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Ophthalmic implants — Intraocular lenses —

Part 10: Phakic intraocular lenses

Implants ophtalmiques — Lentilles intraoculaires —

Partie 10: Lentilles intraoculaires phaques

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 11979-10 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

ISO 11979 consists of the following parts, under the general title *Ophthalmic implants — Intraocular lenses*:

— *Part 1: Vocabulary*

— *Part 2: Optical properties and test methods*

— *Part 3: Mechanical properties and test methods*

— *Part 4: Labelling and information*

— *Part 5: Biocompatibility*

— *Part 6: Shelf-life and transport stability*

— *Part 7: Clinical investigations*

— *Part 8: Fundamental requirements*

— *Part 9: Multifocal intraocular lenses*

— *Part 10: Phakic intraocular lenses*

Ophthalmic implants — Intraocular lenses —

Part 10:
Phakic intraocular lenses

1 Scope

This part of ISO 11979 is applicable to any intraocular lens (IOL) whose primary indication is the modification of the refractive power of a phakic eye, but excludes phakic IOLs (PIOLs) that utilize multifocal or other simultaneous vision optics to address presbyopic loss of accommodation and PIOLs that correct astigmatism.

This part of ISO 11979 addresses specific requirements for PIOLs not addressed in the other parts of ISO 11979.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11979-1, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

ISO 11979-2, *Ophthalmic implants — Intraocular lenses — Part 2: Optical properties and test methods*

ISO 11979-3, *Ophthalmic implants — Intraocular lenses — Part 3: Mechanical properties and test methods*

ISO 11979-4, *Ophthalmic implants — Intraocular lenses — Part 4: Labelling and information*

ISO 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11979-1, ISO 14155-1 and ISO 14155-2 apply.

4 Optical requirements

4.1 General

This clause applies to the optical properties and performance requirements of PIOLs in their final form, as intended for implantation in the human eye.

4.2 Dioptric power

The requirements of ISO 11979-2 apply.

4.3 Imaging quality

The requirements of ISO 11979-2 apply.

NOTE A modified bench (e.g. additional converging lens, a microscope objective of appropriate numerical aperture, etc.) can be needed to quantify the image quality of negative power PIOLs.

4.4 Spectral transmittance

The requirements of ISO 11979-2 apply.

5 Mechanical requirements

Where applicable to the PIOL design, the mechanical requirements given in ISO 11979-3 apply. Furthermore, an analysis of the location of the PIOL surfaces with respect to ocular tissue shall be conducted to establish the minimal anatomical dimensions acceptable for the design and the range of dioptric powers for which it applies.

NOTE Guidance for performing this analysis is provided in ISO 11979-3.

6 Clinical investigation

6.1 General

The general requirements for a clinical investigation given in ISO 14155-1 and the clinical investigation plan requirements in ISO 14155-2 apply. Additional requirements are given in 6.2 and in 6.3.

NOTE Annex A of this part of ISO 11979 contains suggested details concerning a clinical investigation.

6.2 Clinical assessments

The following assessments shall be considered for the clinical investigation plan:

a) visual acuity (VA);

b) refraction;

c) contrast sensitivity;

d) intraocular pressure;

e) corneal status;

f) iritis;

g) IOL decentration;

h) IOL tilt;

i) IOL discoloration;

j) IOL opacity;

k) cystoid macular edema;

l) hypopyon;

m) endophthalmitis;

n) pupillary block;

o) retinal detachment;

p) status of crystalline lens;

q) status of anterior chamber angle;

r) status of iris;

s) pupil size;

t) corneal thickness.

6.3 Other considerations

To minimize the risks associated with the clinical investigation of a new PIOL, subject enrollment shall occur in stages. The subject data from each stage shall be evaluated and found acceptable by the sponsor and the principal investigator prior to the continuation of the clinical investigation. Guidance on phased enrollment is included in Annex A.

Any plans for fellow eye implantation shall be described in the clinical investigation plan. Bilateral implantation shall not be implemented until initial safety and performance data have been collected and evaluated by the sponsor and the principal investigator.

The review of data from at least 50 eyes with six months of follow-up is recommended. Previous clinical experience, i.e. results from well-documented clinical investigations, could be adequate justification to begin bilateral implantation earlier in the study.

