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Short Title

Optimizing the Assessment of Refractive Outcomes after Cataract Surgery

Long Title

Optimizing the Assessment of Refractive Outcomes after Cataract Surgery and Implantation of a Monofocal IOL

Protocol Number:	ILQ732-I001 / NCT02842151
Study Phase:	Not Applicable
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	ACRYSOF® IQ Monofocal IOL (Model SN60WF)
US IND# / IDE#/ EudraCT:	Not Applicable

Investigator Agreement

I have read the clinical study described, herein, 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 Practices (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

Address

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1 GLOSSARY OF TERMS

ACRYSOF IQ Monofocal IOL	Throughout this document, investigational product will be referred to as ACRYSOF IQ Monofocal IOL (Model SN60WF), Model SN60WF and Test Article.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test article) or control article. *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 article or control article.*
Adverse Event (AE)	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). *Note: For subjects, this definition includes events related to the test article, the control article, or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*
Anticipated Serious Adverse Device Effect (ASADE)	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.*
Enrolled Subjects	Any subject who signs an informed consent form (ICF) for participation in the study.
Interventional Study	A study in which prospective subject assignment is decided by a protocol and use of the product is linked to the decision to include the subject in the study. Interventions include, but are not restricted to, drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, and preventive care. Additional diagnostic or monitoring procedures are applied and methods other than epidemiological methods are being used for analysis of the data.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.

Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Pre-screened Subjects	Chart review completed on potential subjects by study site for inclusion/exclusion criteria that do not require study specific testing. This is based on routine clinical testing and/or cataract evaluation.
Screened Subjects	Any subject who is considered for the study and may or may not have signed an ICF.
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 health 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), or any ocular secondary surgical intervention excluding posterior capsulotomy. 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 12 for additional SAEs.*
Significant Non-Serious Adverse Event	A significant non-serious adverse event is a symptomatic, device-related, non-sight threatening adverse event that warrants discontinuation of any contact lens wear for greater than or equal to 2 weeks. *Refer to Section 7 for additional Significant Non-Serious AEs.*
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 ABBREVIATIONS

Abbreviation	Definition
AAS	All implanted analysis set
ACD	Anterior chamber depth
ADE	Adverse device effect
AE	Adverse event
AL	Axial length
AMD	Age-related macular degeneration
ASADE	Anticipated serious adverse device effect
BAS	Best case analysis set
CDVA	Corrected distance visual acuity
CE	European Conformity
CI	Coordinating Investigator
D	Diopter
DoH	Declaration of Helsinki
DFU	Directions for use
EDC	Electronic data capture
eCRF	Electronic case report form
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
LASIK	Laser-assisted in situ keratomileusis
LRI	Limbal relaxing incision
MOP	Manual of procedures
N/A	Not applicable
OD	Right eye
OS	Left eye
PC	Posterior capsulotomy
PCO	Posterior capsular opacification
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedures
SSI	Secondary surgical intervention
UDVA	Uncorrected distance visual acuity
UNSV	Unscheduled visit
US	United States

Abbreviation	Definition
USADE	Unanticipated serious adverse device effect
VA	Visual Acuity

3 PROTOCOL SUMMARY

Investigation Type	Device
Study Type	Interventional (See Glossary of Terms for full definition)
Investigational Product	ACRYSOF IQ Monofocal Intraocular Lens (IOL) (Model SN60WF)
Purpose and Rationale	The purpose of this study is to evaluate whether an automated refraction device can be used to personalize the A-constant as well as standard refraction (ie, to a clinically insignificant difference). Errors/noise from refraction plays a significant role, and it would be important to know if an automated method has any advantages over conventional manifest refraction for A-constant optimization.
Primary Objective	To demonstrate equivalency, at each of the 3 clinical sites, between IOL SRK/T A-constant estimated based on postoperative manifest spherical equivalent refraction at 3 months and IOL A-constant estimated based on postoperative spherical equivalent from autorefraction using *Topcon® KR-1W* at 3 months.
Endpoint(s) and assessments related to Primary Objective(s)	• Automated Refraction • Anterior Chamber Depth (ACD) • Keratometry • Axial Length (AL) • Manifest Refraction • IOL Power (implanted) • White-to-White Distance
Secondary Objectives	Not Applicable

Endpoint(s) and Assessments Related to Secondary Objective(s)	Not Applicable
Safety Endpoints and Assessments	• Adverse Event (AE) rates of ACRYSOF IQ Monofocal IOL (Model SN60WF) and use of the Topcon KR-1W will be collected separately • Intraocular Pressure (IOP) • Slit-Lamp Examination • Dilated Fundus Examination • IOL Observations • Subjective Posterior Capsular Opacification (PCO) Assessment • Posterior Capsulotomy (PC) • Surgical Problems • Other Procedures at Surgery • AEs • Secondary Surgical Interventions (SSIs) • Device Deficiencies
Study Design	Prospective; observer-masked *(examiner performing manifest refraction is masked to the refractive target and refractive error from the surgical planning and the operative visit)*; non-randomized; total duration of a subject's participation in the study is approximately 4.5 months.
Subject Population	Adults (22 years and older) with cataract in one or both eyes requiring surgery with implantation of a monofocal IOL.
Key Inclusion Criteria (See Section 9.1)	• Planned cataract removal by phacoemulsification with implantation of a monofocal IOL • Preoperative keratometric astigmatism ≤ 1.0 D

Key Exclusion Criteria (See Section 9.2)	• History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology • History of recurrent anterior segment /posterior segment inflammation • Clinically significant, in the opinion of the Investigator, any corneal dystrophy or any other corneal abnormality/pathology • Clinically significant, in the opinion of the Investigator, severe dry eye • Diagnosis of amblyopia • Systemic medications that, in the opinion of the Investigator, may confound the outcome or increase the risk of complications to the subject or other medications including anticholinergics, alpha adrenergic blocking agents with similar side effects
Data Analysis and Sample Size Justification	**Data Analysis:** The primary analysis set for effectiveness analyses will be the All-Implanted Analysis Set. This includes all eyes with successful IOL implantation. Analysis based on the study eye will be considered primary. Additional supportive analyses may be conducted using the Best-Case Analysis Set. This includes all eyes successfully implanted with the IOL that had • at least 1 postoperative visit; • no macular degeneration at any time; and • no major protocol violation The Safety Analysis Set will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye) The Safety Analysis Set will be used for the safety analyses. If the 2-sided 90% confidence intervals for the mean difference in IOL A-constants is contained within (-0.15, 0.15), then equivalence will be concluded. Descriptive statistics (mean, median, standard deviation, number of subjects/eyes, minimum, maximum, and (two-sided) 90% confidence interval) will be provided for effectiveness endpoints.

