Title

Postmarket Study of ORA with VerifEye+ and Barrett Toric Calculator used for the Implantation of AcrySof Toric

Protocol Number:	ILX369-P001/NCT03579433
Development Stage of Project:	Product Support
Sponsor Name and Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	ORA with VerifEye+
Investigator Agreement:	I have read the clinical study described herein, and recognize its confidentiality. I agree to conduct this study in accordance with the ethical principles contained within the Declaration of Helsinki, and the described study in compliance with the protocol, Good Clinical Practice (GCP), ISO 14155, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Study Sponsor.
Principal Investigator:	

_____

Signature Date

Name and professional position:

Address:

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1 GLOSSARY OF TERMS

Name of Test product(s)	ORA System with VerifEye+
Name of Test Product(s)	Alcon Toric Calculator (Barrett)
Adverse Device Effect	Adverse event related to the use of an investigational medical device (test product) or control product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test product or control product.*
Adverse Event	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 investigational medical device (test product). *Note: For subjects, this definition includes events related to the test product, the control product, or the procedures involved. For users or other persons, this definition is restricted to events related to the test product.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk management file.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.* Requirements for reporting Device Deficiencies in the study can be found in Section 11.

Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Interventional Clinical Trial	A research trial that prospectively assigns, whether randomly or not, human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, and/or a research trial in which diagnostic or monitoring procedures beyond standard of care are conducted and generate outcomes for use in analysis of data.
Investigational Product	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Non-serious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Postmarketing/Post-authorization study	Any study conducted within the conditions laid down in product labelling and other conditions laid down for the marketing of the product or under normal conditions of use. A postmarketing study falls either within the definitions of an interventional or a non- interventional study and may also fall within the definition of a post-approval study.
Product Complaints	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not

	the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.
Randomized Subjects	Any subject who is assigned a randomized treatment.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject that either resulted in: a. a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* *b.* any potentially sight-threatening event or permanent impairment to a body structure or a body function.

	c. in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* *d.* a medical or surgical intervention to prevent a) or b). *e.* any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 11 for additional SAEs.*
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Bird Flu.

Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk management file.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 LIST OF ACRONYMS AND ABBREVIATIONS

Table 2–1 List of Acronyms and Abbreviations Used in This Protocol

Abbreviation	Definition
AAS	All-Implanted Analysis Set
ADE	Adverse device effect
AE	Adverse Event
BCDVA	Best Corrected Distance Visual Acuity
BSS	Balanced salt solution
CFR	Code of Federal Regulations
CRF	Case Report Form
D	Diopter
DEP	Deviations and Evaluability Plan
DEQ	Defocus equivalent
DFU	Directions for use
EBMD	Epithelial basement membrane dystrophy
eCRF	Electronic case report form
EDC	Electronic data capture
EN	European Standard
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPCMS	Global Product Complaint Management System
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IOL	Intraocular Lens
[redacted]	[redacted]
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
LCD	Liquid crystal display
LogMAR	Logarithm of the minimum angle of resolution
mm	Millimeter

Abbreviation	Definition
mmHg	Millimeter of mercury
MOP	Manual of procedures
[redacted]	[redacted]
N/A	Not applicable
ORA	Optiwave Refractive Analysis
OVD	Ophthalmic viscosurgical device
[redacted]	[redacted]
PI	Principal Investigator
PPS	Per Protocol Analysis Set
[redacted]	[redacted]
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SD	Standard Deviation
[redacted]	[redacted]
SIA	Surgically induced astigmatism
[redacted]	[redacted]
SOP	Standard operating procedure
SS	Safety Analysis Set
SSI	Secondary surgical intervention
[redacted]	[redacted]
US	United States
USADE	Unanticipated serious adverse device effect
VA	Visual acuity
YAG	Yttrium-aluminum-garnet

3 PROTOCOL SUMMARY

Investigational product type	Devices
Study type	Interventional
Investigational products	Investigational Products: The ORA System with VerifEye + is made up of the following components: The ORA System Aberrometer is mounted on a compatible surgical microscope. It measures optical aberrations which are converted to wavefront data to generate refraction data. The refraction data is used for selecting the power of an intraocular lens (IOL). Once a toric IOL is placed in the eye, the aberrometer indicates when the toric marks of the IOL are aligned with the intended axis. A key feature of ORA with VerifEye + is that surgical information is displayed through the microscope oculars. The Cart provides control and power to, and receives and processes data from, the aberrometer. The portable cart is tethered to the ORA System via a cable. The LCD Touchscreen is mounted on the cart and displays operating screens for user input, option selections, and data output. It can also display wavefront analyses. The Alcon Toric IOL Calculator (Barrett) is a tool to assist the treating ophthalmic surgeon in selecting a Toric IOL for adult patients with corneal astigmatism undergoing cataract removal. Accurate keratometry and biometry measurements are required to achieve optimal visual outcomes. The calculator offers two options with the manufacturer's model specific A-constant for IOL calculation: 1. Barrett Toric Calculator algorithm which calculates a patient-specific effective lens position and also

	estimates the effect of posterior corneal astigmatism. Optimum outcomes are achieved with a centroid Surgically Induced Astigmatism (SIA) value. 2. Holladay I Vergence formula which calculates a patient-specific effective lens position, but does not consider posterior corneal astigmatism. The Calculator combines patient specific biometry data and the planned surgery information to recommend a Toric IOL model with the optimal alignment axis within the capsular bag.
Purpose and rationale	The Alcon Toric Calculator (Barrett) is a modern IOL calculator that includes estimates of the posterior corneal astigmatism in the selection of the IOL power. The ORA System with VerifEye + is an intraoperative device that measures the total corneal astigmatism in the aphakic condition which is used for IOL power selection. Also, in the pseudophakic condition, ORA provides guidance for alignment of the Toric axis mark. These modern technologies account for the posterior corneal astigmatism in the IOL power selection and this study is intended to evaluate the visual acuity outcomes when they are used for implantation of a Toric IOL.
Objective(s)	**Primary Effectiveness:** To evaluate the percentage of eyes with best corrected distance visual acuity (BCDVA) of 20/20 or better in eyes implanted with AcrySof® Toric selected by ORA with VerifEye + and Barrett Toric Calculator [redacted]

	[redacted] **Safety:** To evaluate adverse events including secondary surgical interventions related to the investigational device.
Endpoint(s)	Primary Effectiveness: Percentage of eyes with BCDVA of 20/20 or better at 6 months [redacted]

	Safety: 1. Adverse events including secondary surgical interventions related to the investigational device 2. Device deficiencies
Assessment(s)	Effectiveness • Monocular Best Corrected Distance Visual Acuity in logMAR [redacted] Safety • Adverse Events • Device Deficiencies [redacted]
Study Design	This is a prospective, randomized, contralateral, multicenter, postmarket study. A total of 115 subjects will be enrolled to achieve 90 evaluable subjects. Treatments will be randomized between eyes and the eye with the more visually significant cataract, as measured by best corrected distance visual acuity (BCDVA), will undergo surgery first. If the BCDVA is equal between eyes, the right eye will undergo surgery first.

