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Clinical Trial Protocol

Clinical Investigation of the AcrySof® IQ PanOptix™ IOL Model TFNT00

Protocol Number:	ILH297-C003 / NCT03090256
Sponsor Name & Address:	Alcon Research, Ltd. Toranomon Hills Mori Tower 1-23-1 Toranomon, Minato-ku Tokyo, 105-6333 Japan
Project Name / Number:	AcrySof® IQ PanOptix™ IOL Model TFNT00 / A01875
Test Article(s) / Product(s):	AcrySof® IQ PanOptix™ IOL Model TFNT00
Release Date:	See last page for electronic approvals.

Clinical Investigation of the AcrySof® IQ PanOptix™ IOL Model TFNT00

Protocol

Alcon Japan Ltd.

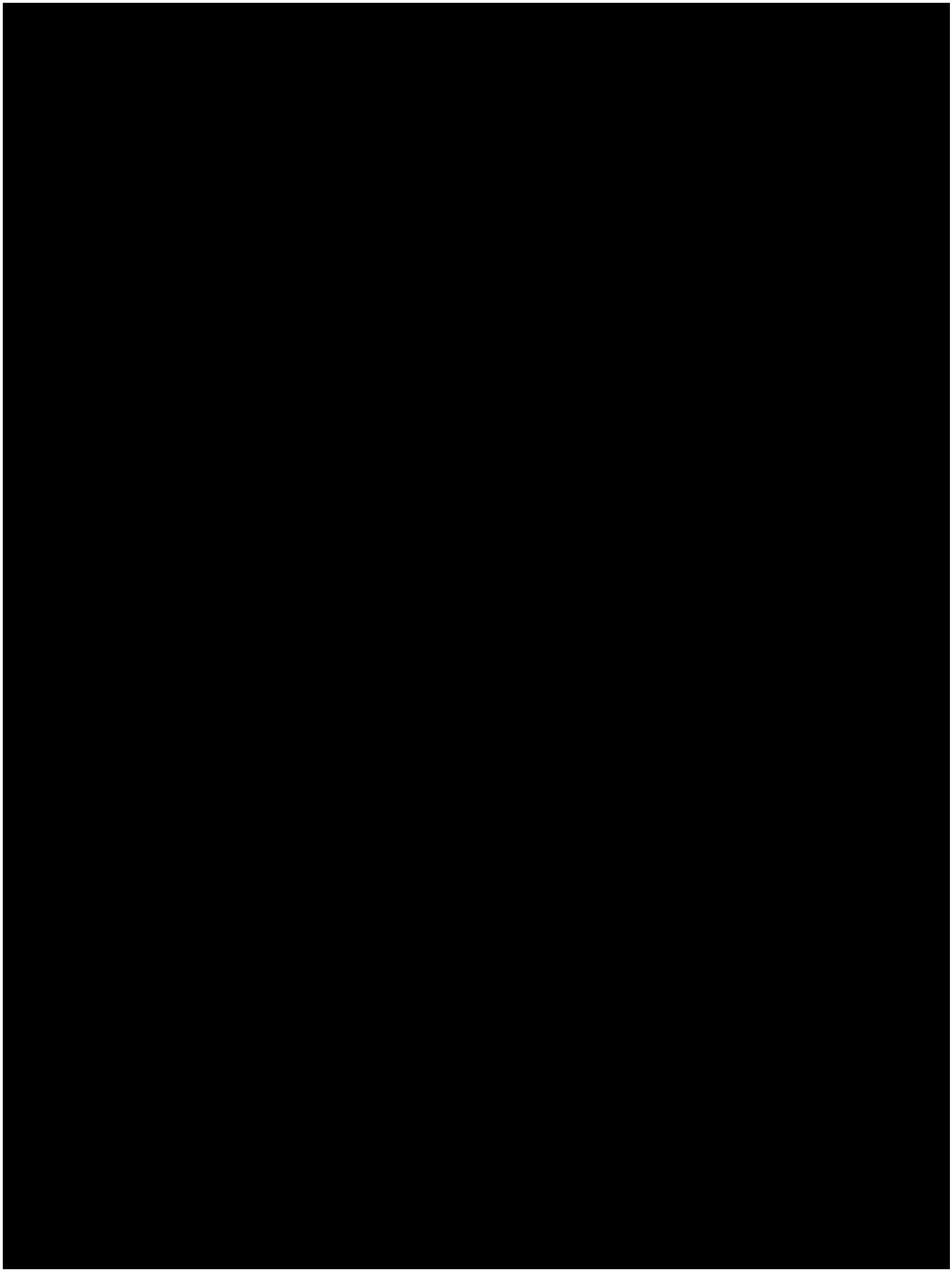
1-23-1, Toranomon, Minato-ku, Tokyo

Protocol No.: ILH297-C003

SUMMARY of the clinical study

Protocol Number	ILH297-C003
Objective(s):	To evaluate effectiveness and safety of the AcrySof IQ PanOptix Intraocular Lens (IOL) Model TFNT00 when implanted to replace the natural lens following cataract removal.
Trial Population:	Japanese subjects with bilateral cataract aged 20 or over
Trial Design:	Multi-center, Non-control, Open-label
Test Article:	AcrySof® IQ PanOptix™ IOL Model TFNT00
Variable(s):	Effectiveness: Primary Effectiveness - Monocular photopic best corrected distance visual acuity (5 m) - Monocular photopic distance corrected intermediate visual acuity (60 cm) - Monocular photopic distance corrected near visual acuity (40 cm) [redacted]
	Safety: Adverse Events Secondary Surgical Intervention related to optical properties Device Deficiencies Fundus visualization Intraocular Pressure Slit Lamp Examination Dilated Fundus Examination IOL Observations Subjective Posterior Capsule Opacification Posterior Capsulotomy Lens decentration and tilt [redacted] Laser Flare meter Subjective symptoms Problems during surgery

Usage	The investigational lens will be placed within the capsular bag after removal of the natural crystalline lens following phacoemulsification.
Eye examinations schedule	Visit 0 : Pre ope Visit 00/00A : Ope (00: 1st eye, 00A: 2nd eye) Visit 1/1A : 1-2 days after implantation (1: 1st eye, 1A: 2nd eye) Visit 2/2A : 7-14 days after implantation (2: 1st eye, 2A: 2nd eye) Visit 3/3A : 30-60 days after implantation (3: 1st eye, 3A: 2nd eye) Visit 4A : 120-180 days after 2nd eye implantation
No. of Subjects:	60 subjects 120 eyes
Anticipated study period	01-Apr-2017 ~ 30-Jun-2018
Medical Monitor	[redacted] Alcon Japan Ltd.
Sponsor	Alcon Japan Ltd.
GCP compliance:	This clinical study is subject to the Good Clinical Practice for Medical Devices (GCP for Medical Devices) (MHLW Notification No.36 dated March, 2005.)



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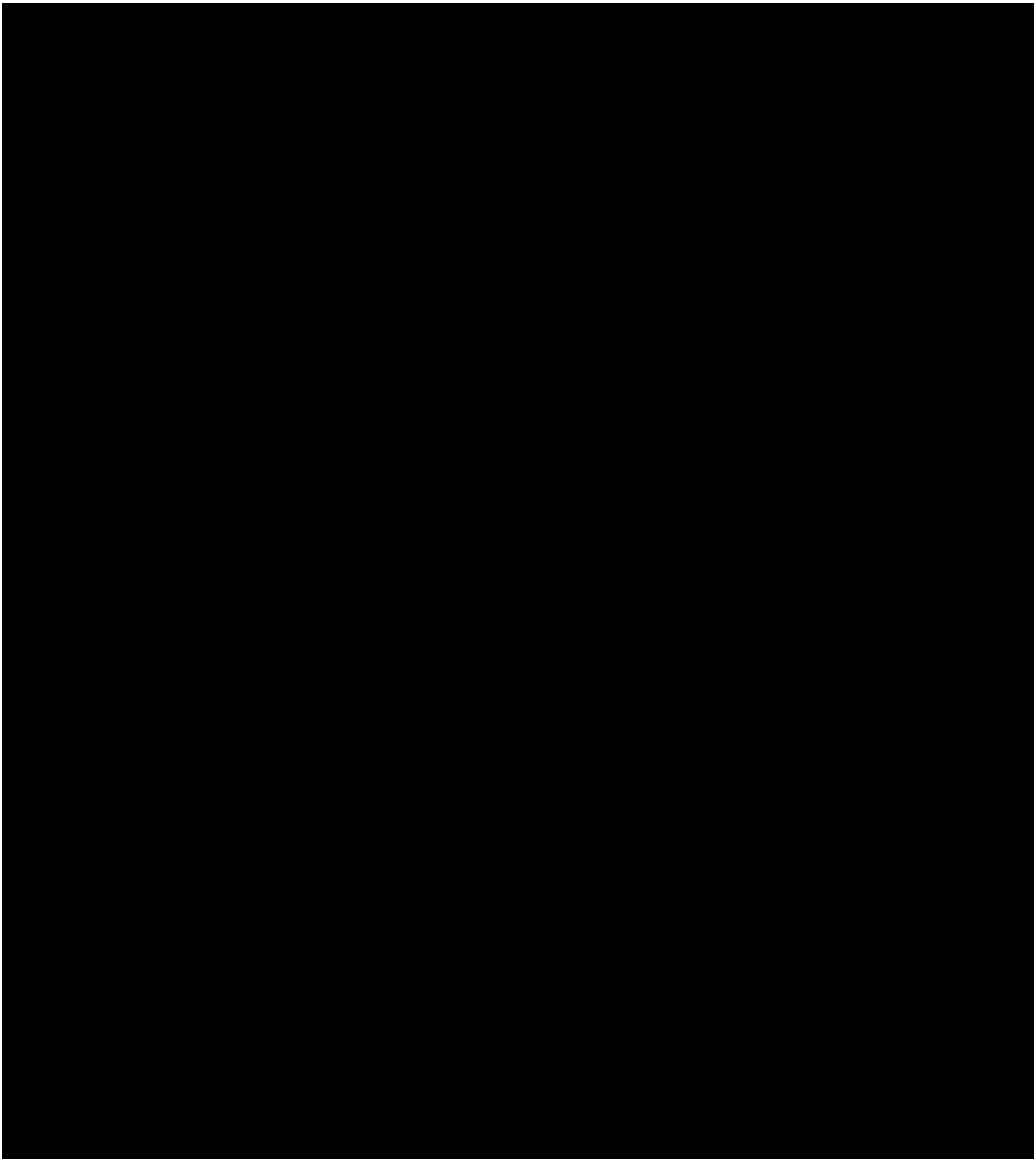

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1. INTRODUCTION

(1) History of development

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, however, bifocal intraocular lenses focusing on far and intermediate or near objects account for most of multifocal intraocular lenses: all the multifocal intraocular lenses approved in Japan are bifocal. Bifocal intraocular lenses have become popular because they correct an intermediate (1 m to 50 cm) or near vision sacrificed in monofocal intraocular lenses and therefore reduce the dependence on corrective devices including eyeglasses. However, bifocal intraocular lenses may not make the patient satisfy enough because they are designed to focus on distant and near or intermediate visions.

