Scope

The discussion topics to be included in draft standards and proposed guidance apply to any intraocular lens (IOL) whose primary indication is the modification of the refractive power of a phakic eye.

References

ANSI Z80.7 - 2001, American national standard for ophthalmics-intraocular lenses
ISO 11979-7 – 2001, Ophthalmic implants – Intraocular lenses – Part 7: Clinical investigations
ISO/DIS 14155-1, Clinical Investigation of Medical Devices - Part 1: General Requirements
ISO/DIS 14155-2, Clinical Investigation of Medical Devices - Part 2: Clinical Investigation Plans
U.S. Code of Federal Regulations 21, Part 812
ANSI Z80.12, Multifocal Intraocular Lenses
Contents

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   8.4 Evaluation of the Natural Lens for Cataractogenesis
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   8.7 Measurement of Intraocular Pressure
   8.8 Patient Questionnaire
9. Study analyses

Attachment A
Sample size

Attachment B
Potential Loss of Endothelial Cell Density Over Time
1. Clinical investigation plan

Each investigator shall contribute a minimum of 20 patients to the study population, but not more than 25% of the patients in the study.

The lost to follow-up patients shall comprise less than 10% of the study population after one year and less than 30% of the study population after three years (if applicable).

Bilateral implantation shall not be implemented until initial safety and effectiveness data have been collected and evaluated by the manufacturer.

Note: 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 trials, may be adequate justification to begin bilateral implantation earlier in the study.

If a formula is to be used to determine the appropriate power for implantation, the formula and its derivation shall also be included. Clinical data shall be evaluated at intervals during the study to validate the accuracy and to refine the power formula if necessary.

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

The clinical protocol shall describe how patient visits in between reporting periods (as defined below) will be handled in the data analyses (e.g., an interim case report form will be used and the data reported separately).

2. Enrollment of patients

To minimize the risks associated with the clinical investigation of a new phakic IOL, patient enrollment shall occur in stages. The patient data from each stage shall be evaluated and found acceptable by the sponsor and the investigator(s) prior to the continuation of the clinical investigation.

The following phased enrollment plans are recommended. Depending on the design of the phakic IOL, a different phase-in may be appropriate. For example, if a significant design change is required for an additional indication, a slower phase-in may be appropriate.

Note: Previous clinical experience, i.e., results from well-documented clinical trials, should be documented and may be used as a justification to support faster enrollment.

For clinical studies for a single refractive indication:

?? Phase I - 10 patients, followed for 6 months

?? Phase II - 100 additional patients. A clinical evaluation of all available data should occur when 50 patients have been followed for 6 months and all 110 patients have been enrolled. If the performance of the phakic IOL is acceptable, the manufacturer may begin the last phase of the investigation.

?? Phase III - remainder of study population
For clinical studies of more than one refractive indication (e.g., myopia and hyperopia or myopia and myopia with myopic astigmatism) ongoing simultaneously:

?? Phase I - 20 patients (no more than 10 of each indication), followed for 6 months

?? Phase II - 150 additional patients (no more than 100 per indication). A clinical evaluation of all available data should occur when 50 patients with one indication have been followed for 6 months. If the performance of the phakic IOL is acceptable, the manufacturer may begin the last phase of the investigation for that indication.

?? Phase III - The remainder of the study population for an individual indication.

For clinical studies of Phakic IOLs that provide astigmatic correction (in addition to a spherical correction), where substantial clinical data has been collected for the spherical correction:

?? Phase II – 100 patients. A clinical evaluation of all available data should occur when 50 patients have been followed for 6 months and all 100 patients have been enrolled. If the performance of the phakic IOL is acceptable, the manufacturer may begin the last phase of the investigation.

?? Phase III – remainder of the study population needed to demonstrate effectiveness of the cylindrical correction

3. Sample size

In general, the sample size required for the safety and effectiveness study will be 300 subjects. Detailed information about calculation of the sample size for the safety and effectiveness study, endothelial cell density study, and contrast sensitivity substudy can be found in Attachment A.