	Descriptive statistics for AEs will be presented separately. **Sample Size Justification:** A minimum of 165 subjects will be enrolled to ensure at least 144 evaluable subjects (48 evaluable subjects per site) complete the study. With 48 evaluable subjects per site, study has 90% chance to show that the mean difference in IOL A-constants calculated with • post-op manifest spherical equivalent refraction at 3 months vs. • post-op spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months is within the equivalence margin of ±0.15 for each site assuming that the mean and the standard deviation of a paired difference are 0 and 0.35 respectively. Standard deviation of 0.35 is based on the standard deviation of the difference in A-constant between the first and the second eye in subjects implanted with ACRYSOF IQ Monofocal IOL [redacted] (ACRYSOF IQ ReSTOR® Multifocal +2.5 D).
Key Words for Posting in Registries	Prospective, interventional, multi-center study; being conducted in the US and Ireland; 183 enrolled 144 completed subjects

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 an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

5 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Visit	Visit 0[1]	Visit 00	Visit 1	Visit 2	Early Exit
Visit Type	**Screening**	**Operative**	**Post-Op**	**Post-Op**	
Day Number	**Day -28-0**	**Day 0**	**Day 20-40**	**Day 80-100**	**N/A**
Informed Consent	X				
Demographics	X				
Medical History	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Inclusion/Exclusion	X	X			
Urine Pregnancy Test[2]	X				
Anterior Chamber Depth	X			X	
Axial Length	X			X	
White-to-White Distance	X			X	
Lens Thickness	X		X	X	
Manifest Refraction	X		X	X	X
Keratometry	X			X	
Autorefraction (*Topcon KR-1W*)	X		X	X	
Uncorrected Distance VA (4 m)	X		X	X	X
Corrected Distance VA (4 m)	X		X	X	X
Pupil Diameter (dilated / undilated)	X	X		X	
Target Residual Refractive Error	X				
IOL Power Calculation	X				
Slit-Lamp Examination	X		X	X	X
Dilated Fundus Examination	X			X	X
Intraocular Pressure	X		X	X	X
Actual Lens Position				X	
Capsulorhexis Diameter				X	
Operative Eye		X			
Lens Information		X			
Folding and Insertion Instrument		X			
Final Incision Size		X			
Incision Location		X			
Problems during Surgery		X			
Other Surgical Procedures		X			
Subjective PCO			X	X	X
Posterior Capsulotomy			X	X	X
IOL Observations			X	X	X
IOL Position Change			X	X	X
Adverse Events	X	X	X	X	X
Secondary Surgical Interventions		X	X	X	X
Device Deficiencies		X	X	X	X

[1] Operative Visit (Visit 00) must occur within 28 calendar days from Screening/Visit (Visit 0)

[2] Women of child-bearing potential only

6 INTRODUCTION

6.1 Rationale and Background

Following cataract surgery, there is a distribution in refractive outcomes relative to the intended refractive target (typically emmetropia). The refractive outcome distribution will have a mean offset (relative to target) as well as some finite spread (eg, standard deviation). Previously we have analyzed the spread in outcomes (for standard-of-care surgery) using an "error budget" analysis. This analysis provides the following estimated for refractive outcome variance (ie, the square of the standard deviation in spherical equivalent error):

- Postoperative refraction – 25.6%
- IOL placement (axial position, decentration, tilt) – 16.8%
- Cornea anterior asphericity – 16.8%
- Cornea posterior/anterior radius ratio – 11.4%
- Corneal anterior radius measurement – 9.8%
- IOL step size – 5.8%
- Cornea refractive index – 4.7%
- Axial length measurement – 3.7%
- IOL manufacturing tolerance – 2.1%
- Vitreous refractive index – 2.1%
- Aqueous refractive index – 0.9%
- Cornea posterior asphericity – 0.2%
- Cornea thickness – 0.1%

The results from the analysis show that:

- Noise in the postoperative refraction is a major contributor
- Uncertainty in the IOL location in the eye is also a large component
- Most of the remaining contributors relate to inadequate preoperative characterization of the eye

Conventional clinical wisdom holds that each surgeon will have unique outcomes due to factors particular to their surgical technique, inherent clinic measurement practices and equipment. The general concept is that surgical technique and in some instances

complications will impact the final resting location of the IOL. Other site-specific factors such as biometry device calibration or postoperative refraction procedure specifics could also influence the offset. Surgeons are encouraged to track outcomes and minimize the offset by "personalizing" the IOL power equation constant(s) related to the IOL position (eg, the "A-constant") (Gale 2009). This requires analyzing preoperative biometry, implanted lens power, and postoperative refraction (typically collected from manifest refraction) for a population of 50+ eyes per IOL model (Sheard 2014). Changes in the A-constant of 0.15 D or less are not considered clinically significant, based on the impact on refractive outcome distributions (Aristodemou 2011).

6.2 Purpose of the Study

The purpose of this study is to evaluate whether an automated refraction device can be used to personalize the A-constant as well as standard refraction (ie, to a clinically insignificant difference). Errors/noise from refraction plays a significant role, and it would be important to know if an automated method has any advantages over conventional manifest refraction for A-constant optimization.

6.3 Risks and Benefits

The IOL being used in this study is a US Food and Drug Administration (FDA)-approved ACRYSOF IQ Monofocal IOL (Model SN60WF). Currently, this IOL represents the industry standard of care for patients who develop cataract and require cataract surgery with a monofocal IOL implantation. This IOL has been well studied in previous Alcon clinical studies and the safety and effectiveness of this IOL has been well documented and established.

However, there may also be previously unidentified risks with use of the Model SN60WF IOL. Any foreseeable risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria, study procedures, and clinical monitoring. Refer to the Directions for Use (DFU) for additional information.

The Topcon KR-1W Wave-Front Analyzer device used to obtain autorefraction data is a non-significant risk device. There is no direct clinical benefit to the subject's participation in this study.

All other test procedures in this study are standard clinical measurements for pre-operative and post-operative cataract surgery; therefore there are very limited non-significant risks to the subject that could emanate from these study assessments.

All devices used in this study to complete assessments are FDA approved and will be used according to the manufacturer's instructions.

7 STUDY OBJECTIVES

7.1 Primary Objective

To demonstrate equivalency[1], at each of the 3 clinical sites, between IOL SRK/T A-constant estimated based on postoperative manifest spherical equivalent refraction at 3 months and IOL A-constant estimated based on postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months[2].

