Alcon A Novartis Division

Clinical Trial Protocol

A Prospective, Randomized, Controlled, Multi-Center Clinical Study of the ACRYSOF® IQ Extended Depth of Focus IOL

Protocol Number:	ILI875-C002
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
[redacted]	[redacted]
Test Article(s) / Product(s):	ACRYSOF IQ Extended Depth of Focus IOL
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), ISO 14155, the ethical principles within the Declaration of Helsinki, this protocol, 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 Sponsor.

Principal Investigator:

Signature Date

Name and Investigator Number:

Address:

Telephone:

Release Date: Refer to e-signature date

1 PROTOCOL SYNOPSIS

Financial Disclosure for US FDA Submission Required?	[X] Yes [ ] No
Test Article(s) / Product(s):	ACRYSOF IQ Extended Depth of Focus (EDF) IOL model number DFT015
Objective(s): Primary	1. ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected intermediate visual acuity (DCIVA) 66 cm from spectacle plane at Visit 4A (120-180 days postoperative) 2. ACRYSOF IQ EDF IOL is non-inferior compared to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic best corrected distance visual acuity (BCDVA) at Visit 4A (120-180d postoperative) 3. Monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR at Visit 4A (120-180d postoperative) 4. ACRYSOF IQ EDF IOL has at least 50% of eyes achieving monocular photopic DCIVA of 0.2 logMAR or better at Visit 4A (120-180d postoperative) A successful outcome on the co-primary effectiveness endpoints is indicated by successful outcomes on all 4 of these endpoints.
Objective(s): Secondary	1. ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected near visual acuity (DCNVA) 40 cm from spectacle plane at Visit 4A (120-180d postoperative) In addition, the following performance targets will also be assessed to demonstrate clinical significance: o At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better, o Percentage of eyes achieving monocular DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher

	than in ACRYSOF IQ Monofocal IOL group 2. ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the Intraocular Lens Satisfaction (IOLSAT) questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?) at Visit 4A (120-180d postoperative) 3. Describe mean monocular photopic uncorrected intermediate visual acuity (UCIVA) 66 cm from spectacle plane outcomes at Visit 4A (120-180d postoperative) 4. Describe mean monocular photopic uncorrected distance visual acuity (UCDVA) outcomes at Visit 4A (120-180d postoperative)
Objective(s): Primary Safety	1. To demonstrate that the adverse event (AE) rates of ACRYSOF IQ EDF IOL are not worse than the historical control safety and performance endpoint (SPE) rates, as defined in IS EN ISO 11979-7:2014, at Visit 4A (120-180d postoperative) 2. To describe monocular mesopic contrast sensitivity test (with and without glare) outcomes at Visit 4A (120-180d postoperative)
Objective(s): Secondary Safety	To estimate rates of severe and most bothersome (separately) visual disturbances as reported by subjects using a questionnaire (QUVID, Questionnaire for Visual Disturbances) at Visit 4A (120-180d postoperative)
Clinical Trial Design:	Prospective, multi-center, randomized, double-masked, parallel-group, safety and performance clinical trial
No. of Subjects:	a) Required for statistical analysis: 200 b) Randomized: 220 c) Approximately enrolled: 240
Region(s):	United States
Clinical Trial Duration:	a) Total expected duration of the clinical investigation: 14 months b) Expected duration of each subject's participation: 7-8 months c) Planned follow-up duration: 6 months d) Estimated time needed to select the number of subjects (ie, enrollment period): 6 months

Clinical Trial Population:	Adults (22 years and older) with cataract in both eyes requiring surgery with implantation of a monofocal IOL	
Treatments:	***Test Article***:	ACRYSOF IQ EDF IOL (Model DFT015)
	Administration:	Routine cataract surgery
	General Description:	Lens powers 18.0 D to 25.0 D in 0.5 D increments
	Duration of Treatment:	IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.
	Control Article:	ACRYSOF IQ Monofocal IOL (Model SN60WF)
	Administration:	Routine cataract surgery
	General Description:	Lens powers 18.0 D to 25.0 D in 0.5 D increments
	Duration of Treatment:	IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.
Inclusion & Exclusion Criteria:	Details can be found in Section 10: Subject Population	
Assessment(s): Performance	Distance visual acuity (VA) (photopic lighting conditions) • Monocular BCDVA • Monocular UCDVA [redacted]	
	Intermediate VA 66 cm (photopic lighting conditions) • Monocular DCIVA • Monocular UCIVA [redacted]	
	Near VA 40 cm (photopic lighting conditions) • Monocular DCNVA [redacted]	
	Defocus curve (photopic lighting conditions)	

	• Monocular [redacted]
	Manifest refraction
	Pupil size • Photopic • Mesopic
	IOLSAT subject survey
Assessment(s): Safety	AEs including secondary surgical interventions (SSIs)
	Device deficiencies (DDs)
	Mesopic monocular distance contrast sensitivity • With glare • Without glare
	QUVID subject survey
	IOP
	Slit lamp examination including • IOL observations • Aqueous Signs • IOL position change (tilt/decentration) • Subjective posterior capsular opacification (PCO) • Posterior capsulotomy
	Dilated fundus examination including fundus visualization
	Intraoperative surgical problems
	Other procedures at surgery (combined and/or additional)
	Incision location
	Final incision size (in event of surgical complication)
Assessment(s) Other	Demographics
	Medical history
	Concomitant medications
	Urine pregnancy test
	Anterior chamber depth
	Axial length
	Keratometry
	Lens information

Planned Analyses

In general, descriptive statistics generated for an endpoint will be based upon the type of parameter (ie, whether the data is 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.

The primary analysis set for effectiveness analyses will be the All-Implanted Analysis

Set (AAS). AAS includes all randomized eyes with successful IOL implantation.

[redacted] BAS includes all eyes successfully implanted that had

- at least 1 postoperative visit
- no preoperative ocular pathology
- no macular degeneration detected at any time
- no previous surgery for correction of refractive errors
- no major protocol violation

Analyses on performance targets are based on point estimates.

Only the first eye of each subject will be included in the primary statistical analysis (as described in IS EN ISO 11979-7:2014).

The statistical hypotheses in support of the primary effectiveness objectives are:

- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic DCIVA distance corrected intermediate visual acuity (66 cm from spectacle plane) at Visit 4A (120-180d postoperative)
- ACRYSOF IQ EDF IOL is non-inferior compared to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic BCDVA best corrected distance visual acuity at Visit 4A (120-180d postoperative). The non-inferiority margin will be 0.1 logMAR.

Analysis of the first primary effectiveness endpoint (DCIVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Analysis of the second primary effectiveness endpoint (BCDVA) will be based on a two-sample t-test, with a type I error rate of 5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated one-sided 95% upper confidence limit will be presented.

Two performance targets in support of the primary effectiveness objectives are:

- Monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR at Visit 4A (120-180d post-operative).
- ACRYSOF IQ EDF IOL has at least 50% of eyes achieving monocular photopic distance corrected intermediate vision of 0.2 logMAR or better at Visit 4A (120-180d post-operative).

For the first performance target (depth of focus), the line plot of the average visual acuity at each defocus level (ie, defocus curve) will be used to estimate the negative

lens induced depth of focus at 0.2 logMAR. The difference in depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ Monofocal IOL will be presented. The defocus data will be presented for overall and by 3 photopic pupil size ranges [< 3.0 mm (small), ≥ 3.0 mm to ≤ 4.0 mm (medium), and > 4.0 mm (large)] and 3 axial length ranges [< 21.0 mm (short), ≥ 21.0 mm to ≤ 26.0 mm (medium), and > 26.0 mm (long)].

For the second performance target (DCIVA), the percentage of eyes achieving distance corrected intermediate visual acuity of 0.2 logMAR or better in each IOL group will be presented.

A success on the 4 co-primary effectiveness endpoints will be indicated by successful outcomes on all 4 of these endpoints (2 hypothesis tests and 2 performance targets). A total of 4 hypothesis tests will be conducted to address the primary and secondary effectiveness objectives of the study. Overall Type I error will be maintained at the 5% level using a sequential testing approach.

Hypothesis tests on secondary effectiveness endpoints will be conducted only after successful outcomes on all 4 co-primary effectiveness endpoints are demonstrated.

The statistical hypothesis in support of the first secondary effectiveness objective is:

- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected near visual acuity (40 cm from spectacle plane) at Visit 4A (120-180d post-operative)

Analysis of the first secondary effectiveness endpoint (DCNVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Two performance targets in support of the first secondary effectiveness objective are:

- At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better
- The percentage of eyes achieving monocular DCNVA 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group.

For the first performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group will be presented and compared against the performance target of 50%. For the second performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in each IOL group will be presented and the difference between the IOL groups (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL)

will be compared against the performance target of 25%.

A success on the first secondary effectiveness endpoint will be indicated by successful outcomes on the hypothesis test and 2 performance targets. A hypothesis test on the second secondary effectiveness endpoint will be conducted only after successful outcomes on the first secondary endpoint are demonstrated.

The statistical hypothesis in support of the second secondary effectiveness objective is:

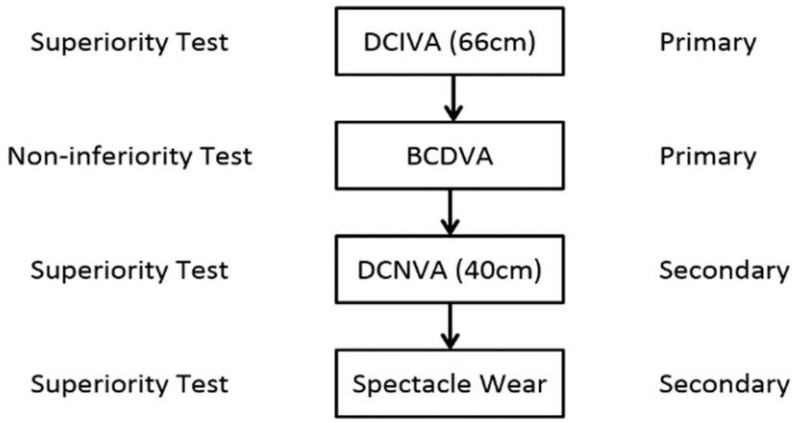
- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?) at Visit 4A (120-180d post-operative)

For the second secondary effectiveness endpoint, a two-sided 95% confidence interval for the difference in proportions (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) will be calculated using the Miettinen-Nurminen method (1985), and ACRYSOF IQ EDF IOL will be determined to be superior to ACRYSOF IQ Monofocal IOL if the lower boundary of the confidence interval is greater than zero. This is equivalent to using a type I error rate of 2.5%, 1-sided.

If the IOLSAT questionnaire generates scores, the cumulative distribution curves showing the percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful. In addition, the frequencies of each item in IOLSAT will be summarized by visit, with counts and percentages.

For the third and the fourth secondary effectiveness endpoints (UCIVA and UCDVA, respectively), the difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Overall type I error will be maintained at 5% level using a sequential testing approach summarized in the figure below.



The Safety Analysis Set will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye).

Descriptive summaries (counts and percentages) for specific AEs, including SSIs, will be presented by IOL group. The one-sided exact 95% lower confidence limit of incidence rates (proportion of eyes with events) observed for each IOL group will be compared to the relevant cumulative and persistent adverse event SPE (safety and performance endpoint) rate. In addition to SPE rates predefined in IS EN ISO 11979-7, the rate of adverse events that may be specifically related to ACRYSOF IQ EDF IOL design features; and any other significant events will be provided. These rates will be accompanied by two-sided exact 95% confidence intervals.

