Alcon

Title:

Clinical Investigation of the Visual Outcomes and Safety of AcrySof® IQ PanOptix® Toric Trifocal IOLs in Asian Population

Protocol Number:	ILX140-P001 / NCT04528069
Development Stage of Project:	Postmarket
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2009
Test Product:	ACRYSOF IQ PanOptix Toric Trifocal Intraocular Lenses (IOLs) (Models TFNT30, TFNT40, TFNT50, TFNT60)

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, all applicable regulatory authority regulations, and conditions of approval imposed by the reviewing IRB or regulatory authority.
- I will supervise all testing of the device involving human subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental regulations.
- I have read and understand the appropriate use of the investigational product(s) as described in the protocol, product information, or other sources provided by the Sponsor.
- I understand the potential risks and side effects of the investigational product(s).
- I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements of the Sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an Investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal Investigator:

Signature Date

Name and professional position:

Address:

Table of Contents

Clinical Investigation of the Visual Outcomes and Safety of AcrySof® IQ PanOptix® Toric Trifocal IOLs in Asian Population 1

Table of Contents 3

List of Tables 6

List of Figures 6

1 GLOSSARY OF TERMS 7

2 LIST OF ACRONYMS AND ABBREVIATIONS 11

3 PROTOCOL SUMMARY 13

4 PROTOCOL AMENDMENTS 21

4.1 Amendments 22

5 INTRODUCTION 22

5.1 Rationale and Background 22

5.2 Purpose of the Study 22

5.3 Risks and Benefits 23

5.3.1 Known and Potential Risks 23

5.3.2 Potential Benefits 24

6 STUDY OBJECTIVES 24

6.1 Primary Effectiveness Objective(s) 24

[redacted]

6.2 Safety Objective(s) 26

[redacted]

7 INVESTIGATIONAL PLAN 27

7.1 Study Design 27

7.2 Rationale for Study Design 27

[redacted]

7.3 Data Monitoring Committee 28

8 STUDY POPULATION 28

8.1 Inclusion Criteria 28

8.2 Exclusion Criteria 29

[redacted]

8.4 Rescreening of Subjects 31
9 TREATMENTS ADMINISTERED 31
9.1 Investigational Product(s) 31
9.2 Other Medical Device or Medication Specified for Use during the Study 33
9.3 Treatment Assignment 33
9.4 Treatment Masking 34
9.5 Accountability Procedures 34
9.6 Changes to concomitant medications, treatments/procedures 34
10 STUDY PROCEDURES AND ASSESSMENTS 35
10.1 Informed Consent and Screening 35
10.2 Visits and Examinations 35
10.2.1 Visit 0: Preoperative Screening Visit 35
10.2.2 Visit 00: Surgery Visit 1st Eye 37
10.2.3 Visit 1: Postoperative for 1st Eye (1-2 Days after Visit 00) 38
10.2.4 Visit 2: Postoperative for 1st Eye (7-14 Days after Visit 00) 39
10.2.5 Visit 00A: Surgery Visit 2nd Eye (recommended 7-14 Days after Visit 00) 39
10.2.6 Visit 1A: Postoperative for 2nd Eye (1-2 Days after Visit 00A) 39
10.2.7 Visit 2A: Postoperative for 2nd Eye (7-14 Days after Visit 00A) 39
10.2.8 Visit 3A: Postoperative for Both Eyes (30-60 Days after Visit 00A) 40
10.2.9 Visit 4A: Postoperative for Both Eyes (90-120 Days after Visit 00A) 40
10.2.10 Visit 5A: Postoperative for Both Eyes (180-210 Days after Visit 00A) 42
10.2.11 Unscheduled Visit 42
10.3 Discontinued Subjects 43
10.3.1 Screen Failures 43
10.3.2 Discontinuations 43
10.3.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product 44
10.3.4 Subject Lost to Follow Up 44
10.4 Subject Pregnant or Lactating 44
10.5 Clinical Study Termination 44
10.5.1 Follow-up of subjects after study participation has ended 45
10.6 Contingency Measures 45
11 ADVERSE EVENTS AND DEVICE DEFICIENCIES 45

11.1 General Information 45
11.2 Specific Events Relevant to this Protocol 46
11.2.1 Device Deficiencies 47
11.3 Monitoring for Adverse Events 47
11.4 Procedures for Recording and Reporting 48
11.5 Intensity and Causality Assessments 49
11.5.1 Intensity (Severity) 49
11.5.2 Causality 49
11.6 Return Product Analysis 50
11.7 Unmasking of the Study Treatment 50
11.8 Follow-Up of Subjects with Adverse Events 50
11.9 Pregnancy in the Clinical Study 50
12 ANALYSIS PLAN 51
12.1 Subject Evaluability 51
12.2 Analysis Sets 51
12.3 Demographic and Baseline Characteristics 51
12.4 Effectiveness Analyses 52
12.4.1 Analysis of Key Effectiveness Endpoint(s) 52
12.4.1.1 Statistical Hypotheses 52
12.4.1.2 Analysis Methods 52
[redacted]
12.5 Handling of Missing Data 54
12.6 Safety Analyses 54
12.6.1 Analysis of Key Safety Endpoint(s) 54
12.6.1.1 Statistical Hypotheses 54
12.6.1.2 Analysis Methods 54
[redacted]
12.8 Sample Size Justification 56
13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS 57
13.1 Subject Confidentiality 57

13.2 Completion of Source Documents and Case Report Forms 57
13.3 Data Review and Clarifications 58
13.4 Sponsor and Monitoring Responsibilities 59
13.5 Regulatory Documentation and Records Retention 59
13.6 Quality Assurance and Quality Control 59
14 ETHICS 60
15 REFERENCES 61
15.1 References applicable for all clinical studies 61
15.2 References for this clinical study 61

List of Tables

Table 2–1 List of Acronyms and Abbreviations Used in This Protocol 11
Table 3–1 Schedule of Study Procedures and Assessments 19
Table 6–1 Primary Objective(s) 25
Table 6–2 Safety Objective(s) 26
Table 9–1 Test Product 31

List of Figures

Figure 11.1–1 Categorization of All Adverse Events 46
Figure 11.1-2 Categorization of All Serious Adverse Events 46

1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as PanOptix Toric Trifocal IOL (Models: TFNT30, TFNT40, TFNT50, TFNT60)
Name of Control Product(s)	N/A
Asian Population	Self-identified as being of Chinese, Japanese, Korean, or Mongolian descent.
Adverse Device Effect	Adverse event related to the use of an investigational medical device (test product) or control product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test product or control product.*
Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (test product). *Note: For subjects, this definition includes events related to the test product, the control product, or the procedures involved. For users or other persons, this definition is restricted to events related to the test product.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk management file.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.*

	Requirements for reporting Device Deficiencies in the study can be found in Section 11.
Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Interventional Clinical Trial	A research trial that prospectively assigns, whether randomly or not, human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, and/or a research trial in which diagnostic or monitoring procedures beyond standard of care are conducted and generate outcomes for use in analysis of data.
Malfunction	Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Non-serious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Postmarketing/Post-authorization study	Any study conducted within the conditions laid down in product labelling and other conditions laid down for the marketing of the product or under normal conditions of use. A postmarketing study falls either within the definitions of an interventional or a non- interventional study and may also fall within the definition of a post-approval study.
Product Complaints	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.