4. Study duration

A study duration of three years is recommended to adequately evaluate the maintenance of endothelial cell density and the rate of cataractogenesis.

5. Study population

The following inclusion criteria are recommended:

?? patient meets specified refractive criteria (spherical and cylindrical components)

?? patient has specified minimum BSCVA in each eye. For myopes, patient has UCVA 20/40 or worse; for hyperopes, patient has difficulty maintaining UCVA 20/40, as evidenced by need for constant contact lens or spectacle wear. *(Note the UCVA inclusion criterion is under discussion.)*

?? patient has less than 0.75 D difference between cycloplegic and manifest refractions
patient has had a stable correction (? 0.5 D), as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history. In addition, patient, whose current method of correction is contact lenses, has demonstrated a stable refraction (? 0.5 D), as determined by MRSE, on two consecutive exam dates. Stability of the refraction is determined by the following criteria: a) 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; b) the two refractions were performed at least 7 days apart.

Patient has the minimum endothelial cell density as given in Table 1 below.

Patient, who is expected to have residual postoperative cylindrical refractive error of ? 1 D, who would receive a phakic IOL providing spherical correction only, has been given the opportunity to experience his/her best spectacle vision with anticipated correction only and is willing to proceed with the surgery.

Patient has given written informed consent.

Patient is willing and able to comply with schedule for follow-up visits.

The following exclusion criteria are recommended:

Patient has an acute or chronic disease or illness that would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, etc.).

Patient is taking systemic medications that may confound the outcome of the study or increase the risk to the patient, including, but not limited to steroids, antimetabolites, etc.

Patient has ocular condition (other than high myopia) that may predispose for future complications, for example:

- History or evidence of current corneal disease (e.g., herpes simplex, herpes zoster keratitis, etc.)
- Evidence of retinal vascular disease
- Prekeratoconus or keratoconus, recurrent erosion syndrome or corneal dystrophy
- Glaucoma or glaucoma suspect by exam findings and/or family history

Patient has had previous intraocular or corneal surgery that might confound the outcome of the study or increase the risk to the patient.

Patient is pregnant, is lactating during the course of the study, or has another condition associated with the fluctuation of hormones that could lead to refractive changes.

Table 1

<table>
<thead>
<tr>
<th>Age at time of enrollment</th>
<th>Minimum endothelial cell density</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 - 25</td>
<td>2800 cells/mm²</td>
</tr>
<tr>
<td>26 - 35</td>
<td>2600 cells/mm²</td>
</tr>
<tr>
<td>36 - 45</td>
<td>2200 cells/mm²</td>
</tr>
<tr>
<td>46 - 55</td>
<td>2000 cells/mm²</td>
</tr>
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</table>
*See Attachment B for general information regarding possible losses of endothelial cell density over time. This information was used to recommend minimum endothelial cell density inclusion criterion. Separate minimum values for ages 26-30 and 31-35 are under consideration.

6. Examination schedule

The following reporting periods are recommended:

?? Preoperative
?? Operative
?? Day 1 (1 day)
?? Week 1 (5-9 days)
?? Month 1 (3-5 weeks)
?? Month 3 (10-14 weeks)
?? Month 6 (21-26 weeks)
?? Month 12 (11-14 months)
?? Month 24 (23-27 months)
?? Month 36 (35-39 months)

The following examinations are recommended:

For all patients:
?? UCVA (distance and near)
?? BSCVA (distance and near)

Note: Manufacturers may wish to perform best contact lens corrected visual acuity (BCLVA) on high myopes and high hyperopes to increase the accuracy of preoperative refractions and power calculations.

?? Manifest and cycloplegic refractions
?? Patient questionnaire
?? Intraocular pressure
?? Slit lamp exam
?? Gonioscopic exam
?? Dilated fundus exam
?? Mesopic pupil size
?? Axial length measurement (preoperatively)
?? Anterior chamber depth (ACD) measurement (if inclusion/exclusion criteria include a minimum or maximum ACD)

Note: If ACD is to be measured by A-scan, intercalibration of equipment at all study sites is recommended.

