Clinical Evaluation of FLACS (Femtosecond Laser Assisted Cataract Surgery) with Combination of LenSx and Centurion

Clinical Study Protocol

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Protocol number: CTB258-P001

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SUMMARY

Protocol number	CTB258-P001
Objectives	To demonstrate less Cumulative Dissipated Energy (CDE), lower endothelial cell less and lower average torsional amplitude with combination of LenSx® and Centurion® (hereafter called LenSx group) than conventional cataract surgery (hereafter called Conventional group).
Population	Adult subjects, 20 years of age or older, with no ocular pathology that confound study outcomes, who require cataract extraction by phacoemulsification both eye.
Study design	Prospective, observer-masked (Specular microscope), randomized, within-subject control, single-center study
Study medical device	LenSx®
Endpoints	Primary Endpoint ・ Cumulative Dissipated Energy (CDE) Secondary Endpoints ・ Percent change of corneal endothelial cell density (ECD) at Visit 5 from Pre-Operative Visit ・ Average torsional amplitude [redacted] Safety Endpoints ・ Average Events ・ Device Deficiencies
Usage	To be used in cataract surgery for continuous curvilinear capsulorrhexis (CCC) and lens fragmentation

Examination/observation schedule	Observation schedule ・ Visit 0 (within 60 days before surgery) ・ Visit 00 (surgery day, during surgery) ・ Visit 1 (1 day after surgery) ・ Visit 2 (4-10 days after surgery) ・ Visit 3 (20-40 days after surgery) ・ Visit 4 (60-120 days after surgery) ・ Visit 5 (150-210 days after surgery)
Target sample size	55 subjects (50 subjects for analyses) LenSx group and Conventional group will be randomly allocated to either eye within a subject.
Planned study period	May 2018 to June 2019 (registration period: May 2018 to October 2018)
Sponsor	Alcon Japan Ltd.
Regulatory requirements	In principle, this study will be conducted in accordance with the Good Clinical Practice (GCP) and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3).

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1 INTRODUCTION

1.1 Circumstances

In recent years, the efficiency and safety of cataract surgery has improved as phacoemulsification machines and intraocular lenses become more advanced. The recent introduction of femtosecond laser has led to improved surgical accuracy and efficiency through the use of femtosecond laser assisted cataract surgery (FLACS) in keratotomy, anterior capsulotomy, nucleus fragmentation etc.[1, 2]. Many of the reports highlight FLACS for its repeatability and precision. It allows making a corneal incision wound as planned and continuous curvilinear capsulorrhexis (CCC) close to perfect circle[3]. Laser nucleus fragmentation is associated with reduced ultrasonic energy than manual surgery, but superiority of outcomes using FLACS has not been established because wide variety of FEMTO and Phaco systems, fragmentation patterns, and various settings of Phaco parameters were used in previous studies.

One of the endpoints for clinical evaluation in cataract surgery is corneal endothelial cell density (EDC) change. To date, techniques[4, 5] and ophthalmic viscoelastic devices (OVD)[6] have been developed for the protection of corneal endothelial cells. The reported possible factors for corneal endothelial cell reduction in cataract surgery include long ultrasonic treatment time and high mean ultrasonic power[7].

FLACS allows finer lens nucleus fragmentation, making it possible to reduce ultrasonic power and ultrasonic treatment time as compared to conventional manual cataract surgery. Thus, we may expect lower corneal EDC reduction rates.

The purpose of this study (CTB258-P001) is to demonstrate the efficacy of LenSx® in cataract surgery by comparing FLACS with minimum grid (200 μm) of lens fragmentation with combination of the latest LenSx® and Centurion® combination to manual conventional surgery without LenSx®.

In principle, this study will be conducted in accordance with the Good Clinical Practice (GCP)

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[1] Zoltan Nagy, Agnes Takacs, Tamas Filkorn, et al. Initial Clinical Evaluation of an Intraocular Femtosecond Laser in Cataract Surgery. J. Refractive Surg. 2009; 25:1053-60

[2] Neil J. Friedman, Daniel V. Palanker, Georg Schuele, et al. Femtosecond laser capsulotomy. J Cataract Refract Surg 2011; 37:1189–1198

[3] Kasu Prasad Reddy, Jochen Kandulla, Gerd U. Auffarth, Effectiveness and safety of femtosecond laser–assisted lens fragmentation and anterior capsulotomy versus the manual technique in cataract surgery. J Cataract Refract Surg 2013; 39:1297–1306

[4] Pirazzoli G, D'Eliseo D, Ziosi M, et al. Effects of phacoemulsification time on the corneal endothelium using phacofracture and phaco chop techniques. J Cataract Refract Surg. 1996; 22:967-969

[5] Miyata K., Nagamoto T., Maruoka S., et al. Efficacy and safety of the soft-shell technique in cases with a hard lens nucleus. J Cataract Refract Surg 2002; 28:1546–1550

[6] Steele AD1, Andrews V. Methylcellulose for endothelial cell protection. Aust N Z J Ophthalmol. 1988; 16: 251-254

[7] 宮井尊史、宮田和典. 白内障手術と角膜内皮. IOL&RS 2006; 4: 367-371

and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3).

1.2 Summary of Known and Possible Risks and Benefits for Subjects

See Appendix B “package insert.”

2 STUDY OBJECTIVES

To demonstrate less Cumulative Dissipated Energy (CDE), lower endothelial cell less and lower average torsional amplitude with combination of LenSx® and Centurion® (hereafter called LenSx group) than conventional cataract surgery (hereafter called Conventional group).

3 TEST ARTICLE

3.1 Test Article

LenSx®

For details of the study medical device, see Appendix B “Package insert.”

3.2 Usage

Connect SoftFit® patient interface to the study medical device. Applanate the study eye using SoftFit® patient interface and set incision pattern parameters on the study medical device. Perform anterior capsulotomy and lens fragmentation. Disconnect SoftFit® patient interface from the study eye and perform phacoemulsification and intraocular lens insertion after making a main incision with a slit knife.

3.3 Instruction on Packaging and Labeling

Not applicable

3.4 Storage and Management

For the storage method, see the instruction manual.

4 SUBJECTS

4.1 Estimated Total Sample Size

55 subjects (50 subjects for analyses)

LenSx group and Conventional group will be randomly allocated to either eye within a subject.

4.2 Inclusion Criteria

Patients meeting all of the following 1)-6)

1) Adults, 20 years of age or older at the time of informed consent, of either gender, diagnosed with cataracts with planned cataract removal by phacoemulsification in both eye.
2) Able to comprehend and willing to sign informed consent and complete all required

postoperative follow-up procedures.

3) Calculated lens power within the available range.
4) Potential postoperative Best Corrected Distance visual acuity (BCDVA) of 0.7 decimal or better in study eye based on Investigator expert medical opinion.
   * NOTE: Subjects with any pathology that could reduce visual potential should not be enrolled in this study.
5) Clear intraocular media other than cataract in both eyes
6) Cataract grade is Grade 2-4 of Emery-Little Classification.

