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Short Title

A Clinical Study of the ACRYSOF® IQ EDF IOL

Long Title

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

Protocol Number:	ILI875-C001 / NCT03010254
Study Phase:	Not applicable
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	ACRYSOF IQ Extended Depth of Focus IOL
US IND#/ IDE#/ EudraCT:	Not applicable
Investigator Agreement:	I have read the clinical study described, herein, recognize its confidentiality. I agree to conduct this study in accordance with the ethical principles contained within the Declaration of Helsinki, and the described study in compliance with the protocol, Good Clinical Practices (GCP), ISO 14155, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Study Sponsor.

Principal Investigator

Signature Date

Name

Address

TABLE OF CONTENTS

TABLE OF CONTENTS 2
List of Tables 5
List of Figures 5
1 GLOSSARY OF TERMS 6
2 ABBREVIATIONS 9
3 PROTOCOL SUMMARY 11
4 PROTOCOL AMENDMENTS 19
4.1 Amendment 1 (Version 2.0) 19
4.2 Amendment 2 (Version 3.0) 20
4.3 Amendment 3 (Version 4.0) 22
5 SCHEDULE OF PROCEDURES AND ASSESSMENTS 24
6 INTRODUCTION 26
6.1 Rationale and Background 26
6.2 Purpose of the Study 27
6.3 Risks and Benefits 27
6.3.1 Known and Potential Risks 27
6.3.2 Potential Benefits 28
7 STUDY OBJECTIVES 29
7.1 Primary Objective 29
7.1.1 Primary Effectiveness Assessment 29
7.2 Secondary Objectives 29
7.2.1 Secondary Effectiveness Assessments 29
[redacted]
7.4 Primary Safety Objective 30
7.4.1 Primary Safety Assessment 30
[redacted]
8 INVESTIGATIONAL PLAN 31
8.1 Study Design 31
8.2 Rationale for Study Design 32
8.3 Rationale for Choice of Control Article 33

8.4 Data Monitoring Committee 33
9 SUBJECT POPULATION....33
9.1 Inclusion Criteria....34
9.2 Exclusion Criteria....34
9.3 Reasons for Discontinuation (During Surgery)....35
9.4 Rescreening of Subjects 36
10 TREATMENT 36
10.1 Other Medical Device Specified for Use during the Study....40
10.2 Treatment Assignment / Randomization 40
10.3 Accountability Procedures 41
10.4 Treatment Masking....41
10.5 Changes to Concomitant Treatments or Procedures 42
11 STUDY PROCEDURES AND ASSESSMENTS BY VISIT 43
11.1 Screening/Preoperative Visit (Visit 0)....43
11.2 Operative Visits (Visit 00/00A)....45
11.3 1-Day Postoperative Visit (Visit 1/1A) 46
11.4 1-Week Postoperative Visit (Visit 2/2A) 47
11.5 1-Month Postoperative Visit (Visit 3A)....47
11.6 3-Month Postoperative Visit (Visit 4A)....48
11.7 6-Month Postoperative Visit (Visit 5A)....50
11.8 Schedule of Procedures and Assessments for Discontinued Subjects....52
11.9 Informed Consent and Screening 54
11.10 Unscheduled Visits....54
11.11 Discontinued Subjects....55
11.11.1 Screen Failures 55
11.11.2 Discontinuations....55
11.12 Clinical Study Termination 56
11.13 Aborted Implantation 56
11.13.1 First Eye Implant....57
11.13.2 Second Eye Implant....57
12 DEVICE DEFICIENCIES AND ADVERSE EVENTS....58
12.1 General Information 58
12.2 Serious Adverse Events (SAEs) 59

12.3 Specific Events Relevant to this Protocol 60
12.3.1 Cumulative Serious Adverse Events 60
12.3.2 Persistent Serious Adverse Events 60
12.3.3 Device Deficiencies 61
12.4 Monitoring for Adverse Events 61
12.5 Procedures for Recording and Reporting 62
12.5.1 Intensity and Causality Assessments 63
12.5.1.1 Intensity (Severity) 63
12.5.1.2 Causality 63
12.6 Return Product Analysis 64
12.7 Unmasking of the Study Treatment 64
12.8 Follow-Up of Subjects with Adverse Events 64
12.9 Pregnancy in the Clinical Study 65
13 ANALYSIS PLAN 65
13.1 Subject Evaluability 65
13.2 Analysis Data Sets 65
13.3 Demographics and Baseline Characteristics 66
13.4 Effectiveness Analyses 66
13.4.1 Analysis of Primary Effectiveness Endpoint 66
13.4.1.1 Statistical Hypotheses 66
13.4.1.2 Analysis Methods 66
13.4.2 Analysis of Secondary Effectiveness Endpoints 67
13.4.2.1 Statistical Hypotheses 67
13.4.2.2 Analysis Methods 68
[redacted] 70
13.5 Handling of Missing Data 70
13.6 Multiplicity 70
13.7 Safety Analysis 71
13.8 Health Economics 73
13.9 Interim Analyses 73
13.10 Non-inferiority Margin 73
13.11 Sample Size Justification 73
14 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS 74

14.1 Subject Confidentiality....74
14.2 Completion of Source Documents and Case Report Forms....75
14.3 Data Review and Clarifications....76
14.4 Sponsor and Monitoring Responsibilities....76
14.5 Regulatory Documentation and Records Retention....77
14.6 Quality Assurance and Quality Control....77
15 ETHICS....78
16 REFERENCES....80

List of Tables

Table 10–1 Test Article....36
Table 10–2 Control Article....38
Table 10–3 Delivery System....40
Table 10-4 Unmasked Individuals....42
Table 11–1 Contact Lens Discontinuation Prior to Preoperative Visit....43

List of Figures

Figure 8–1 Study Design....32
Figure 12–1 Categorization of All Adverse Events....58
Figure 12-2 Categorization of All Serious Adverse Events....59

1 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 informed consent form (ICF).
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in health that either resulted in: a) a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* b) any potentially sight-threatening event or permanent impairment to a body structure or a body function. c) in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.*

	d) a medical or surgical intervention to prevent a) or b), or any ocular secondary surgical intervention excluding posterior capsulotomy. e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 12 for additional SAEs.*
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk management file.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 ABBREVIATIONS

Abbreviation	Definition
AAS	All-implanted analysis set
ADE	Adverse device effect
AE	Adverse event
[redacted]	[redacted]
ARMD	Age-related macular degeneration
ASADE	Anticipated serious adverse device effect
BAS	Best-case analysis set
BCDVA	Best corrected distance visual acuity
CI	Coordinating Investigator
D	Diopter
DCIVA	Distance corrected intermediate visual acuity
DCNVA	Distance corrected near visual acuity
DEP	Deviations and Evaluability Plan
DoH	Declaration of Helsinki
DFU	Directions for use
eCRF	Electronic case report form
EDC	Electronic data capture
EDF	Extended depth of focus
EU	European Union
FLACS	Femtosecond laser-assisted cataract surgery
GCP	Good Clinical Practice
GPCMS	Global Product Complaint System
HA	Health Authority
IA	Interim analysis
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IOL	Intraocular lens
[redacted]	[redacted]
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
ISO	International Organization for Standardization
LASIK	Laser-assisted in situ keratomileusis
LRI	Limbal relaxing incision
MOP	Manual of procedures
OD	Right eye
OS	Left eye
OVD	Ophthalmic viscosurgical devices
[redacted]	[redacted]
[redacted]	[redacted]

SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedures
SPE	Safety performance endpoint
SSI	Secondary surgical intervention
TPS	Trapezoidal phase shift
[redacted]	[redacted]
UNSV	Unscheduled visit
US	United States
USADE	Unanticipated serious adverse device effect
VA	Visual acuity
YAG	Yttrium aluminum garnet

3 PROTOCOL SUMMARY

Investigation Type	Device
Study Type	Interventional
Investigational Product	• ACRYSOF IQ Extended Depth of Focus (EDF) Intraocular Lens (IOL) (Model DFT015) • ACRYSOF IQ Monofocal IOL (Model SN60WF)
Purpose and Rationale	The purpose of the study is to demonstrate the safety and performance of the ACRYSOF IQ EDF IOL at Month 3/Visit 4A (70-100 day post 2nd eye implantation). After all subjects complete Month 3 (Visit 4A), the study database will be locked to conduct planned analyses. Results from these analyses will be used in a clinical study report for submission. The study will be continued until all subjects complete Month 6 (Visit 5A), at which time the study database will be locked to report longer term safety and performance results.
Primary Objective	• To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic distance-corrected intermediate visual acuity (DCIVA) (at 66 cm from spectacle plane) at Month 3/Visit 4A.
Endpoint(s) and assessments related to Primary Objective(s)	• Monocular photopic DCIVA (logMAR) at 66 cm
Secondary Objectives	• To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic best corrected distance visual acuity at Month 3/Visit 4A. • To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic distance corrected near visual acuity (DCNVA) (at 40 cm from spectacle plane) at Month 3/Visit 4A.

