Clinical evaluation of the Clareon® low cylinder power toric IOL versus the Clareon® non-toric IOL

1. TITLE PAGE

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IRB / ERC	REK, Norway
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Test Article:	Clareon® Toric IOL with the AutonoMe ® delivery system

2. GENERAL INFORMATION

Objective	To evaluate visual and refractive outcomes of the Clareon® T2 (low toric) IOL relative to implantation of the Clareon® non-toric IOL. To show the superior clinical performance of Clareon T2 IOL compared to Clareon non-toric IOL
Test Article(s)	Clareon® T2 IOL with the AutonoMe® delivery system
Control Article(s)	Clareon® non-toric IOL with the AutonoMe® delivery system
Sample size	104 subjects implanted with Clareon T2 or the Clareon non-toric IOL in one or both eyes
Study Population	Subjects ≥40 years of age who are interested and eligible for implantation of the Clareon low toric IOL based on Barrett biometric analysis in at least one eye
Number of sites	One site (Norway)
Study Design	Prospective, randomized, two-arm study, 3 months follow-up
Masking	None
Variables	The planned study endpoints (all at the three month visit) would be:

Primary - Uncorrected distance VA (logMAR)

Secondary:

- MRSE (D)
- Eyes with absolute MRSE ≤ 0.50 D
- Manifest refractive cylinder (D)
- Percentage of eyes with ≤ 0.25 D of cylinder
- Percentage of eyes with ≤ 0.50 D of cylinder
- Corrected distance VA (logMAR)
- Mesopic and photopic contrast sensitivity values BCDVA at 4 m
- Low Contrast VA (10%)
- Rotational stability

Exploratory endpoints:

- Sub-category analysis will be performed based on the categorized orientation of the anterior corneal astigmatism (WTR/ATR/OBL).

Duration / Follow-up	Visits will include preoperative, operative, 1 day, and 3 months postoperative

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4. INTRODUCTION

Low power astigmatism (≈ 1D) is observed frequently in a cataract population. Epidemiological data indicates that about a third of adult cataract patients will have a keratometric astigmatism between 0.50 D and 1.00 D. Traditionally, such low power astigmatism has been treated with spherical IOLs, but recent clinical experience both from implantation of multifocal and monofocal IOLs indicate that patients could benefit from implantation of such low power cylinder implants. Our retrospective paper from 2020[1] showed significantly better visual and refractive outcomes using the AcrySof® IQ T2 toric IOL compared to a similar non-toric IOL.

5. OBJECTIVE(S)

To show the superior clinical performance of Clareon T2 IOL compared to Clareon non-toric IOL

HYPOTHESIS:
Clareon T2 will demonstrate better uncorrected distance visual acuity and lower refractive cylinder than the Clareon non-toric IOL.

6. SUBJECTS

6.1. Subject Population

Test subjects will be screened and confirmed as both interested and eligible for implantation of a T2 toric IOL.

A total of 104 subjects will be enrolled.

Exploratory analysis: Anterior corneal astigmatism orientation as measured with the Lenstar LS900 biometer:

- WTR, astigmatism orientation 0 to 30, or 150 to 180 degrees
- ATR, astigmatism orientation between 60 and 120 degrees
- Oblique (OBL), astigmatism orientation 31 to 59, or 121 to 149 degrees

All subjects must meet the inclusion criteria. Prior to enrollment, subjects will be provided information on the study and asked to sign a consent to participate.

6.2. Inclusion Criteria

Subjects are eligible for the study if they meet the following criteria:

Note: Ocular criteria must be met in both eyes.

- are willing and able to understand and sign an informed consent;
- are willing and able to attend all study visits;

- are more than 40 years of age, of either gender and any race;
- have biometry from the LS900 biometer that indicates they are candidates for T2 toric implantation in at least one eye, based on the Barrett Toric Calculator (which includes consideration of posterior corneal astigmatism). This inclusion criterion must be met using the biometry from the day of surgery.
- have good ocular health, with no pathology that compromises visual acuity (outside of residual refractive error)
- Have potential monocular distance visual acuity of 20/32 (0.2 logMAR) or better measured at the time of their screening visit.

6.3. Exclusion Criteria

If any of the following exclusion criteria are applicable to the subject or either eye, the subject should not be enrolled in the study.