The clinical investigation plan shall contain descriptions of the surgical technique, the intraoperative use of ophthalmic viscosurgical devices, and the use of preoperative, intraoperative and postoperative medications. Any variations from these recommendations shall be recorded on the case report forms.

All subjects in a clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation, including subjects whose PIOL was removed or replaced, have reached the final reporting period.

Serious ophthalmic adverse events and all adverse device effects shall be reported using a special case report form and forwarded to the sponsor for investigation. A drop in best spectacle corrected visual acuity of two or more lines shall be considered a serious ophthalmic adverse event. All other ophthalmic adverse events shall be reported using the standard visit case report forms and are collected during monitoring.

If a specific calculation procedure is to be used to determine the appropriate power for implantation, the calculation procedure and its derivation shall also be included in the clinical investigation plan. Clinical data shall be evaluated at intervals during the investigation to refine the power calculation procedure, if necessary.

7 Information supplied by the manufacturer

The requirements of ISO 11979-4 apply, with the following additional information that shall be made available to the user:

a) a summary of the results of the clinical investigation, if any;

b) any recommendations for periodic evaluations after implantation, based on the risk analysis and/ or any clinical investigation performed;

c) any restrictions in the indications for use if necessitated by the anatomical clearance analysis and clinical evaluation.

The general requirements for information provided by the manufacturer with medical devices specified in EN 1041 [1] should be considered. Symbols can be used instead of text, where appropriate. When symbols are used, the requirements of ISO 15223 [2] and EN 980 [3] should be considered.

Annex A
(informative)

Clinical investigation

A.1 Objectives

The objectives of the clinical investigation are to determine the safety and performance of the PIOL.

A.2 Design

The type of clinical investigation recommended is a non-controlled study.

The clinical investigation plan should describe how subject visits in between reporting periods will be handled.

Each investigator should contribute a minimum of 20 subjects, but not more than 25 % of the subjects in the study.

A minimum study duration of three years is recommended to adequately evaluate the maintenance of endothelial cell density and the rate of cataract development. The clinical investigation plan should inform subjects and investigators that longer term follow-up could be necessary.

Guidance for accountability is provided in ISO 11979-7 [4].

A.2.1 Primary endpoint

The recommended primary endpoint is endothelial cell density.

The null hypothesis is that the true rate of decrease in endothelial cell density is less than or equal to the normal rate. The alternative hypothesis is that the true rate is greater than the normal rate. Sample size guidance using this endpoint is provided in Annex B.

A.2.2 Inclusion and exclusion criteria

A.2.2.1 Inclusion criteria

The following inclusion criteria for subjects should be considered:

a) subject meets specified refractive criteria (spherical and cylindrical components);

b) subject has specified minimum best spectacle corrected visual acuity (BSCVA) in each eye;

c) subject has uncorrected visual acuity (UCVA) 0,5 or worse;

d) subject has less than 0,75 D difference between cycloplegic and manifest refractions;

e) subject has had a stable refraction (± 0,5 D; ± 1,0 D for high refractive errors), as expressed by manifest refraction spherical equivalent (MRSE) for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history;

f) subject who is a current contact lens wearer, needs to demonstrate a stable refraction (± 0,5 D), expressed as MRSE, on two consecutive examination dates and stability of the refraction is determined by the following criteria:

   1) contact lenses were not worn for at least 2 weeks (rigid and toric contact lenses) or 3 days (soft contact lenses) prior to the first refraction,

   2) two refractions were performed at least 7 days apart;

g) subject, who is expected to have residual postoperative cylindrical refractive error of ⩾ 1 D, has been given the opportunity to experience his/her best spectacle vision with the anticipated correction.

A.2.2.2 Exclusion criteria

The following exclusion criteria for subjects should be considered:

a) subject has an acute or chronic disease or illness that would increase the operative risk or confound the outcome(s) of the study;

b) subject is taking systemic medications that can confound the outcome of the study or increase the risk to the subject;

c) subject has ocular condition that can predispose for future complications;

d) subject has had previous intraocular or corneal surgery;

e) subject with less than the minimum endothelial cell density (ECD) at time of enrollment as described by Table A.1;

f) subject with coefficient of variation of endothelial cell area ⩾ 0,45 (in both eyes);

g) subject is pregnant, plans to become pregnant, or is lactating during the course of the study, or has another condition associated with the fluctuation of hormones that could lead to refractive changes;

h) monocular subjects;

i) insufficient space for the intended implant;

j) subjects that are not adults.

