Study Protocol

POST-APPROVAL STUDY OF THE TECNIS SYMFONY® TORIC LENSES

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POST-APPROVAL STUDY OF THE TECNIS SYMFONY® TORIC LENSES

PROTOCOL NUMBER: TIOL-205-STPA

SPONSOR:
Johnson & Johnson Surgical Vision, Inc.
1700 E. Saint Andrew Place
Santa Ana, CA 92705 USA
(714) 247-8200

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, ISO 14155:2011 and all 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, Inc. 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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[redacted]

PROTOCOL CHANGE HISTORY

Version	Section(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	Original	N/A
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]

1. SYNOPSIS

PROTOCOL TITLE: Post-Approval Study of the TECNIS Symfony® Toric Lenses

Protocol Number: TIOL-205-STPA

STUDY TREATMENTS:

Toric Study Lenses:

- TECNIS Symfony Toric Extended Range of Vision IOL (Symfony Toric), Model ZXT300
- TECNIS Symfony Toric Extended Range of Vision IOL (Symfony Toric), Model ZXT375

Toric Control Lens:

- TECNIS Symfony Toric Extended Range of Vision IOL (Symfony Toric), Model ZXT150

Other Study Lenses (may be used for fellow eyes):

- TECNIS Symfony Toric Extended Range of Vision IOL (Symfony Toric), Model ZXT225
- TECNIS Symfony Extended Range of Vision IOL (Symfony), Model ZXR00

STUDY OBJECTIVE: The purpose of this post-approval study is to evaluate the rates of bothersome visual symptoms in a larger population in clinical practice for the TECNIS Symfony Toric IOLs with approximately 2.0 D or more of cylinder correction at the corneal plane (Models ZXT300 and ZXT375, higher-cylinder group), compared to the Symfony Toric IOL with approximately 1.0 D of cylinder correction at the corneal plane (Model ZXT150, lower-cylinder group), and to ensure the continued safety of the approved devices.

CLINICAL HYPOTHESIS: The rate of bothersome visual symptom items [redacted] for the Symfony Toric IOL higher-cylinder group will be comparable to that of the lower-cylinder group.

[redacted]

OVERALL STUDY DESIGN:

Structure:	Prospective, multicenter, bilateral, non-randomized, open-label, comparative clinical study
Number of Sites:	Up to 50 sites in the USA
Duration:	6 months; however, any subject that undergoes a lens repositioning procedure due to IOL misalignment, or [redacted] at 6 months, will be followed through 1 year postoperatively.
Administration:	Surgeons will perform routine small-incision, cataract surgery and use the JJSV-recommended implantation systems for lens implantation. Refractive target outcomes will be emmetropia for both eyes.
Visit Schedule:	Subjects will be bilaterally implanted; the second eye is to be implanted within approximately one month after the first-eye surgery. All subjects will undergo a minimum of 9 visits: Preoperative for both eyes; Operative, 1-day and 1-week visits for each eye; and 1-month and 6-month visits for both eyes together. In addition, a 1-year postoperative visit will be required for subjects who undergo a lens repositioning procedure due to IOL misalignment at any time during the study, and for subjects who report [redacted] visual symptoms [redacted] at 6 months.

STUDY POPULATION CHARACTERISTICS:

Condition:	Bilateral cataracts with corneal astigmatism in at least 1 eye of approximately 2.00 D to 3.00 D (higher-cylinder group) or approximately 1.00 D to 1.50 D (lower-cylinder group) based on the combination of preoperative keratometric cylinder,

	the expected effect of surgically-induced astigmatism (SIA), use of the optional posterior corneal astigmatism (PCA) algorithm and TECNIS Symfony Toric Calculator outcomes of ZXT300 or ZXT375 (higher-cylinder group) or ZXT150 (lower-cylinder group).
Number of subjects:	Up to 634 subjects will be enrolled to achieve bilateral implantation in approximately 506 subjects, resulting in approximately 240 evaluable subjects in the higher-cylinder group and 240 evaluable subjects in the lower-cylinder group at 6 months [redacted] This is a bilateral study; both eyes must be implanted with a TECNIS Symfony IOL, either toric (Models ZXT150, ZXT225, ZXT300 or ZXT375) or non-toric (TECNIS Symfony Extended Range of Vision IOL, Model ZXR00). Each eye may have a different TECNIS Symfony IOL implanted, as determined by the surgeon and the TECNIS Symfony Toric IOL calculator; however, at least one eye must be implanted with either a Symfony Toric IOL Model ZXT150 (lower-cylinder group) or a Model ZXT300 or ZXT375 (higher-cylinder group) and the fellow eye must have the same or a lower toric power. The eye with the highest toric power IOL will determine the model group. NOTE: No site may enroll more than 25% of the enrollment total.

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

- Minimum 22 years of age
- Bilateral cataracts for which phacoemulsification extraction and posterior chamber IOL implantation have been planned
- Preoperative keratometric cylinder of:
  - Approximately 2.00 D to 3.00 D resulting in a calculated lens power (using the web-based TECNIS Symfony Toric IOL Calculator) that requires implantation of a ZXT300 or ZXT375 IOL in at least one eye for the subject to be eligible for the higher-cylinder group, or

  - Approximately 1.00 D to 1.50 D resulting in a calculated lens power (using the web-based TECNIS Symfony Toric IOL Calculator) that requires implantation of a ZXT150 IOL in at least one eye for the subject to be eligible for the lower-cylinder group
  - The eye with the higher toric power IOL will determine the model group
  - The fellow eye must be the same or a lower toric power
- Predicted residual refractive cylinder based on the TECNIS Symfony Toric IOL calculator, taking surgically-induced astigmatism into account and using the posterior corneal astigmatism option, must be ≤0.50 D for all toric eyes
- Clear intraocular media other than cataract in each eye
- Availability, willingness, ability and sufficient cognitive awareness to comply with examination procedures and study visits
- Ability to understand, read and write English in order to consent to study participation and complete study questionnaires
- Signed informed consent and HIPAA authorization

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

- Irregular corneal astigmatism
- Any clinically-significant corneal pathology/abnormality other than regular corneal astigmatism
- Previous corneal surgery
- Recent ocular trauma or intraocular surgery that is not resolved/stable or may affect visual outcomes
- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils)
- 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
- Known ocular disease or pathology that, in the opinion of the investigator, may affect visual acuity or require surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.)
- Concurrent participation or participation during 30 days prior to preoperative visit in any other clinical study
- Planned monovision correction
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes

EVALUATION CRITERIA:

The purpose of this post-approval study is to evaluate the rates of bothersome visual symptoms for the higher-cylinder Symfony Toric IOLs, Models ZXT300 and ZXT375, compared to the lower-cylinder Symfony Toric IOL, Model ZXT150. The first primary endpoint is the rate of bothersome visual symptoms [redacted]. The second primary endpoint will be the rate of those having a lot of difficulty with an activity due halos, glare or starbursts as measured in the PRVSQ.

Other endpoints are individual visual symptom ratings included in the PRVSQ, rates of IOL repositioning procedures (secondary surgical intervention) due to IOL misalignment, rates of explants due to visual symptoms, distance visual acuities, mean percent reduction in absolute cylinder, mean refractive cylinder, mean refractive cylinder compared to the preoperatively-predicted cylinder, mean spherical equivalent, spherical equivalent compared to the preoperatively-predicted spherical equivalent, percent of eyes with cylinder and spherical equivalent (MRSE) within 0.50 D and within 1.00 D of the preoperatively-predicted spherical equivalent, rates of medical and/or lens findings, and rates of other adverse events. Preoperatively-predicted values will be based upon those generated from the TECNIS Symfony Toric IOL calculator.

