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Clinical Trial Protocol

Clinical Investigation of Visual Function After Bilateral Implantation of Two Presbyopia-Correcting Trifocal IOLs

Protocol Number:	ILH297-P003 / NCT02691741
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Project Name / Number:	PanOptix Comparative Study / A02622
Test Article(s) / Product(s):	ACRYSOF® IQ PanOptix™ Presbyopia-Correcting IOL Model TFNT00
Release Date:	Refer to e-signature date
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.

Principal Investigator: _____ _____
Signature Date

Principal Investigator Name: _____

Principal Investigator Address: _____

_____

1 PROTOCOL SYNOPSIS

Financial Disclosure for US FDA Submission Required?	☐ Yes ☒ No
Test Article(s) / Product(s):	The ACRYSOF IQ PanOptix Presbyopia-Correcting IOL Model TFNT00 is a single-piece ultraviolet and blue light filtering foldable multifocal IOL. The biconvex optic is 6.0 mm in diameter and the lens has an overall diameter of 13.0 mm. The multifocal optic diffractive structure is in the central 4.5 mm portion of the anterior surface of the optical zone and divides the incoming light to create a +2.17 D intermediate and a +3.25 D near add power (IOL plane). The anterior surface is designed with 0.10 microns of negative spherical aberration to compensate for the positive spherical aberration of the average human cornea. 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 with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence.
Objective(s):	*Primary Objective:* To demonstrate **noninferiority** of ACRYSOF IQ PanOptix presbyopia-correcting IOL Model TFNT00 to the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **intermediate** (60 cm) visual acuity at Visit 4A *Secondary Objectives:* 1. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **intermediate** (60 cm) visual acuity at Visit 4A 2. To demonstrate **noninferiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **distance** (4 m) visual acuity at Visit 4A 3. To demonstrate **noninferiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **near** (40 cm) visual acuity at Visit 4A 4. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **near** (40 cm) visual acuity at Visit 4A. 5. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **distance** (4 m) visual acuity at Visit 4A 6. To **characterize** the binocular defocus curve profiles, contrast sensitivity and patient satisfaction with ACRYSOF IQ PanOptix

	IOL versus the AT LISA tri IOL Model 839MP at Visit 4A	
Clinical Trial Design:	This study is a prospective, multi-center, randomized, double masked, parallel group postmarket trial.	
No. of Subjects:	a) Required for statistical analysis: 152 evaluable completers b) Successfully screened: Approximately 180 c) Bilaterally Implanted: Approximately 160	
Region(s):	Asia, EU, LACAR	
Clinical Trial Duration:	a) Total expected duration of the clinical investigation: 13 months b) Expected duration of each subject's participation: ~7 months c) Planned follow up duration: 6-months post 2nd eye implantation d) Estimated time needed to select the number of subjects (ie, enrollment period): 6 months	
Clinical Trial Population:	Adults subjects, 22 years of age or older, with no ocular pathology that confound study outcomes, who require cataract extraction by phacoemulsification and desire an IOL that provides the potential for near, intermediate and distance vision.	
Treatments:	***Test Article***:	ACRYSOF IQ PanOptix Presbyopia-Correcting IOL Model TFNT00
	Administration:	Routine small incision cataract surgery with IOL implantation.
	General Description:	A range of commonly utilized spherical powers (diopters) will be available.
	Duration of Treatment:	Intraocular lenses are implantable medical devices and are intended for long term use over the lifetime of the cataract subject.
	Control Article:	AT LISA tri IOL Model 839MP
	Administration:	Routine small incision cataract surgery with IOL implantation.
	General Description:	A range of commonly utilized spherical powers (diopters) will be available.
	Duration of Treatment:	Intraocular lenses are implantable medical devices and are intended for long term use over the lifetime of the cataract subject.
Inclusion & Exclusion Criteria:	Details can be found in Section 10: Subject Population	
Performance Assessments	Intermediate Visual Acuity • [redacted] • Binocular uncorrected intermediate VA (60 cm)	

	Distance Visual Acuity • [redacted] • Binocular uncorrected distance VA (4 m)
	Near Visual Acuity (VA) • [redacted] • Binocular uncorrected near VA (40 cm)
Safety Assessments	Adverse Events (AEs) including secondary surgical intervention (SSI)
	Device Deficiencies (DD)
	Surgical Problems
	Intraocular Pressure (IOP)
	Slit Lamp Examination
	IOL Observations
	IOL Position Change
	Subjective Posterior Capsule Opacification (PCO)
	Posterior Capsulotomy
	Fundus Visualization
	Dilated Fundus Examination
Other Assessments	Photopic Pupil Size
	Binocular Uncorrected Defocus Curve
	Binocular Contrast Sensitivity • Photopic without Glare • Photopic with Glare • Mesopic without Glare • Mesopic with Glare
	Subject Satisfaction
Planned Analyses:	Analyses: A total of six hypothesis tests will be conducted to address the primary and secondary objectives of the study. The primary, second secondary and third secondary will be tests of non-inferiority while the first secondary, fourth secondary and fifth secondary will be tests of superiority. Non-inferiority, with a non-inferiority margin of 0.1 logMAR, will be tested for the mean binocular uncorrected photopic visual acuity at each of the following distances, respectively: • Intermediate (60 cm) (primary) • Distance (4 m) (second secondary) • Near (40 cm) (third secondary)

	Superiority will be tested for the mean binocular uncorrected photopic visual acuity at each of the following distances, respectively: • Intermediate (60 cm) (first secondary) • Near (40 cm) (fourth secondary) • Distance (4 m) (fifth secondary) Hypothesis testing will be conducted in the order presented above for both non-inferiority and superiority. A combination of gate-keeping and Bonferroni adjustment strategies will be employed to control the overall type I error rate. Descriptive statistics generated for safety and performance parameters will be based upon the type of parameter (ie, whether the data are categorical or continuous) being analyzed and by 1st and 2nd operative eyes for monocular measures. For categorical parameters, the statistics used to summarize the data descriptively include sample size, number in the category, and percent in the category. For continuous parameters, sample size, mean, median, standard deviation, minimum, and maximum will be presented. Summaries of logMAR visual acuity will also include two-sided 90% confidence intervals. [redacted] Responses to the satisfaction question will be analyzed as a categorical variable. Contrast sensitivity will be scored and analyzed per CSV-1000E instructions. Defocus curves will be generated for binocular defocus data, including 90% confidence intervals, with amount of defocus along the x-axis and logMAR VA at each defocus point along the y-axis. To examine the inter-site variation in outcome, a forest plot will be produced by plotting the difference in means and associated standard error for each site. An interim analysis will be performed when all subjects complete Visit 3A (20-40 days post 2nd eye implantation) in order to support the study publication plan of the test articles for near, intermediate and distance visual acuity, contrast sensitivity, defocus curves and adverse events.

	The interim analysis results will be distributed to a limited audience to limit potential bias in Visit 4A assessments. The clinical trial team with the exception of the Brand Lead will be masked to the interim analysis results.
Sample Size Justification	Sample size estimations are based on minimum sample size needed to achieve 90% power for all hypothesis tests. A type I error rate of 2.5%, one-sided, is used for calculations to account for simultaneous testing in first and second secondary hypotheses. Assuming a dropout rate of 5%, approximately 160 subjects will be bilaterally implanted in 1:1 allocation ratio (test: control) to achieve at least 152 subjects who complete the study. With 152 subjects (76 per group) there is 98% probability that an upper one-sided 97.5% confidence limit on the difference (test-control) in visual acuity will be less than 0.1 logMAR, assuming the mean difference of 0.0 logMAR and a common standard deviation of 0.16 logMAR, the maximum observed for binocular uncorrected distance, intermediate and near visual acuity in a previous Alcon study (C-06-40, ReSTOR +3.0 D IOL). Also, with 76 subjects per group, there is more than 90% power to detect a difference of 0.09 logMAR (4.5 letters) between means in a two sample t-test conducted at a 2.5% chance of a Type I error and assuming a standard deviation of 0.16 logMAR for binocular uncorrected distance, intermediate and near visual acuity.