?? Keratometry (to establish preoperative refractive stability for contact lens wearers and to demonstrate surgery has been astigmatically neutral, where necessary)
?? Assessment of the natural lens for cataractogenesis

Table 2 below contains a recommended examination schedule.
7. Adverse events
Clinical investigators shall file reports of serious intraoperative and postoperative adverse events with the sponsor immediately after learning of their occurrence. All other adverse events shall be documented in the case reports.

The following adverse events, although not an all-inclusive list, should be considered to be reportable as described in 21 CFR 812.150(b)(1):

- Endophthalmitis
- Pupillary block
- Retinal detachment
- Stromal thinning/corneal melting
- Corneal haze/cloudiness, if associated with ≥ 2 lines BSCVA loss
- Secondary surgical intervention*

* Note: Secondary surgical interventions should be reviewed by the sponsor on a case-by-case basis to determine if reporting is appropriate.

The manufacturer should include in the clinical protocol a list of possible adverse events, including any that apply from the list below, that may occur in conjunction with the investigational device. The clinical report forms should include forced-choice listings of these adverse events and allow for the recording of other adverse events not listed.

- Hyphema
- Uveitis/Iritis
- Raised IOP requiring treatment
- Vitreous loss (intraoperative)
- Induction of cataract

- Macular edema
- Corneal haze/cloudiness
- Corneal edema
- Dislocation of device
Table 2

Recommended postoperative examination schedule

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Op</th>
<th>Day 1</th>
<th>Week 1</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 24</th>
<th>Month 36</th>
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</thead>
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<tr>
<td>Distance UCVA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Near UCVA</td>
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<td></td>
<td>X^2</td>
<td>X</td>
<td>X</td>
<td>X^2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Near BSCVA</td>
<td>X</td>
<td></td>
<td>X^2</td>
<td>X</td>
<td>X^2</td>
<td></td>
<td></td>
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<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Cycloplegic refraction</td>
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<td></td>
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<tr>
<td>Dilated fundus exam</td>
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<td>X</td>
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<td></td>
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<td>Mesopic pupil size</td>
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<td>X^6</td>
<td>X</td>
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<tr>
<td>Keratometry</td>
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<td></td>
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<td>X</td>
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<td>Patient questionnaire</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Contrast sensitivity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X^4</td>
<td>X^4</td>
<td>X</td>
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<tr>
<td>Distance BSCVA – mesopic</td>
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<td>X^4</td>
<td></td>
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<td></td>
<td></td>
<td>X</td>
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<td>Specular microscopy</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1 - for hyperopia protocols
2 - for presbyopia protocols
3 - for contact lens wearers
4 - these tests may be performed at either the Month 3 or the Month 6 exam, but must be performed at the same exam for all patients
5 - post-surgery operative day IOP measurements should be considered if pupillary block is a possible complication
6 - should be performed at the same visit as contrast sensitivity testing
7 - if needed to evaluate corneal astigmatism (e.g., to demonstrate astigmatically neutral surgery)
8. Testing methodologies

8.1 Visual Acuity

Distance and near acuity charts, chart illumination, ambient illumination, testing distances and testing procedures should be standardized for all investigators. Reporting of refractions should be standardized across study sites and allow for the identification of patients with mixed astigmatism.

The design of the visual acuity chart and testing procedures with scoring methods are described by Ferris et al. in “New visual acuity charts for clinical research.”

The following conditions, materials and procedures for acuity testing are recommended:

a. Luminance

Chart background luminance should be 85 cd/m\(^2\) (80 - 160 cd/m\(^2\) acceptable range) for photopic testing, and 3 cd/m\(^2\) or less for mesopic testing. Luminance should be identical for all testing centers.

