

Study Protocol

Clinical Investigation of the TECNIS® Next-Generation
Intraocular Lens, Model DEN00V

PROTOCOL NUMBER: PCOL107AHNG

NCT Number: NCT05574959

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**Clinical Investigation of the TECNIS® Next-Generation Intraocular Lens, Model
DEN00V****PROTOCOL NUMBER: PCOL107AHNG****SPONSOR:** Johnson & Johnson Surgical Vision, Inc. (JJSV)

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Investigator Agreement**As an Investigator, I agree to:**

- Implement and conduct this study diligently and in strict compliance with this agreement; the protocol; Good Clinical Practices; 21CFR812, ISO 14155 and all other applicable FDA regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB), FDA or other regulatory authorities; and all other applicable laws and regulations.
- Supervise all testing of the device where human subjects are involved.
- Ensure that the requirements for obtaining informed consent are met.
- Obtain authorization for use/disclosure of health information (e.g., HIPAA authorization or equivalent).
- Maintain all information supplied by Johnson & Johnson Surgical Vision in confidence and, when this information is submitted to an independent IRB or any other group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, and I agree to all aspects.

_____ Investigator Printed Name	_____ Signature	_____ Date
_____ Sub-Investigator Printed Name	_____ Signature	_____ Date
_____ Sub-Investigator Printed Name	_____ Signature	_____ Date

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PERSONNEL AND FACILITIES

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SPONSOR PERSONNEL:

Medical Monitor:

[REDACTED]
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Medical Safety:

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Clinical Science:

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EMERGENCY TELEPHONE NUMBERS:

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PROTOCOL CHANGE HISTORY

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1. SYNOPSIS

PROTOCOL TITLE:	Clinical Investigation of the TECNIS® Next-Generation Intraocular Lens, Model DEN00V
PROTOCOL NUMBER:	PCOL107AHNG
STUDY TREATMENTS:	<u>Investigational Lens</u> TECNIS 1-Piece Soft Acrylic next-generation Extended Depth of Focus (EDF) IOL, Model DEN00V [REDACTED] [REDACTED] <u>Control Lens</u> TECNIS 1-Piece IOL, Model ZCB00 (colorless monofocal IOL or TECNIS® Simplicity™ [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
STUDY OBJECTIVE:	The purpose of this clinical trial is to evaluate the safety and effectiveness of the TECNIS 1-Piece Soft Acrylic IOL, Model DEN00V in comparison to an aspheric monofocal IOL.
CLINICAL HYPOTHESIS:	The TECNIS 1-Piece Soft Acrylic IOL, Model DEN00V provides improved distance-corrected intermediate (DCIVA, 66 cm) visual acuity without compromising distance vision, when compared to the monofocal control, TECNIS 1-piece IOL Model ZCB00. Complication and adverse event rates associated with the DEN00V IOL are within the rates for posterior chamber IOLs given in ISO 11979-7:2018.
OVERALL STUDY DESIGN:	
Structure:	Prospective, multicenter, bilateral, masked (sponsor, subject, and evaluator), randomized clinical trial.
Number of Sites:	Up to 10 sites in the United States
Duration:	6 months

STUDY POPULATION CHARACTERISTICS:

Condition: Bilateral cataracts with otherwise-healthy eyes

Number of Subjects:

Original Enrollment Up to 250 subjects will be enrolled

Inclusion Criteria (all criteria apply to each study eye):

- Minimum 22 years of age;
- Bilateral cataracts for which posterior chamber IOL implantation has been planned;
- Preoperative best corrected distance visual acuity (BCDVA) of 20/40 Snellen or worse with or without a glare source;
- Potential for postoperative BCDVA of 20/30 Snellen or better;
- Corneal astigmatism:
 - Normal corneal topography;
 - ≤ 1.0 D of preoperative keratometric astigmatism;

- Clear intraocular media other than cataract;
- Availability, ability, willingness and sufficient cognitive awareness to comply with examination procedures;
- Signed informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries;
- Ability to understand and respond to a questionnaire in English.

Exclusion Criteria (all criteria apply to each study eye):

- Requiring an intraocular lens power outside the available range of +14.0 D to +26.0 D;
- Any clinically significant pupil abnormalities (non-reactive, fixed pupils, or abnormally shaped pupils);
- Inability to focus or fixate for prolonged periods of time (e.g., due to strabismus, nystagmus, etc.);
- Prior corneal refractive surgery (SMILE, LASIK, LASEK, RK, PRK, etc.);
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study;
- Irregular corneal astigmatism;
- Inability to achieve keratometric stability for contact lens wearers (as defined in preoperative procedures);
- History of intraocular surgery, including prophylactic peripheral iridotomies and peripheral laser retinal repairs;
- Recent ocular trauma that is not resolved/stable or may affect visual outcomes or increase risk to the subject;
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study;
- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration, including pseudoexfoliation, trauma, or posterior capsule defects;
- Use of systemic or ocular medications that may affect vision;
- Prior, current, or anticipated use during the 6-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcomes or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery);
- Poorly controlled diabetes;
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the

- outcomes of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.). Note: controlled ocular hypertension without glaucomatous changes (optic nerve cupping and visual field loss) is acceptable;
- Known ocular disease or pathology that, in the opinion of the investigator:
 - may affect visual acuity;
 - may require surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.);
 - may be expected to require retinal laser treatment or other surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.);
 - Pregnancy, planned pregnancy, presently lactating or another condition associated with hormonal fluctuation that could lead to refractive changes;
 - Concurrent participation or participation within 30 days prior to preoperative visit in any other clinical trial;
 - Desire for monovision correction.

EVALUATION CRITERIA:

The purpose of this clinical study is to evaluate the safety and effectiveness of the investigational IOL Model DEN00V. Clinical endpoints and success criteria for this evaluation are defined as follows:

EFFECTIVENESS

The primary effectiveness endpoints are monocular (first eyes) photopic distance-corrected intermediate visual acuity at 66 cm, distance-corrected depth of focus, and photopic best-corrected distance visual acuity at 4 m.

The secondary effectiveness endpoint is monocular (first eyes) distance-corrected near visual acuity at 40 cm.

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DATA ANALYSIS:

The investigational IOL Model DEN00V will be compared to the control IOL Model ZCB00. The 6-month postoperative visit is the key analysis timepoint for all endpoints, although data will be reviewed at other time points as well. The “first eyes” are the primary eyes and the “second eyes” are the fellow eyes.

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STUDY VISITS AND PROCEDURES

Patient qualification as a study subject will be assessed at the preoperative visit according to the inclusion/exclusion criteria. The Informed Consent Document (ICD) and Authorization for Use/Disclosure of Health Information form (HIPAA authorization) must be signed by any patients who agree to participate in the study prior to undergoing any study-specific procedures. Prior to randomization, the investigator should choose which eye to operate on first for each subject at his/her discretion based on his/her standard clinical practice (e.g., the eye with the worse cataract, poorer best corrected distance vision and/or more severe optical/visual complaints). After determination that all inclusion/exclusion criteria have been met and the first eye is determined the enrolled subjects will be randomized in a 1:1 ratio. Each subject will receive lenses from the same lens group in both eyes, either investigational Model DEN00V or control Model ZCB00. The eye implanted first will be considered the primary study eye.

All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week exam for the first eye but no more than 30 days after the first-eye surgery. After surgery, each eye will be examined at 1 day (1-2 days), 1 week (7-14 days), and 1 month (30-60 days). Based on the date of the second-eye surgery, both eyes will be evaluated at both 6-month visits (120-180 days).

NOTE: *For the 1-month visits, the first and second eyes should be examined at separate visits if the visit intervals do not overlap. However, if the 1-month visit intervals for the first and second eye overlap, both eyes may be examined at a single visit.*

NOTE: *The second 6-month visit must be scheduled within 1-10 days of the first 6-month visit. Both visits must fall within the specified 6-month window (120-180 days).*

Subjects and study personnel performing the postoperative vision testing and refractions will be masked for the duration of the study. Key preoperative data include ocular health and history, axial length, anterior chamber depth, visual acuities, manifest refraction, keratometry, topography, biomicroscopic slit-lamp findings, gonioscopy, ocular symptoms, and biometry. The operative visit will include standard procedures for cataract surgery and IOL implantation. Key postoperative data collection includes

monocular and binocular uncorrected, and distance-corrected visual acuities, questionnaires, contrast sensitivity, defocus curve, slit-lamp findings, non-directed visual symptoms, and adverse events.

2. BACKGROUND/INTRODUCTION

Presbyopia, defined as the age-related loss of accommodative amplitude, affects essentially all human beings beyond the age of 45 and impacts the ability of the eye to focus at near.^{1,2} Current intraocular lens options for cataract patients who desire improved vision across a range of distances include a choice of monovision or multifocality. Patients implanted with standard monofocal lenses often need spectacles for reading or performing other near tasks, even if a monovision option is selected. Patients implanted with multifocal lenses, while being able to read and perform near tasks without spectacles, sometimes experience dysphotopsias (e.g., halos), particularly at night, and may have limited intermediate ability (e.g., may need spectacles to work on a computer). Some accommodating lenses are also available on the market, although their effect depends upon fit within the capsular bag or capsular bag elasticity.