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3 ABBREVIATIONS

Abbreviation	Definition
AAS	All implanted analysis set
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
BAS	Best case analysis set
[redacted]	[redacted]
CE	**C**onformité Européene
CFR	Code of Federal Regulations
CJD	Creutzfeldt-Jacob disease
cm	Centimeter
CM	Clinical Manager
CRF	Case report form
CSM	Clinical site management
D	Diopter
DD	Device deficiency
DFU	Directions for use
EDC	Electronic data capture
EU	Europe
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
IOL	Intraocular lens
IOP	Intraocular pressure
ISO	International Organization for Standardization
MOP	Manual of procedures
LASIK	Laser-assisted in-situ keratomileusis
LCSM	Lead Clinical Site Manager
logMAR	Logarithm of minimum angle of resolution
m	Meter
MedDRA®	Medical Dictionary for Regulatory Activities
mm	Millimeter
PCO	Posterior capsule opacification
PI	Principal Investigator
PP	Per protocol
SADE	Serious adverse device effect
SAE	Serious adverse event
SAS®	SAS statistical software, SAS Institute Inc., Cary, NC
SOP	Standard operating procedures

SS	Safety set
SSI	Secondary surgical intervention
UCDVA	Uncorrected distance visual acuity
UCIVA	Uncorrected intermediate visual acuity
UCNVA	Uncorrected Near Visual Acuity
UNSV	Unscheduled visit
USADE	Unanticipated serious adverse device effect
VA	Visual acuity
WHO	World Health Organization
YAG	Yttrium aluminum garnet

4 GLOSSARY OF TERMS

Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device or comparator, if applicable. *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 investigational medical device or comparator, if applicable.*
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.
Anticipated Serious Adverse Device Effect (ASADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis.
Assessment	A procedure used to generate data required by the study.
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.*
Performance (Clinical)	Behavior of a medical device or response of the subject to that medical device in relation to its intended use, when correctly applied to appropriate subjects.
Malfunction	Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed.
Nonserious Adverse Event	Any adverse event that does not meet the criteria for a serious adverse event.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, operative, postoperative, etc.
Randomization Number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Serious Adverse Device Effect (SADE)	A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

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 b) Permanent impairment of a body function or permanent damage to a body structure c) A condition necessitating medical or surgical intervention to prevent a) or b) d) A condition that requires hospitalization or significant prolongation of existing hospitalization 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.
Subject Number	A number assigned to each subject who enrolls in the study. When combined with the site number, a unique identifier is created for each subject in the study.
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 analysis.

5 AMENDMENTS

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

6 SCHEDULE OF VISITS

	Bin-ocular	1st Eye			2nd Eye			Binocular		Mon-ocular
	Visit 0	**Visit 00**	**Visit 1**	**Visit 2**	**Visit 00A**	**Visit 1A**	**Visit 2A**	**Visit 3A**	**Visit 4A[1]**	**UNSV[2]**
Activity	Day -60 to 0 Preoperative	Day 0 1st Eye Implantation	1-2 Day Post 1st Eye Implantation	7-14 Days Post 1st Eye Implantation	2-21 Days Post Visit 00 2nd Eye Implantation	1-2 Day Post 2nd Eye Implantation	7-14 Days Post 2nd Eye Implantation	20-40 Days Post 2nd Eye Implantation	120-180 Days Post 2nd Eye Implantation	N/A
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[3,4]	X									
Inclusion/Exclusion	X	X			X					
[redacted]										
Randomization		X								
Surgery/Treatment		X			X					
Report Implanted Lens Model		X			X					

		Bin-ocular	1st Eye			2nd Eye				Binocular		Mon-ocular
	Activity	**Visit 0**	**Visit 00**	**Visit 1**	**Visit 2**	**Visit 00A**	**Visit 1A**	**Visit 2A**	**Visit 3A**	**Visit 4A[1]**	**UNSV[2]**
		Day -60 to 0 Preoperative	Day 0 1st Eye Implantation	1-2 Day Post 1st Eye Implantation	7-14 Days Post 1st Eye Implantation	2-21 Days Post Visit 00 2nd Eye Implantation	1-2 Day Post 2nd Eye Implantation	7-14 Days Post 2nd Eye Implantation	20-40 Days Post 2nd Eye Implantation	120-180 Days Post 2nd Eye Implantation	N/A
	Surgical Report (Including: lens power, implant success, target refractive error[6], and success of implantation)		X			X					
	Problems During Surgery		X			X					
	Other Surgical Procedures		X			X					
	Patient Satisfaction									X	
Distance VA (4 m)											X
•	Monocular Uncorrected										

		Bin-ocular	**1st Eye**			**2nd Eye**				**Binocular**		**Mon-ocular**
Activity		**Visit 0**	**Visit 00**	**Visit 1**	**Visit 2**	**Visit 00A**	**Visit 1A**	**Visit 2A**	**Visit 3A**	**Visit 4A[1]**	**UNSV[2]**
		Day -60 to 0 Preoperative	Day 0 1st Eye Implantation	1-2 Day Post 1st Eye Implantation	7-14 Days Post 1st Eye Implantation	2-21 Days Post Visit 00 2nd Eye Implantation	1-2 Day Post 2nd Eye Implantation	7-14 Days Post 2nd Eye Implantation	20-40 Days Post 2nd Eye Implantation	120-180 Days Post 2nd Eye Implantation	N/A
• Binocular Uncorrected									X	X	
Near VA (40 cm)									X	X	
[redacted]											
• Binocular Uncorrected									X	X	
Intermediate VA (60cm)									X	X	
[redacted]											
• Binocular Uncorrected									X	X	
Defocus Curve (Binocular)									X	X	

		Bin-ocular	1st Eye			2nd Eye			Binocular		Mon-ocular
Activity		**Visit 0**	**Visit 00**	**Visit 1**	**Visit 2**	**Visit 00A**	**Visit 1A**	**Visit 2A**	**Visit 3A**	**Visit 4A[1]**	**UNSV[2]**
		Day -60 to 0 Preoperative	Day 0 1st Eye Implantation	1-2 Day Post 1st Eye Implantation	7-14 Days Post 1st Eye Implantation	2-21 Days Post Visit 00 2nd Eye Implantation	1-2 Day Post 2nd Eye Implantation	7-14 Days Post 2nd Eye Implantation	20-40 Days Post 2nd Eye Implantation	120-180 Days Post 2nd Eye Implantation	N/A
Contrast Sensitivity (Binocular)											
• Mesopic without Glare									X	X	
• Mesopic with Glare									X	X	
• Photopic without Glare									X	X	
• Photopic with Glare									X	X	
Slit-Lamp Examination (Including IOL Observations)		X		X	X		X	X	X	X	X
IOL Position Change				X	X		X	X	X	X	X
Subjective PCO				X	X		X	X	X	X	X
Posterior Capsulotomy (Report if performed)				X	X		X	X	X	X	X
Fundus Visualization									X	X	

	Bin-ocular	1st Eye			2nd Eye			Binocular		Mon-ocular
	Visit 0	**Visit 00**	**Visit 1**	**Visit 2**	**Visit 00A**	**Visit 1A**	**Visit 2A**	**Visit 3A**	**Visit 4A[1]**	**UNSV[2]**
Activity	Day -60 to 0 Preoperative	Day 0 1st Eye Implantation	1-2 Day Post 1st Eye Implantation	7-14 Days Post 1st Eye Implantation	2-21 Days Post Visit 00 2nd Eye Implantation	1-2 Day Post 2nd Eye Implantation	7-14 Days Post 2nd Eye Implantation	20-40 Days Post 2nd Eye Implantation	120-180 Days Post 2nd Eye Implantation	N/A
Dilated Fundus Examination	X							X	X	X
IOP	X		X	X		X	X	X	X	X
Adverse Events (Including SSI)	X	X	X	X	X	X	X	X	X	X
Device Deficiencies		X	X	X	X	X	X	X	X	X

[1] If a subject exits early, the Visit 4A procedures should be performed at the last available visit, if at all possible.

[2] UNSV assessments listed are recommended. Only complete assessments required per the PI medical judgment.

[3] Women of child-bearing potential only

[redacted]

[5] Within 10 business days of treatment (Visit 00).

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

7 INTRODUCTION

7.1 Background

Monofocal IOLs are designed to replace the focusing power of the natural lens (typically after cataract surgery) by providing good visual function through a single, fixed, focal length; thus, generally correcting a patient's distance vision. However, many pseudophakic patients implanted with monofocal IOLs ultimately require reading glasses to compensate for the loss of the ability to see clear at intermediate or near distances (presbyopia). Several IOL designs for treating presbyopia in pseudophakic patients exist in modern day clinical practice, including the use of multifocal IOLs. Multifocal IOLs offer the patient an opportunity to have the effects of presbyopia corrected after cataract surgery by providing multiple focal points. The majority of commercially available multifocal IOLs have two optical zones – one that provides distance vision and a second that provides near vision. The ACRYSOF IQ PanOptix Presbyopia IOL Model TFNT00 test IOL (hereto referenced as TFNT00) and the AT LISA tri IOL model 839MP control IOL (hereto referenced as 839MP) improve on commercially available multifocal IOLs by creating an additional focal point for intermediate vision.

The TFNT00 IOL has a trifocal design and provides a near focal point at 40 cm and distance vision similar to the currently marketed ACRYSOF IQ ReSTOR +3.0 D IOL Model SN6AD1, and it has the additional benefit to patients of an intermediate focal point at 60 cm. The TFNT00 IOL has recently received a CE Mark in Europe and is also approved in other countries outside of the European Union.

