe active inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-SC implantation
9. Ocular surgery procedure(s) (excluding selective laser trabeculoplasty and peripheral iridotomy) within 6 months (cataract surgery within 3 months) prior to ARGOS-SC implantation in the study eye that can affect the assessment of IOP by Goldmann Applanation tonometry
10. Ocular disease other than glaucoma that may affect assessment of visual acuity and/or IOP by Goldmann Applanation tonometry/Pascal Dynamic Contour Tonometry (e.g. choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy)
11. Existence of other active medical eye implant and/or other active medical implants in the head/neck region
12. Difficulties or complications during NPGS procedure or implantation of ARGOS-SC sensor, as assessed by surgeon (e.g. perforation of trabeculo-descement's membrane; excessive aqueous filtration through TDM leading to shallow anterior chamber; excessive bleeding; choroidal detachment)
13. Severe generalized disease resulting in a life expectancy shorter than a year
14. Currently pregnant or breastfeeding
15. Participation in any study involving an investigational drug or device within the past 30 days or ongoing participation in a study with an investigational drug or device

16. Patients who are not suitable for the study based on the surgeon's evaluation (e.g. patients affected by Parkinson's disease or essential tremor)
17. Patients unable or unwilling to understand or comply with required study procedures
18. Patients with psychiatric disorders influencing their judgement or autonomy
19. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization.
20. Enrollment of the fellow eye in this clinical study

2.6 Study population

Patients with glaucoma and scheduled for non-penetrating glaucoma surgery

2.7 Study objective

2.7.1 Primary objective

Performance:

To evaluate the limits of agreement between measurements with Goldmann Applanation Tonometry (GAT), Pascal Dynamic Contour Tonometry (DCT) and the ARGOS-SC system in the 12 months following implantation.

2.7.2 Secondary objective

Safety:

To evaluate the safety and tolerability the ARGOS-SC pressure during implantation and throughout a 12 months follow-up period.

Performance:

To evaluate the performance of the ARGOS-SC system up to 12 months after implantation.

2.8 Study variables

2.8.1 Primary performance parameters

- GAT measurements (2 – 3 measurements) at visit V02 – V09
- ARGOS-SC system measurements (2 – 3 measurements) at visit V02 – V09 roughly contemporaneous with the GAT measurements
- Pascal DCT (2 – 3 measurements) at visit V05 – V09 (if available)
- ARGOS-SC system measurements (2 – 3 measurements) at visit V05 – V09 roughly contemporaneous with the Pascal DCT measurements

2.8.2 Safety parameters

- Device deficiency / device malfunction
- Adverse events (AE / ADE / SAE / SADE)

2.8.3 Further ophthalmological parameters

- 24-hours measurements inpatient with GAT and ARGOS-SC every 3 hours at visit V06, V07 and V09.
- User acceptance questionnaire for surgeon (7 items) at visit V01
- User acceptance questionnaire for investigator (24 items) at visit V09
- User acceptance questionnaire for patient (16 items) at visit V09
- Visual acuity (subjective and objective refraction, best corrected visual acuity on study eye at Screening and Visit V02 – V09
- Perimetry: Visual field on both eyes at Screening and visit V06, V07, and V09
- The ANTERION® from Heidelberg Engineering performed: no / yes at V04 – V09
- Anterior eye segment measurement on study eye:
  - Optical coherence tomography (OCT), Central cornea thickness (CCT) at Screening and visit V04 – V09
  - Slit-lamp biomicroscopy (Lids, Conjunctiva, Cornea, Anterior chamber, Iris Pupil, Lens, Anterior vitreous body) at Screening and visit V02 – V09
  - Gonioscpoy (angle open to (Shaffer), pigmentation of Trabecular meshwork)

- Posterior eye segment measurement:
  - Biomicroscopy (dilated, fundus) on study eye at Screening and visit V02 – V09
  - Optical coherence tomography (OCT) on both eyes at Screening and visit V06, V07, and V09