On July 15, 2016, another option was made available to cataract patients when the TECNIS Symphony Extended Range of Vision IOL, Model ZXR00, became commercially available. Utilizing a diffractive technology to elongate the depth of focus, the Symphony IOLs provide cataract patients with good distance vision, and improved intermediate and near vision compared to standard monofocal IOLs.

The investigational IOL in this protocol, is designed to offer a next-generation EDF IOL option to patients that builds upon the benefits of JJSV's TECNIS 1-Piece IOL platform with an EDF refractive technology that provides low levels of visual symptoms.

3. CLINICAL HYPOTHESIS

The TECNIS 1-Piece Soft Acrylic IOL, Model DEN00V provides improved distance-corrected intermediate (DCIVA, 66 cm) visual acuity without compromising distance vision, when compared to the monofocal control, TECNIS 1-piece IOL Model ZCB00.

Complication and adverse event rates associated with the DEN00V IOLs are within the rates for posterior chamber IOLs given in ISO 11979-7:2018.

4. STUDY DESIGN

This study is a 6-month, prospective, multicenter, bilateral, masked (sponsor, subject, and evaluator), randomized clinical investigation of the TECNIS 1-piece Soft Acrylic IOL, Model DEN00V.

The study will be conducted at up to 10 sites in the USA and should enroll up to 250 subjects [REDACTED]

¹ Koretz J.F., Kaufman P.L., Neider M.W. Goeckner P.A. Accommodation and Presbyopia in the Human Eye – Aging of the Anterior Segment. Vision Res. 1989;29: 1685-1692.

² Benjamin, William, J., Borish, Irvin M. Borish's Clinical Refraction, Philadelphia: 1998, W.B. Saunders, pg 109.

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5. ACRONYMS

The following acronyms are used throughout the document:

- BCDVA: best-corrected distance visual acuity
- DCIVA: distance-corrected intermediate visual acuity
- DCNVA: distance-corrected near visual acuity
- UCDVA: uncorrected distance visual acuity
- UCIVA: uncorrected intermediate visual acuity
- UCNVA: uncorrected near visual acuity
- PRSIQ: patient reported spectacle independence questionnaire
- PRVSQ: patient reported visual symptoms questionnaire

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the safety and effectiveness of the investigational IOL Model DEN00V. The key study timeframe for effectiveness and safety endpoints is 6 months based on ISO 11979-7:2018 and ANSI Z80.35-2018 guidance.

6.1 PRIMARY EFFECTIVENESS ENDPOINTS

Effectiveness of the study will be demonstrated if all success criteria for the following 3 primary endpoints are simultaneously met.

1) MONOCULAR PHOTOPIC DCIVA AT 66 CM

Mean (logMAR) monocular DCIVA under photopic conditions at 66 cm for first eyes in the investigational vs. control lens groups at 6 months.

Statistical criterion:

- Statistically significant superiority of mean DCIVA in the investigational lens group vs. control lens group

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2) MONOCULAR DEPTH OF FOCUS

Mean monocular depth of defocus where visual acuity is 0.20 logMAR or better at 6 months (measured only negative direction from zero) for first eyes in investigational vs. control lens groups at 6 months.

Clinical criterion:

- Mean difference between lens groups of at least 0.50 D.

3) MONOCULAR PHOTOPIC BCDVA AT 4 M

Mean (logMAR) monocular BCDVA under photopic conditions at 4 meters for first eyes in the investigational vs. control lens groups at 6 months

Success criterion:

- Statistical non-inferiority in mean BCDVA of investigational lens group vs. control lens group with non-inferiority margin of 0.10 logMAR.

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7. STUDY PRODUCTS

7.1 INTRAOCULAR LENSES

The two intraocular lens models that will be evaluated in this study are the investigational IOL Model DEN00V and the control IOL Model ZCB00.

Investigational IOL Model DEN00V

The Model DEN00V is a TECNIS 1-piece soft acrylic lens with a 6.00 mm optic body diameter and 13.00 mm in overall length designed to further extend the depth of focus. The IOL shares the same anterior aspheric optical profile as the monofocal analog lens, model ZCB00 and a modified refractive posterior surface. [REDACTED]

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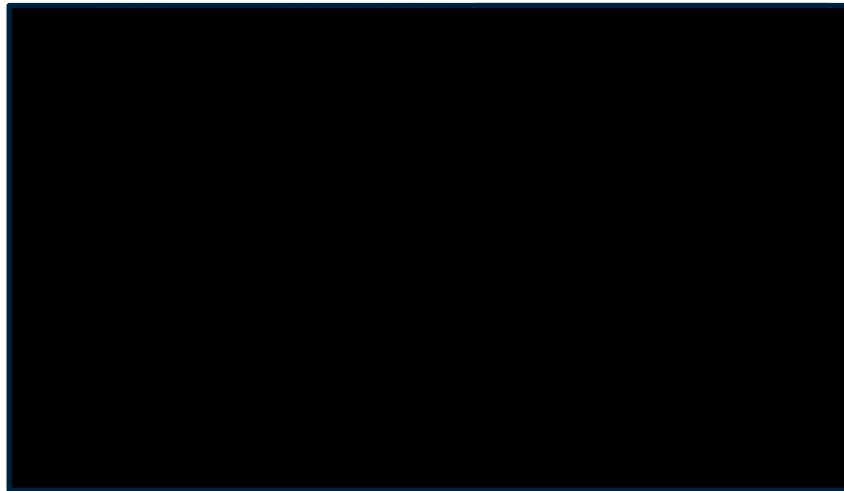
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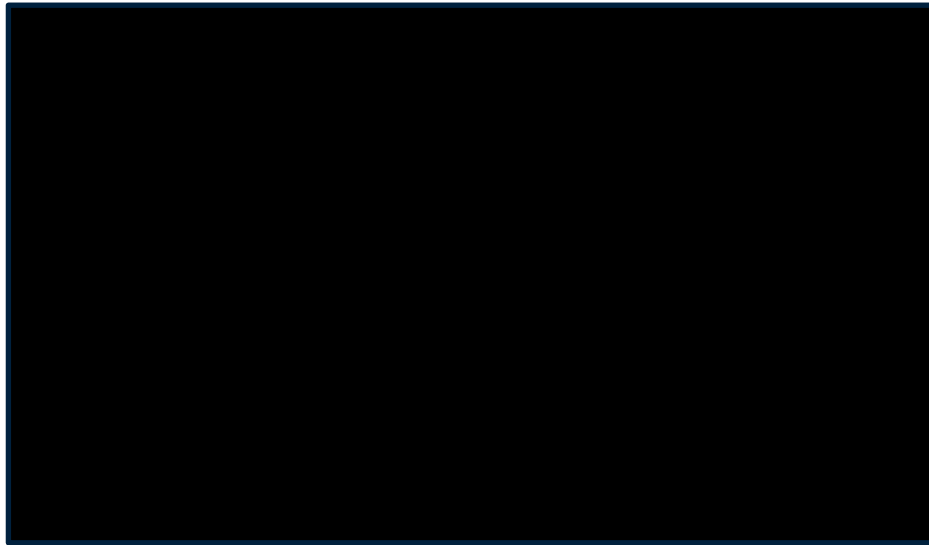


Control IOL Model ZCB00

The control IOL Model ZCB00 shares the same material, general dimensions, geometry, and one-piece soft acrylic lens platform as the SENAR 1-Piece IOL, Model AAB00, which is the mechanical parent of the DEN00V IOL. [REDACTED]

[REDACTED]

[REDACTED]



[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

STORAGE AND DISTRIBUTION

Consignments of the study lens will be supplied to the sites. All study lenses should be stored in the original packaging and kept in a dry place. Lenses should not be stored in direct sunlight or at temperatures greater than 45° C (113° F). Each lens is packaged in a lens tray and sealed in a peel-pouch. The lens is sterile as long as the package has not been opened or damaged and the shelf-life expiration date has not been exceeded. The Principal Investigator is responsible for ensuring that the investigational lenses are only used for subjects enrolled in this study.

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8. STUDY POPULATION

The study will be conducted at up to 10 sites in the U.S.A and up to 250 subjects will be enrolled [REDACTED]

[illegible]

[REDACTED]

8.1 INCLUSION CRITERIA (all study criteria apply to each study eye)

- Minimum 22 years of age;
- Bilateral cataracts for which posterior chamber IOL implantation has been planned;

- Preoperative best-corrected distance visual acuity (BCDVA) of 20/40 Snellen or worse with or without a glare source;
- Potential for postoperative BCDVA of 20/30 Snellen or better;
- Corneal astigmatism:
 - Normal corneal topography;
 - ≤ 1.0 D of preoperative keratometric astigmatism;
- Clear intraocular media other than cataract;
- Availability, willingness and sufficient cognitive awareness to comply with examination procedures;
- Signed informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries;
- Ability to understand and respond to a questionnaire in English.