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

	e. any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 11 for additional SAEs.*
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Bird Flu.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk management file.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 LIST OF ACRONYMS AND ABBREVIATIONS

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

Abbreviation	Definition
ACD	Anterior chamber depth
AAS	All-implanted analysis set
ADE	Adverse device effect
AE	Adverse event
AL	Axial length
[redacted]	[redacted]
BCDVA	Best corrected distance visual acuity
cm	Centimeter
CRF	Case report form
CI	Confidence Interval
D	Diopter
DCIVA	Distance corrected intermediate visual acuity
DCNVA	Distance corrected near visual acuity
DFU	Directions for use
DEP	Deviations and Evaluability Plan
[redacted]	[redacted]
eCRF	Electronic case report form
EDC	Electronic data capture
eIFU	Electronic instructions for use
EU	European Union
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IOL	Intraocular lens
[redacted]	[redacted]
[redacted]	[redacted]
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
LASIK	laser-assisted in situ keratomileusis
logMAR	Logarithm of minimum angle of resolution
LRI	Limbal relaxing incision
m	Meter
MedDRA®	Medical Dictionary for Regulatory Activities
mm	Millimeter
MOP	Manual of procedures
N/A	Not applicable
[redacted]	[redacted]

OD	Right eye
OS	Left eye
OVD	Ophthalmic viscosurgical devices
PI	Principal Investigator
QUVID	Questionnaire for Visual Disturbances
SADE	Serious adverse device effect
SAE	Serious adverse event
SS	Safety analysis set
SD	Standard deviation
SOP	Standard operating procedures
SPH	Sphere
SSI	Secondary surgical intervention
TRRE	Target residual refractive error
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
VA	Visual acuity
YAG	Yttrium-Aluminum Garnet

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional
Investigational products	ACRYSOF® IQ PanOptix® Toric Trifocal Intraocular Lenses (IOLs) (Models: TFNT30, TFNT40, TFNT50, TFNT60)
Purpose and rationale	The present study is intended to confirm the effectiveness and safety of the PanOptix Toric Trifocal in Asian population, especially for visual performance. [redacted]
Objective(s)	To evaluate the clinical performance of the ACRYSOF® IQ PanOptix® Toric Trifocal intraocular lenses (Model TFNT30, TFNT40, TFNT50, TFNT60) when implanted to replace the natural lens following cataract removal in Asian Population. Primary Effectiveness objectives are to describe the following at Month 3 and Month 6 for all operative eyes: • Residual manifest cylinder • IOL rotational stability • Binocular Best Corrected Distance Visual Acuity (BCDVA) (4 m from spectacle plane) in photopic lighting • Binocular Distance Corrected Intermediate Visual Acuity (DCIVA) (60 cm from spectacle plane) in photopic lighting • Binocular Distance Corrected Near Visual Acuity (DCNVA) (40 cm from spectacle plane) in photopic lighting Safety objectives are to describe the following at Month 3 and Month 6 for all operative eyes: • Estimate the cumulative rate of secondary surgical interventions (SSIs) • Evaluate the rates of severe and most bothersome visual disturbances using the QUVID questionnaire • Evaluate the rates of adverse events
Endpoint(s)	Primary Effectiveness Endpoints at Month 3 and 6:

	• Mean monocular residual manifest cylinder for all operative eyes for all IOL models combined • Percent of IOLs with <10 degree rotation for all operative eyes (rotation defined as the difference in IOL axis of orientation from postop day 1) • Mean binocular BCDVA at 4m in photopic lighting condition • Mean binocular DCIVA at 60cm in photopic lighting condition • Mean binocular DCNVA at 40 cm in photopic lighting condition Safety Endpoints: • Rate of SSIs (including rate of SSIs related to optical properties of the IOL and rate of all SSIs) • Rates of severe and most bothersome (separately) visual disturbances reported by QUVID questionnaire for subjects with binocular implantation by visit • Rates of adverse events [redacted]
Assessment(s)	**Effectiveness:** • Distance Visual Acuity at 4 m o [redacted] Binocular BCDVA in photopic [redacted] lighting condition [redacted] • Intermediate Visual Acuity at 60 cm o [redacted] Binocular DCIVA in photopic lighting condition o [redacted] • Near Visual Acuity at 40 cm o [redacted] Binocular DCNVA in photopic [redacted] lighting condition o [redacted] [redacted] • Manifest refraction

	• IOL rotation (compared to actual axis position day 1 postoperative) • [redacted] **Safety:** • Secondary Surgical Interventions (SSIs) • QUVID Subject Survey (binocular) to assess visual disturbances • Adverse Events • [redacted] • Dilated Fundus Examination • [redacted] • Slit-lamp Biomicroscopy Examination [redacted] **Additional:** • Ocular Biometry (Axial Length, Keratometry, and Anterior Chamber Depth with corneal thickness, lens thickness, and white to white both pre and post-operative)
Study Design	Prospective, unmasked, single arm, multi-center, postmarket study; total duration of a subject's participation is approximately 8 months.
Subject population	Adult Asian subjects, 20 years of age or older, who self-identify as being of Chinese, Japanese, Korean, or Mongolian descent, who require bilateral cataract extraction by phacoemulsification and have pre-existing corneal astigmatism, desire an IOL that provides the potential correction for near, intermediate and distance vision as well as for pre-existing corneal astigmatism. Planned number of subjects enrolled/consented: 63 subjects Planned number of implanted subjects: 56 subjects Planned number of completed subjects: 50 subjects
Key inclusion criteria	• Planned bilateral cataract removal followed by posterior chamber IOL implantation with PanOptix Toric (TFNT30,

(See Section <8.1> for a complete list of inclusion criteria)	TFNT40, TFNT50, or TFNT60) • Calculated target residual refractive error within ±0.50 D of emmetropia within the commercially available IOL Power Range in both operative eyes • Preoperative regular corneal keratometric astigmatism with predicted residual refractive astigmatism ≤ 0.50 D in both operative eyes
Key exclusion criteria (See Section <8.2> for a complete list of exclusion criteria)	• Preoperative irregular astigmatism • Clinically significant corneal abnormalities, eg, corneal dystrophy, inflammation, edema, et.al., or corneal irregularity • Glaucoma • History of or current retinal disease • History of current anterior or posterior segment inflammation • Any other planned ocular surgical procedures including but not limited to limbal relaxing incision (LRI)/Astigmatic Keratotomy and laser-assisted in situ keratomileusis (LASIK).
Data analysis and sample size justification	**Data Analysis:** Dataset Definitions: The Safety Analysis Set (SS) will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye). The SS will be the primary set for all safety analyses. All-Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation with at least one post-operative visit and will be the primary analysis set for all effectiveness analyses [redacted]. [redacted]

Analyses:

There are no statistical hypotheses for the safety and effectiveness objectives in this study.

Planned analyses include a descriptive summary of all effectiveness and safety endpoints up to Month 6. [redacted]

[redacted]. IOL rotation will be summarized by sample size, number, percent, and cumulative percent for the following categories of absolute rotation: (< 10 and < 20 degrees) for all models combined.

