Title

Clinical Investigation of AcrySof IQ PanOptix Toric Intraocular Lens Model TFNT20

Protocol Number:	ILX140-C001 / NCT04542525
Development Stage of Project:	Development
Sponsor Name and Address:	Alcon Japan, Ltd. Toranomon Hills Mori Tower 1-23-1 Toranomon, Minato-ku Tokyo, 105-6333 Japan
Test Product:	AcrySof IQ PanOptix Toric Intraocular Lens Model TFNT20

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, current Investigator's Brochure, 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:

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[redacted]

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1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as TFNT20
Name of Control Product(s)	N/A
Adverse Device Effect (ADE)	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 (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (test 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 (ASADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk management file.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.* 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.

Investigational Product	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
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.
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), 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.*
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in Investigator's Brochure.
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
ADE	Adverse device effect
AE	Adverse event
ARMD	Age-related macular degeneration
[redacted]	
cd	Candela
CI	Confidence interval
[redacted]	
CRF	Case report form
D	Diopter(s)
GCP	Good Clinical Practice
IB	Investigator's brochure
ICF	Informed consent form
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Investigational review board
LASIK	Laser-assisted in situ keratomileusis
LRI	Limbal relaxing incision
mm	millimeter
MOP	Manual of procedures
PCO	Posterior capsule opacification
PRK	Photorefractive keratectomy
SAE	Serious adverse event
SADE	Serious adverse device effect
SD	Standard deviation
SOP	Standard operating procedure
SSI	Secondary Surgical Intervention(s)
[redacted]	
VA	Visual acuity
YAG	Yttrium aluminum garnet laser

3 PROTOCOL SUMMARY

This study is a prospective, single-center and non-comparative study. The study will include subjects must be ≥ 20 years of age with cataract who would be eligible to receive a TFNT20 lens in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. Subject with no ocular pathology that could confound study outcome, must require clear cornea cataract extraction, and must desire an IOL that provides the potential for near, intermediate and distance vision and corrects astigmatism. Potential subjects will be screened for enrollment into this clinical trial. Those qualifying will attend a total 5 visits. If the investigational products will be implanted to both eye, the maximum number of visits is total 9 visits. Primary endpoint data will be collected at the final visit, Visit3/3A (30-60 days post implantation). No interim analysis is planned.

Investigational product type	Device
Study type	Interventional
Investigational products	Test Product: AcrySof IQ PanOptix Toric Intraocular Lens Model TFNT20 (hereinafter called "TFNT20") Control Product: Not applicable
Purpose and rationale	The purpose of this study is to evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal. [redacted] this is intended to confirm the safety of the test product and examine its effectiveness as a Toric lens by examining the subject's astigmatism power.
Objective(s)	To evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal.
Endpoint(s)	Primary Effectiveness • Percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) Secondary Effectiveness • Percentage of eyes with ≤ 0.5 D refractive cylinder at Visit 3/3A (Day 30-60)

	• Average manifest refractive cylinder at Visit 3/3A (Day 30-60) [redacted] Safety • Adverse events including SSI • Device deficiencies • Posterior capsular opacification • Posterior capsulotomy • IOL position change (tilt and decentration) • Intraocular pressure • Surgical problems • Slit Lamp Examination • Dilated Fundus Examination • IOL Observations
Assessment(s)	[redacted] Safety • Adverse events including SSI

	• Device deficiencies • Posterior capsular opacification • Posterior capsulotomy • IOL position change (tilt and decentration) • Intraocular pressure • Surgical problems • Slit Lamp Examination • Dilated Fundus Examination • IOL Observations
Study Design	This study is a prospective, single-center and non-comparative study.
Subject population	Subjects must be ≥ 20 years of age with cataract who would be eligible to receive a TFNT20 lens in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. Planned number of subjects implanted: 32 eyes for first surgery (32 subjects) [redacted]
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	• Eligible to be implanted with TFNT20 as determined by a new Alcon Toric calculator in at least one eye that incorporates ocular trends in surgical planning. • Subjects for whom postoperative emmetropia is planned (spherical equivalent ± 0.50 D).
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Irregular corneal astigmatism as assessed by topographer per investigator decision.

	• History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology including retinal vascular occlusive disease, retinal detachment or peripheral retinal laser photocoagulation, ARMD, glaucoma (uncontrolled or controlled with medication) or ocular hypertension, diabetic retinopathy, retinitis pigmentosa and any optic nerve pathology. • History of previous intraocular or corneal (refractive or trauma related) surgery. • Any other planned ocular surgical procedures including but not limited to limbal relaxing incision (LRI)/Astigmatic Keratotomy and LASIK
Data analysis and sample size justification	To enroll more than or equal to 30 eligible T2 eyes used for analysis, at least 30 subjects will be evaluated by a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning and unilaterally or bilaterally implanted with the AcrySof IQ PanOptix IOL (TFNT20). Using a new Alcon calculator that incorporates ocular trends in Toric IOL planning, percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) in T2 group was estimated as 60.9% based on a previous [redacted](T2) study conducted in US. Using the same calculator, the percentage in T0 group was recalculated as 29.2% from the combined result of studies (non-Toric (T0) lenses) conducted in Japan [redacted] Statistical test will be conducted to compare percentage of T2 with a constant of 29.2% as percentage of T0. With 30 eyes from 30 subjects in T2 group, assuming the percentage of T2 is equal to 60.9% [redacted] the statistical power to demonstrate superiority of T2 to T0 is 91.6% with one-sided alpha of 2.5%, using an exact test of binomial proportion.
Anticipated study period	Sep, 2020 ~ Sep, 2021
Key words	Cataract, intraocular lens, Toric, astigmatism
Associated materials	Not applicable.