All measured contrast sensitivity values will be converted to logarithmic form before performing statistical calculations. Analyses of log contrast sensitivity will be performed for each testing condition and spatial frequency. If a subject is unable to see a targeted spatial frequency at any available contrast (including the contrast of the reference patch), the lowest contrast score will be given, preceded by the appropriate inequality symbol (<) to indicate that the actual sensitivity is below the given value. Prior to any averaging or other statistical calculations, all contrast threshold values will be converted to log contrast sensitivity values. The number and percentage of subjects who cannot see any contrast will be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive statistics will include number of eyes, mean, standard deviation, median, minimum, maximum, and additional percentiles (10th, 25th, 75th, and 90th percentiles). Descriptive tables will include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols). The 5th percentile of log contrast sensitivity values will be calculated for the control group, then the percentage of eyes in the test group that achieved a log contrast sensitivity lower than this value will be presented.

For the secondary safety endpoint, descriptive summaries (counts and percentages) for the severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented by IOL group. These rates will be accompanied by two-sided exact 95% confidence intervals.

If the QUVID questionnaire generates scores, the cumulative distribution curves showing the

percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful.

Counts and percentages of subjects who did not have a given visual disturbance at baseline but developed and present at Visit 4A (120-180d postoperative) will be presented.

In addition, the presence and absence of these symptoms, and how frequent, severe, and bothersome they appear will be summarized by visit with counts and percentages.

Sample Size Justifications

Approximately 220 subjects will be randomized to achieve 200 subjects who complete the study.

Effectiveness
The proposed sample size (N = 200; 100 for each IOL group) provides >99% power for the superiority hypothesis test on mean monocular photopic distance corrected intermediate visual acuity (66 cm) when tested at the 2.5% level of significance (one-sided). This assessment assumes:
Difference in DCIVA (66 cm) [logMAR]: Mean (SD) = -0.12 (0.18)

The proposed sample size will provide 84% power for the non-inferiority hypothesis with respect to mean photopic monocular best corrected distance visual acuity when tested at the 5% level of significance (one-sided) with a non-inferiority margin of 0.1 logMAR assuming:
Difference in BCDVA [logMAR]: Mean (SD) = 0.04 (0.16)

The proposed sample size provides >99% power for the superiority hypothesis test on mean photopic monocular distance corrected near visual acuity (40 cm) when tested at the 2.5% level of significance (one-sided). This assessment assumes:
Difference in DCNVA (40 cm) [logMAR]: Mean (SD) = -0.12 (0.18)

The proposed sample size will provide 94% power, with α=2.5%, 1-sided, to detect a difference of 25% in proportion of subjects who respond “Never” to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?), assuming a 50% rate in the ACRYSOF IQ EDF IOL group.

Adverse Events
For any event where zero incidence is observed in 100 operative eyes with ACRYSOF IQ EDF IOL, the one-sided exact 95% upper confidence limit is less than 3%. Thus, with 95% confidence the true adverse event rate is less than 3%.

2 TABLE OF CONTENTS

List of Tables

List of Figures

3 ABBREVIATIONS

Abbreviation	Definition
AAS	All-implanted analysis set
ACD	Anterior chamber depth
ADE	Adverse device effect
AE	Adverse event
AL	Axial length
ARMD	Age-related macular degeneration
ASADE	Anticipated serious adverse device effect
BAS	Best-case analysis set
BCDVA	Best corrected distance visual acuity
BSS	Balanced Salt Solution
CDVA	Corrected distance visual acuity
CI	Coordinating Investigator
cm	Centimeter
D	Diopter
DD	Device Deficiency
DCIVA	Distance corrected intermediate visual acuity
DCNVA	Distance corrected near visual acuity
DEP	Deviations and Evaluability Plan
DOF	Depth of focus
DoH	Declaration of Helsinki
DFU	Directions for use
eCRF	Electronic case report form
EDC	Electronic data capture
EDF	Extended depth of focus
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FDA	US Food and Drug Administration
FLACS	Femtosecond laser-assisted cataract surgery
GCP	Good Clinical Practice
GPCMS	Global Product Complaint System
IB	Investigator's brochure
IDE	Investigational Device Exemption
IEC	Independent ethics committee
ICF	Informed consent form
ICH	International Conference on Harmonization
IOL	Intraocular lens
IOLSAT	Intraocular Lens Satisfaction
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization

LASIK	Laser-assisted in situ keratomileusis
LogMAR	Logarithm of the minimum angle of resolution
LRI	Limbal relaxing incision
m	Meter
mm	Millimeter
mmHg	Millimeters of mercury
MOP	Manual of procedures
MRSE	Manifest refraction spherical equivalent
Nd:YAG	Neodymium-doped yttrium aluminium garnet
N/A	Not applicable
OCT	Ocular Coherence Tomography
OD	Right eye
OVD	Ophthalmic Viscosurgical Device
PC	Posterior capsulotomy
PCO	Posterior capsular opacification
QUVID	Questionnaire for Visual Disturbances
RD	Retinal detachment
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SME	Sponsor Medical Expert
SOP	Standard operating procedures
SPE	Safety performance endpoint
SSI	Secondary surgical intervention
SUN	Standardization of Uveitis Nomenclature
TPS	Trapezoidal phase shift
UCDVA	Uncorrected distance visual acuity
UCIVA	Uncorrected intermediate visual acuity
UCNVA	Uncorrected near visual acuity
UNSV	Unscheduled visit
US	United States
USADE	Unanticipated serious adverse device effect
VA	Visual acuity
YAG	Yttrium Aluminum Garnet

4 GLOSSARY OF TERMS

ACRYSOF IQ Extended Depth of Focus (EDF) IOL (Model DFT015)	Throughout this document, this investigational product (IP) will also be referred to as ACRYSOF IQ EDF IOL, Model DFT015, and test article.
ACRYSOF IQ Monofocal IOL (Model SN60WF)	Throughout this document, this IP will also be referred to as ACRYSOF IQ Monofocal IOL, Model SN60WF, and control 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 Subject	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 a 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 Subject	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.
Randomization Subject	Any subject who is assigned a randomized treatment.
Screened Subject	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) orb), 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 13 for additional SAEs.*
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.*

5 AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the institutional review board/ independent ethics committee (IRB/IEC) prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

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[redacted]

[redacted]

[redacted]

6 SCHEDULE OF VISITS

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
General Assessments and Procedures										
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[4]	X									
Inclusion/Exclusion	X	X			X					
Ophthalmic Assessments										
QUVID questionnaire (for visual disturbance)	X							X	X	X
IOLSAT questionnaire (for spectacle need)	X							X	X	X
Anterior Chamber Depth	X									
Axial Length	X									
Keratometry	X									
Predicted Target Residual Refractive Error[5]	X									
Manifest Refraction (4 m)	X			X			X	X	X	X
Distance VA at 4 m										
• Photopic Uncorrected	X		X	X		X	X	X	X[6]	X
• Photopic Corrected	X			X			X	X	X[6]	X
[redacted]									[redacted]	
[redacted]									X	
Defocus Curve (4 m)									X[6]	
[redacted]	X								X	
Intermediate VA at 66 cm										
• Photopic Uncorrected								X	X[6]	
• Photopic Distance Corrected								X	X[6]	
• [redacted]									X	

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
[redacted]									X	
Near VA at 40 cm										
• [redacted]								X	X[6]	
• Photopic Distance Corrected								X	X[6]	
[redacted]									[redacted]	
[redacted]									X	
[redacted]									X	
Contrast Sensitivity										
• Mesopic without Glare									X	
• Mesopic with Glare									X	
Slit Lamp Examination	X		X	X		X	X	X	X	X
Aqueous Signs			X	X		X	X	X	X	X
IOL Observations			X	X		X	X	X	X	X
IOL Position Change			X	X		X	X	X	X	X
Subjective PCO			X	X		X	X	X	X	X
Posterior Capsulotomy			X	X		X	X	X	X	X
Intraocular Pressure	X		X	X		X	X	X	X	X
Dilated Fundus Exam	X							X	X	X
Fundus Visualization								X	X	X
Surgical Procedure & Assessments										
Cataract Surgery		X			X					
Lens Information		X			X					
Incision Location[7]		X			X					
Final Incision Size[7,8]		X			X					
Problems during Surgery		X			X					
Other Surgical Procedures		X			X					
Adverse Events & Device Deficiencies										
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X
Secondary Surgical Interventions		X	X	X	X	X	X	X	X	X

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
Device Deficiencies		X	X	X	X	X	X	X	X	X

1. Visit 00 (1st eye surgery) must occur within 28 calendar days from Pre-Operative Visit (Visit 0).
2. Visit 00A (2nd eye surgery) must occur between 7 and 14 calendar days after Visit 00.
3. If necessary, Visit 4A may be completed over 2 days within a two-week period. Both days must fall within the specified visit window.
4. In women of child bearing potential only.
5. Data is reported in EDC at the surgical visit, but may be collected at a previous visit.
6. Testing is conducted monocular (bilaterally) [redacted].
7. Capture in source (not captured in EDC).
8. Only measure in cases with surgical complications.
9. Collected from time of consent onward.

7 INTRODUCTION

7.1 Background

Depth of focus (DOF) is the amount of focal plane displacement behind a lens that does not degrade the image quality of a distant object. The distance between the nearest and farthest objects in a scene that appear acceptably sharp depends upon the eye's DOF. Larger DOF allows sharp images of closer objects. A young, healthy human eye provides large DOF due to the large range of accommodation of the crystalline lens; however, the amplitude of depth of focus or accommodation gradually declines with age. For most people, accommodation is completely lost in the mid-fifties. While subjects implanted with a monofocal IOL have good distance vision, quality of vision at intermediate and near is often insufficient to support activities of daily living

Premium IOL solutions, such as multifocal IOLs, provide functional intermediate vision and near vision, but can also result in complaints of visual disturbance. In view of this, there exists a medical need to provide functional vision at intermediate and near distances, while maintaining good distance vision and a visual disturbance profile similar to that of a monofocal IOL. The ACRYSOF IQ EDF IOL was developed to provide an extended depth of focus at intermediate distance (approximately 66 cm) while maintaining distance VA and a safety profile similar to that of the ACRYSOF IQ Monofocal IOL.

[redacted]

A summary of known and potential risks and benefits to humans, as identified in the literature or through preclinical testing and/or prior clinical evaluations, for each investigational product can be found in the respective Directions for Use (DFU) - ACRYSOF IQ model

SN60WF, ACRYSOF IQ EDF model DFT015. Additional relevant information on the test article can be found in the Investigator's Brochure.

7.2 Purpose of the Study

The ACRYSOF IQ EDF IOL was developed to provide an extended DOF for provision of functional intermediate and near vision while maintaining both a distance VA and a safety profile similar to that of the ACRYSOF IQ Monofocal IOL. The purpose of the study is to demonstrate the safety and performance of ACRYSOF IQ EDF IOL at Month 6/Visit 4A.

7.3 Risks and Benefits

The risk of unanticipated adverse device effects with use of ACRYSOF IQ EDF IOL is considered to be low and the benefits of receiving the IOL should outweigh the risks for subjects that qualify for implantation in this study.

7.3.1 Known and Potential Risks

Refer to the IB and DFU for comprehensive risk information on ACRYSOF IQ EDF IOL model DFT015. A summary of this information is found below.

Surgical Complications:

Complications may occur on the surgery day or throughout the postoperative period. As with any type of intraocular surgery, there is a possibility of complications due to anesthesia, drug reactions, and surgical problems. The surgical procedure can exacerbate a pre-existing ocular condition. Possible problems during surgery include corneal endothelial touch, detached Descemet's membrane, iris damage, iris prolapse, iris trauma, iris incarceration, zonular rupture, vitreous loss, capsulorhexis tear, capsular rupture, uncontrollable intraocular pressure (IOP), hyphema, and retinal damage. An IOP increase may occur from the surgical procedure, residual viscoelastic in the eye, or a steroid response to postoperative medications.