	• To demonstrate that mean monocular defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.50 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.20 logMAR (20/32 line) at Month 3/Visit 4A. • To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular mesopic contrast sensitivity with and without glare at Month 6/Visit 5A respectively. • To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire at Month 6/Visit 5A respectively.
Endpoint(s) and Assessments Related to Secondary Objective(s)	• Monocular photopic BCDVA (logMAR) at 4 m • Monocular photopic DCNVA (logMAR) 40 cm • Monocular photopic distance-corrected depth of focus assessed by the mean defocus curve • Monocular mesopic contrast sensitivity at 12 cycles per degree with and without glare respectively • Proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire respectively
Primary Safety Objective	To demonstrate that the adverse event rates of ACRYSOF IQ EDF IOL are not worse than Safety Performance Endpoint (SPE) rates as defined in IS EN ISO 11979-7:2014 at Month 3/Visit 4A.
Assessments related to Primary Safety Objective	• Adverse event rates of ACRYSOF IQ EDF IOL
Study Design	Prospective, randomized, parallel group, multi-center study; assessor and subject masked; total duration of a subject's participation is approximately 7.5 months.
Subject Population	Adults (22 years and older) with cataract in both eyes requiring surgery with implantation of a monofocal IOL.
Key Inclusion Criteria	• Planned cataract removal by routine small incision surgery.

(See Section 9.1 for a complete list of inclusion criteria)	• Calculated IOL power is within the clinical study supply range (18.0-25.0 D in 0.5 D steps). • Preoperative regular astigmatism of less than 1.0 D.
Key Exclusion Criteria (See Section 9.2 for a complete list of inclusion criteria)	• Pregnancy or lactation current or planned during the course of the study. • History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology including retinal vascular occlusive disease, retinal detachment or peripheral retinal laser photocoagulation, ARMD, glaucoma (uncontrolled or controlled with medication) or ocular hypertension, diabetic retinopathy, retinitis pigmentosa and any optic nerve pathology. • Any current anterior or posterior segment inflammation of any etiology, and/or history of any disease producing an intraocular inflammatory reaction. • Clinically significant corneal pathology (epithelial, stromal, and/or endothelial) which would adversely affect the visual outcome based on Investigator expert medical opinion. • Clinically significant severe dry eye that would affect study measurements based on Investigator expert medical opinion • History of previous intraocular or corneal (refractive or trauma related) surgery. • Current or history of amblyopia or monofixation syndrome. • Any other ocular or systemic co-morbidity that, based on Investigator expert medical opinion, may confound the results of this study or prohibit the completion of the study assessments or increase the risk for the subject.

	• Subjects with conditions that increase the risk of zonular rupture during cataract extraction procedure that may affect the postoperative centration or tilt of the IOL. • Any other planned ocular surgical procedures including but not limited to limbal relaxing incision (LRI)/Astigmatic Keratotomy and laser-assisted in situ keratomileusis (LASIK). • Patients who desire monovision correction.
Data Analysis and Sample Size Justification	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] The statistical hypothesis in support of the primary effectiveness objective is: • ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic DCIVA (66 cm from spectacle plane) at Month 3/Visit 4A (70-100 day post 2nd eye implantation) for the first implanted eye. [redacted] The statistical hypothesis in support of the secondary effectiveness objectives are: • ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic BCDVA (4m) at Month 3/Visit 4A (70-100 day post 2nd eye implantation) for the first implanted eye. [redacted] The non-inferiority margin will be 0.10 logMAR.

	• ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic DCNVA (40 cm from spectacle plane) at Month 3 / Visit 4A (70-100 day post-operative) for the first implanted eye. [redacted] • ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean mesopic contrast sensitivity with and without glare at Month 6 / Visit 5A (120-180 day post 2nd eye implantation) for the first implanted eye respectively. [redacted] The non-inferiority margin will be -0.15 log unit. • ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire at Month 6 / Visit 5A (120-180 day post 2nd eye implantation) respectively. Analysis of primary effectiveness endpoints will be based on a two-sample t-test. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated 95% (two-sided) confidence interval will be obtained. Analysis of first secondary effectiveness endpoint will be based on a two-sample t-test. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated one-sided 97.5% upper confidence limit will be obtained. Analysis of second secondary effectiveness endpoint will be based on a two-sample t-test. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated 95% (two-sided) confidence interval will be obtained. For the third secondary effectiveness objective (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 0.20 logMAR. The difference in

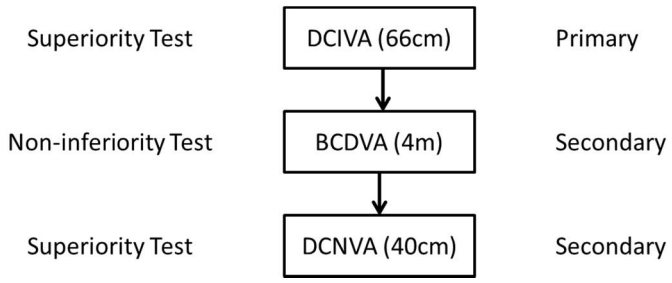
depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ Monofocal IOL will be presented.

Analysis of fourth secondary effectiveness endpoint will be based on a two-sample t-test. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated one-sided 97.5% lower confidence limit will be obtained.

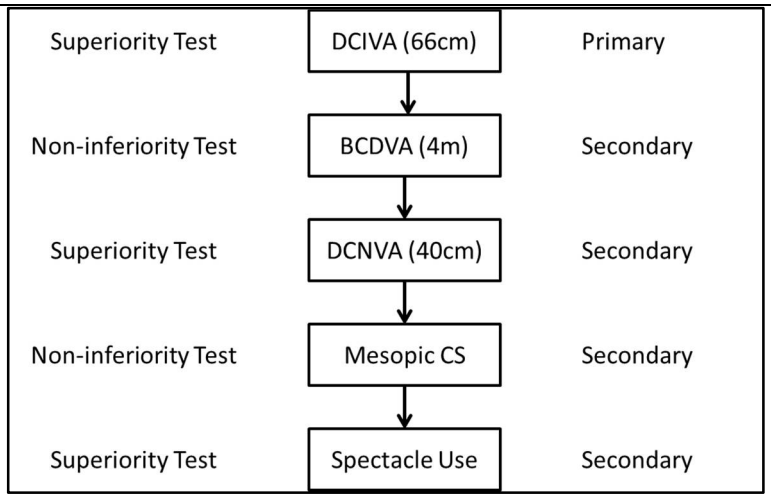
For the fifth secondary effectiveness endpoint, a two-sided 95% confidence interval for the difference in proportions (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) will be calculated using the Miettinen-Nurminen method (1985), and ACRYSOF IQ EDF IOL will be determined to be superior to ACRYSOF 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.

Descriptive statistics (mean, median, standard deviation, number of subjects/eyes, minimum, maximum, and (two-sided) 95% confidence interval) will be provided for effectiveness endpoints, separately for each eye (for monocular measures).

Overall type I error will be maintained at 0.05 level for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analyses using sequential testing approach summarized in the figure below.



The following primary and secondary effectiveness analyses will be performed on the Month 6/Visit 5A (120-180 day post 2nd eye implantation) data using the sequential testing approach summarized in the figure below if the primary and both secondary null hypotheses are rejected for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analysis.



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 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.