Table 3–1 Schedule of Study Procedures and Assessments

Activity	Visit 0/0A (Day-60 to 0)	Visit 00/00A (Day 0)	Visit 1/1A (Day 1-2)	Visit 2/2A (Day 7-14)	Visit 3/3A (Day 30-60)
Informed Consent*	X				
Demographics	X				
Medical History	X	X			
Concomitant Medications	X	X	X	X	X
Urine Pregnancy Test**	X (Visit 0 only)				
Inclusion/Exclusion	X	X			
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Subjective Manifest Refraction	X		X	X	X
Slit-Lamp Examination	X		X	X	X
Fundus exam with dilated pupil	X				X
Keratometry	X		(X)	(X)	X
Target Residual Refractive Error	X				
Calculation by new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning	X				
Topography	X		(X)	(X)	X
Axial Length	X		(X)	(X)	X
Anterior chamber depth	X		(X)	(X)	X
Intraocular Pressure	X		X	X	X
[redacted]		[redacted]	[redacted]		[redacted]
Operation Record****		X			
Posterior capsular opacification			X	X	X
Posterior capsulotomy			X	X	X
IOL observations		X	X	X	X
IOL position change (tilt an decentration)			X	X	X
Adverse Events	X	X	X	X	X
Secondary Surgical Intervention		X	X	X	X
Device Deficiencies	X	X	X	X	X

(X): The data will be captured if the investigator judged to be able to conduct the examination based on the subject's condition.
* When a subject receives the bilateral study lens implantation, written informed consent form prior to the examinations at Visit 0A is needed.
** Women of child-bearing potential only
*** A slit lamp photograph shall be recorded and kept as a source document.
**** Operative eye, lens information, final incision size, surgical problems and other surgical procedures during surgery will be collected.

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 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.

5 INTRODUCTION

5.1 Rationale and Background

The first clinical results of the multifocal intraocular lenses were reported in the United States in 1987. The first Japanese clinical study was performed and reported in the early 1990's [1]. In general, multifocal intraocular lenses are roughly divided into diffractive and refractive types. Diffractive lenses are structured to separate incident light energy to far and near visions, while refractive lenses have an optical zone structure consisting of far and near vision zones arranged in an alternate, concentric manner [2]. Since the diffractive multifocal intraocular lens product, "Alcon® AcrySof® ReSTOR® Single Piece" (medical device approval number: 21900BZX00605000, Alcon Japan Ltd.) was first approved in 2007, various multifocal intraocular lenses have been developed in Japan. As opposed to monofocal intraocular lenses, intraocular lenses with 2 or more focuses are collectively called multifocal intraocular lenses. Actually bifocal intraocular lenses focusing on far and intermediate or near objects account for most of multifocal intraocular lenses in Japan, however three trifocal intraocular lenses, "Alcon Acrysof IQ PanOptix Single Piece (medical device approval number: 23100BZX00042000, Alcon Japan Ltd.)" and "Alcon Acrysof IQ PanOptix Toric Single Piece (medical device approval number: 23100BZX00043000, Alcon Japan Ltd.)", focusing on far, intermediate, and near objects were approved in 2019.

The AcrySof IQ PanOptix Toric IOL is a diffractive multifocal lens with a toric optic to correct pre-existing corneal astigmatism. The ACRYSOF IQ PanOptix Toric IOL is commercially available in 4 cylinder powers to reduce pre-existing corneal astigmatism (ACRYSOF IQ PanOptix Toric IOL TFNT30 - TFNT60), but the TFNT20, having lower cylinder power than approved products, has not been approved.

Levels of astigmatism 0.5 D to 1.0 D are estimated to represent 35.6% of all cataract cases in Japan [3]. For those patients, a lack of astigmatism correction can limit their desired outcome of visual acuity. Correcting astigmatism concurrently during phacoemulsification cataract surgery eliminates the need for additional surgical procedures, such as excimer laser keratectomy and limbal and corneal relaxing incision techniques. For example, the excimer laser can be cost prohibitive [4] and limbal and corneal relaxation incision can have less predictable results compared to Toric IOL options [4) 5) 6) 7) 8)].

The effect of astigmatism on the visual acuity of a multifocal intraocular lens implamted eyes are greater than that of a monofocal intraocular lens, and in particular, reduction of postoperative residual astigmatism is desired for multifocal intraocular lenses [9]. Therefore, even if the cylinder power is low, it is important to reduce cylinder power astigmatism.

The TFNT20, a multifocal IOL with an adequate cylinder power for low cylinder power astigmatism patients, will provide patients, as an additional treatment option, with post-cataract surgery quality of vision as they wish for, and is expected to contribute to the improved quality of vision after cataract surgery.

5.2 Purpose of the Study

The purpose of this study is to evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal. So this is intended to confirm the safety of the test product and examine its effectiveness as a Toric lens by examining the subject's astigmatism power.

At the end of the study, a clinical study report will be prepared in accordance with applicable regulatory requirements and standards.

5.3 Risks and Benefits

[redacted]

The TFNT20, a multifocal IOL with an adequate cylinder power for low cylinder power astigmatism patients, is expected to contribute to the improved quality of vision after cataract surgery.

There may also be unknown risks to use of test product. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight and monitoring.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Endpoint(s)

Objective(s)	Endpoint(s)
To evaluate primary effectiveness of the TFNT20 when implanted to replace the natural lens following cataract removal.	• Percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60)

6.2 Secondary Endpoint(s)

Table 6–2 Secondary Endpoint(s)

Objective(s)	Endpoint(s)
To evaluate secondary effectiveness of the TFNT20 when implanted to replace the natural lens following cataract removal.	• Percentage of eyes with ≤ 0.5 D refractive cylinder at Visit 3/3A (Day 30-60) • Average manifest refractive cylinder at Visit 3/3A (Day 30-60)

[redacted]

6.5 Safety Objective(s)

Table 6–4 Safety Endpoint(s)

Objective(s)	Endpoint(s)
To evaluate safety of the TFNT20 when implanted to replace the natural lens following cataract removal.	• Adverse events including SSI • Device deficiencies • Posterior capsular opacification • Posterior capsulotomy • IOL position change (tilt and decentration) • Intraocular pressure • Surgical problems • Slit Lamp Examination • Dilated Fundus Examination • IOL Observations