2.8.4 Further study variables

- Inclusion criteria at Screening
- Exclusion criteria at Screening
- Demographic data at Screening
- Educational level at Screening
- Medical history at Screening
- Glaucoma anamnesis at Screening
- Previous glaucoma medication (stopped before implantation) (Mock-up Table 3a)
- Concomitant glaucoma medication from V01 – V09 (Mock-up Table 3b)
- Other previous medication (stopped before implantation)
- Other concomitant medication from V01 – V09
- Pregnancy test (for female subjects of childbearing potential) at Screening and before surgery
- Surgery related data (study eye, examination prior surgery, ARGOS-SC implantation, Intraocular lens implantation, complications)
- Visual Function Questionnaire (VFQ-25) at Screening and visit V06, V07, and V09

2.9 Study endpoints

2.9.1 Primary endpoints

Performance:

Level of agreement between measurements made using GAT and the ARGOS-SC system at visit V02 - V09.

The concordance of the intraindividual measurement values of GAT and ARGOS-SC will be indicated by the concordance correlation coefficient r_{ccc} (4.6.1), separate for each visit

Additionally, the absolute difference between the GAT and ARGOS-SC measurement will be scaled in ≤ 5mmHg and > 5 mmHg and the frequency distribution will be displayed (4.6.1, Table 2).

The Bland-Altman (mean-difference) plot and a X-Y plot should illustrate the comparison of the two methods (4.6.1, Figure 1).

The level of agreement between Pascal DCT and ARGOS-SC will be evaluated analogously.

2.9.2 Secondary endpoints

Safety:

- Number of patients experiencing a device-related SAE (SADE) at any time during implantation and in the first 12 months (day 0 to day 360) following it.
- Incidence, nature, severity and seriousness of observed adverse events (AE) and adverse device events (ADE) at any time during implantation and in the 12 months following it.

Performance:

- Repeatability of the ARGOS-SC measurement.
- Comparison of OPA measurements with the repeatability of the ARGOS-SC measurement
- Incidence, nature and seriousness of observed device malfunctions during implantation and in throughout a 12 months follow-up period.

Utility:

- User acceptance of the ARGOS-SC implantation procedure by means of evaluation of implantation procedure questionnaires (surgeon)
- User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of patient acceptance questionnaires (by investigators)
- User acceptance of the ARGOS-SC system at home by means of evaluation of patient acceptance questionnaires (patients)

2.9.3 Further endpoints

NEI VFQ-25 questionnaire:

The 25 items will be converted to a 0 (= worst response) to 100 scale (= best response). Then, the items within sub-scale will be averaged to create 12 sub-scale scores:

- General health (1 item: question 1)
- General vision (1 item: question 2)
- Ocular pain (2 items: question 4 and 19)
- Near activities (3 items: question 5, 6, and 7)
- Distance activities (3 items: question 8, 9, and 14)
- Vision specific: Social functioning (2 items: question 11 and 13)
- Vision specific: Mental health (4 items: question 3, 21, 22 and 25)
- Vision specific: Role difficulties (2 items: question 17 and 18)
- Vision specific: Despendency (3 items: question 20, 23 and 24)
- Driving (2 items: question 15c, 16)
- Color vision (1 item: question 12)
- Peripheral vision (1 item: question 10)

2.10 Study Flow Chart

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09
Indicative Days (D) Visit window	**Up to 28 days before surgery**	**D0**	**D1**	**D3 - 1/+ 2 days**	**D10 +/- 1 day**	**D30 +/- 5 days**	**D90 +/- 10 days**	**D180 +/- 15 days**	**D270 +/- 15 days**	**D360 +/- 15 days**
GENERAL										
Informed consent signed	X									
Allocation of subject 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]								
Non-penetrating glaucoma surgery and ARGOS-SC pressure sensor implantation		X								
Vision related Quality of Life (VFQ-25) questionnaire	X						X	X		X
Visual acuity (ETDRS)[3]	X		X	X	X	X	X	X	X	X
Perimetry[4] (OU)	X						X	X		X
Heidelberg Engineering ANTERION®					X	X	X	X	X	X
External eye photography[5]	X				X	X	X	X	X	X
Implantation procedure questionnaire (surgeon)		X								
User acceptance questionnaire (patient)										X
User acceptance questionnaire (investigator)										X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
AE/ADE/SAE/SADE		X	X	X	X	X	X	X	X	X
Device malfunction		X	X	X	X	X	X	X	X	X
ANTERIOR SEGMENT										
Optical Coherence Tomography[6]	X				X	X	X	X	X	X
Slit-lamp biomicroscopy[7]	X		X	X	X	X	X	X	X	X
Gonioscopy[9]	X						X	X		X