Ambient illumination should be from dim to dark, to maximize pupil size. No surface (including reflective surfaces) within the subject’s field of view should exceed the chart background in luminance.

b. Data Recording Procedures

i. All physical and optical testing distances should be recorded.

ii. All corrective lenses should be recorded.

iii. All acuity measurements should be recorded using MAR notation (minimum angle of resolution in minutes of arc) or other notation convertible to MAR. Examples of acceptable notation include:

- logMAR (common logarithm of MAR)
- decimal notation (reciprocal of MAR)
- standard Snellen notation (actual test distance/test distance that would render MAR = 1)

iv. Jaeger notation for near acuity may be used only after a letter size calibration has established the relationship between the Jaeger values and Snellen or MAR values.

8.2 Specular Microscopy

The main safety concern to be addressed by specular microscopy is the possibility of a chronic loss of endothelial cell density, which, even at a low yearly rate could, over time, lead to corneal edema and decompensation. With an initial loss due to surgical trauma of 10% or less, it can be estimated that a subsequent yearly loss of 2.0% or less should preserve the integrity of the cornea over the life of the patient.
To determine endothelial cell density loss, specular microscopy should be performed preoperatively and at the Month 3 (or Month 6), Month 12, Month 24, and Month 36 exams. Losses due to surgical trauma may be determined by evaluating the cell counts at Month 3 (or Month 6) in comparison to the preoperative measurements. To determine losses over time, measurements from the Month 3 (or Month 6) and later time points should be analyzed.

A yearly rate of cell density loss may be determined by subtracting the measurement at Month 3 from the measurement at Month 36 and dividing by 2.75 years (using Month 6 data, divide by 2.5 years). However, to apply this rate of loss to the remainder of the life of the device requires an assumption that the loss of cell density after Month 3 (or Month 6) occurs in a linear fashion. Therefore, the sample size chosen for this study should be sufficient to detect a yearly loss of 2.0% as well as to demonstrate the linearity of the cell density loss over time (see 2.2 above).

Specular microscopy images should be taken of the central cornea for all phakic IOLs. Peripheral measurements should be taken if warranted by the design or placement of the IOL. The peripheral locations to be photographed should be specified based on the design and/or placement of the implant.

Analyses of specular microscopy data should include the determination of the mean cell density loss over time and a frequency distribution. The mean rate of cell density loss should be calculated via a paired analysis in order to calculate the mean of the differences. A frequency distribution of cell density losses between Month 3 (or Month 6) and Month 36 should also be performed.

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

- difficulty in returning to same location on the cornea at each visit;
- poor image quality (less than 100 countable cells);
- technician error;
- improper reader analysis; and
- 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 should be taken at each visit. The mean density from the three images should be used.

Problems due to poor image quality and/or technician error may be avoided by using appropriate equipment and trained, experienced clinical sites. Non-contact specular microscopes are strongly recommended. The same model of specular microscope should be used at each site. Images should be stored on 35 mm slides, half-inch video, or in electronic format. Specular cameras that can record digitized images on disk or to e-mail are preferable for ease of data transfer.

Prior to the beginning of the study, it is recommended that each site take an initial set of images for an evaluation of image quality. Training (or retraining) should be performed as necessary and include the following important points:
An acceptable image has:
- distinct cells;
- at least 100 identifiable (countable) cells as a minimum, 150 cells preferred; and
- cells that can be grouped in a uniform area.

To capture a good image:
- make sure the patient is comfortable;
- instruct the patient to blink;
- instruct patient not to move and to open eyes wide;
- instruct patient to focus on the green light;
- be patient; and
- if necessary, use the manual setting. (Note that the use of the manual setting may require additional training.)

The use of a reading center is strongly recommended. If the use of a reading center is not possible, the sponsor should 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 should be adequately trained in both specular photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer should be used at each site throughout the study. A back-up technician who is trained should also be available.

The reading center or technician performing the image analysis should be advised of the following recommendations:

- A minimum of 100 cells (ideally 150 cells) in a contiguous area should be counted. The center method for counting cells is recommended.

- The quality of cells in an image is critical. Be aware that the presence of disease can increase variability (e.g., polymegathism/pleomorphism post-contact lens wear, keratoconus). When selecting cells to count, use the area with the fewest distortions (not in shadow, washed-out, or blurred).