Optical bench studies and modeling & simulation studies conducted by Alcon to support the CE mark for the TFNT00 IOL have demonstrated equivalence or superior performance to the marketed trifocal 839MP IOL in simulated expected visual performance, namely VA at near (40cm), intermediate (60cm) and distance (4m). In addition, the studies predict equivalent or superior halo propensity and contrast sensitivity of the TFNT00 IOL to the 839MP IOL.

The purpose of this study is to clinically qualify the bench studies and model predictions of visual performance of the TFNT00 IOL by demonstrating the non-inferiority in binocular visual performance to 839MP IOL and to characterize the low contrast performance and patient satisfaction with both IOLs.

7.2 Clinical Trial Design

This study is a prospective, multi-center, postmarket trial comparing the visual function of 2 presbyopia-correcting trifocal IOLs following bilateral implantation. Both trifocal IOLs are commercially available in the countries where the study is being conducted. The study will

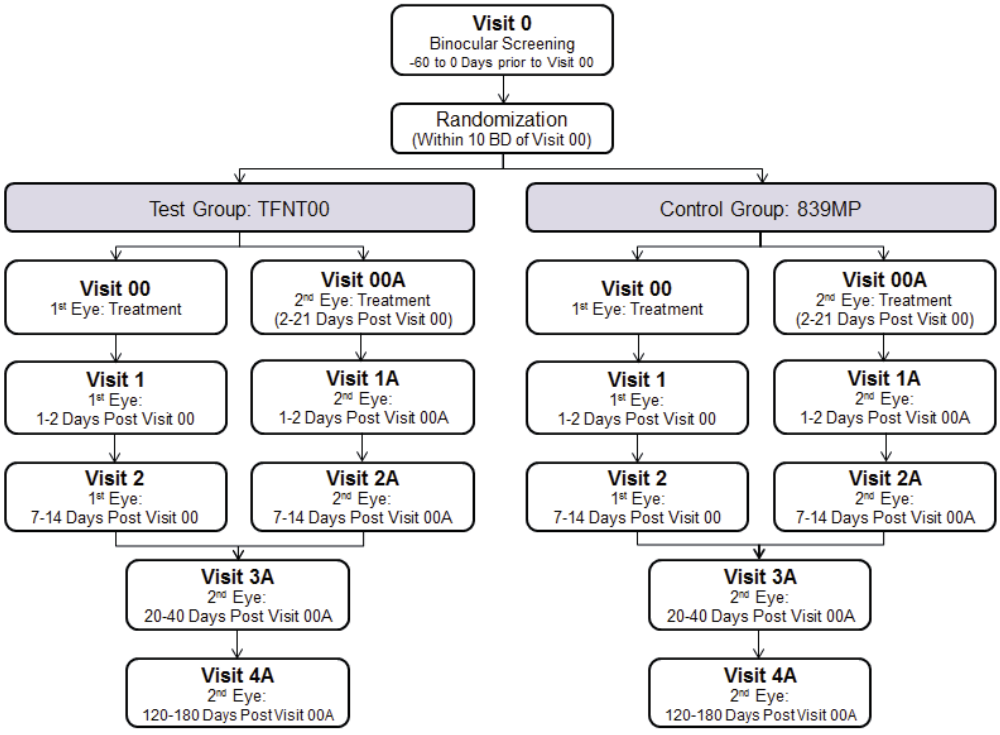
include adults (≥22 years of age) who require bilateral cataract extraction and who desire an IOL that provides the potential for functional near, intermediate and distance vision. Potential subjects will be screened for enrollment into the trial. Those qualifying will attend a total of 9 visits (6 postoperative) over a 7 month period.

Post consent, the EDC system will assign the subject number. Within 10 business days of surgery, qualified subjects will be randomized to either the TFNT00 or 839MP IOL. Randomization is 1:1 test IOL (TFNT00) to control IOL (839MP). In order to reduce bias, the observer (ie, study technician assessing primary and secondary endpoint data) and the subject will remain masked to the treatment assignment. The subject will remain masked for the duration of his/her trial participation, and will be provided with his/her permanent implant card upon study exit.

An interim analysis of the data will be conducted upon the completion of Visit 3A (20-40 days post 2nd eye implantation). Final data analysis will be conducted at study completion.

An overview of the study design is depicted in Figure 7-1.

Figure .7–1 Study Design



8 CLINICAL TRIAL OBJECTIVES

8.1 Primary Objective

The primary objective of this study is to demonstrate **noninferiority** of ACRYSOF IQ PanOptix presbyopia-correcting IOL (TFNT00) to the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **intermediate** (60 cm) visual acuity (UCIVA) at Visit 4A (120-180 days post 2nd eye implantation).

8.2 Secondary Objectives

The first secondary objective of this study is to demonstrate **superiority** of the TFNT00 IOL versus the 839MP IOL in mean photopic binocular uncorrected **intermediate** (60 m) visual acuity (UCIVA) at Visit 4A (120-180 days post 2nd eye implantation).

The second secondary objective of this study is to demonstrate **noninferiority** of the TFNT00 IOL versus the 839MP IOL in mean photopic binocular uncorrected **distance** (4 m) visual acuity (UCDVA) at Visit 4A (120-180 days post 2nd eye implantation).

The third secondary objective of this study is to demonstrate **noninferiority** of the TFNT00 IOL versus the 839MP IOL in mean photopic binocular uncorrected **near** (40 cm) visual acuity (UCNVA) at Visit 4A (120-180 days post 2nd eye implantation).

The fourth secondary objective of this study is to demonstrate **superiority** of the TFNT00 IOL versus the 839MP IOL in mean photopic binocular uncorrected **near** (40 cm) visual acuity (UCNVA) at Visit 4A (120-180 days post 2nd eye implantation).

The fifth secondary objective of this study is to demonstrate **superiority** of the TFNT00 IOL versus the 839MP IOL in mean photopic binocular uncorrected **distance** (4 m) visual acuity (UCDVA) at Visit 4A (120-180 days post 2nd eye implantation).

The sixth secondary objective of this study is to **characterize** the Binocular Defocus Curve profiles, contrast sensitivity and patient satisfaction with the TFNT00 IOL versus the 839MP IOL at Visit 4A (120-180 days post 2nd eye implantation).

8.3 Exploratory Objectives

None.

8.4 Study Endpoints

8.4.1 Effectiveness Endpoints

Primary, secondary, [redacted] effectiveness endpoints are listed below. All endpoints pertain to 120-180 days post 2nd eye implantation (Visit 4A) unless otherwise noted.

Primary Effectiveness

- Mean binocular uncorrected intermediate VA (60 cm)
  Note: For non-inferiority testing

Secondary Effectiveness

- Mean binocular uncorrected intermediate VA (60 cm)
  Note: For superiority testing
- Mean binocular uncorrected distance VA (4 m)
- Mean binocular uncorrected near VA (40 cm)
- Mean photopic binocular defocus curve
- Mean photopic *without* glare binocular distance contrast sensitivity
- Mean photopic *with* glare binocular distance contrast sensitivity
- Mean mesopic *without* glare binocular distance contrast sensitivity
- Mean mesopic *with* glare binocular distance contrast sensitivity
- Subject satisfaction

[redacted]

8.4.2 Safety Endpoints

Safety endpoints are listed below.

- Rates of ocular adverse events, including SSIs related to the optical properties for either eye
- Adverse events
- Device deficiencies
- IOL observations
- Subjective PCO
- Posterior Capsulotomies

9 INVESTIGATIONAL PLAN

9.1 Outline of Clinical Trial

This is a prospective, randomized parallel group post market study in which masked subjects will be randomized to bilateral implantation of either a test IOL (TFNT00) or a control IOL (839MP) in a 1:1 fashion. In addition to the subject, the observer collecting primary and secondary effectiveness data including visual acuity, defocus curves, contrast sensitivity and patient satisfaction will be masked.

Subjects participating in the trial will attend a total of 9 visits study visits over a 7 month period. Of these 9 visits, 1 is preoperative, 2 are operative and the remaining 6 are postoperative visits. Refer to Figure 7-1 above for a study outline diagram. Unscheduled visits may be attended if needed for medical attention.

Primary endpoint data will be collected at the final visit, Visit 4A (120-180 days post 2nd eye implantation). An interim analysis summarizing the visual acuity, contrast sensitivity, defocus curves and AEs will be conducted when all subjects complete Visit 3A (20-40 days post 2nd eye implantation) to support the study publication plan objectives.

Additional details, including a thorough risk-benefit assessment can be found in the sections below.