- [1] A margin of ±0.15 is chosen based on an independent external investigation that has established 0.15 D as the threshold for clinical significance in the A-constant (Aristodemou 2011).
- [2] The 3-month postoperative visit has been established as the point of refractive stability in multiple prior clinical studies.

7.1.1 Primary Effectiveness Endpoints

- IOL A-constants estimated based on preoperative biometry, IOL power and postoperative manifest spherical equivalent refraction at 3 months.
- IOL A-constant estimated based on preoperative biometry, IOL power and postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months.

7.1.2 Primary Effectiveness Assessments

- Autorefraction using *Topcon KR-1W*
- ACD
- AL
- White-to-White Distance
- Keratometry
- Manifest Refraction
- IOL Power Implanted

7.2 [redacted]

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

7.3 Safety Objective

- AE rates for ACRYSOF IQ Monofocal IOL (Model SN60WF) and use of Topcon KR-1W will be collected separately

7.3.1 Safety Endpoint

- Monitor AEs related to the IOL and study assessments at all postoperative visits

7.3.2 Additional Safety Assessments

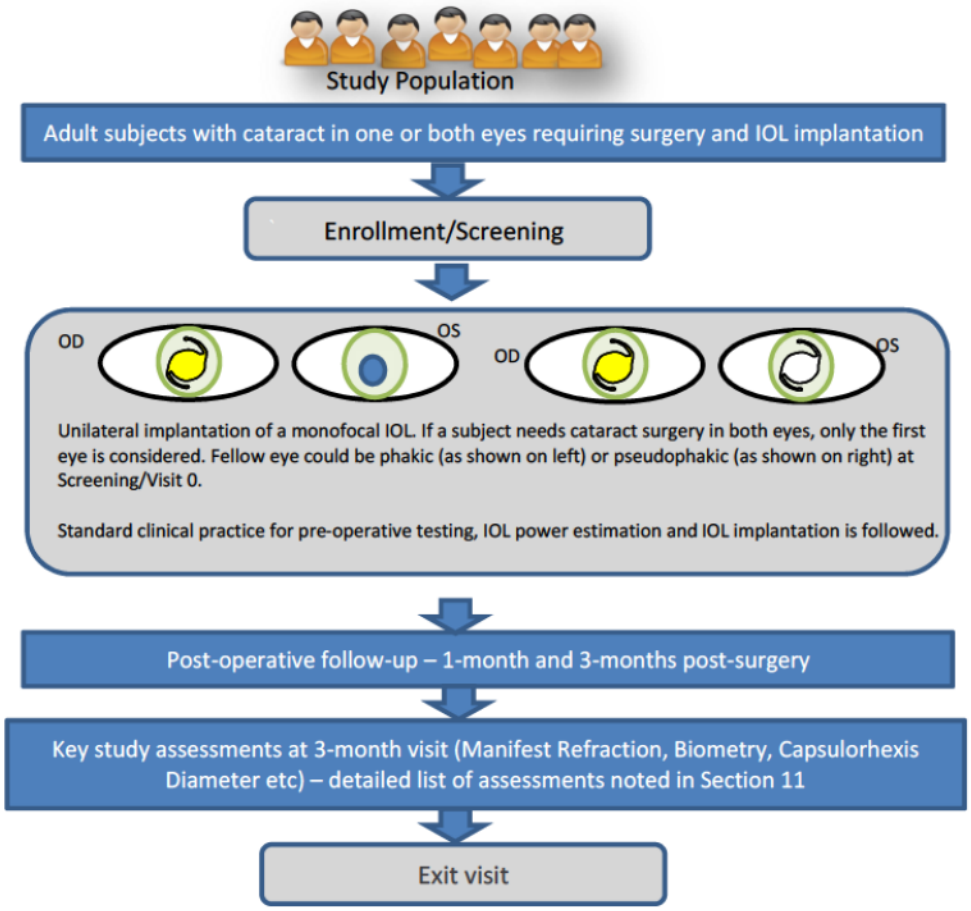
- IOP
- Slit-Lamp Examination
- Dilated Fundus Examination
- IOL Observations
- Subjective PCO Assessment
- PC
- Surgical Problems
- Other Procedures at Surgery
- AEs (including SSIs)
- Device Deficiencies

8 INVESTIGATIONAL PLAN

8.1 Study Design

This is a prospective, observer-masked *(examiner performing manifest refraction is masked to the refractive target and refractive error from the surgical planning and the operative visit),* interventional clinical study. The Investigator will determine the study eye to be included in this study. Only the study eye will be followed throughout the study. At a minimum 165 subjects will be enrolled at up to 3 sites in the United States and Ireland. Subjects require cataract surgery with implantation of a monofocal IOL Model SN60WF in the capsular bag in one or both eyes to qualify for enrollment into this study. One eye will be enrolled per subject. See Figure 8-1 Study Design.

Figure 8–1 Study Design



A total of 4 scheduled visits are planned including the Screening/Visit 0 and the Operative Visit/Visit 00. Scheduled postoperative visits must occur at the following intervals: 20-40 days, and 80-100 days. See Table 8-1 Schedule of Study Visits.

Table 8–1 Schedule of Study Visits

Time From Implantation	Study Visit
Screening / Preoperative (Day -28 to Day 0)	Visit 0
Operative (Day 0)	Visit 00
20-40 days	Visit 1
80-100 days	Visit 2

8.2 Rationale for Study Design

This study **will not** be evaluating an investigational product (IP). It is a study intended to evaluate current available assessments (automated vs. manual) with which manifest refraction data is obtained to understand, if data from an automated refractor can be utilized to optimize the A-constant as well as manual subjective refraction (ie, to a clinically insignificant difference). Thus, the effectiveness analyses will be conducted on single eye outcomes and for this reason only one eye (surgeon determination) will be part of and followed through the entire study. At each of the 3 sites, the examiner performing the manifest refraction at the postoperative follow-up visits will be masked to the refractive target and refractive error from the surgical planning and the operative visit.

8.3 Rationale for duration of treatment/follow-up

The implantation and use of the marketed Model SN60WF IOL is in accordance with the DFU for this IOL.

8.4 Data Monitoring Committee

Not Applicable

8.5 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

Not Applicable

9 SUBJECT POPULATION

The study population consists of male and female subjects 22 years and older with a diagnosis of cataract in one or both eyes requiring surgery with implantation of a monofocal IOL in the capsular bag. Only one eye will be enrolled in the study per surgeon determination. If both eyes are eligible then the eye undergoing surgery first should be

enrolled (as per Figure 8-1). Approximately 3 centers worldwide will participate in this study with a target of approximately 55 subjects per site. Site specific targets may be adjusted based on individual site capabilities. Enrollment projections are as follows:

- 183 subjects are expected to be enrolled (10% screen failure rate is expected)
- 165 eligible subjects that meet inclusion/exclusion criteria (13% discontinuation rate)
- 144 subjects to successfully complete the final study visit (Visit 3)

NOTE: If one or both eyes have cataracts, only the eye being assessed will need to meet the inclusion and exclusion criteria.