Additionally, potential postoperative adverse events include but are not limited to corneal stromal edema, cystoid macular edema, endophthalmitis, hypopyon, iritis, lens dislocation, membrane formation on the IOL, pupillary block, retinal detachment, cyclitic membrane, transient or persistent glaucoma, retinal tear, vitritis, iris touch, pupil ovalization, posterior synechiae, ocular inflammation, ocular discomfort or pain, inflammation, decreased vision, decreased contrast sensitivity, decreased color perception, visual disturbances, and corneal endothelial cell loss.

ACRYSOF IQ EDF IOL Model DFT015:

An IOL replacement or explantation may be appropriate in some cases of significant residual refractive error, ocular infection, subject dissatisfaction, or visual disturbances (eg, glare, halos, starbursts, hazy vision, blurred vision, double vision, visual distortions, and color distortions). In most/majority of cases, spectacles or contact lenses may be prescribed to resolve residual refractive error. Other secondary surgical interventions include, but are not limited to: IOL repositioning, refractive laser treatment, paracentesis, vitreous aspirations, and iridectomy or laser iridotomy for pupillary block, wound leak repair, and retinal detachment repair.

There may also be unknown risks with the use of the ACRYSOF IQ EDF IOL. Any foreseen risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria, study procedures, and clinical monitoring.

7.3.2 Potential Benefits

[redacted] The ACRYSOF IQ EDF IOL may provide benefits to the subject by:

- Extending the range of functional vision to intermediate distances
- Maintaining the distance VA and safety profile similar to ACRYSOF IQ Monofocal IOL
- Providing improved near vision in comparison to a monofocal IOL
- Eliminating the visual disturbances commonly associated with diffractive IOLs

8 CLINICAL TRIAL OBJECTIVES

8.1 Primary Effectiveness Objective(s)

Below are listed the study's co-primary objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCIVA
2. To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic BCDVA
3. To demonstrate that the monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR
4. To demonstrate that ACRYSOF IQ EDF IOL has at least 50% of eyes achieving DCIVA of 0.2 logMAR or better

A successful outcome on the co-primary effectiveness endpoints is indicated by successful outcomes on all 4 of these endpoints.

8.1.1 Primary Effectiveness Endpoint(s)

Below are listed the study's primary effectiveness endpoints.

1. Monocular photopic DCIVA (logMAR) 66 cm from spectacle plane
2. Monocular photopic BCDVA (logMAR)
3. Monocular depth of focus (measured in the negative direction from 0) at 0.2 logMAR
4. Percentage of eyes achieving monocular photopic DCIVA of 0.2 logMAR or better

8.2 Secondary Effectiveness Objective(s)

Below are listed the study's co-secondary objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCNVA

   In addition, the following performance targets will also be assessed to demonstrate clinical significance:

- At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better
- Percentage of eyes achieving monocular DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group

2. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?)
3. To describe mean monocular photopic UCIVA outcomes
4. To describe mean monocular photopic UCDVA outcomes

8.2.1 Secondary Effectiveness Endpoint(s)

Below are listed the study's secondary effectiveness endpoints.

1. Monocular photopic DCNVA (logMAR) 40 cm from spectacle plane
2. Proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire: "Overall, in the past 7 days, how often did you need to wear eyeglasses to see?"
3. Monocular photopic UCIVA (logMAR) 66 cm from spectacle plane
4. Monocular photopic UCDVA (logMAR)

[redacted]

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

8.3 Co-Primary Safety Objective

Below are listed the study's co-primary safety objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. The study's primary safety objective is to demonstrate that ACRYSOF IQ EDF IOL adverse event rates are not worse than the historical control SPE rates, as defined in IS EN ISO 11979-7:2014
2. To describe monocular mesopic contrast sensitivity test (with and without glare) outcomes

8.3.1 Primary Safety Endpoint

The study's primary safety endpoints are

- Rate of ocular adverse events
- Mesopic contrast sensitivity (log units)

8.4 Secondary Safety Objective(s)

To estimate rates of severe and most bothersome (separately) visual disturbances as reported by subjects using a questionnaire at Visit 4A (120-180d postoperative)

8.4.1 Secondary Safety Endpoint(s)

The study's secondary safety endpoint is QUVID-reported visual disturbances rate.

8.4.2 Supportive Safety Endpoint(s)

Supportive safety endpoints include those bulleted below.

- IOP
- Slit lamp findings including IOL observations

- IOL tilt/decentration
- Subjective PCO assessment
- Posterior capsulotomy
- Dilated fundus exam findings including fundus visualization
- Intraoperative surgical problems
- Other procedures at surgery (combined and/or additional)
- Adverse events (including SSIs)
- Device deficiencies

9 INVESTIGATIONAL PLAN

9.1 Study Design

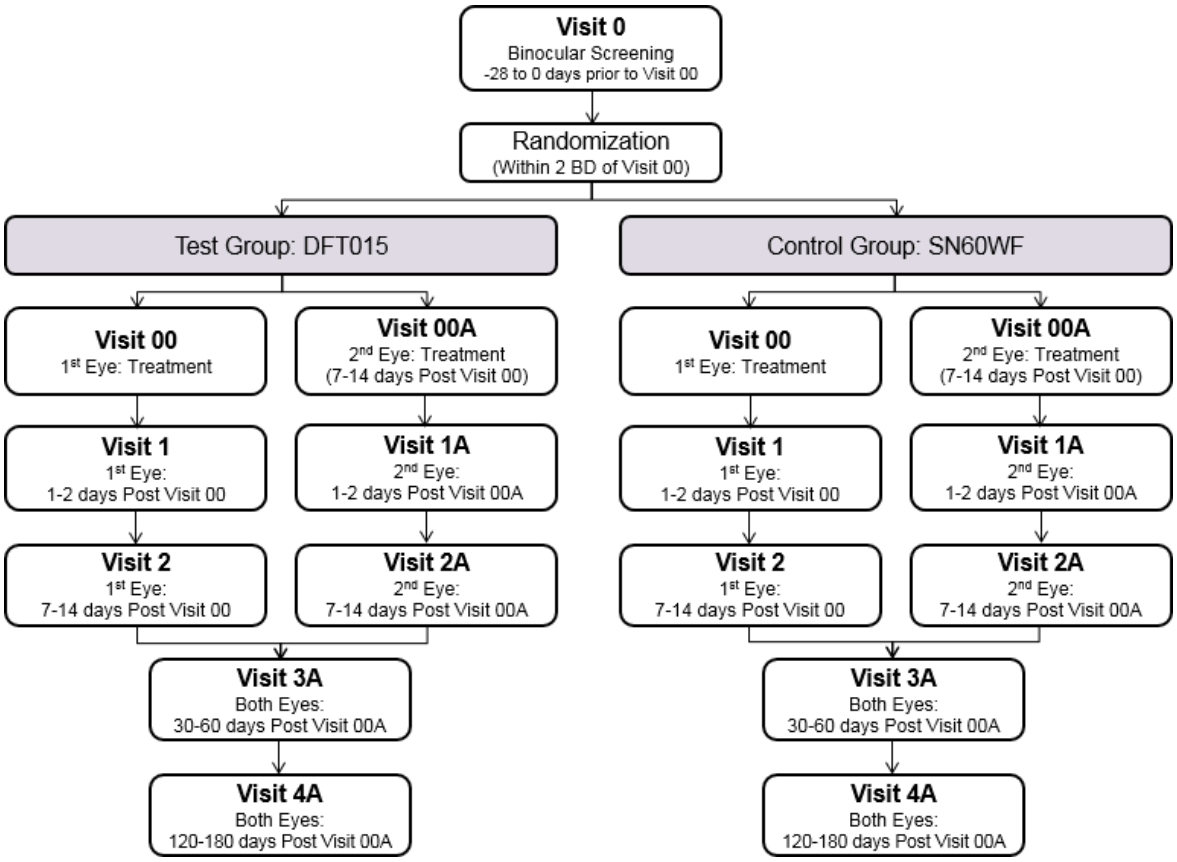
This is a prospective, multi-center, randomized, parallel-group, controlled, assessor- and subject-masked study. Both eyes of a subject must require cataract surgery to qualify for enrollment into this study. To reduce bias, subjects will be randomly assigned in a 1:1 ratio to receive either ACRYSOF IQ EDF IOL model DFT015 (test article) or ACRYSOF IQ Monofocal IOL model SN60WF (control article) in both eyes. To further reduce bias, all subjects and site assessors will be masked to subject treatment assignment until the end of the study.

The first operative eye is defined as the eye with the worse BCDVA. If the BCDVA is the same in both eyes, identify the right eye (OD) as the first operative eye. The second eye implant must occur within 14 days of the first eye implant.

A total of 9 scheduled visits are planned and subject participation is expected to last 7-8 months. The visits include a Screening visit (Visit 0), 2 Operative Visits (Visit 00 and Visit 00A), and 6 postoperative visits at the following intervals: Day 1-2 (Visit 1/1A), Day 7-14 (Visit2/2A), Day 30-60 (Visit 3A), and Day 120-180 (Visit 4A) (See Figure 9-1 Study Design). Primary endpoint data will be collected at the Month 6/ Visit 4A (120-180 day post 2nd eye implantation).

Note: Visit 4A may be completed over 2 days within a 2-week period. Both days must fall within the specified visit window.

Figure 9–1 Study Design Diagram



9.2 Rationale for Study Design

The study is designed to assess performance and safety parameters of interest in compliance with guidance from the draft ANSI Z80.35 Extended Depth of Focus Intraocular Lenses (11 July 2016) and the American Academy of Ophthalmology Task Force Consensus Statement for Extended Depth of Focus Intraocular Lenses (MacRae 2017). Compliance includes subject number requirement (100 per lens model), follow-up period (6 months postoperative), control article (see Section 9.3 below), randomization, masking, and assessments.

9.3 Rationale for Choice of Control Article

ACRYSOF IQ EDF IOL is a modification of the United States (US) Food and Drug Administration (FDA) approved, commercially available control article (ACRYSOF IQ Monofocal IOL). The control article has the same physical properties and is composed of the same material as the test article. Based on optical bench testing and simulation of the test article, the contrast sensitivity under mesopic conditions is expected to be comparable to the

control article. Further, the ACRYSOF IQ Monofocal IOL is well established in the literature and is considered the industry standard of care. For these reasons, the ACRYSOF IQ Monofocal IOL is scientifically the most appropriate control article for this study, and functions to reduce bias.

9.4 Data Monitoring Committee

Not applicable.

10 SUBJECT POPULATION

The study population consists of male and female subjects 22 years of age and older, with a diagnosis of cataract in both eyes, requiring surgery with implantation of a monofocal IOL in the capsular bag. It is aimed to randomize approximately 220 subjects at approximately 12 US investigative sites. Each site will aim to randomize approximately 20 subjects, and no site will randomize more than 55 subjects (25% of total). Site specific targets may be adjusted based on individual site capabilities. Enrollment projections are as follows:

- 240 subjects to be enrolled/sign consent (approximately 10% screen failure rate is expected)
- 220 subjects to be randomized (approximately 10% discontinuation rate is expected)
- 200 subjects to successfully complete the final study visit (Visit 4A)
    - 100 subjects in the ACRYSOF IQ EDF IOL arm
    - 100 subjects in the ACRYSOF IQ Monofocal IOL arm

Sites must check all entry criteria at Screening/Visit 0 and at both surgical visits (Visit 00, Visit 00A). If a subject is excluded post randomization and prior to first eye surgery (IOL does not come in contact with the eye), the subject should be discontinued from participation in the study. Refer to Section 12.6 Discontinued Subjects for further details.