[Rationale for the inclusion criteria]

1) and 3): To confirm the eligibility for this study.
2): To ensure that subjects understand the risks associated with participation in the clinical study and that adequate informed consent is obtained and to enable complete collection of all follow-up study data.
4): To ensure that subjects have the possibility for achieving improved vision postoperatively
5): To select patients who has eligibility of laser procedure
6): To avoid bias of procedure difficulty

4.3 Exclusion Criteria

Exclusion criteria (Prior to Surgery)

Patients meeting any of the following 1)-16).

1) Corneal opacity that would interfere with the laser beam
2) Hypotony or the presence of a corneal implant
3) Residual, recurrent, active ocular or eyelid disease, including any corneal abnormality (for example, recurrent corneal erosion, etc.)
4) Corneal disease that precludes applanation of the cornea or transmission of laser light at 1030 nm wavelength
5) Descemetocele with impending corneal rupture
6) Presence of blood or other material in the anterior chamber
7) Poorly dilating pupil, such that the iris is not peripheral to the intended diameter for the capsulotomy
8) Conditions which would cause inadequate clearance between the intended capsulotomy depth and the endothelium
9) Any contraindication to cataract
10) Corneal endothelial cell density is less than 2000 cells/mm^2
11) Presence of peripheral iridotomy
12) Patients whose cataract grade of both eyes are two different levels
13) Pregnancy current or planned during the course of the study
14) Any subject currently participating in another investigational drug or device study that may confound the results of this investigation
15) Subjects who are expected to require an ocular surgical treatment at any time during the study

(other than Nd:YAG capsulotomy)

16) Disqualified by the investigator or the sub investigator because of systemic or ophthalmic diseases

[Rationale for the exclusion criteria]

1)-9): contraindication/prohibition of the test devise

10) and 11): To avoid factors potentially affecting the secondary efficacy endpoints

12): To avoid the risk of creating a difference in background of both groups

The other criteria were established for general safety consideration.

Exclusion criteria (During Surgery)

Patients whose study eye meets any of the following 1)-6).

1) Eyes with any other additional procedures during the cataract surgery and IOL implant due to intraoperative complications that required further intervention (including but not limited to posterior capture rupture, vitreous loss, etc.)
2) Incomplete CCC by LenSx
3) Significant anterior chamber bleeding
4) Uncontrolled intraocular pressure
5) Bag-sulcus, sulcus-sulcus or unknown placement of the haptics
6) Disqualified by the investigator or the sub investigator because of any clinical reason (adverse event etc.)

[Rationale for the exclusion criteria]

To avoid factors potentially affecting the primary and secondary efficacy endpoints

5 STUDY DESIGN

Prospective, observer-masked (specular microscope only), randomized, within-subject control, single-center study

5.1 Surgical Technique

The surgical techniques of LenSx group and Conventional group are as follows. For the selection of surgeon, see Appendix C.

1) LenSx surgical technique

   LenSx® is used for CCC and lens fragmentation procedure of cataract surgery in this study. Use a slit knife (2.6 mm) to make a main incision by keratotomy, and insert an intraocular lens (IOL, Alcon®UltraSert®AcrySof®IQ Single Piece (Alcon Japan Ltd.)) after phacoemulsification using the Centurion® VISION SYSTEM (Alcon Japan Ltd.). The laser parameters and phaco parameters will be set as described in Section 6.4 2).

   If the LenSx surgery is tried but fails to be completed, perform the manual surgical technique.

2) Conventional surgical technique

CCC and fragmentation will be conducted manually. Use a slit knife (2.6 mm) to make a main incision by keratotomy, and insert IOL (Alcon®UltraSert®AcrySof®IQ Single Piece (Alcon Japan Ltd.)) after phacoemulsification using the Centurion® VISION SYSTEM (Alcon Japan Ltd.). The phacoemulsification parameters will be set as described in Section 6.4 2).

6 STUDY PROCEDURES

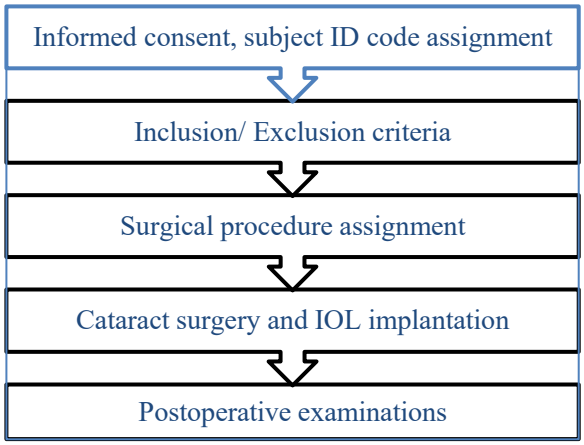
6.1 Outline

The population is patients undergoing cataract surgery by phacoemulsification whose cataract grade is diagnosed as grade 2, 3 or 4 (Emery-Little classification). One eye will be assigned to the LenSx group and the other eye to the Conventional group in a random manner according to the randomization table[8] for cataract surgery. The randomization information will be masked only to the specular microscope observer[9]. Examinations and observations will be performed prospectively from before surgery until around 6 months after surgery. The target sample size is 55 subjects.

6.2 Method of Subject Selection

Subjects will be selected will be following method.

Figure 6-1 Outline of This Study



1) After explanation of the content of study to subject, obtain consent to participate in the clinical study from subject.

[8] The person in charge of randomization will prepare a randomization table using the permuted block method.

[9] A person different from the surgeon will be designated as the specular microscope observer before the start of the study. Specular microscope will be observed by a single observer. The specular microscope observer will assure that masking was maintained by signing the “confirmation of masking” after the end of the study.

2) Subject code will be assigned after obtain consent.
3) Perform examinations/observations (screening tests) necessary for the investigator etc. to assess eligibility according to the inclusion/exclusion criteria and the investigator will assess the qualification.
4) For qualified subjects, LenSx group or Conventional group will be allocated to either eye according to the randomization table.
5) Perform cataract surgery.
   The eye with more aggravated cataract will be operated first. If both eyes are the same, then always pick the right eye. Subjects will be assessed according to the intraoperative exclusion criteria during the surgery.
6) Perform the postoperative examinations.

6.3 Examination/Observation Schedule

As shown in Table 6-1, the examination and observation are carried out for the period from within 60 days before surgery to 150-210 days after surgery.

Table 6-1 Overview of Study Procedure

	Visit 0	Visit 00	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Procedure/Assessment	Day -60	Surgery day, during surgery	Day 1	Day 4-10	Day 20-40	Day 60-120	Day 150-210
Informed Consent	X						
Demographics	X						
Medical History	X						
Inclusion/Exclusion	X	X					
Corneal Endothelial Cell	X						X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDE		X					
Average Torsional Amplitude		X					
[redacted]		[redacted]					
[redacted]		[redacted]					
Slit Examination	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Device Deficiency		X	X	X	X	X	X
Adverse Experiences	X						

6.4 Examinations/Observations

The following examinations/observations will be performed at Visit 0 (before surgery), Visit 00 (surgery day), Visit 1 (1 day after surgery), Visit 2 (4-10 days after surgery), Visit 3 (20-40 days after surgery), Visit 4 (60-120 days after surgery) and Visit 5 (150-210 days after surgery). The same instruments and methods should be used for all measurements at all visits in a site.