Table A.1 — Recommended minimum ECD

Age at time of enrollment years	**Minimum endothelial cell density** cells/mm^2
21 to 25	2 800
26 to 30	2 650
31 to 35	2 400
36 to 45	2 200
⩾ 46	2 000
NOTE With the rate of endothelial cell density decrease unknown during the clinical investigation, minimum endothelial cell density values were selected for this table that are based on conservative assumptions in order to protect the subjects in the investigation. The recommended endothelial cell density (ECD) in this table represents the average minimum ECD necessary to leave 1 000 cells/mm^2 at 72 years of age assuming a 10 % surgical decrease and a yearly rate of decrease of 2 %.	

A.2.3 Enrollment of subjects

A.2.3.1 For clinical studies of a single refractive indication, the following phased enrollment plans are recommended.

a) Phase I: 10 subjects, followed for 6 months.

b) Phase II: 100 additional subjects. A clinical evaluation of all available data is done when 50 subjects have been followed for 6 months and all 110 subjects have been enrolled. If the performance of the PIOL is acceptable, the sponsor can begin the last phase of the investigation.

c) Phase III: remainder of the subjects.

A.2.3.2 For clinical studies of more than one refractive indication ongoing simultaneously, the following phased enrollment plans are recommended.

a) Phase I: 20 subjects (10 of each indication), followed for 6 months.

b) Phase II: 150 additional subjects (no more than 100 per indication). A clinical evaluation of all available data is done when 50 subjects with one indication have been followed for 6 months. If the performance of the PIOL is acceptable, the sponsor can begin the last phase of the investigation for that indication.

c) Phase III: remainder of the subjects for each indication.

A.2.3.3 Depending on the design of the refractive implant, a different phase-in can be appropriate. The data from each stage is evaluated and found acceptable by the sponsor and the principal investigator prior to proceeding to the next stage.

NOTE Previous clinical experience, i.e. results from well-documented clinical investigations, can be used as a justification to support faster enrollment.

A.2.4 Examination schedule

The following reporting periods are recommended for postoperative examination (see Table A.2):

a) preoperative (Preop);

b) operative (Op);

c) Day 1 (1 day);

d) Week 1 (5 to 9 days);

e) Month 1 (3 to 5 weeks);

f) Month 3 (10 to 14 weeks);

g) Month 6 (21 to 26 weeks);

h) Month 12 (11 to 14 months);

i) Month 18 (17 to 21 months);

j) Month 24 (23 to 27 months);

k) Month 30 (29 to 33 months);

l) Month 36 (35 to 39 months).

Table A.2 — Recommended postoperative examination schedule

Study	Preop	Op	Day 1	Week 1	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Distance UCVA	X		X	X	X	X	X	X		X		X
Distance BSCVA	X			X	X	X	X	X		X		X
Near VA with distance spectacle correction	X							X				X
Manifest refraction	X	X [a]		X	X	X	X	X		X		X
Cycloplegic refraction	X					X		X		X		X
Axial length	X											
Anterior chamber [b]	X						X					X
Intraocular pressure	X	X [c]	X	X	X	X	X	X		X		X
Slit lamp exam.[d]	X		X	X	X	X	X	X		X		X
Status of crystalline lens	X					X	X	X	X	X	X	X
Gonioscopic exam.	X						X	X		X		X
Fundus exam. with dilated pupil	X				X			X		X		X
Mesopic pupil size	X						X					X
Pachymetry of corneal thickness	X	X [e]					X					X
Keratometry [f]	X	X						X				X
Subject questionnaire	X						X	X	X	X	X	X
Specular microscopy	X						X	X	X [g]	X	X [g]	X
Substudies												
Contrast sensitivity [h]	X						X					X
Clearance analysis [i]	X					X						

Preop preoperative
Op operative
UCVA uncorrected visual acuity
BSCVA best spectacle corrected visual acuity
VA visual acuity
exam. examination

[a] For contact lens wearers.

[b] Distance from the posterior surface of the cornea to the anterior surface of the crystalline lens.