9.2 Study Design

This study is a prospective, multi-center, postmarket trial comparing the visual function of 2 commercially available presbyopia-correcting trifocal IOLs following bilateral implantation. The study will include adults (≥22 years of age) who require bilateral cataract extraction and who desire an IOL that provides the potential for functional near, intermediate and distance vision. Potential subjects will be screened for enrollment into the trial. Those qualifying will attend a total of 9 visits (6 postoperative) over a 7 month period.

An interim analysis of the data will be conducted upon the completion of Visit 3A (20-40 days post 2nd eye implantation). Final data analysis will be conducted at study completion.

9.3 Rationale for Study Design

The purpose of this study is to clinically qualify the bench studies and model predictions of visual performance of the TFNT00 IOL by demonstrating the non-inferiority in binocular visual performance to 839MP IOL and to characterize the low contrast performance and patient satisfaction with both IOLs.

9.4 Procedures per Study Visit

Section 12 Clinical Trial Procedures contains procedures per study visits.

9.5 Risk Benefit Assessment

9.5.1 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, 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 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.). Alternatively, 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, iridectomy or laser iridotomy for pupillary block, wound leak repair, and retinal detachment repair.

9.5.2 Potential Benefits

The TFNT00 IOL is a single-piece, trifocal diffractive lens with a +3.25 D near ADD and +2.17 D intermediate ADD intended to provide optical performance and spectacle independence similar to the ACRYSOF IQ ReSTOR +3.0 D Multifocal IOL (Model SN6AD1) at near range (40 cm) and distance, with the additional benefit of intermediate vision at 60 cm.

Maxwell (2009) performed a randomized, parallel group, subject masked, multicenter 6 month follow-up study comparing ACRYSOF IQ ReSTOR +3.0 D Add Power IOL (Model SN6AD1) to ACRYSOF ReSTOR +4.0 D Add Power IOL (Model SN6AD3). Both lenses were implanted bilaterally. The effectiveness results at 6 months showed mean uncorrected distance visual acuity of 20/20 and binocular defocus curves demonstrated 20/20 visual acuity at 40 cm. The Patient Reported Outcomes with the SN6AD1 IOL were very favorable with reported spectacle independence rates in 76% of subjects in the ACRYSOF IQ ReSTOR +3.0 D Multifocal IOL (Model SN6AD1), high patient satisfaction, self-rated visual quality and substantial improvements in patient reported outcomes.

The 839MP is a single-piece, trifocal diffractive IOL with a +3.33D near ADD and +1.66D intermediate ADD indicated to provide presbyopia correction in patients with or without cataract. In a case series study comprised of 30 patients who had bilateral implantation of the 839MP IOL after phacoemulsification for either cataract or refractive lens exchange surgery, the effectiveness results at 6 months showed mean uncorrected distance visual acuity of close to 20/20 for mean uncorrected monocular and binocular visual acuity (Law 2014). Similarly, binocular defocus demonstrated 20/30 visual acuity between distance and 33 cm. The majority of patients (77%) were satisfied with their distance, intermediate and near vision at the end of the follow up. Difficulties associated with photic phenomena (night vision, glare and halo perception) decreased significantly over time.

9.5.3 Risk Benefit Assessment

Based on the formal risk assessment, the TFNT00 IOL demonstrates a risk profile that is comparable to the FDA-approved ACRYSOF IQ ReSTOR +3.0 Add Power IOL (Model SN6AD1) [redacted]. Furthermore, it was concluded that the benefits of increased intermediate vision while maintaining visual performance at near distance significantly outweigh the risks of suboptimal surgical outcomes and [redacted] when the TFNT00 IOL is used in cataract surgery. Potential risks following implantation of both the TFNT00 IOL and the 839MP IOL (Law 2014) include visual disturbances such as glare and halos which are known risks for multifocal IOLs. The benefits of improved near and intermediate vision, when weighed against the risks of visual disturbances, result in a benefit to risk profile that is favorable for the both the test and control IOLs (Law 2014).

10 SUBJECT POPULATION

The study population includes approximately 160 subjects to be bilaterally implanted at approximately 15 sites with approximately 10 subjects per site. Enrollment is anticipated to take approximately 6 months.
Note: Randomization of 10 subjects per site is a target recommendation. No minimum or maximum requirement exists.

To participate in the clinical trial, subjects must be ≥ 22 years of age with no ocular pathology that could confound study outcomes, must require clear cornea cataract extraction in both eyes, and must desire an IOL that provides the potential for near, intermediate and distance vision. Additional entry criteria are listed below in Sections 10.1 through 10.3.

Check all entry criteria at baseline (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 12.4 Discontinued Subjects for further details.

If a subject reschedules surgery, and this rescheduling results in preoperative/baseline assessments (Visit 0) falling outside of the -60 to 0 day window, assessments should be repeated, and inclusion/exclusion criteria re-verified. Subjects failing to pass entry criteria may not be re-screened. If subject reschedules surgery after randomization, proceed with the original randomized treatment (ie, do not attempt to re-randomize and do not attempt to assign a new subject number).

10.1 Inclusion Criteria

Below is a list of inclusion criteria. Ocular criteria must be met in both eyes with exception to criterion 4 below.

1. Adults, 22 years of age or older at the time of surgery, of either gender or any race, diagnosed with bilateral cataracts with planned clear cornea cataract removal

2. Able to comprehend and willing to sign informed consent and complete all required postoperative follow-up procedures

3. Calculated lens power between 13.0 and 30.0 D

4. [redacted]

5. [redacted]
   Note: Subjects with any pathology that could reduce visual potential should not be enrolled in this trial

6. Preoperative regular corneal astigmatism of < 1.00 D, in both eyes

7. Clear intraocular media other than cataract in both eyes

10.2 Exclusion Criteria

Below is a list of exclusion criteria. Ocular criteria must be met in both eyes.

1. Subjects who may reasonably be expected to require an ocular surgical treatment at any time during the study (other than YAG capsulotomy)

2. Previous refractive surgery or planned refractive surgery procedures throughout the entire duration of the subjects' participation in the clinical study (including, but not limited to LASIK, astigmatic keratotomy and limbal relaxing incisions);

3. Clinically significant corneal abnormalities including corneal dystrophy (eg, epithelial, stromal, or endothelial dystrophy), inflammation or edema per the Investigator's expert medical opinion.
   Note: conditions including, but not limited to: keratitis, keratoconjunctivitis, keratouveitis, keratopathy, or keratectasia should be excluded

4. Amblyopia

5. Previous corneal transplant

6. Extremely shallow anterior chamber (≤ 2.5 mm), not due to swollen cataract

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

8. Rubella, congenital, traumatic, or complicated cataracts

9. Situations where the need for a large capsulotomy can be anticipated (eg, diabetics, retinal detachment in the fellow eye, peripheral retinal pathology, etc.)

10. Iris neovascularization

11. Glaucoma (uncontrolled or controlled with medication)

12. Subjects with diagnosed degenerative eye disorders

13. History of or current retinal conditions or predisposition to retinal conditions, previous history of, or a predisposition to, retinal detachment or presence of diabetic retinopathy that the Investigator judges could confound outcomes
    Note: Including but not limited to background diabetic retinopathy, diabetic macular edema or proliferative diabetic retinopathy, macular degeneration

14. Optic nerve atrophy

15. Subjects who are expected to require retinal laser treatment.

16. Known color vision deficiencies

17. Pregnancy or lactation current or planned during the course of the study

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

10.3 Exclusion Criteria During Surgery

Below is a list of criteria that when occurring prior to IOL implantation prevent the study lens from being implanted. This is true for both eyes.

19. Any other additional procedures during the phacoemulsification and IOL implant due to intraoperative complications that require further intervention (including but not limited to posterior capture rupture, vitreous loss, zonular dehiscence that may make the IOL implant less stable, etc.)

20. Uncontrolled intraocular pressure

21. Significant anterior chamber bleeding

22. Excessive iris mobility

23. Mechanical or surgical manipulation required to enlarge the pupil prior to or at IOL implantation (pupil size must be at least 4.5 mm or larger just prior to implantation)

24. Capsulorhexis tears or any areas of "can-opener" capsulotomy

25. Unrecognized (pre-existing but discovered during surgery) ocular conditions or complications in which the IOL stability could be compromised, including zonular weakness

26. Zonular or Capsule rupture

27. Intended IOL haptic placement other than bag-bag

11 TREATMENT

Upon signing informed consent, subjects are considered enrolled in the study. All subjects will be assigned a single subject identifier at the screening visit. The subject identifier consists of a combination of a 4 digit investigator number and a 5 digit subject number. The number is automatically generated sequentially by the EDC system. As an example: "4584.00001" (The investigator number and subject number are separated by a "." character). This number will be used throughout the clinical trial.

Within 10 business days of surgery, subjects will be randomized in a 1:1 manner to receive treatment with either the test or control IOL. Throughout the clinical trial, the Investigator will be responsible for the accounting of all investigational products and will ensure that the clinical trial products are used in accordance with the manufacturer's DFU.