Recently, three trifocal intraocular lenses focusing on far, intermediate, and near objects were released in Europe. All the commercially available trifocal intraocular lenses are classified into the diffractive type. FineVision developed by PhysIOL has a 6.15 mm optical zone that serves as a diffractive zone, with an add power of +1.75D and +3.50D and an intermediate and near focal distance (theoretical value) of about 60 and 30 cm, respectively. AT LISA® tri 839 MP (Carl Zeiss Meditec AG) has a 6-mm optical zone that serves as a diffractive zone, with an add power of +1.66D and +3.33D and a focal distance (theoretical value) of about 80 and 40 cm, respectively. These two trifocal intraocular lenses have been reported to provide not only good distance and near, but also intermediate uncorrected visions [3) to 8)]. Neither of them has been approved in Japan.

The remaining one lens is TFNT00 developed by US Alcon (hereinafter called the investigational lens). It was given the CE mark in June 2015 and is now commercially available in EU. As with the Alcon® AcrySof® IQ ReSTOR® Single Piece of Alcon Japan (medical device approval number: 22000BZX00970000; hereinafter called SN6AD1) approved in Japan, the investigational lens provides multiple focuses based on the diffractive structure of the optical zone. SN6AD1 is a bifocal intraocular lens designed to have a diffractive zone with 3.6 mm around the optical part center, with an add power of +3D and a near focal distance (theoretical value) of about 40 cm. The investigational lens is designed to have a diffractive zone with 4.5 mm around the optical part center. This design change of the diffractive zone allows focusing on distance, intermediate, and near objects. The investigational lens has an add power of +2.17D and +3.25D and intermediate and near focal distances (theoretical value) of about 60 and 40 cm, respectively. It has an intermediate focus of 60 cm in addition to the distance and near (40 cm) focuses of SN6AD1. A non-clinical study (simulation with Badal images) performed to compare the visions potentially

achieved with the investigational lens and SN6AD1 showed that the investigational lens had a potential to provide equivalent distance and near visions to SN6AD1 and better intermediate visions at 80 and 60 cm [9].
In general, diffractive lenses are structurally associated with diffraction loss and resulting reduced contrast sensitivity because not all the lights passing through the lens are focused on the retina. [redacted] A clinical study of SN6AD1 (C-07-44) showed an uncorrected distance VA (logMAR) of 0.03 ± 0.14, uncorrected near vision of 0.04 ± 0.12, and normal photopic contrast sensitivity for both distance and near visions at 1 year postoperation[10, 11].
Although these visual acuity values from Badal images were obtained from a simulation, the investigational lens can correct not only distance and near visions, but also an intermediate vision of about 60 cm and is therefore expected to contribute to the improved quality of vision after cataract surgery.
The present study (ILH297-C003) is intended to confirm the safety of the investigational lens and examine its effectiveness as a multifocal lens by examining the vision results at different distances and investigating the postoperative use of eyeglasses by subjects.

(2) Summary of known and possible risks and benefits to subjects

Alcon has received the Approval to Market for TFNT00 with a CE mark in the European Union. But the results of clinical study have not been made available yet. In USA, a clinical study on this lens is in the planning stage. However, the plural clinical studies on same material IOLs were completed and in widespread clinical use in Japan and other countries. These clinical study data is described on investigator's brochure.

2. OBJECTIVE(S)

The objective of this study is to evaluate safety and effectiveness of AcrySof® IQ PanOptix™ IOL Model TFNT00 when implanted to replace the natural lens following cataract removal.

3. TEST ARTICLE(S)

(1) Investigational lens

AcrySof® IQ PanOptix™ IOL Model TFNT00 (+3.25D and +2.17D add power)

Construction

Single-piece construction lens consisting of the optic and the haptic made of the same material, optic diameter: 6.0 mm, overall length: 13.0 mm, [redacted] (See Fig.3-1)

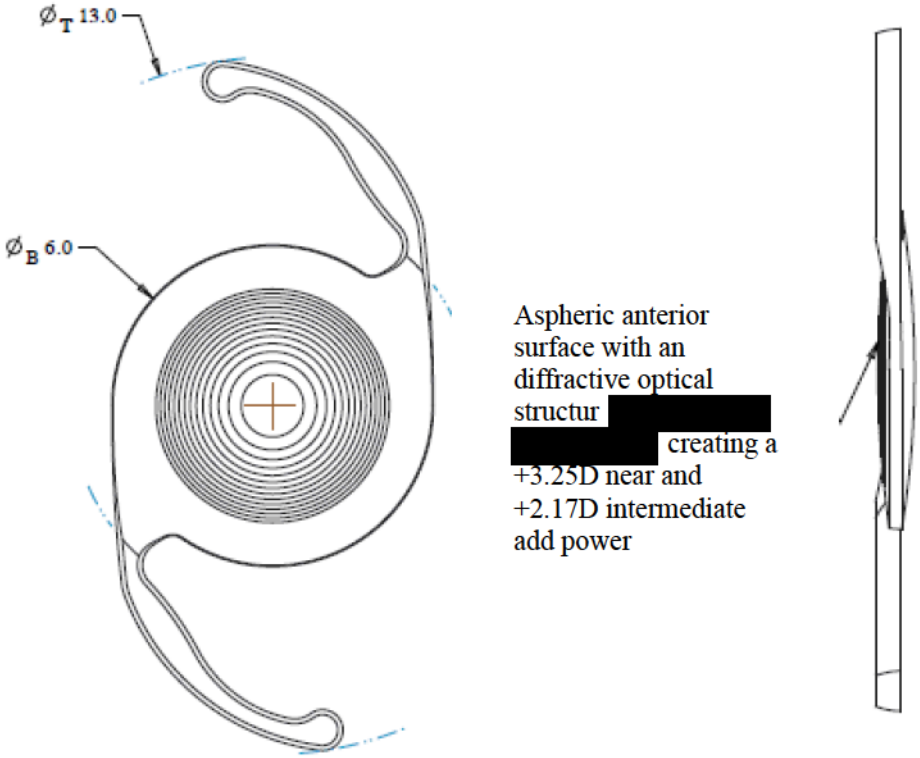

Fig.3-1 Product Drawing (TFNT00)

Optic

Material: Cross-linked, acrylate/methacrylate copolymer with a chemically bonded ultraviolet and blue light absorber*

* : N-2-[3-(2-methylphenylazo)-4-hydroxyphenyl] ethyl methacrylamide [redacted]

Edge thickness: 0.21±0.05 mm

Add power: +3.25D、+2.17D

Refractive power: 12.5～26.5D (in 0.5 D increments)

Haptic

Material: Same as the optic material

Shape: Modified-L

Angulation: 0°

(2) Usage

The investigational lens will be placed within the capsular bag after removal of the natural crystalline lens following phacoemulsification. Bilateral implantation of the investigational lens is planned for all subjects. The lens is implanted first to the eye with more advanced cataract. If both eyes have a similar degree of cataract, perform the surgery first for the right eye. The time of surgery for the remaining eye (2nd eye) will be within 30days from the first surgery which will be decided by the investigators based on the results of the examination and observation at Visit 1 (1-2 days after 1st eye implantation).

[Justification for the intended use]

Since the investigational lens, like conventional IOLs, is a posterior chamber lens which is widely implanted following cataract extraction, phacoemulsification is adopted. To assess the binocular vision, the investigational lens will be implanted to bilateral eyes. Considering the safety of the study subjects, the time of implant to the remaining eye (2nd eye) will be decided based on the results of the 1st implant.

(3) Instructions on package and labeling

Pack each investigational lens into 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 investigational lens:

- 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).

<Carton of the investigational lens>

(Side view)

Model:	Barcode	For Use of Clinical study	Illustration of the lens
Serial No	A-constant: ***.*		

(Front view)

Storage methods:

Keep the lens not at a high temperature/humidity and away from direct light.

Do not keep the lens at 45°C or higher.

Precautions:

- This product is a sterilized product used only once. Do not re-sterilize or re-use the once opened product.
- Do not use the product if the package has a tear or if the package is opened and the sterility is not assured.

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<Adhesive label>

(Investigational lens Control Label)

For Use of Clinical study	Model: Refractive power: Serial No.:

(Copy of the investigational lens information given to study subjects)

Model:	**Refractive power:**
Name of study subject:	
Implant eye:	**right / left**
Overall length including the haptic:	
Optic diameter:	
Serial No.:	
Date of surgery:	
Surgeon:	

(4) Storage and Management

The investigational lens storage manager appointed at each study site appropriately stores and manages the investigational lens according to the investigational lens management operating procedure provided by Sponsor beforehand, and prepares the inventory on which the receipt and delivery of the product, such as use of the product by each investigator, are recorded.