DATA ANALYSIS:

The key time frame for analysis will be the 6-month visit. The first primary endpoint for this study will be the rate of bothersome visual symptoms, [redacted]. The second primary endpoint will be the rate of those having a lot of difficulty with an activity due to halos, glare or starbursts as measured in the PRVSQ. The primary endpoint results will be compared between higher-cylinder toric IOL subjects and lower-cylinder toric control IOL subjects at the 6-month visit. The frequency, proportion and 95% Confidence Interval (CI) will be reported for higher-cylinder and lower-cylinder control subjects. This will be done for the higher-cylinder (ZXT300 and ZXT375) and lower-cylinder (ZXT150) groups.

Descriptive statistics will be used for reporting results. Visual acuity data will be reported by acuity line achieved. For questionnaire items, the frequency and proportion for each response will be reported. For refractive data, descriptive statistics will include mean, standard deviation, median, minimum and maximum and also the percent achieving absolute values within 0.50 D and 1.00 D of preoperatively-predicted values.

The frequency and proportion of primary and fellow eyes with adverse events or medical/lens findings will also be reported.

STUDY VISITS AND PROCEDURES:

Inclusion and exclusion qualifications will be assessed at the preoperative visit according to the inclusion/exclusion criteria. The Informed Consent Document 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. Each subject will receive Symfony IOLs in both eyes, according to the TECNIS Symfony Toric IOL calculator, and will be placed in either the higher-cylinder group or the lower-cylinder control group based on the IOL with the highest toric power.

Key preoperative data include ocular health and history, distance visual acuities, manifest refraction, keratometry, biomicroscopic slit-lamp findings, ocular symptoms and biometry. The operative visit will include standard procedures for cataract surgery and IOL implantation. Key postoperative data collection includes non-directed visual symptoms, questionnaires, distance visual acuities, manifest refraction, keratometry, slit-lamp findings and adverse events.

2. BACKGROUND/INTRODUCTION

Amongst patients undergoing cataract surgery, approximately 35-41% of cataract patients have ≥ 0.75 diopter of corneal astigmatism, with 15%-20% having ≥ 1.5 D of corneal astigmatism.[1,2] Although there are various modalities to reduce the amount of astigmatism during cataract surgery (e.g., limbal relaxing incisions, etc.), toric IOLs are now commonly used for correction of aphakia and pre-existing ocular astigmatism.

The TECNIS Symfony Extended Range of Vision IOLs were designed in response to a patient need for lenses that can provide good distance vision, improved intermediate and near vision compared to standard monofocal IOLs, and less dysphotopsia compared to a multifocal IOL. The Symfony IOLs utilize diffractive technology to mitigate the effects of presbyopia by providing an extended depth of focus, while keeping visual symptoms to a minimum and reducing chromatic aberration. In addition, the Symfony Toric IOLs include an anterior aspheric optic with a toric surface to correct for ocular astigmatism.

On July 15, 2016, JJSV received USA FDA approval (P980040/S065) for the TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, and the TECNIS Symfony Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300 and ZXT375, for the visual correction of aphakia and pre-existing corneal astigmatism of 1 diopter or greater. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. [redacted]

[redacted]

3. CLINICAL HYPOTHESIS

The rate of bothersome visual symptom items [redacted] for the Symfony Toric IOL higher-cylinder group will be compared to the rate for the lower-cylinder group. The bothersome visual symptom items of interest are halos, glare, and starbursts.

4. STUDY DESIGN

This study is a prospective, multicenter, bilateral, non-randomized, open-label, comparative, 6-month clinical study conducted at up to 50 sites in the USA. Subjects who meet the inclusion/exclusion criteria will be bilaterally implanted with Symfony IOLs, with either 1) Model ZXT300 or ZXT375 IOLs (higher-cylinder group), or 2) control Model ZXT150 (lower-cylinder control group) IOL, implanted in at least one eye, according to the TECNIS Symfony Toric IOL calculator. The fellow eye will be allowed to have any Symfony IOL implanted, according to the TECNIS Symfony Toric IOL calculator, provided it is the same or a lower toric power as the primary eye. The eye with the highest toric power IOL will determine the model group.

JUSTIFICATION OF STUDY DESIGN

[redacted]

5. ACROYNYMS

The following acronyms are used throughout the document:

- UCDVA: uncorrected distance visual acuity
- BCDVA: best corrected distance visual acuity
- D: diopters

6. STUDY OBJECTIVES AND ENDPOINTS

The objective of this post-approval study is to evaluate the rate of bothersome visual symptoms [redacted] at 6 months for the Symfony Toric IOLs with approximately 2.0 D or more of cylinder correction at the corneal plane (Models ZXT300 and ZXT375) in a larger population in clinical practice compared to the control IOL (Symfony Toric Model ZXT150 IOL), and to ensure the continued safety of the approved devices.

Study endpoints will be evaluated at 6 months postoperatively.

6.1 PRIMARY ENDPOINT:

The primary co-endpoints are the rate of bothersome visual symptoms and the rate of difficulty with an activity due to the symptoms at 6 months postoperative. [redacted] The rate of difficulty with an activity due to the symptoms is determined by the percentage of subjects who respond "Yes" to the question "Is there anything you have a lot of difficulty with, or do not do, because of (visual symptom) at 6 months postoperative. [redacted]

- [redacted]
- [redacted]
- [redacted]

The frequency and proportion of subjects reporting one or more of these items [redacted] via PRVSQ questionnaire will be used to determine the primary endpoint. This rate will be calculated for the higher-cylinder (ZXT300 and ZXT375) and lower-cylinder (ZXT150) groups.

6.2 OTHER ENDPOINTS:

- Other questionnaire responses, such as rates of degree of bother
- Rates of IOL repositioning procedures (secondary surgical intervention) due to IOL misalignment
- Rate of explants related to visual symptoms
- Rates of other adverse events
- Monocular uncorrected distance visual acuity
- Monocular best corrected distance visual acuity

- Mean percent reduction in absolute cylinder
- Mean refractive cylinder and mean refractive cylinder compared to preoperatively-predicted cylinder
- Mean spherical equivalent and mean spherical equivalent compared to preoperatively-predicted spherical equivalent
- Percent of eyes with absolute cylinder within 0.50 D and within 1.00 D of preoperatively-predicted cylinder
- Percent of eyes with spherical equivalent within 0.50 D and within 1.00 D of preoperatively-predicted spherical equivalent
- Rates of medical and/or lens findings

7. STUDY PRODUCTS

7.1 INTRAOCULAR LENSES

TECNIS Symfony IOLs, both toric and non-toric, are posterior-chamber, 1-piece, aspheric, hydrophobic acrylic foldable IOLs and are to be implanted in the capsular bag following cataract extraction. The Symfony IOLs have a spherical posterior optic with a diffractive surface to provide an extended depth of focus and an anterior aspheric optic; the Symfony Toric IOLs also have a toric surface to correct for ocular astigmatism.

The TECNIS Symfony Toric Model Series ZXT IOLs included in this study are intended for cataract patients with pre-existing corneal astigmatism that, when taking surgically-induced astigmatism into account and using the TECNIS Symfony Toric Calculator's PCA algorithm, have approximately 2.00 D to 3.00 D (higher-cylinder group) or 0.75 D – 1.50 D (lower-cylinder group) of predicted corneal astigmatism to be corrected (**Table 1**).