Descriptive statistics generated for all endpoints will be based upon the data type (ie, whether the data are categorical or continuous) being analyzed. For categorical endpoints, sample size, number in the category, and percent in the category will be presented. For continuous endpoints, sample size, mean, median, standard deviation, minimum, maximum, and two-sided 95% confidence intervals will be presented.

Visual acuity will be summarized as a continuous measure.

[redacted]

Sample Size Justification:

	The choice of sample size is not based on statistical considerations. Approximately 56 subjects will be bilaterally implanted to obtain data for at least 50 subjects (100 eyes) at Month 6, assuming a dropout rate of 10% over a 6-month period. The precision estimates below are presented for individual eye summaries. All eye summaries will have increasedprecision. 
Key words	Prospective, multi-center, single arm, postmarket study.
Associated materials	Surgical disposables used in conjunction with the IP (eg, OVDs, cartridges) as per the DFU and standard of care.

Table 3–1 Schedule of Study Procedures and Assessments

	Both Eyes	First Operative Eye			Second Operative Eye			Both Eyes		
	Visit 0 (Preop)	Visit 00 (Op)	Visit 1 Day 1 - 2	Visit 2 Day 7 - 14	Visit 00A (Op)*	Visit 1A Day 1 - 2	Visit 2A Day 7 - 14	Visit 3A Day[1] 30-	Visit 4A Day[1] 90-120	Visit 5A Day[1] 180-210
Informed Consent	X									
Demographics	X									
Medical History[3]	X									
Concomitant Medications[3]	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X									
Inclusion/Exclusion	X	X			X					
Ocular Biometry (Axial Length, Keratometry, Anterior Chamber Depth with corneal thickness, lens thickness preop, white-to-white)	X									X
ALCON® Online Toric IOL Calculator (Barrett) (Intended AxisPlacement)	X									
Actual axis of IOL orientation			X [1]			X[2]			X	X
[redacted]	[redacted]								[redacted]	[redacted]
[redacted]	[redacted]							[redacted]		
Target (Predicted) Residual Refractive Error (include spherical and cylinder)	X									
Administer Treatment(s)		X [1]			X[2]					
Operative Eye		X[1]			X[2]					
Surgical Problems		X[1]			X[2]					
Other Procedures at Surgery		X[1]			X[2]					
Incision Site		X[1]			X[2]					

		Both Eyes	First Operative Eye			Second Operative Eye			Both Eyes		
		Visit 0 (Preop)	Visit 00 (Op)	Visit 1 Day 1 - 2	Visit 2 Day 7 - 14	Visit 00A (Op)[1]	Visit 1A Day 1 - 2	Visit 2A Day 7 - 14	Visit 3A Day[1] 30-	Visit 4A Day[1] 90-120	Visit 5A Day[1] 180-210
Final Incision Size			X[1]			X[2]					
Lens Information			X[1]			X[2]					
IOL Damage			X[1]			X[2]					
Manifest Refraction		X			X[1]			X[2]	X	X	X
Distance Visual Acuity (4 m) in photopic condition	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Best Corrected	[redacted]			[redacted]			[redacted]	[redacted]	[redacted] X[b]	[redacted] X[b]
[redacted]											
Intermediate Visual Acuity (60 cm) in photopic condition	[redacted]								[redacted]	[redacted]	[redacted]
	Distance Corrected								[redacted]	[redacted] X[b]	[redacted] X[b]
Near Visual Acuity (40 cm) in photopic condition	[redacted]								[redacted]	[redacted]	[redacted]
	Distance Corrected								[redacted]	[redacted] X[b]	[redacted] X[b]
[redacted]											
[redacted]											
Slit Lamp Examination)		X		X[1]	X[1]		X[2]	X[2]	X	X	X
[redacted]											

	Both Eyes	First Operative Eye			Second Operative Eye			Both Eyes		
	Visit 0 (Preop)	Visit 00 (Op)	Visit 1 Day 1 - 2	Visit 2 Day 7 - 14	Visit 00A (Op)*	Visit 1A Day 1 - 2	Visit 2A Day 7 - 14	Visit 3A Day[1] 30-	Visit 4A Day[1] 90-120	Visit 5A Day[1] 180-210
Dilated Fundus Examination	X			X[1]			X[2]	X	X	X
[redacted]										
QUVID Subject Survey	X[b]								X[b]	X[b]
Secondary Surgical Interventions			X[1]	X[1]		X[2]	X[2]	X	X	X
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events[3]	X	X	X	X	X	X	X	X	X	X

NOTE:

* IOL implantation in the second eye is recommended to occur within 7-14 days from first eye implantation.

X: The 1st operative eye and the 2nd operative eye (if applicable) separately

X[1]: Only the 1st operative eye

X[2]: Only the 2nd operative eye (if there is a 2nd operative eye)

X[b]: Binocular examination (if there is a 2nd operative eye)

[1] Based on the 2nd eye post-operative surgery date (Visit 00A)

[2] In women of child bearing potential only

[3] Refer to Section 9.6 and Section 9.6, eCRF Guidelines, and MOP for collection and documentation requirements. Concomitant medications and medical history must be fully documented in the subject source documents. eCRF data will be Targeted:

•Medical History: All ocular history, targeted systemic history*

•Concomitant Medications: All ocular medications, targeted systemic medications

*Pre-populated dropdown field

4 PROTOCOL AMENDMENTS

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

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

4.1 Amendments

There are no amendments. This is the first version of the protocol.

5 INTRODUCTION

5.1 Rationale and 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 subject's distance vision. However, many pseudophakic subjects implanted with monofocal IOLs ultimately require reading glasses to compensate for the loss of the ability to see clearly at intermediate or near distances. Several IOL designs for compensating the accommodation in pseudophakic subjects exist in modern day clinical practice, including multifocal IOLs. Multifocal IOLs offer subjects an opportunity to overcome the loss of near and intermediate vision by providing multiple focal points. The majority of commercially available multifocal IOLs provide two optical zones for distance and near vision.

Toric intraocular lenses correct aphakia as well as any pre-existing or surgically induced corneal astigmatism (Horn, 2007; Bauer, 2008). This provides a benefit to patients due to freedom from spectacles for distance vision which is an important consideration when choosing an intraocular lens (Lane, 2006; Laurendeau et al, 2009). Approximately two-thirds of patients who undergo cataract surgery have corneal astigmatism between 0.25 and 1.25 D which can significantly limit the desired 20/20 visual acuity if the astigmatism is uncorrected (Riley et al., 2001; Ferrer-Blasco, 2009).

The ACRYSOF IQ PanOptix Toric Trifocal Intraocular lens to be implanted in this study is approved in the EU and Australia, along with other countries. It provides distance vision, intermediate vision at approximately 60 cm, and near vision at approximately 40 cm, and corrects for corneal astigmatism. It is indicated for primary implantation in the capsular bag in the posterior chamber of the eye for the visual correction of aphakia and pre-existing corneal astigmatism, in adult patients with or without presbyopia who desire near, intermediate and distance vision with increased spectacle independence.