4. SUBJECTS

(1) Estimated Total Sample Size

60 subjects 120 eyes

(2) Inclusion Criteria

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

1) Adults, 20 years of age or older at the time of informed consent, of either gender, diagnosed with bilateral cataracts;
2) Able to comprehend and sign a statement of informed consent;
3) Willing and able to complete all required postoperative visits;
4) Calculated lens power within the available range;
5) Planned cataract removal by phacoemulsification;
6) Potential postoperative BCDVA of 0.5 decimal or better in both eyes;
7) Subject with preoperative astigmatism < 1.0 D
   Note: Corneal incisions made to reduce astigmatism will not be allowed during the course of the study.
8) Clear intraocular media other than cataract in both eyes;
9) The subject must be able to undergo second eye surgery within 30 days of the first eye surgery.

[Justification for the inclusion criteria]

1 and 5: Cataract extraction is the indication of the clinical study.

2 and 3: One of GCP requirements

4: Essential condition for implant of the investigational lens.

6, 7, 8 and 9: Conditions to minimize the potential non-IOL factors which may affect the visual acuity data

(3) Exclusion Criteria

[Exclusion Criteria Prior to Surgery]

The patient who meets any criteria specified in the following 1) through 21).

1) Significant irregular corneal aberration as demonstrated by corneal topography;
2) Inflammation or edema (swelling) of the cornea affecting post-operative visual acuity;
3) Subjects with diagnosed degenerative visual disorders (e.g. macular degeneration or other retinal disorders) that are predicted to cause future acuity losses to a level worse than 0.5 decimal for BCDVA;

4） Subjects who may be expected to require ocular surgery (other than blepharo-surgery, laser surgery of fundus and YAG capsulotomy) during the study;
5） Previous refractive surgery;
6） Amblyopia;
7） Clinically severe corneal dystrophy (eg., epithelial, stromal, or endothelial dystrophy), keratitis, keratoconjunctivitis, keratouveitis, keratopathy, or kerectasia;
8） Diabetic retinopathy;
9） Extremely shallow anterior chamber, not due to swollen cataract;
10） Microphthalmos;
11） Previous retinal detachment;
12） Previous corneal transplant;
13） Recurrent severe anterior or posterior segment inflammation of unknown etiology;
14） Rubella or traumatic cataract;
15） Iris neovascularization;
16） Glaucoma;
17） Aniridia;
18） Optic nerve atrophy;
19） Pregnancy;
20） Any subject currently participating in another investigational drug or device study.
21） Disqualified by the investigator or the sub-investigator because of physical or ophthalmic diseases

[Exclusion Criteria During Surgery]
The patient who meets any criteria specified in the following 1) through 8).

1） Mechanical or surgical manipulation required to enlarge the pupil; pupil size must be at least 4.5 mm or larger just prior to implantation;
2） Other planned ocular surgery procedures for the duration of the study;
3） Excessive iris mobility;
4） Significant vitreous loss;
5） Significant anterior chamber hyphema;
6） Uncontrollable intraocular pressure;
7） Zonular or capsular rupture or tear;
8） Bag-sulcus, sulcus-sulcus or unknown placement of the haptics.

In the event of zonular damage, capsulorhexis tear, or decentered capsulorhexis during surgery, the surgeon should decide whether the stability of the IOL would be compromised by the complication. If the IOL stability would be compromised, the study IOL should not be implanted, the subject should be discontinued from the study, and the surgeon should make arrangements to implant an alternative non-study IOL.

[Justifications for the exclusion criteria]

{Exclusion Criteria Prior to Surgery}

9, 12, 13, 17 and 20: Factors potentially affecting effectiveness evaluability and criteria to secure safety of study subjects

1, 2, 4, 5, 6, 7, 8, 11, 18 and 19: Factors potentially affecting effectiveness evaluability

3, 10, 14, 15, 16 and 21: Criteria to secure safety of study subjects

{Exclusion Criteria During Surgery}

1: Factors potentially affecting effectiveness evaluability

2-7: Criteria to secure safety of study subjects

5. STUDY DESIGN

Multi-center, single-arm and non-masked study

6. STUDY PROCEDURE

(1) Outline

The investigational lens will be implanted to both eyes in subjects with bilateral cataract. Registration of patients and the implantation of the investigational lens will be conducted in consideration of securing 120 eyes in 60 subjects as the analysis subjects. As shown in (4) of this section, subjects will be followed for 120 to 180 postoperative of the second implant for effectiveness and safety evaluation of the investigational lens.

(2) Eligibility Assessment and Subject Identification Code Allocation

Subjects are selected and subject code is assigned according to the following procedures.

1. After explanation of the content of study to subject, obtain consent to participate in the clinical study from the qualified subject. Subject code will be assigned after obtain consent.
2. Perform tests/observations (screening tests) necessary for the assessment according to the inclusion/exclusion criteria and the investigator will assess the qualification. In the case of meeting the exclusion criteria during surgery, do not implant the investigational lens to the eye and do not enroll the eye in the clinical study.
3. The same subject code will be used for both the first and second implants. Prior to the second implant, obtain consent to continuously participate in the clinical study from the subjects.

(3) Surgical Technique

The lens is implanted first to the eye with more advanced cataract (1st eye). If both eyes have a similar degree of cataract, perform the surgery first for the right eye. The time of surgery for the remaining eye (2nd eye) will be within 30days from the first surgery which will be decided by the investigator based on the results of the examination and observation at Visit 1 (1-2 days after 1st eye implantation).

Each investigator should use his or her standard surgical technique on all subjects. A continuous tear capsulorhexis should be performed to open the anterior capsule. Implant of the investigational lens will follow

phacoemulsification. The investigational lens, including both haptics, should be placed within the capsular bag. If the standard surgical technique cannot be applied or if the investigational lens cannot be implanted, the subject should be discontinued from the study and an approved and marketed lens should be implanted instead of the investigational lens. All study subjects should receive the investigator's standard regimen of preoperative, operative, and postoperative medications.

(4) Eye Examinations Schedule

As shown in Table 6-1, the examination and observation are carried out for the period from before surgery day 120 to 180 after surgery of second eye. At Visit 0 and Visit 4A, the examination and observation of both eyes are carried out on the same day.

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.

Table 6-1 Eye Examinations Schedule

PROCEDURES/ MEASUREMENTS/ STATUS	Visit 0 (Preop)	Visit 00 (Op)	Visit 00A (Op)	Visit 1 (d1-2)	Visit 1A (d1-2)	Visit 2 (d7-14)	Visit 2A (d7-14)	Visit 3 (d30-60)	Visit 3A (d30-60)	Visit 4A (d120-180)
Informed Consent*	X									
Demographics	X									
Inclusion/Exclusion Criteria	X	1st	2nd							
Urine Pregnancy Test (female only)	X									
[redacted]										
Intraocular Pressure	B			1st	2nd	1st	2nd	1st	2nd	B
Laser Flare Meter (mydriatic)						1st	2nd			(1st) (2nd)
Slit Lamp Examination	B			1st	2nd	1st	2nd	1st	2nd	B
Dilated Fundus Examination	B					1st	2nd			B
Fundus visualization						1st	2nd			B
IOL Observations				1st	2nd	1st	2nd	1st	2nd	B
Lens decentration and tilt				1st	2nd	1st	2nd	1st	2nd	B
Subjective Posterior Capsule Opacification / Posterior Capsulotomy				1st	2nd	1st	2nd	1st	2nd	B
[redacted]										
Subjective Symptoms	Xb								Xb	Xb
Operation Records**		1st	2nd							
Ocular Concomitant Medications	B	1st	2nd	1st	2nd	1st	2nd	1st	2nd	B
Secondary Surgical Interventions				1st	2nd	1st	2nd	1st	2nd	B
Device Deficiencies	◄									►
Adverse Events	◄									►

1st: First eye, 2nd: Second eye, B: Both eyes (1st eye and 2nd eye), Xb: Binocular Testing, X: Conduct [redacted], (1st) (2nd): If there is any inflammation sign at Visit 2 or Visit 2A, perform examination again.
* : Consent continuously participate of this clinical study is obtained between 1st and 2nd implant.
** : Operative Eye, Problems During Surgery, Other Procedures at Surgery, Insertion Instrument, Incision Site, Final Incision Size, anterior capsulotomy size, and Lens Information

(5) Examinations Procedure

Below examination and observation are carried out at Visit 0, Visit 00/00A, Visit 1/1A, Visit 2/2A, Visit 3/3A and Visit 4A. The same instruments and methods should be used for all measurements at all visits in each site.

1）Preoperative Examination (Visit 0)

・ 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.

・ Demography

Sex, age, systemic complication, ophthalmologic surgical history

・ Urine Pregnancy Test (female subjects only)

Perform a urine pregnancy test if the subject is female and of childbearing potential.

・ Visual acuity

Measure the monocular visual acuity about both eyes. Measure the visual acuity [redacted] using the 100% contrast chart at each measurement distance as below. [redacted]

[redacted]

[redacted]

・ Subjective Symptoms

To the following inquiries by the investigator or co-investigator, the subject will declare the following Subjective symptoms.

[redacted]

- Target Residual Refractive Error

  Indicate the amount of postoperative refractive error (±) anticipated based on the power calculation software used for the lens power that is chosen. [redacted]

[redacted]

- Intraocular pressure

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

- 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.

- Ocular concomitant medications

  Indicate the type of concomitant ocular medications used by the subject at the time of the examination.

- Inclusion/exclusion criteria

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

- Adverse Events, Device Deficiencies

  Presence/absence of adverse events and device deficiencies are recorded since informed consent.