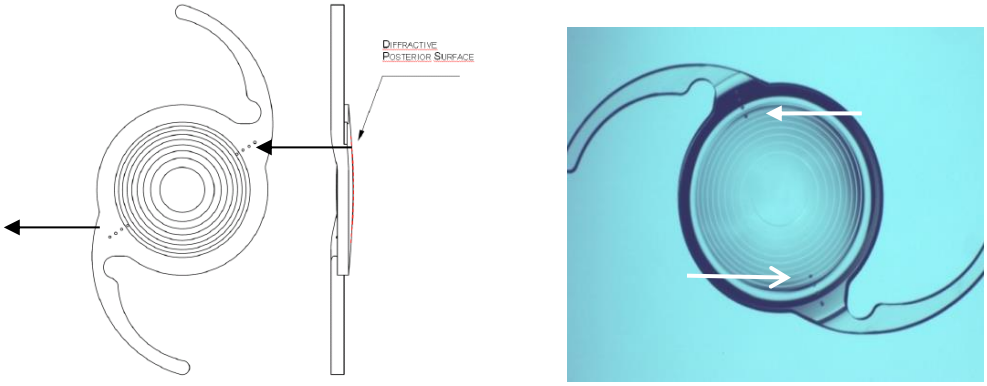
TABLE 1
Symfony Toric IOL Astigmatism Correction Range

ZXT IOL Model	Cylinder Power (D)		Correction Range Based on Combined Corneal Astigmatism (Preoperative Kcyl[a] + SIA[b])
	IOL Plane	Corneal Plane	
ZXT150	1.50	1.03	0.75 – 1.50 D
ZXT225	2.25	1.55	1.50 – 2.00 D
ZXT300	3.00	2.06	2.00 – 2.50 D
ZXT375	3.75	2.57	2.50 – 3.00 D

[a] Keratometric cylinder
[b] Surgically-induced astigmatism
[c] Model ZXT225 eyes may be included in the study; however, the fellow eye must require either a ZXT300 or ZXT375 IOL. Model ZXT225 is not the subject of this study.

The Model ZXT IOLs have two sets of four axis orientation marks 180° apart in the outer periphery of the anterior optic surface (**Figure 1**) to indicate the meridian of the lowest power (flat meridian). These axis orientation marks are for proper alignment of the flat meridian of the IOL with the steep meridian of the corneal curvature.

FIGURE 1: Drawing and Photograph of a Model Series ZXT IOL



INDICATION

The TECNIS Symfony Toric Extended Range of Vision IOLs, including Models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model Series ZXT IOLs are intended for capsular bag placement only. Note that Model ZXT225 may be included in the study; however, the fellow eye must require either a Model ZXT300 or ZXT375 IOL. Model ZXT225 is not the subject of this study.

The TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. Note that Model ZXR00 will only be implanted in fellow eyes for this study.

STORAGE AND DISTRIBUTION

All lenses will be obtained from the site's own inventory. 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.

Table 2 lists the general design characteristics of the Symfony Toric IOLs:

TABLE 2
Lens Characteristics of the Symfony Toric Model ZXT

CHARACTERISTICS	Symfony Toric IOL Model Series ZXT
Lens Design	1-piece foldable posterior-chamber lenses with a toric-aspheric anterior surface, a diffractive design on the posterior surface, and a maximum and a minimum radii of curvature perpendicular to each other
Lens Model	Surface-treated SENSAR® soft acrylic (hydrophobic acrylic with a covalently-bound UV absorber)
DIMENSIONAL FEATURES	
Overall Diameter	13.0 mm
Optical Center Thickness	0.7 mm (20.0 D Lens)
Haptic Angle	No angulation, but offset from the optic body
Optic Body Diameter	6.0 mm
Haptic Material	Same as optic
Haptic Width	0.39 mm
Haptic Thickness	0.46 mm
Haptic Style	TRI-FIX Design Modified C, integral with optic
Other Features	Axis orientation marks
OPTICAL FEATURES	
Optic Shape	Biconvex
Anterior Optic Profile	Toric aspheric with a maximum and a minimum radii of curvature perpendicular to each other
Posterior Optic Profile	Spherical
Optic Edge Design	PROTEC™ squared posterior edge
Dioptric Power Range	+5.0 to +34.0 D in 0.50 D increments
Cylinder Power Range	1.50 D, 2.25 D[b], 3.00 D and 3.75 D (at the IOL plane)
Refractive Index	1.47 (at 35° C)
Theoretical A-constant[a]	118.8 for ultrasound biometry 119.3 for optical biometry

[a] For lens power calculations, the investigator's personalized A-Constant or Surgeon Factor for the TECNIS Symfony Model ZXR00 IOL or TECNIS Symfony Toric Model ZXT IOLs is to be used.

[redacted]

7.2 IOL IMPLANTATION SYSTEMS

[redacted]

8. STUDY POPULATION

All study subjects will be enrolled from the normal surgical cataract population at up to 50 sites in the U.S.A. This study will include only subjects intended to undergo bilateral primary phacoemulsification cataract extraction and IOL implantation who have either approximately 2.00 D to 3.00 D (higher-cylinder group) or approximately 1.00 D to

1.50 D (lower-cylinder control group) of corneal astigmatism requiring correction in at least one eye. The lenses to be implanted will be calculated using the TECNIS Symfony Toric Calculator and based on the combination of preoperative keratometric cylinder, the expected effect of SIA and the PCA algorithm. [redacted] The eye with the highest toric power IOL will determine the model group.

Up to 634 subjects will be enrolled to achieve approximately 506 bilaterally implanted subjects, resulting in approximately 480 evaluable subjects at 6 months, 240 in the higher-cylinder group and 240 in the lower-cylinder group. [redacted] The eye implanted with the highest toric power IOL will determine the model group.

All patients who sign the informed consent will be enrolled in the study and subjects that meet the inclusion and exclusion criteria (Section 8.1 and 8.2) in both eyes will be offered treatment in the study. Eligibility criteria may not be waived by the investigator. Any questions regarding patient eligibility are to be discussed with JJSV prior to subject treatment. Those subjects who meet the criteria and agree to participate will be enrolled in either the higher-cylinder group or the lower-cylinder group, according to the TECNIS Symfony Toric IOL calculator. Subjects will be treated sequentially at each site until the total recruitment goals for each lens model are met.

8.1 INCLUSION CRITERIA:

Note: All criteria apply to each eye unless otherwise indicated:

- Minimum 22 years of age
- Bilateral cataracts for which phacoemulsification extraction and posterior chamber IOL implantation have been planned
- Preoperative keratometric cylinder of:
  - Approximately 2.00 D to 3.00 D resulting in a calculated lens power (using the web-based TECNIS Symfony Toric IOL Calculator) that requires implantation of a ZXT300 or ZXT375 IOL in at least one eye for the subject to be eligible for the higher-cylinder group, or

  - Approximately 1.00 D to 1.50 D resulting in a calculated lens power (using the web-based TECNIS Symfony Toric IOL Calculator) that requires implantation of a ZXT150 IOL in at least one eye for the subject to be eligible for the lower-cylinder group
  - The eye with the higher toric power IOL will determine the model group
  - The fellow eye must be the same or a lower toric power
- Predicted residual refractive cylinder based on the TECNIS Symfony Toric IOL calculator, taking surgically-induced astigmatism into account and using the posterior corneal astigmatism option, must be ≤0.50 D for all toric eyes
- Clear intraocular media other than cataract in each eye
- Availability, willingness, ability and sufficient cognitive awareness to comply with examination procedures and study visits
- Ability to understand, read and write English in order to consent to study participation and complete study questionnaires
- Signed informed consent and HIPAA authorization

8.2 EXCLUSION CRITERIA:

Note: All criteria apply to each eye

- Irregular corneal astigmatism
- Any clinically-significant corneal pathology/abnormality other than regular corneal astigmatism
- Previous corneal surgery
- Recent ocular trauma or intraocular surgery that is not resolved/stable or may affect visual outcomes
- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils)
- 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
- Known ocular disease or pathology that, in the opinion of the investigator, may affect visual acuity or require surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.)
- Concurrent participation or participation during 30 days prior to preoperative visit in any other clinical study
- Planned monovision correction
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes

9. INVESTIGATOR APPROVAL

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select ophthalmic surgeons who have completed a residency in ophthalmology (or its documented equivalent) and are licensed to practice medicine and perform surgery at his/her investigative site. [redacted]. 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 only make changes to a protocol after notifying and obtaining approval from JJSV, the FDA, and the Institutional 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 study-related duties
- Be responsible for protecting the rights, safety and welfare of subjects under the investigator's care
- Maintain confidentiality as required by HIPAA or similar laws and regulations
- Shall not obtain written informed consent of any subject to participate or allow any subject to participate before FDA and IRB approval are obtained
- Document in each subject's case history that informed consent was obtained prior to participation in the study
- Report to JJSV any adverse experiences and/or device defects or malfunctions that occur during the course of 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, etc.) and/or the IRB
- Submit progress reports on the study to JJSV and the reviewing IRB at regular intervals, but no less often than yearly as required by the FDA Guidance Document on PAS "Procedures for Handling Post-Approval Studies Imposed by PMA Order," dated June 15, 2009.