[c] Post-surgery operative day IOP measurements are considered if pupillary block is a possible complication.

[d] Tilt and decentration of the PIOL are included in the slit lamp assessment.

[e] If required for the surgical procedure.

[f] To establish preoperative refractive stability for contact lens wearers and to demonstrate postoperative corneal stability, where necessary.

[g] These evaluations are optional (in the case of specular microscopy data, they can be useful to demonstrate the trend associated with the outcomes given the variability of the ECD measurements).

[h] Contrast sensitivity testing is performed on all subjects preoperatively and repeated postoperatively on those subjects that are part of the contrast sensitivity substudy and on all subjects that develop crystalline lens opacity at all remaining visits.

[i] Methods such as ultrasonic biomicroscopy or Scheimpflug photography can be used.

A.3 Evaluations

A.3.1 Visual acuity and refraction

Distance and near acuity charts, chart illumination, ambient illumination, testing distances and testing procedures are standardized for all investigators. Reporting of refractions is standardized across study sites.

The design of the visual acuity chart and testing procedures with scoring methods are described by Ferris *et al*. [5].

A.3.1.1 Luminance

Chart background luminance is 85 cd/m^2 (80 cd/m^2 to 160 cd/m^2 is the acceptable range) for the photopic testing. The chart background luminance is identical at all testing centres.

Ambient illumination is from dim to dark with no surface (including reflective surfaces) within the subject's field of view to exceed the chart background luminance.

A.3.1.2 Chart distance

For testing at a fixed distance, the chart distance should be precisely defined, no head movements relative to the charts are allowed. For distance acuity testing, the best correction to the chart distance should be used after adjusting the chart to optical infinity (e.g. + 0,25 D for a 4 m chart). When determining the best distance refraction for treatment, however, the refraction should be adjusted to the refractive correction at infinity (e.g – 0,25 D for a 4 m chart distance) if the chart is not at optical infinity.

A.3.1.3 Data recording procedures

Record all:

a) test distances;

b) refractive corrections;

c) measured visual acuities in log MAR notation, or other notation convertible to log MAR.

A.3.2 Specular microscopy

The main safety concern to be addressed by specular microscopy is the possibility of a progressive decrease in endothelial cell density, which could lead to corneal decompensation.

Specular microscopy images are taken of the central cornea. Peripheral measurements are taken if warranted by the design or placement of the PIOL. The peripheral locations to be photographed are specified based on the design and/or placement of the implant.

To determine endothelial cell density decrease, specular microscopy is performed preoperatively and at 6, 12, 24, and 36 months. Given the variability of the measurements, consider performing the examination also at 18 and 30 months to increase the sensitivity of the trend analysis. Decreases due to surgical trauma can be determined by evaluating the cell counts at Month 6 in comparison to the preoperative measurements. To determine decreases over time, measurements from the 6 month examination and later time points are analysed.

Operated fellow eyes with the experimental PIOL can be used in the endothelial cell density analysis after correcting for the correlation between eyes. This can be accomplished in many statistical packages using the general estimating equations method. The net effect of this technique is to adjust the standard errors (and thus the confidence intervals) for the slope estimates to account for the observed correlation between fellow eyes.

A.3.2.1 Collection of data

The methods used for the collection and analysis of specular microscopy data are critically important to minimize the variability associated with these measurements. Common sources of variability in specular microscopy are:

a) returning to same location;

b) poor image quality (less than 100 countable cells);

c) technician error;

d) improper reader analysis;

e) maintaining equipment calibration/alignment.

There are several ways to reduce this variability. Sponsors should implement as many of these recommendations as possible.

To address differences in location of the image within a given area of the cornea, three acceptable images are taken at each visit. The mean density from the three images is used.

Non-contact specular microscopes are strongly recommended. The same model of specular microscope is used at each site.

Prior to the beginning of the study, each site takes an initial set of images for evaluation of image quality. Training (or retraining) is performed as necessary and includes the following important points:

A preferred image has distinct cells, with at least 100 countable cells (150 cells preferred) that can be grouped in a uniform area.

The use of a reading centre is strongly recommended. If the use of a reading centre is not possible, the sponsor has to establish a protocol for the collection and analysis of images to be used by each participating site. The person responsible for taking and accepting the images is adequately trained in both specular photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer is used at each site throughout the study. A back-up technician who is trained is also available.