2）Surgery Day (Visit 00/00A)

Record surgical information at Visit 00 (1st eye) and Visit 00A (2nd eye) respectively, 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.

- Qualification during the surgery.

  Assess qualification according to the inclusion/exclusion criteria during the surgery.

- Incision Site

  Record the incision site (sclera, at limbus, or cornea).

・ Anterior capsulorhexis Diameter

Indicate anterior capsulorhexis diameter (mm) to the nearest 0.1 mm.

・ Final Incision Size

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

・ Insertion Instrument

Indicate which approved instrument and cartridge was used to fold and insert the IOL through the wound.

・ 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.

・ Ocular concomitant medications

Indicate the type of concomitant ocular medications (e.g. adrenocorticosteroid, chemotherapy, NSAIDs, IOP reducing drug) used during the surgery.

・ 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 CRF and the Study Participants Card.

・ Adverse events and Device deficiencies

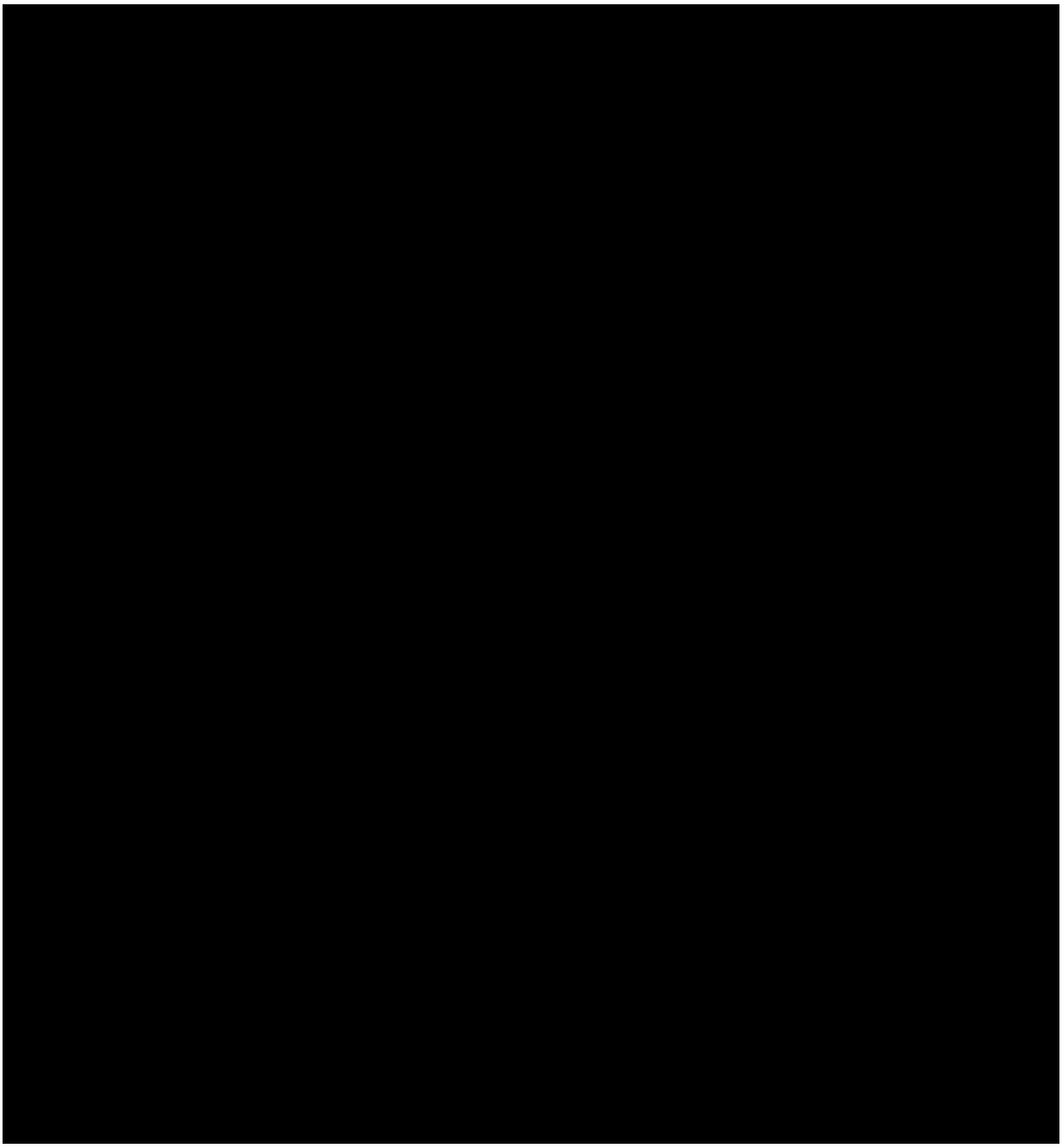
Presence/absence of adverse events and device deficiencies are recorded.

3）Postoperative Examinations

Below examination and observation are carried out at Visit 1/1A, Visit 2/2A, Visit 3/3A and Visit 4A.

・ Visual acuity

Visual acuity is tested under photopic [redacted] using the 100% contrast chart at each measurement distance as below. [redacted]

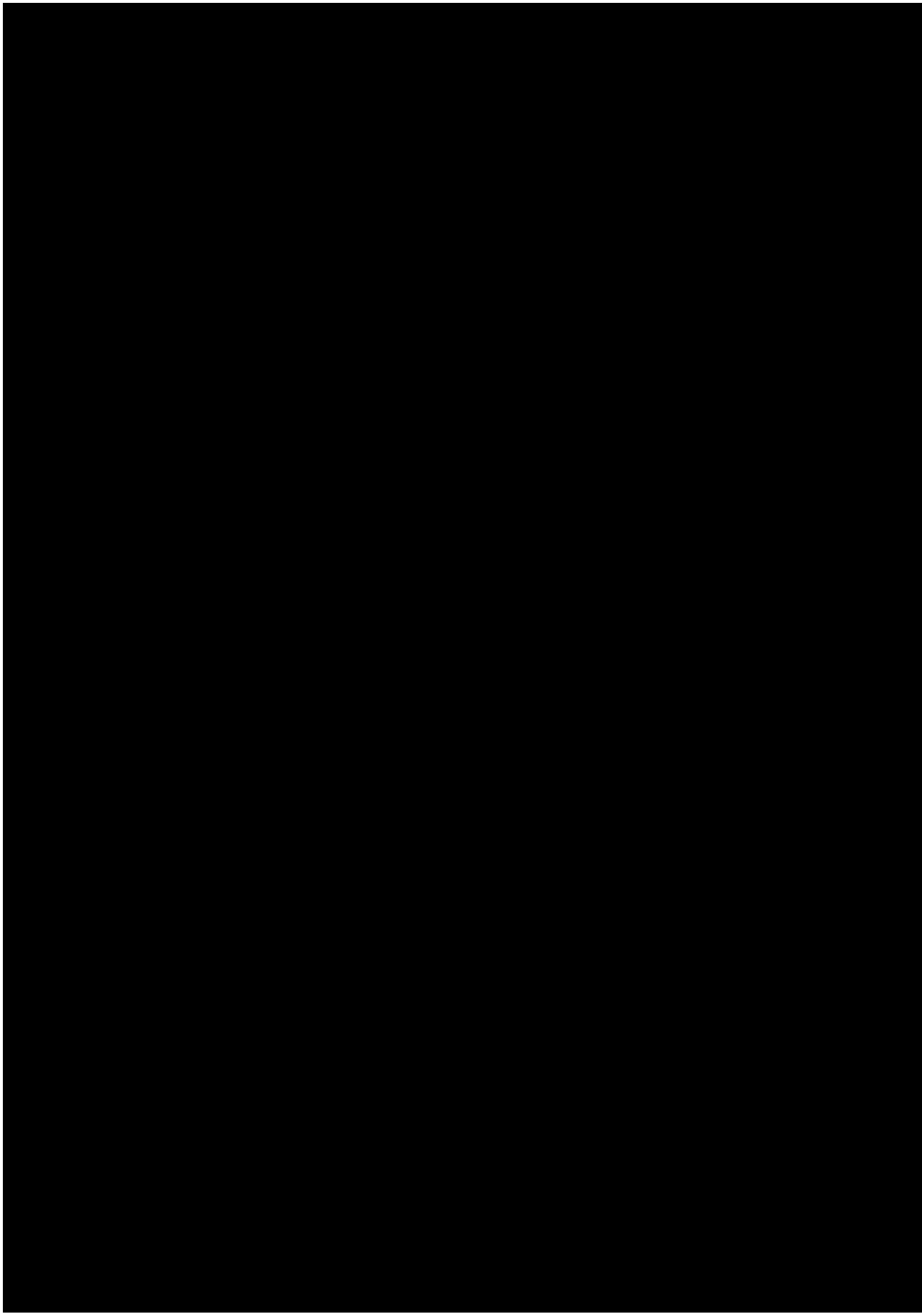


[redacted]

[redacted]

・ Subjective Symptoms (Visit 3A, Visit 4A: Binocular)

To the following inquiries by the investigator, the subject will declare the following Subjective symptoms.



[redacted]

- Intraocular Pressure (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

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

- Laser Flare Meter (Visit 2/2A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  Perform examination using a laser flare meter at mydriatic condition. If there is any inflammation sign at Visit 2 or Visit 2A in laser flare mater and Slit lamp examination, perform examination again at Visit 4A.

- Slit Lamp Examination (non-mydriatic or mydriatic)
  (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  Record the presence or absence of clinically significant ophthalmologic findings.

- Dilated Fundus Examination (Visit 2/2A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  Record the presence or absence of clinically significant ophthalmologic findings.

- Fundus visualization (Visit 2/2A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  Indicate whether the investigational lens has caused any loss in fundus visualization that would alter a surgeon's ability to administer retinal treatment, as compared to experience with monofocal IOLs.