- 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 subjects to the IRB and JJSV
- Submit a final report to JJSV and reviewing IRB within 3 months after termination or completion of the study or the investigator's part in the study
- 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 course of the study 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, all other applicable laws and regulations and all conditions of approval imposed by the reviewing IRB and FDA
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately informed about the protocol, the study devices, 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 study 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. [redacted] 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.

[redacted]

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.

10. STUDY TIMELINE

[redacted]

[redacted]

11. EXPERIMENTAL PLAN

11.1 OVERVIEW

This study will be conducted in accordance with U.S. Code of Federal Regulations, the Declaration of Helsinki, ISO 14155:2011 and all other applicable laws and regulations. The study will not begin until regulatory and IRB approvals have been obtained.

This study will be a prospective, multicenter, bilateral, non-randomized, open-label, comparative, 6-month clinical study conducted at up to 50 U.S. sites. Subjects will be bilaterally implanted with Symfony lenses. [redacted] Subjects will be examined postoperatively at 1 day, 1 week, 1 month and 6 months following the second-eye surgery. A 1-year examination will be required only if the subject reports any of the 3 bothersome visual symptom items of interest at the 6-month examination, or if the subject experiences an IOL repositioning procedure due to IOL misalignment during the study.

Key preoperative data include ocular health and history, visual acuities, manifest refraction, keratometry, biomicroscopic slit-lamp findings, ocular symptoms and biometry. The operative visit will include standard procedures for cataract surgery and

IOL implantation. Key postoperative data collection includes non-directed visual symptoms, questionnaires, distance visual acuities, manifest refraction, keratometry, slit-lamp findings and adverse events. A chart summary of all examination procedures required at each study visit is provided in **Appendix A**.

11.2 VISIT SCHEDULE

The study visit schedule for all study subjects is outlined below in **Table 4**. Additional visits may be conducted at the discretion of the investigator; however, routine follow-up visits without reports of ocular adverse event(s) or spontaneous reports of any of the 3 bothersome visual symptom items of interest are not considered study visits and will not be reported in the study database. [redacted]

TABLE 4
Study Visit Schedule

Visit	[redacted]	Exam	[redacted]
1		Preoperative Exam	
2		Eye Surgery	
3		1 day	
4		1 week	
5		d Eye Surgery	
6		1 day	
7		1 week	
8		1 month	
9		6 months	
10[a]		1 year[a]	

[a] [redacted].

11.3 PREOPERATIVE PROCEDURES

Subjects will be considered eligible for treatment only after the current IRB-approved informed consent form is signed and all eligibility criteria are met. 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.

[redacted] Documentation (via the TECNIS Symfony Toric IOL calculator) of the toric power lens choice for each eye of each subject is required.

Preoperative testing to be performed includes the following:

- Informed consent documentation
- Subject demographic information
- Ocular history, including presence of ocular pathology for each eye
- Potential best-corrected distance visual acuity for each eye (Note: Snellen 20/30 or better is recommended for study inclusion; may be performed by surgeon estimation)
- Monocular uncorrected distance visual acuity (Snellen) for each eye
- Monocular best corrected distance visual acuity (Snellen) for each eye
- Manifest refraction (Snellen) for each eye
- Keratometry for each eye by keratometer only (no Sim-K allowed)
- Intraocular pressure for each eye
- Ocular medications for each eye
- Cataract type and density for each eye
- Fundus exam for each eye (dilated with ophthalmoscopy or undilated with a wide-field retinal imaging system, e.g., Optomap. The same method should be used for pre- and postoperative examinations)
- Medical and lens findings for each eye from a biomicroscopic slit-lamp exam
- Axial length, vertex distance, spherical equivalent IOL power and spherical equivalent targeted refraction (emmetropia, within ±0.50 D) for each eye using the investigator's preferred biometry method (IOLMaster, LenStar, or ultrasound)
- A-constant or Surgeon Factor used for spherical equivalent IOL power determination for each eye
- Surgeon-estimated surgically-induced astigmatism (SIA) and planned incision location for each eye
- Documentation of the TECNIS Symfony Toric IOL calculator choice of ZXT toric power for each eye and corresponding residual refractive cylinder and axis, as well as documentation of inclusion of the optional posterior corneal astigmatism algorithm

- PRVSQ Subject Questionnaire (**Appendix B**)

LENS POWER CALCULATIONS AND IOL SELECTION:

[redacted]

In order to verify subject eligibility and to optimize toric IOL selection and axis placement, investigators will use the web-based TECNIS Symfony Toric IOL calculator (www.TecnisToricCalc.com) to determine the appropriate IOL model for each eye. Note that the TECNIS Symfony Toric IOL calculator provides toric IOL options based on predicted astigmatism, i.e., the vector sum of pre-existing corneal astigmatism and the expected effect of SIA. For this study, subjects are to have corneal astigmatism in at least one eye that, when taking SIA into account and using the PCA algorithm, has approximately 2.00 D to 3.00 D (higher-cylinder group) or 1.00 D to 1.50 D (lower-cylinder group) of corneal astigmatism to be corrected, and subjects must qualify for implantation of the suitable toric IOL by the TECNIS Symfony Toric IOL calculator.

[redacted] Predicted residual refractive cylinder must be ≤0.50 D for all toric eyes. For all subjects, the IOL model selections chosen by the investigator via the TECNIS Symfony Toric IOL calculator are to be printed and maintained as source documentation.

[redacted]

11.4 STUDY LENS SUPPLY

[redacted].

11.5 OPERATIVE PROCEDURES

The investigator should use his or her standard, small-incision, cataract extraction surgical technique. All lenses should be folded for implantation and inserted into the capsular bag using one of the JJSV-validated insertion systems. [redacted] If exited during the first-eye surgery, the subject will be considered a screen failure. [redacted]

Following lens insertion, Symfony Toric IOLs are to be precisely aligned with the intended axis of placement using the imaginary line formed by the axis orientation marks at each of the haptic/optic junctions of the IOL, identifying the flat meridian of the optic. Special care should be taken to ensure proper positioning of the Symfony Toric IOL at the intended axis following viscoelastic removal and/or inflation of the capsular bag at the end of the surgical case. All viscoelastic must be carefully removed from the capsular bag. Residual viscoelastic and/or over-inflation of the bag may allow the lens to rotate, causing misalignment of the Symfony Toric IOL from the intended axis.

Operative case report forms will collect the following information:

- Date of surgery
- Operative eye
- IOL model, power and serial number
- Use of intraoperative wavefront analysis
- Incision location
- Surgical complications
- Other surgical procedures
- IOL placement (e.g., within capsular bag, proper alignment, etc.)
- Wound closure (e.g., suture required)
- Adverse events

11.6 POSTOPERATIVE PROCEDURES

Postoperatively, all subjects will be examined according to the schedule in Section 11.2, Visit Schedule.

Beginning with the 1-month visit, prior to any testing being performed at any follow-up visit, the subject will be asked how their vision has been since the last visit [redacted] and the PRVSQ questionnaire will be administered.