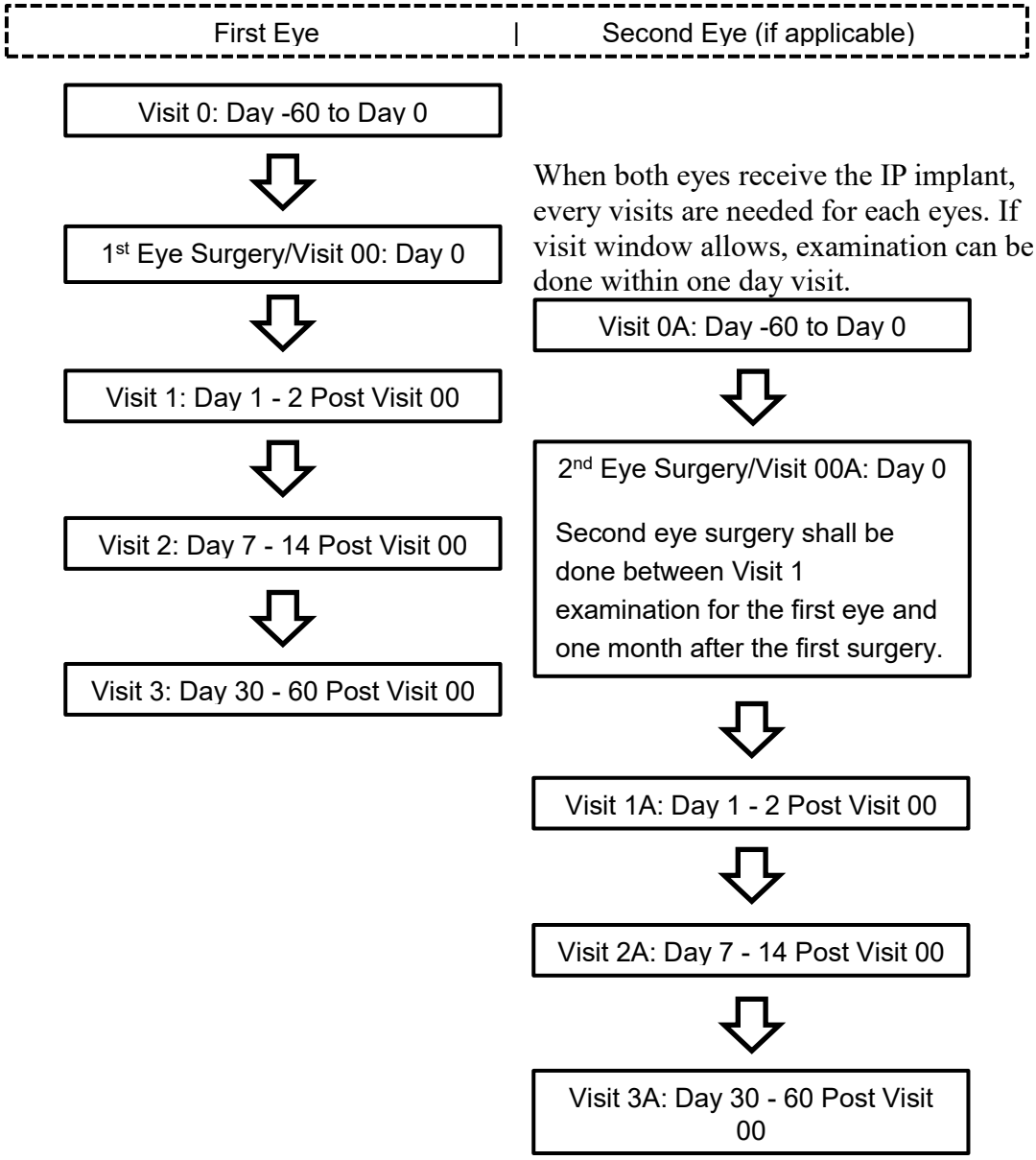
7 INVESTIGATIONAL PLAN

7.1 Study Design

This study is a prospective, single-center and non-comparative study. The study will include subjects must be ≥ 20 years of age with cataract who would be eligible to receive a TFNT20 lens in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. Subject with no ocular pathology that could confound study outcome, must require clear cornea cataract extraction, and must desire an IOL that provides the potential for near, intermediate and distance vision and corrects astigmatism. Potential subjects will be screened for enrollment into this clinical trial. Those qualifying will attend a total 5 visits, 1 is preoperative, 1 is operative and 3 are postoperative visits. If the test products will be implanted to both eye, the maximum number of visits is 9 visits, 1 is preoperative, 2 are operative and 6 are postoperative visits. Unscheduled visits may be attended if needed for medical attention.

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

Figure .7-1 Study Design



7.2 Rationale for Study Design

The purpose of this clinical study is to evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning.

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

Not applicable.

7.3 Rationale for Duration of Treatment/Follow-Up

Follow-up period required to properly evaluate effectiveness of astigmatism reduction of IP are set up.

7.4 Data Monitoring Committee

Not applicable

8 STUDY POPULATION

The study population includes approximately 30 subjects to be enrolled at 1 site.

To participate in the clinical trial, subjects must be ≥ 20 years of age with cataract who would be eligible to receive a TFNT20 lens in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. Subject with no ocular pathology that could confound study outcome, must require clear cornea cataract extraction, and must desire an IOL that provides the potential for near, intermediate and distance vision and corrects astigmatism. Additional entry criteria are listed below in Sections 8.1 through 8.3.

Check all entry criteria at baseline (Visit 0/0A) and at both surgical visits (Visit 00/00A).

If the implantation was aborted and the IOL did **not** touch the eye, then the subject is required to discontinue from the study and standard of care for IOL implantation is followed. Refer to Section 10.3 Discontinued Subjects for further details. If the implantation was aborted and the IOL did touch the eye, then the subject is followed for safety evaluation on this eye only.

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria: Among the criteria listed below, ocular criteria relates to the study eye only.

1. Adults, 20 years of age or older at the time of informed consent for participating in this study, of either gender, Japanese patient diagnosed with age-related cataract.
2. Planned routine cataract surgery (need determined by the expert opinion of the investigator).
3. Eligible to be implanted with the TFNT20 as determined by a new Alcon Toric calculator in at least one eye that incorporates ocular trends in surgical planning.
4. To qualify for fellow eye implant with TFNT20, subject must have no clinically significant findings at the Visit 1 examination of the first implanted eye.

Note: This criterion only applies to subjects who are eligible for both eyes and wishes to be implanted into fellow eye with TFNT20.

5. Willing and able to complete all required postoperative visits.

6. Subjects for able to comprehend and sign the informed consent form for participating in this study.
   For the subjects who are eligible for both eyes and wishes to be implanted into fellow eye with TFNT20, subject has to comprehend and sign the informed consent form for the second eye surgery and the study examinations prior to the examinations at Visit 0A.