9.1 Inclusion Criteria

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

1. Subject must be able to understand and sign an IEC/ IRB approved ICF
2. Willing and able to attend all scheduled study visits as required per protocol
3. Adults (22 years or older at the time of enrollment in the study) diagnosed with cataract in one or both eyes
4. Planned cataract removal by phacoemulsification with implantation of a monofocal IOL; laser refractive procedures for incisions (primary and sideport), capsulorhexis and lens fragmentation are allowed
5. Preoperative keratometric astigmatism $\leq$ 1.0 D

9.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Women of childbearing potential, defined as all women who are physiologically capable of becoming pregnant and who are not postmenopausal for at least 1 year or are less than 6 weeks since sterilization, are excluded from participation if any of the following apply:
    a. they are currently pregnant
    b. have a positive urine pregnancy test result at Screening/Visit 0
    c. intend to become pregnant during the study period
    d. are breast-feeding

2. History of any condition with associated fluctuation of hormones that could lead to refractive changes

3. History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology including retinal vascular occlusive disease, retinal detachment or peripheral retinal laser photocoagulation, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, retinitis pigmentosa and any optic nerve pathology

4. History of recurrent anterior segment /posterior segment inflammation

5. Clinically significant, in the opinion of the Investigator, any corneal dystrophy or any other corneal abnormality/pathology (epithelial, stromal or endothelial) including but not limited to the following: keratitis, keratoconjunctivitis and keratouveitis

6. Clinically significant, in the opinion of the Investigator, severe dry eye

7. History of previous intraocular or corneal surgery

8. Diagnosis of amblyopia

9. Systemic medications that, in the opinion of the Investigator, may confound the outcome or increase the risk of complications to the subject (eg, Tamusolin Hydrochloride – Flomax) or other medications including anticholinergics, alpha adrenergic blocking agents with similar side effects (eg, small pupil/floppy iris syndrome)

10. Concurrent participation in another clinical study that, in the Investigator's opinion, may confound the results of the current study

11. Any other ocular or systemic co-morbidity that, in the opinion of the Investigator, may confound the results of this study or prohibit the completion of the study assessments or increase the risk for the subject

12. Subjects with conditions that increase the risk of zonular rupture during cataract extraction procedure that may affect the postoperative centration or tilt of the lens

13. Any other planned ocular surgical procedures including but not limited to limbal relaxing incision (LRI)/Astigmatic Keratotomy and laser-assisted in situ keratomileusis (LASIK)

9.3 Exclusion Criteria at Time of Surgery

1. Surgical complications including but not limited to loss of zonular integrity/zonular weakness, zonular rupture, anterior or posterior capsule rupture, any evidence of fluid misdirection during the cataract procedure with progressive shallowing of the anterior chamber, uncontrollable IOP

2. Mechanical or surgical manipulation of the pupil

3. Excessive iris mobility

4. Inability to place the IOL in the capsular bag due to surgical complications

NOTE: Subjects who satisfy any of the Exclusion Criteria at the Time of Surgery noted in Section 9.3 will be followed for safety if they are implanted or the IOL touches the eye; and data from these subjects will not be part of the effectiveness data set.

9.4 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

10 TREATMENT

Throughout the clinical study, the Investigator is responsible for the accounting of all IP and must ensure that the clinical study product is used in accordance with the manufacturer's DFU.

Site temperature monitoring of IOLs is not required.

10.1 Investigational Product

Table 10–1 Test Article

Test Product	ACRYSOF IQ Monofocal IOL (Model SN60WF)
Manufacturer	Alcon
Indication for use	Implantation for visual correction of aphakia secondary to removal of a cataractous lens in subjects with and without presbyopia, who desire distance vision.
Intended Purpose in the current study	Implantation for visual correction of aphakia secondary to removal of a cataractous lens in subjects with and without presbyopia, who desire distance vision.

Product description and parameters available for this study	Optic Type: Biconvex Toric Aspheric Optic
	Optics Material: Ultraviolet and blue light filtering Acrylate/ Methacrylate Copolymer
	Optic Powers: 6.0-34.0 D in 0.50 D steps
	Index of Refraction: 1.55
	Haptic Configuration: STABLEFORCE® Haptics
	Haptic Material: Ultraviolet and blue light filtering Acrylate Methacrylate Copolymer (Boettner 1962)
	Optic Diameter (mm): 6.0
	Overall Length (mm): 13.0
	Haptic Angle: 0°
Formulation	N/A
Usage	IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.
Number/Amount of Product to be Provided to the Subject	The Investigator is to keep a current record of the dispensing of all products. This record will be made available to the Sponsor's monitor to account for all products. Any discrepancy and/or deficiency must be recorded, with an explanation.
Packaging description	Each IOL will be individually packaged and will have a unique serial number. The IOL package will contain the following items: • The IOL • A subject registration card (Lens Implant Card) • A subject identification card • Adhesive labels containing the IOL information and unique serial number • A package insert containing directions for use
Labeling description	Product must be locally procured by the site via commercial channel and will arrive in country compliant commercial packaging with commercial label.

Storage conditions	Once designated for study use, product must be stored in a safe, secure location with limited access separated from general stock. Transportation of product from one address to another must be documented and a Transportation Log (or similar documentation) utilized for appropriate accountability.
Final Disposition	At the conclusion of the study, remaining product may be returned to the Investigator's general stock. **NOTE:** Return deficient product to the manufacturer following each manufacturer's respective complaint process. Refer to Section 12.5 for further details on the return process for Alcon product. Additionally, the Investigator must follow any recalls from the distributor/manufacturer.
Supply	The Investigator will locally procure the IP through their standard commercial channel.
Additional information	In order to implant IOLs in study subjects, the surgeons participating in the study must be licensed ophthalmologists with cataract surgery experience and trained on the protocol. Each surgeon will follow their standard of care to implant the IOL following respective DFU instructions for IOL implant.

10.1.1 Other Medical Device Specified for Use During the Study

The Topcon KR-1W Wave-Front Analyzer will be used to capture autorefraction values for the primary endpoint. This device is CE Marked, FDA approved and will be used following the manufacturer's instructions.

10.2 Treatment Assignment / Randomization

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system. Subjects will not be randomized in this study. All subjects will be implanted with Model SN60WF IOL in the selected study eye and measured on automated refraction device, Topcon KR-1W preoperatively and at postoperative visits.