The reading centre or technician performing the image analysis is advised of the following recommendations.

— A minimum of 100 cells (ideally 150 cells) in a contiguous area are counted.

— The centre method for counting cells is recommended.

— When selecting cells to count, use the area with the fewest distortions (not in shadow, washed-out, or blurred).

NOTE The quality of cells in an image is critical. Be aware that increased variability in the data can be seen in some subjects (e.g. polymegethism/pleomorphism post-contact lens wear).

A calibration grid can be obtained from the specular microscope manufacturer. The study monitor should check the calibration at each site on a yearly basis.

A.3.3 Crystalline lens status

The crystalline lens should be evaluated preoperatively and at each of the postoperative intervals after 1 month. The level of evaluation should be commensurate with the risk of lens opacities/lens changes identified by the risk analysis performed by the manufacturer.

For PIOLs where the design or surgical procedure could lead to lens changes, a grading system such as the LOCS III [6], [7], [8] or a quantitative method should be used to evaluate all eyes for lens changes and to evaluate those changes over time.

When lens opacity is observed, photographs should also be taken when first observed and at each subsequent visit to document any progression of the opacity. Also, when crystalline lens opacities are detected, contrast sensitivity testing is performed on that subject at each postoperative evaluation after the opacity is observed.

Analyses should include:

a) the number of subjects with lens changes (i.e. any change in the appearance of the lens, with stratification by the type of change);

b) contrast sensitivity and visual acuity outcomes for the subjects with lens opacities for determination of clinical significance.

For PIOLs for which lens changes are not an identified risk, qualitative observations can be adequate.

A.3.4 Mesopic pupil size

Pupil size is measured for all eyes in the study, with eye illumination identical to that used for mesopic contrast sensitivity testing. The pupil size is determined with a method capable of an accuracy of $\pm$ 0,5 mm at mesopic conditions. The measurement of pupil size is performed in conjunction with the contrast sensitivity testing.

A.3.5 Aqueous cell and flare assessment

The slit lamp examination includes the measurement of aqueous cell and flare by a standard grading system.

For the evaluation of aqueous cells and flare, use a slit beam 0,3 mm wide and 1 mm high, and use the following grading:

a) Cells

- none (0) = no cells seen,
- mild (+1) = 1 to 5 cells seen,
- moderate (+2) = 6 to 15 cells seen,
- severe (+3) = 16 to 30 cells seen,
- very severe (+4) = $>$ 30 cells seen;

b) Flare

- none (0) = no Tyndall effect,
- mild (+1) = Tyndall effect barely discernible,
- moderate (+2) = Tyndall beam in anterior chamber is moderately intense,
- severe (+3) = Tyndall beam in anterior chamber is severely intense,
- very severe (+4) = Tyndall beam is very severely intense. The aqueous has a white and milky appearance.

A.3.6 Measurement of intraocular pressure

Intraocular pressure is measured using Goldmann applanation tonometry. Other methods can be used with a scientific justification, but the same method is used by all investigators.

A.3.7 Corneal thickness

Corneal thickness is measured with pachymetry. The same method is used by all investigators.

A.3.8 Subject questionnaire

A validated subject questionnaire is administered to all subjects. The questionnaire includes questions regarding glare, halos, double vision, spectacle/contact lens use, and night driving. The time of onset of visual symptoms is addressed. These types of questionnaires are described in References [9] and [10] in the Bibliography. The results of the subject questionnaire are stratified by fellow eye status (untreated, implanted with same PIOL, treated with other refractive surgery, etc.).

A.3.9 Contrast sensitivity

Measure sinusoidal grating contrast sensitivity at far under mesopic and mesopic with glare conditions. For this purpose, gratings produced on either charts or monitors can be used, provided that they are validated. Use the same test system at all sites.

The sine-wave gratings are accurately produced on a chart (reflective or transmissive) or a high-resolution monitor.

NOTE Methods to minimize high-frequency artifacts that can affect the data are to blur the outer edges of the grating and to surround all edges by a uniform field equal to the grating in space-averaged luminance. Further information about the effects of sharp edges on gratings are provided in Thorn [11].