7. Clear intraocular media other than cataract.

8. Subjects for whom postoperative emmetropia is planned (spherical equivalent ± 0.50 D).

9. Potential postoperative BCDVA of 0.5 decimal or better.

8.2 Exclusion Criteria Prior to Cataract Surgery

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study. Among the criteria listed below, ocular criteria relates to the study eye only.

1. Any disease or pathology, other than cataract, that (in the expert opinion of the investigator) is expected to reduce the postoperative BCDVA to a level worse than 0.5 decimal

2. Prior retinal detachment.

3. Irregular corneal astigmatism as assessed by topographer per investigator decision.

4. Pregnancy or lactation, current or planned, during the course of the study.

5. Participation in another concurrent clinical trial.

6. Pupil less than 6mm after dilation.

7. History of anterior segment (corneal, anterior chamber, sulcus) or posterior segment (uveal, vitreo-retinal) pathology including retinal vascular occlusive disease, retinal detachment or peripheral retinal laser photocoagulation, ARMD, glaucoma

(uncontrolled or controlled with medication) or ocular hypertension, diabetic retinopathy, retinitis pigmentosa and any optic nerve pathology.

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

9. Any other planned ocular surgical procedures including but not limited to LRI/Astigmatic Keratotomy and LASIK

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

11. Presence or history of any condition or finding that makes the subject unsuitable as a candidate for cataract surgery or study participation or may confound the outcome of the study, in the opinion of the Investigator.

8.3 Exclusion Criteria During Cataract Surgery

The patient who meets any criteria specified in the following 1) through 9).

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

2. Mechanical or surgical intervention required to manipulate the pupil.

3. Excessive iris mobility.

4. Significant vitreous loss.

5. Significant anterior chamber hyphema.

6. Zonular or capsular rupture.

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

8. Haptic placement other than bag-bag.

9. Incision other than temporal location

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): TFNT20

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

Table 9–1 Test Product

Test Product	TFNT20
Indication for use and intended purpose in the current study	The TFNT20 is intended for primary implantation in the capsular bag in the posterior chamber of the human eye for the visual correction of aphakia and pre-existing corneal astigmatism, secondary to removal of a cataractous lens in adult patients who desire near, intermediate, and distance vision with increased spectacle independence.
Product description and parameters available for this study	Single-piece construction lens consisting of the optic and the haptic made of the same material. The optic diffractive structure is in the central 4.5 mm portion of the optic zone (6.0mm), overall length: 13.0 mm, on the anterior surface and divides the incoming light to create a +2.17 D intermediate and a +3.25 D near add power. The posterior surface of Model TFNT20 is toric, and is designed with 1.00 D of cylinder power (0.68 D at the corneal plane in an average pseudophakic human eye [10]). The flat meridian of the AcrySof IQ PanOptix Toric IOL is identified with the indentations on the posterior surface of the optic in the form of dots. The details of the test product can be found in the Investigator's Brochure (#IB-0175).
Formulation	Not applicable.

Usage	The investigational product will be placed within the capsular bag after removal of the natural crystalline lens following phacoemulsification.
Packaging description	Pack each test product into the carton.
Labeling description	The carton with labeling of: ・ Name and address of the Sponsor ・ Purpose (for use in clinical study) ・ Lens model, serial number and refractive power, A-constant ・ Method of storage and precautions The package contains the following adhesive labels besides the test products: ・ Investigational lens control labels (to be attached to Investigational lens Control Log, medical record) ・ Copy of the investigational lens information given to study subjects (to be attached to the Study Participants Card).
Storage conditions	Keep the lens not at a high temperature/humidity and away from direct light. Do not keep the lens at 45°C or higher.
Supply	Refer to the management manual of test product for a detailed description.

The TFNT20 must be maintained within specified environmental condition, per the labeling.

A temperature log must be maintained documenting appropriate IP storage conditions as described in the management manual of test product, and must be made available for inspection.

More information on the test product can be found in the Investigator's Brochure (#IB-0175) and management manual of test product.

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

No other medical devices or medications are required to be used in conjunction with the treatments during the clinical study.

9.3 Treatment Assignment / Randomization

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system.

The investigational product will be placed within the capsular bag after removal of the natural crystalline lens. When both eyes are eligible, the eye which has smaller anticipated residual refractive astigmatism based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning shall be the first eye, and the eye which has lager anticipated residual refractive astigmatism shall be the second eye. If both eyes have same anticipated residual refractive astigmatism, the eye with advanced cataract shall be the first eye and the fellow eye should be the second eye.

9.4 Accountability Procedures

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

- Return to the Study Sponsor investigational products associated with a device deficiency. Refer to Section 11 of this protocol for additional information on the reporting of device deficiencies and to the management manual of test product 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 management manual of test product.

9.5 Changes to concomitant medications, treatments/ procedures

Changes in concomitant treatments after Visit 0 are not allowed unless needed for the proper medical care and treatment of the subject for a specific medical condition.

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 blood transfusions).

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

The use of spectacles and contact lenses (excluding refraction corrective contact lens for orthokeratology) is permitted. However, concomitant application of other ways of correcting refraction, possibly affecting evaluation of the investigational lens, is prohibited during the study. For example, laser in situ keratomileusis, PRK and refraction corrective contact lens (orthokeratology).

10 STUDY PROCEDURES AND ASSESSMENTS

Below examinations and observations are carried out at Visit 0/0A, Visit 00/00A, Visit 1/1A, Visit 2/2A and Visit 3/3A. The same instruments and methods should be used for all measurements at all visits. Examinations and observations are outlined in tabular format in Section 6 of this protocol. Both the examination and the observation may be per Visited on the same day if the day is within the window for the examination and observation of the eye concerned (first or second operated eye). Also examination and observation can be performed separately over days if these are performed within the set window.

10.1 Description of Study Procedures and Assessments

10.1.1 Preoperative Examination (Visit 0/0A)

- Informed consent
  Routine test conducted for cataract subjects is performed. Subjects still qualifies after these tests are explained this study. Ensure that the subject has read, understood, and signed and dated a statement of informed consent prior to undergoing any study specific testing. Even though routine test was operated before informed consent, these data can be use as study data.

- Demographics
  Confirm sex , age and race/ethnicity.