	The Barrett Toric Calculator via the Alcon Toric Calculator will be used for IOL power selection preoperatively. Sites that have LenSx will use it for primary and secondary incisions, capsulorhexis, and phacofragmentation consistently in both eyes for all subjects. Sites that don't have LenSx will use standard manual procedures. For the eyes in the ORA with VerifEye + study group, the IOL power and axis and axis mark alignment will be provided by ORA. For eyes in the Barrett Toric study group, the IOL power and axis will be provided by the Barrett Toric Calculator and axis alignment will be done manually (ie, without ORA guidance). The study will be conducted at up to 10 sites in the US. Surgery will be done on each eye on different days 7 to 14 days apart. Total follow-up duration is 6 months. There will be 10 visits in total. Refer to the Overview of Study Procedures Table for an overview of the visit schedule and the assessments to be performed at each visit.
Subject population	Subjects who require cataract surgery and a Toric IOL in both eyes. Subjects will be required to have preoperative keratometric astigmatism of 0.75 D to 3.00 D and require the AcrySof IQ® Toric SN6AT3 – 6 as determined by Alcon Toric Calculator. [redacted]
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	Inclusion Criteria: 1. 22 years of age or older 2. Preoperative keratometric astigmatism of 0.75 to 3.00 D 3. Planned implantation of AcrySof IQ Toric SN6AT3 – T6 as determined by the Alcon Toric Calculator 4. Potential postoperative visual acuity of 0.04 logMAR (20/20) or better

	5. Willing and able to complete all required postoperative visits 6. Able to comprehend and sign the informed consent form
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	Exclusion Criteria: 1. Unclear intraocular media other than cataract 2. Axial length < 21.5 and > 27.0 mm 3. Significant irregular corneal astigmatism as measured by a corneal topographer 4. Unstable tear film per Investigator judgement 5. Significant anterior or posterior segment disease 6. Prior intraocular or corneal surgery 7. Prior retinal detachment 8. Pregnancy or lactation, current or planned, during the course of the study. 9. Participation in another concurrent clinical trial per the PI judgement 10. Presence or history of any condition or finding that makes the subject unsuitable as a candidate for cataract surgery or study participation or may confound the outcome of the study, in the opinion of the Investigator. Exclusion Criteria During Surgery 11. Intra-op complications such as but not limited to posterior capsular tear, wound burn and need to place a suture 12. ORA or Alcon Toric Calculator recommends an IOL other than AcrySof IQ Toric SN6AT3-T6
Data analysis and sample size justification	No formal statistical hypothesis testing is planned in support of the primary objective. Rather the data will be summarized using descriptive statistics by treatment group. There will be two effectiveness analysis sets. The All Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA. The Per Protocol Analysis Set (PPS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA and with no major protocol deviations. The primary analysis set for effectiveness is the PPS.

Safety Analysis Set (SS) will include all eyes with attempted implantation with any IOL (successful or aborted after contact with the eye) and will be used for the safety analyses.

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In general, descriptive statistics generated for effectiveness and safety parameters will be based upon the type of parameter (ie, whether the data were categorical or continuous) being analyzed. For categorical parameters, the statistics used to summarize the data descriptively included sample size, number in the category, and percent in the category. For continuous parameters, sample size, mean, median, standard deviation, minimum, and maximum will be presented.

For visual acuity endpoints, the number and percentage of the logMAR categories and Snellen categories will be provided respectively.

- logMAR categories: the number and percentage of eyes with visual acuity of
  - 0.00 logMAR or better: ≤ 0.00 logMAR
  - 0.10 logMAR or better: ≤ 0.10 logMAR
  - 0.20 logMAR or better: ≤ 0.20 logMAR
  - 0.30 logMAR or better: ≤ 0.30 logMAR
- Snellen categories: the number and percentage of eyes with visual acuity of
  - 20/20 Snellen or better: ≤ 0.04 logMAR
  - 20/25 Snellen or better: ≤ 0.14 logMAR

	• 20/32 Snellen or better: ≤ 0.24 logMAR • 20/40 Snellen or better: ≤ 0.34 logMAR In addition, descriptive statistics including sample size, mean, median, standard deviation, number of subjects/eyes, minimum, maximum and (two-sided) 95% confidence interval will be presented. Descriptive statistics for adverse events (including SSIs) will be presented for study eyes. The rates of all adverse events will be provided with counts and percentages, and these rates will be accompanied by two-sided exact 95% confidence intervals. In order to estimate the percent of eyes with BCDVA of 20/20 or better (ie, ≤ 0.04 logMAR) at 6 months postop, the 95% confidence interval for the percent of eyes with BCDVA of 20/20 or better at 6 months postop will be calculated based on the binomial distribution. With a sample size of 90 eyes, per the binomial distribution, the width of the 95% confidence interval ranges from 4.0% to 21.5%. As an example, for an observed outcome of 70%, the 95% confidence interval per binomial distribution is (59.4%, 79.2%) with a width of 19.8%.
Key words	ORA, Verifeye+, Barrett, Toric, IOL

Table 3–1 Schedule of Study Procedures and Assessments

	Both eyes	1st Operative Eye			2nd Operative Eye			Both eyes			
	Visit 0 Day -30 to 0 Preoperative	Visit 00 Day 0 Operative	Visit 1 Day 1-2 Post Visit 00	Visit 2 Day 7-14 Post Visit 00	Visit 00A 7-14 days Post Visit 00	Visit 1A Day 1-2 Post Visit 00A	Visit 2A Day 7-14 days Post Visit 00A	Visit 3A Day 30-45 days Post Visit 00A	Visit 4A Day 80 – 100 days Post Visit 00A	Visit 5A Day 120 – 180 days Post Visit 00A	Early Exit
Informed Consent	X										
Demographics	X										
Medical, ocular history	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X			X						
Urine Pregnancy Test	X										
[redacted]	[redacted]							[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monocular Best Corrected Distance Visual Acuity	X			X			X	X	X+	X+	X+
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Both eyes	1st Operative Eye			2nd Operative Eye			Both eyes					
		Visit 0 Day -30 to 0 Preoperative	Visit 00 Day 0 Operative	Visit 1 Day 1-2 Post Visit 00	Visit 2 Day 7-14 Post Visit 00	Visit 00A 7-14 days Post Visit 00	Visit 1A Day 1-2 Post Visit 00A	Visit 2A Day 7-14 days Post Visit 00A	Visit 3A Day 30-45 days Post Visit 00A	Visit 4A Day 80 – 100 days Post Visit 00A	Visit 5A Day 120 – 180 days Post Visit 00A	Early Exit		
	ORA measurement including reticle orientation, aphakic		X			X								
	Preoperative IOL selection with Alcon Toric Calculator	X												
	Cataract Surgery		X			X								
	Lens Information		X			X								

Printed By: Print Date:

	Both eyes	1st Operative Eye			2nd Operative Eye			Both eyes			
	Visit 0 Day -30 to 0 Preoperative	Visit 00 Day 0 Operative	Visit 1 Day 1-2 Post Visit 00	Visit 2 Day 7-14 Post Visit 00	Visit 00A 7-14 days Post Visit 00	Visit 1A Day 1-2 Post Visit 00A	Visit 2A Day 7-14 days Post Visit 00A	Visit 3A Day 30-45 days Post Visit 00A	Visit 4A Day 80 – 100 days Post Visit 00A	Visit 5A Day 120 – 180 days Post Visit 00A	Early Exit
capture, pseudophakic capture											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Device Deficiencies		X	X	X	X	X	X	X	X	X	X

[redacted]

4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the Study Sponsor and must be approved by the IRB/IEC and global and regional Health Authorities, as applicable, prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.