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

**8.3 Contrast Sensitivity**

Contrast sensitivity testing should be performed under mesopic and mesopic with glare conditions. Contrast sensitivity should be measured at spatial frequencies as close as possible to 1.5, 3, 6, 12, and 18 cycles/degree. Patients should be tested with their habitual correction (spectacles or contact lenses) preoperatively and with best spectacle correction postoperatively, but results should be stratified by type of preoperative habitual correction. Sponsors are encouraged to enroll similar numbers of patients with each type of preoperative correction method.

The chart luminance should be 3 cd/m² or less and the ambient illumination should be lower than the chart luminance. In order to limit pupil constriction and maintain uniform glare conditions across the test chart, the glare source should be an array of two or more small spots symmetrically positioned around the chart. The level of glare should be the minimum necessary to significantly
reduce the contrast sensitivity of young adult patients with normal corneas and normal vision, but
the illumination should not be so great as to completely wash out the target in these young,
normal patients. The reduction in contrast sensitivity due to glare in normal patients should be a
mean loss of between 0.15 and 0.45 log units at 6 cycles/degree (for grating charts). A small pilot
study of normal patients may be necessary to determine an appropriate glare level.

Control data may be obtained from preoperative measurements of best spectacle-corrected
noncataractous eyes or from a sample of normal patients with the same age, gender and refractive
error distributions as the postoperative test patients. The patient population should be large
enough to detect a 0.15 log unit difference in contrast sensitivity. (See A.3 for sample size
calculations.)

8.4 Evaluation of the Natural Lens for Cataractogenesis (this section under discussion)

The natural lens should be evaluated preoperatively and at each of the postoperative intervals.
The level of evaluation should be commensurate with the risk of cataractogenesis/lens changes
identified by the risk analysis performed by the manufacturer. For phakic IOLs where the design
or surgical procedure may lead to lens changes, a grading system or quantitative method should
be used to evaluate lens changes over time. For IOLs for which lens changes are not an identified
risk, qualitative observations may be adequate.

Analyses should include:

?? the number of patients with lens changes (i.e., any change in the appearance of the lens, with
stratification by the type of change)
?? the number of patients with clinically significant lens opacities - the term “clinically
significant” to be defined

8.5 Mesopic Pupil Size

Pupil size should be measured for all eyes in the study, with eye illumination identical to that
used for mesopic contrast sensitivity testing. The measurements should be made with an infrared
pupilometer or other calibrated infrared camera. Contrast sensitivity and pupil measurement
should begin only after the eye has had time to fully adapt to the testing conditions
(approximately 10 minutes).

8.6 Slit Lamp Exam

The slit lamp exam should include the measurement of aqueous cell and flare by a standard
grading system and an evaluation for the presence of corneal edema, pupillary irregularities, iris
atrophy and pigment dispersion. A gonioscopic exam using a consistent grading system at each
site should also be conducted.

The following system is recommended for grading of aqueous cell and flare using a slit beam 0.3
mm wide and 1.0 mm long:

<table>
<thead>
<tr>
<th>Cells</th>
<th>(0)</th>
<th>= no cells seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>(+1)</td>
<td>= 1-5 cells seen</td>
</tr>
<tr>
<td>moderate</td>
<td>(+2)</td>
<td>= 6-15 cells seen</td>
</tr>
<tr>
<td>severe</td>
<td>(+3)</td>
<td>= 16-30 cells seen</td>
</tr>
<tr>
<td>very severe</td>
<td>(+4)</td>
<td>= &gt; 30 cells seen</td>
</tr>
</tbody>
</table>
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.

8.7 Measurement of Intraocular Pressure

Intraocular pressure should be measured using Goldmann applanation tonometry. Other methods may be used with a scientific justification, but the same method should be used throughout the study.

8.8 Patient Questionnaire

A validated patient questionnaire should be administered to all patients. The questionnaire should include questions regarding glare, halos, double vision, spectacle/contact lens use, and night driving. The time of onset of visual symptoms should also be addressed. One such questionnaire is described in Vitale S, Schein OD, Meinert CL and Steinberg EP. “The Refractive Status and Vision Profile.” Ophthalmology 2000; 107:1529-1539. A second questionnaire is the NEI Refractive Quality of Life Questionnaire (in publication, Ophthalmology). The results of the patient questionnaire should be stratified by fellow eye status (untreated, implanted with same phakic IOL, treated with other refractive surgery, etc.).