- Medical history
  Confirm systemic and ophthalmologic complication, ophthalmologic surgical history.

- Concomitant medications
  Indicate the concomitant medications used by the subject at the time of the examination.

- Urine pregnancy test (female subjects only)
  Perform a urine pregnancy test if the subject is female and of childbearing potential.

- Inclusion/exclusion criteria
  Ensure that the subject meets inclusion/exclusion criteria and meet all qualifications for participation.

- Visual acuity

[redacted]

[redacted]

- Manifest refraction
  Measure using an automated refractometer, and then perform a manifest refraction using the 100% contrast chart at 5m, under photopic lighting condition (100-180 cd/m^2).

- Slit lamp examination
  Record the presence or absence of clinically significant ophthalmologic findings.

- Dilated fundus examination
  Record the presence or absence of clinically significant ophthalmologic findings.

- Keratometry
  Keratometry will be performed using an automated keratometer.

- Target residual refractive error
  Indicate the amount of postoperative refractive error (±) anticipated based on the power calculation softwareused for the lens power that is chosen. The target for all eyes shall be emmetropia (based on the distance focus power).

- Calculation by a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning
  Calculate the IOL model by a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. The formula should be the Holladay Total SIA formula. Record the Anticipated Residual Refractive Astigmatism and Indicated IOL Alignment.

- Topography

Corneal topography should be measured and indicate whether the astigmatism is regular or irregular. Irregular astigmatism is an exclusion criterion and these subjects should not be enrolled in the study.

- Axial length
  Obtain the axial length by A-mode or IOL master.

- Anterior chamber depth (ACD)
  The ACD should be measured from the apex of the cornea to the anterior surface of the natural crystalline lens with A-mode or IOL master.

- Intraocular pressure
  Perform tonometry using a contact or a non-contact ocular tonometer.

- Adverse events, Device deficiencies
  Presence/absence of adverse events and device deficiencies are recorded since informed consent.

10.1.2 Surgery Day (Visit 00/00A)

Record surgical information at Visit 00/00A. If subjects wish to be implanted into both eyes with TFNT20, obtain consent in continuation of the study from each subject prior to the surgery on the 2nd eye.

- Operative eye
  Indicate which eye is being implanted.

- Exclusion criteria during surgery
  Assess qualification according to the inclusion/exclusion criteria during the surgery. The incision site for this study is defined as temporal (± 15°, or approximately 1 mm, for the horizontal meridian (OS: 0°, OD: 180°)).

- Final incision size
  Indicate final incision size (mm) to the nearest 0.1 mm.

- Problems during surgery

Indicate what problems, if any, occurred during surgery. If any exclusion criteria occur, discontinue the subject from the clinical study.

- Other procedures at this surgery
  Any other procedures performed at this surgery should be indicated. Since other procedures at this surgery are included in the exclusion criteria, discontinue the subject from the clinical study.

- Lens information
  Provide the IOL information (IOL model, refractive power, serial No.) also in the event of discontinuation of implant. Attach the adhesive label contained in the package of the investigational lens to the Study Participants Card.

- IOL axis orientation (dilated)
  Record the orientation (in degrees; 0 ~180 degrees) of the investigational lens axis (designated by indentations on the IOL optic). [redacted]

- Medical history
  Confirm systemic and ophthalmologic complication, ophthalmologic surgical history.

- Concomitant medications
  Indicate the concomitant ocular medications used during the surgery.

- IOL observation
  Observe the IOL surface and the inside of the haptic and optic of the investigational lens with a slit-lamp microscope, and record the presence/absence of visible abnormal findings (debris on IOL surface, forceps marks on IOL surface, IOL discoloration, IOL opacities, IOL scratch, membrane generated on IOL, pigmentation on IOL, surface haze, other.). And regarding the observed findings, evaluate the clinical significance. If the problem may negatively affect postoperative visual acuity, etc., handle it as the clinical significant, and if possible, take photos.

- Adverse events, Device deficiencies
  Presence/absence of adverse events and device deficiencies are recorded since informed consent.

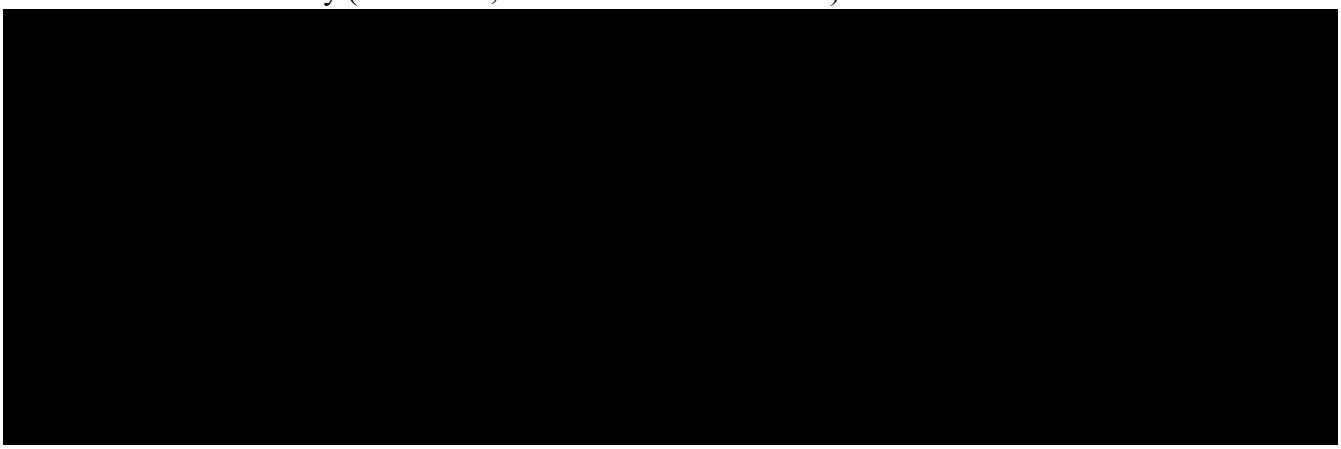
- Secondary surgical intervention

Record the presence/absence of any postoperative surgical procedure that may be caused by the investigational lens. The SSI include iridotomy/ iridectomy for pupillary block, vitrectomy for pupillary block, adjustment of the position of the investigational lens, removal of the investigational lens due to inflammation, exchange of the investigational lens, etc., but not limited to them. Meanwhile, retinal reattachment surgery and posterior capsule resection are not included as SSI.