If a subject requires a lens repositioning procedure due to IOL misalignment at any time during the study, or if a subject reports a [redacted] visual symptom [redacted] at 6 months for any of the 3 items of interest (halos, glare or starbursts) contained in the PRVSQ, the subject will also undergo a visit at 1 year.

1-Day Visit: Postoperative procedures require a serious and/or device-related adverse event review.

1-Week Visit: Postoperative procedures require a serious and/or device-related adverse event review.

1-Month Visit: Postoperative procedures will include the non-directed subject question; administration of the PRVSQ questionnaire, distance visual acuities, manifest refraction, keratometry, intraocular pressure and biomicroscopic slit-lamp examination. A spectacle and/or contact lens prescription will be offered to each subject.

6-Month Visit: Postoperative procedures will include the non-directed subject question, administration of the PRVSQ questionnaire, manifest refraction, distance visual acuities, intraocular pressure, keratometry and a slit-lamp exam. If the subject indicates a [redacted] visual symptom [redacted] for any of the 3 items of interest (halos, glare or starbursts) contained in the PRVSQ, the subject will be required to return for a 1-year postoperative visit.

1-Year Visit (if required): Postoperative procedures will include the non-directed subject question, administration of the PRVSQ questionnaire, manifest refraction, distance visual acuities, intraocular pressure, keratometry and a slit-lamp exam.

If refractive correction is required during the study postoperatively, spectacles or contact lenses will be prescribed; however, no additional refractive enhancement procedures (LRI, AK, etc.) are allowed until after completion of the 6-month study visit. [redacted]

The postoperative case report form will collect the following information for scheduled study visits (see Section 11.7, *Postoperative Procedures* for information to be collected for unscheduled visits):

- Confirmation of offering of spectacle and/or contact lens prescription: 1-month visit only
- Non-directed subject question responses at every visit.
- PRVSQ questionnaire: 1-month, 6-month and 1-year visits. Following completion of the questionnaire by the subject, the questionnaire is to be reviewed by the site personnel for reports of very or extremely bothersome visual symptoms of interest (halos, glare or starbursts) that impact daily living under overall conditions.
- Keratometry: 1-month, 6-month and 1-year visits
- Monocular uncorrected distance visual acuity at 4 m (Snellen or ETDRS): 1-month, 6-month and 1-year visits
- Manifest refraction (Snellen or ETDRS): 1-month, 6-month and 1-year visits; manifest refraction is to be performed using the Maximum Plus refraction method as detailed in **Appendix C**.
- Monocular best corrected distance visual acuity at 4 m (Snellen or ETDRS): 1-month, 6-month and 1-year visits
- Medical and lens findings from biomicroscopic slit-lamp exam: 1-month, 6-month and 1-year visits; findings of aqueous cells and flare, corneal edema, posterior capsule striae, posterior capsular opacification and IOL glistenings are to be rated using standardized grading scales provided in **Appendix D**.
- Ocular medications: In the event of a serious and/or device-related adverse event.
- Intraocular pressure: 1-month, 6-month and 1-year visits
- Fundus exam, if medically indicated
- Occurrence of Nd:YAG capsulotomy(ies)
- Occurrence of any adverse events

11.7 UNSCHEDULED VISITS

A visit is considered an unscheduled study visit when it occurs other than at the specified 1-day, 1-week, 1-month or 6-month study visits AND at which a serious or device-related adverse event is reported OR if the subject has a spontaneous report of any of the 3 visual symptom items of interest (halos, glare or starbursts) after the 1 month postoperative visit. [redacted].

Testing to be performed at an unscheduled visit due to a serious or device-related adverse event is at the discretion of the Investigator. If the event results in an IOL

repositioning procedure (secondary surgical procedure), keratometry is to be performed and the PRVSQ questionnaire is to be administered PRIOR to the IOL repositioning.

At any unscheduled visit where the subject spontaneously reports any of the 3 visual symptom items of interest (halos, glare or starbursts), the PRVSQ questionnaire is to be administered.

Following completion of a PRVSQ questionnaire by the subject, the questionnaire is to be reviewed by the site personnel [redacted].

At any unscheduled visit where any of the 3 [redacted] visual symptom items of interest [redacted] are reported via PRVSQ to impact daily living under overall conditions, monocular distance visual acuities, manifest refraction, keratometry and biomicroscopic slit-lamp examinations will be performed.

Data to be collected on unscheduled visit forms include:

- Serious or device-related adverse event, date of onset, classification, prognosis and treatment
- Non-directed subject question
- PRVSQ questionnaire - in the event of a spontaneous report of any of the 3 visual symptoms of interest ([redacted]) or prior to an IOL repositioning procedure
- Manifest refraction (Snellen or ETDRS) - if a serious or device-related event occurs or if any of the 3 visual symptom items of interest [redacted] are reported via PRVSQ
- Uncorrected and best-corrected monocular distance visual acuity (Snellen or ETDRS) - if a serious or device-related event occurs or if any of the [redacted] visual symptom items of interest [redacted] are reported via PRVSQ
- Keratometry - if a serious or device-related event occurs or if any of the [redacted] visual symptom items of interest ([redacted] reported via PRVSQ
- Slit-lamp examination – findings of aqueous cells and flare, corneal edema, posterior capsule striae, posterior capsular opacification and IOL glistenings are to be rated using standardized grading scales provided in **Appendix D**.
- Fundus exam, if performed
- Ocular medications - if a serious or device-related event occurs

11.8 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 will 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.

SUBJECT FOLLOW-UP

To minimize subjects lost to follow-up, compensation will be provided for the subject's time and participation in the study at the 1- and 6-month postoperative exams, as well as the 1-year visit, if required. Additionally, sites will be compensated for completion of the 1-day, 1-week, 1- and 6-month exams as well as the 1-year visit, if required. Sites will be provided frequent listings of upcoming 1-month, 6-month and 1-year visits. It is anticipated that at least 95% of implanted subjects will be available for the 6-month study visit (i.e., no more than a 5% lost-to-follow-up rate at 6 months postoperatively). [redacted]

SUBJECT EARLY EXIT

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 (e.g., subject moved/unable to locate, subject uncooperative/refuses further study participation, subject ill/unable to travel). [redacted] If a subject is exited from the study, the investigator will, if at all possible, have the subject return for a final study visit.

If a subject is exited early from the study, the investigator will complete an Exit Case Report Form 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, effort should be made by the investigator to follow the subject until resolution of the adverse event. In this situation, additional information will be documented in the SAE/ADE form, not on an Unscheduled Visit form.

Following study completion or early exit, 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.

[redacted]

11.9 PROTOCOL DEVIATIONS

Any departure from the protocol procedures represents a protocol deviation. Protocol deviations may be subject-based (e.g., inclusion/exclusion criteria, informed consent deviation, etc.) or procedural-based (e.g., out-of-interval visits, non-compliance with testing procedures, etc.). All protocol deviations will be documented using protocol deviation case report forms.

Any deviation made to protect the life or physical well-being of a subject in an emergency, as well as any use of a study device without obtaining informed consent, must be reported to JJSV within 5 working days. Protocol deviations will be monitored by JJSV, and if the non-compliance is persistent or egregious, JJSV may take action, including but not limited to termination of the investigator's participation in the study. The investigator is also responsible for informing the reviewing IRB of instances of protocol non-compliance in accordance with the IRB requirements.

12. ADVERSE EVENTS AND PRODUCT COMPLAINTS

12.1 ADVERSE EVENT AND COMPLAINT DEFINITIONS

Adverse Event (AE)

An adverse event is defined (following 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. All adverse events will be recorded in the subject's case report forms.

NOTE: Findings typical of early postoperative healing (e.g., corneal edema, cells and flare, elevated intraocular pressure, etc.) will not be considered an ocular adverse event in the first postoperative month.

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 in-patient 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,
- 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

A Serious Adverse Event/Adverse Device Effect (SAE/ADE) form will be completed by the investigative site for any SAE.