8.2 EXCLUSION CRITERIA (all study criteria apply to each study eye)

- Requiring an intraocular lens power outside the available range of +14.0 D to +26.0 D;
- Any clinically significant pupil abnormalities (non-reactive, fixed pupils, or abnormally shaped pupils);
- Inability to focus or fixate for prolonged periods of time (e.g., due to strabismus, nystagmus, etc.);
- Prior corneal refractive surgery (SMILE, LASIK, LASEK, RK, PRK, etc.);
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study;
- Irregular corneal astigmatism;
- Inability to achieve keratometric stability for contact lens wearers (as defined in preoperative procedures);
- History of intraocular surgery, including prophylactic peripheral iridotomies and peripheral laser retinal repairs;
- Recent ocular trauma that is not resolved/stable or may affect visual outcomes or increase risk to the subject;
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study;
- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration, including pseudoexfoliation, trauma, or posterior capsule defects;
- Use of systemic or ocular medications that may affect vision;

- Prior, current, or anticipated use during the 6-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcomes or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery);
- Poorly controlled diabetes;
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the outcomes of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.). Note: controlled ocular hypertension without glaucomatous changes (optic nerve cupping and visual field loss) is acceptable;
- Known ocular disease or pathology that, in the opinion of the investigator:
 - may affect visual acuity;
 - may require surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.);
 - may be expected to require retinal laser treatment or other surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.);
- Pregnancy, planned pregnancy, presently lactating or another condition associated with hormonal fluctuation that could lead to refractive changes;
- Concurrent participation or participation within 30 days prior to preoperative visit in any other clinical trial;
- Desire for monovision correction.

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select ophthalmic surgeons who have completed residency in ophthalmology (or its documented equivalent) and are licensed to practice medicine and perform surgery at his/her investigative site. Each site will have one designated principal investigator; some sites may have additional implanting sub-investigators/surgeons.

Investigators will be selected from surgeons who are experienced in small-incision surgery and have implanted TECNIS 1-piece IOLs in cataract patients. Investigators should have established personalized A-constants for the TECNIS 1-piece IOL Model ZCB00. Additionally, investigators should have established their personalized A-constant for the TECNIS 1-piece IOL Model ZCB00. All sites are required to have adequate staff support for reporting and subject follow-up, as well as the necessary instrumentation to conduct study testing.

9.2 INVESTIGATOR OBLIGATIONS

Investigators are required to fulfill the following obligations:

- Conduct the study in accordance with the relevant and current protocol. Investigator will make changes to a protocol only after notifying and obtaining approval from JJSV, the FDA and the Investigational Review Board (IRB), except when necessary to protect the safety, rights, or welfare of subjects.
- Personally conduct and supervise the study.
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- Be responsible for protecting the rights, safety, and welfare of subjects under the investigator's care and be responsible for the control and documentation of the devices under investigation.
- Inform patients that the device(s) are being used for investigational purposes and that requirements relating to obtaining informed consent and IRB approval are met according to 21CFR50, 21CFR56, 21CFR812 and all other applicable laws and regulations.
- Maintain confidentiality as required by HIPAA or similar laws and regulations.
- Shall not obtain written informed consent from any subject to participate or allow any subject to participate before obtaining FDA and IRB approval.
- Document in each subject's case history that informed consent was obtained prior to participation in the study as required by 21CFR812.
- Report to JJSV and the reviewing IRB any adverse experiences that occur during the study in accordance with applicable laws and regulations.
- Maintain adequate and accurate records in accordance with applicable laws and regulations and make available all study documents and subject medical records for inspection by either JJSV, duly authorized regulatory agencies (e.g., FDA, PMDA, Health Canada, MOH, etc.) and/or the IRB.
- Submit progress reports on the investigation to JJSV and the reviewing IRB at regular intervals, but no less often than yearly as required by 21CFR812.150.
- Ensure the IRB that is responsible for initial and continuing review of the study complies with applicable laws and regulations.
- Report all changes in research activity and all unanticipated problems involving risks to patients to the IRB and JJSV.
- Supervise and permit investigational device use and disposition in accordance with applicable regulations and protocol requirements. Upon completion of enrollment or termination of the study or the investigator's part of the study, or at JJSV's request, return to JJSV any remaining supply of the investigational device.
- Provide sufficient accurate financial information to JJSV to allow JJSV to submit complete and accurate certification or disclosure statements as required by

21CFR54. Promptly update this information if any relevant changes occur during the investigation or for up to one year following completion of the study.

- Comply with all other obligations of clinical investigators and requirements according to all applicable FDA regulations (e.g., 21CFR812), all other applicable laws and regulations, and all conditions of approval imposed by the reviewing IRB and the FDA.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are adequately informed about the protocol, the investigational device, their study-related duties and functions and agree to fulfill their obligations in meeting the above commitments.

Investigators shall provide adequate time and resources to conduct and report on the study. The Investigator, or delegate, shall notify JJSV of any change in the conduct of the study including changes in study personnel assigned to the study project, location of the investigational device(s), or maintenance of study records, etc.

9.3 INVESTIGATOR APPROVAL

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Study Files/Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV. Study sites will obtain IRB approvals and fulfill any other site-specific regulatory requirements. The investigator is required to report to JJSV within five working days any withdrawal of approval by the reviewing IRB for his/her participation in the investigation.

Prior to the start of subject enrollment, the following documents must be signed and returned to JJSV:

- Confidentiality Agreement
- Clinical Study Agreement
- Investigator Agreement/Protocol Signature page
- Clinical Investigator Brochure Signature page
- Financial Disclosure form
- Signed and dated copy of investigator's current curriculum vitae
- Copy of the investigator's current medical license
- Hospital/Ambulatory Surgery Center Clinical Study Acknowledgement, if required

By signing the study documents, the investigator agrees to conduct this study according to the obligations above and all other applicable regulatory and legal requirements.

9.4 INVESTIGATOR INFORMATION

Information on the principal investigator at each investigative site, the address details for each investigative site and the emergency contact details for the principal investigator of each site are listed in a separate document— Study Investigator Information.

10. EXPERIMENTAL PLAN

10.1 OVERVIEW

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155 and all other applicable regional laws and regulations. The study will not begin until regulatory and IRB approvals have been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed.

This study will be a prospective, multicenter, bilateral, masked (sponsor, subject, and evaluator), randomized trial conducted at up to 10 sites in the U.S.A. Up to 250 subjects will be enrolled [REDACTED]

After signing the informed consent, for each subject meeting all eligibility criteria, the investigator should choose which eye to operate on first at his/her discretion based on his/her standard clinical practice (e.g., the eye with the worse cataract, poorer best-corrected distance vision and/or more severe optical/visual complaints). Following the selection of the first eye the subject will be randomized to receive lenses from the same lens group in both eyes, either the investigational Model DEN00V or the control Model ZCB00. All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week postoperative exam for the first eye, but no more than 30 days after the first-eye surgery. [REDACTED]

[REDACTED]

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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

10.3 PREOPERATIVE PROCEDURES

All subjects enrolled in the study must sign the current IRB-approved informed consent document and meet the eligibility criteria. The informed consent form must be signed before any study-specific examinations are performed, and this must be documented in the source documents. An Authorization for Use/Disclosure of Health Information Form (HIPAA authorization) or similar medical treatment privacy law documentation must also be signed.

All preoperative testing for the study must be completed within 60 days prior to the first surgery. Data from routine (non-study-specific) preoperative cataract examinations performed prior to the informed consent process may be included, provided these tests are conducted no more than 60 days prior to the first-eye surgery and the test date(s) are documented on the preoperative Case Report Form (CRF). If a test/exam is required by the protocol but not part of the routine testing the investigator performs for the cataract evaluation, that test/exam is study-specific and is not to be performed until after informed consent has been signed by the subject. The subject may be randomized and scheduled for surgery only after informed consent, preoperative study examination, and review of all required entrance criteria are completed (including lens power determination).

After the informed consent process, completion of the preoperative study examination, and determination that the subject meets all the required entrance criteria (including lens power determination), the subject may be randomized and scheduled for surgery.

As the Informed Consent Form is signed at the beginning of the preoperative study exam, some subjects may not qualify after study-specific testing is performed. Subjects will be considered screen-failures if they do not qualify, or if they qualify but decide not to participate further in the study, or if they decide not to proceed with surgery. These subjects will be exited from the study.

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10.4 RANDOMIZATION AND MASKING

Randomization of the subject will occur following the selection of the first eye. Randomization will be first stratified by site. Within each site, the random assignment will be further stratified based on age group (<70 years vs. ≥ 70 years), sex and cataract severity of the first eye (trace/mild vs. moderate/severe). The randomization list will be created by a JJSV biostatistician who is independent and not involved in the study activities. The randomization code will be uploaded into the electronic data capture system (EDC). Using computer-generated randomization code stratified by site, age group, sex and cataract severity of the first eye, subjects will be randomized (1:1) to bilaterally receive the investigational IOL Model DEN00V or control IOL Model ZCB00.

[REDACTED]
[REDACTED]
[REDACTED]

As part of the informed consent process, the investigator or delegate will explain to the subject the requirements of a randomized study and the differences expected between the two lens models: investigational DEN00V and the control ZCB00. The surgeon and the operative staff will know which lens type is implanted. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The subjects and the study technicians performing the postoperative vision tests are to be masked through study completion. [REDACTED]

10.5 STUDY LENS SUPPLY

[REDACTED]

The investigational lenses will be obtained from a site consignment that is supplied by the Sponsor after IRB approval. Two lenses (primary and back-up) should be available for each case. Unused back-up lenses are to be returned to the site consignment. At the completion of study enrollment, any remaining consignment lenses will be shipped back to the Sponsor after reconciliation of investigational lens inventory by a Sponsor Clinical Research Associate (CRA). The storage, access, and use of all investigational lenses must be controlled. Complete lens accountability must be always maintained [REDACTED]

10.6 OPERATIVE PROCEDURES

The investigator should use his or her standard, small-incision, cataract extraction surgical technique. Lenses should be folded for implantation and inserted into the

capsular bag using one of the Sponsor-validated insertion systems [REDACTED]
[REDACTED] to the Directions for Use (DFU).