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Table 6-2

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[redacted]		[redacted]		[redacted]	[redacted]
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5 INTRODUCTION

5.1 Background

In modern cataract surgery, spectacle freedom for the patient, either for distance vision, near vision, or both, is becoming more important. Globally, key cataract technology advancements (eg, monofocal, Toric, and foldable IOLs; ultrasound, optical and intraoperative biometry; phacoemulsification and femtosecond laser assisted surgery), have resulted in important reductions in residual refractive error and improved uncorrected distance visual acuity (UCDVA), both of which are highly correlated with patient satisfaction following cataract surgery (Nordan 1991, Kirwan 2015).

However, while the potential for significant postoperative residual refractive error has been reduced, it remains the most frequent cataract surgery complication. Approximately 30-60% of patients undergoing monofocal IOL implantation and 15-30% of patients undergoing toric IOL procedures require spectacle correction for distance correction as a result of a non-emmetropic refraction (Agresta 2012, Brandser 1997, Steinert 1999, Connors 2002). The large majority of these patients have residual refractive errors that are less than 2.00 D of magnitude (Brandser 1997, Olsen 1995, Wegener 1998).

The major causes for residual refractive error following cataract surgery include:

- Estimation errors for postoperative IOL position, preoperative axial length measurement and limitations of IOL calculation formulas that affect both spherical and Toric IOLs (Norrby 2008, Hirnschall 2014).

- Pre-existing corneal astigmatism (reported to exceed 1.00 D in approximately one-third of cataract patients) and imprecise preoperative measurement of corneal astigmatism (Ferrer-Blasco 2009, Lekhanont 2011).
- Surgical variations in the size and central position of the capsulorhexis which may influence the final position of the IOL inside the bag and are surgeon-dependent, and surgically induced astigmatism (SIA; McIntyre 2012).
- Healing process, such as anterior movement of the IOL resulting from postoperative capsular bag fibrosis and contraction (McIntyre 2012).

When spectacle or contact lens correction is not adequate or desired, secondary surgical procedures currently available to address residual refractive error include excimer laser corneal surgery, astigmatic keratotomy, piggyback (second) IOL placement and IOL exchange. Incorrect lens power remains one of the major causes cited for the removal of intraocular lenses (Steinert 1999, Connors 2002, Mamalis 2001).

5.2 Purpose of the Study

The purpose of the study is to evaluate the visual acuity outcomes when two modern technologies (Barrett Toric Calculator and ORA with VerifEye+) are used for implantation of a Toric IOL. There are also exploratory measurements which will be used to determine the effectiveness of each device.

At the end of the study, a clinical study report will be prepared in accordance with applicable regulatory requirements and standards.

There are no immediate plans to submit the results of this study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing.

5.3 Risks and Benefits

5.3.1 ORA System with VerifEye+

The ORA System with VerifEye+ is designed to provide intraoperative measurement of the refractive power of eyes during cataract removal and IOL implantation. The ORA System provides real time confirmation to ophthalmic surgeons with respect to the correctness of the IOL selection for the patient during the surgical procedure potentially reducing the frequency of revision surgery and possibly refractive surprises. In addition, the ORA system helps with the following:

- Judging the axis placement of the Toric IOL.
- Measurement of refractive power of the eye intraoperatively
- Confirmation of proper IOL selection

Harm is defined as physical injury or damage to the health of people, or damage to property or environment. The Risk Management File identifies harms, which are known as potential AEs associated with the ORA System with VerifEye.

Below is a summary of the identified harms:

- Temporary user discomfort (Blurred Vision)
- Decreased vision
- Visual Disturbance
- Microbial Infection
- Unexpected Postoperative Refraction Intervention Required
- Injury Due To Interference With Other Equipment
- Globe Rupture
- Blindness

The following conditions may make it difficult to obtain accurate readings using the ORA System:

- Patients having progressive retinal pathology such as diabetic retinopathy, macular degeneration, or any other pathology that the physician deems would interfere with patient fixation;
- Patients having corneal pathology such as Fuchs', EBMD, keratoconus, advanced pterygium impairing the cornea, or any other pathology that the physician deems would interfere with the measurement process;
- Patients for whom the preoperative regimen includes residual viscous substances left on the corneal surface such as lidocaine gel or viscoelastics;
- Visually significant media opacity, such as prominent floaters or asteroid hyalosis, will either limit or prohibit the measurement process;
- Patients having received retro or peribulbar block or any other treatment that impairs their ability to visualize the fixation light;

- Use of iris hooks during an ORA system image capture will yield inaccurate measurements.

In addition:

- Significant central corneal irregularities resulting in higher order aberrations might yield inaccurate refractive measurements.
- Post refractive keratectomy eyes might yield inaccurate refractive measurement.
- The safety and effectiveness of using the data from the ORA System have not been established for determining treatments involving higher order aberrations of the eye such as coma and spherical aberrations.

There may also be unknown risks to use of the ORA System with VerifEye+. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight and monitoring.

Refer to the ORA System DFU for additional information.

5.3.2 Alcon Toric Calculator (Barrett)

The Toric IOL Web-based Calculators, including the updated Alcon Online Toric IOL Calculator, provide clinically significant benefits in regard to assisting the ophthalmic surgeon in calculations related to IOL selection and placement. This benefit is substantiated by clinical evidence and published literature demonstrating an overall improvement in refractive status across the general population of patients following IOL implantation.

The key harm is unexpected postoperative refraction resulting in intervention, which was identified in a comprehensive review of the post-market clinical experience surveillance data incorporated in the RMF for existing Alcon Toric IOL Web-based IOL Calculators (TDOC-0050559; Risk Management File for the Alcon Online Toric IOL Calculator). The affected population includes cataract patients implanted with an AcrySof Toric, AcrySof IQ Toric, AcrySof ReSTOR® Toric 3.0, AcrySof ReSTOR Toric 2.5 or AcrySof Cachet® IOL, previously calculated with existing Web-based IOL calculators.

Unexpected post-operative refraction errors may occur as a result of a combination of factors which may include the calculator algorithm (underestimation of the corneal plane equivalent power of the cylinder), steps between IOL cylinder powers, and other sources of surgical and measurement error. In addition, iatrogenic as well as inherent patient/subject dependent healing processes following surgery may also contribute to unexpected postoperative

refraction error as shown by Jeon, et al (2014) who reported a myopic shift in the refractive spherical equivalent.