Subjects are tested with best corrected spectacle correction preoperatively and postoperatively. Preoperatively, mesopic contrast sensitivity is measured on all subjects; mesopic contrast sensitivity with glare is measured on the subjects in the contrast sensitivity substudy. Postoperatively, mesopic contrast sensitivity testing is performed on subjects who develop lens opacity at each form after the opacity is observed. Mesopic contrast sensitivity and mesopic contrast sensitivity with glare testing is performed on all subjects in the contrast sensitivity substudy.

At the first contrast sensitivity evaluation, a full practice trial (all spatial frequencies) on one eye is performed.

Testing is performed twice for each subject at each test condition, and the average of the log contrast sensitivity values is reported.

Plot the results as graphs of contrast sensitivity against spatial frequency and report them.

a) Subjects

The number of subjects to be tested is determined as described in Annex B. All subjects should be best case. Include in the clinical investigation plan (CIP) a description of how subjects are selected for the contrast sensitivity substudy. For example, testing sequentially enrolled subjects that meet the best case criteria is one way to minimize selection bias.

Stratify the test results by pupil size on each 0,5 mm.

b) Lighting conditions

The chart luminance is about 3 cd/m^2 and the ambient illumination is lower than the chart luminance. Standardize light levels, ambient illumination, chart luminance and glare source luminance across all investigators and sites.

A pilot study to validate the proposed glare testing condition is recommended. The minimum level of glare is the amount necessary to significantly reduce the contrast sensitivity of young adults with normal corneas and normal vision, but not so great as to completely wash out the target in these young, normal adults. A small pilot study of normal adults may be necessary to determine an appropriate glare level. The reduction in contrast sensitivity due to glare in normal adults should be a loss of about 0,10 log units at 6 cycles/degree. Subjects in this pilot study that show an increase in contrast sensitivity performance should be excluded in the analysis to determine the appropriate glare level.

For “look-in” contrast sensitivity viewing systems, unless the pupil can be measured while each subject looks into the instrument, the subject’s head should be moved from the system to measure pupil size. It is therefore critical that the room lighting be calibrated to be identical to the test lighting inside the “look-in” instrument.

c) Spatial frequencies

Measure contrast sensitivity at spatial frequencies as close as possible to 1,5, 3, 6, and 12 cycles/degree.

d) Indeterminite data

Use the instructions for the test system chosen to clarify in the CIP how indeterminite data are treated in the analysis. It should be confirmed that the percentage of subjects with indeterminite data is consistent with the equipment manufacturer’s population norms at the mesopic luminance.

A.3.10 Clinical clearance analysis

The clearance of the PIOL is determined for all subjects in Phase I of the clinical investigation at the pre-operative and the six month evaluations (e.g. by ultrasonic biomicroscopy, Scheimpflug photography). The substudy confirms the clearances between the PIOL and the ocular tissue and is used to validate the theoretical anatomical clearance analysis that was performed as part of the risk assessment. The data from this substudy is used to modify the minimum anterior chamber depth inclusion criteria, if necessary.

A.4 Study analyses

A.4.1 Safety analyses

A.4.1.1 Three different types of analyses are performed to assess the effects of the PIOL on the endothelial cells, as described in a) to c). Endothelial cell coefficient of variation and preoperative contact lens status should be considered in the outcome analysis.

a) Mean analysis

Analyses of specular microscopy data include the determination of the mean endothelial cell density decrease over time. The mean rate of endothelial cell density decrease is calculated via a paired analysis in order to calculate the mean of the differences between each reporting period. A mean endothelial cell density decrease between Month 6 and Month 36 should also be determined.

b) Regression analysis

An average yearly rate of endothelial cell density decrease and the 90 % confidence interval around this average yearly rate of endothelial cell density decrease can be determined from regression analysis of the postoperative specular microscopy data. A regression analysis is performed from the number of endothelial cells at each follow-up examination. An average regression trend is determined from the individual subject data using all the data for subjects with at least two or more evaluations, taking into account the necessary adjustments for correlations between eyes for the fellow eye data and utilizing the exact time after implantation and not the case report form number in the analysis.