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[REDACTED]

A horizontal bar chart consisting of 25 black bars. The bars are arranged in five groups of five. The lengths of the bars vary significantly, with some being very short and others nearly spanning the width of the chart area. There are gaps between the groups of bars.

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10.7 POSTOPERATIVE PROCEDURES

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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
Defocus Curve	4 m	Photopic (85 cd/m ²)	Monocular (first eye) Binocular	No adjustment; ETDRS Rx only

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10.8 EXIT OF SUBJECTS

An Exit Case Report Form will be completed for all subjects, either when they complete the study or if they exit early.

It is the responsibility of the investigator to provide complete follow-up data to JJSV for each subject, and every attempt should be made to gather that complete follow-up data for all subjects enrolled as missing data can have a negative effect on the study results. Patients who would be traveling, relocating or otherwise unavailable for postoperative follow-up visits should not be chosen for this clinical study.

Subjects will be discontinued from the study if the study lens is removed or if the subject dies. Subjects will be considered "lost-to-follow-up" from the study only if irretrievably lost for unavoidable reasons such as: subject moved/unable to locate, subject uncooperative/refuses further study participation, subject ill/unable to travel.

Documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons. In the event of subject relocation, efforts must be made by the investigator to secure follow-up information (i.e., slit-lamp findings and general visual acuity, etc.) from the subject's new physician.

A subject will be considered a non-randomized screen failure if he/she does not meet the inclusion/exclusion criteria or if consent is withdrawn prior to randomization.

A subject will be considered a randomized screen failure if the subject is randomized but does not undergo surgery or receive a study lens in both eyes for various reasons including but not limited to the planned implant being aborted due to surgical complications, the subject withdrawing consent prior to treatment or the subject died prior to treatment. If a subject receives at least one study lens, he/she is to be followed according to the protocol.

If a subject is exited early from the study, the investigator will complete an Exit Case Report Form in EDC indicating the reason for study exit. In the event of a lens removal or other serious adverse event, the subject may be exited from the study; however, efforts must be made by the investigator to follow the subject until resolution of the adverse event.

Following study completion or early exit, subjects will be informed about which lens model they received. Additionally, all study subjects are to be instructed to undergo regular eye examinations at least yearly and also to return to their doctor if any eye complications are experienced in the interim.

Completion of the clinical investigation is defined as last visit of the last subject and when follow-up visits are completed for the clinical investigation.

[illegible]

-
- | Response | Percentage |
|-----------------------------|------------|
| U.S. should take action | 85% |
| U.S. should not take action | 15% |

[illegible]

11. ADVERSE EVENTS AND PRODUCT COMPLAINTS

11.1 ADVERSE EVENT DEFINITIONS

Adverse Event (AE)

An adverse event is defined (per ISO 14155) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

Serious Adverse Event (SAE)

An adverse event is considered serious (following ISO 14155) if it is an untoward occurrence which may or may not be related to use of the study device that

- is sight- or life-threatening,
- results in death,
- requires inpatient hospitalization or prolongation of hospitalization (a planned hospitalization for a pre-existing condition without a serious deterioration in health is not considered a serious adverse event),

- results in permanent impairment of a body structure or body function including chronic diseases,
- necessitates medical or surgical intervention to prevent permanent impairment to a body structure or function, or
- results in fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

Device-Related Adverse Event/Adverse Device Effect (ADE)

A device-related adverse event is defined as any adverse event that is believed to be definitely, probably, or possibly related to the study device (following the guidelines in **Section 11.4, Causal Relationship**). A device-related event is also considered an adverse device effect (ADE; following ISO 14155) resulting from the use of the study device that may result from user error, insufficiencies, or inadequacies in the instructions for use, deployment, implantation, installation, operation of any malfunction of the device.

Study-Specific Serious Anticipated Adverse Events

The following is a list including, but not limited to, ocular serious adverse events (SAE) that are anticipated and must be reported to JJSV for this study. Any other potentially sight-threatening events may also be considered serious based on the judgment of the Investigator and must be reported appropriately. All adverse events should be identified and recorded in the CRFs. Any events that are unlikely but anticipated (i.e., endophthalmitis) will be reported to the FDA and other appropriate regulatory agencies.

The following list of adverse events categories are provided in ISO 11979-7:2018.

Cumulative Serious Adverse Events

These are adverse events that have occurred at any time up to a specified timepoint postoperatively:

- Cystoid macular edema
- Hypopyon
- Endophthalmitis
- Lens dislocated from posterior chamber
- Pupillary block
- Retinal detachment
- Secondary surgical intervention

NOTE: Wound “burps” during the first week postoperatively, suture removal, planned blepharoplasty and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

Persistent Serious Adverse Events

These are adverse events present at the final study visit.

- Corneal stromal edema

- Cystoid macular edema
- Iritis
- Raised IOP requiring treatment

All investigators must use standardized definitions to serious adverse events [REDACTED] in accordance with the American Academy of Ophthalmology Task Force Consensus Statement (Masket et al., 2017) in **Appendix Q**.

Secondary Surgical interventions (SSIs)

Secondary Surgical Interventions will be sub-categorized into exchange, removal, and repositioning. [REDACTED]

[REDACTED] The investigator should determine whether a secondary surgical intervention (SSI) is 'related' or 'not related' to the optical properties of the investigational lens.

- Exchange: The investigational device is replaced with the same lens model
- Removal: The investigational device is removed and replaced with a non-investigational lens, or no lens is implanted
- Reposition: The existing IOL is surgically moved to another location or rotated.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE)

Any UADE (USA 21CFR 812.3(s)) or USADE (ISO 14155) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (i.e., this protocol), application (including a supplementary plan or application), or risk assessment, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Health Threat

A serious health threat (following ISO 14155) is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subject, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.2 PRODUCT COMPLAINT/DEVICE DEFICIENCY DEFINITION

A product complaint/device deficiency is defined (21 CFR 820.3(b) and ISO 14155) as any alleged deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device. This may include malfunctions, use error and inadequacies in labeling. Product complaints can pertain to any marketed JJSV device

being used in the study as well as the investigational device. The investigator is to assess whether the deficiency could have led to a serious adverse event without suitable action or intervention or under less fortunate circumstances.

11.3 ADVERSE EVENT AND COMPLAINT REPORTING REQUIREMENTS

All adverse events and any complaint encountered using any JJSV product, regardless of severity and whether or not attributed to the study device(s), are to be reported to the Sponsor and recorded on the case report form corresponding to the visit during which awareness of the event occurred. Adverse events are also to be reported to the reviewing IRB as per the IRB's reporting requirements. If required, adverse events will be reported to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations.

Reporting of adverse events shall follow the USA Code of Federal Regulations (21CFR812) for sites in the USA. General guidelines are provided below:

Adverse Event Reporting

An adverse event that is not serious or device-related is to be reported to JJSV in a timely manner. Notification of non-serious and non-device related adverse events will occur by recording events on the CRF when noted. Such adverse events are also to be reported to the reviewing IRB per their reporting requirements.

Complaints/Device Deficiency Reporting

A general product complaint or device deficiency is to be reported to the Sponsor in a timely manner. Notification of complaints/device deficiencies will occur by recording complaints on the CRF at the visit the complaint occurs (e.g., operative visit) and/or by a phone call to the Sponsor.

Any device deficiency that could have led to a serious adverse event without suitable action or intervention, or under less fortunate circumstances, must be reported to the sponsor immediately (no later than 24 hours after detection). Device deficiencies that could have led to a serious adverse event should also be reported to the investigator's IRB per their reporting requirements.

Serious and/or Device-Related Adverse Event Reporting

Serious and/or device related events (ADEs) are to be documented using the Detailed Adverse Event CRF. In the event of a serious adverse event (SAE), which may or may not be related to use of the study device, JJSV must be notified immediately (no later than 48 hours after detection). Any SAE is to be reported by phone (and/or email) and by submitting the completed Detailed Adverse Event CRF. Any SAE or device-related AE should also be reported to the investigator's IRB per their reporting requirements.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE) Reporting

If during the study, a serious adverse event occurs that may reasonably be regarded as device-related and was not previously expected in nature, severity, or degree of incidence, the investigator is to report the UADE/USADE to JJSV within 48 hours, and to the investigator's IRB as soon as possible (and no later than 10 working days after learning of the event for sites in the USA as required by 21CFR812).

11.4 CAUSAL RELATIONSHIP

The investigator should always be alert to adverse events that may be related to the study device or the use of the study device (i.e., the procedure specific to the initial application of the device). An attempt should be made in every case to determine the causality of the event. The following definitions are to be used as guidelines in determining the relationship between the event and the study device and/or use of the device.

Definitely related:	If the event is associated with the device and/or the use of the device beyond a reasonable doubt, a causal relationship exists between the adverse event and the device and/or the use of the study device.
Probably related:	There is a reasonable possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event cannot be reasonably explained by another cause.
Possibly related:	The adverse event has not been determined to be related to the device or the use of the device, but no other cause has been identified and the device and/or the use of the study device cannot be ruled out as a possible cause.
Unlikely to be related:	The possibility of a potential causal relationship between adverse event and the device and/or the use of the device could exist, but the adverse event can be reasonably explained by another cause.
Not related:	There is no possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event can be attributed to another cause.