10.1.3 Postoperative Examinations (Visit 1/1A, Visit 2/2A and Visit 3/3A)

Below examination and observation are carried out at Visit 1/1A, Visit 2/2A and Visit 3/3A.

- Visual acuity (Visit 1/1A, Visit 2/2A and Visit 3/3A)



- Manifest refraction (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Measure using an automated refractometer, and then perform a manifest refraction using the 100% contrast chart at 5m, under photopic lighting condition (100-180 cd/m^2).

- Slit lamp examination (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Record the presence or absence of clinically significant ophthalmologic findings.

- Dilated fundus examination (Visit 3/3A)
  Record the presence or absence of clinically significant ophthalmologic findings.

- Keratometry (Visit 1/1A and Visit 2/2A (if needed). Visit 3/3A.)
  Keratometry will be performed using an automated keratometer.

- Topography (Visit 1/1A and Visit 2/2A (if needed). Visit 3/3A.)

Corneal topography should be measured and indicate whether the astigmatism is regular or irregular.

- Axial length (Visit 1/1A and Visit 2/2A (if needed). Visit 3/3A.)
  Obtain the axial length by A-mode or IOL master.

- Anterior chamber depth (ACD) (Visit 1/1A and Visit 2/2A (if needed). Visit 3/3A.)
  The ACD should be measured from the apex of the cornea to the anterior surface of the natural crystalline lens with A-mode or IOL master.

- Intraocular pressure (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Perform tonometry using a contact or a non-contact ocular tonometer.

[redacted]

- Posterior Capsule Opacification (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Indicate the presence/absence of PCO. If PCO is present, it will be graded as clinically non-significant, clinically significant or clinically significant requiring YAG as follows:

  1. *Clinically Non-significant*: Early development of PCO, including fibrosis and proliferation of lens epithelial cells, observable by slit-lamp biomicroscopy. Causes no apparent decrease in VA subjectively (e.g., glare) or objectively (e.g., decrease in visual acuity).
  2. *Clinically Significant*: Increased PCO with early subjective and objective VA changes but does not require posterior capsulotomy.
  3. *Clinically Significant Requiring YAG*: Clinically significant PCO adversely affecting subject's VA and requiring posterior capsulotomy.

- Posterior capsulotomy (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Indicate whether a posterior capsulotomy was performed or not. If it was performed, report the date of the procedure and size.

- IOL observation (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Observe the IOL surface and the inside of the haptic and optic of the investigational lens with a slit-lamp microscope, and record the presence/absence of visible abnormal

findings (debris on IOL surface, forceps marks on IOL surface, IOL discoloration, IOL opacities, IOL scratch, membrane generated on IOL, pigmentation on IOL, surface haze, other.). And regarding the observed findings, evaluate the clinical significance. If the problem may negatively affect postoperative visual acuity, etc., handle it as the clinical significant, and if possible, take photos.

- IOL position change (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Tilt and/or decentration should be reported if greater than 10 degrees or 0.5mm.

- Adverse events, Device deficiencies (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Presence/absence of adverse events and device deficiencies are recorded since informed consent.

- Secondary surgical intervention (Visit 1/1A, Visit 2/2A and Visit 3/3A)
  Record the presence/absence of any postoperative surgical procedure that may be caused by the investigational lens. The SSI include iridotomy/ iridectomy for pupillary block, vitrectomy for pupillary block, adjustment of the position of the investigational lens, removal of the investigational lens due to inflammation, exchange of the investigational lens, etc., but not limited to them. Meanwhile, retinal reattachment surgery and posterior capsule resection are not included as SSI.

10.2 Unscheduled Visits

When a subject makes an unscheduled visit for adverse events etc., inquire about the reason for the visit and retain the record. The investigator will perform examinations/observations those are necessary and retain the record. If the visit is associated with any ophthalmologic symptom, identify the eye and retain the record.

If during an Unscheduled Visit the subject is discontinuing the IP or discontinuing from the study, the Investigator must conduct Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments and Section 10.1, as possible.

10.3 Discontinued Subjects

10.3.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent, not meeting the inclusion/excursion criteria.

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

The subject is discontinued in the following cases:

1) The investigational lens was removed for reasons of adverse events.
2) The investigator (or sub-investigator) judged it necessary to replace the investigational lens with another IOL.
3) The investigator (or sub-investigator) judged it necessary to discontinue the subject from the study.
4) The subject canceled the consent once issued.
5) The subject requested discontinuation of the study.
6) Continuation of the study was judged as impossible because of subject's referral or move during the study.
7) Other (discontinuation is necessary)

Upon discontinuation of the study, if the investigator or sub-investigator decided the examination or observation is necessary, the examination or observation should be carried out as far as possible under the subject's consent, and the date and reason of discontinuation are entered in the electric case report form. In case where continuation of the study is difficult because of discontinued visit of the subject to the clinic, the subject is followed over telephone, by mail or other appropriate means and the reason for discontinued visit, survival/death of the subject, presence/absence of adverse events, etc., are entered in the electric case report form.

If the investigational lens remained implanted in the subject after discontinuation of the study, the subject is informed as to the necessity of receiving periodical ophthalmological follow-up to assure safety at 30 – 60 days after surgery, and the subject is asked to extent cooperation as much as possible.

10.4 Clinical Study Termination

If discontinuation of the entire study has become inevitable for reasons of reports on serious safety information from any participating study site or overseas, problems pertaining to the quality of the investigational lens, and so on, the Sponsor is required to immediately inform the investigator and the head of each study site of discontinuation of the study and its reason in writing.

10.4.1 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.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test article). Refer to the Glossary of Terms and figures below for categories of AEs and SAEs.