Sample Size Justification:

Effectiveness

The proposed sample size (N = 234; 130 Bilateral EDF IOL and 104 Bilateral Monofocal IOL) provides >99% power for the superiority hypothesis test on mean monocular DCIVA (66 cm) when tested at the 0.025 level of significance (one-sided). This assessment assumes:

- Difference in DCIVA (66 cm) [logMAR]: Mean (SD) = -0.12 (0.18)

The proposed sample size provides 81% power for the non-inferiority hypothesis with respect to mean monocular BCDVA (4 m) when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of 0.10 logMAR assuming:

	• Difference in BCDVA (4 m) [logMAR]: Mean (SD) = 0.04 (0.16) The proposed sample size provides >99% power for the superiority hypothesis test on mean monocular DCNVA (40 cm) when tested at the 0.025 level of significance (one-sided). This assessment assumes: • Difference in DCNVA (40 cm) [logMAR]: Mean (SD) = -0.12 (0.18) The proposed sample size provides 74% power for the non-inferiority hypothesis with respect to mean monocular mesopic contrast sensitivity value when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of -0.15 log unit assuming: • Difference in contrast sensitivity [log unit]: Mean (SD) = -0.02 (0.38) The expected sample size (N = 131) provides 84% power, with α=0.025, 1-sided, to detect a difference of 25% in proportion of subjects who respond “Never” to Q1 and Q3 of the spectacles use questionnaire respectively, assuming a 50% response rate in the ACRYSOF IQ EDF IOL group. Approximately 260 subjects will be randomized to achieve 234 subjects who complete the study. It is expected that approximately 131 subjects will respond to spectacle use questionnaire in this study. <u>Adverse Events</u> For any event where zero incidence is observed in130 operative eyes with ACRYSOF IQ EDF IOL, the one-sided exact 95% upper confidence limit is less than 2.3%. Thus, with 95% confidence the true adverse event rate is less than 2.3%.

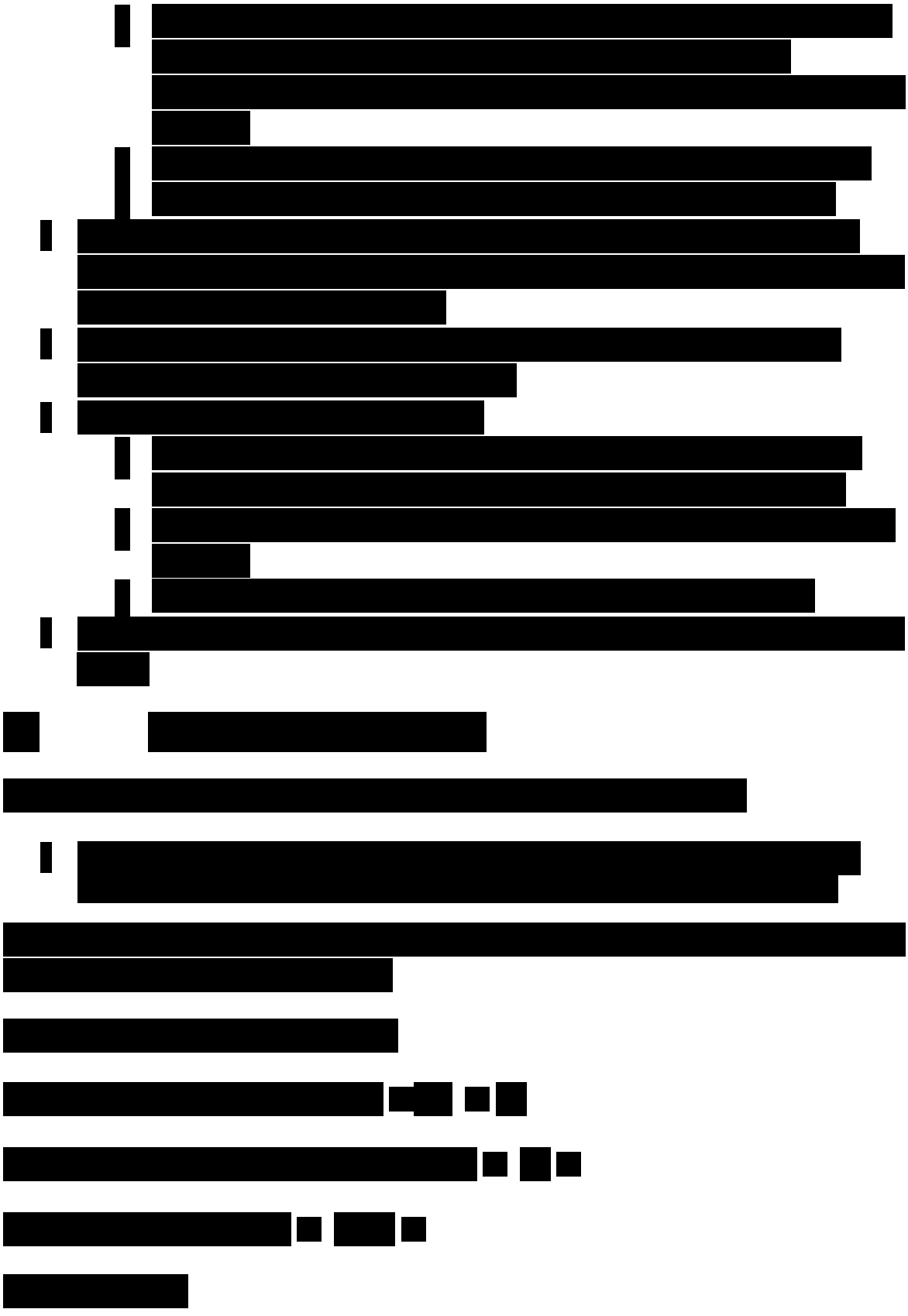
Key Words for Posting in Registries	Prospective, multi-center, randomized, parallel group, controlled, assessor and subject masked study; being conducted in approximately 4 countries outside the US.

4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the Study Sponsor and must be approved by an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

[redacted]

[redacted]



5 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Visit	Visit 0 Pre-Op	Visit 00 OP[1]	Visit 1	Visit 2	Visit 00A: OP[2]	Visit 1A	Visit 2A	Visit 3A	Visit 4A[3]	Visit 5A[3]	Early Exit
Eye	**Both Eyes**	**1st Eye**	**1st Eye**	**1st Eye**	**2nd Eye**	**2nd Eye**	**2nd Eye**	**Both Eyes**	**Both Eyes**	**Both Eyes**	
Day Number	**Day -28-0**	**Surgery**	**Day 1-2**	**Day 7-14**	**Surgery**	**Day 1-2**	**Day 7-14**	**Day 30-60**	**Day 70-100**	**Day 120-180**	**N/A**
Informed Consent	X										
Demographics	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X			X						
Urine Pregnancy Test[4]	X										
[redacted]	[redacted]										
[redacted]	X										
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]										[redacted]	[redacted]
Spectacle Use Questionnaire										X	X
Distance VA at 4 m											
• [redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Photopic corrected	X			X			X	X	X	X[5]	X
Intermediate VA at 66 cm											
• [redacted]								[redacted]	[redacted]	[redacted]	
• Photopic Distance Corrected								X	X	X[5]	
Near VA at 40 cm											
• [redacted]									[redacted]	[redacted]	
• Photopic Distance Corrected									X	X[5]	
Defocus Curve (4 m)									X[5]	X[5]	
Contrast Sensitivity											
• Mesopic without Glare									X	X[5]	
• Mesopic with Glare									X	X[5]	
[redacted]									[redacted]	[redacted]	
[redacted]											
[redacted]										[redacted]	
[redacted]										[redacted]	
[redacted]									[redacted]		
Target Residual Refractive Error[6]	X										
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	X							X	X	X	X
[redacted]								[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		X	X		X	X	X	X	X	X

Visit	Visit 0 Pre-Op	Visit 00 OP[1]	Visit 1	Visit 2	Visit 00A: OP[2]	Visit 1A	Visit 2A	Visit 3A	Visit 4A[3]	Visit 5A[3]	Early Exit
Eye	**Both Eyes**	**1st Eye**	**1st Eye**	**1st Eye**	**2nd Eye**	**2nd Eye**	**2nd Eye**	**Both Eyes**	**Both Eyes**	**Both Eyes**	
Day Number	**Day -28-0**	**Surgery**	**Day 1-2**	**Day 7-14**	**Surgery**	**Day 1-2**	**Day 7-14**	**Day 30-60**	**Day 70-100**	**Day 120-180**	**N/A**
Operative Eye		X			X						
[redacted]											
Incision Location[7]		X			X						
Final Incision Size[7]		X			X						
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Secondary Surgical Interventions		X	X	X	X	X	X	X	X	X	X
Device Deficiencies		X	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 after a minimum of 7 calendar days and a maximum of 28 calendar days after Visit 00 (1st eye surgery).

[3] If necessary Visits 4A and 5A may be completed over 2 days within a two week period. All visits must be completed within the specified visit window.