1) Visit 0 (Before surgery)

The investigator should provide an adequate explanation to subjects on this study to obtain written voluntary consent from them. Each subject who has provided consent will be given a subject ID code and assessed according to the inclusion/exclusion criteria.

After consent, the following examinations/observations will be performed. Results of general examinations performed for cataract surgery before consent may be adopted as clinical study data if they are obtained within 60 days before surgery.

- Demography
  Sex, age (at consent), ophthalmic medical history, ophthalmic surgical history, and ophthalmic complications will be investigated.

- Specular microscope (observer-masked)
  The central corneal endothelial cell density, [redacted] will be measured. These observations will be performed by the same observer masked to randomization information, who is not the surgeon.

[redacted]

[redacted]

- Slit lamp Examination
  The eye condition will be observed by the slit lamp microscopy. The presence or absence of clinically significant ophthalmologic findings will be recorded.
  The lens condition will be graded according to the Emery-Little classification (Appendix D).

- Preoperative adverse experiences
  Adverse experiences occurring from consent to before surgery will be recorded.

2) Visit 00 (Surgery day, during surgery)

Confirm the assigned surgical techniques.

- Exclusion criteria (during surgery)

  Confirm the exclusion criteria of during surgery.

- Femtosecond laser surgery device

  LenSx® (Alcon Japan Ltd.) will be used. The same software version of LenSx® should be used for all subjects. The parameters will be set as follows.

  LENS PARAMETERS

LENS METHOD	FRAG
DIAMETER	6.0 mm
ENERGY	15.00 μJ
SPOT SEPARATION	20 μm
LAYER SEPARATION	30 μm
FRAG SIZE	200 μm

  CAPSULOTOMY PARAMETERS

DIAMETER	5.5 mm
ENERGY	7.00 μJ
SPOT SEPARATION	5 μm
LAYER SEPARATION	4 μm

- Recording of surgical techniques

  The surgical techniques of anterior capsulotomy and lens fragmentation will be recorded.

  "Anterior capsulotomy"

  01 – Completed with the assigned surgical techniques

  02 – Not completed with the assigned surgical techniques

  "Lens fragmentation"

  01 – Completed with the assigned surgical techniques

  02 – Not completed with the assigned surgical techniques

- Incision making

  In both of the groups, the corneal incision (main incision) will be made by using a slit knife (2.6 mm). Side ports may also be made if necessary.

- Ophthalmic viscoelastic device (OVD)
  PROVISC® (Alcon Japan Ltd.) will be used as the OVD. However, other OVDs may be added if medically considered necessary for adverse events or the prevention of adverse events.

- Intraocular irrigation solution
  BSS PLUS® Irrigating Solution 0.0184% (Alcon Japan Ltd.) will be used as the intraocular irrigation solution.

- Phacoemulsification
  A cataract surgery device called CENTURION® VISION SYSTEM (Alcon Japan Ltd.) will be used for phacoemulsification. The parameters will be set as follows.

Phaco power (%)	0
Torsional power (%)	50
Vacuum (mmHg)	600
Aspiration flow (mL/min)	40
Ultrasonic mode (pulse)	Continuous

- [redacted]

- IOL insertion
  Alcon® UltraSert® AcrySof® IQ Single Piece (Alcon Japan Ltd.) will be inserted.

- Cumulative Dissipated Energy (CDE)
  CDE will be recorded after the U/S portion.

- Average torsional amplitude
  The average torsional amplitude will be recorded after the U/S portion.

- [redacted]
- [redacted]

- Adverse events, device deficiencies
  Adverse events and device deficiencies will be recorded.

3) Visits 1, 2, 3, 4, 5 (after surgery)

- Specular microscope (observer-masked) (Visit 5)
  The central corneal endothelial cell density, [redacted] These observations will be performed by the same observer masked to randomization information, who is not the surgeon.

- [redacted]

- [redacted]

- Slit lamp microscopy
  The presence or absence of clinically significant ophthalmologic findings will be recorded.

- Adverse events and device deficiencies
  Adverse events and device deficiencies will be 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.

6.5 Planned Study period

May 2018 to June 2019

7 CONCOMITANT THERAPIES

No concomitant therapy will be prohibited.

8 DISCONTINUED SUBJECTS

8.1 Discontinued Subjects

The subject is discontinued in the following cases:

1) Upon onset of adverse events which make study continuation difficult.
2) Upon cancellation of the subject to discontinue the study.

3) Upon request of the subject to discontinue the study.
4) Continuation of the study was judged as impossible because of subject's referral or move during the study.
5) Other, if the investigators judge it necessary to discontinue this study.

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 reason of discontinuation are entered in the 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 case report form.

8.2 Discontinuation of the Entire Study

If discontinuation of the entire study has become inevitable for reasons of reports on serious safety information, problems pertaining to the quality of the test articles, 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 STATISTICAL ANALYSIS

9.1 Subject Evaluability

Subject evaluability based on pre-specified deviations and their impact on analysis sets will be determined prior to database lock.

9.2 Datasets

The data sets for the efficacy and safety analyses in this study are defined as follows.

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 cataract surgery using test device. The Treatment-Emergent Safety Analysis Set will include all eyes for which cataract surgery is performed with test device (regardless of success or failure).

2) Full Analysis Set (FAS)

The FAS will include eyes with successful cataract surgery for which anterior capsulotomy and lens fragmentation have been completed using the assigned surgical techniques.

3) Per Protocol Set (PPS)

The PPS will include all eyes with successful cataract surgery for which anterior capsulotomy and lens fragmentation have been completed using the assigned surgical techniques and meeting the following conditions, data of at least one postoperative observation are available, and the study medical device has been successfully inserted.

- at least 1 postoperative visit; and
- no major protocol violation. The PPS will exclude visits by individual subjects and observed data that do not meet the clinical study protocol criteria.

The Pre-Treatment Safety Analysis Set will be the set that will be used to summarize occurrence of adverse experiences prior to exposure to cataract surgery using test device. The Treatment-Emergent Safety Analysis Set will be used for safety analysis after cataract surgery using test device.

The FAS and PPS will be used for primary effectiveness analysis in the study, with priority given to FAS results. [redacted]

9.3 Demographic Factors and Baseline Characteristics

For all analysis datasets (Safety Analysis Set, FAS and PPS), demographics (sex, age, cataract grade) will be summarized. For sex and cataract grade, the N and percentage will be summarized. For age (<60, 60-69, 70-79, ≥ 80), the N and percentage, and descriptive statistics (arithmetic mean, standard deviation, N, median, minimum and maximum) will be summarized.

9.4 Efficacy Analysis

The objective of this study is to demonstrate superiority of less-invasiveness of LenSx group to Conventional group..