Unexpected post-operative refraction has been identified as harm in the risk assessment of the Toric IOL Web-based Calculators; this risk has been further mitigated and reduced as far as possible for calculator-related factors through design risk control measures by implementing Holladay I formula and the Universal II (Barrett) formula in the updated Calculator and the provision of instructions for use.

Overall, the clinically significant benefits of the IOL Web-based Calculators, including the Alcon IOL Online Toric Calculator are considered to outweigh the overall risks.

Refer to the Alcon Toric Calculator DFU for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
To evaluate the percentage of eyes with BCDVA of 20/20 or better in eyes implanted with AcrySof Toric selected by ORA with VerifEye + and Barrett Toric Calculator	Mean Monocular BCDVA in logMAR

6.2 Secondary Objective(s)

Not Applicable.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	QoV questionnaire

6.4 Safety Objective(s)

Table 6–3 Safety Objective(s)

Objective(s)	Endpoint(s)
Evaluation of adverse events including secondary surgical interventions related to the investigational device	Adverse events
Device deficiencies	Device deficiencies

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, randomized, contralateral, multicenter, postmarket study. A total of 115 subjects will be enrolled to achieve 90 evaluable subjects. Treatments will be randomized between eyes and the eye with more visually significant cataract as measured by BCDVA will

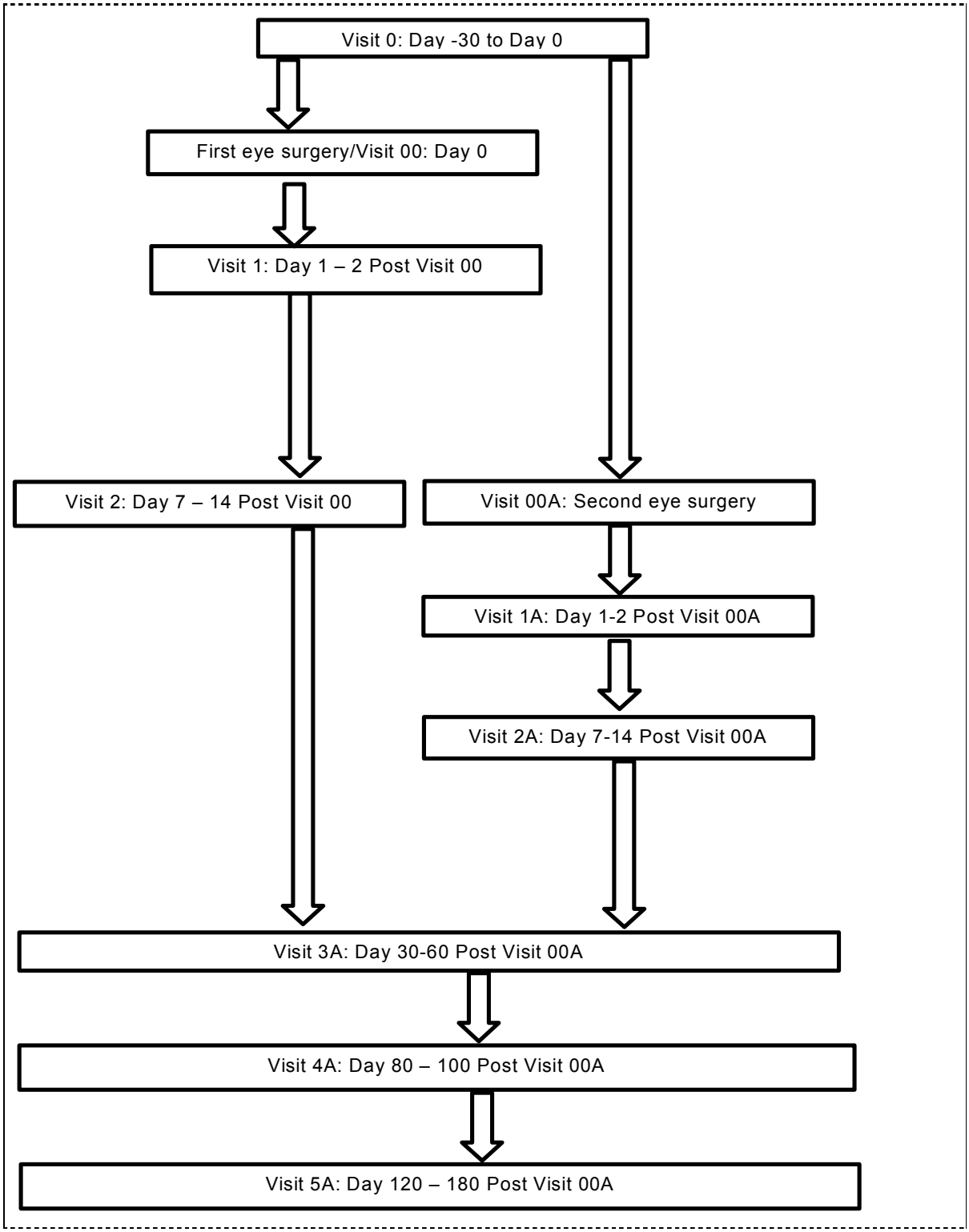
undergo surgery first. If the BCDVA is equal between eyes, the right eye will undergo surgery first.

The Barrett Toric Calculator via the Alcon Toric Calculator will be used for IOL power selection preoperatively. Sites that have LenSx will use it for primary and secondary incisions, capsulorhexis, and phacofragmentation consistently in both eyes for all subjects. Sites that don't have LenSx will use standard manual procedures.

For the eyes in the ORA with VerifEye + study group, the IOL power and axis and axis mark alignment will be provided by ORA. For eyes in the Barrett Toric study group, the IOL power and axis will be provided by the Barrett Toric Calculator and axis alignment will be done manually (ie, without ORA guidance).

The study will be conducted at up to 10 sites in the US. Surgery will be done on each eye on different days 7 to14 days apart. Total follow-up duration is 6 months. There will be 10 visits in total. Refer to the Overview of Study Procedures Table for an overview of the visit schedule and the assessments to be performed at each visit.

Figure 7–1 Study Flow Chart



7.2 Rationale for Study Design

This is a prospective, randomized, contralateral eye, multicenter postmarket study. Treatments will be randomized between eyes to mitigate bias. Contralateral design can control for environmental and patient specific factors. There is no masking in the study because it will be obvious to the surgeon which methodology is being used. Purpose and Timing of Interim Analyses and Resulting Design Adaptations

There will be an interim analysis performed using the 1-month follow up data. This will be performed after the last subject has completed their 1-month follow up visit. There are no expected design adaptations planned using the results of this analysis.

7.3 Rationale for Duration of Treatment/Follow-Up

A six month follow-up duration was chosen because it is expected that the visual acuity and refraction variables will be stabilized by then.

7.4 Rationale for Choice of Control Product

- Not applicable.

7.5 Data Monitoring Committee

- Not applicable

8 STUDY POPULATION

The study population consists of male and female subjects at least 22 years old who require cataract surgery and a Toric IOL in both eyes. It is aimed to enroll approximately 115 subjects at approximately 10 sites in the US. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 12 weeks.