[4] In women of child bearing potential only.

[5] Monocular (bilaterally) [redacted]

[6] Data is reported in EDC at the surgical visit, but may be collected at a previous visit.

[7] Captured in source. Not collected in EDC.

6 INTRODUCTION

6.1 Rationale and Background

Depth of focus 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 depth of focus. Larger depth of focus allows sharp images of closer objects. A young, healthy human eye provides large depth of focus 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. Specifically, intermediate vision has become increasingly significant to subjects because of daily tasks related to computers, mobile devices and other technologic advances.

Premium IOL solutions, such as multifocal IOLs, provide functional intermediate 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 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 visual acuity (VA) and a safety profile similar to that of the ACRYSOF IQ Monofocal IOL Model SN60WF.

Extended depth of focus is achieved on the anterior surface through Trapezoidal Phase Shift (TPS) technology (TDOC-0016353, Optical Design of Toric Extended Depth of Field IOL). The TPS structure consists of two radial steps in an aspheric central zone that smoothly connects to an outer annular zone. The curvature of the outer annular zone is identical to anterior surface of the non-toric, base design for the ACRYSOF IQ Toric IOL which compensates the 0.2 micron spherical aberration from the cornea. The TPS structure widens the depth of focus by creating interfering wavefronts from the tops and bottoms of the two steps. The combination of the central TPS zone and the outer annular zone transfers enough distance contrast under photopic conditions to provide a continuous range of vision. The ACRYSOF IQ EDF IOL provides an additional benefit by not using diffractive structures that typically induce visual disturbances. The EDF behavior is pupil dynamic; under mesopic conditions when the pupil size increases, the extended depth of focus is reduced and the performance of the ACRYSOF IQ EDF IOL is similar to a monofocal IOL.

6.2 Purpose of the Study

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 Model SN60WF. The purpose of the study is to demonstrate the safety and performance of the ACRYSOF IQ EDF IOL at Month 3/Visit 4A. After all subjects complete Month 3/Visit 4A, the study database will be locked to conduct planned analyses. Results from these analyses will be used in a clinical study report for submission. The study will be continued until all subjects complete Month 6/Visit 5A, at which time the study database will be locked to report longer term safety and performance results.

6.3 Risks and Benefits

6.3.1 Known and Potential Risks

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.

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, etc.). 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.

Based on the above, the risk of unanticipated adverse device effects with use of this 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.

Refer to the Investigator's Brochure (IB) and Directions for Use (DFU) for additional information on the IOLs being used in this study.

6.3.2 Potential Benefits

The EDF design extends the depth of focus of a monofocal IOL to +1.5 D by introducing a two-step phase shift to the incoming wavefront through Alcon's proprietary technology, TPS. The EDF IOL provides benefits to the subject by:

- Extending the range of functional vision to intermediate distances (approximately 66 cm) while
- Maintaining the distance VA and safety profile similar to ACRYSOF IQ monofocal IOL (SN60WF) and
- Providing improved near vision in comparison to a monofocal IOL
- Eliminating the visual disturbances commonly associated with diffractive IOLs

The ACRYSOF IQ EDF IOL incorporates the TPS principle in the IOL optic and is designed to increase the subjective depth of focus and provide improved functional vision at intermediate distances. The anterior aspheric surface of the ACRYSOF IQ EDF IOL is designed with negative spherical aberration to compensate for the positive spherical aberration of the normal cornea. The magnitude of asphericity of the ACRYSOF IQ EDF IOL (Model DFT015) is identical to the CE Marked, Health Authority (HA)-approved (in applicable countries) and commercially available ACRYSOF IQ Monofocal IOL (Model SN60WF).

7 STUDY OBJECTIVES

7.1 Primary Objective

- To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCIVA (at 66 cm from spectacle plane) at Month 3/Visit 4A (70-100 day post 2nd eye implantation).

7.1.1 Primary Effectiveness Assessment

- Monocular photopic DCIVA (logMAR) at 66 cm

7.2 Secondary Objectives

- To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic BCDVA (at 4 m) at Month 3/Visit 4A.

- To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCNVA (at 40 cm from spectacle plane) at Month 3/Visit 4A.

- To demonstrate that mean monocular defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.50 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.20 logMAR (20/32 line) at Month 3/Visit 4A.

- To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean mesopic contrast sensitivity with and without glare at Month 6/Visit 5A respectively.

- To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond “Never” to Q1 and Q3 of the spectacle use questionnaire at Month 6/Visit 5A respectively.

7.2.1 Secondary Effectiveness Assessments

- Monocular photopic BCDVA (logMAR) at 4 m
- Monocular photopic DCNVA (logMAR) at 40 cm
- Monocular photopic distance corrected depth of focus from defocus curve assessment

- Monocular mesopic contrast sensitivity at 12 cycles per degree with and without glare respectively
- Proportion of subjects who respond “Never” to Q1 and Q3 of the spectacle use questionnaire respectively

[redacted]

7.4 Primary Safety Objective

To demonstrate that the adverse event rates of ACRYSOF IQ EDF IOL are not worse than SPE rates as defined in IS EN ISO 11979-7:2014 at Month 3/Visit 4A.

7.4.1 Primary Safety Assessment

- AE rates of ACRYSOF IQ EDF IOL

[redacted]

8 INVESTIGATIONAL PLAN

8.1 Study Design

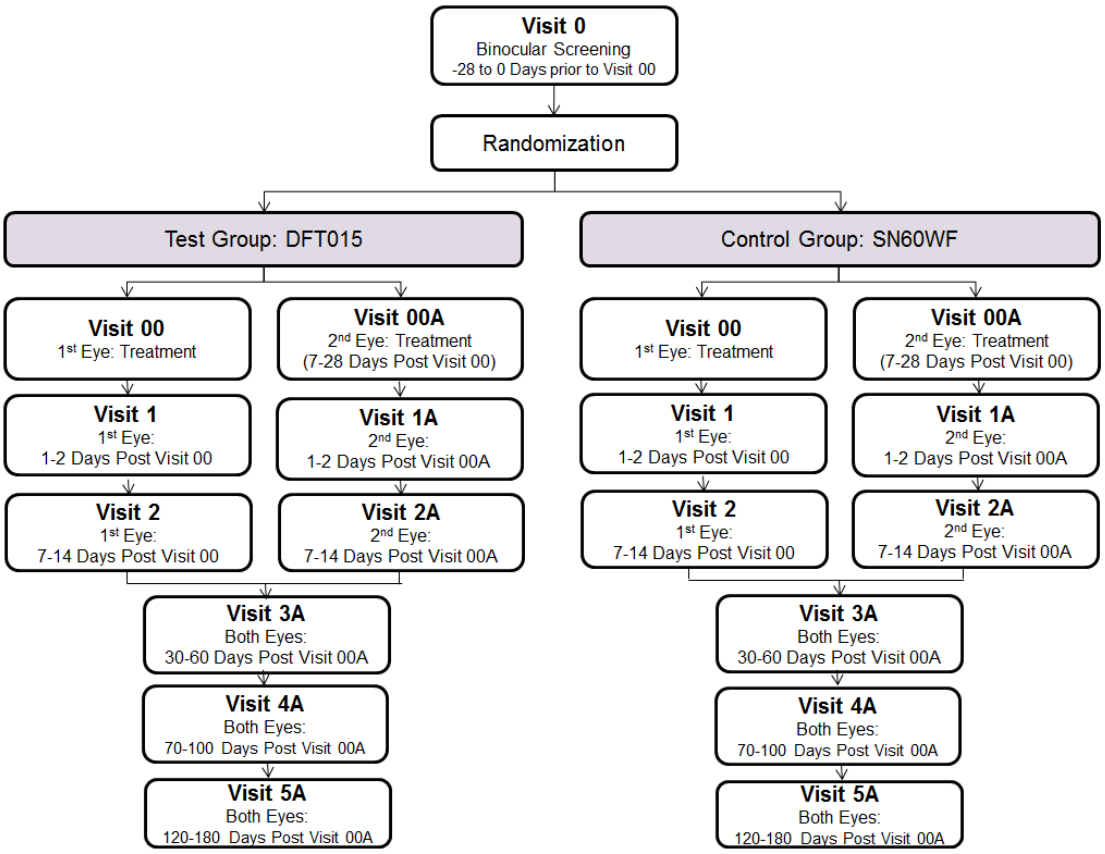
This is a prospective, multi-center, randomized, parallel group, controlled, assessor and subject masked study. Both eyes of a subject must require cataract surgery to qualify for enrollment into this study. Subjects will be randomly assigned in a 5:4 ratio to receive either Model DFT015 (test article) or Model SN60WF (control article) in both eyes. The first surgical 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 surgical eye. The second eye implant must occur within 28 days of the first eye implant.