Figure .11-1 Categorization of All Adverse Events

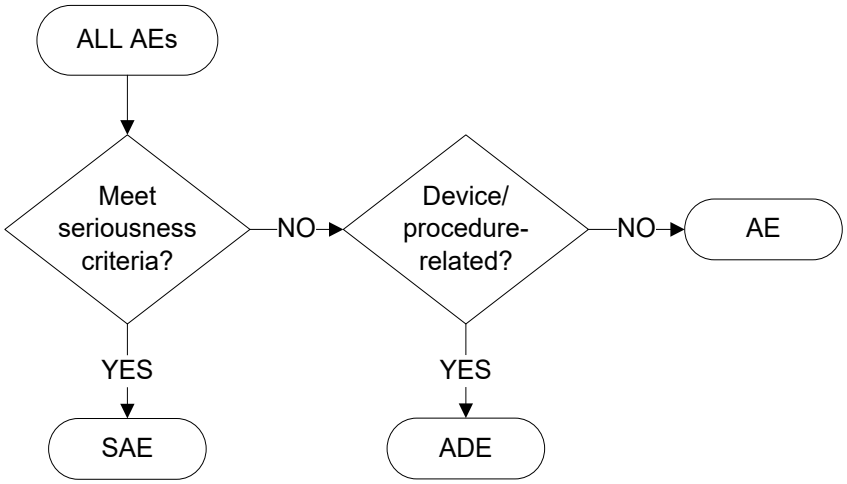
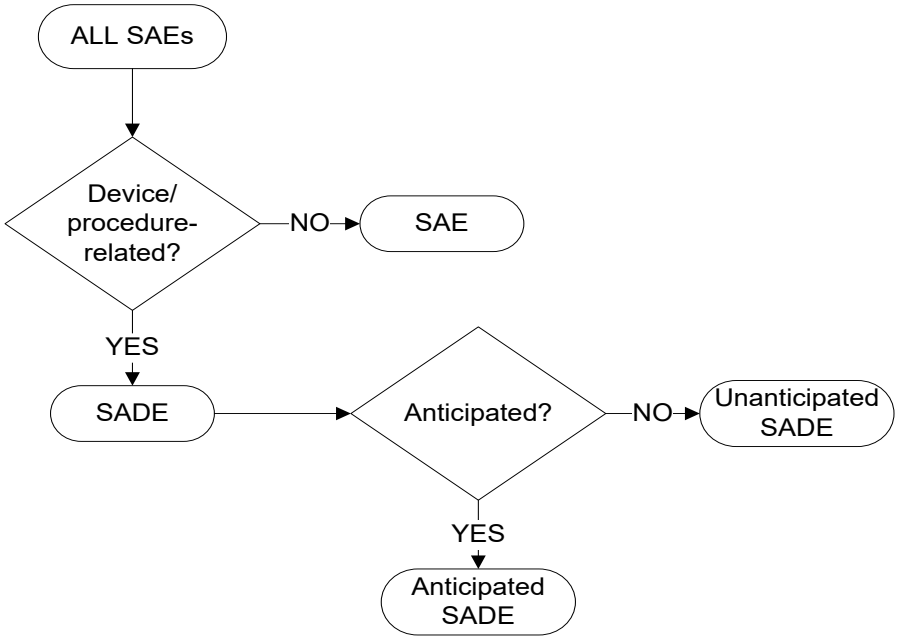


Figure .11-2 Categorization of All Serious Adverse Events



11.2 Procedures for Recording and Reporting

If any serious adverse event occurs, the investigator will report the type of the serious adverse event to Alcon Japan within 24 hours after confirming the event. After obtainment of detailed information on the serious adverse event, the investigator will prepare a report and immediately submit it to Alcon Japan and the head of the study sites.

[redacted]

All adverse events (related and unrelated to the medical device or test procedures) will be entered in the Adverse Event form. Surgically-related post-operative conditions that are normal consequences of the ocular surgery (see MOP) and not clinically relevant will be only reported as adverse events at the discretion of the investigator.

In addition, the investigator must document all serious adverse events (related and unrelated) on the Serious Adverse Event Form. Any device deficiencies will be entered in the device deficiency form within 24 hours after confirming the event.

Adverse events will also be reported for any clinically relevant change from informed consent in any protocol specific safety parameter evaluated during the study, based upon an assessment by the investigator following exposure to an investigational product.

Regarding the relationship with the investigational lens, a judgment will be made whether “not related” or “related.” Adverse events will be reported for any change in an ongoing medication and/or addition of a new medication, based upon an assessment by the investigator.

In addition, for all device deficiencies that have occurred, the details of it and the condition in which it have occurred will be entered in the device deficiency form within 24 hours after confirming the event.

Study Sponsor contact information is provided in the Manual of Procedures (MOP).

Causality and Intensity Assessments

For every AE, the Investigator must assess the causality as Related or Not Related to the medical device or test procedure in the study.

Causality

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

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.

The Investigator must document any action taken (ie, medication, intervention, or treatment plan) and outcome of the AE or device deficiency when applicable.

11.3 Unmasking of the Study Information

Not applicable; this study is a single treatment study.

11.4 Follow-Up of Safety Information

The Investigator is responsible for adequate and safe medical care of patients during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. For subjects who are experiencing ongoing unresolved adverse events at the time of their study completion or early discontinuation from the study, it is

recommended that the investigator schedule an appropriate follow-up visit in order to determine the outcome of the event.

11.5 Pregnancy in the Clinical Study

If the subject becomes pregnant during the study, the investigator or sub-investigator will report it to Alcon Japan immediately. However, pregnancy is not included in adverse event. Subjects who become pregnant during the study will not be discontinued; however, all data will be excluded from the Best-Case Analysis Set (BAS).

12 ANALYSIS PLAN

12.1 Subject Evaluability

Final subject evaluability must be determined prior to locking the database, based upon the Deviations and Evaluability Plan.

12.2 Analysis Sets

Analysis datasets used for safety and effectiveness analyses of this study are defined as follows.

Safety Analysis Set
The treatment-emergent safety analysis set will include all eyes with attempted implantation with the test article (successful or aborted after contact with the eye).

All-Implanted Analysis Set (AAS)
All-Implanted Analysis Set (AAS) will include all eyes with successful test article implantation.

Best-Case Analysis Set (BAS)
Best-Case Analysis Set (BAS) will include all eyes with successful test article implantation that had

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

12.3 Demographic and Baseline Characteristics

For all analysis datasets (Safety Analysis Set, AAS and BAS), demographics (sex, age [<60, 60-69, 70-79, ≥80], systemic complication [None/Yes, details] and past ocular surgery [None/Yes, details]) will be summarized with the number and percent of subjects in each category for the variable. Age will also be summarized with descriptive statistics (mean, standard deviation, number of subjects or eyes, median, min and max).