- IOL observation (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  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 mark on IOL surface, glistening, formation of membrane on IOL, pigmentation on IOL, etc.). 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, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

  Tilt and/or decentration should be reported if greater than 10 degrees or 0.5mm.

- Posterior Capsule Opacification (PCO) (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

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:

- Posterior capsulotomy (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

Indicate whether a posterior capsulotomy was performed or not. If it was performed, report the date of the procedure and size.

- Ocular concomitant medications (Visit 1/1A, Visit 2/2A, Visit 3/3A Monocular (1st or 2nd eye), Visit 4A: Both eyes）

Indicate the type of concomitant ocular medications used by the subject at the time of the examination.

- Secondary surgical intervention (Visit 1/1A, Visit 2/2A, Visit 3/3A: Monocular (1st or 2nd eye), Visit 4A: Both eyes)

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.

- Adverse events and Device efficiencies (Visit 1/1A, Visit 2/2A, Visit 3/3A and Visit 4A)

Presence/absence of adverse events and device efficiencies are recorded.

4）Unscheduled Visits Examinations

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.

(6) Anticipated study period

01-Apr-2017 ~ 30-Jun-2018

7. CONCOMITANT THERAPY

(1) Permissible concomitant therapy

The use of spectacles and contact lenses is permitted.

(2) Prohibited concomitant therapy

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).

8. DISCONTINUED SUBJECTS

(1) Discontinued Subjects

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 least 6 months after surgery, and the subject is asked to extent cooperation as much as possible.

(2) Discontinuation of the entire study

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.

9. Analysis Plan

9.1 Subject Evaluability

The final subject evaluability will be determined prior to database lock. Analysis datasets used for safety and effectiveness analyses of this study are defined as follows.

9.1.1 Safety Analysis Set

The pre-treatment safety analysis set will include all subjects who consented to participate in the study. The pre-treatment safety analysis set will be the set that will be used to summarize occurrence of adverse experiences prior to exposure to the test article. 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).

9.1.2 All-Implanted Analysis Set (AAS)

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

9.1.3 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

9.2 Analysis Dataset

Analysis datasets used for effectiveness and safety analyses are as follows.

9.2.1 Dataset for Primary Effective Analysis

AAS and BAS will be used for primary effectiveness analysis. The primary analysis set for effectiveness analyses will be the AAS.

[redacted]

9.2.3 Dataset for Safety Analysis

Pre-treatment safety analysis set will be used for adverse experiences prior to exposure to the test article. The treatment-emergent safety analysis set will be used for all safety variables after contact with the test article.

9.3 Demographics 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, median, min and max).

9.4 Effectiveness Analysis

The objective of this study is to describe safety and effectiveness of the investigational lens (TFNT00) when implanted to replace the natural lens following cataract removal. Monocular analysis will be performed at both first and second eyes. Binocular analysis will be performed for binocular testing parameters.

9.4.1 Primary Analysis

Primary effectiveness variables are as follows.

- Monocular photopic best corrected distance visual acuity (5 m)
- Monocular photopic distance corrected intermediate visual acuity (60 cm)
- Monocular photopic distance corrected near visual acuity (40 cm)

9.4.1.1 Statistical Hypothesis

No formal hypothesis testing is planned.

9.4.1.2 Analysis Method

Decimal monocular photopic best corrected distance visual acuity (5 m) and decimal monocular photopic distance corrected intermediate visual acuity (60 cm) will be categorized as follows.

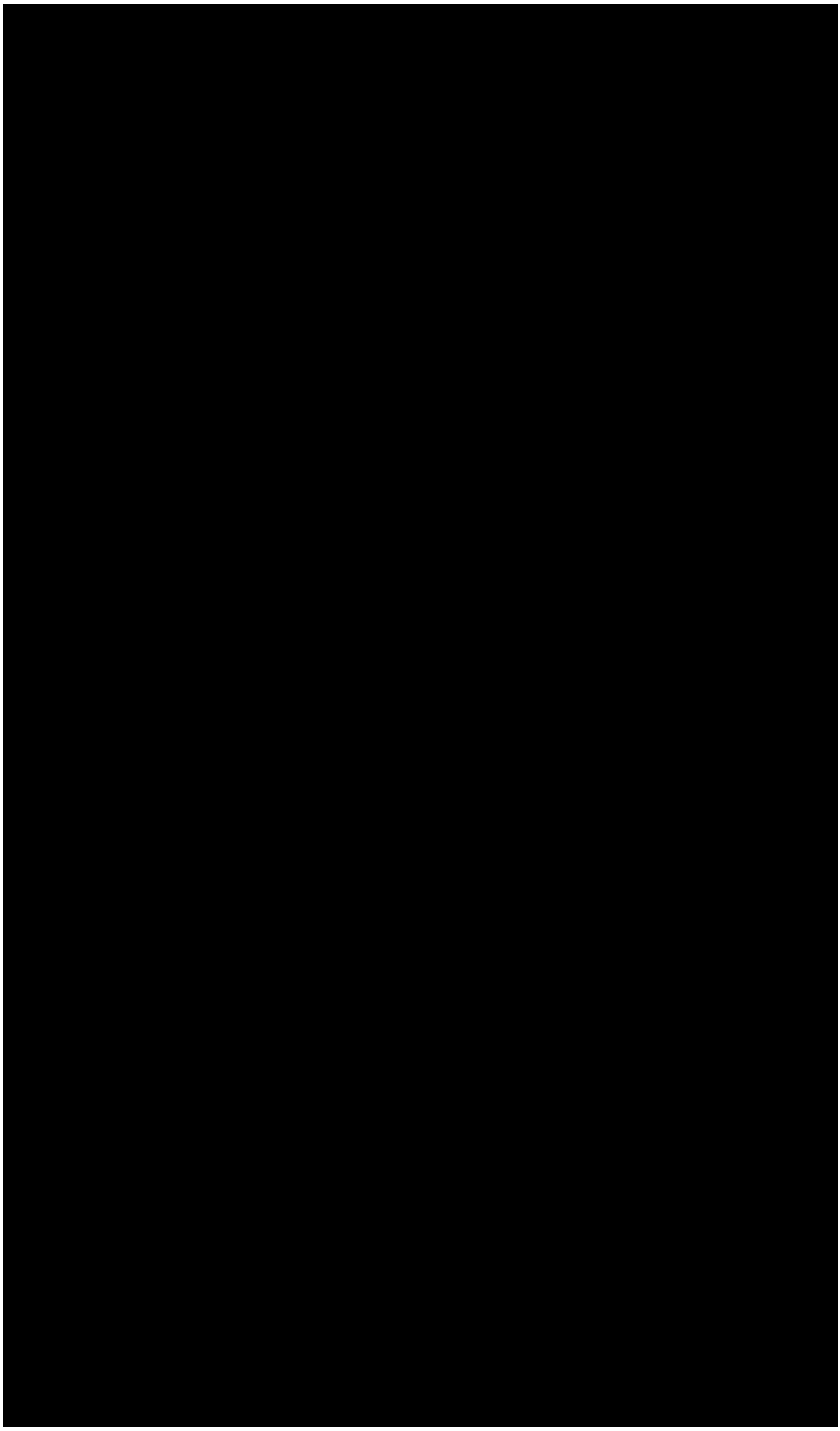
- < 0.5
- 0.5 - < 0.7
- 0.7 - <1.0
- 1.0 -

Decimal monocular photopic distance corrected near visual acuity (40 cm) will be categorized as follows.

- < 0.4
- 0.4 -

The N and percent of each category will be provided by visit. For these decimal visual acuity, descriptive statistics (geometric mean, dispersion factor (DF), N, median, min and max) will be provided by visit. Descriptive statistics (arithmetic mean, standard deviation, N, median, min and

max) will also be provided for logMAR visual acuity by visit.



9.5 Handling of Missing Data

No missing data will be imputed.

9.6 Safety Analysis

Patient listings will be provided for adverse experiences occurred from informed consent to exposure to the test article using Pre-Treatment Safety Analysis Set. Safety variables below 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.

- Secondary Surgical Interventions related to the optical properties of the IOL
- Adverse Events (including secondary surgical interventions not-related to the optical properties of the IOL)
- Device Deficiencies
- Fundus visualization
- Intraocular Pressure
- Slit Lamp Examination
- Dilated Fundus Examination
- IOL Observations
- Subjective Posterior Capsule Opacification
- Posterior Capsulotomy
- Lens decentration and tilt
- [redacted]
- Laser Flare meter

- Subjective symptoms
- Problems during surgery

9.7 Interim Analysis

No interim analysis is planned.

9.8 Sample Size Justification

The 60 eligible subjects will be bilaterally implanted with the AcrySof IQ PanOptix IOL (TFNT00). The purpose of this study is to describe safety and effectiveness of the investigational lens. The sample size is not determined on the basis of a statistical power calculation. With a sample size of 60, a two-sided 95% CI for the mean based on the t-statistic will extend 0.26*SD units from the observed mean. Also, a 95% confidence interval of 50% (30/60) is (36.8%, 63.2%) based on the exact method.

10. ADVERSE EVENTS and DEVICE DEFICIENCIES

A device deficiency and an adverse event will be collected from the time informed consent is signed.

(1) General Information

Definitions

Device Deficiency - any alleged deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device.

Adverse Event (AE) - any untoward medical occurrence in a subject, user, or other persons regardless of whether or not the event has a causal relationship with the medical device(s) or test procedure(s) in the study. Secondary surgical intervention is also reported as an adverse event (Additional information addressing adverse events is presented in Supplemental Attachment B: Definition of Adverse Events)

Nonserious Adverse Event - an adverse event that does not meet the criteria for a serious adverse event.

Serious Adverse Event (SAE) - an adverse event that led to any of the following:

- Death
- A serious deterioration in health that:

A) resulted in 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, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.