9. Study analyses

Based on the risk analysis, safety and effectiveness analyses appropriate to the specific phakic IOL and intended patient population should be selected from the following list.

Safety Analyses

?? Endothelial cell density loss as measured between the preoperative and the Month 3 postoperative exams.
?? Endothelial cell density loss between the Month 3 and Month 36 exams.
?? Percentage of eyes that lose 2 lines or more BSCVA
?? Percentage of eyes that have a postoperative BSCVA worse than 20/40 (if 20/20 or better BSCVA preoperatively)
?? Percentage of eyes that have an induced manifest refractive astigmatism of greater than 2 D of absolute cylinder.
?? Rates of adverse events.
?? Rate of cataractogenesis.
Effectiveness Analyses

?? Percentage of eyes that achieve predictability (attempted versus achieved) of the MRSE of ≥ 1.00 D.

?? Percentage of eyes that achieved predictability of the MRSE of ≥ 0.50 D.

?? 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 change of less than or equal to 0.50 D of MRSE between two refractions performed at least 3 months apart.

?? Mean change in MRSE between visits as determined by a paired analysis.

?? Percentage of eyes that achieve an UCVA of 20/40 or better (for those eyes with BSCVA of 20/20 or better preoperatively and are targeted for emmetropia).

?? Percentage of eyes that achieve UCVA of 20/20 or better (for those eyes with BSCVA of 20/20 or better preoperatively and are targeted for emmetropia).

?? Percentage of eyes that achieve an UCVA equal to or better than the preoperative BSCVA (for those eyes targeted for emmetropia)

?? Percentage of eyes that achieve 0.3 LogMAR or better uncorrected near visual acuity (UCNVA) (appropriate for phakic IOLs intended for near VA correction).

?? Percentage of eyes that achieve 0.1 LogMAR or better UCNVA (appropriate for phakic IOLs intended for near VA correction)
Attachment A

Sample size

A.1 Safety and effectiveness study

The sample size for this study should be adequate to evaluate the primary endpoint selected based on the risk analysis. The recommended primary safety endpoint is the evaluation of the rates of adverse events. The sample size should be adequate to detect adverse events with an expected rate of 0.1% or greater.

The null hypothesis ($H_0$) is that the true adverse event rate ($p_t$) is less than or equal to a target value (fixed) control rate ($p_c$). The alternative hypothesis ($H_1$) is that the true adverse event rate ($p_t$) is larger than the control rate ($p_c$).

$$H_0: p_t = p_c$$
$$H_1: p_t > p_c$$

For an adverse event such as intraocular infection, a target value of 0.1% may be used, based on the aphakic intraocular lens experience (see ISO 11979-7 Annex D for more information). For an adverse event with an expected rate (or point estimate) of 0.1%, with a sample size of 300 evaluable patients, an observed rate of 1.0% is the minimum rate detectable as statistically significantly greater than the expected rate with 80% power. Allowing for sampling error, the maximum number of patients with this adverse event in a population of 300 patients would be statistically significantly greater than the expected rate of 0.1%.

The following assumptions were used for this calculation: $\alpha = 0.05$, 80% power, one-sided alternative. The calculated result is based on the use of the binomial distribution, as mathematically described below, to test the null hypothesis that the true adverse event rate is less than or equal to the control rate or point estimate. The alternative hypothesis would be that the rate of the adverse event is greater than the control rate, where

- $p$ is the control adverse event rate (or point estimate);
- $n$ is the sample size;
- $x$ is the observed number of adverse events from the investigation.

The maximum of allowable events, “$x$”, can be obtained using an inverse-input binomial probability calculator, by setting the left-tail probability value equal to 0.95, for the given sample size (n) and control rate (p) or by using PASS2000 statistical software, using the One Proportion Power Analysis, setting $p_0=0.001$, $p_1=0.01$, $n=300$ and $\alpha = 0.05$, $\beta = 0.20$.