10.1 Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill **all** of the below listed criteria. When criteria are ocular, both eyes must meet criteria.

1. Adults (22 years or older at the time of participation in the study) diagnosed with cataract in both eyes
2. BCDVA of 0.3 logMAR (20/40 Snellen) or worse either with or without a glare source present (e.g., Brightness Acuity Tester).
3. Clear intraocular media other than cataract
4. Planned cataract removal by routine small incision surgery
5. Calculated lens power between 18.0 and 25.0 D [when targeted for emmetropia (0.00 D)]

6. Willing and able to complete all required postoperative visits
7. Able to comprehend and sign an IRB/IEC approved statement of informed consent
8. Potential postoperative BCDVA of 0.2 logMAR (20/32 Snellen) or better in each eye based on Investigator's medical opinion
9. Preoperative keratometric astigmatism of less than 1.0 D in both operative eyes

10.2 Exclusion Criteria

Subjects fulfilling **any** of the below listed criteria are not eligible for inclusion in this study. When criteria are ocular, the subject is not eligible if either eye meets the criteria.

1. Any disease or pathology, other than cataract, that (in the expert opinion of the Investigator) is expected to reduce the potential postoperative best corrected distance visual acuity (BCDVA) to a level worse than 0.2 logMAR (including, but not limited to the following: amblyopia, clinically severe corneal dystrophy (e.g., epithelial, stromal, or endothelial dystrophy), diabetic retinopathy, extremely shallow anterior chamber, not due to swollen cataract, microphthalmos, previous retinal detachment, previous corneal transplant, recurrent severe anterior or posterior segment inflammation of unknown etiology, iris neovascularization, uncontrolled glaucoma, aniridia, or optic nerve atrophy, epiretinal membrane, macular degeneration, or diagnosis of pseudoexfoliation)
2. History of recurrent anterior segment/posterior segment inflammation.
3. Clinically significant (in the Investigator's opinion) corneal pathology (epithelial, stromal, endothelial) or ocular surface disease that would adversely affect the visual outcome including but not limited to old significant corneal scars (including Salzman's nodular degeneration), corneal irregularity (including dry eye syndrome), active or inactive keratitis with compromise of the refractive capability of the cornea, keratoconjunctivitis sicca with compromise of visual function, active keratouveitis, endothelial dystrophy (Fuch's and non-guttate), keratoconus, etc.
4. Clinically significant ocular surface disease that would affect study measurements based on Investigator expert medical opinion
5. History of previous intraocular or corneal surgery

6. Pregnant/lactating or has another condition with associated fluctuation of hormones that could lead to refractive changes

7. History of amblyopia or monofixation syndrome with poor stereoscopic vision

8. Current or recent use of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha1A adrenoceptor (e.g. Flomax (tamsulosin HCL), Hytrin, or Cardura) that in the opinion of the investigator would potentially require mechanical or surgical manipulation to enlarge the pupil

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

10. Any other ocular condition 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

11. Subjects with conditions that, in the Investigator's opinion, increase the risk of zonular rupture during cataract extraction procedure (eg, pseudoexfoliation syndrome, Marfan syndrome) that may affect the postoperative centration or tilt of the lens

12. Any other planned ocular surgical procedures including but not limited to limbal relaxing incision (LRI), astigmatic keratotomy, laser-assisted in situ keratomileusis (LASIK), and retinal laser treatment within the study time frame

13. Patients who desire monovision correction

10.3 Reasons for Non-Implantation

Below are listed reasons to not implant the study lens, where study lens refers to both the test lens and the control lens.

1. Surgical complications including but not limited to loss of zonular integrity/zonular weakness, zonular rupture, anterior capsular rupture interfering with the stability of the IOL, 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

If the study implantation is aborted due to a reason for non-implantation, follow standard of care and implant a non-study lens. In the event the first eye is not implanted and the IOL **did not** touch the eye, the subject is discontinued from the study. If the implantation is aborted and the IOL **did** touch the eye (first operative eye), then the second eye should not be implanted and the subject is encouraged to attend all follow-up study visits for safety evaluation on this eye only. In the event the second eye is not implanted, the subject continues in the study. Refer to Manual of Procedures (MOP) Section 5.4 for complete details on subject discontinuation and/or follow-up when a lens is not implanted.

10.4 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

11 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 and IB.

Table 11–1 Test Article

Test Product	ACRYSOF IQ EDF IOL (Model DFT015)
Manufacturer	Alcon
Indication for use	The ACRYSOF IQ EDF IOL model DFT015 IOL is intended for primary implantation for the visual correction of aphakia in adult patients with < 1.00 D of preoperative corneal astigmatism, in whom a cataractous lens has been removed by extracapsular cataract extraction. Compared to a monofocal aspheric IOL, the lens may provide a continuous extended DOF, with improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The lens is intended for capsular bag placement only.
Intended Purpose in the current study	This IOL is intended for primary implantation in the capsular bag in the posterior chamber for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients. The lens is intended to provide distance vision and a continuous range of functional vision between distance and intermediate and improved near acuity.
Product description and parameters available for this study	Optic Type - Biconvex Aspheric Optic
	Optics Material – Ultraviolet and blue light filtering Acrylate/ Methacrylate Copolymer
	Optic Powers: 18.0 to 25.0 D in 0.5 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.
Amount of Product to be Provided to the Subject	Following randomization, each subject will be bilaterally implanted with the control or test article.
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	Packaged in a standard Alcon IOL carton. The carton is labeled with the following information: name of the lens, model number, overall diameter, optic diameter, diopter power, serial number, name of the manufacture, storage condition, expiration date, sterile, and single use. Each package is also labeled *"Exclusively for Clinical Investigations"* and *"Caution – Investigational device. Limited by Federal (or United States) law to investigational use".*
Storage conditions	The IP 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.
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. • Subjects in this protocol must be targeted for an emmetropic postoperative refraction (ie, the lens power selected must be that which has a predicted residual refraction closest to emmetropia (0.00 D)). • More information on the test article can be found in the IB

	(0138) and DFU for ACRYSOF IQ EDF IOL.
Supply	A designated amount of IOLs will be supplied to the site by the Sponsor.

Table 11–2 Control Article

Control Product	ACRYSOF IQ Monofocal IOL (Model SN60WF)
Manufacturer	Alcon
Indication for use	The ACRYSOF IQ Monofocal IOL model SN60WF IOL is indicated for the replacement of the human lens to achieve visual correction of aphakia in adult patients following cataract surgery. This lens is intended for placement in the capsular bag.
Intended Purpose in the current study	This lens is indicated for the replacement of the human lens to achieve visual correction of aphakia in adult patients following cataract surgery. This lens is intended for placement in the capsular bag.
Product description and parameters available for this study	Optic Type: Biconvex Aspheric Optic
	Optics Material: Ultraviolet and blue light filtering Acrylate/ Methacrylate Copolymer
	Optic Powers: 18.0-25.0 D in 0.5 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.
Amount of Product to be Provided to the	Following randomization, each subject will be bilaterally implanted

Subject	with the control or test article.
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	This lens is marketed in the countries conducting this clinical study. In countries where applicable, an additional label will be added to the marketed product noting, "*Investigational Device"* and "*To Be Used by Qualified Investigators Only"* or alternate country required text (text in English and translation as appropriate).
Storage conditions	IP 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.
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. • Subjects in this protocol must be targeted for an emmetropic postoperative refraction (ie, the lens power selected must be that which has a predicted residual refraction closest to emmetropia (0.00 D)). • More information on the control article can be found in the DFU for ACRYSOF IQ Monofocal IOL.
Supply	A designated amount of IOLs will be supplied to the site by the Sponsor.

11.1 Other Medical Device Specified for Use during the Study

Table 11–3 Delivery System

Delivery System	Qualified Diopter Range	
	ACRYSOF IQ EDF IOL (Model DFT015)	**ACRYSOF IQ Monofocal IOL (Model SN60WF)**
MONARCH® II/III C Cartridge with: • MONARCH II (green) handpiece • MONARCH III (blue) handpiece	**18.0 – 25.0 D**	**18.0 – 25.0 D**
MONARCH III D Cartridge **only** with: • MONARCH III (blue) handpiece	**18.0 – 25.0 D**	**18.0 – 25.0 D**

11.2 Treatment Assignment / Randomization

Subjects will be randomized in a 1:1 ratio to receive either ACRYSOF IQ EDF IOL or ACRYSOF IQ Monofocal IOL. Randomization will be stratified by site. After signing the ICF, the subject is considered enrolled. After which he/she will be assigned a subject number by the electronic data capture (EDC) system. The Investigator (or delegate) will initiate randomization in EDC:

- after confirming the subject meets eligibility criteria
- post lens power calculation and IOL power selection for both lens types (ie, the power calculation for both the ACRYSOF IQ EDF IOL and the ACRYSOF IQ Monofocal IOL must be conducted prior to randomization)
- within 2 business days of the first eye operative visit (Visit 00)

11.3 Accountability Procedures

Upon receipt of IP, the Investigator or delegate must conduct an inventory of all IOLs by serial number, complete study specific confirmation of receipt procedures, and retain any required documentation in the Investigator's clinical study records. Throughout the study, the Investigator or delegate must maintain records of IP use for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of IP supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. All IP sent to the Investigator must be accounted for by Study Sponsor personnel, and in no case be used in an unauthorized manner.

If possible, investigational and control products associated with a DD must be returned to the Study Sponsor. Refer to Section 13 of this protocol for additional information on the reporting of device deficiencies and to the MOP for information on return of study products associated with these events.

The Investigator is responsible for proper disposition of all unused IPs at the conclusion of the study, according to the instructions provided by the Sponsor.

11.4 Treatment Masking

The assessor and subject will be masked in this study. Subjects will be masked to treatment assignment for the entire duration of the study. Site personnel performing the manifest refraction, all VA assessments (including defocus curve testing), and all contrast sensitivity assessments will remain masked with regard to treatment assignment until after the final database lock. Should a subject safety concern arise, refer to Section 13.10 Unmasking of the Study Treatment. ***Note:*** Any unmasking of assessor or subject must be reported to Alcon.

After the subject is implanted with the appropriate lens, a generic implant card is provided to the subject. The implant card will not reveal his/her treatment assignment. The treatment assignment will only be revealed to the study subject after the final database lock and when investigative sites are notified by the Study Sponsor.

Masked study personnel must avoid seeking information that may compromise masking. Unmasked study personnel must not disseminate information that is potentially unmasking to any masked personnel. A list of unmasked individuals can be found in Table 10-4 below.

Table 11-4 Unmasked Individuals

Unmasked Individual	Extent of Unmasking	Rationale
Investigator	Unmasked to IP treatment assignment	Investigator will be implanting the IOL and will have knowledge of the treatment assigned to study subjects
Site Personnel (not completing assessments noted Section 11.4)	Unmasked to IP treatment assignment	Site personnel involved with operative visits and data entry into EDC
Monitor	Unmasked to IP treatment assignment	Monitor will complete IP accountability and monitoring responsibilities

11.5 Changes to Concomitant Treatments or Procedures

After the subject is enrolled (signed an ICF) 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.

12 CLINICAL TRIAL PROCEDURES

12.1 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 ICF. Additionally, the individual obtaining consent from the subject must sign and date the ICF. 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.

12.2 Clinical Trial Assessments

The following section outlines the assessments to be performed in this clinical study. Assessments are described in detail in the ILI875-C002 MOP, and are outlined in tabular format in Section 6 of this protocol.