A total of 10 scheduled visits are planned including the Screening/Visit 0 and two Operative Visits/Visit 00 and Visit 00A. Postoperative visits must occur at the following intervals: Day 1-2, Day 7-14 (after each surgery), Day 30-60, Day 70-100 and Day 120-180 (after 2nd eye surgery). See Figure 8-1 Study Design.

NOTE: Months 3 and 6 (Visits 4A and 5A) may be completed over 2 days within a two week period. All visits must be completed within the specified visit window.

Primary endpoint data will be collected at the Month 3/ Visit 4A (70-100 day post 2nd eye implantation). An interim database lock will be conducted when all subjects have completed this visit. All subjects will continue to be followed until Month 6/Visit 5A (120-180 day post 2nd eye implantation) for further characterization of the performance and safety profile of the ACRYSOF IQ EDF IOL (Model DFT015).

Figure 8–1 Study Design



8.2 Rationale for Study Design

The test article for this study is the ACRYSOF IQ EDF IOL. This IOL is a modification of the CE Marked, HA-approved (in applicable countries) and commercially available ACRYSOF IQ Monofocal IOL which is well established in the literature and is also the industry standard of care. This study will aim to assess all parameters of interest including performance and safety at Month 3/Visit 4A. Since there is no clinical experience with the ACRYSOF IQ EDF IOL, all subjects will be followed up to Month 6/Visit 5A for further safety assessments.

All subjects and site assessors will be masked to subject treatment assignment until the end of the study. Subjects will be randomized to the test or control arm. The primary and secondary analyses will be conducted on monocular first eye implanted outcomes. [redacted]

8.3 Rationale for Choice of Control Article

The control article for this study is the CE Marked, HA-approved (in applicable countries) and commercially available ACRYSOF IQ Monofocal IOL (Model SN60WF). Currently, this IOL represents the industry standard of care for subjects who develop cataract and require cataract surgery with a monofocal IOL implantation. Model SN60WF has been well studied in previous Alcon clinical trials and the safety and effectiveness of this IOL have been well established. The control article has the same physical properties and is composed of the same material as the test article, ACRYSOF IQ EDF IOL (Model DFT015). The only difference between these two IOLs is the presence of the TPS optics in the test article, which is designed to provide improved functional vision at intermediate distances.

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. Therefore, Model SN60WF is scientifically the most appropriate control article for this study.

8.4 Data Monitoring Committee

Not Applicable.

9 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 260 subjects in approximately 16 centers globally, with a target of approximately 16 subjects randomized per site. Site specific targets may be adjusted based on individual site capabilities. Enrollment projections are as follows:

- 260 subjects to be randomized (10% discontinuation rate is expected)
- 234 subjects to successfully complete the final study visit (Visit 5A)
    - 130 subjects in the Model DFT015 arm

- 104 subjects in the Model SN60WF arm

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 1st eye surgery (IOL does not come in contact with the eye), the subject should be discontinued from participation in the study. Refer to Section 11.11 Discontinued Subjects for further details.

9.1 Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria in both eyes (where applicable):

1. Subject must be able to understand and sign an IEC/ IRB approved ICF.
2. Willing and able to attend all scheduled study visits as required per protocol.
3. Adults (22 years or older at the time of enrollment in the study) diagnosed with cataract in both eyes.
4. Planned cataract removal by routine small incision surgery.
5. Calculated IOL power is within the clinical study supply range (18.0-25.0 D in 0.5 D steps).
6. Preoperative regular astigmatism of less than 1.0 D, measure by automated keratometry in both eyes.

9.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria in either eye (where applicable) are not eligible for inclusion in this study:

1. Pregnancy or lactation current or planned during the course of the study.
2. History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology including retinal vascular occlusive disease, retinal detachment or peripheral retinal laser photocoagulation, age-related macular degeneration (ARMD), glaucoma (uncontrolled or controlled with medication), ocular hypertension, diabetic retinopathy, retinitis pigmentosa and any optic nerve pathology.

3. Any current anterior or posterior segment inflammation of any etiology, and /or history of any disease producing an intraocular inflammatory reaction.

4. Clinically significant corneal pathology (epithelial, stromal, and/or endothelial) which would adversely affect the visual outcome based on Investigator expert medical opinion. These ocular pathologies include but are not limited to old significant corneal scars (including Salzman's nodular degeneration), 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), etc.

5. Clinically significant severe dry eye that would affect study measurements based on Investigator expert medical opinion.

6. History of previous intraocular or corneal (refractive or trauma related) surgery.

7. Current or history of amblyopia or monofixation syndrome.

8. Any subject currently participating in another investigational drug or device study that may confound the results of this investigation.

9. Any other ocular or systemic co-morbidity that, based on Investigator expert medical opinion, may confound the results of this study or prohibit the completion of the study assessments or increase the risk for the subject.

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

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

12. Patients who desire monovision correction.

13. Patients participating in the UK who are aviators falling under Civil Aviation Authority (CAA) regulation.

9.3 Reasons for Discontinuation (During Surgery)

14. Surgical complications including but not limited to loss of zonular integrity/zonular weakness, zonular rupture, anterior or posterior capsule rupture, any evidence of

fluid misdirection during the cataract procedure with progressive shallowing of the anterior chamber, uncontrollable IOP, etc.

15. Mechanical or surgical manipulation of the pupil.

16. Excessive iris mobility.

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

If the implantation was aborted and the IOL **did not** touch the eye (1st eye), then the subject is required to discontinue from the study and standard of care for IOL implantation is followed. If the implantation was aborted and the IOL **did** touch the eye (1st eye), then 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 5.3 for further detail.

9.4 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

10 TREATMENT

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

NOTE: Femtosecond laser-assisted cataract surgery (FLACS) is permitted for Investigators that currently use this procedure as part of their standard of care for cataract surgery, however it is **NOT** required. May **ONLY** be used for the following:

- Primary and sideport incisions
- Capsulorhexis
- Lens fragmentation

Table 10–1 Test Article

Test Product	ACRYSOF IQ EDF IOL (Model DFT015)
Manufacturer	Alcon
Indication for use	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.
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.
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 and Wolter, 1962)
	Optic Diameter (mm): 6.0
	Overall Length (mm): 13.0
	Haptic Angle: 0°
Formulation	N/A
Usage	IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.
Number/Amount of Product to be Provided to the Subject	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".* ***NOTE:*** In countries where applicable, an additional label will be added noting "*Investigational Device"* and *"To Be Used by Qualified Investigators Only"* (text in English and translation as appropriate).
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. More information on the test article can be found in the IB (0138) and DFU for ACRYSOF IQ EDF IOL (Model DFT015).
Supply	A designated amount of IOLs will be supplied to the site by the Sponsor.

Table 10–2 Control Article

Control Product	ACRYSOF IQ Monofocal IOL (Model SN60WF)
Manufacturer	Alcon
Indication for use	The ACRYSOF® IQ posterior chamber intraocular 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.

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 and Wolter, 1962)
	Optic Diameter (mm) – 6.0
	Overall Length (mm) – 13.0
	Haptic Angle - 0°
Formulation	N/A
Usage	IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.
Number/Amount of Product to be Provided to the Subject	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	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. More information on the control article can be found in the DFU for ACRYSOF IQ Monofocal IOL (Model SN60WF).
Supply	A designated amount of IOLs will be supplied to the site by the Sponsor.

10.1 Other Medical Device Specified for Use during the Study

Table 10–3 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**

10.2 Treatment Assignment / Randomization

Subjects will be randomized in a 5:4 ratio to receive either ACRYSOF IQ EDF IOL or ACRYSOF IQ Monofocal IOL respectively.

Only after signing the informed consent form (ICF), a subject will be assigned a subject number by the electronic data capture (EDC) system.

The Investigator, or delegate, at Operative Visit / Visit 00 will initiate randomization in EDC after confirming that the subject meets all the eligibility criteria and confirming the subject is eligible for randomization. Randomization must be completed no more than two business days prior to the first operative visit, unless there is a valid reason to randomize earlier. After randomization is initiated, all eligible subjects will be randomized to one of two treatment arms.