If a different primary endpoint is chosen, the manufacturer should document the statistical basis

$$\Pr\{X \leq x \mid n, p, \alpha = 0.05\} = \sum_{i=0}^{x} \binom{n}{i} p^i (1-p)^{n-i}$$

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for the sample size.

A.2 Endothelial cell density study

The loss of endothelial cell density over time should be determined by evaluating measurements taken at the Month 3 (or Month 6) through Month 36 exams. Two measurements should be taken at each visit and the mean cell density should be used. The number of patients should be sufficient to detect a yearly endothelial cell loss of 2.0% and to demonstrate linearity of the cell loss over time. A sample size of 200 subjects should be sufficient; however, in order to ensure that 200 analyzable photographs are obtained, it is recommended that all subjects be evaluated. Additional statistical information is provided below.

One approach to determining an appropriate sample size is to set an upper bound of the 90% confidence interval (C.I.) around the observed loss using the following formula:

$$\text{Upper 90\% C.I.} = X + Z_{a}(s/\sqrt{N})$$

where \(X\) is the observed total cell loss after 2.75 years (then divided by 2.75 to calculate the yearly loss), \(Z_{a} = 1.28\) for a one-sided upper 90% C.I., \(s\) is the assumed standard deviation of 5%, and \(N\) is the sample size.

If the upper bound is set to 5.5% (representing a 2.0% per year loss) and a standard deviation of 5% is assumed, a sample size of 200 patients would ensure with 90% confidence that the true population loss is 2.0% per year or less. The observed loss must be greater than 1.83% per year for the 90% C.I. to exceed 2.0%. A sample size of 200 patients should also be sufficient to demonstrate linearity.

If, due to measurement error, the standard deviation is larger, for example, 10%, and the sample size is 200 patients, an observed loss of greater than 1.67% per year would cause the 90% C.I. to exceed 2.0%. The sample size may be increased to allow for a larger observed loss in cases where the standard deviation is larger than 5% (e.g., with a sample size of 300 patients the observed loss must be 1.73% for the upper 90% C.I. to exceed 2.0%). Similarly, if the standard deviation is less than 5%, the sample size may be decreased accordingly.

Note: If the upper 90% C.I. exceeds 2%, additional justification should be provided by the manufacturer, such as the upper C.I. that falls below 2.0% and an explanation of efforts taken to minimize variability.

A.3 Contrast sensitivity substudy

Contrast sensitivity losses should be determined by comparing measurements obtained at the Month 3 or Month 6 visit (should be after the point of refractive stability) and at the Month 36 visit with preoperative measurements.

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 can be determined from the following equation:\(^1\):

\(^1\) Lin, S.C. (1995) “Sample size for therapeutic equivalence based on confidence interval,” Drug Information Journal, Vol. 29, pp 45-50. This article is for two-sided therapeutic equivalence. Non-inferiority problems produce the same sample equations, but with different choices of confidence and
where the subscript ‘d’ refers to the paired differences. Table B.1 provides parameter definitions. The paired differences subtract control values from the treatment values. Usually, the mean of the paired differences is assumed to be zero.

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

\[ n \geq \frac{2(z_{1-\alpha/2} + z_{1-\beta} )^2 }{\sigma_d^2} \text{ for } \sigma_d \geq 0 \]

for the sample size. For example, non-inferiority in a paired comparison of means solves this equation for the sample size:

\[ n \geq \frac{2(z_{1-\alpha} + z_{1-\beta} )^2 }{\sigma_d^2} \text{ for } \sigma_d \geq 0 \]

The subscript ‘d’ refers to paired difference. The abbreviation lci stands for lower confidence interval. 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 analyzed directly by numerical methods.