Subjects will be required to have preoperative keratometric astigmatism of 0.75 to 3.00 D and require the AcrySof IQ Toric SN6AT3 – 6 as determined by Alcon Toric Calculator.

[redacted]

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form.
2. Willing and able to attend all scheduled study visits as required per protocol.
3. 22 years of age or older
4. Preoperative keratometric astigmatism of 0.75 to 3.00 D
5. Planned implantation of AcrySof IQ Toric SN6AT3 – T6 as determined by the Alcon Toric Calculator
6. Potential postoperative visual acuity of 0.04 logMAR (20/20) or better

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study.

1. Pregnancy:
    a. they are currently pregnant,
    b. have a positive urine pregnancy test result at Screening,
    c. intend to become pregnant during the study period,
    d. are breast-feeding.

    Subjects who become pregnant during the study will not be discontinued; however, data will be excluded from the effectiveness analyses because pregnancy can alter refraction and visual acuity results.
2. Unclear intraocular media other than cataract

3. Axial length < 21.5 and > 27.0 mm

4. Significant irregular corneal astigmatism as measured by a corneal topographer

5. Unstable tear film per Investigator judgement

6. Significant anterior or posterior segment disease

7. Prior intraocular or corneal surgery

8. Prior retinal detachment

9. Participation in another concurrent clinical trial per the PI judgement

10. Presence or history of any condition or finding that makes the subject unsuitable as a candidate for cataract surgery or study participation or may confound the outcome of the study, in the opinion of the Investigator

Exclusion Criteria during Surgery

11. Intra-operative complications such as, but not limited to, posterior capsular tear, wound burn and need to place a suture

12. ORA or Alcon Toric Calculator recommends an IOL other than AcrySof IQ Toric SN6AT3-T6

8.3 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): ORA with VerifEye+
Alcon Toric Calculator

Table 9–1 Test Product

Test Product	ORA System with VerifEye+
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	The ORA System uses wavefront aberrometry data in the measurement and analysis of the refractive power of the eye (ie, sphere, cylinder, and axis measurements) to support cataract surgical procedures.
Product description and parameters available for this study	The ORA System uses wavefront aberrometry data in the measurement and analysis of the refractive properties of the eye. The ORA System method of determining the refractive state of the eye is performed intraoperatively during the aphakic state (after natural lens removal) during cataract surgery. This additional information provided by the ORA System can be collected only after the natural lens is removed and may contribute to the provider's plan and patient's outcome when seeking a refractive correction. Preoperatively, a patient who has been diagnosed with a treatable refractive condition could elect to have the ORA System utilized during cataract surgery to allow the surgeon to measure the total corneal impact on refraction, and variables that may impede the refractive goal.
Packaging description	N/A
Storage conditions	N/A
Supply	N/A

More information on this test product can be found in the Directions for Use.

Table 9–2 Test Product

Test Product(s)	Alcon Toric Calculator
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for Use	The Alcon Online Toric IOL calculator is a tool intended to assist the ophthalmic surgeon in selecting a toric IOL and placement axis for adult patients with corneal astigmatism undergoing cataract removal.
Product description and parameters available for this study	IOL Web-based Calculators and the Alcon Online Toric IOL Calculator are a family of IOL accessories that use software-driven algorithms to assist the surgeon in necessary calculations and are intended to be displayed in the Microsoft® Internet Explorer® or similar browser. The IOL Web-based Calculators and the Alcon Online Toric IOL Calculator are accessories to AcrySof Toric IOLs. The family of Toric IOL Calculators help to predict the amount of postoperative corneal astigmatism that needs to be corrected in order to optimize IOL model selection and axis placement within the capsular bag. The Barrett Toric formulas will be used in this study.
Formulation	N/A
Storage conditions	N/A
Supply	N/A

More information on this test product can be found in the Directions for Use.

9.2 Other Medical Device or Medication Specified for Use During the Study

No other medical devices or medications outside of the standard of care are required to be used in conjunction with the treatments during the clinical study.

9.3 Treatment Assignment / Randomization

Subjects will be randomized in a 1:1 ratio to receive treatment with ORA System with VerifEye+ or the Barrett Toric Calculator in the first treated eye, respectively. Since this is a contralateral study, each subject should have one eye treated with each technique.

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system.

A randomization list will be generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned to treatment according to the randomization list uploaded in the IRT system. The randomization list will be generated and maintained by the Study Sponsor.

9.3.1 IRT

At Visit 0, all eligible subject eyes will be randomized via the IRT system to one of the treatment arms. The Investigator or delegate will access the IRT system after confirming that the subject meets all the eligibility criteria. A randomization number will be automatically assigned to the subject according to the subject randomization list. The IRT system will inform the site user of the treatment assignment to be used for the subject eye.

9.4 Treatment masking

All members associated with the study (at the site and the Study Sponsor) are unmasked to the assigned treatment.

9.5 Accountability Procedures

Not applicable.

9.6 Changes to concomitant medications, treatments/ procedures

After the subject is enrolled into the study, the Investigator must instruct the subject to notify the study site about:

- Any new medications
- Alterations in dose or dose schedules for current medications
- Any medical procedure or hospitalization that occurred or is planned
- Any non-drug therapies (including physical therapy and blood transfusions).

The Investigator must document this information in the subject's case history source documents.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 Informed Consent and Screening

The Investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures.

The Investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

10.2 Description of Study Procedures and Assessments

Detailed descriptions of assessments and procedures are provided in the MOP. All devices are to be used per the standard of care and the DFU. The Investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

10.2.1 Demographics

Obtain demographic information including age, race, ethnicity, and sex.

10.2.2 Medical History

Collect medical history information, including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications. Throughout the subject's participation, obtain information on any changes in medical health and/or the use of concomitant medications.

10.2.3 Adverse Event Collection: Safety Assessment

Assess and record any adverse events that are observed or reported, including those associated with changes in concomitant medication dosing since the previous visit.

Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or randomized).

10.2.4 Device Deficiencies: Safety Assessment

Assess and record any device deficiencies that are reported or observed, including those associated with changes in concomitant medication dosing since the previous visit. Requirements for reporting device deficiencies in the study can be found in Section 11.
Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or randomized).

[redacted]

10.2.8 Visual Acuity: Effectiveness

Visual acuity testing for both eyes must be performed prior to any assessment requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye.

[redacted]

[redacted]

10.3 Study Visit Procedures

10.3.1 Visit 0: Day -30 to Day 0 (for both eyes)

Upon signing informed consent, patients are considered enrolled. Subjects will be assigned a single subject identifier at the screening visit. The subject identifier consists of a combination of a 4 digit Investigator number and a 5 digit subject number. The number is automatically generated sequentially by the electronic data capture (EDC) system. As an example: "4584.00001" (the Investigator number and subject number are separated by a "." character).

Below is a list of study procedures to be undertaken at Visit 0. Procedures should be performed in the order presented below unless otherwise stated. All assessments must be documented in the source documentation and eCRFs (if applicable).

For a potential subject meeting all entry criteria via pre-screening, invite him/her to participate in the study, and carry out the informed consent process if he/she is interested.

NOTE: Subjects must formally consent to participate in the study prior to undergoing any study specific testing.