If an adverse event is believed to be definitely, probably, or possibly related to the study device and/or the use of the device, the event will be considered related to the study device and/or the use of the device.

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[REDACTED]

12. PROTOCOL CHANGES/AMENDMENTS

If the investigator wishes to modify any procedure and/or the design of the study, he or she must contact and obtain consent from JJSV regarding the proposed changes prior to implementation. Any modifications (including additional data collection) require approval by the FDA and all other appropriate regulatory agencies, as well as approval of the governing IRBs prior to implementation.

13. ETHICS REVIEW AND PATIENT WELFARE

13.1 INSTITUTIONAL REVIEW BOARD (IRB)

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV.

The investigator is responsible for notifying the IRB of reportable adverse events as well as any other circumstance in which additional procedures outside the protocol were conducted to eliminate apparent hazards to subjects.

13.2 INFORMED CONSENT

The informed consent document will be provided as a physical or electronic document to each study subject for review prior to consenting. If using the electronic document, the study subject will be given an electronic tablet with the preloaded IRB-approved study specific informed consent. The current version of the IRB-approved study informed consent must be signed by each study subject prior to any study-specific examinations being performed. The IRB approved- informed consent is to be signed and dated by the subject as well as by the person who conducted the informed consent discussion. Consent will be documented with required signatures on the physical document or on the electronic document. The signed informed consent will be maintained by the investigator as a permanent part of the subject's medical records. A copy of the signed

and dated form is to be provided to the subject. If the electronic document is used for consenting, study subjects can elect to receive either a printed or electronic copy of the informed consent documents. Signed and submitted informed consent documents will be available as PDFs in an electronic consent repository. The investigator will provide JJSV written acknowledgement on the preoperative case report form that a signed agreement of informed consent has been obtained and is in the investigator's possession for each subject. As required by 21CFR812 Part G, the site shall document in the source documents that informed consent was obtained prior to participation in the study for each subject enrolled.

NOTE: *The informed consent process also includes obtaining the subject's signature on an Authorization for Use/Disclosure of Health Information for Research Form or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries.*

NOTE: *The Sponsor will secure appropriate insurance for study subjects prior to study start.*

14. DOCUMENTATION

14.1 SOURCE DOCUMENTS

Source documents must be kept for all study subjects. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as results of any diagnostic tests or procedures such as topographies or laboratory tests with photographs or instrument printouts.

Each site is expected to adhere to the clinic's own standard documentation requirements for medical charts/clinic notes. For the purposes of this clinical study, the medical charts/clinic notes must also include, at a minimum, the following data that will be considered source data and will be reviewed by the Sponsor:

- Subject's name and study identification number
- Subject's contact information
- Study protocol number and the Sponsor name (JJSV)
- A statement that informed consent was obtained prior to participation in the study (including the date)
- Evidence of subject eligibility
- Dates of all subject visits and surgeries throughout the duration of the study
- Implant serial number identification (NOTE: This is masked information, and may only be reviewed by unmasked study staff)
- Concurrent medications
- Corrected and uncorrected distance visual acuity (NOTE: M&S electronic data and near visual acuity score sheets are considered source documentation and are to be retained by the site. A paper copy of the M&S results will be printed and certified by the site)
- Manifest refraction

- Occurrence and status of any operative complications, postoperative medical or lens findings and adverse events
- Occurrence and status of any subject complaints, e.g., ocular/visual symptoms
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for early exit.

14.2 SUBJECT CONFIDENTIALITY

Subjects will be assigned a unique subject number at the time of enrollment as a means of identification on study documents. Subject confidentiality will be maintained by recording only the subject number on the CRFs. Subject names may possibly be disclosed to JJSV or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to protect and maintain confidentiality of personal information to the extent permitted by applicable laws and regulations.

14.3 CASE REPORT FORM COMPLETION

This study will use an electronic data capture system. All study staff responsible for entering data into the system must complete certification prior to using the system. The investigator is responsible for ensuring that data are properly recorded on each subject's case report forms and related documents. Prior to database lock, the investigator will verify completeness and accuracy of data submitted to JJSV.

14.4 STUDY SUMMARY

A final investigator's summary will be provided to JJSV and the reviewing IRB within 3 months after termination or the completion of the study or the investigator's part of the investigation.

15. MONITORING

The Sponsor will perform three types of monitoring to ensure compliance with regulations: data monitoring, administrative monitoring, and safety monitoring.

15.1 DATA MONITORING

To ensure a well-controlled clinical trial, the Sponsor will follow specific data monitoring procedures, routinely generate reports, and periodically review safety and effectiveness data. To avoid bias, any analyses generated prior to site closures will not be disseminated to any of the investigative sites.

An electronic data capture system (EDC) will be used to transmit case report forms from the investigative site to the Sponsor. Requests for data clarification will be handled through this same system.

To minimize data omissions and inconsistencies on clinical reports and to ensure that data are accurately transcribed to computer data files, the Sponsor will follow internal data processing procedures that include automated and manual quality control checks to

identify any data discrepancies. Any such items will be resolved and documented as needed in EDC.

Prevention of Missing Data

Methods used to safeguard against missing data that can have deleterious effects on the study integrity and reliability of its outcomes will include training study staff via online conferencing, centralized and/or on-site programs. In addition, subjects will be encouraged at the time of informed consent to avoid missing study visits, as missing data may affect the study reliability and diminish the scientific value of their contribution to the study.

15.2 ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that study devices, subjects, and forms can be traced and will allow monitoring of investigator progress and compliance. Accountability and traceability of study devices will be monitored by trained JJSV personnel.

Device Accountability

Complete lens accountability will be maintained at the investigative site by maintaining records of all clinical study products received from and returned to the Sponsor. A site log will be used to track all investigational lenses for date of receipt, eye implanted, serial number, lens power, use and disposition/return to the Sponsor. This site log and any other study lens information will be maintained in the operating room study binder. During periodic investigative site monitoring visits, Sponsor personnel will review site lens inventory records and logs to ensure IOL accountability compliance and investigational lens traceability.

Site Monitoring Plan

Prior to performing any study implants, the requirements of the study and reporting mechanisms will be explained to each investigator either personally at the investigative site or at a formal study investigator meeting. When necessary, a pre-study site qualification visit may be performed to assess the adequacy of the site to perform the study for sites that have not previously worked with the Sponsor or have undergone significant changes or have not been visited in the past year. An initial site visit will be conducted (either in-person or via a web-based meeting) prior to the first implant for all sites.

Throughout the duration of the study, site visits to monitor compliance to this protocol will be made at each investigative site. During interim site monitoring visits, the Sponsor will review informed consent documents and subject eligibility, and the data on study case report forms will be verified against subject charts and other source documents to ensure complete and accurate reporting. The subject files will also be reviewed to assure that all adverse events and any issues encountered with JJSV products have been reported in a timely fashion.

The Sponsor will also review source documents to verify that all required items have been documented in the subject medical charts. Refer to **Section 14.1**, Source Documents, for a list of items that are required for source documentation. In addition to subject files, study logs will be checked and conformance to lighting levels for visual acuity tests will be verified.

Training on study-specific procedures may also be conducted during monitoring visits. For this study in particular, a training/monitoring visit is likely to occur just prior to or during the first of the 1-month and 6-month visits, wherein the most extensive vision testing occurs.

Upon study completion, a final close-out site visit to each site will be made to monitor the last of the subject data records and finalize any outstanding study issues.

A separate Study Monitoring Plan will be established prior to study start that will define the type and frequency of monitoring visits and frequency of record monitoring.

15.3 SAFETY MONITORING

The Medical Monitor will review and assess any reports of serious and/or device-related adverse events as well as device deficiencies that could have led to a serious adverse event. If necessary, the medical monitor will discuss these events with the reporting investigator(s), without being specific about lens type. If unmasking is required by the Medical Monitor to protect the safety of the subject(s), a request will be submitted and approved by Head of Clinical Sciences and Head of Biostatistics prior to release of the randomization code for only the subject(s) involved and the IRB/IEC will be notified. The medical monitor will also be available to answer all questions from investigators. The medical monitor, as well as any other qualified personnel designated by JJSV, shall also review interim progress reports, as applicable.

16. PUBLICATIONS

Refer to the Clinical Study Agreement for information regarding JJSV publication policies. JJSV will complete the final clinical study report and any associated publications accordance with legal requirements and the ethical principles. If applicable, Clinical Investigation will be registered in a publicly accessible database and results will be made publicly available per the legal requirements.

17. RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

Investigational IOL, Model DEN00V

The investigational IOL Model DEN00V is designed to provide far, and intermediate and near vision; however, glasses may still be needed to improve distance vision and/or to have useful vision for intermediate or near tasks. Visual symptoms, particularly dysphotopsias such as halos, night glare, starbursts, etc., are expected to be less than with a standard multifocal IOL; however, such symptoms may still occur. Dysphotopsias

may become less noticeable over time; however, the IOL may be removed if necessary. There may be a reduction in contrast sensitivity under certain conditions compared to a monofocal lens. Due to the optic design caution should be used when interpreting results of autorefractors.