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

### Table A.1
#### Parameter Definitions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(\alpha)</td>
<td>Confidence interval level</td>
</tr>
<tr>
<td>1-(\beta)</td>
<td>Power or probability that confidence interval limit is within the non-inferiority margin</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>Non-inferiority margin – assumed to be positive</td>
</tr>
<tr>
<td>(z_{1-\alpha})</td>
<td>Standard normal quantile for confidence level</td>
</tr>
<tr>
<td>(z_{1-\beta})</td>
<td>Standard normal quantile for power (coverage probability)</td>
</tr>
<tr>
<td>(\mu)</td>
<td>Population mean</td>
</tr>
<tr>
<td>(\sigma)</td>
<td>Population standard deviation</td>
</tr>
<tr>
<td>(N)</td>
<td>Sample size</td>
</tr>
<tr>
<td>(\bar{x})</td>
<td>Sample mean</td>
</tr>
</tbody>
</table>
The following table provides a convenient list of standard normal quantiles that will be used throughout.

<table>
<thead>
<tr>
<th>?</th>
<th>(1-?)</th>
<th>$z_{1.9}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>0.975</td>
<td>1.960</td>
</tr>
<tr>
<td>0.050</td>
<td>0.950</td>
<td>1.645</td>
</tr>
<tr>
<td>0.100</td>
<td>0.900</td>
<td>1.282</td>
</tr>
<tr>
<td>0.150</td>
<td>0.850</td>
<td>1.036</td>
</tr>
<tr>
<td>0.200</td>
<td>0.800</td>
<td>0.842</td>
</tr>
<tr>
<td>0.500</td>
<td>0.500</td>
<td>0.000</td>
</tr>
</tbody>
</table>

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 must be chosen. Values for these parameters should be chosen based on experience or published literature. Examples have been provided below to clarify the use of the above equations.

**Examples:**

For the following examples, power has been assumed to be 90% with a 95% 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 may be used if deemed appropriate. Standard deviations used in the examples were chosen based on published literature and experience, however these values may differ among testing equipment or lighting conditions. The manufacturer should choose the expected standard deviation based on literature or experience.

**Example:**

For a contrast sensitivity study comparing postoperative data to preoperative data for the same subject (paired sample), the sample size needed would be 61 subjects for a 0.4 log unit standard deviation. Therefore, with 61 patients 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:

$$n \geq \frac{0.4(1.645 - 1.282)^2}{0.15^2} \geq 60.92 \geq 61$$
### Attachment B
Potential Loss of Endothelial Cell Density Over Time

<table>
<thead>
<tr>
<th>Age at time of implant</th>
<th>Cell density at time of implant*</th>
<th>Estimated rate of cell loss (per year)</th>
<th>Age when cell density &lt; 1200 cells/mm²**</th>
<th>Age when cell density &lt; 1000 cells/mm²**</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>3000</td>
<td>1.5%</td>
<td>76</td>
<td>88</td>
</tr>
<tr>
<td>21</td>
<td>3000</td>
<td>2.0%</td>
<td>63</td>
<td>72</td>
</tr>
<tr>
<td>21</td>
<td>3000</td>
<td>2.5%</td>
<td>55</td>
<td>62</td>
</tr>
<tr>
<td>35</td>
<td>2500</td>
<td>1.5%</td>
<td>90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>35</td>
<td>2500</td>
<td>2.0%</td>
<td>77</td>
<td>86</td>
</tr>
<tr>
<td>46***</td>
<td>2000</td>
<td>1.5%</td>
<td>74</td>
<td>86</td>
</tr>
<tr>
<td>46</td>
<td>2000</td>
<td>2.0%</td>
<td>68</td>
<td>77</td>
</tr>
</tbody>
</table>

* Initial cell densities taken from Moller-Pedersen (Cornea 16(3):333-338, 1997). Rate of loss associated with normal aging assumed to be approximately 0.6%/year, from Bourne et al. (IOVS 38(3):779-782, 1997).

** Assuming a surgical loss of 10% and normal loss of 0.6%/year from 21 until age of implant

*** With normal aging, cell density at age 46 should be approximately 2400 cells/mm², but this exercise assumes a worst-case situation, given the proposed inclusion criterion of a minimum of 2000 cells/mm² for patients age 46 and older.