POSTERIOR SEGMENT										
Slit-lamp biomicroscopy[9]	X		X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)[10](OU)	X						X	X		X
Fundus photography[11]	X						X	X		X
Goldmann Applanation Tonometry[12]	X		X	X	X	X	X	X	X	X
Pascal Dynamic Contour Tonometry[12]	X					X	X	X	X	X
ARGOS-SC pressure sensor measurement[12]			X	X	X	X	X	X	X	X
24-hours measurements inpatient with GAT and ARGOS-SC over 24h[13]							X	X		X
ARGOS-SC pressure sensor self-measurement[14]		X	X	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.

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

[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] Anterior segment OCT is performed to evaluate effects on change in chamber angle after non-penetrating glaucoma surgery and to assess corneal thickness.

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

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

[11] Posterior segment biomicroscopy is performed by means of indirect ophthalmoscopy on a slit lamp with the aid of a 90D or “Superfield” or comparable lenses. For this examination the pupil needs to be dilated by the use of mydriatic agents. 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 thickness (RNFLT) and if possible Minimum rim width at Bruch membrane opening (BMO-MRW).

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

[14] V02 to V09 IOP measurements will be made in series of 2 GAT measurements (in case of a difference of more than 2 mmHg, a third GAT measurement is required) followed by 3 directly consecutive ARGOS-SC system measurements; *if DCT is available:* V05 to V09 additionally followed by 2 Pascal DCT measurements (in case of a difference difference of more than 2 mmHg, a third Pascal DCT measurement is required) and 3 directly consecutive ARGOS-SC system measurements.

[15] Patient’s admission at the site for a 24h series of measurements with GAT and ARGOS-SC sensor. Measurements with EYEMATE-SC sensor will be done automatically via an externa antenna**.** GAT will be done every three hours, if it is possible even at night. If night measurements are not possible every three hours at night, the last measurement should take place between 22 and 24 o’clock and the three-hours rhythm should be resumed between 5 and 7 o’clock on the next morning.

[16] All patients will receive a MESOGRAPH reading device after implantation in order to measure the IOP daily at home. Measurements will 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.

3 General Considerations

3.1 Responsibility

All tables, graphics and listings, and the statistical analysis will be produced by *CRO Dr. med. Kottmann GmbH & Co. KG*. The reconditioning / coding of diseases and drugs will be conducted by *Implandata Ophthalmic Products.*

3.2 Statistical Analysis Plan (SAP)

The Statistical Analysis Plan (SAP) will be finalized prior to data base lock. The SAP will incorporate all CIP amendments prepared for the study. In case of an amendment to the CIP after the SAP finalization date, an amendment to this SAP may be written.

The SAP will be produced and signed by CRO Dr. med. Kottmann GmbH & Co. KG and approved in writing by the sponsor.

3.3 Statistical analyses in SAS

All tables, graphics and statistical analyses will be performed using the statistical software SAS®, version 9.4.

3.4 Tables and graphics

The pertinent population of a table / graphic will be mentioned in the header.

3.5 Descriptive statistics

Descriptive statistics calculated for continuous variables will be

- number of patients
- number of valid patients
- mean
- standard deviation
- minimum
- maximum
- median
- percentiles (if indicated)

All continuous parameter will be tested for normal distribution by using Shapiro-Wilk-Test.

For categorical variables

- number of patients
- number of valid and/or missing values
- absolute frequencies (n)
- relative frequencies (%)

3.6 General missing data handling

In tables of continuous and categorial data the number of cases and the number of valid cases will be reported. The missing values will not be included in the calculation of percentages except when it appears reasonable on occasion.

If the calculation of periods requires the full date format dd-mm-yyyy, missing entries will be set to the first possible day of the month for a missing day. In case of a missing month, the first possible month of a year will be set.