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 12.4, 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.

An SAE/ADE form will be completed by the investigative site for any ADE.

Study-Specific Serious Anticipated Adverse Events

The following is a list including, but not limited to, ocular adverse events that are anticipated and must be reported to JJSV for this study. Any events that are unlikely but anticipated (i.e., endophthalmitis) will be reported to the FDA.

- Endophthalmitis/Intraocular infection
- Hypopyon
- Hyphema
- Lens dislocation
- Cystoid macular edema
- Mechanical pupillary block
- Rhegmatogenous retinal detachment/tear
- Persistent corneal edema
- Persistent iritis/uveitis
- Toxic anterior segment syndrome (TASS)
- Persistent elevated IOP requiring treatment

- Tilt, decentration, residual refractive error or axis misalignment resulting in secondary surgical intervention (e.g., repositioning)
- Visual symptoms requiring secondary surgical intervention
- Residual refractive error resulting in a secondary surgical intervention
- Residual lens remnants resulting in a secondary surgical intervention

[redacted]

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.

An SAE/ADE form will be completed by the investigative site for any UADE or USADE.

12.2 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. Product complaints can pertain to any marketed JJSV device being used in the study. 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.

12.3 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 IOLs used in this study, are to be reported to JJSV 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.

All serious adverse events, whether anticipated or unanticipated, all adverse device effects and all device complaints, deficiencies or malfunctions with or without an adverse event, shall be reported per the USA Code of Federal Regulations (21CFR812) for sites in the USA as follows:

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.

Serious and/or Device-Related Adverse Event Reporting

SAE's and/or ADEs are to be documented using the Serious Adverse Event/Adverse Device Effect (SAE/ADE) CRF. In the event of an SAE, JJSV must be notified immediately (no later than 24 hours after detection). Any SAE/ADE is to be reported by phone, email and/or by submitting a completed SAE/ADE 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 study-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 24 hours, and to the investigator's IRB as soon as possible. Any UADE or USADE is to be reported by phone, email and/or submitting a completed SAE/ADE CRF.

Complaints/Device Deficiency Reporting

A general product complaint or device deficiency is to be reported to JJSV in a timely manner. Notification of complaints/device deficiencies will occur by either recording complaints on the "Complaint Form" CRF and/or by contacting 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.

12.4 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.

12.5 ADVERSE EVENT FOLLOW-UP

For every serious or device-related adverse event, appropriate measures should be undertaken to treat and/or monitor the subject until resolution occurs. Obtain and maintain in the subject's files all pertinent medical data relating to the event including the subject's medical records and medical reports and/or judgments from colleagues or outside specialists who assisted in the treatment and follow-up of the subject. The

investigator should keep JJSV closely informed as to the outcome of serious and/or device-related adverse events, thereby allowing JJSV to comply with the appropriate regulatory reporting requirements. The SAE/ADE CRF within the electronic data capture system should be updated as needed each time the subject returns to the investigator or other specialist(s) for follow-up of serious and/or device-related adverse event until resolution of the event. Any subject who is exited from the study due to a serious and/or device-related adverse event will be followed until the outcome is determined.

13. PROTOCOL CHANGES AND PROCEDURES

If the investigator desires 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.

14. ETHICS REVIEW AND PATIENT WELFARE

14.1 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.

14.2 INFORMED CONSENT

The current version of the IRB-approved study informed consent form must be signed and dated by each study subject prior to any study-specific examinations being performed. The approved informed consent form is to be signed and dated by the subject as well as by the person who conducted the informed consent discussion. The signed informed consent form will be maintained by the investigator as a permanent part of the subject's medical records. A signed and dated copy is to be provided to the subject. [redacted]

Note: The informed consent process also includes obtaining the subject's signature on an Authorization for Use/Disclosure of Health Information for Research Form.

[redacted]

15. DOCUMENTATION

15.1 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. However, 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 JJSV:

- 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)
- Dates of all subject visits and surgeries throughout the duration of the study
- Implant serial number identification
- Concurrent medications
- Corrected and uncorrected distance visual acuity, if done
- Manifest refraction, if done
- 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.

15.2 SUBJECT CONFIDENTIALITY

Subjects will be assigned a site/subject number to maintain subject confidentiality. 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 maintain confidentiality of personal information to the extent permitted by applicable laws and regulations.

15.3 CASE REPORT FORM COMPLETION

This study will use an electronic data capture system using electronic case report forms. Case report forms will be completed in accordance with instructions provided to the site prior to study start. The investigator is responsible for ensuring that data are properly recorded in each subject's electronic case report forms and related documents. Prior to database lock, the investigator will verify completeness and accuracy of data submitted to JJSV.

15.4 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.

16. MONITORING

[redacted]

16.1 DATA MONITORING

In order to ensure a well-controlled clinical trial, JJSV will follow specific data monitoring procedures. [redacted]

[redacted]

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 [redacted] 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.

16.2 ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that subjects and case report forms can be traced and will allow monitoring of investigator progress and compliance.

Device Accountability

As the study IOLs are commercially available, supply records for the lenses will solely be the responsibility of the site and managed by their customary methods.

Site Monitoring Plan

16.3 MEDICAL OVERSIGHT

The medical monitor will be available throughout the clinical trial to review study results and to answer any questions from investigators. The medical monitor will review and assess any reports of serious and/or device-related adverse events and discuss these with the reporting investigator(s) as necessary. The medical monitor, as well as any other qualified personnel designated by JJSV, shall also review study reports.

17. PUBLICATIONS

[redacted]

18. RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

RISKS OF THE SYMFONY TORIC IOLS

The Symfony Toric IOLs are intended to compensate for corneal astigmatism and to mitigate the effects of presbyopia and provide a continuous range of high-quality vision by extending the depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity; however, glasses may still be needed to improve distance vision and/or to have useful vision for intermediate or near tasks. The Symfony Toric IOLs may cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL. Some visual effects associated with the Symfony Toric IOL may be expected due to the lens design that delivers elongation of focus. These may include a perception of halos, glare, or starbursts around lights under nighttime conditions. In addition, rotation of the Symfony Toric IOL away from its intended axis can reduce its astigmatic correction. Misalignment greater than 30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. These risks are not unlike other lenses of this kind.

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.

RISK MANAGEMENT

Subjects will be closely monitored thought the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to JJSV according to Section 12, Adverse Events and Product Complaints. Additionally, JJSV will monitor incoming data following the procedures outlined in Section 16, *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 16.3, *Medical Oversight*).

POTENTIAL BENEFITS

The clinical performance of the Symfony Toric IOL, Models ZXT150, ZXT300 and ZXT375, is expected to be similar to the non-toric Symfony IOL, Model ZXR00 (USA FDA approval P980040/S065), with respect to mitigating the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens is expected to provide improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. In addition, the Symfony Toric IOLs are expected to be similar to the TECNIS Toric Model Series ZCT IOLs (USA FDA approval P980040/039) for reduction in residual refractive cylinder.

CONCLUSION

The hazards/risks associated with the Symfony Toric IOL, Models ZXT150, ZXT300 and ZXT375, are acceptable and within those of JJSV's other advanced optic IOLs. The potential clinical benefits of these lenses outweigh the residual risks when the device is used as intended.

19. RECORD 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 an electronic copy of the completed case report forms should be maintained by the investigator.

[redacted]

- All case report forms
- All adverse event information (adverse event forms, follow-up letters, etc.)
- IRB and regulatory approval documentation
- Study correspondence
- Study agreements
- Site visit documentation
- Protocol(s) and the reason for any deviations from the protocol
- Subject log(s)
- Directions for Use
- Completed subject informed consent forms and medical privacy forms (e.g., Authorization for Use/Disclosure of Health Information or equivalent

documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries)

- Subject medical chart/clinic notes

20. TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event that high levels of complications and/or adverse events occur that are unexpected in nature and/or severity and are possibly related to use of the study device. The clinical investigation may be suspended if the Medical Monitor or 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. JJSV 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 should continue to be followed through completion of the study visit schedule.