12.2.1 Prohibited Procedures

Refractive surgical procedures are prohibited in the study eye at surgery and throughout the duration of the subject's participation in the clinical study. Prohibited procedures include, but are not limited to, LASIK, astigmatic keratotomy and limbal relaxing incisions (qualify as LRI outside of PI's predetermined placement of corneal incision locations). Retinal laser treatments are also prohibited.

12.2.2 Screening/Preoperative Visit (Visit 0)

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

To ensure corneal stability subjects who wear contact lenses must discontinue use prior to the preoperative visit measurements. Discontinuation guidelines are provided below in Table 12-1.

Table 12–1 Contact Lens Discontinuation Prior to Preoperative Visit

Type of Contact Lens	Minimum Time to Stop Wearing before Preoperative
Hard or rigid gas permeable lenses	3 weeks
Daily wear soft lenses	2 weeks
Soft extended-wear lenses	2 weeks

Below is a list of study procedures to be done at Visit 0. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in the source documentation and, if applicable, electronic case report form (eCRF).

Data from the Investigator's previous routine clinical evaluation (eg, slit lamp exam) may be used, if the data 1) meet the requirements of this protocol and MOP, and 2) were collected within the -28 to 0 day preoperative time period.

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 he/she is interested. Refer to Section 16 Ethics.

3. Collect subject demographic, medical history information, and concomitant medication use.

4. Perform a urine pregnancy test, **IF** the subject is a woman of childbearing potential.

5. Assess anterior chamber depth (ACD) and axial length (AL) with an optical biometer. *[Both Eyes, Bilateral]*

6. Perform keratometry measurements with a biometer. From this measure, determine if the subject qualifies with <1.00 D of keratometric astigmatism in both eyes. *[Both Eyes, Bilateral]*

7. For both the ACRYSOF IQ EDF IOL and the ACRYSOF IQ monofocal IOL select and document the subject's required lens power. The power selected must be that which has a predicted residual refraction closest to emmetropia (0.00 D). Refer to the MOP for acceptable formulas. *[Both Eyes, Bilateral]*
   Note: This determination may be made any time after required biometry has been collected and must be made prior to randomization. Lens power cannot be changed post randomization.

8. Perform manifest refraction. *[Both Eyes, Bilateral]*
   Note: UCDVA testing may be performed prior to manifest refraction.

9. Assess UCDVA and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*

10. Identify the first operative eye for this study. To reduce bias, first operative eye is defined as the eye with the worse BCDVA, or the right eye if the VA is equal in both eyes.
    Note: This determination may be made at any time after BCDVA measurement.

11. Measure photopic pupil size with subject fixated on 4m VA chart under photopic conditions. *[Both Eyes, Bilateral]*
    Note: Pupil diameter should be measured under the same photopic light conditions as the VA tests.

12. Conduct slit lamp examination. *[Both Eyes, Bilateral]*

13. Perform tonometry to measure IOP. *[Both Eyes, Bilateral]*

14. Conduct dilated fundus examination. *[Both Eyes, Bilateral]*

15. Assess for and record any AEs. Refer to Section 13 for further details.

16. Evaluate subject against all entry criteria. If subject fails criteria, screen fail the subject.

17. Provide the QUVID and IOLSAT questionnaires to the subject for completion.
    Note: Questionnaires may be completed any time after entry criteria have been met. Subjects screen failing should not be given the questionnaire.

18. Proceed with scheduling study surgery(ies).

12.2.3 Operative Visits (Visit 00/00A)

Visit 00: Day 0, Monocular First Eye

Visit 00A: 7-14 Days Post First Implantation, Monocular Second Eye

***Note*:** The Visit 00A window may overlap with other study visit windows (eg, Visit 2). In this case, both visits may be conducted on the same day at the discretion of the Investigator.

Each study surgeon should follow his/her routine cataract procedure for all study surgeries, and according to the site's documented surgical protocol.

It is permitted to have 1 study-trained surgeon at each site perform IOL implantations. For surgeons with experience prior to the start of the trial, femtosecond laser-assisted cataract surgery (FLACS) is permitted, however it is **NOT** required. The laser may **ONLY** be used for the following:

- Primary and sideport incisions
- Capsulorhexis
- Lens fragmentation

Use of any intraoperative power assessment is not permitted during surgery.

Below is a list of study procedures to be completed at Visit 00 and Visit 00A. It is recommended that procedures are performed in the order described below unless otherwise stated. Activities involving multiple delegated staff members may be performed in parallel. All assessments must be documented in source documentation and, if applicable, eCRF.

1. In preparation for the operative visit, randomize the subject. It is recommended that subjects are contacted prior to randomization to 1) confirm willingness to continue trial participation, and 2) confirm scheduled surgical date and time.
   Note: Randomization must occur within 2 business days of the scheduled first eye surgery. Lens power cannot be changed after the subject is randomized.

2. Document any changes to ocular and non-ocular concomitant medications.

3. Prior to treatment, review inclusion/exclusion criteria and ensure the subject has been properly consented for participation in the study.

4. Prepare subject for surgery in accordance to site specific operating procedures. *[Operative Eye Only, Monocular]*

5. Perform surgery and implantation with the randomized IOL. *[Operative Eye Only, Monocular]* Implantation may be attempted twice. After 2 aborted implants, the subject must be implanted with a non-study IOL (IOL not provided as part of study consignment).

6. If a surgical complication occurs, measure and record incision size at the completion of IOL implantation. *[Operative Eye Only, Monocular]*

7. Record incision location. *[Operative Eye Only, Monocular]*

8. Record any intraoperative surgical problems, complications or other procedures that occur during surgery. Other procedures include those performed outside of routine cataract surgery whether combined and/or additional. *[Operative Eye Only, Monocular]*
   ***Note*:** Other planned procedures at the time of surgery are exclusionary.

9. Record the lens information that is located on the IOL sticker. Both successful and aborted (if applicable) test and control article information should be recorded. *[Operative Eye Only, Monocular]*

10. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.

11. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.2.4 1-Day Postoperative Visit (Visit 1/1A)

Visit 1: 1-2 Day Post First Eye Implantation, Monocular First Eye

Visit 1A: 1-2 Days Post Second Eye Implantation, Monocular Second Eye

Below is a list of study procedures to be completed at Visit 1 and Visit 1A. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in source documentation and, if applicable, eCRF.

1. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.

2. Assess UCDVA under photopic conditions at 4 m. *[Operative Eye Only, Monocular]*

3. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any. *[Operative Eye Only, Monocular]*

4. Grade cell and flare according to Standardization of Uveitis Nomenclature (SUN) system (SUN Working Group, 2005). Refer to MOP for grading scheme. *[Operative Eye Only, Monocular]*

5. Observe and record any IOL position changes (ie, tilt and decentration) occurring since the previous visit. *[Operative Eye Only, Monocular]*

6. Assess subjective PCO, and record information for any posterior capsulotomy (PC)

that has occurred since surgery, if applicable. *[Operative Eye Only, Monocular]*

7. Perform tonometry to measure IOP. *[Operative Eye Only, Monocular]*
8. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.
9. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.2.5 1-Week Postoperative Visit (Visit 2/2A)

Visit 2: 7-14 Days Post First Eye Implantation, Monocular First Eye

Visit 2A: 7-14 Days Post Second Eye Implantation, Monocular Second Eye

Below is a list of study procedures to be completed at Visit 2 and Visit 2A. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in source documentation and, if applicable, eCRF.

1. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.
2. Perform manifest refraction. *[Operative Eye Only, Monocular]*
   NOTE: UCDVA testing may be performed prior to manifest refraction.
3. Assess UCDVA and BCDVA under photopic conditions at 4 m. *[Operative Eye Only, Monocular]*
4. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any. *[Operative Eye Only, Monocular]*
5. Grade cell and flare according to SUN system (refer to MOP for grading scheme). *[Operative Eye Only, Monocular]*
6. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit. *[Operative Eye Only, Monocular]*
7. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable. *[Operative Eye Only, Monocular]*
8. Perform tonometry to measure IOP. *[Operative Eye Only, Monocular]*

9. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.
10. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.2.6 1-Month Postoperative Visit (Visit 3A)

Visit 3A: 30-60 Days Post Second Eye Implantation, Bilateral

Below is a list of study procedures to be completed at Visit 3A. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in source documentation and, if applicable, eCRF.

1. Provide the QUVID and IOLSAT questionnaires to the subject for completion. Questionnaires should be completed by the subject prior to administration of any other assessment.
2. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.
3. Perform manifest refraction. *[Both Eyes, Bilateral]*
   Note: UCDVA testing may be performed prior to manifest refraction.
4. Assess monocular UCDVA and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*
5. Assess monocular UCIVA and DCIVA under photopic conditions at 66 cm. *[Both Eyes, Bilateral]*
6. Assess monocular UCNVA and DCNVA under photopic conditions at 40 cm. *[Both Eyes, Bilateral]*
7. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any. *[Both Eyes, Bilateral]*
8. Grade cell and flare according to SUN system (refer to MOP for grading scheme). *[Both Eye, Bilateral]*
9. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit. *[Both Eyes, Bilateral]*
10. Assess subjective PCO, and record information for any PC that has occurred since

surgery, if applicable. *[Both Eyes, Bilateral]*

11. Perform tonometry to measure IOP. *[Both Eyes, Bilateral]*

12. Conduct dilated fundus exam noting any issues with fundus visualization due to the lens optic. *[Both Eyes, Bilateral]*

13. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.

14. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.2.7 6-Month Postoperative Visit (Visit 4A)

Visit 4A: 120-180 Days Post Second Eye Implantation, Bilateral [redacted]

This visit may be completed over 2 days within a two-week period. Both days must fall within the specified visit window. Below is a list of study procedures to be completed at Visit 4A. It is recommended that procedures are performed in the order described below unless otherwise stated. If a subject appears fatigued, or requests a break from testing, provide a rest. All assessments must be documented in source documentation and, if applicable, eCRF.

1. Provide the QUVID and IOLSAT questionnaires to the subject for completion. Questionnaires should be completed by the subject prior to administration of any other assessment.

2. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.

3. Perform manifest refraction. *[Both Eyes, Bilateral]*
Note: UCDVA testing [redacted] monocular [redacted]) may be performed prior to manifest refraction.

4. Assess <u>monocular</u> UCDVA and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*

[redacted]

[redacted]

8. Perform monocular defocus curve testing. *[Both Eyes, Bilateral]*

[redacted]

11. Assess monocular UCIVA and DCIVA under photopic conditions at 66 cm. *[Both Eyes, Bilateral]*

[redacted]

15. Assess monocular [redacted] DCNVA under photopic conditions at 40 cm. *[Both Eyes, Bilateral]*

[redacted]

[redacted]

20. Perform monocular mesopic *without* glare contrast sensitivity testing. *[Both Eyes, Bilateral]*

21. Perform monocular mesopic *with* glare contrast sensitivity testing. *[Both Eyes, Bilateral]*

22. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any. *[Both Eyes, Bilateral]*

23. Grade cell and flare according to SUN system (refer to MOP for grading scheme). *[Both Eye, Bilateral]*

24. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit. *[Both Eyes, Bilateral]*

25. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable. *[Both Eyes, Bilateral]*

26. Perform tonometry to measure IOP. *[Both Eyes, Bilateral]*

27. Conduct dilated fundus exam noting any issues with fundus visualization due to the lens optic. *[Both Eyes, Bilateral]*

28. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.

29. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.3 Schedule of Procedures and Assessments for Discontinued Subjects

For subjects that discontinue from the study post-implantation, it is recommended to complete the applicable assessments noted in the Schedule of Visits (Section 6) for an Early Exit Visit. All assessments must be documented in source documentation and, if applicable, eCRF. It is recommended that procedures are performed in the order described below unless otherwise stated.

1. Provide the QUVID and IOLSAT questionnaires to the subject for completion.
   Note: The questionnaire should be completed by the subject prior to administration of

any other assessment.

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

3. Perform manifest refraction. *[Both Eyes, Bilateral]*
Note: UCDVA testing may be performed prior to manifest refraction.

4. Assess UCDVA and BCDVA. *[Both Eyes, Bilateral]*

5. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any. *[Both Eyes, Bilateral]*

6. Grade cell and flare according to SUN system (refer to MOP for grading scheme). *[Both Eye, Bilateral]*

7. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit. *[Both Eyes, Bilateral]*

8. Assess subjective PCO, and record information for any PC that has occurred since surgery, if applicable. *[Both Eyes, Bilateral]*

9. Perform tonometry to measure IOP. *[Both Eyes, Bilateral]*

10. Conduct dilated fundus exam noting any issues with fundus visualization due to the lens optic. *[Both Eyes, Bilateral]*

11. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.

12. Evaluate for and record any DDs. Refer to Section 13 for further detail.

12.4 Unscheduled Visits

An unscheduled visit (UNSV) is defined as follows:

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

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).

With exception to the questionnaires, assessments captured at the UNSV are dictated by the Investigator per their medical judgment. The below listed assessments are recommended. All assessments must be documented in source documentation and, if applicable, eCRF. It is recommended that procedures are performed in the order described below unless otherwise stated.

1. Mandatory: Provide the QUVID and IOLSAT questionnaires to the subject for completion.
   Note: Questionnaires should be completed by the subject prior to administration of any other assessment.
2. Document any changes to medical/ocular history and ocular and non-ocular concomitant medications.
3. Perform manifest refraction.
   Note: UCDVA testing may be performed prior to manifest refraction.
4. Assess UCDVA and BCDVA.
5. Perform slit lamp examination including IOL observations (if any).
6. Grade cell and flare according to SUN system (refer to MOP for grading scheme).
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. Conduct dilated fundus examination including fundus visualization.
11. Evaluate for and record any AEs including SSIs. Refer to Section 13 for further detail.
12. Evaluate for and record any DDs. Refer to Section 13 for further detail.

Assessments are not limited to the above list. 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.

12.5 Missed Visit

If a subject misses a scheduled visit, reschedule the subject within the same visit period. Show diligence in trying to schedule the subject for all visits, and document all attempts to contact the subject in the subject's chart. In chart documentation, include dates, times, method of contact, etc.

If attempts to contact the subject are unsuccessful, document the date the subject is considered lost to follow-up. If a subject is unable to return for the final study visit, complete the Exit Case Report Form with the appropriate reason for discontinuation. Complete the subject's Exit Case Report Form after the last window closes, indicating the subject is lost to follow-up.

12.6 Discontinued Subjects

12.6.1 Screen Failures

Subjects who discontinue from the study prior to the randomization 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 enter the subject in EDC. Subjects failing screening may not be rescreened.

12.6.2 Discontinuations

Discontinued subjects are individuals who have signed an ICF and who voluntarily withdraw or are withdrawn from the study by the Investigator post randomization. Subjects may discontinue from the 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. The Investigator must document the reason for study discontinuation in the subject's case history source documents and complete the exit form in EDC.

For subjects discontinuing from the study, the Investigator should complete Early Exit procedures if the subject is willing and able, and if in the opinion of the Investigator it is safe

for the subject to do so. 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.

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

Note: Subjects not implanted at the time of surgery (first operative eye) and the study IOL **did not** touch the eye (refer to Section 10.3) must be captured as discontinuations.

12.6.3 Aborted Implantation

Implantation may be attempted twice. After two aborted implants, the subject must be implanted with a non-study provided IOL.

If an implantation is aborted and the study IOL **did not** touch the eye (first operative eye), then the subject is required to discontinue from the study and standard of care for IOL implantation is followed. If the implantation is aborted and the study IOL **did** touch the eye (first operative eye), then the second eye should not be implanted but the subject is encouraged to attend all follow-up study visits for safety evaluation on this eye only. Refer to Manual of Procedures (MOP) Section 5.4 for complete details on subject discontinuation and/or follow-up when a lens is not implanted.

If the IOL implantation is attempted and aborted due to Device Deficiency, then a Device Deficiency form must be completed and the IOL must be returned to the Study Sponsor in appropriate safe packaging.

12.7 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-studytreatment options as needed.

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

13 DEVICE DEFICIENCIES AND ADVERSE EVENTS

An adverse event (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 and figures for categories of AEs and SAEs.

13.1 General Information

An AE is any untoward medical occurrence in a subject who is administered a clinical trial treatment (eg, implanted with an investigational device) regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the clinical trial treatment, whether or not related to the treatment. Below are Figures that categorize AEs and SAEs.

Figure 13–1 Categorization of All Adverse Events

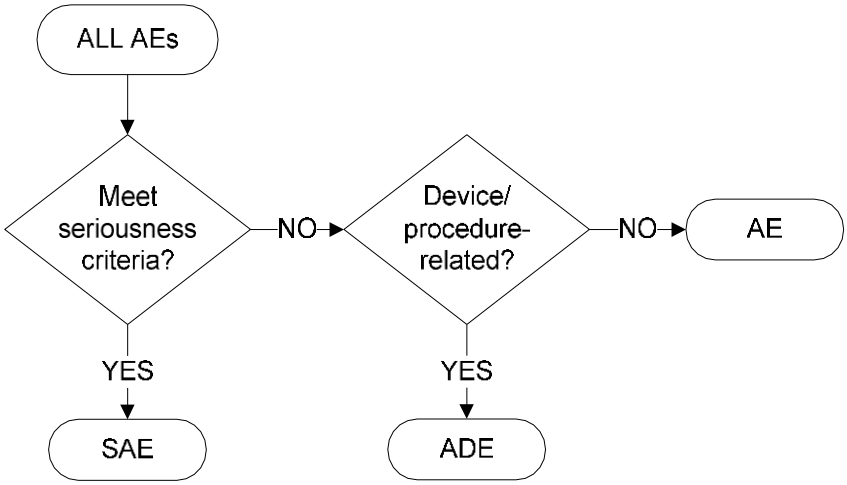
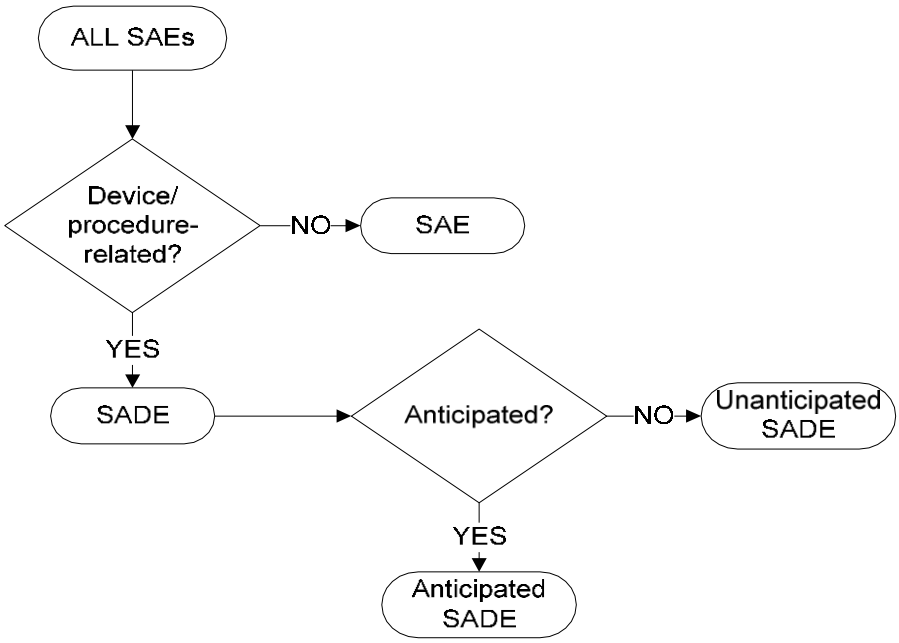


Figure 13–2 Categorization of All Serious Adverse Events



13.2 Serious Adverse Events (SAEs)

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.

13.3 Specific Events Relevant to this Protocol

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

13.3.1 Cumulative Serious Adverse Events

(Total number of Adverse Events that have occurred at any time up to a specified timepoint postoperatively)

- Cystoid macular edema
- Hypopyon
- Endophthalmitis
- Lens dislocation from posterior chamber
- Pupillary block
- Retinal detachment
- Secondary surgical intervention (excluding PC)

13.3.2 Persistent Serious Adverse Events

(Adverse Events present at the conclusion of the clinical investigation)

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

This list is consistent with the categories provided in IS EN ISO 11979-7:2014. A persistent AE is an AE that is present at the conclusion of a clinical investigation per IS 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 13.5.

13.4 Supportive Characterization of Ocular Adverse Events

Additional supportive characterizations of ocular adverse events will be assessed by the investigator according to the terms and definitions in Section 18, Appendices, Table 18-1. This table is a modified version of the "The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses" (Masket, 2017).

13.5 Secondary Surgical Interventions (SSI)

Secondary Surgical Interventions reporting will be sub-categorized using the following terminology: exchange, removal, and repositioning. Indications and associated definitions for these outcomes are provided in Section 18, Appendices, Table 18-2 (Masket, 2017).

13.6 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. 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
- Suspect product contamination

- Lack of effectiveness

13.7 Monitoring for Adverse Events

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

- "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 ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the subject's responses to any questionnaire utilized 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 and will be distinguished between protocol defined AEs and questionnaire related AEs.

13.8 Procedures for Recording and Reporting

AEs 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 ICF 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 resolve within a week post-operatively and do not result in any untoward long-term visual outcome impact as clinically assessed by the investigator.

For each recorded event, the ADEs and SAEs documentation must include: 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 and control 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:

- **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, should be faxed to the Study Sponsor at 1-817-302-1927.**
- **UADEs and USADEs must be reported to the Sponsor and to the IRB as soon as possible, but not later than 10 working days after the Investigator's or site's awareness (§812.150(a)(1)).**
- **The Sponsor must immediately conduct an evaluation of UADEs and USADEs and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).**

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 1-817-302-1927 or FTW.medical_safety@alcon.com 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.

Any AEs and device deficiencies for non-study marketed devices/products (i.e. BSS, OVD, Delivery systems etc.) 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 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.

13.8.1 Intensity and Causality Assessments

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:

13.8.1.1 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.

13.8.1.2 Causality

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

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 test procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or test 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).

13.9 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 should be returned and must include the Complaint # that will be provided by the Study Sponsor after the case is entered in the Study Sponsor's Global Product Complaint System (GPCMS).

13.10 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate Study Sponsor representative prior to unmasking the information if there is sufficient time. Depending upon the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the Study Sponsor. The Study Sponsor must be informed in all cases in which the code was broken and of the circumstances involved. Additionally, the Study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

13.11 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 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. 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).

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

13.12 Pregnancy in the Clinical Study

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.

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 determine the 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 European Union (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 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.

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.

14.7 Publication of the Clinical Trial

Any information other than that which is disclosed upon registration should not be discussed with persons outside the study. The protocol, study data, and information related to the study or to Alcon's products or research programs that is provided by Alcon (Confidential Information) are to be kept confidential, and not disclosed directly or indirectly to any third party other than those involved in the study who has a need to know.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Alcon, Inc. Alcon reserves the right of prior review of any publication or presentation of information related to the study. Alcon may use these data now and in the future for presentation or publication at Alcon's discretion or for submission to government regulatory agencies.