3.7 Analysis populations

The following populations will be defined for analysis:

- **Safety-Analysis Set (SAF)**: The safety analysis set will comprise all patients that gave written informed consent to participate in the study and the ARGOS-SC pressure sensor implantation was attempted, defined as introduction of the ARGOS-SC pressure sensor into the study eye, whether or not the implantation was successful.
- **Per protocol set (PP)**

  The Per Protocol Set (PP) will comprise all subjects in whom an ARGOS-SC pressure sensor was successfully implanted and for whom the full data set including IOP measurements made in the clinic and safety data according to protocol are available until 3 months (V06) after surgery. Because IOP measurements conducted outside the clinic will be made at varying times under varying conditions, they are not anticipated to be comparable to those made in the clinic and will not be included in the Per-Protocol evaluation of agreement.

Performance analyses will be based on the SAF and PP, the safety analyses on the SAF.

3.8 Major protocol violations

In general, major protocol violations are

- Substantial violation of inclusion or exclusion criteria
- Missing primary or secondary performance parameters
- Extensive time window violation

4 Data Analysis

4.1 General methodological considerations

4.1.1 Methods for handling dropouts

All patients will be analysed as far as documented.

4.1.2 Methods for handling missing data

Missing data will not be replaced.

4.1.3 Methods for handling outliers

Outliers which cannot be justified will be excluded from the analysis.

4.1.4 Level of significance

All statistical test will be performed with a two-tailed alpha (α) of 0.10, all confidence intervals which will be calculated will be 95% confidence intervals.

Test results $p<0.05$ will be regarded as 'significant', test results with p-values $p<0.10$ as 'remarkable' or as 'trends / tendencies'.

4.1.5 Interim analysis

An interim analysis is planned when all patients have completed the follow-up visit V07 (day 180), an additional evaluation of safety and performance of ARGOS-SC implant is to be carried out after all patients have undergone the follow-up visit V06 (day 90). (Addendum I to Clinical Investigation Plan ARGOS-SC).

4.1.6 Equivalence / Non-inferiority study

Not applicable.

4.1.7 Subgroup analysis

In order to permit investigation of their impact on performance and safety, information will be collected prospectively on the following variables:

- Gender
- Medical History (primary underlying ophthalmic illness or injury necessitating the non-penetrating glaucoma surgery)
- Pre-treatment
- Concomitant medications
- Post-surgical complications
- Successful implantation
- Age groups
- Country of investigational site
- Educational level

Which subgroup analyses are actually performed will be decided at a final data review meeting preceding the statistical analysis, based on the actual distribution of subjects in the study population.

4.2 Definition of baseline and endpoints, and derived variables

Baseline values are determined in the Screening visit before the implantation procedure.

Post values are defined as the values after the implantation procedure.

Change from baseline (Δ) is defined as the difference between the baseline value obtained before implantation procedure and the post value after implantation procedure separately for each visit:

$$\Delta = \text{Post value} - \text{Baseline value}$$

Percent change from baseline is defined as the change from baseline divided by the baseline value times 100%:

$$\%\Delta = ((\text{Post value} - \text{Baseline value}) / (\text{Baseline value})) \times 100$$

In case of measurements / assessments before (pre) and after (post) implantation the change from baseline and the percent change from baseline (if indicated) will be calculated.

In case of ordinal scales, shift tables (before vs. after) may be used instead of differences.

4.3 Disposition of patients

The number and percentage of screened, enrolled, implanted subjects and those who complete the follow-up will be tabulated for the safety set. The number of screening failures and early withdrawals will be tabulated with the reason for termination. The reasons for premature termination are classified as follows:

- Death
- Adverse events / Serious adverse events
- Lost to follow-up
- Voluntary withdrawal not for adverse event
- Other

4.4 Demographic data and other baseline characteristics

- Inclusion criteria
- Exclusion criteria
- Demographic data
- Educational level
- Medical history
- Glaucoma anamnesis
- Concomitant glaucoma medication at start of study
- Other Concomitant medication at start of study
- Pregnancy test (for female subjects of childbearing potential)

4.5 Surgery data

Surgery related data (study eye, examination prior surgery, ARGOS-SC implantation, Intraocular lens implantation, complications)

4.6 Analysis of endpoints

4.6.1 Performance endpoints

The evaluation uses the following methods to analyze the agreement between two different measurement methods

Bland-Altman Plot:

Bland and Altman introduced the Bland-Altman plot to describe agreement between two quantitative measurements by constructing limits of agreement. These statistical limits are calculated by using the mean and the standard deviation (s) of the differences between two measurements. To check the assumptions of normality of differences and other characteristics, they used a graphical approach.