11.1 Investigational Products

Test Article: ACRYSOF IQ PanOptix Presbyopia-Correcting IOL Model TFNT00

The TFNT00 IOL is a CE Marked device that is commercially available in the countries of the participating Investigators as well as other countries across the globe.

The lens is an ultraviolet and blue-light filtering foldable multifocal IOL of single-piece design with a central optic and two open-loop haptics. The optic is 6.0 mm in diameter and the lens has an overall diameter of 13.0 mm. The optic consists of a proprietary high refractive index hydrophobic acrylic material with a blue light filtering chromophore which filters light in a manner that approximates the human crystalline lens in the 400-475 nm blue light wavelength range (Boettner 1962). It is biconvex and consists of a soft acrylic material capable of being folded prior to insertion, allowing placement through an incision smaller than the optic diameter of the lens. After surgical insertion into the eye, the lens gently unfolds to its intended shape. The optic diffractive structure is in the central 4.5 mm portion of the optic zone and divides the incoming light to create a +2.17 D intermediate and a +3.25 D near add power. The anterior surface is designed with negative spherical aberration to compensate for the positive spherical aberration of the cornea.

The lens is available in a diopter range of 13.0 – 30.0 D in 0.5 D increments and 31.0 D – 34.0 D in 1.0 D increments. The manufacturer suggested A-constant for optical biometry equipment is 119.1.
Note: Subjects in this study required a lens power between **13.0 and 30.0 D**. While available, IOLs out of this power range will not be utilized for this study.

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; and
- A package insert containing directions for use.

More information on the test article can be found in the Package Insert/Directions for Use (DFU).

The 839MP IOL is a CE Marked device approved for use and commercially available in the countries with participating Investigators as well as other countries across the globe.

The lens is a foldable multifocal IOL made from 25% hydrophilic acrylic material with hydrophobic surface properties. The lens has a total diameter of 11.0 mm with 360^{o} square edge and can be inserted through a corneal incision ≥1.8 mm. The IOL is a single-piece design with a central optic and 4 haptics with 0^{o} angulation. The optic is 6.0 mm in diameter with a diffractive structure in the central 4.3 mm portion of the optic zone. The diffractive structure divides the incoming light to create a +1.66 D intermediate and a +3.33 D near add power. The posterior surface is designed with negative spherical aberration (-0.18) to compensate for the positive spherical aberration of the cornea.

The lens is available in a diopter range of 0.0 – 32.0 D in 0.5 D increments. The manufacturer suggested A-constant for optical biometry equipment is 118.6.
Note: Subjects in this study required a lens power between **13.0 and 30.0 D**. While available, IOLs out of this power range will not be utilized for this study.

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; and
- A package insert containing directions for use.

More information on the test article can be found in the Package Insert/DFU.

Other national regulations for labeling may apply for studies conducted outside the United States or for studies using previously approved products.

11.2 Usage

Intraocular lenses are implantable medical devices and are intended for long term use over the lifetime of the pseudophakic subject. Lenses utilized in this trial are intended for presbyopic correction allowing the pseudophakic subject to see across a range of distances with foci at near, intermediate and far distances. See Section 11.1 Investigational Products for details related to near and intermediate add power specific to each lens.

In order to implant the test and control articles, the surgeons participating in the study must be licensed ophthalmologists with cataract surgery experience. Each surgeon will use his/her standard of care to implant the lens following respective Package Insert/DFU instructions for each device.

11.3 Accountability Procedures

The Investigator will procure *both* investigational products (test and control lenses). Details related to the procurement, labeling, handling, dispensing and final disposition are outlined below. The product must be tracked/accounted for through all steps of the procedure.

11.3.1 Procurement

The Investigator shall locally procure each product (test lens and control lens) through his/her standard commercial channel.

11.3.2 Labeling

Product is locally procured via commercial channel and will arrive in country compliant commercial packaging with commercial label.

11.3.3 Handling

Once designated for trial use, product will 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.

11.3.4 Dispensing

The Investigator is to keep a current record of the dispensing of all test articles. This record will be made available to the Sponsor's monitor to account for all test articles. Any discrepancy and/or deficiency must be recorded, with an explanation.

11.3.5 Final Disposition

At the conclusion of the trial, remaining product may be returned to the Investigator's general stock.

Note: Return deficient product to the manufacturer following the each manufacturer's respective complaint process. Refer to Section 13.3 for further details on the return process for Alcon product. Additionally, the investigator must follow any recalls from the distributor/manufacturer.

12 CLINICAL TRIAL PROCEDURES

12.1 Clinical Trial Assessments

The following section outlines the assessments to be performed in this clinical trial. Assessments are described in detail in the ILH297-P003 Manual of Procedures (hereto referred to as the MOP), and are outlined in tabular format in Section 6 of this protocol.

12.1.1 Preoperative Visit (Visit 0)

Visit 0: -60 to 0 Days Prior to Visit 00, Binocular Visit

Below is a list of study procedures to be undertaken at Visit 0. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in source documentation and case report forms (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 -60 to 0 day preoperative time period.

1. Review non-study specific inclusion/exclusion criteria (eg, age, previous ocular history) to ensure that a potential subject meets all qualifications for participation in the study.

2. For a potential subject meeting all entry criteria via pre-screening, invite him/her to participate in the study, and carry out the informed consent process if he/she is interested. Refer to Section 16.2 Informed Consent Procedures.
   Note: Subjects must formally consent to the trial prior to any study specific testing.

3. Document demographics, ocular and non-ocular medical history, ocular and non-ocular concomitant medications and pregnancy status (where applicable).

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

5. [redacted]

6. [redacted]

7. Document the target residual refractive error based the IOL calculation power. [redacted]
   [Both Eyes, Bilateral]

8. [redacted]

9. [redacted]

10. Conduct slit lamp examination.
    [Both Eyes, Bilateral]

11. Conduct dilated fundus examination.
    [Both Eyes, Bilateral]

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

13. Record any AEs. Refer to Section 13 for further detail.

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

15. [redacted]

16. Proceed with scheduling surgery.

12.1.2 Operative Visit (Visit 00/00A)

Visit 00: Day 0, Monocular 1st Eye
Visit 00A: 2-21 Days Post 1st Eye Implantation, Monocular 2nd Eye

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

Note: the Visit 00A window may overlap with other study visit windows (eg, Visit 1, Visit 2). In this case, both visits may be conducted on the same day at the discretion of the Investigator.

1. In preparation for the operative visit, randomize the subject. Randomization should be performed within 10 business days of Visit 00. 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 trial.

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

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

9. Record any adverse events including SSIs.
   Note: Serious adverse events (SAEs) including SSIs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

10. Record any device deficiencies. Refer to Section 13 for further detail.

12.1.3 1-Day Postoperative Visit (Visit 1/1A)

Visit 1: 1-2 Days 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 undertaken 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 case report forms (if applicable).

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

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

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

4. Assess subjective PCO, and record information for any posterior capsulotomy that has occurred since surgery, if applicable.
   [Operative Eye Only, Monocular]

5. Perform tonometry to measure the IOP.
   [Operative Eye Only, Monocular]

6. Record any AEs including SSIs.
   Note: SAEs including SSIs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

7. Record any device deficiencies. Refer to Section 13 for further detail.

12.1.4 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 2nd Eye

Below is a list of study procedures to be undertaken 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 case report forms (if applicable).

1. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. Perform slit lamp examination of the anterior segment. Include documentation of IOL observations, if any.
   [Operative Eye Only, Monocular]
7. Observe any IOL position changes (ie, tilt and decentration) occurring since the previous visit.
   [Operative Eye Only, Monocular]
8. Assess subjective PCO, and record information for any posterior capsulotomy that has occurred since surgery, if applicable.
   [Operative Eye Only, Monocular]
9. Perform tonometry to measure the IOP.
   [Operative Eye Only, Monocular]

10. Record any AEs including SSIs.
    Note: SAEs including SSIs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

11. Record any device deficiencies. Refer to Section 13 for further detail.

12.1.5 1-Month Postoperative Visit (Visit 3A)

Visit 3A: 20-40 Days Post 2nd Eye Implantation, Binocular

Below is a list of study procedures to be undertaken 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 case report forms (if applicable).

1. Record changes in medical/ocular history and ocular and non-ocular concomitant medications.
2. [redacted]
3. [redacted]
4. [redacted]
5. Assess binocular uncorrected distance visual acuity.
   [Both Eyes, Binocular]
6. [redacted]
7. Assess binocular uncorrected near (40 cm) visual acuity.
   [Both Eyes, Binocular]
8. [redacted]
9. Assess binocular uncorrected intermediate (60 cm) visual acuity.