GENERAL RISKS OF CATARACT SURGERY AND IOL IMPLANTATION

There are risks and complications associated with cataract surgery and IOL implantation in general. These can include worsening of vision, hemorrhage, loss of corneal clarity, inflammation, infections, retinal detachment, pupil changes, glaucoma, etc.

Complications can result in poor vision, loss of vision or loss of the eye. Any events that are unlikely but anticipated (e.g., endophthalmitis) will be reported to the FDA.

Potential risks and complications include:

- Endophthalmitis / Intraocular infection
- Hypopyon
- Hyphema
- IOL dislocation
- Persistent cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Persistent corneal stromal edema
- Persistent iritis
- Persistent raised intraocular pressure (IOP) (i.e., is present at the last study visit) requiring treatment
- Toxic anterior segment syndrome
- Secondary surgical intervention (including implant repositioning, removal, AC tap, or other surgical procedure)
- Any other adverse event that leads to permanent visual impairment or requires surgical or medical intervention to prevent permanent visual impairment.

RISK MANAGEMENT

Subjects will be closely monitored throughout the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to the Sponsor according to **Section 11.0**, Adverse Events and Product Complaints.

Additionally, the Sponsor will monitor incoming data following the procedures outlined in **Section 15.0**, Monitoring. The Medical Monitor will ensure subjects are not exposed to additional risks by monitoring serious adverse events, device-related adverse events, and device-deficiencies that could have led to serious adverse events (**Section 15.3**, Safety Monitoring).

POTENTIAL BENEFITS

The general clinical performance of the investigational IOL Model DEN00V is expected to be similar to the control IOL Model ZCB00 regarding distance visual acuity and safety outcomes. Improved vision in the intermediate to near range, as well as functionality for certain tasks, may be achieved with the investigational IOL compared to the control IOL.

CONCLUSION

The hazards/risks associated with the investigational IOL Model DEN00V are acceptable and within the range of those of other advanced-optic IOLs from JJSV. The potential clinical benefits of the investigational device outweigh each individual risk and the overall residual risk when the device is used as intended.

18. RECORDS RETENTION

All study-related correspondence, subject records, consent forms, Authorization for Use/Disclosure of Health Information Forms or similar medical treatment privacy law documentation, records of the distribution and use of all study products, and original case report forms should be maintained by the investigator.

The essential documents must be retained for a period of time as indicated in applicable country laws and regulations for the investigative site. The essential documents should be retained for at least two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least two years after the formal discontinuation of the clinical development of the investigational product (IP). The essential documents should not be destroyed without prior written agreement between the Investigator and JJSV. JJSV must be notified before the disposal of any essential documents, even if retention requirements are met.

Sponsor must be notified if the Investigator wishes to assign the study records to another party or move them to another location.

- All case report forms
- All adverse event information (detailed adverse event forms, follow-up letters, etc.)
- Investigational supply records/inventory
- IRB approval documentation
- Study correspondence
- Study agreements
- Site visit documentation
- Protocol(s) and the reason for any deviations from the protocol
- Subject log(s)
- Clinical Investigator's Brochure

- Completed subject informed consent forms and medical privacy forms (e.g., Authorization for Use/Disclosure of Health information)
- Subject medical chart/clinic notes

19. TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event of high levels of complications and/or adverse events that are unexpected in nature and/or severity and evaluated as to causality relative to the study device. The clinical investigation may be suspended if the Medical Monitor or the IRB, upon review and evaluation of the clinical data, finds unacceptable clinical performance or the level of single or total complications and/or adverse events unacceptable for continuation of the investigation.

If causality is shown not to be related to the study device, the study may be resumed in accordance with the IRB and regulations of the FDA. The study will be terminated if causality is shown to be related to the study device.

Additionally, the investigator or JJSV may stop a subject's participation at any time. The Sponsor may also stop the study at any time for reasons it determines appropriate. However, no suspension of the study would be made to disadvantage the study subjects. Following suspension of the study for any reason, all study subjects who have already received treatment would continue to be followed through completion of the study visit schedule.

20. STATISTICAL METHODS

This section highlights the analyses planned for key study endpoints. The 6-month postoperative visit is the primary analysis time point for all endpoints, although data will be summarized at all other time points when collected. Further details will be provided in the Statistical Analysis Plan (SAP).

20.1 ANALYSIS POPULATION

- **ITT:** Intent-to-treat (ITT) population will consist of all subjects randomized. Subjects will be analyzed per planned randomization schema.
- **Safety:** Safety Population (SP) will consist of all subjects for whom a study IOL touched the eye. Subjects will be analyzed per IOL received or attempted.
- **Per-Protocol:** First-eye Per-Protocol Population (first-eye PP) will include the first eyes with an investigational or control lens implanted, evaluated within the proper study interval and without clinically relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints) as determined prior to database lock.
- **Best-case safety population:** will consist of eyes in the safety population with no pre-operative ocular pathology, no macular degeneration detected at any time, and no previous surgery for the correction of refractive error.

20.2 MISSING DATA HANDLING RULES

The primary and secondary effectiveness endpoints analyses are based on the first-eye data. Missing values for the primary (DCIVA and BCDVA) and secondary (DCNVA) effectiveness endpoints, regardless of being collected from bilateral subjects or unilateral subjects, will be handled as described below. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The observed case data analysis (ignoring missing data) will be performed for completeness.

20.3 INTERIM ANALYSIS

There is no planned interim analysis for this study.

20.4 EFFECTIVENESS ENDPOINTS ANALYSIS

The ITT population will be the primary analysis set for the primary endpoints (DCIVA and defocus) and the secondary effectiveness endpoint. [REDACTED]

[REDACTED]

Effectiveness of the lens and study success will be demonstrated if all success criteria for the following three primary endpoints are simultaneously met based on the ITT multiple imputation analysis for DCIVA and BCDVA and ITT observed case for defocus curve.

To control the overall study Type I error rate at 0.05 level, all the hypothesis tests on the primary endpoints must show statistical significance simultaneous (statistical success) before testing the secondary effectiveness endpoint (DCNVA) at full one-sided alpha level of 0.025.

[REDACTED]

Primary Effectiveness Endpoints

MONOCULAR PHOTOPIC DCIVA AT 66 CM

The first primary endpoint is the mean (logMAR), monocular (first eye) DCIVA (66 cm) under photopic conditions at 6 months. The mean, SD, median, minimum, maximum and two-sided 95% C.I. will be reported by IOL group. The comparison between lens groups will be performed using a one-sided, two-sample t-test at the alpha level of 0.025. Note that a lower or more negative logMAR values denote better visual acuity. The null hypothesis is that the mean monocular DCIVA logMAR value for eyes in the investigational group is worse than or equal to that for control eyes. The alternate hypothesis is that the mean monocular DCIVA logMAR value for eyes in the investigational lens group is better than that for control eyes.

$H_0: \mu_c - \mu_t \leq 0$ (DEN00V is worse than (higher logMAR) or equal to control)

$H_1: \mu_c - \mu_t > 0$ (DEN00V is better (lower logMAR) than control)

where

μ_t = the mean logMAR DCIVA for investigational (DEN00V)

μ_c = the mean logMAR DCIVA for control (ZCB00)

Statistically significant superiority of the investigational lens will be achieved if pvalue ≤ 0.025 . The clinical performance criterion is the median logMAR DCIVA value at 66 cm to be at least 0.20 logMAR in the investigational lens group.

MONOCULAR DEPTH OF FOCUS

The second primary endpoint is the mean monocular depth of defocus where visual acuity is 0.20 logMAR or better at 6 months (measured only negative direction from zero) for first eyes in investigational vs. control groups at 6 months. The mean visual acuity at each diopter of defocus will be plotted to obtain a defocus curve for both lens groups. The diopter of defocus where mean visual acuity crossing the 0.20 logMAR threshold will be calculated for each IOL group [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

MONOCULAR PHOTOPIC BCDVA AT 4 M

The third primary effectiveness endpoint is the mean (logMAR) first-eye, monocular BCDVA (4 m) at 6 months postoperative. The mean, SD, median, minimum, maximum and two-sided 90% CI for BCDVA will be reported by IOL group. The hypothesis is that the investigational lens is non-inferior to the control lens. This is demonstrated by the

lower limit of the 90% two-sided confidence interval (CI) of the difference in mean (logMAR) first-eye monocular BCDVA (4 m) at 6 months not exceeding the non-inferiority margin of -0.10 logMAR. The two-sided 90% confidence interval will be calculated using the two-sample t-test statistic.

$H_0: \mu_c - \mu_t \leq -0.10$ (DEN00V is inferior to control)

$H_1: \mu_c - \mu_t > -0.10$ (DEN00V is not inferior to control)

where

μ_t = mean logMAR BCDVA for investigational (DEN00V)

μ_c = mean logMAR BCDVA for control (ZCB00)

The statistical criterion requires the lower bound of the 2-sided 90% confidence interval for the difference between the IOLs to be greater than -0.10 logMAR.