The resulting graph is a scatter plot XY, in which the Y axis shows the difference between the two paired measurements (x-y) and the X axis represents the average of these measures ((x+y)/2). In other words, the difference of the two paired measurements is plotted against the mean of the two measurements. Bland-Altman recommended that 95% of the data points should lie within ± 2s of the mean difference. This is the most common way to plot the Bland-Altman method.

The bias is computed as the value determined by one method minus the value determined by the other method. If one method is sometimes higher, and sometimes the other method is higher, the average of the differences will be close to zero. If it is not close to zero, this indicates that the two assay methods are systematically producing different results.

Concordance correlation coefficient

Concordance correlation coefficient (r_{ccc}) measures the agreement between two variables X and Y. Lawrence Lin has defined the form of the concordance correlation r_{ccc} as[1]

$$r_{ccc} = 2\, r\, s_x\, s_y / ((s_x^2 + s_y^2) + (m_x - m_y)^2)$$

with

$r = s_{xy}/(s_x\, s_y)$ (Pearson correlation coefficient)
m_x = mean of X
m_y = mean of Y
s_x = standard deviation of X
s_y = standard deviation of Y
s_{xy} = covariance of x and Y

The concordance correlation r_{ccc} has an range of -1 to 1. Values near +1 indicate strong concordance between *x* and y, values near -1 indicate strong discordance and values near zero indicate no concordance. There is no clear-cut agreement as to how to interpret the values, although one approach is to interpret Lin's r_{ccc} as for Pearson's correlation coefficient (e.g. values less than .20 are poor, while values greater than .80 are excellent).

The following values will be calculated:

- Calculation of the average of the (up to) 3 IOP measurements using GAT (GAT_{mean})
- Calculation of the average of the (up to) 3 IOP measurements using ARGOS-SC ($ARGOS1_{mean}$)
- Calculation of the average of the (up to) 3 IOP measurements using DCT (DCT_{mean})
- Calculation of the average of the (up to) 3 IOP measurements using OPA (OPA_{mean})
- Calculation of the average of the (up to) 3 IOP measurements using ARGOS-SC ($ARGOS2_{mean}$)
- Difference IOP_{d1}= $ARGOS1_{mean}$ - GAT_{mean}
- Mean IOP_{mean1}= ($ARGOS1_{mean}$ + GAT_{mean})/2
- Difference IOP_{d2}= $ARGOS2_{mean}$ - DCT_{mean}
- Mean IOP_{mean2}= ($ARGOS2_{mean}$ + GAT_{mean})/2

  $ARGOS1_{mean}$ / GAT_{mean} / IOP_{d1} (statistical parameters, concordance correlation coefficient r_{ccc}, Bland-Altman-Plot with IOP_{mean1} vs. IOP_{d1}, plot of $ARGOS1_{mean}$ vs. GAT_{mean}), separate for each visit

  $|IOP_{d1}| \leq 5$ mmHg (N, %)

  $ARGOS2_{mean}$ / DCT_{mean} / IOP_{d2} (statistical parameters)

  $|IOP_{d2}| \leq 5$ mmHg (N, %)

4.6.2 Safety endpoints

Incidences of adverse events stratified by:

- expectedness: expected event / unexpected event (N, %)
- severity: mild / moderate / severe (N, %)
- causal relationship to medical device: none / unlikely / possible / probable / definite (N, %)
- causal relationship to other: none / unlikely / possible / probable / definite (N, %)
- seriousness: yes / no (N, %)
- outcome: recovered / recovered with sequelae / recovering / not recovered / death / unknown (N, %)

(if indicated).