21. STATISTICAL METHODS

This section highlights the analyses to be performed for key study endpoints. The 6-month postoperative visit is the critical analysis time point for all endpoints. Outcomes for subjects implanted with the higher-cylinder IOLs (ZXT300 and ZXT375) and the lower-cylinder control lens (ZXT150) will be reported separately. Descriptive statistics will typically include mean, standard deviation, minimum, maximum for continuous data with frequency and proportion reported for categorical data.

21.1 ANALYSIS POPULATION

For the primary endpoint, the primary analysis population will be all bilaterally-implanted subjects having available data at the 6-month visit, with data reported separately for the higher- and lower-cylinder groups. Data will also be reported for all subjects, including bilateral subjects and those with only one eye implanted (having a phakic lens, a cataract or other IOL in the fellow eye). [redacted]

[redacted]

In addition to the primary population analyses discussed above, additional analyses will also be performed for the primary endpoint to evaluate the [redacted] at the six-month visit who did not undergo repositioning or IOL removal. [redacted]

For other questionnaire items, bilaterally-implanted subjects with data at six months postoperative will be used for analysis. Refraction, monocular visual acuity, medical/lens findings and adverse event data will be reported for primary eyes (first eye implanted) and fellow eyes. Data will be reported separately for the higher-cylinder group (ZXT300, ZXT375) and the lower-cylinder control eyes (ZXT150).

21.2 PRIMARY ENDPOINT

The primary endpoints are the rate of bothersome visual symptoms and the rate of reported difficulty with an activity due to visual symptoms at 6 months postoperative. [redacted]

- [redacted]
- [redacted]
- [redacted]

The first primary endpoint is the rate of bothersome visual symptoms, [redacted]. The second primary endpoint is the rate of reported difficulty with an activity due to one or more visual symptoms, determined by a "Yes" response to the question "Is there anything you have a lot of difficulty with, or do not do, because of [visual symptom]") at 6 months postoperative.

The frequency and proportion of subjects with bothersome visual symptoms for one or more visual symptoms, and the frequency and proportion of subjects reporting difficulty with an activity due to one or more visual symptoms will be reported along with the two-sided, 95% confidence interval at the 6-month visit.

Justification of Effect Size:

Using an assumed value of 20% for bothersome visual symptoms or difficulty with an activity due to visual symptoms, and a sample size of 240 evaluable subjects per group, a two-sided 95% confidence interval will estimate the observed rate of bothersome visual symptoms to within 4.2 percentage points.

21.3 ADDITIONAL ENDPOINTS

The frequency and proportion of subjects with each response will be reported for the individual visual symptom items for overall and with and without correction.

The frequency and proportion achieving each acuity level will be reported for monocular visual acuity.

Descriptive statistics will be reported for mean percent reduction in cylinder, refractive cylinder, cylinder vs preoperatively-predicted cylinder, spherical equivalent and spherical equivalent vs preoperatively-predicted spherical equivalent. The frequency and proportion of eyes within 0.50 D and within 1.00 D of the preoperatively-predicted values will be reported for refractive cylinder and spherical equivalent. Percent reduction in cylinder will be calculated for each eye using the following formula:

100*((Postop Ref. Cyl. - Preop K. Cyl.)/(Target Ref. Cyl. - Preop K. Cyl.))
Key: Ref. Cyl.=absolute refractive cylinder; K. Cyl.=keratometric cylinder;

Refractive data will be referred to the corneal plane prior to determining percent reduction in cylinder.

Enrollment data, demographic data, subject accountability data and operative complications/procedures will be reported using descriptive statistics. Visual symptom findings, adverse events and other key data will be reported at 1 year for subjects who experienced a repositioning procedure during the study or who were reported with bothersome visual symptoms at the 6-month visit.

The frequency and proportion of primary and fellow eyes with medical/lens findings will also be reported. In addition, rates of IOL repositioning procedures (secondary surgical intervention) due to IOL misalignment, rates of explants related to visual symptoms, rates of refractive procedures performed during the study period, and other adverse events will be reported.

21.4 INTERIM REPORTS

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

21.5 SAMPLE SIZE CALCULATIONS

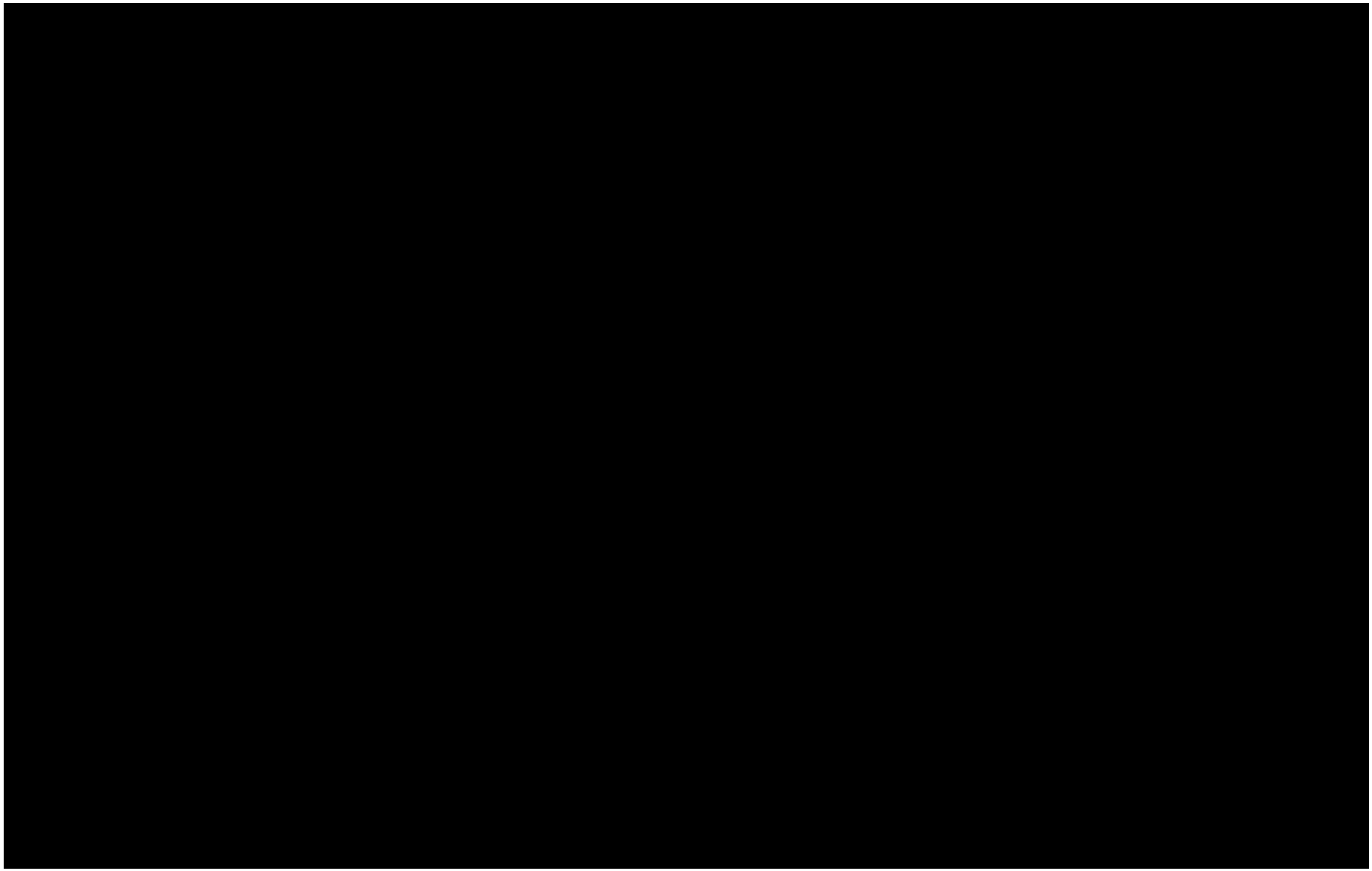
With a sample size of 240 subjects and assuming a 20% rate of bothersome visual symptoms or difficulty with an activity due to visual symptoms, a two-sided 95% confidence interval will estimate the observed rate of bothersome visual symptoms to within 4.2 percentage points.