[Both Eyes, Binocular]

10. Perform defocus testing.
    [Both Eyes, Binocular]

11. Perform mesopic without glare contrast sensitivity testing.
    [Both Eyes, Binocular]

12. Perform mesopic with glare contrast sensitivity testing.
    [Both Eyes, Binocular]

13. Perform photopic without glare contrast sensitivity testing.
    [Both Eyes, Binocular]

14. Perform photopic with glare contrast sensitivity testing.
    [Both Eyes, Binocular]

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

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

17. Assess subjective PCO, and record information for any posterior capsulotomy that has occurred since surgery, if applicable.
    [Both Eyes, Bilateral]

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

19. Perform tonometry to measure the IOP.
    [Both Eyes, Bilateral]

20. Record any AEs including SSIs.
    Note: SAEs including SSIs must be entered into EDC within 24 hours of the

Investigator's knowledge. Refer to Section 13 for further detail.

21. Record any device deficiencies. Refer to Section 13 for further detail.

12.1.6 6-Month Postoperative Visit (Visit 4A)

Visit 4A: 120-180 Days Post 2nd Eye Implantation, Binocular

Below is a list of study procedures to be undertaken at Visit 4A. It is recommended that procedures are performed in the order described below unless otherwise stated. All assessments must be documented in source documentation and case report forms (if applicable).

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

2. Administer patient satisfaction question. For question, refer to Appendix Section 18.1.

3. [redacted]

4. [redacted]

5. [redacted]

6. Assess binocular uncorrected distance visual acuity.
   [Both Eyes, Binocular]

7. [redacted]

8. Assess binocular uncorrected near (40 cm) visual acuity.
   [Both Eyes, Binocular]

9. [redacted]

10. Assess binocular uncorrected intermediate (60 cm) visual acuity.
    [Both Eyes, Binocular]

11. Perform defocus testing.
    [Both Eyes, Binocular]

12. Perform mesopic without glare contrast sensitivity testing.
    [Both Eyes, Binocular]

13. Perform mesopic with glare contrast sensitivity testing.
    [Both Eyes, Binocular]

14. Perform photopic without glare contrast sensitivity testing.
    [Both Eyes, Binocular]

15. Perform photopic with glare contrast sensitivity testing.
    [Both Eyes, Binocular]

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

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

18. Assess subjective PCO, and record information for any posterior capsulotomy that has occurred since surgery, if applicable.
    [Both Eyes, Bilateral]

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

20. Perform tonometry to measure the IOP.
    [Both Eyes, Bilateral]

21. Record any AEs including SSIs.
    Note: Serious adverse events (SAEs) including SSIs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

22. Record any device deficiencies. Refer to Section 13 for further detail.

12.2 Unscheduled Visits

An unscheduled visit (UNSV) is defined as follows:

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

An UNSV may or may not result in the capture of an adverse event. Likewise an adverse event 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 his/her medical judgment. The following assessments are recommended.

- Concomitant medications
- Monocular uncorrected distance VA
- Slit lamp exam including IOL position change
- Subjective PCO and posterior capsulotomy assessment
- Fundus exam
- IOP
- Adverse events
- Device deficiencies

Note: Assessments are not limited to the above list.

If the subject is discontinued at the unscheduled visit, perform all Early Exit procedures. Refer to Section 6 SCHEDULE OF VISITS. For safety purposes, if an UNSV is required after the final study visit, document the visit. Refer to Section 13.5 for further detail.

12.3 Missed Visits

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

If a subject is unable to return for the final study visit, complete the Exit Case Report Form with the appropriate reason for discontinuation. If attempts to contact the subject are unsuccessful, document the date the subject is considered lost to follow-up. Complete the subject's Exit Case Report Form after the last window (Visit 4A) closes, indicating the subject is lost to follow-up.

12.4 Discontinued Subjects

Discontinued subjects withdraw, or are withdrawn from the study after signing consent, and prior to completing all study visits. Subjects signing consent, but withdrawing or withdrawn prior to randomization shall be considered discontinued due to screen failure, and the failed entry criterion documented (eg, inclusion criterion 2, exclusion criterion 5). Refer to Section 10 SUBJECT POPULATION.

Subjects may discontinue study participation at any time and for any reason. Subjects may be discontinued from the study at any time if in the medical opinion of the PI or designated, qualified medical personnel, continued participation poses a health risk to the subject. Subject numbers from discontinued subjects will not be reissued. Discontinued subjects will not be replaced.

12.5 Clinical Trial Termination

The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause. The Investigator also may terminate the study at his/her site for reasonable cause. Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities (where applicable) of the termination/ suspension

and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons.

If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s), and provide written instructions for study termination and applicable subject follow-up.

13 DEVICE DEFICIENCIES AND ADVERSE EVENTS

13.1 General Information

Product Complaint

Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.

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.

- **Malfunction** is defined as a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed.
- **Use error** is defined as the act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user.

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 (IOL)
- Lack of efficacy

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 medical device.

Serious Adverse Event (SAE)

Adverse event that led to any of the following:

- Death
- A serious deterioration in the health of the subject that either resulted in:
    a) A life-threatening illness
    b) Permanent impairment of a body function or permanent damage to a body structure
    c) A condition necessitating medical or surgical intervention to prevent a) or b)
    d) A condition that requires hospitalization or significant prolongation of existing hospitalization
    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

Non-serious adverse event

Any adverse event that does not meet seriousness criteria described above.

Adverse Device Effect (ADE)

Adverse event related to the use of a 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.

Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

Serious Public Health Threat

Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).

Figure. 13–1 Categorization of All Adverse Events

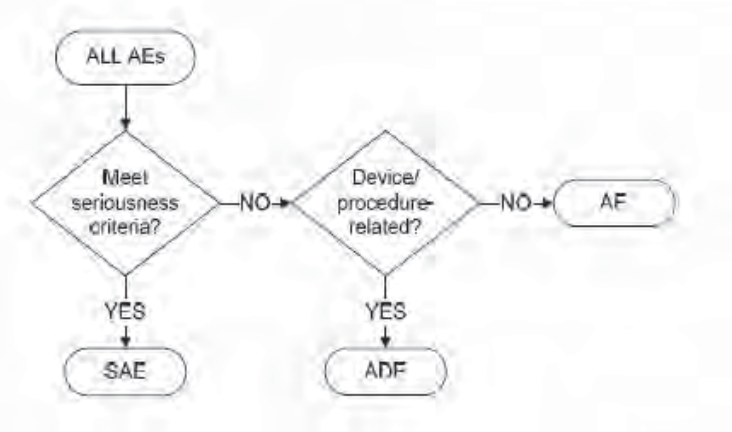
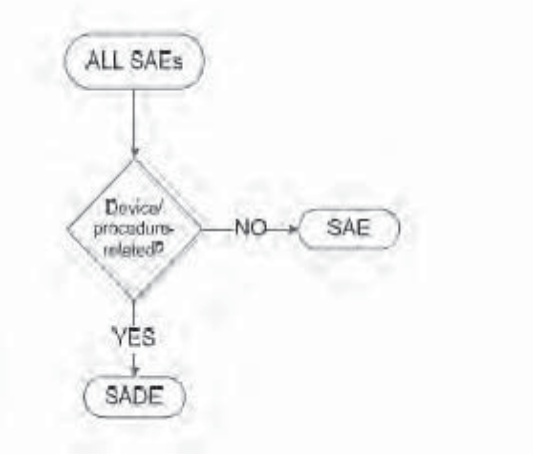


Figure. 13–2 Categorization of All Serious Adverse Events



Specific Events Relevant to this Protocol

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

Cumulative Serious Adverse Events

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

Persistent Serious Adverse Events

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

This list is consistent with the categories provided in EN ISO 11979-7:2014. A persistent AE is an AE that is present at the conclusion of a clinical investigation per EN ISO 11979-1:2012. Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and should be reported appropriately as delineated in Section 13.2.

13.2 Recording and Reporting Adverse Events and Device Deficiencies

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

A separate eCRF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event.

The site must submit all available information to the Study Sponsor as follows:

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs (related AEs) that do not meet seriousness criteria and Device Deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.

Please also include a printed copy of the completed Device Deficiency and/or the SAE-ADE 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.
- Document all relevant information from Discharge Summary, Autopsy Report, Certificate of Death etc., if applicable, in narrative section of the Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF.

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

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 according to the requirements of regulatory authorities or IRB/IEC.

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

In the very unlikely event of a Serious Public Health Threat being detected, the site must contact the Study Sponsor and the accredited ethics committee immediately.

Intensity and Causality Assessments

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

Causality

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

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:

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.

If an AE reported for an Investigator's subject is upgraded to a SAE or if a SAE reported by an Investigator as not related that is subsequently upgraded to be related by the study Sponsor, the Investigator will receive a notification by the study Sponsor.

13.3 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 as specified in the MOP and must include the Complaint # which will be provided by study Sponsor.