9.4.1 Primary analysis

The primary endpoint is Cumulative Dissipated Energy (CDE) at Visit 00 (surgery day).

9.4.1.1 Statistical hypotheses

The null hypothesis (H_0) and the alternative hypothesis (H_1) for the primary analysis are as follows.

$$H_0 : \mu_{(LenSx)} = \mu_{(Conv)}$$
$$H_1 : \mu_{(LenSx)} < \mu_{(Conv)}$$

, where each of $\mu_{(LenSx)}$ and $\mu_{(Conv)}$ denotes the mean of CDE for LenSx and Conventional surgery in population.

9.4.1.2 Analysis methods

The descriptive statistics of CDE at Visit 00 (surgery day) will be calculated for each of the surgical techniques (arithmetic mean, standard deviation, N, median, minimum and maximum) and the means will be estimated using 95% confidence intervals based on the MMRM (mixed model for repeated measures). The superiority of LenSx to Conventional will be tested if there is a significant difference in mean between the surgical techniques (MMRM-based t-test, significance level: one-sided 2.5%).

9.4.2 Secondary efficacy analysis

The secondary endpoints are as follows.

- Percent change of corneal endothelial cell density (ECD) at Visit 5 (150-210 days after surgery) from Pre-Operative Visit
- Average torsional amplitude at Visit 00 (surgery day)

9.4.2.1 Statistical hypotheses

The null hypothesis (H_0) and the alternative hypothesis (H_1) for the secondary analysis are as follows.

< Percent ECD change (Visit 5) >	< Average torsional power (Visit 00) >
$H_0: \mu_{(LenSx)} = \mu_{(Conv)}$	$H_0: \mu_{(LenSx)} = \mu_{(Conv)}$
$H_1: \mu_{(LenSx)} > \mu_{(Conv)}$	$H_1: \mu_{(LenSx)} < \mu_{(Conv)}$

, where each $\mu_{(LenSx)}$ and $\mu_{(Conv)}$ denotes the means of the parameters for LenSx and Conventional surgery in population.

9.4.2.2 Analysis methods

The descriptive statistics of ECD, absolute and percent ECD change and average torsional power will be calculated for each of the surgical techniques (arithmetic mean, standard deviation, N, median, minimum and maximum) and the means will be estimated using 95% confidence intervals based on the MMRM (mixed model for repeated measures). The hypothesis on percent ECD change from before surgery to Visit 5 (150-210 days after surgery) will be tested only if the superiority is demonstrated in the primary analysis. The hypothesis on average torsional power at Visit 00 (surgery day) will be tested only if there is a significant difference in percent ECD change (both MMRM-based t-test, significance level: one-sided 2.5%).

[redacted]

[redacted]

9.5 Handling of Missing Data

Missing data will not be imputed.

9.6 Multiplicity

In the primary analysis, multiplicity will not be an issue since there is only one primary endpoint. For the 2 secondary endpoints, the hypotheses will be tested in the pre-specified order only if the superiority is demonstrated in the primary analysis. Therefore, the type I family-wise error (FWE) for the total of 3 hypothesis tests (primary analysis (once) and secondary analysis (twice)) is controlled (one-sided 2.5%). [redacted]

9.7 Safety Analysis

Lists of untoward safety events occurring from consent to before cataract surgery will created. The incidences and proportions of adverse events and deficiencies occurring after cataract surgery will be calculated by surgical technique.

9.8 Sample Size Justification

The 50 evaluable subjects will be enrolled for this study. For CDE, treatment difference was assumed 1.9% with common standard deviation of 1.2%. The sample size was simulated in Table 1 varying correlation coefficient between both eyes because intra-subject positive correlation between both eyes is assumed for endpoints in this study.

Table 9.8-1 Statistical Power for CDE (N=50)

Correlation between Both Eyes	Actual Power
0	>0.999
0.25	>0.999
0.50	>0.999
0.75	>0.999
0.99	>0.999

Also, for ECD, treatment difference and common standard deviation of ECD percent change from Baseline at Visit 5 was assumed 5.5% with common standard deviation of 11%. The sample size was simulated in Table 2 in the same manner as CDE.

Table 9.8-2 Statistical Power for ECD (N = 50)

Correlation between Both Eyes	Actual Power
0	0.688
0.25	0.808
0.50	0.934
0.75	0.998
0.99	>.999

Considering 8% dropout rate, 55 subjects will be enrolled for this study.

10 ADVERSE EVENTS AND DEVICE DEFICIENCIES, etc.

10.1 General Information

Refer to the Glossary of Terms below for categories of Adverse Experiences, AEs and SAEs.

Adverse Experience:

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects from consent to before cataract surgery will be recorded.

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects after cataract surgery (including during cataract surgery), users or other persons, whether or not related to the investigational medical device (test article). *For subjects, this definition includes events related to the test article or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*

Serious Adverse Event:

Adverse event that led to any of the following, or that needed treatment not to lead to the following results:

- 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 congenital anomaly/birth defect,

  e) a medically important event or reaction.

Non-serious Adverse Event

Adverse event that does not meet the criteria for a serious adverse event.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device (test article).

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test article.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Safety Information:

Information about quality, efficacy and safety for medical device and information which is needed for appropriate use, including:

- Use error
- Abnormal Use
- Product tampering
- Product counterfeiting
- Product theft

10.2 Procedure for Reporting of Serious Adverse Events (SAE)

The investigator will report the serious adverse event or the risk of causing serious adverse event to Alcon 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 and the head of the medical institutions.

[redacted]

When the SAE is correspond to “Death or a life-threatening ADE” or “Serious and unexpected ADE other than Death or a life-threatening event”, the sponsor will immediately notify them to heads of all medical institutions and all investigators by document.

10.3 Report of Adverse Events and Evaluation of the Causal Relationship

All adverse experiences from consent to before cataract surgery and adverse events after signed informed consent will be documented on the Adverse Event Case Report Form (CRF).

For every AE, the investigator will assess the casual relationship of the medical device at “related” or “ not related”.

10.4 Intensity Assessment of Adverse Events

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:

Intensity:

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.

10.5 Follow-up of Subjects / Subjects with Adverse Events

In the event of acknowledging any adverse events, the investigators should immediately take appropriate actions irrespective of the presence or absence of causal relationship with the test article. And the investigators will make a follow-up of the adverse event if it is possible. When the subject needs medical treatment, the investigators should inform the subject of the matter.

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.

10.6 Subject Pregnancy

Women [redacted] planning to become pregnant during this study period or women who are pregnant at the time of study entry are excluded from participation.

10.7 Provision of Safety Information

Investigators provide safety information which is needed to make a detailed report on demand from the sponsor.

11 ETHICS

11.1 Independent Ethics Committee

Prior to the start of the study, the Independent ethics committee (IEC) of each participating institution 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, questionnaire 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 welfare of the subjects.

The inspection and examination by the IEC may be performed again also during a certain period of time after the start of the study or when the head of the participating institution sees the necessity of additional inspection/examination so that the study may be monitored continuously.