B) resulted in an any potentially sight-threatening event or permanent impairment to a body structure or a body function.

C) required in-subject hospitalization or prolongation of an existing hospitalization.

NOTE: Hospitalization that is standard of practice following a surgical procedure for the device type would not be a SAE. In general, hospitalization signifies that the individual remained at the

hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether

"hospitalization" occurred, the event should be considered serious.

D) resulted in a medical intervention to prevent A) or B) or any surgical intervention(excluding posterior capsulotomy).

E) resulted in 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.

Adverse Device Effect - any untoward and unintended response to a medical device (adverse device effect that cannot be denied the relations with the medical device), including any event resulting from device malfunction, insufficiencies or inadequacies in the instructions for use, or user error.

Serious Adverse Device Effect - an adverse device effect that has resulted in any of the consequences/characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

(2) Reporting of serious adverse events (SAE)

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.

Contact for emergent communication (e.g. reporting of SAE)

Contact	Company telephone/facsimile	Email	Home telephone/ Cellular phone
[redacted]	TEL [redacted] FAX	[redacted]	[redacted]

(3) Report of adverse events and evaluation of the causal relationship

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 Appendix B) 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 screening 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.

(4) Intensity Assessment

For every AE, the investigator must assess the intensity (severity). Events should be classified as mild, moderate, or severe. These classifications should be based on the following definitions:

(5) Follow-up of Subjects / Subjects with Adverse Events

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.

(6) Subject Pregnancy

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).

11. ETHICS

(1) Institutional review board

Prior to the start of the study, the institutional review board (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.

(2) Ethical consideration

The study is implemented after a contract on implementation of the study is concluded between the Sponsor and each study site following inspection and authorization of the study by the IRB of each study site.

If deemed necessary to ensure safe implementation of the study, the protocol of this study may be revised in accordance with the provisions set forth in “Section 12. PROTOCOL AMENDMENTS” This study is carried out in accordance with the principles set forth in 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).

(3) Protection of subjects’ privacy

To protect the privacy of individual subjects, only the identification codes are used to represent the subjects whose data are used in case report form, etc., so that leakage of the identifiable individual information about the subjects can be prevented.

(4) Specifications to secure safety of study subjects

1) Actions to take for adverse events

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.

2) Supply of new information

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.

3) Avoiding emergent risks

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.

(5) 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.

(6) 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.

12. PROTOCOL AMENDMENTS

When the protocol is revised, the sponsor and the investigator will exchange an agreement in writing. The revised protocol, etc. will be reviewed and approved by the IRB of the study site before new subjects are enrolled, depending on the necessity.

13. CONSIDERATIONS FOR DOCUMENTATION AND COMPLETION OF CASE REPORT FORM

The Investigator, or coordinator etc. will complete the electronic case report form by himself or herself based on source data in accordance with the protocol and the preparation procedure of the electronic case report form.

14. MONITORING

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that:

1. The rights and well-being of the subjects are protected.
2. The reported data are accurate, complete, and verifiable from the source documents.
3. The study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current Good Clinical Practices (GCPs), and with applicable regulatory requirements.

15. RETENTION OF THE RECORDS

The records for this clinical study shall be stored properly: At expiration of the retention period of the records, the sponsor will notify the study sites thereof.

Study sites and investigators shall preserve the protocol, source documents, informed consent forms agreed, informed consent form and other written information, records on handling of the study devices and other documents required by the provisions of MHLW Ordinance No. 36 date March 23, 2005. Above documents should be retained either three years after the date of termination or completion of the clinical study or approval of the importing of the devices (in case of termination of the development, three years after the date of the termination) whichever date is later.

16. REFERENCES

1) Bissen-Miyajima H.: Multifocal IOL; 3-12, 2008
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5) Mojzis P, Kukuckova L, Majerova K, Liehneova K, Piñero DP. Comparative analysis of the visual performance after cataract surgery with implantation of a bifocal or trifocal diffractive IOL. J Refract Surg. 2014;30(10):666-72.
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8) Cochener B, Vryghem J, Rozot P, Lesieur G, Chevalier JP, Henry JM, David T, Lesueur L, Gatinel D, Ganem C, Blanckaert J, Van Acker E, Heireman S, Ghekiere S. Clinical outcomes with a trifocal intraocular lens: a multicenter study. J Refract Surg. 2014;30(11):762-8.
9) In-house reference: TDOC-0050087 Clinical Evaluation Report for:ACRYSOF IQ PANOPTIX IOL Model TFNT00
10) Bissen-Miyajima H., Hayashi K., Yoshino M., Nakamura K., Yoshida M.: Atarashii Ganka 27(12); 1737-1742, 2010
11) In-house reference : CSR Supplement (C-07-44 date of preparation 2010/2/4)

Signature page

The sponsor and the Investigator agree to conduct the study in accordance with the details and procedures described in this study protocol and electronic CRF.

Investigator

Medical institution: [_____]

Affiliation and position: [_____]

Name: [_____]

(Signature or seal)

Date:_____

Sponsor

Study manager

Alcon Japan Ltd. Development department

Name (signature): [_____]

Date:_____

APPENDIX

[redacted] [redacted]

Clinical Investigation of the AcrySof® IQ PanOptix™ IOL

Model TFNT00

Protocol Appendix

A Definition of Term
B Definition of Adverse Events
C Clinical Trial System, Participating Facilities and Principal Investigators
D Confidentiality and Publication of the Study
E Direct Access to Source Data and Documents
F Quality Control and Quality Assurance of the Study
G Obligations of Investigators
H Informed consent
[redacted]

Alcon Japan Ltd.

1-23-1, Toranomon, Minato-ku, Tokyo

Protocol No.: ILH297-C003

APPENDIX A: Definition of Term

Corneal edema - Fluid in stromal layer of cornea with or without epithelial edema.

Hyphema - Blood in the anterior chamber, present over a period of time.

Hypopyon - Accumulation of white blood cells in the anterior chamber.

Intraocular infection/Endophthalmitis - Inflammation of ocular tissue including confirmed infection and sterile inflammation.

Iritis - Inflammation of the iris causing pain, tearing, blurred vision, small pupil (miosis), and a red congested eye, as evidences by flare and/or cell in the anterior chamber.

Lens Dislocation – Displacement of the lens from its intended place.

Macular degeneration - Deterioration of macular tissue usually evident as a loss of pigment from the pigment epithelial layer. Included in this category are central serous chorioretinopathy, choroidal neovascular membrane and pigment epithelial detachment.

Macular edema - Swelling of macular tissue from excess fluid accumulation in the macular area diagnosed by clinical symptoms and/or fluoroscopic exam. This includes cystoid macular edema.

Membrane formation on IOL - Outgrowth of epithelial cells from the capsularhexis onto the surface of the IOL.

Pigment precipitates on IOL - Iris pigment deposits on the surface of the IOL.

Pupillary block - Blockage of normal aqueous flow through the pupil.

Retinal detachment - Separation of the retina from the pigment epithelium layer.

Secondary Surgical Intervention - Any secondary surgical procedure that can reasonably be expected to be IOL-related. This includes, but is not limited to, iridectomy for pupillary block, vitreous aspiration for pupillary block, repositioning of the lens, IOL removal for inflammation, and IOL replacement. This excludes posterior capsulotomy.

Vitreous detachment - Separation of vitreous gel from the retinal surface.

Vitritis – Inflammatory intraocular reaction (with clouding and cells) in the vitreous. Often accompanies inflammation of the ciliary body, iris, choroid, or retina. Can be sterile or due to infection.

Raised IOP Requiring Treatment - A persistent elevation of intraocular pressure secondary to cataract surgery that requires medical and/or surgical treatment.

Synechiae - Iris adhesion to adjacent ocular structures.

APPENDIX B: Definition of Adverse Events

Following findings are not regarded as AE because that it is a series of wound healing reaction related to cataract surgery. However, when investigator judged it is not wound healing reaction, it is treated as AE.

- Edema or haze around sclerocorneal incision: Occurred by 1 month post surgery
- Fold or swelling of Descemet's membrane at central cornea: Occurred by 1 month post surgery
- Post surgery inflammation: Occurred by 3 months post surgery
- Raised IOP related to post operation inflammation and fibrin reaction: Occurred by 1 month post surgery

Investigator (or sub-investigator) should judge when the events below occurred after the test IOL implantation whether the events is AE or not.
If the events are regarded as AE, investigator must fill out AE forms in the electric case report forms.

- IOP: 10mmHg or more than 10 mmHg change from Visit 0 after 1 month post surgery
- Slit lamp findings (anterior and posterior segment): Worse than Visit 0
  (Ocular finding which is caused by inflammation related to cataract surgery is excluded.)
- Best corrected distance visual acuity: Worse than Visit 0 at the last exam (Visit 4A)

APPENDIX C: Clinical Trial System, Participating Facilities and Principal Investigators

1. Clinical Trial System

(1) Sponsor

Alcon Japan Ltd.

Representative: [redacted]

[redacted]

TEL: [redacted] FAX: [redacted]

(2) Study Supervisor

[redacted], Alcon Japan, Ltd.

(3) Study Manager

[redacted], Alcon Japan, Ltd.

(4) Persons in Charge of Monitoring (delegate)

[redacted], Alcon Japan, Ltd.

(5) Medical Monitor

[redacted] Alcon Japan, Ltd.

2. Medical Institutions and Investigators

No.	Clinical study site	Job title	Principal investigator	Location
[redacted]				

APPENDIX D: Confidentiality and Publication of the Study

All information related to this clinical study including the protocol and therapeutic results are the property of the sponsor, and the investigator and other medical staff engaged in the clinical study must keep such information confidential.

The sponsor can submit the results of this clinical study to the health authority for the purpose of obtaining an approval for manufacture (import) and publish them in the congresses or medical journals. When publishing the results of this clinical study in the congresses or medical journals, the investigators and other medical staff must obtain prior approval from the sponsor. The sponsor can confirm the contents of presentation beforehand.