Incidences of device deficiency stratified by:

- involved component: ARGOS-SC sensor / MESOGRAPH reader (N, %)
- did this device deficiency involve the patient: no / yes (N, %)
- consequences of the device deficiency (ARGOS-SC sensor): none / recalibration / discontinued use / explanation (N, %)
- consequences of the device deficiency (MESOGRAPH reader): none / discontinued use / discontinued use with a replacement device (N, %)

4.6.3 Further endpoints

- User acceptance of the ARGOS-SC implantation procedure by means of evaluation of implantation procedure questionnaires (investigators) at V01 (statistical parameters)
- User acceptance of the ARGOS-SC system at the investigational site by means of evaluation of patient acceptance questionnaires (by investigators) at V09 (statistical parameters)
- User acceptance of the ARGOS-SC system at home by means of evaluation of patient acceptance questionnaires (patients) at V09 (statistical parameters)
- Repeatability of the ARGOS-SC measurement (statistical parameters)
- Concomitant glaucoma medication is shown separately as follows:
    - Previous glaucoma medication (stopped before implantation): in total (N,%) and stratified by ingredients (N, %) (Mock-up Table 3a)
    - Concomitant glaucoma medication (medication given during V01 – V09): in total (N, %) and stratified by ingredients (N, %) (Mock-up Table 3b)

- Other concomitant medication is shown separately as follows:
  - Previous medication (stopped before implantation): in total (N, %) and stratified by ingredients (N, %)
  - Concomitant medication (medication given during V01 – V09): in total (N, %) and stratified by ingredients (N, %)
- NEI VFQ-25 questionnaire:
  - 25 items in course of study (statistical parameters)
  - 12 sub-scales in course of study (statistical parameters)
  - Changes from baseline of the 12 sub-scales (statistical parameters)

  The changes from baseline of the 12 sub-scales will be analysed by means of paired t-Test (in case of normal distribution) or the Wilcoxon sign rank test (in case of non-normal distribution). The Mixed Model repeated measurement (MMRM) analysis of covariance for repeated measures in mixed models (V06, V07, V09 vs. Screening) will be used in addition.
- Daily IOP self-measurement profiles (patients) will not be included into the evaluation.

4.7 Other topics of data analysis: Coding

- Reconditioning / coding of adverse events, diagnoses, and concomitant diseases will be conducted by *Implandata Ophthalmic Products*
- Coding of concomitant medication by ingredients will be conducted by *Implandata Ophthalmic Products*

5 Mock-up tables and figures

Table 1(dummy data)

Demographic data		
Gender	N	50
	male	20 (40.0%)
	female	30 (60.0%)
Age [years]	N	
	Mean	
	Mean [95% CI]	
	Standard dev.	
	25.-Percentile	
	Median	
	75.-Percentile	
	Minimum	
	Maximum	

Table 2

IOP measurements: GAT and ARGOS-SC						
		Visit V02	**Visit V03**	**Visit V04**	**Visit V05**	**Visit V06**
GAT	N	22	22	21	22	17
	Mean	7.36	9.82	12.81	13.05	12.24
	Mean [95% CI]	5.03|9.70	7.19|12.45	10.45|15.17	10.93|15.16	10.13|14.34
	SD	5.26	5.93	5.18	4.78	4.10
	25.-Percentile	3.00	6.00	7.00	10.00	11.00
	Median	5.50	8.50	13.00	13.00	12.00
	75.-Percentile	9.00	12.00	17.00	17.00	14.00
	Minimum	2.0	2.0	6.0	4.0	4.0
	Maximum	24.0	27.0	22.0	24.0	19.0
ARGOS-SC	N	21	21	20	22	17
	Mean	8.24	10.52	15.05	14.95	12.65
	Mean [95% CI]	5.77|10.7	8.23|12.82	11.53|18.57	12.10|17.81	9.25|16.04
	SD	5.42	5.05	7.51	6.45	6.60
	25.-Percentile	5.00	7.00	8.50	11.00	9.00
	Median	7.00	9.00	15.50	14.50	12.00
	75.-Percentile	11.00	14.00	20.00	18.00	14.00
	Minimum	2.0	3.0	4.0	4.0	5.0
	Maximum	24.0	22.0	31.0	29.0	33.0
Difference	N	21	21	20	22	17
	Mean	0.81	0.71	2.20	1.91	0.41
	Mean [95% CI]	-0.17|1.79	-0.86|2.29	0.31|4.09	0.41|3.41	-1.84|2.67
	SD	2.16	3.47	4.05	3.38	4.39
	25.-Percentile	0.00	-2.00	-0.50	0.00	-2.00
	Median	1.00	1.00	2.50	2.00	0.00
	75.-Percentile	2.00	4.00	3.50	5.00	1.00
	Minimum	-2.0	-7.0	-5.0	-4.0	-4.0
	Maximum	6.0	6.0	13.0	7.0	15.0