10.3 Accountability Procedures

The Investigator or delegate must procure the IP through their standard commercial channel. Once designated for study use, the IP will be stored in a safe, secure location with limited access separated from general stock. Transportation of IP from one address to another must

be documented and a Transportation Log (or similar documentation) utilized for appropriate accountability. Throughout the study, the Investigator or delegate must maintain records of IP use for each subject. This record must be made available to the Sponsor's monitor for the purposes of verifying the accounting of IP supplies. Any discrepancies and/or deficiencies must be recorded along with an explanation. All IP must be accounted for by Study Sponsor personnel, and in no case be used in an unauthorized manner.

- If possible, return to the Study Sponsor, IP associated with a device deficiency. Refer to Section 12 of this protocol for additional information on the reporting of device deficiencies and to the Manual of Procedures (MOP) for information on return of IP associated with these events.

The Investigator is responsible for proper disposition of all unused IP at the conclusion of the study to the Investigator's general stock.

10.4 Treatment Masking

The examiner performing the manifest refraction must be masked to the refractive target and refractive error from the surgical planning and the operative visit, respectively.

10.5 Changes to Concomitant Treatments or 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.

11 STUDY PROCEDURES AND ASSESSMENTS BY VISIT

The following section outlines the assessments to be performed in this clinical study. Assessments are described in detail in the ILQ732-I001 MOP, and are outlined in tabular format in Section 5 of this protocol.

AEs, SAEs including SSIs and device deficiencies are assessed and reported at all scheduled and unscheduled visits (UNSV) for each subject, beginning at the time the informed consent is obtained.

11.1 Screening/Preoperative Visit (Visit 0)

Visit 0: -28-0 Days Prior to Visit 00

Below is a list of study procedures to be done at Visit 0. All assessments must be documented in the source documentation and electronic case report form (eCRF), if applicable.

NOTE: At the Screening/Preoperative Visit (Visit 0) all assessments to be completed monocularly on the study eye only, where applicable.

NOTE: Per the Investigator's discretion, data from previous cataract evaluation visit(s) may be used. This data may come from more than one routine visit conducted within 4 months of the Screening/Visit 0 with the exception of those assessments that are crucial to the IOL power calculation.

NOTE: To ensure the stability of refraction, subjects who currently wear contact lenses they must discontinue their use prior to completing the Screening/Preoperative Visit (Visit 0) as follows:

- Hard or rigid contact lenses - 3 weeks
- Soft contact lenses – 2 weeks

1. Review study specific inclusion/exclusion criteria (eg, age, previous ocular history) to ensure that a potential subject meets all qualifications for participation in the study.
2. 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 they are interested. Refer to Section 11.7 Informed Consent Procedures.
3. Perform a urine pregnancy test, **IF** the subject is a woman of childbearing potential.
4. Assess ACD, AL and white-to-white distance.
5. Perform keratometry measurements to evaluate the curvature of the anterior surface of the eye.
6. Assess lens thickness.

7. Capture aberrometry, topography, keratometry, pupillometry and autorefraction with the Topcon KR-1W Wave-Front Analyzer.
8. Perform manifest refraction.
9. Measure and record uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA)
10. Document the target residual refractive error based on the IOL calculation power.
11. Measure and record photopic pupil diameter (dilated and undilated).
12. Conduct slit-lamp examination.
13. Conduct dilated fundus examination.
14. Perform tonometry to measure IOP.
15. Record any AEs. Refer to Section 12 for further details.
16. Evaluate subject against all entry criteria. If subject fails criteria, screen fail the subject.
17. Identify the surgical eye for this study (determined by the Investigator)
18. Proceed with scheduling the surgery.

11.2 Operative Visit (Visit 00)

Visit 00: Day 0, Study Eye Implantation

Below is a list of procedures to be completed at Visit 00. Activities involving multiple delegated staff members may be performed in parallel. All assessments must be documented in source documentation and eCRF, if applicable.

1. Prior to surgery, review inclusion/exclusion criteria and ensure the subject has been properly consented for participation in the study.
2. Document any changes to ocular and non-ocular concomitant medications.
3. Record operative eye.
4. Measure and record photopic pupil diameter (dilated and undilated).

5. Prepare subject for surgery in accordance to site-specific operating procedures.

6. Record the folding and insertion instrument used.

7. Record the final incision size and incision site.

8. Record any surgical problems, complications, or other procedures that occur during surgery. Other procedures include those performed outside of routine cataract surgery.

9. Record the lens information that is located on the IOL sticker. Both successful and aborted (if applicable) IOL information should be recorded.

10. Record any AEs including SSIs.

    NOTE: SAEs including SSIs must be entered into the eCRF system within 24 hours of the Investigator's knowledge. Refer to Section 12 for further details.

11. Record any device deficiencies. Refer to Section 12 for further details.

11.3 Postoperative Visit (Visit 1)

Visit 1: 20-40 Days Post Study Eye Implantation

Below is a list of procedures to be completed at Visit 2. All assessments must be documented in source documentation and eCRF, if applicable.

NOTE: All postoperative assessments to be completed monocularly on the operative eye only, as applicable.

1. Document any changes to medical/ocular history and ocular and non-ocular concomitant medications.

2. Record lens thickness of the IOL.

3. Capture aberrometry, topography, keratometry, pupillometry and autorefraction with the Topcon KR-1W Wave-Front Analyzer.

4. Perform manifest refraction.

5. Measure and record UDVA and CDVA.

6. Perform slit-lamp examination of the anterior segment. Include documentation of IOL observations, if any.

7. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit.

8. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable.

9. Perform tonometry to measure IOP.

10. Record any AEs including SSIs

    NOTE: SAEs including SSIs must be entered into the eCRF within 24 hours of the Investigator's knowledge. Refer to Section 12 for further details.

11. Record any device deficiencies. Refer to Section 12 for further details.

11.4 Postoperative Visit (Visit 2)

Visit 2: 80-100 Days Post Study Eye Implantation

Below is a list of procedures to be completed at Visit 3. All assessments must be documented in source documentation and eCRF, if applicable.

NOTE: All postoperative assessments to be completed monocularly on the operative eye only, as applicable.

1. Document any changes to medical/ocular history and ocular and non-ocular concomitant medications.

2. Assess ACD, AL and white-to-white distance.

3. Assess lens thickness of the IOL.

4. Perform keratometry measurements to evaluate the curvature of the anterior surface of the eye.

5. Capture aberrometry, topography, keratometry, pupillometry and autorefraction with the Topcon KR-1W Wave-Front Analyzer.