5.2 Purpose of the Study

The present study is intended to evaluate the clinical performance of the PanOptix Toric Trifocal in an Asian population, and to demonstrate that the addition of the toric component to the PanOptix trifocal design reduces pre-existing astigmatism while providing functional

vision at all distances (from 40 cm to infinity) with significantly fewer patients reporting any need for eyeglasses. These resulting data will be used in support of one or more regional Health Authority submissions.

5.3 Risks and Benefits

5.3.1 Known and Potential Risks

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

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

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

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

Refer to the Directions for Use (DFU) for additional information on the IOLs being used in this study.

5.3.2 Potential Benefits

The ACRYSOF IQ PanOptix Toric Trifocal Intraocular lens is a single-piece, trifocal diffractive lens with a near add power of +3.25 D and an intermediate add power of +2.17 D at the IOL plane, and also includes a toric component. This IOL is intended to provide vision to aphakic subjects at near, intermediate, and distance and to correct pre-existing corneal astigmatism. (The potential benefits of the PanOptix Toric Trifocal IOL include:

- Potential postoperative mean 20/25 Snellen (about 0.1 logMAR) or better uncorrected visual acuity at all distances (from 40 cm to infinity) and
- Correction of preexisting corneal astigmatism and
- Improved near and intermediate vision in comparison to a monofocal IOL

Based on the above, the risk of unanticipated adverse device effects with use of this IOL is considered to be low, and the benefits of receiving the IOL should outweigh the risks for subjects that qualify for implantation in this study.

6 STUDY OBJECTIVES

The objective of this study is to evaluate the clinical performance of the ACRYSOF IQ PanOptix Toric Trifocal intraocular lenses (Models: TFNT30, TFNT40, TFNT50, TFNT60) when implanted to replace the natural lens following cataract removal in an Asian population.

6.1 Primary Effectiveness Objective(s)

The following are the Primary Effectiveness objectives and endpoints at Month 3 and Month 6 for all operative eyes:

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
Residual Manifest Cylinder	Mean monocular residual manifest cylinder for all operative eyes for all IOL models combined
IOL Rotational Stability	Percent of IOLs with <10 degree rotation for all operative eyes (rotation defined as the difference in IOL axis of orientation from postop day 1)
Binocular Best Corrected Distance Visual Acuity (BCDVA) (4 m from spectacle plane) in photopic lighting	Mean binocular BCDVA at 4m in photopic lighting condition
Binocular Distance Corrected Intermediate Visual Acuity (DCIVA) (60 cm from spectacle plane) in photopic lighting	Mean binocular DCIVA at 60cm in photopic lighting condition
Binocular Distance Corrected Near Visual Acuity (DCNVA) (40 cm from spectacle plane) in photopic lighting	Mean binocular DCNVA at 40 cm in photopic lighting condition

[redacted]

[redacted]

6.2 Safety Objective(s)

The following are the Safety objectives and endpoints at Month 3 and Month 6 for all operative eyes:

Table 6–2 Safety Objective(s)

Objective(s)	Endpoint(s)
Estimate the cumulative rate of secondary surgical interventions (SSIs)	Rate of SSIs (including rate of SSIs related to optical properties of the IOL and rate of all SSIs)
Evaluate the rates of severe and most bothersome visual disturbances using the QUVID questionnaire	Rates of severe and most bothersome (separately) visual disturbances reported by QUVID questionnaire for subjects with binocular implantation by visit
Evaluate the rates of adverse events	Rates of adverse events

[redacted]

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, unmasked, multi-center, single arm, postmarket study in an Asian population. Both eyes of a subject with regular corneal astigmatism must require cataract surgery to qualify for enrollment into this study. Each site should implant approximately 50% of eyes with TFNT30 and 50% of eyes with TFNT40, TFNT50, and TFNT60 combined (approximately at 1:1 ratio). Sites should strive to have at least one implant in each astigmatism level (TFNT40, TFNT50, and TFNT60).

It is recommended that the eye with the highest astigmatism is implanted first. If the astigmatism is the same in both eyes, it is at the surgeon's discretion to determine which eye is implanted first. It is recommended that the second eye implant occurs within 7 to 14 days of the first eye implant.

A total of 10 scheduled visits are planned including the Screening/Visit 0 and two Operative Visits/Visit 00 and Visit 00A. Postoperative visits must occur at the following intervals: Day 1-2, Day 7-14, Day 30-60, Day 90-120 and Day 180- 210 (after the second eye surgery).

7.2 Rationale for Study Design

The test article for this study is the ACRYSOF IQ PanOptix Toric Trifocal IOL, models TFNT30-TFNT60. The study design elements are according to scientific standards and the duration of follow-up is appropriate for the evaluation of visual and safety outcomes following recovery and stabilization of vision post cataract surgery for an established IOL platform. This study will aim to evaluate the clinical performance of the ACRYSOF IQ PanOptix Toric Trifocal IOLs at Month 3/Visit 4A and Month 6/Visit 5A in an Asian population. These results will be used as supplementary clinical data for approval of the PanOptix Toric Trifocal IOLs in China or other regions as applicable.

[redacted]

[redacted]

7.3 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population consists of male and female subjects 20 years of age and older that self-identify as being of Chinese, Japanese, Korean, or Mongolian descent, with a diagnosis of cataract in both eyes with regular corneal astigmatism requiring surgery with implantation of an intraocular lens in the capsular bag. It is aimed to enroll (consent) approximately 63 subjects (126 eyes) in approximately 4-5 sites in Australia, with a target of approximately 13-16 subjects per site. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 16 weeks. Assuming a 10% screening failure rate and 10% dropout rate, data from approximately 50 subjects (100 eyes) will be available for statistical analysis at 6 months. Enrollment projections are as follows:

- Approximately 63 subjects to be enrolled (sign consent) (a 10% screen failure rate is estimated)
- Approximately 56 subjects to be bilaterally implanted (a 10% dropout rate is estimated)
- Minimum 50 subjects to successfully complete the final study visit (Month 6, Visit 5A)

[redacted]

Check all entry criteria at Screening/Visit 0 and at both surgical visits (Visit 00, Visit 00A). If a subject is excluded following enrollment 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 8.3 Reasons for Discontinuation (During Surgery) for further details.