10.3 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, return to the Study Sponsor investigational and control products associated with a device deficiency. Refer to Section 12 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.

10.4 Treatment Masking

The assessor and subject will be masked in this study. Subjects will be masked to their treatment assignment for the entire duration of the study. Site personnel performing the [redacted] and all VA testing, which will include BCDVA, [redacted] DCIVA, [redacted], DCNVA, [redacted] defocus curve testing and contrast sensitivity, will remain masked with regard to treatment assignment until after the final database lock (Visit 5A). Alcon and site personnel will not reveal the treatment assignment to study subjects at any time during the study.

After the subject is implanted with the appropriate lens, a generic implant card is provided to the subject that will not reveal their 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.

This level of masking will be maintained throughout the conduct of the study. Unmasking will occur only after all planned study data have been validated, and the database locked. Unmasking will also occur at the time of the interim database lock, with treatment related information being revealed only to designated personnel.

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 10-4 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 10.4)	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

10.5 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.

11 STUDY PROCEDURES AND ASSESSMENTS BY VISIT

The following section outlines the assessments to be performed in this clinical study. Assessments are described in detail in the ILI875-C001 MOP, and are outlined in tabular format in Section 5 of this protocol.

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

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

Subjects who currently wear contact lenses must discontinue their use to ensure corneal stability prior to the preoperative visit measurements as noted in Table 11-1.

Table 11–1 Contact Lens Discontinuation Prior to Preoperative Visit

Type of Contact Lens	Minimum Time to Stop Wearing before Pre-Op Visit
Hard or rigid gas permeable lenses	3 weeks
Daily wear soft lenses –Toric/Spherical	2 weeks
Soft extended-wear lenses	2 weeks

11.1 Screening/Preoperative Visit (Visit 0)

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

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 electronic case report form (eCRF), if applicable.

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 11.9 Informed Consent Procedures.

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.

[redacted]

[redacted] *]*

[redacted]

8. Measure and record [redacted] and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*

[redacted]

12. Record any AEs. Refer to Section 12 for further details.

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

14. Document the target residual refractive error based on the IOL calculation power. *[Both Eyes, Bilateral]*
NOTE: This assessment may be done at any time after required biometry has been collected.

15. Identify the surgical eye for this study (determined by preoperative BCDVA).

16. Proceed with scheduling the surgery.

11.2 Operative Visits (Visit 00/00A)

Visit 00: Day 0, Monocular 1st Eye

Visit 00A: 7-28 Days Post 1st Implantation, Monocular 2nd Eye

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 assessment must be documented in source documentation and eCRF (if applicable).

***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.

NOTE: It will be permitted to have two study-trained surgeons at each site perform IOL implantations. However, the same surgeon must complete both the left (OS) and right (OD) IOL implants on a subject.

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.

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

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

4. Record operative eye.

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

6. Perform surgery and implantation with the randomized IOL. *[Operative Eye Only, Monocular]*

7. At completion of IOL implantation measure and record incision size. *[Operative Eye Only, Monocular]*

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

[redacted]

11. Record any adverse events including SSIs. Refer to Section 12 for further detail.

12. Record any device deficiencies. Refer to Section 12 for further detail.

11.3 1-Day Postoperative Visit (Visit 1/1A)

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

Visit 1A: 1-2 Days Post 2nd Eye Implantation, Monocular 2nd 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 eCRF (if applicable).

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

2. [redacted]

[redacted]

7. Record any adverse events including SSIs. Refer to Section 12 for further detail.

8. Record any device deficiencies. Refer to Section 12 for further detail.

11.4 1-Week Postoperative Visit (Visit 2/2A)

Visit 2: 7-14 Days Post 1st Eye Implantation, Monocular 1st Eye

Visit 2A: 7-14 Days Post 2nd Eye Implantation, Monocular 1st 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 eCRF (if applicable).

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

[redacted]

[redacted] Measure and record [redacted] and BCDVA under photopic conditions at 4 m. *[Operative Eye Only, Monocular]*

[redacted]

8. Record any adverse events including SSIs. Refer to Section 12 for further detail.

9. Record any device deficiencies. Refer to Section 12 for further detail.

11.5 1-Month Postoperative Visit (Visit 3A)

Visit 3A: 30-60 Days Post 2nd 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 eCRF (if applicable).

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

[redacted]

3. Measure and record <u>monocular</u> [redacted] and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*

4. Measure and record <u>monocular</u> [redacted] and DCIVA under photopic conditions at 66 cm. *[Both Eyes, Bilateral]*

[redacted]

10. Record any adverse events including SSIs. Refer to Section 12 for further detail.

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

11.6 3-Month Postoperative Visit (Visit 4A)

Visit 4A: 70-100 Days Post 2nd Eye Implantation, Bilateral

Below is a list of study procedures to be completed at Visit 4A. All assessments must be documented in source documentation and eCRF (if applicable). 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. If the visit is conducted

over multiple sessions or days, seek advice from Alcon staff regarding best practices. For example:

- Conducting primary and secondary outcome assessments day 1; and
- Conducting distance, intermediate and near VA testing in an early session and defocus testing in a later session on day 1.

1. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.
2. Measure photopic pupil size. *[Both Eyes, Bilateral]*
3. [redacted].
4. Measure and record <u>monocular</u> [redacted] and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*
5. Perform <u>monocular</u> defocus curve testing. *[Both Eyes, Bilateral]*

[redacted]

7. Measure and record <u>monocular</u> [redacted] and DCIVA under photopic conditions at 66 cm. *[Both Eyes, Bilateral]*
8. Measure and record <u>monocular</u> [redacted] and DCNVA under photopic conditions at 40 cm. *[Both Eyes, Bilateral]*

[redacted]

[redacted]

17. Record any adverse events including SSIs. Refer to Section 12 for further detail.

18. Record any device deficiencies. Refer to Section 12 for further detail.

11.7 6-Month Postoperative Visit (Visit 5A)

Visit 5A: 120-180 Days Post 2nd Eye Implantation, Bilateral with Binocular Testing

Below is a list of study procedures to be completed at Visit 5A. All assessments must be documented in source documentation and eCRF (if applicable). 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. If the visit is conducted over multiple sessions or days, seek advice from Alcon staff regarding best practices. For example:

- Conducting primary and secondary outcome assessments day 1; and
- Conducting distance, intermediate and near VA testing in an early session and defocus testing in a later session on day 1.

1. Provide questionnaires ([redacted] Spectacle Use) to the subject for completion. The 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. [redacted]

4. Perform manifest refraction. *[Both Eyes, Bilateral]*

[redacted]

5. Measure and record monocular [redacted] and BCDVA under photopic conditions at 4 m. *[Both Eyes, Bilateral]*

[redacted]

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

[redacted]

9. Measure and record monocular [redacted] and DCIVA under photopic conditions at 66 cm. *[Both Eyes, Bilateral]*

[redacted]

11. Measure and record monocular [redacted] and DCNVA under photopic conditions at 40 cm. *[Both Eyes, Bilateral]*

[redacted]

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

[redacted]

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

[redacted]

17. Perform monocular photopic *without* glare contrast sensitivity testing. *[Both Eyes, Bilateral]*

[redacted]

25. Record any adverse events including SSIs. Refer to Section 12 for further detail.

26. Record any device deficiencies. Refer to Section 12 for further detail.

11.8 Schedule of Procedures and Assessments for Discontinued Subjects

Subjects that discontinue from the study, it is recommended to complete the assessments noted in the table in Section 5 for an Early Exit Visit.

1. Provide questionnaires (Quality of Vision and Spectacle Use) to the subject for completion. The 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.

[redacted].

4. Measure and record [redacted] and BCDVA.

[redacted]

9. Record any adverse events including SSIs. Refer to Section 12 for further detail.

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

11.9 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, have the individual obtaining consent from the subject 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.

11.10 Unscheduled Visits

An 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
- 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).

The assessments captured at the UNSV are dictated by the Investigator per their medical judgment. The following assessments are recommended:

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

[redacted].

3. Measure and record [redacted] and BCDVA.

[redacted]

[redacted]

[redacted]

[redacted]

NOTE: 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 according to Section 5, Schedule of Study Procedures and Assessments.

11.11 Discontinued Subjects

11.11.1 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.

11.11.2 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.

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

For subjects discontinuing from the study, the Investigator should complete Early Exit procedures according to Section 5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS, if the subject is willing and able, and if in the opinion of the Investigator

it is safe for the subject to do so. 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.