[REDACTED]

[REDACTED]

20.5 PRIMARY SAFETY ENDPOINTS

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20.8 SAMPLE SIZE CALCULATIONS

The study sample size satisfies the requirements for a Level B modification of a parent lens per ISO/TR 22979:2017(E) and ANSI Z80.35-2018 which requires a minimum of 100 bilaterally implanted evaluable subjects in each IOL group. The screen failure rate is assumed to be around 10%, and the dropout rate up to 6 months is assumed to be

approximately 10%. Accounting for the screen failure rate and the dropout rate, the study will enroll approximately 250 subjects [REDACTED]

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1. Monocular Photopic Distance Corrected Intermediate Visual Acuity (66 cm)

For monocular (first-eye), distance-corrected intermediate visual acuity (DCIVA), with 100 subjects in each lens group there is over 90% power to detect a 0.10 logMAR or greater difference in mean visual acuity between the investigational and control lens groups using a one-sided two-sample t-test at a one-sided alpha of 0.025 and assuming a standard deviation of 0.16 logMAR.

2. Monocular Depth of Focus

There is no statistical comparison for this endpoint; therefore, no formal sample size calculation was performed.

3. Monocular Photopic Best-Corrected Distance Visual Acuity (4 m)

For monocular (first-eye), best-corrected distance visual acuity (BCDVA), with 100 subjects in each lens group there is over 90% power to conclude non-inferiority in visual acuity between the investigational and control lens groups at one-sided alpha of 0.05 with non-inferiority margin of 0.10 logMAR, assuming no difference between the IOLs and a standard deviation of 0.12 logMAR. The two-sided 90% confidence interval will be calculated using the two-sample t-test statistic.

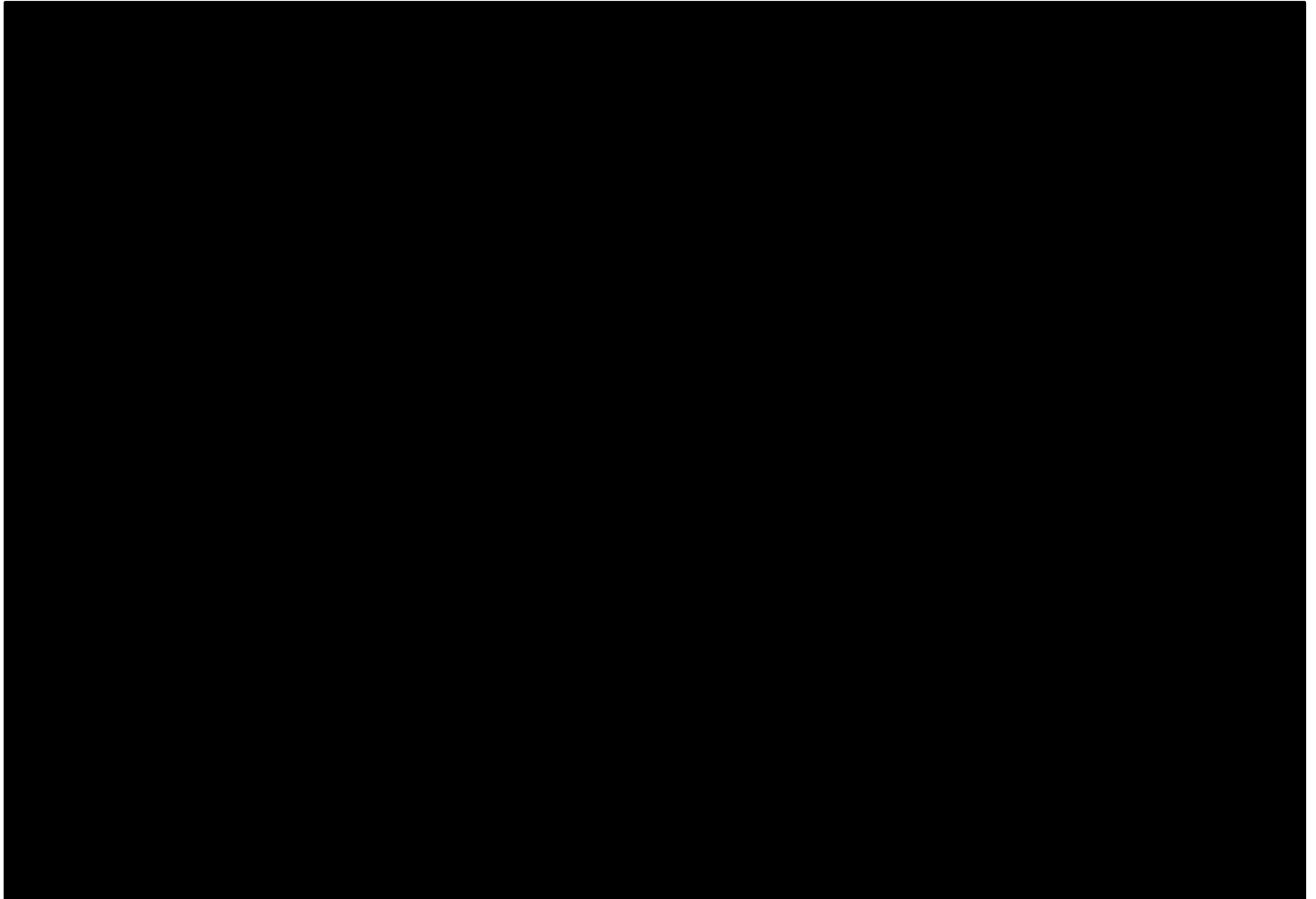
4. Monocular Photopic Distance Corrected Near Visual Acuity (40 cm)

For monocular (first-eye), distance-corrected near acuity (DCNVA), with 100 subjects in each lens group there is over 90% power to detect a 0.10 logMAR or greater difference in mean visual acuity between the investigational and control lens groups at using a one-sided two-sample t-test at a one-sided alpha of 0.025 and assuming standard deviation of 0.16 logMAR.

Because the gate keeping testing approach applies for testing the primary endpoints first, followed by the secondary endpoint, the sample size calculation for the secondary endpoint of DCNVA at 40 cm was performed at the nominal one-sided 0.025 alpha level.

21. FUNDING

The funding of this clinical trial will be provided by the sponsor, Johnson & Johnson Surgical Vision, and is documented in the Clinical Study Agreement between the sponsor and the investigator/institution.