The foregoing obligations of confidence and non-use assumed by an Investigator or member of the Investigator's team shall not apply to: (a) information that at the time of disclosure is in the public domain; (b) information that thereafter lawfully becomes part of the public domain other than through disclosure by or through the Investigator or a member of the Investigator's team; (c) information that, as evidenced by an individual's written records, was known to this individual prior to Alcon's disclosure; (d) information that is lawfully disclosed to by a third party not under any obligation of confidence to Alcon; or (e) information that is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Alcon.

In signing this protocol, the Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this Statement shall survive the completion of the study.

15 ANALYSIS PLAN

15.1 Subject Evaluability

The final subject evaluability will be determined using the Deviations and Evaluability Plan (DEP) prior to breaking the code for masked treatment assignment and locking the database.

15.2 Analysis Data Sets

The primary analysis set for effectiveness analyses will be the all-implanted analysis set (AAS). AAS includes all randomized eyes with successful IOL implantation.

Additional supportive analyses will be conducted using the best-case analysis set (BAS). BAS includes all eyes successfully implanted that had

- at least 1 postoperative visit
- no preoperative ocular pathology
- no macular degeneration detected at any time
- no previous surgery for the correction of refractive errors
- no major protocol violation

The Safety Analysis Set will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye).

15.3 Demographics and Baseline Characteristics

Summary statistics will be provided for demographic and baseline characteristics by IOL 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.

15.4 Performance Analyses

A success on co-primary effectiveness endpoints would be indicated by successful outcomes on all 4 of these endpoints (2 hypothesis tests and 2 performance targets). A total of 4 hypothesis tests will be conducted to address the primary and secondary effectiveness objectives of the study. Overall Type I error will be maintained at the 5% level using a sequential testing approach.

Hypothesis tests on secondary effectiveness endpoints will be conducted only after successful outcomes on all 4 co-primary effectiveness endpoints are demonstrated.

Analyses on performance targets are based on point estimates.

Only the first eye of each subject will be included in the primary statistical analysis (as described in IS EN ISO 11979-7:2014).

15.4.1 Primary Performance

The co-primary effectiveness endpoints are:

- Monocular distance corrected intermediate visual acuity (DCIVA) at 66 cm
- Monocular best corrected distance visual acuity (BCDVA)
- Monocular depth of focus assessed by the mean defocus curve evaluation
- Percentage of eyes achieving monocular distance corrected intermediate visual acuity (DCIVA) of 0.2 logMAR or better at 66 cm

15.4.1.1 Statistical Hypotheses

The statistical hypotheses in support of the primary effectiveness objectives are:

- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected intermediate visual acuity (66 cm from spectacle plane) at Visit 4A (120-180d postoperative)

The null and alternative hypotheses for the first co-primary analysis are:

$$H_0: \mu_{DFT015VA} \geq \mu_{SN60WFVA}$$
$$H_A: \mu_{DFT015VA} < \mu_{SN60WFVA}$$

where $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic DCIVA at 66 cm for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

- ACRYSOF IQ EDF IOL is non-inferior compared to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic best corrected distance visual acuity at Visit 4A (120-180d postoperative). The non-inferiority margin will be 0.1 logMAR.

The null and alternative hypotheses for the second co-primary endpoint are:

$$H_0: \mu_{DFT015VA} - \mu_{SN60WFVA} \geq \Delta$$
$$H_A: \mu_{DFT015VA} - \mu_{SN60WFVA} < \Delta$$

where Δ refers to the non-inferiority margin, set at 0.10 logMAR, and $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic BCDVA for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

Two performance targets in support of the primary effectiveness objectives are:

- Monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR at Visit 4A (120-180d postoperative).
- ACRYSOF IQ EDF IOL has at least 50% of eyes achieving monocular photopic distance corrected intermediate vision of 0.2 logMAR or better at Visit 4A (120-180d postoperative).

15.4.1.2 Analysis Methods

Analysis of the first primary effectiveness endpoint (DCIVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Analysis of the second primary effectiveness endpoint (BCDVA) will be based on a two-sample t-test, with a type I error rate of 5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated one-sided 95% upper confidence limit will be presented.

Data poolability will be analyzed by testing a treatment by site interaction effect: first, the interaction effect between treatment and site will be tested using an alpha of 0.15; second, if the interaction effect is found significant, the final analysis model will include site as a random effect.

For the first performance target (depth of focus), the line plot of the average visual acuity at each defocus level (ie, defocus curve) will be used to estimate the negative lens induced depth of focus at 0.2 logMAR. The difference in the depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ Monofocal IOL will be presented. The following sensitivity analyses will be performed on the depth of focus endpoint:

- Exclude extreme outliers (individual depth of focus values less than Q1 – 3*IQR or greater than Q3 + 3*IQR)

- Exclude mild outliers (individual depth of focus values less than Q1 – 1.5*IQR or greater than Q3 + 1.5*IQR), where Q1 = 25th percentile, Q3= 75th percentile, and IQR = Q3 – Q1.

The depth of focus data will be presented by IOL group, 3 photopic pupil size ranges [<3.0 mm (small), ≥3.0 mm to ≤4.0 mm (medium), and >4.0 mm (large)] and three axial length ranges [<21.0 mm (short), ≥21.0 mm to ≤26.0 mm (medium), and >26.0 mm (long)]. Descriptive summary statistics (number of eyes, mean, median, standard deviation, minimum, and maximum) on individual depth of focus value will be presented by IOL group.

For the second performance target (DCIVA), the percentage of eyes achieving distance corrected intermediate visual acuity of 0.2 logMAR or better in each IOL group will be presented.

15.4.2 Secondary Performance

The secondary effectiveness endpoints are:

- Monocular distance corrected near visual acuity at 40 cm
- Proportion of subjects who respond “Never” to Q1 of the IOLSAT questionnaire: “Overall, in the past 7 days, how often did you need to wear eyeglasses to see?”
- Monocular uncorrected intermediate visual acuity at 66 cm
- Monocular uncorrected distance visual acuity

15.4.2.1 Statistical Hypotheses

The statistical hypothesis in support of the first secondary effectiveness objective is:

- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected near visual acuity (40 cm from spectacle plane) at Visit 4A (120-180d postoperative)

The null and alternative hypotheses for the first secondary analysis are:

$$H_0: \mu_{DFT015VA} \geq \mu_{SN60WFVA}$$
$$H_A: \mu_{DFT015VA} < \mu_{SN60WFVA}$$

where $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic DCNVA at 40 cm for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

The statistical hypothesis in support of the second secondary effectiveness objective is:

- ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?) at Visit 4A (120-180d postoperative).

The null and alternative hypotheses for the second secondary analysis are:

$$H_0: \pi_{DFT015Q1} \leq \pi_{SN60WFQ1}$$
$$H_A: \pi_{DFT015Q1} > \pi_{SN60WFQ1}$$

where $\pi_{DFT015Q1}$ and $\pi_{SN60WFQ1}$ refer to the proportion of subjects who responded "Never" for the test and control lenses.

There are no hypothesis tests associated with the third and the fourth secondary effectiveness endpoints (UCIVA and UCDVA, respectively).

15.4.2.2 Analysis Methods

Analysis of first secondary effectiveness endpoint (DCNVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Two performance targets in support of the first secondary effectiveness objective are:

- At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better
- The percentage of eyes with DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group.

For the first performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group will be presented and compared against the performance target of 50%. For the second performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in each IOL group will be presented and the difference between the IOL groups (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) will be compared against the performance target of 25%.

A success on the first secondary effectiveness endpoint will be indicated by successful outcomes on the hypothesis test and two performance targets. A hypothesis test on the second secondary effectiveness endpoint will be conducted only after successful outcomes on the first secondary endpoint are demonstrated.

For the second secondary effectiveness endpoint, a two-sided 95% confidence interval for the difference in proportions (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) will be calculated using the Miettinen-Nurminen method (1985), and ACRYSOF IQ EDF IOL will be determined to be superior to ACRYSOF IQ Monofocal IOL if the lower boundary of the confidence interval is greater than zero. This is equivalent to using a type I error rate of 2.5%, 1-sided.

If IOLSAT questionnaire generates scores, the cumulative distribution curves showing the percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful.

In addition, the frequencies of each item in IOLSAT will be summarized by visit with counts and percentages.

For the third and the fourth secondary effectiveness endpoints (UCIVA and UCDVA, respectively), the following descriptive statistics will be provided for each IOL group:

- 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
- Descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum and (two-sided) 95% confidence interval will be presented for overall, by preoperative corneal cylinder (≤ 0.5 D vs. > 0.5 D), and by residual corneal cylinder (≤ 0.5 D vs. > 0.5 D).

In addition, the difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

First implanted eyes and second implanted eyes assessments will be in separate tables.

[redacted]

Visual Acuity Endpoints

In general, for visual acuity endpoints, the following descriptive statistics will be provided for each IOL group:

- 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
- Descriptive statistics including sample size, mean, median, standard deviation, number of eyes, minimum, maximum and the confidence interval will be presented.

Additionally, these descriptive statistics will be provided for the first two co-primary and the first secondary visual acuity endpoints, for first eye and second eye, by age categories (<65 years vs. ≥65 years), by investigative site, by adverse event (study eyes with ocular adverse events vs. study eyes without ocular adverse events) and by preoperative ocular pathology (study eyes with vs. study eyes without) for both the AAS and BAS. Listings of these visual acuity endpoints at every visit for each eye will also be provided.

In addition, the difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

First implanted eyes, second implanted eyes [redacted] will be in separate tables.

Defocus curve evaluation at Visit 4A (120-180d postoperative)

Descriptive statistics (mean, median, standard deviation, number of eyes/subjects, minimum, maximum, and two-sided 95% confidence intervals) will be provided for the logMAR VA measured on the ETDRS chart at each defocus level for all eyes/subjects. The mean logMAR VA measured on the ETDRS chart at each defocus value will be displayed graphically for all eyes/subjects, separately for first implanted eye, second implanted eye and binocular assessments. Mean logMAR visual acuity will be plotted versus defocus value, including two-sided 95% confidence intervals and standard deviations, with the amount of defocus along the x-axis and logMAR VA at each defocus point along the y-axis. The defocus tables and plots will be generated overall and by site.

In addition, monocular defocus curves for the first implanted eye and second implanted eye will be presented, by treatment group, for the following photopic pupil ranges: [<3.0 mm (small), ≥3.0 mm to ≤4.0 mm (medium), and >4.0 mm (large)] and three axial length ranges [<21.0 mm (short), ≥21.0 mm to ≤26.0 mm (medium), and >26.0 mm (long)].

Manifest refraction

Descriptive statistics (number of eyes, mean, median, standard deviation, minimum, and maximum) on manifest refraction spherical equivalent (MRSE= sphere + ½ cylinder) will be provided by IOL group.

First implanted eyes and second implanted eyes will be in separate tables.

[redacted]

15.5 Handling of Missing Data

The AAS and BAS do not include any imputed values. Although missing data will occur, the influence of missing data is expected to be minimal. The following sensitivity analyses will be conducted to address missing values for the first two co-primary effectiveness endpoints and first secondary effectiveness endpoint.