13.4 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study (see Section 9.2) 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 of all cases in which the code was broken and of the circumstances involved. Additionally, the study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

13.5 Follow-Up of Subjects with Adverse Events

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

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

All complaints received after study completion (ie, after database lock) 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 report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

13.6 Pregnancy in the Clinical Trial

Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case–by-case basis. An Alcon form will be utilized to capture all pregnancy related information until birth of the child.

14 DATA REVIEW AND HANDLING

14.1 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 electronic case report forms (eCRFs) exists and are accessible for verification by the monitor. It is required that the author of each entry in the source documents be identifiable (eg, initials or signature and date). At a minimum, source documents should include the following information for each subject:

- Subject identification (name, date of birth or age, sex)
- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol-specific procedures were performed
- Results of study testing, as required by the protocol
- Test article accountability records
- Documentation of SAEs and other safety parameters (as 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

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

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. Data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on a source document shall be dated, initialed, and explained if necessary, and shall not obscure the original entry (ie, an audit trail shall be maintained); this applies to both written and electronic changes and corrections. eCRFs shall be signed and dated by the Principal Investigator or his/her authorized designee(s).

14.2 Data Review and Clarifications

Upon completion of the eCRFs, targeted data will be reviewed by the assigned Sponsor global clinical site management (CSM) team for accuracy and completeness. The planned source document verification and overall monitoring activities for this study are outlined in a

separate document, the Protocol Monitoring Plan. Corrections and/or any necessary additions to the data will be applied and if required, queries will be generated. Designated investigative staff are expected to respond to data queries in a timely manner and ensure that the corrections and changes made to the data are reflected in the subjects' source documentation.

Deviations from this protocol, regulatory requirements and GCP must be recorded. An explanation of the deviation should be included, as applicable. In addition, corrective and preventive action should be identified, implemented and documented within the study records. Prior to study start, a plan for data validation will be completed by Alcon clinical data management, and agreed upon by the study clinical manager (CM) and other team members.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List. Medical history and adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) terminology. Upon completion of the study and once the database is declared completed and accurate, the database will be locked and data will be available for data analysis. Any changes to the database after lock will be implemented upon agreement between the Sponsor's clinical trial management, medical safety clinical data management and biostatistics departments, and will be completed following the Sponsor's procedures for changes to a database after database lock.

15 ANALYSIS PLAN

15.1 Subject Evaluability

The final subject evaluability will be determined prior to breaking the code for masked treatment assignment and locking the database. All eyes will be analyzed as implanted.

15.2 Analysis Data Sets

The all-implanted analysis set (AAS) will include all eyes with successful test or control article bilateral implantation.

The best-case analysis set (BAS) will include all eyes successfully implanted with the test or control article that had at least one postoperative visit, and with no macular degeneration at any time, and no major protocol deviations. Subjects who become pregnant at any time during the study will also be excluded from the BAS.

All eyes with attempted test or control article implantation (successful or aborted after contact with the eye) will be considered evaluable for the Safety Set (SS).

The primary analysis set for performance analyses will be the AAS for all performance endpoints, except for binocular defocus and contrast sensitivity for which it will be considered supportive. The BAS will be the primary set for binocular defocus and contrast sensitivity. [redacted] The SS will be used for analysis of safety endpoints.

15.3 Demographics and Baseline Characteristics

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

15.4 Performance Analyses

A total of six hypothesis tests will be conducted to address the primary and secondary objectives of the study.

The primary, second secondary and third secondary will be tests of non-inferiority while the first secondary, fourth secondary and fifth secondary will be tests of superiority. A combination of gate-keeping and Bonferroni adjustment strategies will be employed to

control the overall type I error rate at 0.05. The hypothesis tests and the testing order (multiplicity adjustment) are outlined in Figure 15-1.

15.4.1 Primary Performance

The primary objective is to demonstrate non-inferiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected intermediate (60 cm) visual acuity (UCIVA) at Visit 4A.

15.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{TFNT00VA} - \mu_{839MPVA} \geq \Delta$$

$$H_A: \mu_{TFNT00VA} - \mu_{839MPVA} < \Delta$$

where, Δ refers to the non-inferiority margin, set at 0.1 logMAR, and $\mu_{TFNT00VA}$, $\mu_{839MPVA}$, refer to the mean binocular high contrast UCIVA for the test and control lenses, respectively.

15.4.1.2 Analysis Methods

The primary hypothesis will be tested by generating a two-sided 90% confidence interval using repeated measures analysis of variance at a type I error rate of 5%, 1-sided. Tests at each visit will be reported with Visit 4A (120-180 days) prospectively identified as the primary time point of interest. The upper bound of the two-sided 90% confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TFNT00 IOL will be concluded non-inferior to the 839MP IOL for UCIVA.

The two sided 90% confidence intervals will be reported for the difference between the treatment groups at each visit.

15.4.2 Secondary Performance

The first secondary objective is to demonstrate superiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected intermediate (60 cm) visual acuity (UCIVA) at Visit 4A.

The second secondary objective is to demonstrate non-inferiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected distance (4 m) visual acuity (UCDVA) at Visit 4A.

The third secondary objective is to demonstrate non-inferiority of the TNFT00 IOL to the 839MP IOL in mean photopic binocular uncorrected near (40 cm) visual acuity (UCNVA) at Visit 4A.

The fourth secondary objective is to demonstrate superiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected near (40 cm) visual acuity (UCNVA) at Visit 4A.

The fifth secondary objective is to demonstrate superiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected distance (4 m) visual acuity (UCDVA) at Visit 4A.

The sixth secondary objective is to characterize the Binocular Defocus Curve profiles, contrast sensitivity and patient satisfaction with the TFNT00 IOL versus the 839MP IOL at Visit 4A.

The secondary endpoints are UCNVA, UCIVA, UCDVA, Binocular Defocus, Contrast Sensitivity and Patient Satisfaction.

15.4.2.1 Statistical Hypotheses

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

$$H_0: \mu_{TFNT00VA} \geq \mu_{839MPVA}$$

$$H_A: \mu_{TFNT00VA} < \mu_{839MPVA}$$

where $\mu_{TFNT00VA}$, $\mu_{839MPVA}$, refer to the mean binocular high contrast UCIVA, UCNVA or UCDVA for the test and control lenses, respectively.

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

$$H_0: \mu_{TFNT00VA} - \mu_{839MPVA} \geq \Delta$$

$$H_A: \mu_{TFNT00VA} - \mu_{839MPVA} < \Delta$$

where, Δ refers to the non-inferiority margin, set at 0.1 logMAR, and $\mu_{TFNT00VA}$, $\mu_{839MPVA}$, refer to the mean binocular high contrast UCDVA or UCNVA for the test and control lenses, respectively.

15.4.2.2 Analysis Methods

For the superiority hypothesis tests, treatment group comparison for UCIVA will be made and the first secondary objective will be demonstrated if $p<0.025$ from a repeated measures analysis of variance at a Type I error rate of 2.5%. Tests at each visit will be reported with Visit 4A (120-180 days) prospectively identified as the primary time point of interest. The two-sided 95% confidence intervals will be reported for the difference between treatment groups at each visit. For the fourth and fifth secondary objectives, superiority will be demonstrated if $p<0.05$ (or $p<0.025$, depending on the gatekeeping) for UCNVA and UCDVA at Visit 4A (120-180 days), respectively.

For the non-inferiority hypothesis test of UCDVA, the second secondary objective, treatment group comparisons will be tested by generating a two-sided 95% confidence interval from a repeated measures analysis of variance, with site included as a covariate, at a Type I error rate of 2.5%. The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response and least squares means will be used to estimate the treatment effect at each visit with Visit 4A (120-180 days) prospectively identified as the primary point of interest. The upper bound of the two-sided 95% confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TNFT00 IOL will be concluded non-inferior to the 839MP IOL for UCDVA. The two-sided 95% confidence intervals will be reported for the difference between the treatment groups at each visit.

For the non-inferiority hypothesis test of UCNVA, the third secondary objective, treatment group comparisons will be tested by generating a two-sided 95% (or 90%, depending on the gatekeeping) confidence interval from a repeated measures analysis of variance, with site included as a covariate, at a Type I error rate of 2.5% (or 5%). The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response and least squares means will be used to estimate the treatment effect at each visit with Visit 4A (120-180 days) prospectively identified as the primary point of interest. The upper bound of the two-sided 95% (or 90%) confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TNFT00 IOL will be concluded non-inferior to the 839MP IOL for UCNVA. The two-sided 95% (or 90%) confidence intervals will be reported for the difference between the treatment groups at each visit.