To achieve 240 higher-cylinder group subjects and 240 lower-cylinder group subjects evaluable at 6 months, assuming an initial 20% screen-fail rate and a 5% lost-to-follow-up rate, up to 634 total subjects will be enrolled.

22. REFERENCES

1. [redacted]

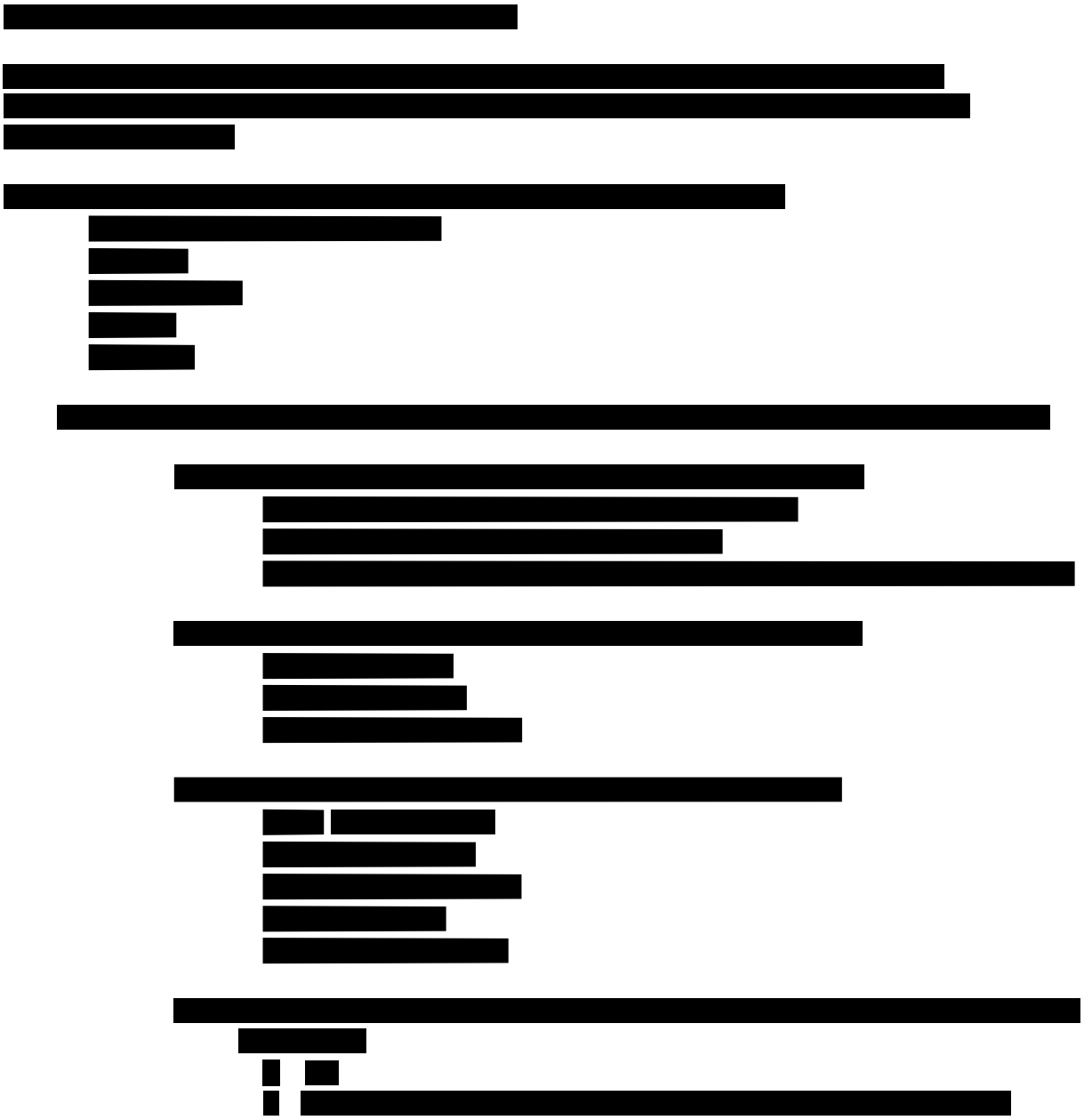
APPENDIX A - SUMMARY OF EXAMINATIONS FOR EACH VISIT



APPENDIX B - PATIENT-REPORTED VISUAL SYMPTOMS QUESTIONNAIRE (PRVSQ V2)

Patient Reported Visual Symptoms Questionnaire

[redacted]



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[redacted]

[redacted]

APPENDIX C - MAXIMUM [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]

APPENDIX D - SLIT-LAMP EXAM RATINGS

[redacted]

CELLS

Grade	Cells in Field (Field is a 1x1 mm slit beam)
0	<1
0.5+	1 - 5
1+	6 - 15
2+	16 - 25
3+	26 - 50
4+	>50

FLARE

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

B. Ratings of Corneal Edema

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

Amount	Grade	Description
None	**0**	Normal transparency: a. No epithelial or sub-epithelial haziness b. No microcysts c. No stromal cloudiness
Trace	**+1**	a. Barely discernible localized epithelial or sub-epithelial haziness, and/or b. 1 to 20 microcysts, and/or c. Barely discernible localized stromal cloudiness
Mild	**+2**	a. Faint but definite localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness, and/or b. 21-50 microcysts
Moderate	**+3**	a. Significant localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness and/or b. 51-100 microcysts
Severe	**+4**	a. Definite widespread epithelial or stromal cloudiness, giving dull glass appearance to cornea or numerous coalescent bullae (please note the number and location of bullae), and/or b. >100 microcysts or bullae, and/or c. Numerous striae (please note the number and location of striae or folds)

C. Posterior Capsule Striae Grading Scale

The following five-point grading scale is to be used for rating striae in the posterior capsule:

Amount	Grade	Description
None	0	None
Trace	+1	One detectable, barely noticeable striae
Mild	+2	One or two prominent striae
Moderate	+3	Three or more prominent striae, but visibility of retina is not impacted
Severe	+4	Three or more prominent striae affecting visualization of retina

D. Posterior Capsule Opacification Grading Scale

Below is the five-point grading scale to be used for PCO determination:

Amount	Grade	Description
None	0	Normal posterior capsule with no area of opacity. Red reflex bright.
Trace	+1	Some loss of transparency involving the posterior capsule. Red reflex fairly bright
Mild	+2	Mild loss of transparency with cloudiness extending through most of the posterior capsule. There may be a few Elschnig's pearls in the posterior capsule. Red reflex mildly diminished.
Moderate	+3	Moderate loss of transparency with difficulty visualizing the retina. There may be multiple Elschnig's pearls in the posterior capsule. Red reflex markedly diminished.
Severe	+4	Posterior capsule very opaque with inability to view the retina. The posterior capsule may have confluent Elschnig's pearls and fibrous scarring. Red reflex barely visible.

E. IOL Glistenings

Use the following scale to grade IOL glistenings, using a slit beam 2.0 mm wide and 10.0 mm long:

Amount	Grade	Description
None	0	No glistenings visible
Rare	+0.5	<10 glistenings visible
Trace	+1	10-19 glistenings visible
Mild	+2	20-29 glistenings visible
Moderate	+3	30-39 glistenings visible
Severe	+4	≥ 40 glistenings visible