12.4 Effectiveness Analyses

The objective of this study is to evaluate safety and effectiveness of the investigational lens (TFNT20, T2 hereafter) when implanted to replace the natural lens following cataract removal.

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

Primary effectiveness variables are as follows.

- Percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60)

12.4.1.1 Statistical Hypotheses

The primary analysis will be performed using an exact test of binomial proportion (one-sided alpha = 2.5%). The null (H_0) and alternative (H_1) hypotheses are;

$$H_0: \pi(T2) = 29.2\%$$

$$H_1: \pi(T2) > 29.2\%$$

, where $\pi(T2)$ is the population proportion of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) for T2 group. The 29.2% is the percentage of non-Toric (T0, hereafter) group estimated from historically combined studies [redacted] that would have qualified for T2 according to the new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning.

12.4.1.2 Analysis Methods

All eligible eyes will be used for the analysis. For unilaterally implanted subjects, only the eligible eye, for bilaterally implanted subjects, both eyes will be used for the analysis. The superiority of T2 to T0 regarding refractive cylinder is to be demonstrated when there is a statistically significant difference between the outcome in this study and the historical threshold of 29.2%.

12.4.2 Analysis of Secondary Effectiveness Endpoint(s)

Secondary effectiveness variables are as follows.

- Percentage of eyes with ≤ 0.5 D refractive cylinder at Visit 3/3A (Day 30-60)
- Average manifest refractive cylinder at Visit 3/3A (Day 30-60)

12.4.2.1 Statistical Hypotheses

No confirmative statistical hypothesis testing is planned for secondary effectiveness variables

12.4.2.2 Analysis Methods

For continuous variables, descriptive statistics (mean, standard deviation, N, median, min and max) will be provided for actual value and change from baseline at each visit. For categorical variables, N and percent will be provided for each category at each visit. Any additional p-values from t-statistics or chi-square type statistics will be provided accordingly only for descriptive purpose.

[redacted]

12.5 Handling of Missing Data

No missing data will be imputed.

12.6 Safety Analyses

The safety endpoints are:

- Adverse events including secondary surgical intervention (SSI)
- Device deficiencies
- Posterior capsular opacification
- Posterior capsulotomy
- IOL position change (tilt and decentration)
- Intraocular pressure
- Surgical problems
- Slit Lamp Examination
- Dilated Fundus Examination
- IOL Observations

Patient listings will be provided for adverse experiences occurred from informed consent to exposure to the test article. Safety variables above will be analyzed using Treatment-Emergent Safety Analysis Set. For continuous variables, descriptive statistics (mean, standard deviation, N, median, min and max) will be provided for actual value and change from baseline at each visit. For categorical variables, N and percent will be provided for each category at each visit.

12.7 Interim Analyses and Reporting

No interim analysis is planned.

12.8 Sample Size Justification

To enroll more than or equal to 30 eligible T2 eyes used for analysis, at least 30 subjects will be evaluated by a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning and unilaterally or bilaterally implanted with the AcrySof IQ PanOptix IOL (TFNT20).

Using a new Alcon calculator that incorporates ocular trends in Toric IOL planning, percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) in T2 group was estimated as 60.9% based on a previous [redacted] (T2) study conducted in US. Using the same calculator, the percentage in T0 group was recalculated as 29.2% from the combined result of studies (non-Toric T0 lenses) conducted in Japan [redacted]. Statistical test will be conducted to compare percentage of T2 with a constant of 29.2% as percentage of T0. With 30 eyes from 30 subjects in T2 group, assuming the percentage of T2 is equal to 60.9% [redacted], the statistical power to demonstrate superiority of T2 to T0 is 91.6% with one-sided alpha of 2.5%, using an exact test of binomial proportion.

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/ethnicity)
- Documentation of subject eligibility

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

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the 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. (Note: Even though routine test was operated before informed consent, these data can be use as study data.) Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, e-mail, written and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

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.

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.

At expiration of the retention period of the records, the sponsor will notify the study sites thereof.

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 pursuant to the provisions of the protocol, Article 14 Paragraph 3 and Article 80-2 of the Pharmaceutical and Medical Device Act, the Ministerial Ordinance on Clinical Studies of Medical Devices (No. 36, Ministry of Health, Labor and Welfare, March 23, 2005) and the Notification about Enforcement of the Ministerial Ordinance on Clinical Studies of Medical Devices (No. Yakushoku-0720003, Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare, July 20, 2005).
- 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. Prior to the start of the study, the IRB of each study site is required to inspect and evaluate the planned study as to the acceptability of implementing the study, appropriateness of the contents of the protocol, case report form and informed consent document, and other matters related to the study from the ethical, scientific and medical points of view, with an ultimate goal of protecting the human rights and well-being of the subjects. The inspection and examination by the IRB may be performed again also during a certain period of time after the start of the study or when the head of the study site sees the necessity of additional inspection/examination so that the study may be monitored continuously. At the end of the study, the Investigator must notify the head of the investigational site about the study's completion. The IRB also must be notified if the study is terminated prematurely. Finally, the Investigator must submit the summary of progress

about clinical study to the head of the investigational site at intervals stipulated by the IRB and report it to the IRB.

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.

Specifications to secure safety of study subjects

In the event of acknowledging any adverse events, the investigator or the sub-investigator should immediately take appropriate actions irrespective of the presence or absence of causal relationship with the investigational lens.

In the case of obtaining safety-related new and significant information related to the clinical study, the sponsor should supply the information in writing to the investigator and the head of the study site and take necessary actions.

In the event of deviating from the study protocol to avoid the emergent risk and secure safety of the study subject or because of other unavoidable clinical reasons, the investigator will retain the record and submit the documentation and justification of the protocol deviation to the sponsor and the head of the study site.

Compensation for health hazards

If any subject has sustained health hazards arising from this study, best healthcare is provided to that subject. The Sponsor needs to be covered by insurance for liability arising from medical devices.

Payment to subjects

As a reward to the cooperation of each subject with the study, the Sponsor pays an amount of money, predetermined through negotiation with each participating study site, to each subject. This payment is not intended to force any subject to remain in the study.

15 REFERENCES

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