To apply this rate of decrease to the remainder of the life of the device requires an assumption that the decrease of endothelial cell density after Month 6 occurs in the same fashion (e.g. linear), as occurred during the investigation.

c) Frequency analysis

Analyses of specular microscopy data also include frequency analyses. The percentage endothelial cell density decrease for each subject is calculated via a paired analysis. Histograms are constructed with a frequency distribution of the percentage endothelial cell decreases between each two consecutive reporting periods, and between the 6 and 36 month reporting periods. The mean loss between each two reporting periods is calculated. These frequency analyses are modified to correct for the correlation between test and fellow eyes with the PIOL.

A.4.1.2 Determination of the percentage of eyes that lose two lines or more BSCVA.

A.4.1.3 Determination of the percentage of eyes that have a postoperative BSCVA worse than 0,5 that were 1,0 or better preoperatively.

A.4.1.4 Determination of the percentage of eyes that have an induced manifest refractive astigmatism of greater than 2 D of cylinder.

A.4.1.5 Determination of the rate of cataract development.

A.4.2 Performance analyses

A.4.2.1 Determination of the percentage of eyes that achieve predictability (attempted versus achieved) of the MRSE of ± 1,00 D.

A.4.2.2 Determination of the percentage of eyes that achieved predictability of the MRSE of ± 0,50 D.

A.4.2.3 Determination of the percentage of eyes that achieve a change of less than or equal to 1,00 D of MRSE between two refractions performed at least 3 months apart.

A.4.2.4 Determination of the mean change in MRSE between visits as determined by a paired analysis.

A.4.2.5 Determination of the percentage of eyes that achieve an UCVA of 0,5 or better (for those eyes with BSCVA of 1,0 or better preoperatively and are targeted for emmetropia).

A.4.2.6 Determination of the percentage of eyes that achieve UCVA of 1,0 or better (for those eyes with BSCVA of 1,0 or better preoperatively and are targeted for emmetropia).

A.4.2.7 Determination of the percentage of eyes that achieve an UCVA equal to or better than the preoperative BSCVA (for those eyes targeted for emmetropia).

Annex B
(informative)

Statistical sample size considerations

B.1 Statistical symbols

The following symbols are defined here for use within this annex.

a) Confidence interval parameters:

- $1-\alpha$ confidence interval level
- $1-\beta$ power
- δ non-inferiority margin, assumed to be positive
- L_{lcl} lower confidence limit, i.e. lower limit of the confidence interval
- $z_{1-\alpha}$ standard normal quantile for confidence level
- $z_{1-\beta}$ standard normal quantile for power (coverage probability)

b) Normal distribution statistics and parameters:

- μ population mean
- σ population standard deviation
- n sample size
- $\bar{x}$ sample mean

c) Hypothesis testing parameters:

- α Type 1 error rate for the hypothesis
- β Type 2 error rate for the hypothesis

B.2 Sample size guidance

B.2.1 General

For non-inferiority hypothesis testing for studies in which postoperative data to preoperative data of the same subject are compared, the sample size required for paired differences is determined from the following equation from Lin [12]:

$$n = \sigma_d^2 \left[\frac{(z_{1-\alpha} + z_{1-\beta})}{\delta + \mu_d} \right]^2 \quad \text{for } \mu_d > -\delta$$

where subscript "d" refers to the paired differences.

The paired differences are determined by subtracting preoperative values from the treatment values. Usually, the mean of the paired differences is hypothesized to be zero (therefore $d = \delta$). This sample size equation is also appropriate for estimating a mean from a single sample by a confidence interval of a pre-specified length. One merely drops the subscript "d" and sets delta to the desired confidence interval length.

The above sample size formula for treatment differences is based on solving the probability statement

$$1 - \beta = \Pr[L_{\text{lcl}} > -\delta]$$

for the sample size. For example, the equation used to determine sample size when evaluating non-inferiority in a paired comparison of means is

$$\begin{aligned} 1 - \beta &= \Pr[L_{\text{lcl}} > -\delta] \\ &= \Pr[\bar{x}_d - z_{1-\alpha}\sigma_d^2/n > -\delta] \end{aligned}$$

where

subscript "d" refers to paired differences;

L_{lcl} is the lower confidence limit of the difference.

The resulting sample size equations have boundary conditions for the expected values and non-inferiority margins. If the boundary conditions are not met, then the probability statement above should be analysed directly by numerical methods.