6. Record actual lens position, the plane bisecting the IOL.

7. Record capsulorhexis diameter.

8. Perform manifest refraction.

9. Measure and record UDVA and CDVA.

10. Measure and record photopic pupil diameter (dilated and undilated).

9. Perform slit-lamp examination of the anterior segment. Include documentation of IOL observations, if any.

10. Conduct dilated fundus examination.

11. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit.

12. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable.

13. Perform tonometry to measure IOP.

14. Record any AEs including SSIs

    NOTE: SAEs including SSIs must be entered into eCRF within 24 hours of the Investigator's knowledge. Refer to Section 12 for further details.

15. Record any device deficiencies. Refer to Section 12 for further details.

11.5 Schedule of Procedures and Assessments for Discontinued Subjects

Subjects that discontinue from the study, all efforts must be made to complete the assessments noted in the table in Section 5 for an Early Exit Visit.

NOTE: All assessments to be completed monocularly on the operative eye only, as applicable.

1. Document any changes to medical/ocular history and ocular and non-ocular concomitant medications.

2. Perform manifest refraction.

3. Measure and record UDVA and CDVA.

4. Perform slit-lamp examination of the anterior segment. Include documentation of IOL observations, if any.

5. Conduct dilated fundus examination.

6. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit.

7. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable.

8. Perform tonometry to measure IOP.

9. Record any AEs including SSIs

   NOTE: SAEs including SSIs must be entered into eCRF within 24 hours of the Investigator's knowledge. Refer to Section 12 for further details.

10. Record any device deficiencies. Refer to Section 12 for further details.

11.6 Informed Consent and Screening

The subject must sign the ICF **BEFORE** any study specific procedures or assessments can be performed.

The Investigator must explain the purpose and nature of the study, and have the subject read, sign, and date the IEC/IRB approved informed consent document. Additionally, have the individual obtaining consent from the subject sign and date the informed consent document.

The Investigator 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.

11.7 Unscheduled Visits

An UNSV is defined as follows:

- Ocular examination that is not standard of care and not required by the protocol
- Examination conducted by the study staff
- New findings, or a change to a previous finding was discovered
- Not site standard of care/routine

An UNSV may or may not result in the capture of an AE. Likewise an AE may be captured without the report of an UNSV (eg, AE identified subsequent to study eye examination by non-study personnel).

During all UNSVs, it is recommended that the Investigator complete the following procedures as appropriate for the operative eye:

1. Document any changes to medical/ocular history and ocular and non-ocular concomitant medications.
2. Perform manifest refraction.
3. Measure and record uncorrected and best corrected distance VA.
4. Perform slit-lamp examination of the anterior segment. Include documentation of IOL observations, if any.
5. Conduct dilated fundus examination.
6. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit.
7. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable.
8. Perform tonometry to measure IOP.
9. Record any AEs including SSIs.

   NOTE: SAEs including SSIs must be entered into eCRF within 24 hours of the Investigator's knowledge. Refer to Section 12 for further details.
10. Record any device deficiencies. Refer to Section 12 for further details.

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 UNSV the subject is discontinuing from the study, then the Investigator must conduct Early Exit/Exit procedures according to Section 5, Schedule of Study Procedures and Assessments.

11.8 Discontinued Subjects

11.8.1 Screen Failures

Subjects who discontinue from the study prior to the Operative Visit (Visit 00) will be categorized as screen failures.

The Investigator may replace a subject who fails study Screening/Visit 0, but the subject number must not be re-used. The Investigator must document the reason for screen failure in the subject's case history source documents and electronic data capture (EDC).

11.8.2 Discontinuations

Discontinued subjects are individuals who have signed informed consent and who voluntarily withdraw or are withdrawn from the study by the Investigator at the Visit 00/Operative Visit and/or prior to completing all study visits.

Subjects that meet Exclusion Criteria at the time of surgery (refer to Section 9.3) must be captured as discontinuations.

Discontinued subjects will not be replaced; subject numbers of discontinued subjects must not be re-used.

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

If a subject discontinues from the study after Visit 00/Operative Visit, 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 should complete all Early Exit procedures according to Section 5 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 discontinuation in the subject's case history source documents and complete the exit form in EDC.

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.

11.9 Clinical Study Termination

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

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 IEC/IRB 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.

11.10 Aborted Implantation

11.10.1 Aborted Initial Implantation

IF the IOL implant was aborted and the test article did not touch the eye **THEN**

- A second attempt is permitted
- If the subject is required to discontinue from the study, follow standard of care for IOL implantation

IF the IOL implant was aborted and the test article did touch the eye **THEN**

- A second attempt is permitted
- If the subject is discontinued from the study
  - Encourage the subject to attend all follow-up study visits for safety evaluation on this eye only
  - Standard of care followed for IOL implantation

11.10.2 Aborted Second Implantation

IF the second attempt to implant the IOL was aborted and the test article did not touch the eye on either attempt **THEN**

- Subject must be discontinued from the study
- Standard of care followed for IOL implantation

IF the second attempt to implant the IOL was aborted and the test article did touch the eye on either attempt **THEN**

- This eye must be followed for all study visits for safety evaluation only
- Standard of care followed for IOL implantation

12 DEVICE DEFICIENCIES AND ADVERSE EVENTS

12.1 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 clinical investigation.

Figure 12–1 Categorization of All Adverse Events

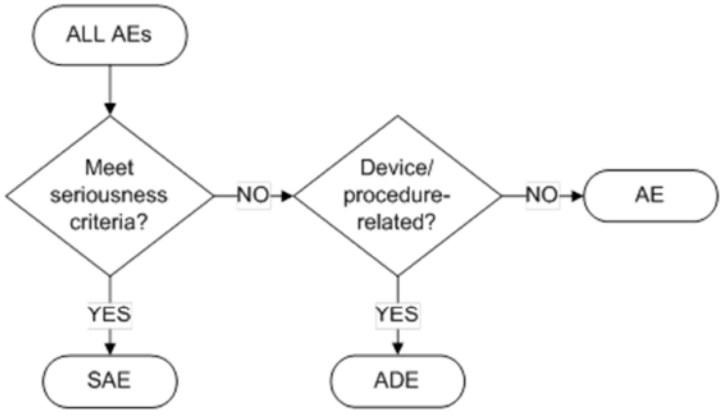
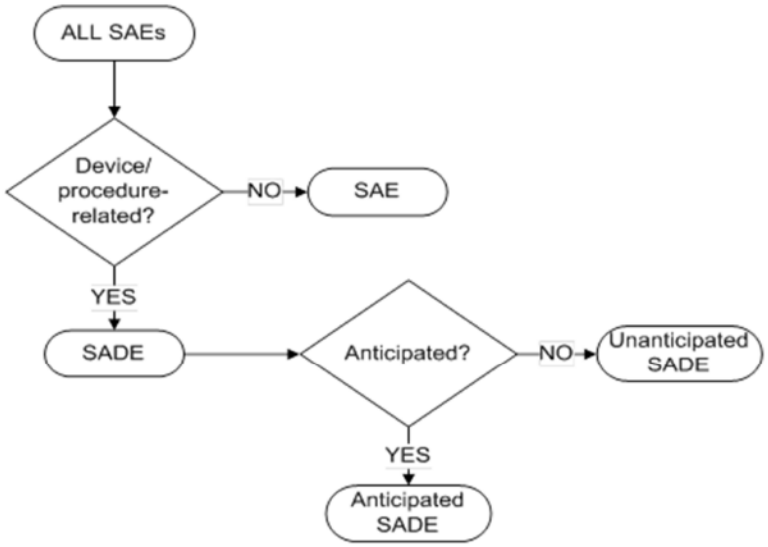