8.1 Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill [redacted] the following criteria in both eyes (where applicable):

1. Asian Adults, 20 years of age or older at the time of surgery, diagnosed with bilateral cataracts who has pre-existing regular corneal astigmatism with planned bilateral cataract removal by phacoemulsification with a clear cornea incision and followed by posterior chamber IOL implantation
2. Able to comprehend and willing to sign informed consent and complete all required postoperative follow-up procedures
3. Calculated target residual refractive error within ±0.5 D of emmetropia within the available lens power range in both operative eyes
4. Preoperative regular corneal keratometric astigmatism with predicted residual refractive astigmatism ≤ 0.50 D in both operative eyes

[redacted]

[redacted]

8.2 Exclusion Criteria

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

[redacted]

2. Clinically significant corneal abnormalities, e.g., corneal dystrophy, inflammation, edema, et.al. or corneal irregularity (including dry eye syndrome) per the investigator's expert medical opinion or corneal endothelial cell less than 2000/mm2; Note: conditions including but not limited to keratitis, keratoconjunctivitis, keratouveitis or keratectasia should be excluded
3. History of or current retinal disease, or predisposition to retinal disease, or presence of ischemic optic neuropathy and other retinopathy which can lead to optic atrophy, or other degenerate retinal disease that the investigator judges could confound study outcomes; Note: Including but not limited to background diabetic retinopathy, diabetic macular edema or proliferative diabetic retinopathy and macular degeneration

[redacted]

[redacted]

6. Glaucoma (uncontrolled or controlled with medication) and iris/anterior chamber angle neovascularization

[redacted]

11. Subjects with history of previous refractive surgery or corneal surgery, or reasonably be expected to require a ocular treatment/surgery at any time during the study or any other ocular Surgery in either eye within 3 months prior to screen visit

[redacted]

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

If the implantation was aborted and the IOL **did** touch the eye (1st eye), then the subject is encouraged to attend all follow-up study visits for safety evaluation on this eye only.

8.4 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): ACRYSOF IQ PanOptix Toric Trifocal Intraocular Lenses (IOLs) (Models: TFNT30, TFNT40, TFNT50, TFNT60)

Control Product(s) (If applicable): Not applicable

Table 9–1 Test Product

Test Product	ACRYSOF IQ PanOptix Toric Trifocal Intraocular Lenses (IOLs) (Models: TFNT30, TFNT40, TFNT50, TFNT60)
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	The ACRYSOF IQ PanOptix Toric Trifocal Intraocular lens is indicated for primary implantation in the capsular bag in the posterior chamber of the eye for the visual correction of aphakia and pre-existing corneal astigmatism, in adult patients in whom a cataractous lens has been removed.
Product description and parameters available for this study	• Optic Type: Single-piece IOL with diffractive aspheric optic • Optics Material: Ultraviolet light and blue light filtering Acrylate/Methacrylate Copolymer • Optic Powers (spherical equivalent diopters): +6.0 through +30.0 diopter in 0.5 diopter increments; +31.0 through +34.0 diopter in 1.0 diopter increments with a +2.17 diopter intermediate and a +3.25 diopter near add power

<table>
<tr><td></td><td>

IOL Cylinder Powers:

<table>
<tr><th rowspan="2">PanOptix Toric Trifocal Model</th><th colspan="2">Cylinder Power</th></tr>
<tr><th>IOL Plane</th><th>Corneal Plane[a]</th></tr>
<tr><td>TFNT30</td><td>1.50</td><td>1.03</td></tr>
<tr><td>TFNT40</td><td>2.25</td><td>1.55</td></tr>
<tr><td>TFNT50</td><td>3.00</td><td>2.06</td></tr>
<tr><td>TFNT60</td><td>3.75</td><td>2.57</td></tr>
</table>
[a] Based on an average pseudophakic human eye

Index of Refraction: 1.55
Haptic Configuration: STABLEFORCE™ Modified-L Haptics
Haptic Material: Ultraviolet light and blue light filtering Acrylate/Methacrylate Copolymer
Optic Diameter (mm): 6.0
Overall Length (mm): 13.0
Haptic Angle: 0°

</td></tr>
<tr><td>Formulation</td><td>N/A</td></tr>
<tr><td>Usage</td><td>IOLs are implantable medical devices and are intended for long-term use over the lifetime of the pseudophakic subject.</td></tr>
<tr><td>Number/Amount of product to be provided to the subject</td><td>Each subject will be bilaterally implanted with the test articles.</td></tr>
<tr><td>Packaging description</td><td>Alcon standard commercial package contains below items:

The IOL
A subject registration card in case it is needed for the Alcon market (Lens Implant Reply Card)
A subject identification card, for the patient (Implant Card)
Adhesive labels containing the IOL information and unique serial number
eIFU Reference Card, providing information to access the IFU at ifu.alcon.com

</td></tr>
</table>

Labeling description	Packaged in a standard Alcon IOL carton. The carton is labeled with the following information: name of the lens, model number, overall diameter, optic diameter, diopter power, serial number, name of the manufacture, storage condition, expiration date, sterile, and single use.
Additional information	In order to implant IOLs in study subjects, the surgeons participating in the study must be licensed ophthalmologists with cataract surgery experience and trained on the protocol. More information on the test article can be found in the DFU for ACRYSOF IQ PanOptix Toric Trifocal IOL (Models: TFNT30, TFNT40, TFNT50, TFNT60).

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

Each surgeon will use his/her standard of care to implant the lens following the respective IFU instructions. Alcon qualified delivery systems and OVDs should be used (per the IFU).

9.3 Treatment Assignment

Subjects will be implanted bilaterally with PanOptix Toric Trifocal IOL (Models: TFNT30, TFNT40, TFNT50, TFNT60) based on the recommendation of the ALCON® Online Toric IOL Calculator with the Barrett Toric Algorithm from www.myalcon-toriccalc.com. [redacted]

The implantation of TFNT20 is not allowed per protocol.

Each site's enrollment should not be more than 50% of the total number of subjects enrolled in the study but should target approximately 25% enrollment of subjects (approximately 13-16 subjects per site implanted).

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

9.4 Treatment Masking

All members associated with the study (at the site and the Study Sponsor) are unmasked to the assigned treatment. Masking is not required in this study since there is a single treatment group.

Measures to minimize bias include objective primary endpoints and consistent training procedures across study sites.

9.5 Accountability Procedures

Throughout the study, the Investigator or delegate must maintain records of IOLs implanted for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting study IOLs implanted. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation.

Return to the Study Sponsor any study IOLs associated with a device deficiency. Refer to Section 11 of this protocol for additional information on the reporting of device deficiencies and to the MOP for information on return of study products associated with these events.

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

9.6 Changes to concomitant medications, treatments/procedures

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

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

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

10 STUDY PROCEDURES AND ASSESSMENTS

The following section outlines the assessments performed in this clinical study. The Investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

Assessments are described in detail in the MOP, and are outlined in Table 3–1, Schedule of Study Procedures and Assessments.

During the course of the study, it is possible that the window of visits may overlap; in such cases the subject may complete both visits on the same day at the discretion of the Investigator (and the data would be entered for each respective visit in EDC).

10.1 Informed Consent and Screening

The Investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Upon signing informed consent, the subject is considered enrolled in the study. (Note that data from exams and assessments specified in Section 10.2.1 that were completed within 90 days of screening can be used as per discretion of Investigator.)

Additionally, the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document. The subject should be provided with enough time for his/her decision on participation in the study and should have options to discuss with his/her family members or relatives about the participation in the investigation.

The Investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations. Note that the applicable privacy regulation requirements must be met.

10.2 Visits and Examinations

10.2.1 Visit 0: Preoperative Screening Visit

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

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.

Data from the Investigator's previous routine clinical evaluation may be used and this data may be used from more than one routine visit, as long as the visits are less than 90 days old and fulfill Visit 0 requirements.

As part of routine practice, subjects who are enrolled and wear contact lenses must discontinue use for the appropriate amount of time to ensure corneal stability.

Note: Subjects must formally consent to the trial prior to any study-specific testing that is not standard of care.