Summaries of logMAR visual acuity will also include two-sided 90% confidence intervals. A composite visual acuity endpoint comprising binocular uncorrected visual acuity at Distance (4 m) and Near (40 cm) will be summarized as a categorical variable with the following

categories: 20/20 or better (≤0.04 logMAR), 20/32 or better (≤0.14 logMAR) and 20/40 or better (≤0.24 logMAR).

Defocus curves will be generated for binocular defocus data, including two-sided 90% confidence intervals, with the amount of defocus along the x-axis and logMAR VA at each defocus point along the y-axis. To examine inter-site variation in outcome, forest plots of near, intermediate and distance visual acuity will be produced by plotting the difference in means and associated standard error for each site.

Contrast Sensitivity will be scored and analyzed per contrast sensitivity unit instructions.

Responses to the satisfaction question will be analyzed as a categorical variable.

15.5 Handling of Missing Data

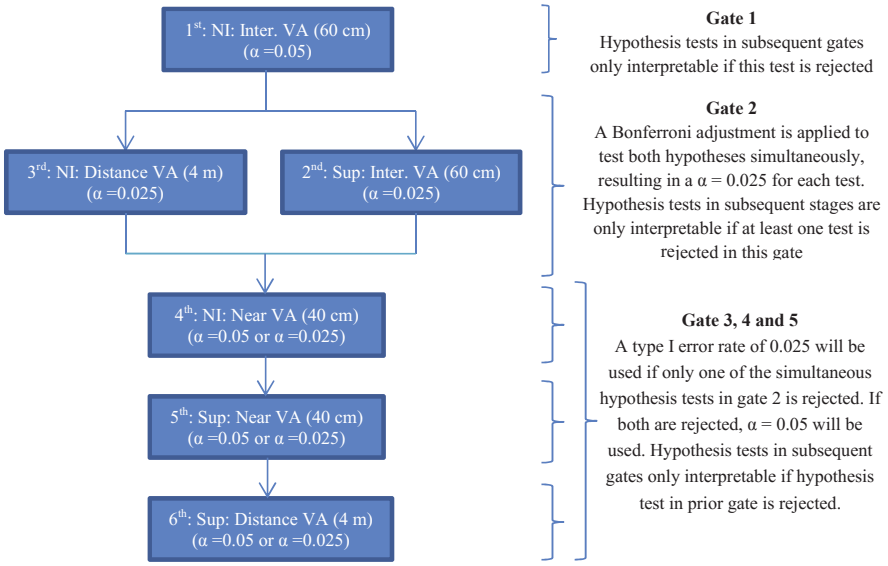
The AAS and BAS do not include any imputed values. Although missing data will occur, the influence of the missing data is expected to be minimal.

15.6 Multiplicity

A total of six hypothesis tests will be conducted to address the primary and secondary objectives of the study.

A combination of gate-keeping and Bonferroni adjustment strategies will be employed to control the overall type I error rate. The hypothesis tests and the testing order (multiplicity adjustment) are outlined in Figure 15-1.

Figure .15–1 Multiple Testing Strategy



15.7 Safety Analysis

Adverse Events

All information obtained on AEs will be displayed by treatment and subject.

The number and percentage of all ocular adverse events, including secondary surgical interventions (SSIs) for either eye, will be tabulated by preferred term with a breakdown by treatment and implanted eye. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

The number and percentage of all adverse events will also be tabulated with a breakdown by treatment.

Device Deficiencies

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

IOL Observations

The number and percentage of all IOL observations will be tabulated with a breakdown by treatment and implanted eye.

Subjective Posterior Capsule Opacification

The number and percentage of eyes within each category of subjective posterior capsule opacification will be tabulated with a breakdown by treatment and implanted eye.

Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy will be tabulated with a breakdown by treatment and implanted eye.

Other Safety Assessments

All other safety assessments (including intraocular pressure, slit lamp examination, IOL position change, fundus visualization, dilated fundus examination and surgical problems) will be summarized. Number and percentage will be presented for categorical variables and descriptive statistics including mean, standard deviation, minimum and maximum will be presented for continuous variables.

15.8 Interim Analyses

An interim analysis will be performed when all subjects complete Visit 3A (20-40 days post 2nd eye implantation) in order to support the study publication plan of the test articles for near, intermediate and distance visual acuity, contrast sensitivity, defocus curves and adverse events. The interim analysis results will be distributed to a limited audience to limit potential bias in Visit 4A assessments. The clinical trial team with the exception of the Brand Lead will be masked to the interim analysis results.

15.9 Adaptive Study Design

Not applicable.

15.10 Sample Size Justification

The multiplicity adjustment strategy is outlined in Figure 15.-1. Sample size estimations are based on the minimum sample size needed to achieve 90% power for all hypothesis tests. A type I error rate of 2.5%, one-sided, is used for calculations to account for simultaneous testing in Gate 2 (see Figure 15-1).

Assuming a dropout rate of 5%, approximately 160 subjects will be bilaterally implanted in 1:1 allocation ratio (test: control) to achieve at least 152 subjects who complete the study. With 152 subjects (76 per group) there is 98% probability that an upper one-sided 97.5% confidence limit on the difference (test-control) in visual acuity will be less than 0.1 logMAR, assuming the mean difference of 0.0 logMAR and a common standard deviation of 0.16 logMAR, the maximum observed for binocular uncorrected distance, intermediate and near visual acuity in a previous Alcon study (C-06-40, ReSTOR +3.0 D IOL).

Also, with 76 subjects per group, there is more than 90% power to detect a difference of 0.09 logMAR (4.5 letters) between means in a two sample t-test conducted at a 2.5% chance of a Type I error and assuming a standard deviation of 0.16 logMAR for binocular uncorrected distance, intermediate and near visual acuity.

16 ADMINISTRATIVE PROCEDURES

16.1 Regulatory and Ethical Compliance

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice, Code of Federal Regulations (CFR), and laws and regulations of foreign countries, whichever affords greater protection to subjects. The trial shall also be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs) and all other applicable regulations. The Investigator and all clinical trial staff will conduct the clinical trial in compliance with this protocol. The Investigator will ensure that all personnel involved in the conduct of the clinical trial are qualified to perform their assigned duties through relevant education, training, and experience.

16.2 Informed Consent Procedures

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

16.3 Responsibilities of the Investigator and IRB/IEC

Before clinical trial initiation, this protocol, the informed consent form (and assent form, if applicable), any other written information provided to subject, and any advertisements planned for subject recruitment must be approved by an Institutional Review Board /

Independent Ethics Committee (IRB/IEC). A master list of IRBs/IECs for this clinical trial can be found in the Trial Master File. The Investigator must provide documentation of IRB/IEC approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subjects, and subject compensation programs. The IRB/IEC must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the clinical trial or in the case of early termination, the Investigator will notify the IRB/IEC of the clinical trial's final status. Finally, the Investigator will report to the IRB/IEC on the progress of the clinical trial at intervals stipulated by the IRB/IEC.

16.4 Sponsor and Monitoring Responsibilities

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored, following the Protocol Monitoring Plan, 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; the equipment used to assess variables in the clinical investigation is maintained and calibrated per manufacturer instructions and Sponsor requirements; the study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current Good Clinical Practice (GCP), and with applicable regulatory requirements.

All investigative sties will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. The assigned CSM will contact each site at appropriate intervals. The Lead Clinical Site Manager (LCSM) will determine the frequency of site visits. Closeout visits will take place after the last visit of the last subject.

16.5 Regulatory Documentation and Records Retention

Essential documents must be retained by the investigator in compliance with the medical device directive and its local transposition as well as other applicable national and international regulations. The investigator(s)/institution(s) must comply with record retention stipulations outlined in the Clinical Study Agreement. Additionally the Investigator will be supplied with further instruction at study completion.

16.6 Clinical Trial Results

The Investigator will notify the accredited ethics committee of the end of the study as required by the ethics committee. The end of the study is defined as database lock. In case the

study is ended prematurely, the Investigator will notify the accredited ethics committee, including the reasons for the premature termination. Within one year after the end of the study, the Investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited ethics committee as required.

16.7 Publication of the Clinical Trial

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

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

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. You shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Alcon's products or a research program that is provided by Alcon to you (the "Confidential Information"). All such persons must be instructed not to further disseminate this information to others. You shall not use the Confidential Information for any purpose other than the study.

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

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

17 REFERENCES

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Maxwell WA, Cionni RJ, Lehmann RP, Modi SS. Functional outcomes after bilateral implantation of apodized diffractive aspheric acrylic intraocular lenses with a +3.0 or +4.0 diopter addition power. Randomized multicenter clinical study. J Cataract Refract Surg. 2009; 35(12):2054-61.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
02/19/2016 23:00:00	[redacted]	[redacted]
02/22/2016 14:26:25	[redacted]	[redacted]
02/22/2016 17:46:23	[redacted]	[redacted]
02/24/2016 19:47:16	[redacted]	[redacted]