11.2 Ethical Consideration

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

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 the protocol. This study will be conducted in accordance with GCP and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3), in principle.

11.3 Protection of Subjects’ Privacy

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

11.4 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 subinvestigator should immediately take appropriate actions irrespective of the presence or absence of causal relationship with the test article.

2) Supply of new information

In the case of obtaining safety-related new and significant information related to the clinical trial, the sponsor should supply the information in writing to the investigator and the subinvestigator 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.

11.5 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 clinical trial.

11.6 Payment to Subjects

[redacted] the Sponsor pays an amount of money, predetermined through negotiation with each participating medical institution, to each subject. This payment is not intended to force any subject to remain in the study.

12 PROTOCOL AMENDMENTS

When the protocol, etc. are revised, the sponsor and the investigator will exchange an agreement in writing. Subjects are enrolled, depending on the necessity.

13 CONSIDERATIONS FOR DOCUMENTATION AND COMPLETION OF CASE REPORT FORM

The investigator, etc. will complete the case report form by himself or herself based on source data in accordance with the protocol and the preparation procedure of the case report form. After preparation of the case report form, he or she will sign and date it, and submit it to the sponsor through the person in charge of monitoring.

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:

- The rights and well-being of the subjects are protected.
- The reported data are accurate, complete, and verifiable from the source documents.
- The study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current GCP, Ethical Guidelines for Clinical Studies and with applicable regulatory requirements, in principle.

The monitor will report the monitoring results to study manager.

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 medical institutions thereof.

Medical institutions and investigators shall preserve the protocol, source documents, informed consent forms agreed, informed consent form and other written information, records on GCP and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3). Above documents excluding medical records should be retained either five years after the date of completion of the study, or three years after the date of publication/presentation the final study result whichever date is later. The storage period of clinical record depend on Medical Practitioners Act and other related regulations.

16 CONFIDENTIALITY AND PUBLICATION OF 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 and use the results as “Information on Proper Use” of the product. Sponsor will register the summary of the study to open database (The Database Center of the National University Hospitals, JAPIC Clinical Trials Information, or JMACCT Clinical Trials Registry, etc.) before conducting the study, and will properly update it based on the revision of the protocol or study progression.

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.

After completion of the study, sponsor and the investigators will report the result of the study after taking necessary steps for protecting the right and benefits of the subjects, related persons, sponsor, investigators, and so on.

17 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 access to source data will be performed so that the sponsor or the regulatory authority 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.

18 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) and Quality assurance SOP of the Sponsor.

Quality Assurance will evaluate that the study is properly conducted according to the protocol, Standard Operation Procedures of Medical Affairs/ Clinical Development Group / Clinical Biometrics, GCP and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3) and its amendments.

19 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 consent for the subject to participate in the trial from the subject or legally acceptable representative thereof, in accordance with GCP.

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.

Investigator(s) and sub-investigators shall inform the subject's the primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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.

After this study, the investigator shall provide the best treatment for the subjects using the result of this study.

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 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 IEC, the trial protocol(s) or CRF is corrected.

Submission of Documents to the IEC

Before and during the trial period, the investigator(s) shall keep current those documents that are

subject to review by the IEC 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 the IEC 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 IEC 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 IEC 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 IEC. 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 IEC 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 IEC, 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.

Recording and Reporting the CRF

The Investigator or sub-investigators shall prepare CRFs in accordance with the trial protocol(s), affix thereto his or her signature or personal seal, and submit them to the sponsor. The investigator shall retain copies of the CRFs submitted.

The investigator shall inspect CRFs prepared by sub-investigators prior to their submission to the sponsor, and upon confirming that there is no problem, affix thereto his or her signature or personal seal. The investigator shall also inspect modifications or revisions to CRFs undertaken by sub-investigators, and confirm that there is no problem.

The investigator shall ensure that the data in the CRFs and all other documents submitted to the sponsor are accurate, complete, legible, and submitted in a timely manner, and that a subject identification code is used for identifying subjects.

Data in the CRFs that are based on original materials shall not conflict with the original materials. When there is any discrepancy with the original, the investigator shall prepare a record explaining the reason therefore, submit it to the sponsor, and retain a copy.

In modifying or correcting CRFs, the investigator or sub-investigators shall follow the manual provided by the sponsor. If there is any modification or correction whatever in a CRF, it must be dated and the signature or personal seal affixed. An explanation of the change must be provided if the change is critical. Further the modification or correcting shall not be such as to render the initial writing unclear (i.e., an audit trail shall be maintained).

The investigator should submit records of modification and correction of the case report form to the Sponsor and retain a photocopy of each record.

Reports, etc. in the Course of the Trial

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

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 sponsor, the director of the institution and, via the director of the institution, to the IEC.

Except in cases in which the trial protocol(s), etc. 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 adverse device effects.

With respect to serious adverse events or serious adverse device effects, including cases of death, shall submit to the sponsor, director of the institution or IEC 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.

20 INFORMED CONSENT

Time to obtain consent

The investigator or sub-investigator will obtain written consent by the trial subject prior to the commencement of the study.

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

(1) The investigator (or sub-investigator) who has given explanations will sign and date the consent document.
(2) 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.)
(3) 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.

(4) 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.

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

(6) 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.

(7) 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.

(8) 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 Explanatory Documents

(1) The fact that the clinical study involves research.

(2) The purpose of the trial.

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

(4) 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).

(5) 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.)

(6) When the persons to be enrolled as trial subjects are patients, the availability of other medical treatments for their condition, and the potential major benefits and risks of such treatments as are available.

(7) The expected duration of the subjects' participation in the trial.

(8) 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.

(9) Handling of investigational products in case of withdrawing from the clinical study.

(10) That the trial monitor, auditor, IEC, 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.

(11) That the subjects' confidentiality will be protected even when the results of the clinical study are published.

(12) The person in the study site 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.

(13) The compensation and medical treatment the trial subjects can receive should they develop a health problem associated with the trial.

(14) The number of subjects expected to be enrolled in the trial (including discrete variable).

(15) That if information is received that may affect the will of the subjects regarding the subjects' ongoing participation in the trial, that information will be passed on promptly to the subjects.

(16) The circumstances under which or the reasons subjects will be withdrawn from the trial.

(17) The specifics about any expense the trial subjects will have to pay.

(18) 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).

(19) Responsibilities of the trial subjects.

(20) Information about Institutional review board.

(21) The name of the study and the fact that the head of medical institute approved the conduct of the study

(22) The procedure of disclosure of information

(23) The fact that the documents related to protocol and procedure of the study are available, as far as there is no interruption regarding protection of personal information and originality of the study, depending on the request from subject etc.. Also procedure of its access.

(24) Handling of personal information (including the procedure of anonymity, if applicable)

(25) The procedure of storing and disposal of the information

(26) Conflict of Interest of the investigator, medical institution etc. regarding the study, including funding source, personal income and so on.

(27) If there is a possibility that the sample or information of subjects might be used in future study or provided to other research institution, the fact and assumed contents when informed consent is obtained.