1. After the subject signs the **consent,** assess **inclusion/exclusion criteria** as assessments are completed. The subject must meet all inclusion criteria and must not meet any exclusion criteria prior to surgery.
2. Obtain the subject's **demographic** information (including age, race, ethnicity, and sex) and collect **medical history** information, including information on all **concomitant medications** used within the past 30 days. Include herbal therapies, vitamins and all over-the-counter as well as prescription medications. (Document full medical history and concomitant medications in source throughout the study. Document all ocular medical history and targeted systemic medical history in the study database. Likewise, document all ocular medications and targeted systemic medications in the study database. Refer to MOP for reporting requirements.)
3. Perform a **urine pregnancy test**, IF the subject is a woman of childbearing potential only (defined as all women who are physiologically capable of becoming pregnant and who are not postmenopausal for at least 1 year or are less than 6 weeks since sterilization).
4. Complete subject **questionnaire**: QUVID [redacted]
5. Adjust room to **photopic lighting conditions** for distance (4 m).

[redacted]

7. Perform **manifest refraction** (OD, OS).
8. Measure and record **BCDVA** at 4 m (OD, OS).

9. Perform **slip-lamp examination** of the anterior segment of both eyes.
10. Measure optical **biometry** according to the Investigator's standard of care noting all available measurements including **keratometry**, crystalline lens thickness, white-to-white, anterior chamber depth (ACD) with corneal thickness and axial length (AL).

    Use standard of care to select lens power for implantation. It is suggested to choose the power that will result in the closest outcome to emmetropia and targeted residual refractive error must be within ± 0.5 D of emmetropia. Use the ALCON® Online Toric IOL Calculator with the Barrett Toric Algorithm from www.myalcon-toriccalc.com to screen subjects in the study and select toric lens model for each eye. Choose the toric model (TFNT30, TFNT40, TFNT50, or TFNT60) that results in the least amount of residual astigmatism that is within 0.5 D. If the model with the least residual astigmatism requires flipping the axis, it is the surgeon's choice to use that model or the next model that allows the lowest residual astigmatism without flipping the axis, as long as the result is still within 0.5 D. Implantation of a TFNT20 in the study is not allowed.

    Document the subject's required lens power and model (PanOptix Toric Trifocal TFNT30, TFNT40, TFNT50, or TFNT60) for each eye. Document the predicted/targeted residual refractive error (TRRE), the predicted residual refractive cylinder and intended axis placement for each eye based on the selected lens power and model.

[redacted]

12. Perform a **dilated fundus** examination of both eyes.
13. Record any **adverse events**.

[redacted]

16. Ensure that all inclusion/exclusion criteria have been met and that all preoperative screening assessments have been performed. Upon meeting eligibility criteria, subjects will be scheduled for surgery.

10.2.2 Visit 00: Surgery Visit 1st Eye

It is recommended that surgery occur as soon after screening as possible or within 30 days of the screening visit.

1. Record **Operative eye**.

2. Record **concomitant medications** for ocular and non-ocular conditions.
3. Verify **inclusion/exclusion criteria**. Subjects must meet all requirements to proceed to surgery.
4. Prepare subject for surgery in accordance to site specific operating procedures and ensure that all IOL power calculations have been completed.
5. Perform **surgery** and **implantation** with the IOL to which the subject was calculated to receive per the ALCON® Online Toric IOL Calculator with the Barrett Toric Algorithm.
6. Record any **surgical problems, complications** or other procedures (including SSIs) that occurred during surgery. Other procedures include those performed outside of routine cataract surgery. **Other planned procedures at the time of surgery are exclusionary.**
7. Record **final incision size** and **incision location**.
8. Record **lens information** that is located on the IOL sticker. Both successful and aborted (if applicable) test article information should be recorded.

[redacted]

10. Record any **adverse events**.

[redacted]

10.2.3 Visit 1: Postoperative for 1st Eye (1-2 Days after Visit 00)

1. Record **concomitant medications** for ocular and non-ocular conditions.
2. Adjust room to **photopic lighting conditions** for distance (4 m).

[redacted]

4. Perform **slit-lamp examination** of the anterior segment.

[redacted]

7. Record the **actual axis of IOL orientation**.

[redacted]

9. Record **secondary surgical interventions** that have occurred since surgery, if applicable.
10. Record any **adverse events**.

[redacted].

10.2.4 Visit 2: Postoperative for 1st Eye (7-14 Days after Visit 00)

1. Record **concomitant medications** for ocular and non-ocular conditions.
2. Adjust room to **photopic lighting for distance** at 4 m.

[redacted]

4. Perform **manifest refraction** at 4 m. [redacted]

[redacted]

6. Perform **slit-lamp examination** of the anterior segment.

[redacted]

10. Perform a **dilated fundus examination.**
11. Record **secondary surgical interventions** that have occurred since surgery, if applicable.
12. Record any **adverse events** (both volunteered and elicited).

[redacted]

10.2.5 Visit 00A: Surgery Visit 2nd Eye (recommended 7-14 Days after Visit 00)

Follow all procedures listed in Section 10.2.2 for the 2nd operative eye.

10.2.6 Visit 1A: Postoperative for 2nd Eye (1-2 Days after Visit 00A)

Follow all procedures listed in Section 10.2.3 for the 2nd operative eye.

10.2.7 Visit 2A: Postoperative for 2nd Eye (7-14 Days after Visit 00A)

Follow all procedures listed in Section 10.2.4 for the 2nd operative eye.

10.2.8 Visit 3A: Postoperative for Both Eyes (30-60 Days after Visit 00A)

1. Record **concomitant medications** for ocular and non-ocular conditions.
2. Adjust room to **photopic lighting conditions for distance** at 4 m.

[redacted]

4. Perform **manifest refraction** at 4 m for each eye. [redacted]

[redacted]

8. Perform **slit-lamp examination** of the anterior segment for each eye.

[redacted]

14. Perform a **dilated fundus examination** for each eye.
15. Record **secondary surgical interventions** that have occurred since surgery, if applicable.
16. Record any **adverse events** (both volunteered and elicited).

[redacted]

10.2.9 Visit 4A: Postoperative for Both Eyes (90-120 Days after Visit 00A)

1. Complete subject questionnaire at the beginning of the visit prior to any other testing: QUVID [redacted]
2. Record **concomitant medications** for ocular and non-ocular conditions.

3. Adjust room to **photopic lighting conditions for distance** at 4 m.

[redacted]

5. Perform **manifest refraction** at 4 m for each eye. [redacted]

6. Measure [redacted] binocular **BCDVA** at 4 m in photopic lighting conditions.

[redacted]

8. Adjust equipment for intermediate assessment at 60 cm, measure [redacted] binocular **DCIVA** (with -0.25 D SPH power for best distance correction) in photopic lighting conditions.

9. Adjust equipment for near assessment at 40 cm, measure [redacted] binocular **DCNVA** (with -0.25 D SPH power for best distance correction) in photopic light condition.

[redacted]

13. Perform **slit-lamp examination** of the anterior segment.

[redacted].