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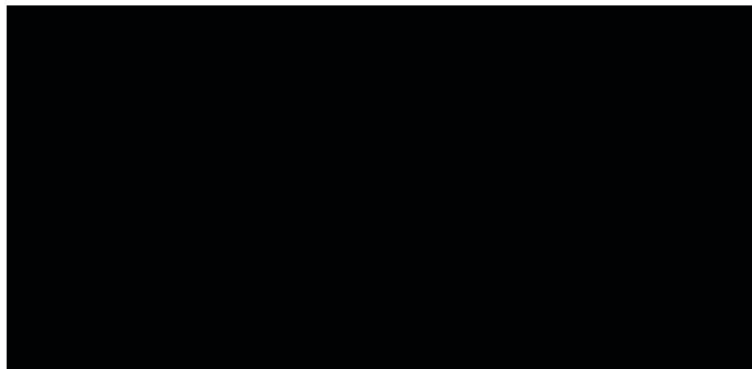
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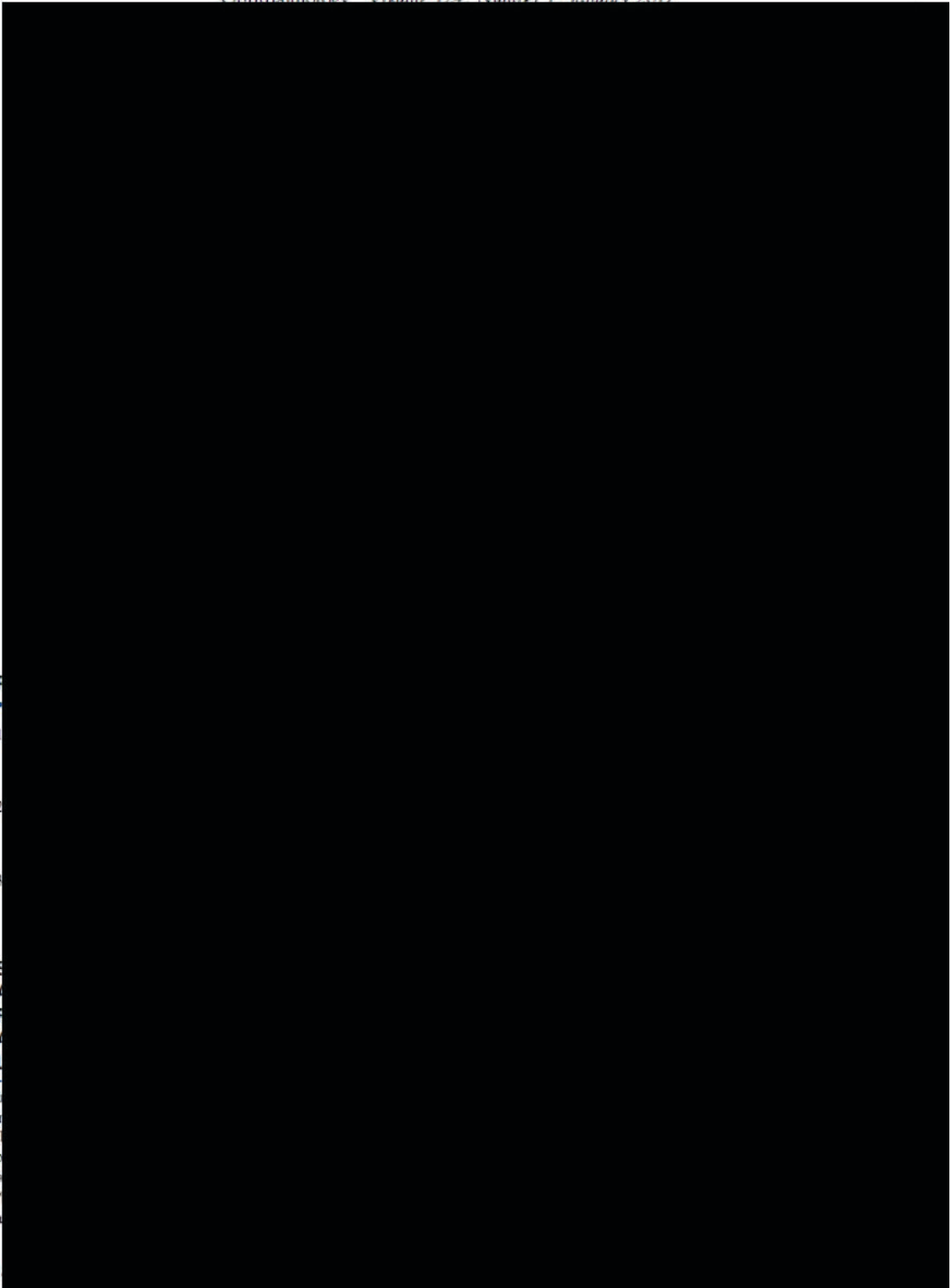
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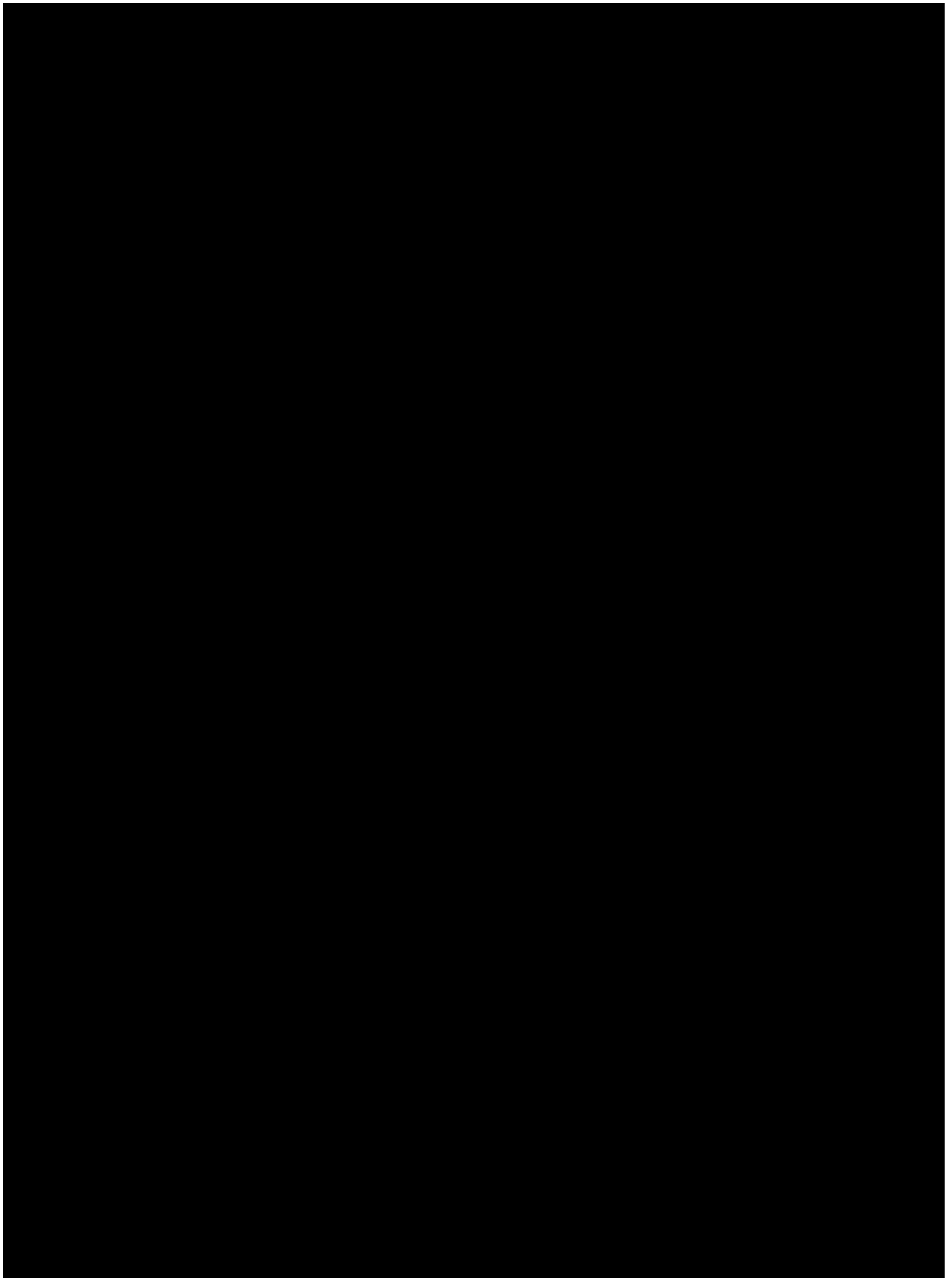
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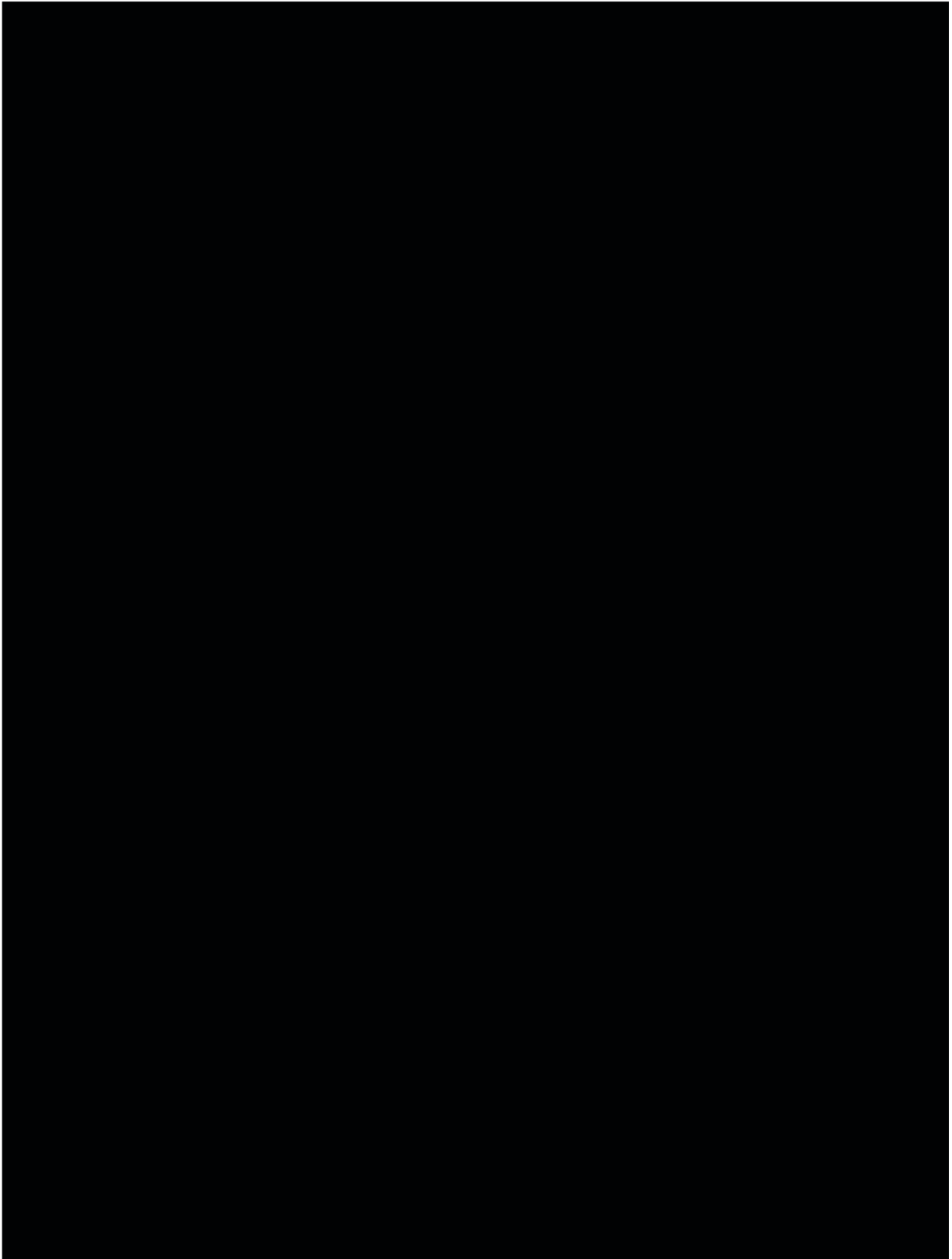
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Ophthalmology, Volume 124, Number 1, January 2017



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