Figure 12–2 Categorization of All Serious Adverse Events



12.2 Serious Adverse Events

A serious adverse event is an AE 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 SAE. 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 AEs. 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) or any ocular secondary surgical intervention (excluding PC).

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.

12.3 Specific Events Relevant to this Protocol

In addition to reporting all AEs (serious and non-serious) meeting the definitions, the Investigator must report any occurrence of the following as an SAE:

12.3.1 Cumulative Serious Adverse Events

- Cystoid macular edema
- Hypopyon
- Endophthalmitis
- Lens dislocation
- Pupillary block
- Retinal detachment
- Secondary surgical intervention

12.3.2 Persistent Serious Adverse Events

- Corneal stromal edema
- Cystoid macular edema
- Iritis
- Raised IOP requiring treatment

This list is consistent with the categories provided in I.S. EN ISO 11979-7:2014. A persistent AE is an AE that is present at the conclusion of a clinical investigation per I.S. EN ISO

11979-1. Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and must be reported appropriately as delineated in Section 12.6.

12.4 Terminology

12.4.1 Adverse Device Effect

An ADE is an AE related to the clinical investigation. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the device.

12.4.2 Serious Adverse Device Effect

A SADE is an ADE that has resulted in any of the consequences characteristic of a SAE.

12.4.3 Anticipated Serious Adverse Device Effect

An ASADE is a SADE which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

12.4.4 Unanticipated Serious Adverse Device Effect

An USADE is a SADE which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

12.4.5 Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This definition includes malfunctions, use errors, and inadequate labeling. Malfunction is defined as a 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. Use error is defined as an act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user; this includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

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 must determine the applicable category for the identified or suspect device deficiency and report any subject harm separately. Examples of device deficiencies include the following:

- Failure to meet product specifications (eg, incorrect IOL power,)
- IOL defect
- Broken IOL optic
- Broken IOL haptic
- Scratched IOL optic
- Unsealed device packaging
- Lack of efficacy
- Autorefractor errors and other diagnostic equipment related deficiencies

12.5 Return Product Analysis

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

Alcon Products associated with device deficiencies and/or product related AEs must be returned as specified in the MOP and must include the Complaint # and which will be provided by the Study Sponsor.

12.6 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator must 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?"

AEs must be reported for any clinically relevant change, in the opinion of the Investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes in any protocol-specific ocular or systemic parameter 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.

12.7 Procedures for Recording and Reporting

All AEs must be documented on the AE electronic case report form (eCRF) by the site and are monitored on a routine basis by the Study Sponsor.

AEs are collected from the time of informed consent. Any pre-existing medical conditions or symptoms present in a subject are not considered AEs in the study. 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.

The Investigator must promptly document all ADEs and SAEs with details including the date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must promptly document all device deficiencies 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:

- **ADEs or SAEs are documented on the *Adverse Device Effect and Serious Adverse Event* eCRF within 24 hours of the Investigator's or site's awareness.**
- **Device deficiencies are documented on the *Device Deficiency* eCRF within 24 hours of the Investigator's or site's awareness. Please include a printed copy of the completed *Device Deficiency* eCRF with product returns.**
- **Additional relevant information after initial reporting is to be entered into the eCRF as soon as the data become available.**
- **Document any changes to concomitant medications on the appropriate eCRFs.**
- **All relevant documentation such as Discharge Summary, Autopsy Report, Certificate of Death etc, must be faxed to the Study Sponsor at** [redacted]

NOTE: Should the EDC system become non-operational, the site must complete the appropriate paper *Adverse Device Effect and Serious Adverse Event Form* or *Device Deficiency Form*. The completed form is faxed to the Study Sponsor at [redacted] within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes operational.

Sponsor representatives and their contact information are 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 IEC/IRB.

12.7.1 Intensity and Causality Assessments

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

12.7.1.1 Causality

Related An AE may be classified as either definitely related or possibly related to the clinical investigation. Where a direct cause and effect relationship with the clinical investigation has not been demonstrated, but there is a reasonable possibility that the AE was caused by the clinical investigation, then causality should be assumed until it can be demonstrated that the AE is not related to the clinical investigation.

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).

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

12.7.1.2 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.

12.8 Unmasking of the Study Information

This study is not masked. However the examiner performing manifest refraction is masked to the refractive target and refractive error from the surgical planning and the operative visit.

12.9 Follow-Up of Safety Information

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 must 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. Any additional data from these follow-up procedures performed up to 6 months after subject exit must be documented and available upon the Study Sponsor's request.

12.10 Pregnancy in the Clinical Study

If a woman becomes pregnant during the study, this information must be documented by Medical Safety in the appropriate documentation. Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case-by-case basis. An Alcon prepared form will be utilized to capture all pregnancy-related information until birth of the child.

13 ANALYSIS PLAN

13.1 Subject Evaluability

The final subject evaluability will be determined prior to locking the database.

13.2 Analysis Data Sets

13.2.1 Safety Analysis Set

All subjects with attempted IOL implantation (successful or aborted after contact with the eye) in at least one eye will be considered evaluable and included in the safety analysis set. The safety analysis set will be used for the safety analyses. Additionally, any AE experienced by a subject during the screening period will be presented separately in the safety analysis.

13.2.2 All Implanted Analysis Set (AAS)

All subjects with successful IOL implantation in the study eye will be included in the AAS. The primary analysis set for the primary and exploratory analyses will be the AAS.

13.2.3 Best Case Analysis Set (BAS)

BAS will include the subjects in AAS with the eye with the IOL which had

- at least 1 postoperative visit,
- no macular degeneration at any time; and
- no major protocol violation

The BAS is a supportive analysis set for the primary and exploratory analyses.