16. Record the **actual axis of IOL orientation**.

[redacted]

20. Perform a **dilated fundus examination** for each eyes.

21. Record **secondary surgical interventions** that have occurred since surgery, if applicable.

22. Record any **adverse events** (both volunteered and elicited).

[redacted].

10.2.10 Visit 5A: Postoperative for Both Eyes (180-210 Days after Visit 00A)

Follow all procedures listed in Section 10.2.9 for each eye **AND** measure optical **biometry,** according to the Investigator's standard of care (used at Visit 0), noting all available measurements including **keratometry**, white-to-white, anterior chamber depth (ACD) with corneal thickness and axial length (AL).

10.2.11 Unscheduled Visit

If a subject is examined more than once during any of the scheduled follow-up periods, or between scheduled follow-up periods due to a potential issue, an unscheduled visit form should be completed, reporting any study parameters or any relevant data collected at this visit. If, during the visits specific for the second eye, a clinical observation is made on the first eye implanted, an unscheduled visit form should be completed to record the first eye data. The following exams and assessments are recommended and should be completed per the Investigator's expert opinion; in the event this is not possible, the data that is available should be reported.

1. Complete subject **questionnaires** at the beginning of the visit: QUVID [redacted] questionnaire[redacted].
2. Record **concomitant medications** for ocular and non-ocular conditions.
[redacted]
4. Perform **manifest refraction** at 4 m.
[redacted]
6. Perform **slit-lamp examination** of the anterior segment of both eyes.
[redacted]
[redacted]
9. Record the **actual axis of IOL orientation**.
[redacted]
11. Perform a **dilated fundus examination** for each eyes.
12 [redacted]
13. Record **secondary surgical interventions** for the operative eye(s) that have occurred since surgery, if applicable.
14. Record any **adverse events** (both volunteered and elicited).

[redacted]

10.3 Discontinued Subjects

10.3.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to administering treatment are considered screen failures. The Investigator must document the reason for screen failure in the subject's case history source documents.

Subject numbers must not be re-used.

10.3.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the Investigator after informed consent is signed and before the last visit is completed.

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

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

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

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

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

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

Subjects who discontinue the IP (ie, have study lens explanted) will continue in the study through Visit 5A and be followed for safety. At minimum, safety examinations must include the assessments associated with appropriate medical care. Standard post-surgical assessments are bulleted below:

- UCDVA and/or BCDVA
- Slit-lamp Examination
- Dilated Fundus Examination

10.3.4 Subject Lost to Follow Up

If a subject unavoidably misses a scheduled exam, he/she should be rescheduled within the same exam period. The investigational site should show diligence in trying to schedule the subject for all exams. The site must document all attempts to contact the subject in the subject's chart, including dates, times, method of contact, etc. If a subject is unable to return for the Final Study Visit, the Exit Case Report Form should be completed with the appropriate reason for discontinuation indicated. If attempts to contact the subject are unsuccessful, then the Exit Case Report Form for that subject is completed after the last window closes and documented as Lost to Follow-up. The date at which the subject was considered lost to follow-up should also be recorded.

10.4 Subject Pregnant or Lactating

Subjects who become pregnant after having a study IOL implanted (or the study IOL touches the eye) or are lactating during the study will not be discontinued; however, all data from that point forward will be excluded from the BAS analyses because these conditions can alter refraction and visual acuity results. Pregnancy, or women who are lactating, should be noted within the source documentation for each visit, and at which time the subject is pregnant or lactating.
The Investigator must notify the sponsor within 24 hours of learning that a subject is pregnant; reporting procedures are noted in Section 11.9.

10.5 Clinical Study Termination

The Study Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time.
If the clinical study is prematurely terminated or suspended by the Study Sponsor:

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

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

10.5.1 Follow-up of subjects after study participation has ended

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

10.6 Contingency Measures

To overcome challenges that may arise during unexpected events which could interrupt the conduct of the trial as planned (eg, natural disasters or a public health emergency), contingency measures may be implemented. The intent of contingency measures would be to address the care of enrolled subjects during such unexpected events. It is not expected that contingency measures would affect study design; however, if necessary, the protocol would be amended accordingly. Written notification describing these contingency measures will be provided to the IRB and other regulatory agencies, as applicable. During such events, Investigators must continue to use medical judgement in the care of subjects and follow national and local guidance, as well as IRB reporting requirements. Additional information can be found in the MOP.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test product).

Refer to the Glossary of Terms and figures for categories of AEs and SAEs.

Figure 11.1–1 Categorization of All Adverse Events

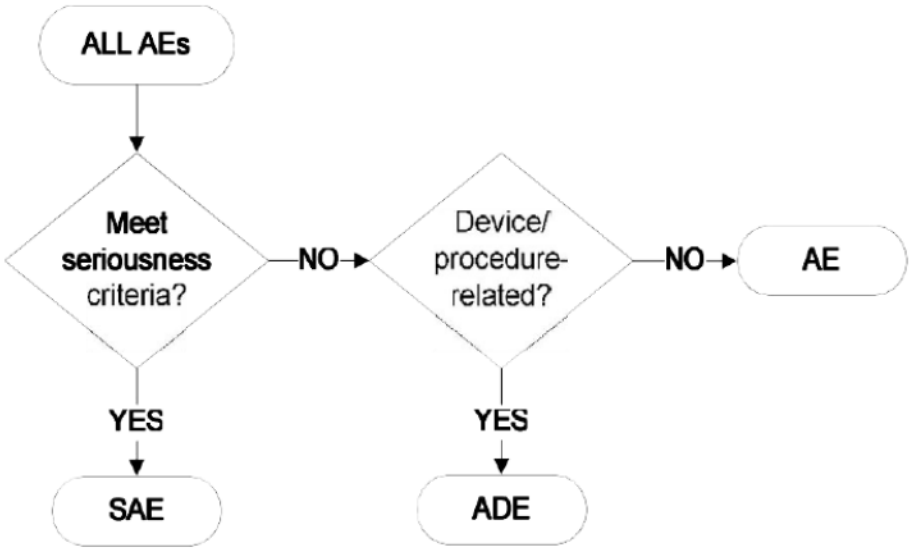
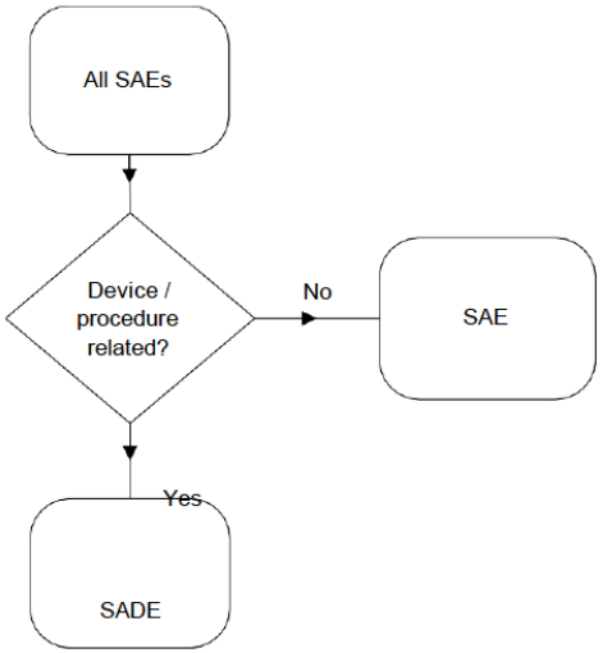


Figure 11.1-2 Categorization of All Serious Adverse Events



11.2 Specific Events Relevant to this Protocol

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

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

Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and must be reported appropriately as delineated in Section 11.4.