Revision of Informed Consent Form and Explanatory Documents

If the investigator acknowledges the necessity of revising the explanatory 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 explanatory document and have the revision approved by the IEC.

21 CONFLICT OF INTEREST

Alcon Japan Ltd. is sponsor of this clinical study. Alcon Japan Ltd. and head of the medical institution will sign a contract for the clinical study. Financial cost of the study will be sponsored by Alcon Japan Ltd in accordance with the contract.

Financial information to medical institutions paid by Alcon Japan Ltd. is disclosed at Homepage of Alcon Japan Ltd.

Signature Page

The Sponsor and the Principal Investigator agree to conduct the study in accordance with the details and procedures described in this study protocol.

The Sponsor and the Principal Investigator agree to conduct the study in accordance with the details and procedures described in this study protocol.

Principal Investigator

Medical Institution : [_____]

Affiliation and position : [_____]

Name (Signature) : [_____]

(Signature)

Date : _____

Sponsor

Director, Clinical Development, Alcon Japan, Ltd.

Name (Signature) : [_____]

(Signature)

Date : _____

Clinical Evaluation of FLACS (Femtosecond Laser Assisted Cataract Surgery) with Combination of LenSx and Centurion

Clinical Study Protocol Supplemental Attachment

A Clinical Study System, Participating Facilities and Principal Investigators
B LenSx® Package Insert
C Selection of Surgeon
D Emery-Little Classification

Alcon Japan Ltd.

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

Protocol No.：CTB258-P001
Version No.2：May 18 2018

Appendix A　Clinical Study System, Participating Facilities and Principal Investigators

1. Clinical Study System

1.1 Sponsor

Alcon Japan Ltd.

[redacted]

1.2 Study Supervisor

[redacted]

1.3 Clinical Development Director

[redacted]

1.4 Study Manager

[redacted]

1.5 Persons in Charge of Monitoring (delegate)

[redacted].

1.6 Statistical Analysis Manager

[redacted]

1.7 Data Management Manager

[redacted]

1.8 Input of Study Data and Data Analysis

[redacted]

1.9 Input of Study Data and Data Analysis

[redacted]

1.10 Sponsor Medical Expert

[redacted]

2. Medical Institutions and Investigators

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix B　LenSx® Package Insert

4-20　LenSx§　眼科用レーザー手術装置
**2016年12月 改訂（第4版）
*2016年3月 改訂（第3版）

医療機器承認番号：22600BZX00350000

機械器具31 医療用焼灼器
高度管理医療機器　眼科用パルスレーザ手術装置　JMDNコード：70635000
*（高度管理医療機器　眼科用レーザ角膜手術装置　JMDNコード：70638000）
特定保守管理医療機器　設置管理医療機器

LenSx§ 眼科用レーザー手術装置

【警告】
〈使用方法〉
1. レーザ光の直視による危険
治療目的以外ではレーザビームを直視しないこと。
［レーザ光により網膜等へ影響が生じる可能性がある］
2. レーザ反射光による危険
ガラスや金属製品等の反射性材料は、レーザを反射するので、目的部位以外にはレーザビームを当てないようにし、使用する器具類は反射しない処置を施したものを用意すること。［レーザ光により人体へ影響が生じる可能性がある］

*【禁忌・禁止】
〈使用方法〉
1. 可燃性気体や蒸気を含んでいる可能性のある臓器、体腔、管腔領域における医療用途のレーザ発振時には、火災・爆発のリスクに対する保護措置がとられていることを確認すること。
〈適用対象（患者）〉
2. 下記の患者に対しては本装置を使用しないこと。［レーザによる処置が不十分となり、重篤な合併症を引き起こす恐れがある］
［白内障手術に用いる場合］
(1) レーザの透過を妨げる角膜混濁の患者
(2) 低眼圧症又は角膜インプラントが挿入されている患者
(3) 角膜異常を合併する再発性/活動性の眼疾患もしくは眼瞼疾患の患者（再発性の角膜びらん等）
(4) 小児

［白内障手術における前嚢切開又は水晶体分割に用いる場合］
(1) 角膜の圧平が困難又は波長1030nmのレーザの透過を妨げる角膜疾患の患者
(2) 切迫角膜破裂を伴うデスメ膜瘤の患者
(3) 血液又はその他物質が前房内に確認された患者
(4) 瞳孔が散瞳しにくい（虹彩が予定前嚢切開径より大きく拡張しない）患者
(5) 予定前嚢切開深度と角膜内皮の間に十分な空間がない患者（予定前嚢切開の全領域において、角膜内皮下端と前嚢表面との距離が、予定前嚢切開上端と前嚢表面との距離よりも短い患者）
(6) 白内障手術又は角膜移植術の適応でない患者

［白内障手術における角膜切開に用いる場合］
(1) 角膜切開の既往により術中に発生するバブルが溜まる可能性がある空間が角膜内にある患者
(2) 角膜厚が本装置の処置範囲を超える患者

［角膜フラップ作製又は層状切除に用いる場合］
(1) 活動性の外眼部炎症の患者
(2) 白内障（核性近視）の患者
(3) ぶどう膜炎や強膜炎に伴う活動性の内眼部炎症の患者
(4) 重症の糖尿病や重症のアトピー性疾患など、創傷治癒に影響を与える可能性の高い全身性あるいは免疫不全疾患の患者
(5) 妊娠中又は授乳中の患者
(6) 角膜病変の患者
(7) 角膜浮腫の患者
(8) 低眼圧の患者
(9) 緑内障の患者
(10) 角膜インプラントの既往歴のある患者
(11) 円錐角膜の患者
(12) 小児

【形状・構造及び原理等】
［構成］
本製品は以下のユニットより構成される。
1. 本体
2. フットスイッチ

［外観寸法］（幅）×（奥行）×（高さ）
(1) 本体：610×762×1219mm
(2) フットスイッチ：152×152×144mm

［電気的定格］
定格電源電圧：VAC100
定格電源周波数：50/60Hz
電源入力：12A

［機器の分類］
レーザのクラス：クラス4
電撃に対する保護の形式による分類：クラスI
電撃に対する保護の程度による装着部の分類：BF形装着部
水の有害な侵入に対する保護の程度による分類：IPX0

取扱説明書を必ずご参照ください

*[作動・動作原理]

本装置は、前嚢切開、水晶体分割、角膜切開、角膜フラップ作製及び層状切除機能を有するスキャニングスポット型フェムトセカンドレーザである。組織の切開・分割は、波長1030nm(近赤外線)のフェムト秒レーザと組織との相互作用により誘起される光切断により行われる。この超短パルス(800フェムト秒未満)のレーザを一秒間に数千回走査することにより、連続的な組織の切開・分割といった外科的な効果が得られる。コンピュータ制御によってレーザを目的とする焦点位置に照射することにより、組織の光切断位置をコントロールする。

*[性能及び安全性に関する規格]