11.12 Clinical Study Termination

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

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

- The Study Sponsor must:
  - Immediately notify the Investigator(s) and subsequently provide instructions for study termination.
  - Inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The Investigator must:
  - Promptly notify the IEC/IRB of the termination or suspension and of the reasons.
  - Provide subjects with recommendations for post-study treatment options as needed.

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

11.13 Aborted Implantation

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 supplied by the Study Sponsor. Specific guidance with regards to aborted implantation is detailed below.

In the sections below, the IOL touching the eye is defined as the time point when any IP first touches the eye.

***NOTE*:** No more than two attempts to be made to implant the control or test article.

11.13.1 First Eye Implant

- **IF** the first attempt to implant the control or test article was aborted **THEN** a second attempt is permitted (regardless if the IOL touches the eye or not).

- **IF** the second attempt to implant the control or test article was aborted and the IOL did not touch the eye on either attempt **THEN s**ubject must be discontinued from the study.

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

    - This eye must be followed for all study visits for safety evaluation only
    - The test or control article must **NOT** be implanted

11.13.2 Second Eye Implant

- **IF** the first attempt to implant the control or test article was aborted **THEN** a second attempt is permitted (regardless if the IOL touches the eye or not).

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

    - Subject must not be implanted with the control or test article
    - Standard of care followed for the second eye IOL implantation
    - The first eye will be followed for all study visits

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

    - The control or test article must **NOT** be implanted in the second eye
    - The second eye must be followed for all study visits for safety evaluation only
    - The first eye will also be followed for all study visits
    - Standard of care followed for IOL implantation of the second eye

12 DEVICE DEFICIENCIES AND ADVERSE EVENTS

12.1 General Information

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.

Figure 12–1 Categorization of All Adverse Events

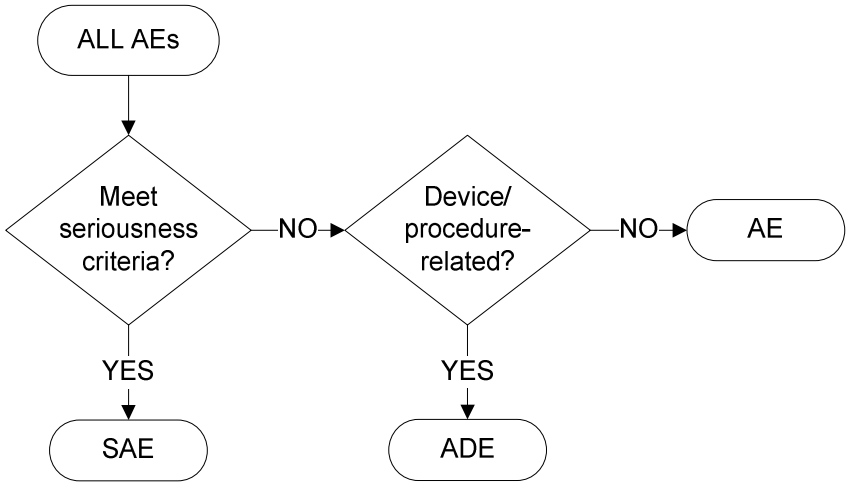
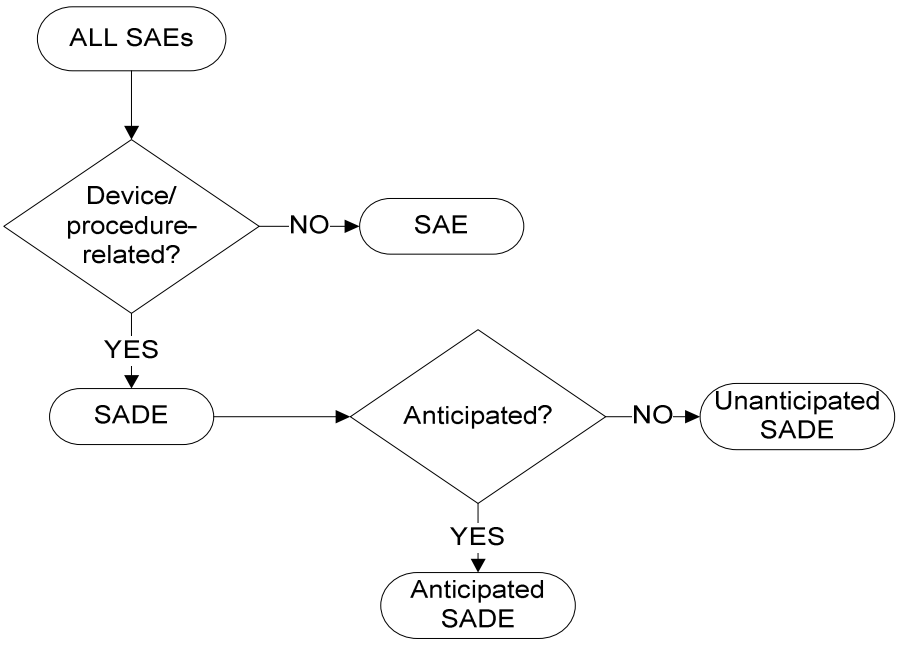


Figure 12-2 Categorization of All Serious Adverse Events



12.2 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.

12.3 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:

12.3.1 Cumulative Serious Adverse Events

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

12.3.2 Persistent Serious Adverse Events

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

This list is consistent with the categories provided in I.S. EN ISO 11979-7:2014. A persistent AE is an AE that is present at the conclusion of a clinical investigation per I.S. EN ISO 11979-1. Any other potentially sight-threatening event may also be considered

serious based on the judgment of the Investigator and must be reported appropriately as delineated in Section 12.6.

12.3.3 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

12.4 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.

12.5 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 post-operative findings that are typically observed following ocular surgery. These are not considered AEs if they can be reasonably expected to resolve within a week and not result in any untoward long term visual outcome impact.

For each recorded event, the 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.**

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 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.

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.

12.5.1 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:

12.5.1.1 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.

12.5.1.2 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).

12.6 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 # which will be provided by the Study Sponsor after the case is entered in the Study Sponsor's Global Product Complaint System (GPCMS).

12.7 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. Dependent 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.

12.8 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.

12.9 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.

13 ANALYSIS PLAN

The primary time point of interest is Month 3/Visit 4A except mesopic contrast sensitivity and spectacle use questionnaire. After all subjects complete Month 3/Visit 4A, the study database will be locked to conduct planned analyses. Results from these analyses will be used in a clinical study report for submission. The study will be continued until all subjects complete Month 6/Visit 5A (120-180 days post 2nd eye implantation), at which time the study database will be locked to report longer term safety and performance results.

13.1 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.

13.2 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.

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

13.3 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, SD, minimum and maximum will be presented for continuous variables.

13.4 Effectiveness Analyses

A total of three 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 0.05 level using a sequential testing approach.

13.4.1 Analysis of Primary Effectiveness Endpoint

The primary endpoint is monocular photopic DCIVA at 66 cm.

13.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis are:

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

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

where $\mu_{DFT015VA}$, $\mu_{SN60WFVA}$, refer to the mean monocular photopic DCIVA at 66 cm for the test and control lenses, respectively, in the first implanted eye. [redacted]

13.4.1.2 Analysis Methods

For the primary effectiveness analysis, treatment group comparison for photopic DCIVA will be made and the primary objective will be demonstrated if (one-sided) $P < 0.025$ from a two-sample t-test.

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 should include site as a random effect.

Descriptive statistics (mean, median, SD, number of eyes, minimum, maximum and [two-sided] 95% confidence interval) will also be provided for monocular photopic DCIVA, separately for each eye.

13.4.2 Analysis of Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are

- monocular BCDVA at 4 m
- monocular DCNVA at 40 cm
- monocular depth of focus assessed by the mean defocus curve
- monocular mesopic contrast sensitivity at 12 cycles per degree with and without glare respectively
- proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire respectively

13.4.2.1 Statistical Hypotheses

The null and alternative hypotheses for the first secondary analysis 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 BCDVA at 4 m for the test and control lenses, respectively, in the first implanted eye. [redacted]

The null and alternative hypotheses for the second 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. [redacted]

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

$$H_0: \mu_{DFT015CS} - \mu_{SN60WFCS} \leq \Delta$$

$$H_A: \mu_{DFT015CS} - \mu_{SN60WFCS} > \Delta$$

where Δ refers to the non-inferiority margin set at -0.15 log unit, and $\mu_{DFT015CS}$ and $\mu_{SN60WFCS}$ refer to the mean monocular mesopic contrast sensitivity score (log unit) for the test and control lenses, respectively, in the first implanted eye. [redacted]

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

$$H_0: \pi_{DFT015} \leq \pi_{SN60WF}$$
$$H_A: \pi_{DFT015} > \pi_{SN60WF}$$

where π_{DFT015} and π_{SN60WF} refer to the proportion of subjects who responded "Never" for the test and control lenses.