APPENDIX E: Direct Access to Source Data and Documents

The investigator and the study site must make source data available to the sponsor or the regulatory authority at their request. Such direct examination of source data will be performed so that the sponsor may confirm whether the clinical study is conducted in accordance with the protocol and whether data of the case report form are indicated accurately.

With reference to [Evaluation] and [Comment of the investigator, etc.], there are no source data and they are information directly indicated on the case report form.

APPENDIX F: Quality Control and Quality Assurance of the Study

Quality control and Quality assurance shall be carried out in accordance with GCP standard operational procedures (SOP) of the Sponsor.

APPENDIX G: Obligations of Investigators

Selection of Trial Subjects

In the selection of trial subjects, investigator(s) and sub-investigators shall, from the standpoint of human rights and on the basis of the standards for selection and exclusion set forth in the trial protocol(s), carefully consider whether to request participation in the trial, taking into consideration such factors as the subject's general state of health, symptoms, age, sex, capacity to consent, dependency on investigator(s), etc., and participation in other trials.

Obtaining Consent of Subjects

Investigator(s) and sub-investigators shall obtain from the subject or legally acceptable representative thereof, in accordance with GCP, consent for the subject to participate in the trial.

Medical Treatment of Subjects

The investigator shall have the responsibility for all decisions on medical treatment relating to the trial.
The director of the institution and the investigator shall ensure that the subject is provided with adequate medical treatment for all trial-related adverse events that constitute clinical problems during and after the subject's participation in the trial. Further, when an investigator or sub-investigator becomes aware of the need for medical treatment of an adverse event, he or she shall so inform the subject.
The investigator or sub-investigator shall conform whether the subject has another attending physician, and with the consent of the subject, inform the attending physician of trial participation.
If a subject desires to withdraw or withdraws participation during the trial, the subject is not obliged to clarify the reason for withdrawal, but the investigator or sub-investigator shall make appropriate efforts, based on full respect for the rights of the subject, to determine the reason.

Agreement on and Compliance with Trial Protocol(s)

Prior to reaching an agreement with the sponsor on the trial protocol(s) and case report forms (CRF), the investigator shall confer with the sponsor on the basis of the trial protocol(s), CRF and current investigator's brochure(s), and other required materials and information submitted by the sponsor, and shall give full consideration to the ethical and scientific suitability of conducting the trial. The same shall apply if the trial protocol(s) or CRF are revised.
The investigator shall reach agreement with sponsor on the content of the trial protocol(s) and CRFs, and as evidence of agreement to comply with the trial protocol(s), the investigator and sponsor shall date and affix their signatures or personal seals to a trial contract or alternative document. The same shall apply if the trial protocol(s) or CRFs are revised, or if, due to a directive of the director of the institution based on the opinion the IRB, the trial protocol(s) or CRF is corrected.

Submission of documents to the IRB

Before and during the trial period, the investigator(s) shall keep current those documents that are subject to review by the IRB and are to be submitted by the investigator(s). If these documents are augmented, updates or revised, all must be submitted promptly to the director of the institution.

Directive and Decisions of the Director of the Study site

When IRB gives its approval to conduct the trial on condition of certain revisions, and the investigator has been informed in writing of the directives and decisions of the director of the institution based thereon, the investigator shall commence the trial in accordance with these directives and decisions.

When the IRB gives its approval to continue a trial in progress or to continue a trial on condition of certain revisions, and the investigator has been informed in writing of the directives and decisions of the director of the institution based thereon, the investigator shall continue the trial in accordance with these directives and decisions.

When the IRB cancels its approval to an item related to a trial in progress (including its termination or suspension) and the investigator has been informed in writing of the directives and decisions if the director of the institution based thereon, the investigator shall comply with these directives and decisions.

Use, etc., of the Investigational Product(s)

The investigator shall ensure that the investigational product(s) are used only in accordance with methods that comply with the approved trial protocol(s).

Deviations etc. from Trial Protocol(s)

The investigator or sub-investigators shall not undertake any deviation from or modification of the trial protocol(s) without prior written agreement between the investigator and the sponsor and written approval based on prior inspection by the IRB. This is not, however, applicable in the case of changes related solely to cases that are medically unavoidable in order to avoid imminent danger to the subject, or in the case of management matters (e.g., a change in telephone number).

The investigator or sub-investigators shall keep a record of all actions deviating from the trial protocol(s). The investigator or sub-investigators shall prepare a record describing the reason(s) etc. therefore, submit the record regarding to deviation in order to avoid imminent danger to the subject to the sponsor, and retain a copy.

The investigator or sub-investigators may undertake deviations from or modification of the trial protocol(s) within prior written agreement between the investigator and the sponsor and written approval based on prior inspection by the IRB in medically unavoidable situation, in order to avoid imminent danger to the subject, In such an event, the investigator notify as soon as possible the sponsor, as well as the director of the institution and, via the director of the institution, to the IRB, of the nature of and reasons for the deviation or modification, together with a proposal for revision of the trial protocol(s), if appropriate, and obtain their approval, and at the same time shall obtain in writing the approval of the director of the institution and, via the director of institution, the agreement of the sponsor.

Filling and submitting electronic case report forms, etc

The Principal Investigator or the sub investigator etc. should fill the electronic case report forms for individual patients in accordance with the preparation procedure of the electronic case report form. The Principal Investigator will e-sign all electronic case report forms including those which would be filled in by the Sub-investigator etc. after checking it to verify. If the Sub-investigator etc. have modified or corrected the electronic case report form, the Principal Investigator should confirm that the electronic case report form is free of errors and should e-sign the electronic case report forms. An electronic copy of the electronic case report forms should be retained by the Principal Investigator.

The Principal Investigator should assure that the electronic case report form and all other reports are correct, complete, and easily understandable and submitted at an appropriate timing. It should also be assured that identification codes are used for distinction between individual patients.

The Principal Investigator or the Sub-investigator etc. should follow the manual of the electronic case report form prepared by the Sponsor when modifying or correcting the electronic case report form. If the electronic case report form is revised, added to or deleted, the revision/addition/deletion must be kept as an audit trail, and the name of the person that has entered (revised) the information, the date of the entry (revision) and the description of the information entered must be recorded. The reason for any significant change or revision to the electronic case report form is also required to be recorded.

Reports, etc. in the Course of the Trial

In order to be available for ongoing review by the IRB, the investigator shall submit to the sponsor annually, or more frequently when requested by the IRB, a written overview of the status of the trial.

With respect to any trial modification that could have a significant effect on the conduct of the trial or could increase the risk to subjects, the investigator shall promptly submit a written report to the director of the institution and, via the director o the institution, to the IRB.

Except in cases in which the trial protocol(s) or investigator's brochure(s) provide that urgent notification is not required, the investigator shall notify the sponsor promptly of all serious adverse events. After the urgent notification, a detailed written report shall be made in due course.

With respect to adverse events that are specified in the trial protocol(s) as serious for evaluation the safety of the investigational product(s), the investigator shall report to the sponsor, observing the reporting requirements and deadlines set forth in the trial protocol(s).

The investigator shall report all serious adverse events to the director of the institution promptly and in writing. In this case, the investigator shall identify those of the reported serious adverse events involving serious and unpredictable device deficiencies.

With respect to serious adverse events or device deficiencies, including cases of death, shall submit to the sponsor, director of the institution or IRB any additional information (autopsy reports, final treatment records or other requisite information that they may request).

Termination or Suspension of the Trial

When for any reason the trial is terminated or suspended, the investigator shall notify the subjects promptly to that effect, and shall ensure that subjects receive appropriate medical treatment and post-treatment.

When the investigator terminates or suspends the trial, the investigator shall notify the director of the institution promptly and in writing to that effect, and shall provide a detailed written explanation for the termination or suspension.

Completion of the Trial

When the trial is completed, the investigator shall notify the director of the institution in writing to that effect, and report in writing an overview of the trial results.

Storage of records

The investigator shall retain essential documentation relating to the conduct of the trial in accordance with the directives of the director of the institution.

APPENDIX H: Informed consent

Time to obtain consent

The investigator or sub-investigator will obtain written consent by the trial subject prior to the commencement of study specific examination. Prior to the second implant, obtain consent to continuously participate in the clinical study from the subjects.

Methods for explaining to trial subjects

The investigator (or sub-investigator) will give explanations to trial subjects. Study collaborators can give supplemental explanations.

The explanations should be given based on the explanation/consent document using terms which are the most easy to understand (non-technical terms). Questions made by trial subjects should be answered appropriately in the way the trial subjects can understand.

Methods for obtaining consent

The investigator (or sub-investigator) who has given explanations will sign and date the consent document.

If any study collaborator has given supplemental explanations, the study collaborator will also sign and date the consent document. (Study collaborators are not allowed to solely give all necessary explanations to trial subjects.)

Supply the trial subject with the consent document and explanation document describing aforementioned necessary information and take sufficient time for the trial subject to decide whether or not he/she should participate in the clinical study.

Before obtaining consent, take sufficient time for the trial subject to sufficiently review the consent items and ask any questions. Answer the questions in a convincing manner.

Obtain the trial subject's spontaneous written consent to participate in the clinical study.

After obtaining the consent document signed and dated by the trial subject, the investigator (or sub-investigator) will enter the date of consent in the CRF and in the medical record. All consent documents must be retained.

Supply the trial subject with the copy (duplicate for the trial subject) of the consent document and the explanation document before the trial subject participates in the clinical study.

If the explanation document or consent document is subject to revision during the participation of the trial subject, follow the above procedures and re-obtain consent.

Items mentioned for the written Informed Consent Form and other explanatory documents

The written Informed Consent Form and other explanatory documents must mention the following, at least.

The fact that the clinical study involves research.

The purpose of the trial.