- [redacted]
- Document demographics, ocular and nonocular medical history, ocular and nonocular concomitant medications.
- Perform a urine pregnancy test, if the subject is a woman of childbearing potential.
- [redacted]
- Measure and record BCDVA measurement (monocular) - (refer to MOP for details).
- [redacted]
- Identify target refraction.
- [redacted]
- Record any device deficiency and AEs.

10.3.2 Surgery Visit (Visit 00 and Visit 00A)

Visit 00: Day 0 (implant for first eye)

Visit 00A: 7-14 days after surgery for Eye 1 (implant for second eye)

Below is a list of study procedures to be undertaken at the surgery visit. Procedures should be performed in the order presented below. Activities involving multiple delegated staff members may be performed in parallel. All assessments must be recorded in source documentation and eCRFs (if applicable).

Procedures performed in ORA group:

- Subjects will be randomized and undergo surgery using the ORA system.
- Document any changes to ocular and nonocular concomitant medications.
- Prepare subject/operative eye for surgery in accordance with site-specific operating procedures.
- Ensure that the subject was randomized to ORA and it is utilized for the surgery.
- Perform the surgical procedure using standard of care.
- Record aphakic refraction and aphakic SE.
- Record IOL power recommended by ORA and predicted post-operative SE.
- Record implanted IOL power and predicted post-operative SE.
- Record any surgical problems, complications, or other procedures that occur during surgery.
- Record any device deficiencies and adverse events. Refer to Section 11 for further detail.

Procedures performed in Barrett Toric Calculator group:

- Subjects will be randomized and undergo surgery using the Barrett Toric Calculator.
- Take preoperative measurements for IOL calculation.
- Prepare subject/operative eye for surgery in accordance with site-specific operating procedures.
- Document any changes to ocular and nonocular concomitant medications.
- Ensure that the subject was randomized to Barrett Toric Calculator and it is utilized.
- Perform surgical procedure using standard of care.
- Record implanted IOL power and anticipated residual refractive astigmatism.
- Record any surgical problems, complications, or other procedures that occur during surgery.
- Record any device deficiencies and adverse events. Refer to Section 11 for further detail.

10.3.3 Visit 1/1A (Day 1 for Eye 1/2)

- Document any changes to ocular and nonocular concomitant medications.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Record any device deficiencies and adverse events. Refer to Section 11 for further detail.

10.3.4 Post-Surgery Visit (Visits 2, 2A, 3A, 4A and 5A)

Below is a list of study procedures to be undertaken at post-surgery visits. Procedures should be performed in the order presented below. All assessments must be recorded in source documents and eCRFs (if applicable).

- [redacted]
- Document changes in ocular and nonocular concomitant medications at Visits 2, 2A, 3A, 4A, and 5A.
- [redacted]
- [redacted]
- Perform BCDVA (monocular) assessment at Visits 2, 2A, 3A, 4A, and 5A. Refer to MOP for details.
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- Record any device deficiencies and AEs. Refer to Section 11 for further detail.
- Document subject exit from study at Visit 5A.

10.4 Unscheduled Visits

If a subject visit occurs between any regularly scheduled visits, this visit must be documented as an Unscheduled Visit. During all unscheduled visits, the Investigator must conduct the following procedures:

- Collect Adverse Event information
- Record changes in medical condition or concomitant medication

The Investigator may perform additional procedures for proper diagnosis and treatment of the subject. The Investigator must document this information in the subject's case history source documents.

If during an Unscheduled Visit the subject is discontinuing from the study, the Investigator must conduct Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments, as possible.

10.5 Discontinued Subjects

10.5.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to randomization/surgical procedure.

The Investigator must document the reason for screen failure in the subject's case history source documents.

Subject numbers must not be re-used.

10.5.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the Investigator after randomization/surgical procedure.

Subject numbers of discontinued subjects must not be re-used.

Subjects may discontinue from study or study treatment at any time for any reason. Subjects may also be discontinued from study treatment at any time if, in the opinion of the Investigator, continued treatment poses a risk to their health.

If a subject discontinues from study treatment, every effort must be made to keep the subject in the study and to continue with the study assessments as specified in the schedule of study procedures and assessments until the final visit.

For subjects discontinuing from the study, the Investigator must complete all Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments, if the subject is willing and able, and if in the opinion of the Investigator it is safe for the subject to do so.

The Investigator must document the reason for study or treatment discontinuation in the subject's case history source documents.

To ensure the safety of all subjects who discontinue early, Investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

10.5.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product

Not applicable.

10.6 Clinical Study Termination

The Study Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time.

If the clinical study is prematurely terminated or suspended by the Study Sponsor:

- The Study Sponsor must:
    - Immediately notify the Investigator(s) and subsequently provide instructions for study termination.
    - Inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The Investigator must:
    - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.

- Provide subjects with recommendations for post-study treatment options as needed.

The Investigator may terminate the site's participation in the study for reasonable cause.

10.6.1 Follow-up of subjects after study participation has ended

Following this study, the subject will return to their eye care professional for their routine eye care.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is 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 investigational medical device (test article). Refer to the Glossary of Terms for categories of AEs and SAEs.

Figure 11–1 Categorization of All Adverse Event

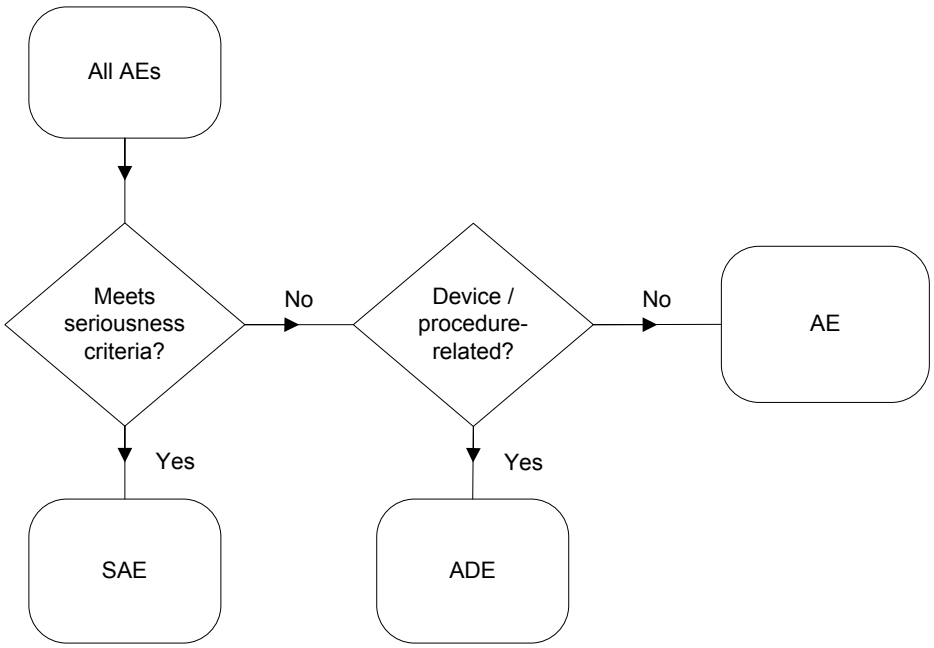
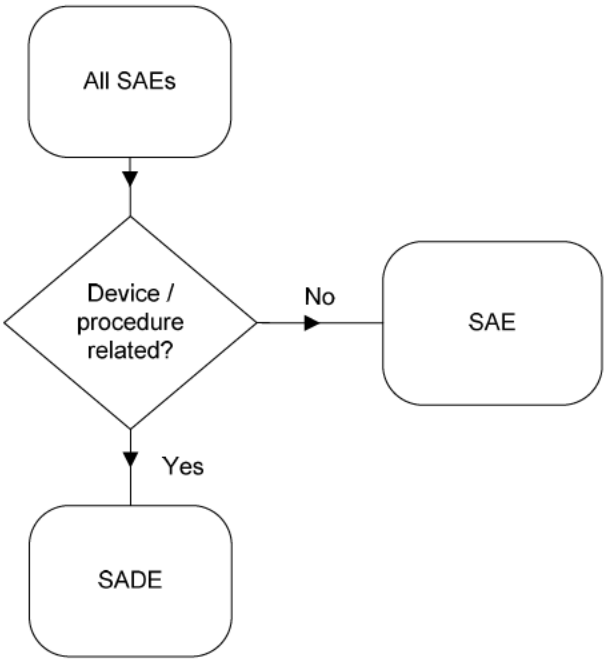