13.4.2.2 Analysis Methods

The statistical model associated with the above hypotheses for the first secondary effectiveness analysis will be tested by generating a one-sided 97.5% upper confidence limit based on the difference in means (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) using a two-sample t-test. The upper bound of the one-sided 97.5% confidence limit will be compared to the margin, 0.10 logMAR. If the upper bound is less than the margin, the null hypothesis will be rejected and it will be concluded that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL for BCDVA at 4 m.

Descriptive statistics (mean, median, SD, number of eyes, minimum, maximum and (two-sided) 95% confidence interval) will also be provided for monocular BCDVA at 4 m, separately for each eye.

For the second secondary effectiveness analysis, treatment group comparison for photopic DCNVA will be made and the objective will be demonstrated if (one-sided) $P < 0.025$ from a two-sample t-test.

Descriptive statistics (mean, median, SD, number of eyes, minimum, maximum and (two-sided) 95% confidence interval) will also be provided for monocular DCNVA at 40 cm, separately for each eye.

For the third secondary effectiveness analysis (depth of focus), the line plot of the average VA at each defocus level (ie, defocus curve) will be used to estimate the negative lens induced depth of focus at 0.20 logMAR. The difference in depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ Monofocal IOL will be presented.

The hypotheses for the fourth secondary effectiveness analysis will be tested by generating a one-sided 97.5% lower confidence limit based on the difference in means (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) using a two-sample t-test. The lower bound of the one-sided 97.5% confidence limit will be compared to the margin, -0.15 log unit. If the lower bound is greater than the margin, the null hypothesis will be rejected and it will be concluded that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL for monocular mesopic contrast sensitivity. Monocular mesopic contrast sensitivity without glare at 12 cycles per degree will best tested followed by monocular mesopic contrast sensitivity with glare at 12 cycles per degree.

For the fifth 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. Response to Q3 of spectacle use questionnaire will best tested followed by response to Q1 of spectacle use questionnaire.

[redacted]

[redacted]

13.5 Handling of Missing Data

The following sensitivity analyses will be conducted to address missing values for the primary endpoint.

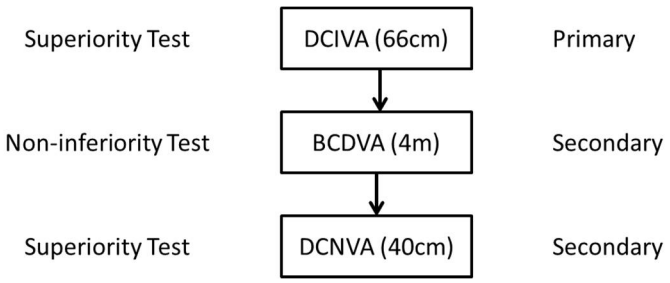
1. Multiple imputation (such as fully conditional specification) method will be used to impute and estimate the treatment effect.

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

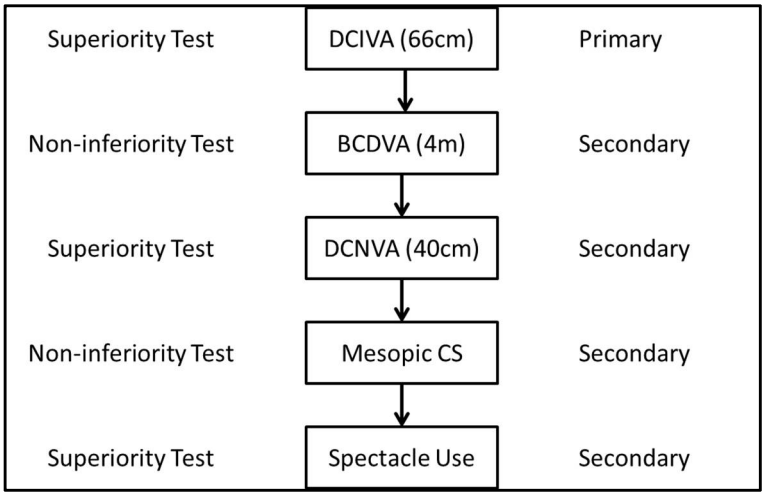
The details will be described in the Statistical Analysis Plan.

13.6 Multiplicity

Overall type I error will be maintained at 0.05 level for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analyses using the sequential testing approach summarized in the figure below.



The following primary and secondary effectiveness analyses will be performed on the Month 6/Visit 5A (120-180 day post 2nd eye implantation) data using the sequential testing approach summarized in the figure below if the primary and both secondary null hypotheses are rejected for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analysis.



13.7 Safety Analysis

Adverse Events and Device Deficiencies

Descriptive summaries (counts and percentages) for specific AEs 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 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.

Mesopic and photopic contrast sensitivity (with and without glare)

Descriptive statistics (mean, median, SD, number of subjects, minimum, maximum, and 95% confidence intervals) will be provided for [redacted] monocular [redacted] distance contrast sensitivity by IOL group.

[redacted]

[redacted]

13.8 Health Economics

Not Applicable.

13.9 Interim Analyses

Not Applicable.

13.10 Non-inferiority Margin

The non-inferiority margin used for the first secondary objective analysis will be 0.10 logMAR which equals 1 line in logMAR VA. The non-inferiority margin used for the fourth secondary objective analysis will be -0.15 log unit.

13.11 Sample Size Justification

Effectiveness

The proposed sample size (N = 234; 130 Bilateral ACRYSOF IQ EDF IOL and 104 Bilateral ACRYSOF IQ Monofocal IOL) provides >99% power for the superiority hypothesis test on mean monocular DCIVA (66 cm) when tested at the 0.025 level of significance (one-sided) assuming the difference in means is -0.12 logMAR (SD = 0.18).

The proposed sample size (N = 234; 130 Bilateral ACRYSOF IQ EDF IOL and 104 Bilateral ACRYSOF IQ Monofocal IOL) provides 81% power for the non-inferiority

hypothesis with respect to mean monocular BCDVA (4 m) when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of 0.10 logMAR assuming the difference in means is 0.04 logMAR (SD = 0.16).

The proposed sample size (N = 234; 130 Bilateral ACRYSOF IQ EDF IOL and 104 Bilateral ACRYSOF IQ Monofocal IOL) provides >99% power for the superiority hypothesis test on mean monocular DCNVA (40 cm) when tested at the 0.025 level of significance (one-sided) assuming the difference in means is -0.12 logMAR (SD = 0.18).

The proposed sample size (N = 234; 130 Bilateral ACRYSOF IQ EDF IOL and 104 Bilateral ACRYSOF IQ Monofocal IOL) provides 74% power for the non-inferiority hypothesis with respect to mean monocular mesopic contrast sensitivity value when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of -0.15 log unit assuming the difference in mean is -0.02 log unit (SD = 0.38).

The expected sample size (N = 131) will provide 84% power, with α=0.025, 1-sided, to detect a difference of 25% in proportion of subjects who respond “Never” to Q1 and Q3 of the spectacles use questionnaire respectively, assuming a 50% rate in the ACRYSOF IQ EDF IOL group.

Approximately 260 subjects will be randomized to achieve 234 subjects who complete the study. It is expected that approximately 131 subjects will respond to spectacle use questionnaire in this study.

Adverse Events

For any event where zero incidences is observed in 130 operative eyes with ACRYSOF IQ EDF IOL, the upper limit of the 95% 1-sided exact binomial confidence interval is less than 2.3%. Thus, with 95% confidence the true adverse event rate is less than 2.3%.

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 United States (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.

15 ETHICS

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

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

The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. The Investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

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

Voluntary informed consent must be obtained from every subject prior to the initiation of any screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved ICF. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential

benefits associated with the IP, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject according to local regulations.

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

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

16 REFERENCES

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

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

Ophthalmic implants – Intraocular lenses – Part 7: Clinical investigations, ISO 11979-7 (2014).

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

TDOC- 0016353, Optical Design of Toric Extended Depth of Field IOL.

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