1. 処置用レーザの発振波長：1030nm
2. スポット径：≦5.3μm
3. パルス幅：600－800fs
4. 繰返し周波数：50kHz(白内障手術の場合)
   150kHz(フラップ作製及び層状切除の場合)
5. 最大パルスエネルギー：15μJ(白内障手術の場合)
   2.6μJ(フラップ作製及び層状切除の場合)
6. OCT発振波長：820－880nm
7. OCT最大出力：3.0mW
8. 前嚢切開パラメータ
   切開径：3 － 8 mm
9. 水晶体分割パラメータ
   (1)チョップパターン
      切開径：3 － 6 mm
      前房側オフセット：500－2000μm
      後房側オフセット：800－2000μm
   (2)シリンダーパターン
      切開径：1 － 6 mm
      前房側オフセット：500－2000μm
      後房側オフセット：800－2000μm
   (3)フラグパターン
      切開径：3 － 6 mm
      前房側オフセット：500－2000μm
      後房側オフセット：800－2000μm
10. 角膜切開パラメータ
   (1)メイン創口切開
      切開幅：1 － 4 mm
   (2)サイドポート切開
      切開幅：0.8－3.0mm
   (3)角膜弧状切開
      切開径：6 －12mm
11. フラップ作製パラメータ
   (1)フラップ径：8.5－9.5μm
   (2)フラップ厚：110－190μm

*[使用目的又は効果]

1. 白内障手術における前嚢切開、水晶体分割及び角膜切開に用いる。
2. 角膜屈折矯正手術(LASIK)、その他角膜層状切除の必要な手術又は処置における角膜フラップ作製又は層状切除に用いる。

〈使用目的又は効果に関連する使用上の注意〉
(白内障手術に用いる場合)

1. 水晶体震盪又はチン小帯脆弱の既往がある患者への有効性、安全性は確立されていないことから、慎重に適用すること。

*[使用方法等]

1. 白内障手術に用いる場合
   (1)キースイッチを「0」位置から「1」位置に回す。
   (2)システムのウォームアップ及びセルフチェックが終わった後、患者データを入力する。
   (3)切開パターン(Capsule(前嚢切開)、Lens(水晶体分割)、Cornea Arcuate(角膜弧状切開)、Cornea Primary(メイン創口切開)又はCornea Secondary(サイドポート切開))を選択し、各切開パターンのパラメータを設定する。
   (4)SoftFit®患者インターフェースのコーンを本体のレーザ照射部に装着し、回して固定し、吸引ポートを本体の吸引ポート接続部に接続する。
   (5)柔らかい先端を有する綿棒等を用いてSoftFitインサートをバイアルから取り出す。
   (6)SoftFitインサートの凹面を下にして指先に乗せる。
   (7)コーンの処置眼との接触面にSoftFitインサートを設置する。
   (8)SoftFitインサートが乾燥する場合には、バイアル内の保存液でSoftFitインサートを濡らす。
   (9)ジョイスティックを操作し、SoftFit患者インターフェースを処置眼に乗せる。
   (10)手術ディスプレイに表示される白色の圧平インジケータが黄色のエリアに入ったら、ディスプレイの左下に表示される「PI SUCTION」ボタンを押して吸引を開始する。
   (11)予定切開パターンが手術ディスプレイの術野のライブ画像及びOCT画像上に重ねて表示されるので、各画像を利用して切開パターンの位置、深さ等を微調整する。
   (12)全ての調整が終わったら、手術ディスプレイに表示される「VERIFY&ACCEPT」ボタンを押す。
   (13)処置開始の準備ができたら、フットスイッチを踏み込む。
   (14)処置完了のメッセージがディスプレイに表示されたら、フットスイッチを離す。吸引は自動で止まり、患眼が吸引から解放される。
   (15)ジョイスティックを反時計回りに回してデリバリーシステムを上昇させる。
   (16)キースイッチを「1」位置から「0」位置に回す。

2. 角膜フラップ作製又は層状切除に用いる場合
   (1)キースイッチを「0」位置から「1」位置に回す。
   (2)システムのウォームアップ及びセルフチェックが終わった後、患者データを入力する。
   (3)切開パターンのパラメータを設定する。
   (4)Laser患者インターフェースのコーンを本体のレーザ照射部に装着し、回して固定し、吸引ポートを本体の吸引ポート接続部に接続する。
   (5)ジョイスティックを操作し、Laser患者インターフェースを処置眼に乗せる。この時、フラップの予定切開パターンが手術ディスプレイの術野のライブ画像及びOCT画像上に重ねて表示される。
   (6)手術ディスプレイに表示される白色の圧平インジケータが緑色のエリアに入ったら、ディスプレイの左下に表示される「PI SUCTION」ボタンを押して吸引を開始する。
   (7)処置開始の準備ができたら、フットスイッチを踏み込む。
   (8)処置完了のメッセージがディスプレイに表示されたら、フットスイッチを離す。吸引は自動で止まり、患眼が吸引から解放される。

(9)ジョイスティックを反時計回りに回してデリバリーシステムを上昇させる。
(10)キースイッチを「1」位置から「0」位置に回す。

〈使用方法等に関連する使用上の注意〉
1. 患者インターフェースを処置眼に接続した後、接続を解除するまで本体のデリバリーシステムを動かさないこと。
2. 患者インターフェースによる圧平は処置中に眼圧を増加させるため、圧平時間が最短になるよう注意すること。不完全な圧平は不均一な切開や不完全な切開の原因となる。
3. 患者は局所麻酔に耐えられる必要がある。眼圧が高い患者には、医師の管理下でのみステロイド薬を使用すること。
4. プライマリー切開やセカンダリ切開は、レーザの正確な照射を妨げる部位(角膜環や血管形成部位等)を避けて設置し、レーザ照射後はスパーテル等を用いて完成させること。また、前房消失や房水漏出に備えて創口を塞ぐ準備をしておくこと。
5. OCTの画像が不鮮明又は分断されている場合には処置を中止すること。
6. 本装置によるレーザ照射後は、速やかに水晶体再建術を継続・終了すること。レーザ照射後の水晶体に対する処置が遅延すると、前房炎症や眼圧上昇を引き起こす可能性がある。

【使用上の注意】
**〈使用注意〉(次の患者には慎重に適用すること)
1. 角膜フラップ作製又は層状切除の場合
(1)向精神薬(ブチロフェノン系抗精神病薬など)を服用している患者
(2)全身性の結合組織疾患を持つ患者
(3)乾性角結膜炎の患者
(4)角膜ヘルペスの既往歴のある患者
(5)屈折矯正手術の既往歴のある患者
(6)術前検査により、角膜拡張症等の増悪により術後の残存角膜実質層が250μmより薄くなることが予想される場合