Figure 11–2 Categorization of All Serious Adverse Events



11.1.1 Specific Events Relevant to this Protocol

There are no specific adverse events included in this protocol.

In addition to all AEs [serious (excluding posterior capsulotomy performed for PCO) and nonserious] meeting the definitions, any potentially sight-threatening event may be considered serious based on the judgment of the Investigator and should be reported appropriately as delineated in Section 11.3.

11.1.2 Device Deficiencies

A device deficiency may or may not be associated with subject harm (ie, ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should determine the applicable category for the identified or suspect device deficiency and report any subject harm separately.

11.2 Monitoring for Adverse Events

At each visit, after the subject has the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"

- "Have there been any changes in the medicines you take since your last study visit?"

Changes in any protocol-specific parameters and/or questionnaires evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant, in the opinion of the Investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.3 Procedures for Recording and Reporting

Adverse events are collected from the time of informed consent. Any pre-existing medical conditions or signs/symptoms present in a subject prior to the start of the study (ie, before informed consent is signed) are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

In addition, aqueous cells and flare, corneal edema, raised IOP and superficial punctate keratitis are examples of early postoperative findings that are typically observed following ocular surgery. These are not considered AEs if they can be reasonably expected to resolve within a week and not result in any untoward long term visual outcome impact.

For each recorded event, the ADE and SAE documentation must include the following: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness, and causality. In addition, the Investigator must document all device deficiencies reported or observed with test articles on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.
- A printed copy of the completed Serious Adverse Event and Adverse Device Effect and/or Device Deficiency eCRF must be included with product returns.
- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.

- Document all relevant information from Discharge Summary, Autopsy Report, Certificate of Death, etc, if applicable, in narrative section of the Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF.

Note: Should the EDC system become non-operational, the site must complete the appropriate paper *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency Form*. The completed form is emailed to the Study Sponsor to FTW.medical_safety@alcon.com according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for non-study marketed devices/products (ie, AcrySof IQ Toric IOL SN6AT3-6, Alcon OVDs and BSS and Alcon surgical systems) will be considered and processed as spontaneous (following the post-market vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study Sponsor representatives may be contacted for any protocol related question and their contact information is provided in the Manual of Procedures that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor may request copies of applicable portions of the subject's medical records. The Investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

11.3.1 Intensity and Causality Assessments

Where appropriate, the Investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the Investigator must assess the causality (Related or Not Related to the medical device or study procedure). An assessment of causality will also be performed by Study Sponsor utilizing the same definitions, as shown below:

Intensity (Severity)

Mild	An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the Investigator must assess the causality (Related or Not Related to the medical device or study procedure). An assessment of causality will also be performed by Study Sponsor utilizing the same definitions, as shown below:

Causality

Related	An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.
Not Related	An AE classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

The Study Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The Study Sponsor will notify the Investigator of any AEs that is upgraded from non-serious to serious or from unrelated to related.

11.4 Return product analysis

Study Sponsor representatives and their contact information are provided in the Manual of Procedures that accompanies this protocol.

Alcon products associated with device deficiencies and/or product related AEs should be returned and must include the Complaint # which will be provided by Study Sponsor after the

case is entered in the Study Sponsor's Global Product Complaint Management System (GPCMS).

11.5 Unmasking of the Study Treatment

Not applicable; this study is open-label.

11.6 Follow-Up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The Investigator should provide the Study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ongoing at time of subject exit from study, any additional information received at follow-up should be documented in the eCRFs up to study completion (ie, database lock).

All complaints received after this time period will be considered and processed as spontaneous (following the post-market vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

The Investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements

11.7 Pregnancy in the Clinical Study

Women of childbearing potential are not excluded from participation. If a woman becomes pregnant during the study, the pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case–by-case basis. An Alcon form will be utilized to capture all pregnancy-related information until birth of the child.

12 ANALYSIS PLAN

12.1 Subject Evaluability

The final subject evaluability will be determined using the Deviations and Evaluability Plan (DEP) prior to locking the database.

12.2 Analysis Sets

There will be two effectiveness analysis sets. The All Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA. The Per Protocol Analysis Set (PPS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA and with no major protocol deviations. The primary analysis set for effectiveness is the PPS.

Safety Analysis Set (SS) will include all eyes with attempted implantation with any IOL (successful or aborted after contact with the eye) and will be used for the safety analyses.

12.3 Demographic and Baseline Characteristics

Summary statistics will be provided for demographic and baseline characteristics by treatment group. Number and percentage will be presented for categorical variables and descriptive statistics including mean, standard deviation (SD), minimum, and maximum will be presented for continuous variables.

12.4 Effectiveness Analyses

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to evaluate the percentage of eyes with BCDVA of 20/20 or better in eyes implanted with AcrySof Toric selected by ORA with VerifEye + and Barrett Toric Calculator. The primary endpoint is percentage of eyes with BCDVA of 20/20 or better at 6 months.

12.4.1.1 Statistical Hypotheses

No hypothesis testing of the primary effectiveness endpoint is planned.

12.4.1.2 Analysis Methods

The following descriptive statistics will be provided by treatment group:

- logMAR categories: the number and percentage of eyes with visual acuity of
    - 0.0 logMAR or better: ≤0.00 logMAR
    - 0.1 logMAR or better: ≤0.10 logMAR
    - 0.2 logMAR or better: ≤0.20 logMAR
    - 0.3 logMAR or better: ≤0.30 logMAR

- Snellen categories: the number and percentage of eyes with visual acuity of
    - 20/20 Snellen or better: ≤0.04 logMAR
    - 20/25 Snellen or better: ≤0.14 logMAR
    - 20/32 Snellen or better: ≤0.24 logMAR
    - 20/40 Snellen or better: ≤0.34 logMAR
- Descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum and two-sided 95% confidence interval

[redacted]

[redacted]

12.5 Handling of Missing Data

The AAS does not include any imputed values. Although missing data will occur, the influence of missing data is expected to be minimal.