- Amblyopia
- Previous radial keratotomy, or other corneal surgery besides LASIK or PRK (e.g. corneal transplant, DSAEK, lamellar keratoplasty)
- Previous anterior or posterior chamber surgery (e.g., vitrectomy, laser iridotomy)
- Diabetic retinopathy
- Macular degeneration
- History of retinal detachment
- Subjects who have an acute or chronic disease or illness that would confound the results of this investigation (*e.g.*, immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, and any other such disease or illness)
- Keratoconus

Pregnancy has a known effect on the stability of refractions and visual acuity. As such, subjects who become pregnant during the study will not be discontinued but their data may be excluded from analyses of effectiveness.

Note: This above list of exclusion criteria is not all inclusive. The investigator will use medical judgment to exclude patients that have disease/conditions that may compromise study results, and patients that are not ideal participants.

7. STUDY DESIGN

7.1. Study Design

This study is a prospective randomized two-arm study of visual outcomes after successful cataract surgery with IOL implantation. Clinical evaluations will include measurement of

visual acuity (VA), manifest refraction, postoperative biometry and low contrast visual acuity.

The primary outcome measure will be the uncorrected monocular distance VA. The secondary measures will include the best-corrected monocular distance VA, best corrected low contrast monocular distance VA, the residual refraction, and postoperative anterior corneal astigmatism.

7.2. Methods Used to Minimize Bias

Biometric analysis and IOL calculations will indicate that study eyes are essentially equivalent from the point of view of astigmatism (inclusion criteria). Subjects' eyes will be randomized such that one half of the study cohort receives the T2 IOL while the other receives a non-toric IOL.

The measurement of visual acuity will be conducted in a systematic fashion to minimize bias. Individuals conducting visual acuity measures will be instructed to perform the same testing in the same fashion for all subjects, with the same level of encouragement to subjects in each group.

All data collection will be completed through provided Case Report Forms (CRFs) or computer files generated by automated test equipment. All site personnel involved in the study will be trained in conducting study-specific procedures.

8. STUDY PROCEDURE

8.1. Informed Consent / Subject enrollment

No subject will be enrolled into the study who does not meet the inclusion/exclusion criteria and does not sign the current approved informed consent document. Informed consent will be obtained prior to collecting any data for the study. The original signed documents will be maintained by the investigator as a permanent part of the subject's medical records. A signed copy will be provided to the subject.

8.2. Visits and Examinations

Subjects will participate in 4 study visits: a screening visit, an operative visit, a 1 day and a 3-month visits. The visit schedule, complete with window Table 9.2-1. Details of each study visit, including testing to be conducted, are provided below.

Table 8.2-1. Visit Schedule

Visit Number	Visit Name	Visit Window
1	Preoperative	-30 to 0 days from surgery
2	Operative	0 from surgery
3	1 day postoperative	1-2 days postoperative
4	3 months postoperative	90 (±20) days postoperative

8.2.1. Preoperative

At the preoperative exam, subjects will be consented, qualified for the study (compared with inclusion/exclusion criteria), and assigned a study ID/subject number. Subject numbers will be assigned sequentially in the order of enrollment. Pre-operative qualification should take place no more than 30 days prior to surgery.

A medical history will be taken, and exams will include the tests described below:

- manifest refraction,
- visual acuity
- biometry measurements
- In addition, all site-specific, routine, usual standard of care preoperative measures should be undertaken.

Measurements should be made as described in section 8.3 below.

- Standard of care ocular surface evaluation
  - Questionnaire (SPEED questionnaire pre-op
  - Noninvasive BUT
  - Oculus Keratography
  - Fluorescein staining of cornea and conjunctiva

All patients will be prescribed and treated with preservative free artificial tears every day for 3-4 weeks before surgery (until the day of surgery). Additionally, they will perform hot facemask treatment for 3 minutes followed by manual massage of the eyelids to improve their meibomian gland function.

Preservative free steroid and NSAID eyedrops will be prescribed and started 2 days ahead of surgery and gradually discontinued over 3 weeks postoperative.

8.2.2. Operative (Surgery)

A biometry measurement to determine IOL power will be repeated on the day of surgery. Only subjects whose biometry on the day of surgery indicate they meet the biometric inclusion criteria will be enrolled. Subjects who are not eligible will be exited from the study, but their keratometric data will be retained for analysis purposes.