13.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions for categorical parameters and descriptive statistics (number, mean, standard deviation, and median, minimum, maximum) for continuous parameters. Demographic characteristics will include age, gender, race and ethnicity.

Demographics and baseline characteristics summaries will be presented for the AAS for overall and by site.

13.4 Effectiveness Analyses

13.4.1 Primary Effectiveness

The primary objective of this study is to demonstrate equivalency at each of the 3 clinical sites, between IOL SRK/T A-constant estimated based on postoperative manifest spherical equivalent refraction at 3 months and IOL SRK/T A-constant estimated based on postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months. The primary endpoints to be used for the primary analysis are:

- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative manifest spherical equivalent refraction at 3 months and
- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months.

The primary analysis data set will be the AAS.

13.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu(diff) \leq -0.15 \; or \; \mu(diff) \geq 0.15$$

$$H_1: -0.15 < \mu(diff) < 0.15$$

Where $\mu(diff)$ refers to the mean difference between the endpoints listed in Section 13.4.1 for each site. This hypothesis will be assessed separately for each site with a paired t-test.

13.4.1.2 Analysis Methods

Two-sided 90% confidence interval will be constructed for the mean of the paired difference between the two estimated SRK/T A-constants separately for each site. If the two-sided 90% confidence interval fall within (-0.15, 0.15), then equivalence will be concluded.

Descriptive statistics (mean, median, standard deviation, number of eyes, minimum, maximum, and two-sided 90% confidence interval) will be provided for each site for the effectiveness endpoints and also for the difference.

13.4.2 Secondary Effectiveness

There are no secondary effectiveness analyses in this study.

13.4.2.1 Statistical Hypotheses

Not Applicable

13.4.2.2 Analysis Methods

Not Applicable

13.4.3 [redacted]

[redacted]

- [redacted]

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

13.4.3.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

[redacted]

[redacted]

13.5 Handling of Missing Data

All data obtained in evaluable subjects will be included in the analysis. No imputation for missing data will be carried out.

13.6 Multiplicity

No alpha adjustment will be applied for testing multiple hypotheses.

13.7 Safety Analysis

The safety analyses will include the following safety assessments:

- Adverse events including SSIs
- Slit-lamp examination
- Dilated fundus examination
- Surgical problems
- Subjective PCO
- PC
- IOL observations
- IOL position change
- IOP
- Device deficiencies

Descriptive statistics generated for safety parameters will be based upon the type of parameter (ie, whether the data are categorical or continuous) being analyzed. For categorical parameters, the statistics used to summarize the data will include 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

13.8 Interim Analyses

No formal interim analyses are planned.

13.9 Adaptive Study Design

No adaptations are planned in this study.

13.10 Sample Size Justification

A minimum of 165 subjects will be enrolled to ensure at least 144 evaluable subjects (48 evaluable subjects per site) complete the study.

With 48 evaluable subjects per site, study has 90% chance to show that the mean difference in IOL A-constants calculated with postoperative manifest spherical equivalent refraction at 3 months and postoperative spherical equivalent from autorefraction at 3 months is within the

equivalence margin of ±0.15 for each site assuming that the mean and the standard deviation (SD) of a paired difference are 0 and 0.35 respectively.

The SD of 0.35 is based on the SD of the difference in the estimated A-constant between the first and the second eyes in subjects implanted with ACRYSOF IQ Monofocal IOL [redacted] (ACRYSOF IQ ReSTOR Multifocal +2.5 D).

14 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

14.1 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 ICF 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.

External researchers who request permission to use anonymized data from studies for a new medicine or new indication of a medicine (studies for approved medicinal products, small molecule generics, and devices are excluded) must be approved by a central independent review panel that will adjudicate the scientific request and the competency of the external researcher(s), as well as the determine applicability to current standard operating procedures (SOPs). If approved, a data sharing agreement will be executed between the Study Sponsor and the external researcher(s), committing to a specified analysis and publication timeline.

Anonymized data will be released to external researchers only after EU and/or US submission of the investigational drug/biologic for the study indication. The Study Sponsor will not be able to influence the analyses that are performed by external researchers using the data from this study once the anonymized data are released.

14.2 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 eCRFs exist and are accessible for verification by the site monitor, and all discrepancies must be appropriately documented via the query resolution process. Study 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 eCRF are consistent with the original source data.

Only designated individuals at the site will complete the eCRFs. The eCRFs 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 eCRFs are accurate and complete. The only subject identifiers recorded on the eCRFs will be subject number, and subject demographic information.

14.3 Data Review and Clarifications

A targeted review of eCRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the eCRFs 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 eCRF.

14.4 Sponsor and Monitoring Responsibilities

The Study Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. 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.

All sites must have a site initiation. Prior to screening subjects or performing the informed consent process on any subject, the site must receive a Site Activation Notification from an appropriate Study Sponsor representative. 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 or after database lock.

A Coordinating Investigator (CI) may be identified by the Study Sponsor. In cases where a CI is required, the Study Sponsor will select the CI based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role. The CI will be bound by confidentiality obligations described in a separate confidentiality agreement between the CI and the Study Sponsor.

Additionally, a Study Sponsor representative will provide training on proper operation of the Topcon KR-1W Wavefront Analyzer and other study assessments as appropriate. Detailed instructions are covered in the MOP. A copy of collected images form study assessments may be sent electronically to the Sponsor. These images must be masked to subject identification information.

14.5 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 not subject to regulatory inspection and is to be kept separately.

Additionally, the Investigator must keep study records and source documents until the Study Sponsor provides written approval for their destruction. 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 (generally 2 years after discontinuing clinical development or after the last marketing approval).

14.6 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.

15 ETHICS

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

- The Declaration of Helsinki (DoH), and in compliance with the International Conference on Harmonization (ICH) E6 GCP Consolidated Guideline
- ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice
- SOPs of the Study Sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations.

The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. 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.

Before clinical study initiation, this protocol, the ICF, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an

IEC/IRB. The Investigator must provide documentation of the IEC/IRB approval to the Study Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), ICF, all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC/IRB must be provided with a copy of the any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator must notify the IEC/IRB about the study's completion. The IEC/IRB also must be notified if the study is terminated prematurely. Finally, the Investigator must report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent must be obtained from every subject prior to the initiation of any screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved ICF. 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, 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 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 in 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 in www.clinicaltrials.gov regardless of outcome as required by current regulations and, if applicable, in other public databases as required by local country regulations.

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, as required by the IEC/IRB.

16 REFERENCES

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