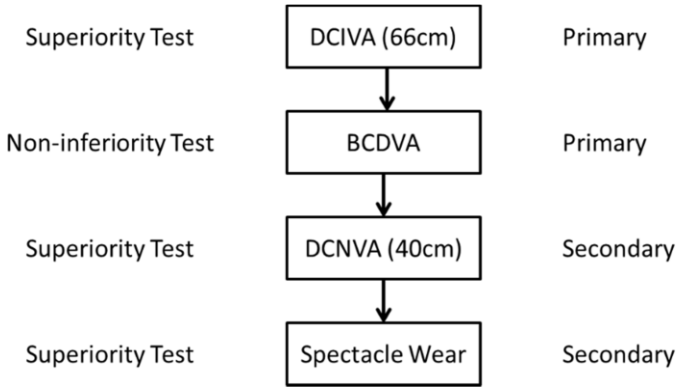
1. Multiple imputation with a fully conditional specification method will be used to impute and estimate the treatment effect.

2. The sensitivity of inferences to departures from the MAR assumption will be examined using a pattern-mixture model approach with a control-based pattern imputation (Ratitch 2011).

The details will be described in the Statistical Analysis Plan.

15.6 Multiplicity

Overall type I error will be maintained at 5% level using the sequential testing approach summarized in the figure below.



15.7 Safety Analysis

15.7.1 Primary Safety

Co-primary safety endpoints are adverse events and monocular mesopic contrast sensitivity (with and without glare).

15.7.1.1 Adverse Events

Descriptive summaries (counts and percentages) for specific AEs including SSIs will be presented by IOL group. The one-sided exact 95% lower confidence limit of incidence rates (proportion of eyes with events) observed for each IOL group will be compared to the cumulative and persistent adverse event SPE rates. In addition to SPE rates predefined in IS EN ISO 11979-7, the rate of adverse events that may be specifically related to ACRYSOF IQ EDF IOL design features; and any other significant events will be provided. These rates will be accompanied by two-sided exact 95% confidence intervals.

The number and percentage of all adverse events will be tabulated with a breakdown by IOL group and implanted eye. A listing of all adverse events will also be provided.

The number and percentage of secondary surgical interventions (SSIs) that may be related to optical characteristics of the lens will be tabulated with a breakdown by IOL group and implanted eye.

15.7.1.2 Mesopic contrast sensitivity (with and without glare)

All measured contrast sensitivity values will be converted to logarithmic form before performing statistical calculations. Analyses of log contrast sensitivity will be performed for each testing condition and spatial frequency. If a subject is unable to see a targeted spatial frequency at any available contrast (including the contrast of the reference patch), the lowest contrast score will be given, preceded by the appropriate inequality symbol (<) to indicate that the actual sensitivity is below the given value. Prior to any averaging or other statistical calculations, all contrast threshold values will be converted to log contrast sensitivity values. The number and percentage of subjects who cannot see any contrast will be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive statistics will include number of eyes, mean, standard deviation, median, minimum, maximum, and additional percentiles (10th, 25th, 75th, and 90th percentiles). Descriptive tables will include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols). The 5th percentile of log contrast sensitivity values will be calculated for the control group, then the percentage of eyes in the test group that achieved a log contrast sensitivity lower than this value will be presented.

In addition, for mesopic contrast sensitivity, descriptive summary statistics will be presented by IOL group and 3 mesopic pupil size ranges: <3.0 mm (small), ≥3.0 mm to ≤4.0 mm (medium), and >4.0 mm (large).

15.7.2 Secondary Safety

Secondary safety endpoint is:

- Rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire

For the secondary safety endpoint, descriptive summaries (counts and percentages) for the severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented by IOL group. These rates will be accompanied by two-sided exact 95% confidence intervals.

If QUVID questionnaire generates scores, the cumulative distribution curves showing the percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful.

Counts and percentages of subjects who did not have a given visual disturbance at baseline but developed and present at Visit 4A (120-180d postoperative) will be presented.

In addition, the presence and absence of these symptoms, and how frequent, severe, and bothersome they appear will be summarized by visit with counts and percentages.

15.7.3 Supportive Safety

Intraocular pressure

Descriptive statistics (mean, median, SD, number of eyes, minimum, and maximum) will be presented for IOP by IOL group and implanted eye. A listing of all eyes with an increase or decrease in IOP of more than 10 mmHg at any visit compared to the same eye at baseline will also be provided.

Slit-lamp examination

The number and percentage of all slit lamp examination findings will be tabulated by IOL group and implanted eye. A listing of abnormal slit lamp examination findings will also be provided.

Dilated fundus exam

The number and percentage of all dilated fundus examination findings will be tabulated by IOL group and implanted eye. A listing of abnormal dilated fundus examination findings will also be provided.

IOL observations

The number and percentage of all IOL observations will be tabulated by IOL group and implanted eye.

IOL tilt/decentration

The number and percentage of all eyes with IOL tilt/decentration will be tabulated by IOL group and implanted eye. A listing of all IOL tilt/decentration assessments will also be provided.

Subjective posterior capsular opacification

The number and percentage of eyes within each category of subjective posterior capsule opacification will be tabulated by IOL group and implanted eye. A frequency table of the "worst case" posterior capsule opacification (including capsulotomy) will be presented by IOL group and implanted eye. In addition, the difference in the rate (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented. A listing of eyes with clinically significant posterior capsule opacification, clinically significant posterior capsule opacification requiring YAG or posterior capsulotomy will be presented.

Posterior capsulotomy

The number and percentage of eyes with PC will be tabulated by IOL group and implanted eye. In addition, the difference in the rate (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Surgical problems

The number and percentage of all surgical problems will be tabulated by IOL group and implanted eye. A listing of all surgical problems will also be provided.

Other procedures at surgery

A listing of all other procedures at surgery will be provided.

Device Deficiencies

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

15.8 Interim Analyses

Not Applicable.

15.9 Adaptive Study Design

Not Applicable.

[redacted]

16 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.

17 REFERENCES

Boettner EA, Wolter JR. Transmission of the ocular media. Invest Ophthalmol. 1962;1:776-83.

ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice.

Draft ANSI Z80.35 Extended Depth of Focus Intraocular Lenses, 2016 July.

Masket S, Rorer E, Stark W, Holladay JT, MacRae S, Tarver ME, et al. Special Report: The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses. Ophthalmology. 2017; 124(1):142-144.

MacRae S, Holladay JT, Glasser A, Calogero D, Hilmantel G, Masket S, et al. Special report: American Academy of Ophthalmology Task Force consensus statement for extended depth of focus intraocular lenses. Ophthalmology. 2017; 124(1):139-141.

McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. Mosby-Year Book; 1989.

IS EN ISO 11979-7:2014 Ophthalmic implants – Intraocular lenses – Part 7: Clinical investigations.

Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop.Am J Ophthalmol. 2005; 140(3):509–516.

Ratitch B, O'Kelly M. Implementation of pattern-mixture models using standard SAS/STAT procedures. Proceedings of PharmaSUG; 2011 May 8-11; Nashville, TN.

Retzlaff JA, Sanders DR, Kraff MC. Development of SRK/T intraocular lens implant power calculation formula. J. Cataract Refract Surg. 1990;16(3):333-40.

Simpson MJ, Charman WN. The effect of testing distance on intraocular lens power calculation. J Refract Surg. 2014;30(11):726..

Optical Design of Toric Extended Depth of Field IOL. Fort Worth (TX): Alcon Research, Ltd.; 2013 June. Technical Report No.: TDOC-0016353,

Miettinen OS and Nurminen M. (1985). Comparative analysis of two rates. *Statistics in Medicine*, 4:213-226.

18 APPENDICES

18.1 Adverse Event Tables

Below are the tables referred to in Section 13 DEVICE DEFICIENCIES AND ADVERSE EVENTS.

Table 18–1 Additional Supportive Characterizations of Ocular Adverse Events

Adverse Event	Definition
Anterior uveitis	Anterior segment inflammation characterized by grade 1+ cell or greater using SUN criteria that is persistent for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation. (Note that any iritis present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event.).
Clinically significant cystoid macular edema	Macular edema diagnosed by clinical examination and adjunct testing (e.g., OCT, FA) resulting in BCDVA of ≤ 20/40 at ≥1 month
Visually significant corneal edema	Corneal swelling (stromal or epithelial) resulting in CDVA of 20/40 or worse at Form 3 (Visit 3A) or later. (Note that any corneal stromal edema present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event.).
Endophthalmitis	Intraocular inflammation requiring diagnostic vitreous tap and intraocular antibiotics
Mechanical pupillary block	Shallowing of anterior chamber due to obstruction of aqueous humor flow from the posterior to anterior chamber through the pupil by the crystalline lens, vitreous face, or implanted device
Increased IOP	Elevation of IOP by ≥10 mmHg above baseline to a minimum of 25 mmHg. (Note that any "raised IOP requiring treatment" present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event.).
Rhegmatogenous RD	Partial or complete RD associated with retinal tear
Toxic anterior segment syndrome	Acute, noninfectious inflammation of the anterior segment that starts within 24 to 48 hrs after surgery, usually resulting in hypopyon and commonly presenting with corneal edema, that improves with steroid treatment
Secondary IOL intervention	
Exchange	The investigational device is replaced with the same lens model
Removal	The investigational device is removed and replaced with a non-investigational lens or no lens is implanted
Reposition	The existing IOL is surgically moved to another location or rotated

CDVA = corrected distance visual acuity; FA = fluorescein angiography; IOL = intraocular lens; IOP = intraocular pressure; OCT = optical coherence tomography; RD = retinal detachment; SUN = Standardization of Uveitis Nomenclature

Table 18-2 Definitions of Indications for Device Exchange, Removal, or Reposition

Indication	Definition
Capsular block syndrome	Hyper-distention of the lens capsular bag due to the IOL optic blocking egress of fluid through the anterior capsulotomy typically inducing a myopic refractive error
Cataract	Any opacification of the crystalline lens with or without reduced visual acuity
Chronic anterior uveitis	Persistent anterior segment inflammation characterized by grade ≥1+ cell using SUN criteria
Endothelial cell loss	Chronic endothelial cell loss at a rate greater than that due to normal aging
Incorrect IOL power	Postoperative refractive error different from predicted and not due to a calculation or other user error
Iris pigment epithelium loss	New or worsening iris transillumination defects or increase in pigmented cells in the anterior chamber noted after the 1-wk visit when assessed before instillation of any dilating drops Note: If there is a transillumination defect preoperatively, then a photograph should be taken, and then at each subsequent visit, a photograph should be taken and compared with the preoperative photograph via a standardized photographic method
Lens optic abnormality	Unanticipated visual outcome (e.g., acuity, contrast sensitivity, symptoms) associated with opacification, vacuoles, microvacuoles, or subsurface nanoglistenings and not due to other causes
Malpositioned IOL	Decentration, tilt, or rotation of IOL requiring reoperation
Early	If noted before 120 days postoperatively
Late	If noted at ≥120 days postoperatively
Damaged IOL	Crack of lens optic, breakage, or deformity of haptic, or other damage to the IOL; may include changes induced by Nd:YAG laser anterior or posterior capsulotomy
Pupil ovalization	Progressive deformation of the pupil with elongation of the pupil in the meridian of the long axis of the IOL Documentation to be made under photopic conditions NOTE: A consensus statement regarding a proposed methodology for standardizing assessment of pupil ovalization is available (Appendix 1, Masket 2017).
Pain	Graded as ≥4 on the standardized pain numeric rating scale of current pain intensity from 0 (no pain) to 10 (worst possible pain) Refer to the MOP for the standardized numeric pain scale (McCaffery 1989).
Peripheral anterior synechiae	Progressive closure of the anterior chamber angle due to propagation of anterior synechiae in the absence of obvious anterior uveitis
Patient-reported undesirable optical phenomena	Dysphotopsia (positive or negative or both), monocular diplopia, intolerable glare, halos, or other visual symptoms, not due to 1 of the indications listed

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