IOP measurements: GAT and ARGOS-SC						
		Visit V02	**Visit V03**	**Visit V04**	**Visit V05**	**Visit V06**
Absolute difference	N	21	21	20	22	17
	≤ 5 mmHg	20 (95.2%)	18 (85.7%)	18 (90.0%)	17 (77.3%)	16 (94.1%)
	> 5 mmHg	1 (4.8%)	3 (14.3%)	2 (10.0%)	5 (22.7%)	1 (5.9%)
	r_{ccc}	0.91	0.80	0.76	0.78	0.68

Figure 1: Example Bland-Altman Plot (dummy data)

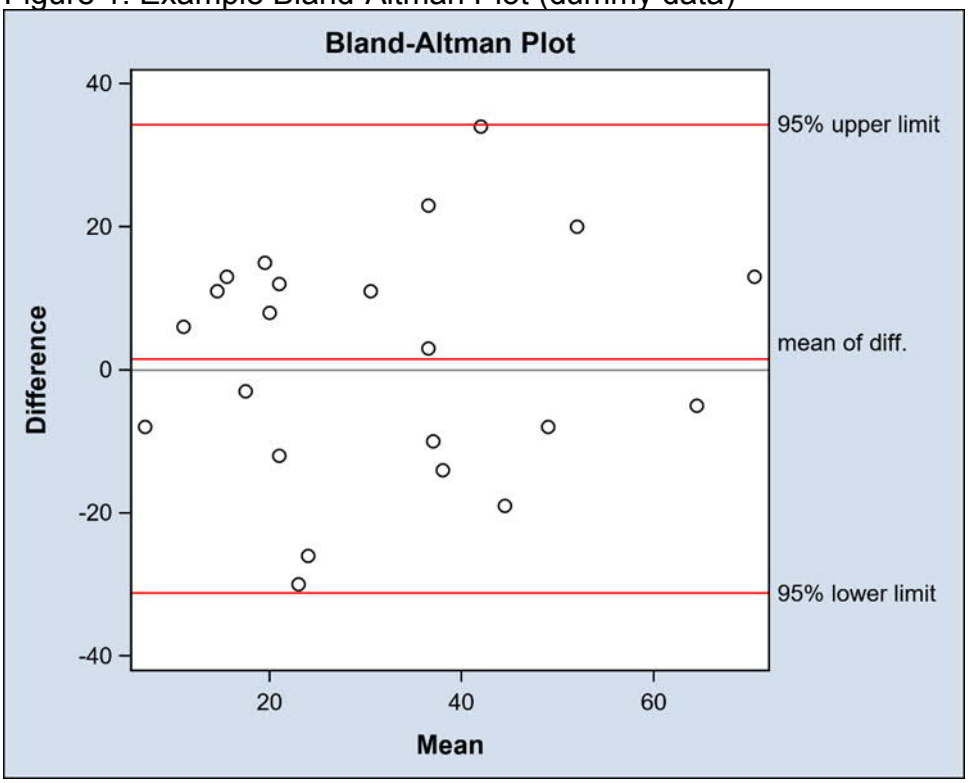

Table 3a

Previous medication due to glaucoma	
Drug / ingredients	
Brinzolamides	
….	
Total	N (%)

Table 3b

Concomitant medication due to glaucoma				
Drug / ingredients	**Begin**	**+**	**-**	**End**
Brimonidine	10	15	3	22
Brinzolamides				
Total				

Begin: administration at V01
\+ started during the study
\- stopped during the study
End: administration at end of study

6 References

[1]Lawrence I-Kuei Lin (March 1989). "A concordance correlation coefficient to evaluate reproducibility". Biometrics. 45 (1): 255–268