11.2.1 Device Deficiencies

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

- Failure to meet product specifications (eg, incorrect IOL power)
- IOL defect
- Broken IOL optic
- Broken IOL haptic
- Scratched IOL optic
- Unsealed device packaging
- Suspect product contamination
- Lack of effectiveness

11.3 Monitoring for Adverse Events

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

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

Changes in any protocol-specific ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter that is clinically relevant, in the opinion of the Investigator, is to

be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.4 Procedures for Recording and Reporting

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

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

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

- ADEs or SAEs are documented on the *Adverse Device Effect and Serious Adverse Event* eCRF within 24 hours of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.
- A printed copy of the completed Serious Adverse Event and Adverse Device Effect and/or Device Deficiency eCRF must be included with product returns.
- Additional relevant information after initial reporting 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 *Adverse Device Effect and Serious Adverse Event Form* or *Device Deficiency Form*. The completed form is emailed to the Study Sponsor at

MSUS.safety@alcon.com within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes operational.

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

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

11.5 Intensity and Causality Assessments

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

11.5.1 Intensity (Severity)

Mild An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.

Moderate An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.

Severe An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

11.5.2 Causality

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

Related An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.

Not Related An AE classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

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

11.6 Return Product Analysis

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

Recoverable Alcon Products associated with device deficiencies and/or product related AEs should be returned to the Sponsor with the appropriate return forms.

11.7 Unmasking of the Study Treatment

Not applicable; this study is open-label, unmasked study.

11.8 Follow-Up of Subjects with Adverse Events

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

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

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

11.9 Pregnancy in the Clinical Study

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

12 ANALYSIS PLAN

12.1 Subject Evaluability

Subject evaluability will be determined prior to the [redacted] final database lock, based upon the Deviations and Evaluability Plan (DEP).

12.2 Analysis Sets

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

All-Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation with at least one post-operative visit and will be the primary analysis set for all effectiveness analyses [redacted]

[redacted]

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

[redacted]

12.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by IOL model (TFNT30 vs TFNT40/TFNT50/TFNT60) and all models combined using descriptive statistics based on the type of variable for AAS and SS. Demographics include age, sex, race and nationality. Baseline characteristics include BCDVA, axial length, anterior chamber depth, keratometry, corneal astigmatism. [redacted]

For categorical variables, number and percentage of eyes/subjects in each category for non-missing data will be presented such as sex, age group (< 65 years; ≥ 65 years), and race. For continuous variables, the number of non-missing eyes/subjects, mean, standard deviation, median, minimum, and maximum values will be presented.

12.4 Effectiveness Analyses

This is a single arm descriptive study. No formal statistical hypothesis testing is planned for any endpoint, rather, the data will be summarized using descriptive statistics.

Binocular endpoints will be summarized at the subject level [redacted]

12.4.1 Analysis of Key Effectiveness Endpoint(s)

All effectiveness endpoints will be summarized for each visit with Month 3 and 6 visit results being the key endpoint.

- Mean monocular residual manifest cylinder for all operative eyes for all IOL models combined
- Percent of IOLs with < 10 degree rotation for all operative eyes (rotation defined as the difference in IOL axis of orientation from postop day 1)
- Mean binocular BCDVA at 4m in photopic lighting condition
- Mean binocular DCIVA at 60cm in photopic lighting condition
- Mean binocular DCNVA at 40 cm in photopic lighting condition

12.4.1.1 Statistical Hypotheses

No hypothesis testing of the key effectiveness endpoints is planned.

12.4.1.2 Analysis Methods

Monocular residual manifest cylinder will be summarized by visits by IOL model (TFNT30 vs TFNT40/TFNT50/TFNT60) and all models combined for first eye and second eye and all eyes combined with descriptive statistics (the number of observations, mean, median, standard deviation, minimum, maximum, and two-sided 95% CI of the mean).

IOL rotation will be summarized by sample size, number, percent, and cumulative percent for the following categories of absolute rotation: (< 10 and < 20 degrees) for all models combined.

Binocular photopic BCDVA, DCIVA and DCNVA will be summarized by visits with descriptive statistics.

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.5 Handling of Missing Data

No missing data will be imputed.

12.6 Safety Analyses

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters. Descriptive statistics will be provided by all model combined for first and second eyes that undergo attempted implantation.

12.6.1 Analysis of Key Safety Endpoint(s)

The key safety endpoints are:

- Rate of SSIs (including rate of SSIs related to optical properties of the IOL and rate of all SSIs)
- Rates of severe and most bothersome (separately) visual disturbances reported by QUVID questionnaire for subjects with binocular implantation by visit
- Rates of adverse events

12.6.1.1 Statistical Hypotheses

No hypothesis testing of the key safety endpoints is planned.

12.6.1.2 Analysis Methods

Rate of SSIs for either eye will be summarized by operative eye.

Descriptive summaries (counts and percentages) for rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented. These rates are accompanied by two-sided 95% CIs.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Ocular AEs will be summarized by operative eye. Descriptive tables (count and percentage) and listing will be generated for AEs based upon the categories of ocular and monocular AEs, serious and non-serious AEs, as appropriate.

[redacted]

[redacted]

12.8 Sample Size Justification

The choice of sample size is not based on statistical considerations.

Approximately 56 subjects will be bilaterally implanted to obtain data for at least 50 subjects (100 eyes) at Month 6, assuming a dropout rate of 10% over a 6 month period. The precision estimates below are presented for individual eye summaries. All eye summaries will have increased precision.

For visual acuity, with a sample size of 50 eyes and assuming a standard deviation of 0.18 logMAR [redacted] a two-sided

95% confidence interval based on large sample z statistics will extend 0.05 logMAR from the observed mean.

For residual cylinder, a two-sided 95% confidence interval based on large sample z statistics will extend 0.11 D from the observed mean, assuming a standard deviation of 0.40 D [redacted]

For any event where a zero incidence is observed in 50 eyes implanted with study IOL, the upper exact binomial 95% confidence limit is less than 6%. Thus, with 95% confidence, the true adverse event rate is less than 6%.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

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

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

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor,

and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the Study Sponsor and are independent of study site staff.

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

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

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

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

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

13.3 Data Review and Clarifications

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

13.4 Sponsor and Monitoring Responsibilities

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

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

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

13.5 Regulatory Documentation and Records Retention

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

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

13.6 Quality Assurance and Quality Control

The Study Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all

data are reliable and have been processed correctly. Agreements made by the Study Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

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

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

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

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

Voluntary informed consent must be obtained in writing from every subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject. The Investigator must have a defined process for obtaining consent. Specifically,

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

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

15 REFERENCES

15.1 References applicable for all clinical studies

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

[redacted]

[redacted]

Signature Page for V-CLN-0001833 v1.0