12.6 Safety Analyses

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters.

The safety endpoints are:

- Adverse events including SSIs
- Device deficiencies

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis.

Adverse events including SSIs

Descriptive summaries (counts and percentages) for AEs including SSIs will be presented by treatment group. Individual subject listings will be provided for AEs.

Device Deficiencies

The number and percentage of all device deficiencies will be tabulated with a breakdown by treatment group. A listing of all device deficiencies will also be provided.

[redacted]

12.7 Interim Analyses and Reporting

There is one interim analysis in this study. The objective of the interim analysis is to assess the effectiveness and safety of each treatment group when all subjects complete Visit 3A (30-60 days post Visit 00A).

12.8 Sample Size Justification

In order to estimate the percent of eyes with BCDVA of 20/20 or better (ie, $\leq$ 0.04 logMAR) at 6 months post-operative, the 95% confidence interval of the percent of eyes with BCDVA of 20/20 or better at 6 months post-operative will be calculated based on the binomial distribution. With a sample size of 90 eyes, per the binomial distribution, the width of the 95% confidence interval ranges from 4.0% to 21.5%. As an example, for an observed outcome of 70%, the 95% confidence interval per binomial distribution is (59.4%, 79.2%) with a width of 19.8%.

For different number of available eyes at 6 months (70, 75, 80, 85, 90, 95, and 100) and different observed percent of eyes with BCDVA of 20/20 or better at 6 months (70%, 75%, and 80%), the table below summarizes the corresponding confidence intervals and the width of the confidence intervals. With a sample size of at least 70 eyes at 6 months postoperatively, the width of confidence interval is less than 23% if the observed rate is $\geq$ 70%.

Table 12-1 95% Confidence Interval and Width per Binomial Distribution

Number of Eyes at 6 Months	Observed Percent of Eyes with BCDVA of 20/20 or Better		
	70%	75%	80%
70	(57.9%, 80.4%) 22.5%	(64.0%, 85.2%) 21.2%	(68.7%, 88.6%) 19.9%
75	(59.0%, 80.6%) 21.6%	(63.3%, 84.0%) 20.7%	(69.2%, 88.4%) 19.2%
80	(58.7%, 79.7%) 21.0%	(64.1%, 84.0%) 19.9%	(69.6%, 88.1%) 18.6%
85	(59.7%, 80.0%) 20.3%	(64.7%, 84.0%) 19.3%	(69.9%, 87.9%) 18.0%
90	(59.4%, 79.2%) 19.8%	(65.4%, 84.0%) 18.6%	(70.2%, 87.7%) 17.4%
95	(60.3%, 79.4%) 19.2%	(64.8%, 83.1%) 18.3%	(70.5%, 87.5%) 17.0%
100	(60.0%, 78.8%) 18.7%	(65.3%, 83.1%) 17.8%	(70.8%, 87.3%) 16.5%

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Study Sponsor will collect a copy of the enrollment log ***without any identifying subject information***. All documents submitted to the Study Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information will be transmitted to the Study Sponsor.

The Study Sponsor may release anonymized study data to external researchers for purposes of future research directly related to the study objectives, or future research that is beyond the scope of the current study objectives. The Informed Consent Form explains this to study subjects. Anonymization means that all identifiable information will be removed from the dataset and all links to the subjects in the study will be removed. Anonymization of the data will maintain confidentiality of the subjects who participate in the study so that they cannot be identified by external researchers. The anonymized data set will contain records from all of the subjects in the current study, but the anonymization process might change the data set in some ways, so external researchers will be informed that they might not be able to duplicate some of the results from this study.

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor, and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the Study Sponsor and are independent of study site staff.

If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility

- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Only designated individuals at the site will complete the CRFs. The CRFs must be completed at regular intervals following the clinical study visit schedule. It is expected that all data reported have corresponding entries in the source documents. The Principal Investigator is responsible for reviewing and certifying that the CRFs are accurate and complete. The only subject identifiers recorded on the CRFs will be subject number, and subject demographic information.

13.3 Data Review and Clarifications

A review of CRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the CRFs have been completed, additional data clarifications, and/or additions may be needed as a result of the data cleaning process. Data clarifications are documented and are part of each subject's CRF.

13.4 Sponsor and Monitoring Responsibilities

The Study Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals according to the study monitoring plan. The clinical investigation will be monitored to ensure that the rights and well-being of the subjects are protected, the reported data are accurate, complete, and verifiable from the source documents, and the study is conducted in compliance with the current approved protocol (and amendments[s], if applicable), with current GCP, and with applicable regulatory requirements.

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate Study Sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

A Coordinating Investigator may be identified by the Study Sponsor to review and endorse the final study report. In cases where a Coordinating Investigator is engaged, the Study Sponsor will select the Coordinating Investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

Additionally,

> Alcon may have an expert Sponsor Observer present during subject visits to make observations during the study visit.
>
> The Sponsor Observer must be supervised by the Investigator or designee to ensure the Sponsor Observer's presence or activities do not bias the outcome of the study, affect the quality of the research data, and/or compromise the rights and welfare of the subject. The Sponsor Observer will not intervene with the standard of care provided to study subjects or make safety-related decisions or assessments. The activities of Sponsor Observers will be described in the Informed Consent.

13.5 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Study Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is to be kept separately.

Additionally, the Investigator must keep study records and source documents consistent with the terms of the clinical study agreement with the Study Sponsor. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, then the Study Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

13.6 Quality Assurance and Quality Control

The Study Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring

and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Study Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

This clinical study must be conducted in accordance with the ethical principles contained within:

- The Declaration of Helsinki, and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155:2011, and the applicable US FDA 21 CFR Regulations.
- SOPs of the Study Sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations.
- Notifications and timelines for reporting protocol deviations should be based upon applicable Ethics Committee requirements

The Investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. Deviations from this protocol, regulatory requirements and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The Investigator must provide documentation of the IRB/IEC approval to the Study Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the Package Insert, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the study, the Investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the Investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent (file in subject's medical records) and must provide a duplicate copy to each subject according to local regulations.

The Study Sponsor assures that the key design elements of this protocol will be registered on www.clinicaltrials.gov as required by current regulations and, if applicable, other public databases as required by local country regulations. In addition, results of this study will be made publicly available on www.clinicaltrials.gov regardless of outcome as required by current regulations and, if applicable, in other public databases as required by local country regulations.

15 REFERENCES

15.1 References applicable for all clinical studies

- EN ISO 11979-7:2014 Ophthalmic implants – Intraocular lenses – Part 7: Clinical Investigations
- ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice

15.1.1 US references applicable for clinical studies

- 21 CFR Part 11 - Electronic Records; Electronic Signatures

- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- The California Bill of Rights

15.2 References for this clinical study

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Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted] Woo Kim [redacted]	[redacted]
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