Also note that if the non-inferiority margin is set to zero, then these sample size formulae simplify into the usual sample size formulae for one-sided hypothesis tests. In all cases, the sample sizes are rounded up to the next largest integer.

In order to calculate sample size using the above equations, the acceptable difference between means (non-inferiority margin), the standard deviation, the power level and the confidence interval are chosen. Values for these parameters are chosen based on experience and published literature. Examples are provided below to clarify the use of the these formulae.

Table B.1 provides a convenient list of standard normal quantiles that are used in the examples.

Table B.1 — Normal quantiles to use in equations

α **or** β	$(1-\alpha)$ **or** $(1-\beta)$	$z_{1-\alpha}$ **or** $z_{1-\beta}$
0,025	0,975	1,960
0,050	0,950	1,645
0,100	0,900	1,282
0,150	0,850	1,036
0,200	0,800	0,842
0,500	0,500	0,000

B.2.2 Sample size guidance for safety and performance evaluation

B.2.2.1 General

Select the primary endpoint based on a risk analysis of possible adverse events. Endothelial cell density decreases are used in the example in B.2.2.2 as the primary endpoint for sample size determination. Endothelial cell density decreases are determined by comparing measurements obtained at the postoperative visits with preoperative measurements.

B.2.2.2 Example

For the following example, power has been selected to be 90 % ($\beta = 0{,}10$) with a 95 % ($\alpha = 0{,}05$) confidence interval level. The confidence interval length has been set at a level that would result in a clinically significant decrease in central endothelial density over the lifetime of the subject. For specular microscopy studies, a rate of decrease of 1,7 % per year would result in a significant difference in final central endothelial cell density over the lifetime of the subject. After 40 years, a subject with a yearly loss of 0,5 % per year would have twice the endothelial cell density as a subject who had a yearly loss of 2,2 % per year. Other values can be used as deemed appropriate.

Standard deviations used in this example were chosen based on published literature and experience, however these values can differ depending on the testing equipment, method used and whether a central reading centre is used to evaluate the images. The manufacturer should choose the expected standard deviation based on literature and experience.

It is desired to estimate the mean percent loss in central endothelial cell loss using a one-sided 95 % upper confidence interval that should not exceed 1,7 % per year. Using the sample size formula for a single mean, 300 subjects are required so that there is a 90 % probability that a one-sided upper 95 % confidence interval on the mean percent loss will fall below 1,7 % per year assuming a standard deviation in percent loss of 10 %.

$$n = 0{,}1^2\left[\frac{(1{,}645 + 1{,}282)}{0{,}017}\right]^2 = 296{,}4 \cong 300$$

The data from any fellow eyes implanted with the PIOL that are available at the completion of the clinical investigation should be included in the endothelial cell density evaluation, after correcting for the correlation between the paired eyes to increase the sensitivity to detect any trends in the regression analysis of the data.

B.2.3 Sample size guidance for substudy

B.2.3.1 General

Contrast sensitivity decreases are determined by comparing measurements obtained at the Month 6 visit (anticipated to be after the point of refractive stability) and at the Month 36 visit with preoperative measurements.

B.2.3.2 Example

For this example, power has been assumed to be 90 % ($\beta = 0{,}10$) with a 95 % ($\alpha = 0{,}05$) confidence interval level. The detectable difference has been set at one half the difference that is typically considered clinically significant. For contrast sensitivity studies, clinical significance is often set at 0,3 log units for 2 or more spatial frequencies. Other values can be used if deemed appropriate. Standard deviations used here were chosen based on published literature and experience, however these values can differ among testing equipment or lighting conditions. The manufacturer should choose the expected standard deviation based on literature and experience.

As shown in the calculation below, for a contrast sensitivity study comparing postoperative data to preoperative data for the same subject (paired sample), the sample size needed is 61 subjects for a 0,4 log unit standard deviation. Therefore, with 61 subjects there is a 90 % probability that a one-sided upper 95 % confidence interval level on the mean paired difference will fall below 0,15 log units (selected for this example as one half of the clinically significant value of 0,3 log units). Solving for this equation:

$$n = 0{,}4^2\left[\frac{(1{,}645 + 1{,}282)}{0{,}15}\right]^2 = 60{,}92 \cong 61$$

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