The name and title of the investigator or sub-investigator, and how he or she can be contacted.

The trial method (including the aspects of the trial that are experimental, subject’s inclusion/exclusion criteria, and when the trial is randomized, the probability of randomization for each treatment).

The expected clinical benefits, and the foreseeable risks or inconveniences to the subjects. (If any benefits for the subject will not be expected, it must be informed to the subject.)
When the persons to be enrolled as trial subjects are subjects, the availability of other medical treatments for their condition, and the potential major benefits and risks of such treatments as are available.
The expected duration of the subjects' participation in the trial.
That participation in the trial is voluntary; that the trial subject can refuse to participate in the trial or can withdraw from the trial at any time and that the subjects will not be disadvantaged or lose any benefit to which they are entitled if they refuse to enroll in the trial or if they withdraw from the trial after enrolling.
The handling of investigational product; if the subjects decied to diccontinue participation of clinical trial.
That the trial monitor, auditor, IRB, and regulatory authorities are allowed to examine the source data; that the confidentiality of the trial subjects will be protected when those data are examined by those persons; and that the subjects authorize the perusal of those data by those persons by sealing and/or signing the written consent form.
That the subjects' confidentiality will be protected even when the results of the clinical study are published.
The person in the study site conducting the trial whom the subjects should contact for further information about the trial or their rights, or if they develop a health problem associated with the trial.
The compensation and medical treatment the trial subjects can receive should they develop a health problem associated with the trial.
The number of subjects expected to be enrolled in the trial (including discreate variable).
That if information is received that may affect the wishes of the subjects regarding the subjects' ongoing participation in the trial, that information will be passed on promptly to the subjects.
The circumstances under which or the reasons subjects will be withdrawn from the trial.
The specifics about any expense the trial subjects will have to pay.
The specifics about any cash or the like that will be paid to the trial subjects (including the arrangement for calculating the sum to be paid).
Responsibilities of the trial subjects.
Information about Institutional review board.

Revision of consent document

If the investigator acknowledges the necessity of revising the explanation document used for obtaining consent, in the case of the obtainment of the information which may affect the trial subject's intention to continuously participate in the clinical study or in other cases, immediately revise the explanation document and have the revision approved by the IRB.

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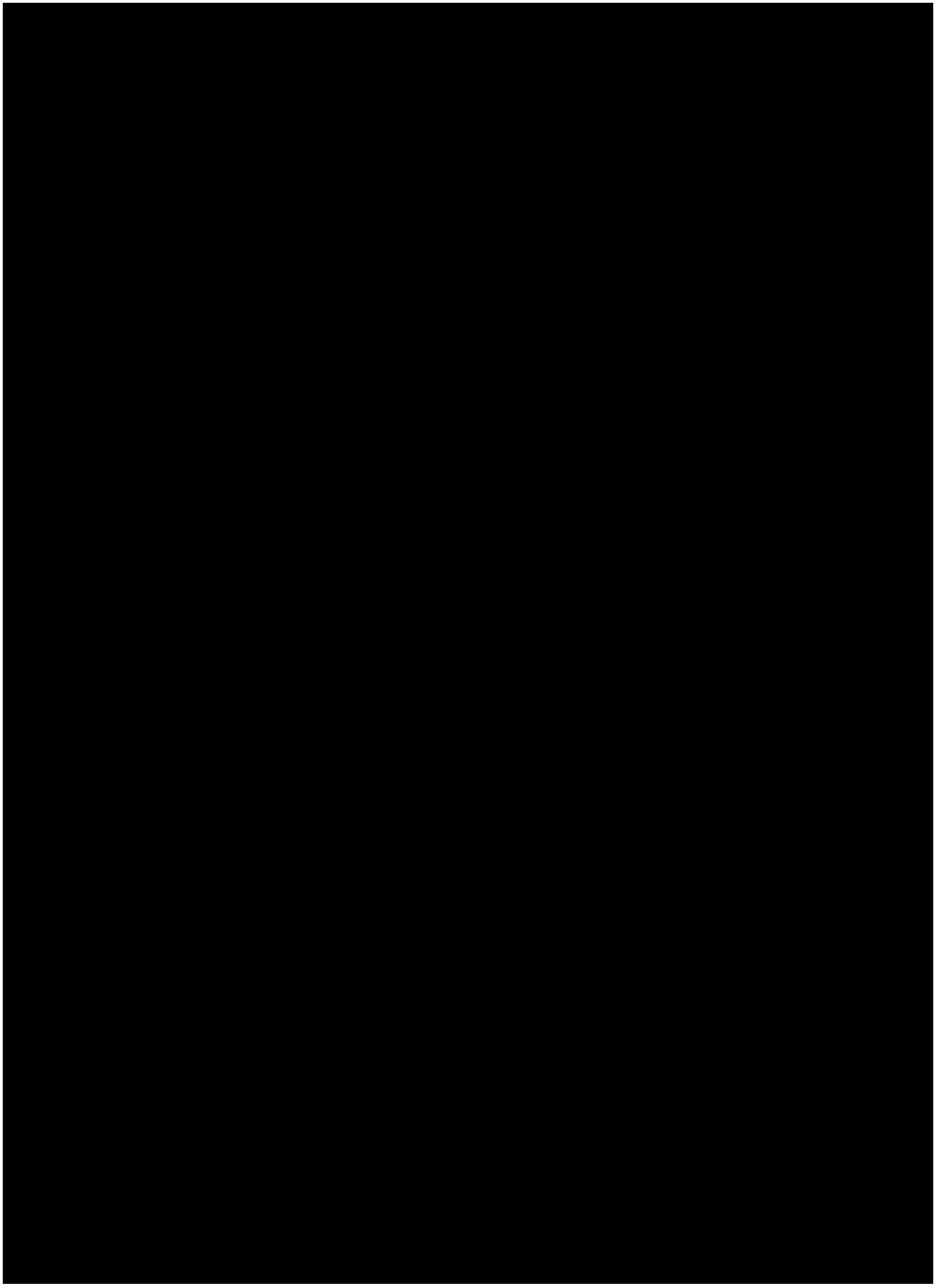

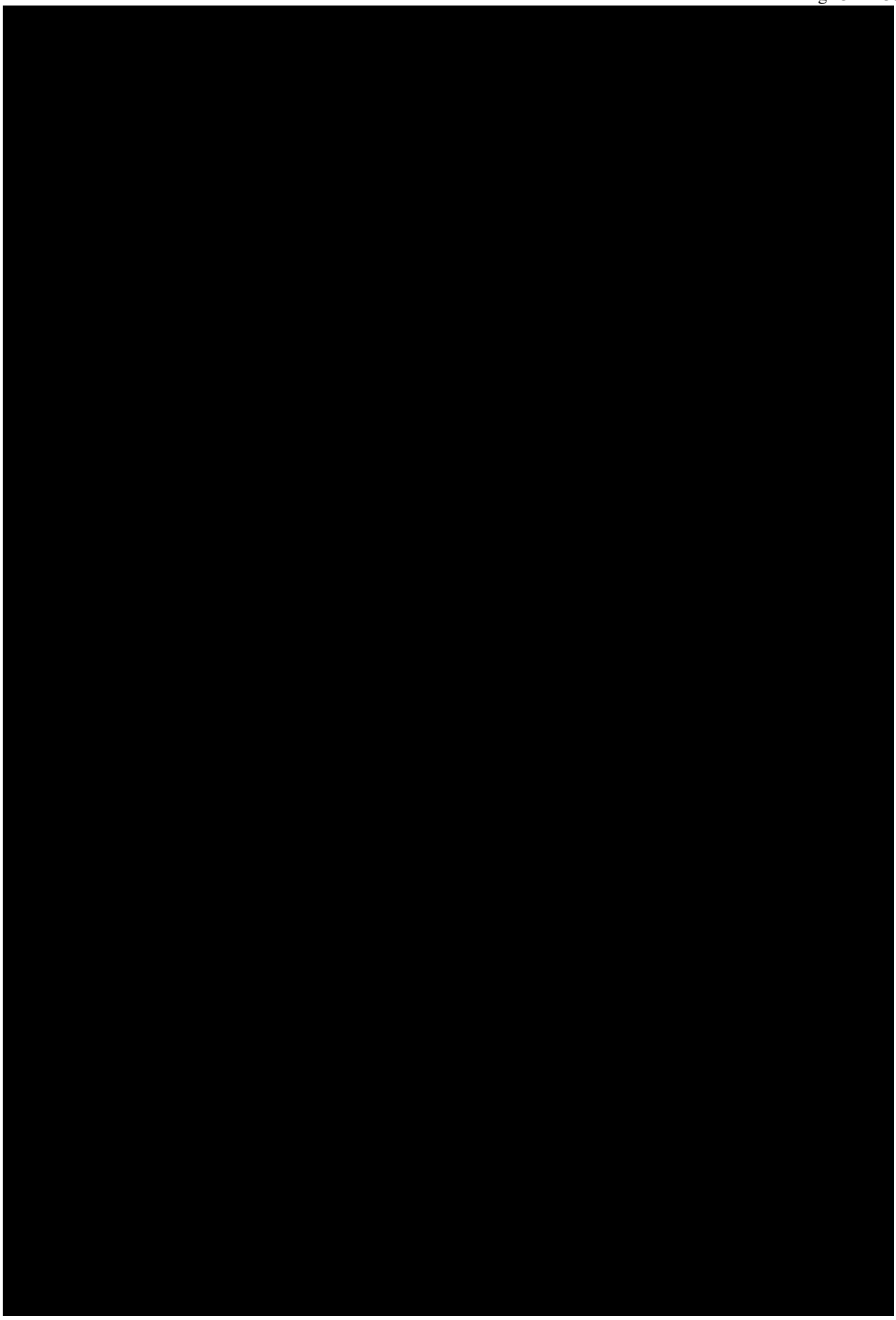

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