〈重要な基本的注意〉
1. 取扱説明書に記載のない処置、操作又は調整等を行うと、患者及び職員が危険な状態に晒される可能性がある。
2. 本装置を設置した室内で携帯電話又はポケットベル等を使用しないこと。
3. 訓練された技術者のみが、本装置の包装開封、設置及び修理を行う。弊社フィールドサービス担当者以外は本装置のカバーを取り外さないこと。[本装置内部の高電圧電気回路に触れると、重大なけが又は死に至る可能性がある。また、眼が本装置内部の平行ビームに曝露されると、網膜に障害を引き起こす可能性がある。]
4. 使用していない間は、キースイッチからマスターキーを本装置から抜き、使用が認められていない者が使用できないように安全な場所に置くこと。
5. 本装置及びフットスイッチの周囲は乾燥させておくこと。本装置から水漏れがある場合には、使用を中止し、弊社フィールドサービス担当者に速やかに連絡すること。
6. 電源コードに擦り切れや損傷がある場合、本装置を使用せずコードを取り換えること。
7. 電源コードを歩行者から保護すること。[つまずく危険がある]
8. 処置中に本装置のプラグが抜けてしまうのを避けるよう注意すること。
9. レーザが使用中の際には部屋のドアに警告表示を行い、管理区域に入る者に使用中であることを知らせること。また、レーザの使用中は部屋のドアを閉めておくこと。
10. 弊社のフィールドサービス担当者のみが本装置を移動させること。本装置を移動する必要がある場合、弊社フィールドサービス担当者に連絡すること。
11. 設置するときは、本体後面にあるペダルを踏んでローラーの回転を防ぐこと。また、処置中はペダルを踏んだ状態にしておくこと。
12. 仰向けで横になり動かないことが可能な患者にのみ使用すること。
13. 安全なレーザ照射を実行するため、レーザ照射時間は最短とすること。

〈相互作用〉
〈併用禁忌〉(併用しないこと)
LenSx® 眼科用レーザ手術装置用でないアクセサリ類は使用しないこと。[システムの性能に影響を与え、患者に危害を与えるおそれがある。]

〈不具合・有害事象〉
*[有害事象]
1. 白内障手術の場合
(1)後嚢破損
(2)前嚢切開、水晶体分割及び角膜切開の偏位
(3)不完全な前嚢切開、水晶体分割及び角膜切開処置又は中断
(4)前嚢の亀裂
(5)角膜縫通傷又は角膜上皮欠損
(6)眼痛
(7)感染症
(8)出血
(9)眼球組織への損傷
(10)房水漏出、前房消失
(11)眼圧上昇

2. 角膜フラップ作製又は層状切除の場合
(1)角膜浮腫
(2)角膜疼痛
(3)角膜上皮増殖
(4)角膜上皮欠損
(5)感染
(6)フラップの偏位
(7)フラップ形成不全
(8)フラップ裂傷又は不完全なリフトオフ
(9)フリーキャップ

【臨床成績】
白内障患者を対象として米国にて臨床試験を1試験実施した。白内障手術手技のうち、前嚢切開、水晶体分割、角膜切開について、片眼は本装置を用いて(レーザ群)、対側眼は従来の手技を用いて(マニュアル群)手術を実施した。
なお、本試験で用いた本装置の各設定値の範囲は、前嚢切開の切開径4.2～5mm、水晶体分割の分割数はチョップパターン2～3(切開径4.2～4.7mm)、シリンダーパターン1～4(切開径2.5～4.5mm)、水晶体分割のオフセット値は前房側500μm、後房側800μmであった。
白内障手術を受けた65例がITT解析の対象となった。レーザ群の65例全例においてSoftFit患者インターフェースの圧平が成功した。レーザ群65例のうち64例に本装置による前嚢切開、水晶体分割を実施し、全例が前嚢切開と水晶体分割の完全例であった。また、レーザ群の65例に本装置を用いた角膜切開を実施し、メイン創口切開とサイドポート切開で部分的にブレードによる切開が必要となったそれぞれ4例(6.2%)を除いて、いずれも完全例であった。

本装置による前嚢切開の真円度は、レーザ群で0.8978±0.0048（平均値±標準偏差，以下同様）、マニュアル群で0.8875±0.0079であり、マニュアル群と比較して平均値、標準偏差ともに差がみられた（対応のあるt検定p<0.0001，Pitmanの検定p=0.0004）。一方，前嚢切開のサイズは5mmの設定に対して、レーザ群で4.9780±0.1909mm、マニュアル群で4.9828±0.4624mmであり平均値に差（対応のあるt検定p=0.7160）は認められなかったが、レーザ群の標準偏差はマニュアル群に比し小さかった（Pitmanの検定p<0.0001）。
白内障のグレード別の超音波時間は、白内障のグレードが「硬い」でレーザ群が40.5±26.1秒、マニュアル群で50.8±13.1秒であり大きな差が認められた（対応のあるt検定p=0.0140）。また、白内障のグレード別のCDEでは、「中等度」でレーザ群が6.170±2.757、マニュアル群で7.242±2.159であり、「硬い」でレーザ群が8.666±5.119、マニュアル群が10.749±4.487であり大きな差が認められた（対応のあるt検定p=0.0378，p=0.0194）。
臨床試験で確認されたもっとも浅い前房深度は2.53mmであった。
なお、本装置との因果関係が否定できない有害事象及び不具合は認められなかった。

【保管方法及び有効期間等】
保管方法に関しては取扱説明書を参照すること。

【保守・点検に係る事項】
1. 保守・点検に関する詳細は、本装置の取扱説明書に従うこと。
2. 弊社のサービス担当者による保守サービスを６ヶ月に１回実施する。

【製造販売業者及び製造業者の氏名又は名称等】
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Appendix C　Selection of Surgeon

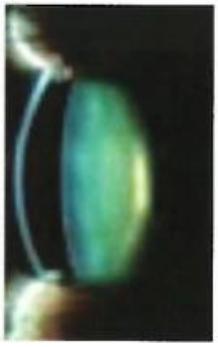
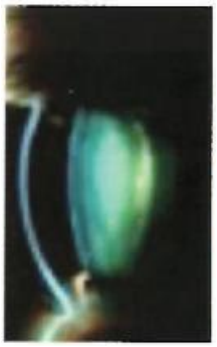
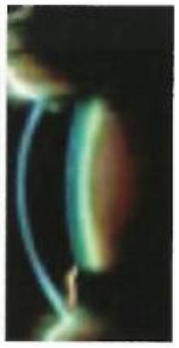
Regarding combination of LenSx and Centurion (hereafter called LenSx group) and conventional cataract surgery (hereafter called Conventional group), the surgeons of this study surgery will be decided as follows.

Surgeon A and Surgeon B should be the same person respectively for all surgery of this study.

Group	Surgical Procedure	Surgeon
LenSx	Anterior capsulotomy and lens fragmentation by LenSx	Surgeon A
	Surgical procedure after the above mentioned procedure	Surgeon B
Conventional	All of the surgical procedure	Surgeon B

Appendix D　Emery-Little Classification

The lens condition will be graded according to the following Emery-Little classification. More than two people different from the surgeon will classify the lens condition of each patients.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Transparent or milky white	White	Yellow	Amber	Brown or black
				

Reference：大鹿哲郎　編集『眼手術学　5. 白内障』 P.15, 株式会社 文光堂, 2012