All subjects will undergo cataract surgery with implantation of either Clareon T2 or T0, randomly assigned. If both eyes are eligible for inclusion in the study, then the same lens will be implanted in both eyes. The surgeon's usual standard of care with regard to treatment and medication will be used for all study subjects. Surgery planning and IOL sphere power calculation will be performed using the

surgeon's preferred method, with an initial a-constant provided by Alcon. If a toric IOL is used, planning will be performed with the Alcon Barrett Toric calculator that takes the effects of posterior corneal astigmatism into account. Verion will be used for intraoperative alignment of the toric axis.
The main incision location for both groups will be 12 o'clock.

Surgical findings will be recorded and any adverse events/serious adverse events (AEs/ SAEs) occurring during surgery will be noted at this visit. Any other problems during surgery and comments regarding surgery will be documented.

Any subject whose surgery is not completed successfully will be documented in the appropriate case report form. These subjects will be monitored for safety, but clinical performance data may be excluded from the analysis.

8.2.3. Postoperative 1 Day

All routine, usual standard of care postoperative measures should be undertaken. In addition, the subject will undergo VA testing in accordance with the specifications below (Section 9.3). Adverse events will be monitored. The axis orientation of the toric IOL will be recorded. If there is a misalignment between planned and obtained toric axis of >10 degrees, the patient will be scheduled for an extra visit. If the toric misalignment is still present at this visit, re-rotation to the correct axis will be performed.

8.2.4. Postoperative 3 Months
All routine, usual standard of care postoperative measures should be undertaken. In addition, the subject will undergo a manifest refraction, VA, low contrast acuity and contrast sensitivity testing (Section 9.3). Any device deficiencies or adverse events will be monitored.

8.2.5. Exit Procedures
In the event of premature exit from the study, all study related examinations should be completed where possible. The Exit CRF should be completed, noting that the subject did not complete the study and the reason for premature study exit. If no premature exit from the study occurs, the Exit CRF should be completed at the end of Visit 5 (Postoperative 3 Months).

8.3. Study Methods and Measurements

Study examination procedures are outlined below.

8.3.1 Contrast sensitivity

Patients will be tested monocularly, best-corrected, using the M&S Technologies' Clinical Trial Suite (CTS) contrast sensitivity system. Instructions for device use will be followed to obtain mesopic and photopic contrast sensitivity values at 4 m.

Low Contrast VA
M&S Technologies contrast sensitivity system will be used to measure best corrected mesopic and photopic low contrast (10%) VA with and without glare at 4 m.

A Gossen Starlite 2 photometer will be used to confirm the light level of the examination room (Photopic and Mesopic conditions)

8.3.2. Manifest Refraction

Perform manifest refraction with the 100% contrast ETDRS chart under photopic lighting conditions (>85 cd/m^2). Document refraction results with sphere, cylinder and axis readings. If uncorrected visual acuity is not improved by manifest refraction, use zero for sphere and cylinder and draw a line through the blank for the axis. This refraction will be considered the best distance correction for the purposes of further testing.

Note: Each subject should be manually refracted to his/her best correction by an ophthalmologist, optometrist, or a skilled technician using a phoropter or trial lenses and a distance target.

8.3.3. Visual Acuity (VA)

Follow the instructions for the M&S Technologies Clinical Trial Suite to collect relevant visual acuity data.

Perform all visual acuity testing monocularly.

Rotational stability is defined as the toric IOL axis' difference between two timepoints. The axis stability will be evaluated with OCT technology postoperative. We will look at two different scenarios. A) Primary misalignment (or early rotational error) found at the Day 1-2 visit or B) Late rotation (e.g. correct axis at visit 1-2 and later axis drift, 3 month. For both categories, an axis drift from planned to achieved of >5 degrees would be defined as misalignment.

Rotational stability manually by selecting the IOL toric marks on the front view pictures of the dilated eye obtained with the pupilar camera of Anterion OCT. Measure the position of the toric IOL at least in two different time points (early post-op and at 3 months post-op). Less than or equal to 5° will be considered a rotationally stable position.

8.3. Discontinued Subjects

Discontinued subjects are those who do not complete the study. If any subject is discontinued their results will be recorded to the point of discontinuation, but not used in data analysis.

9. ANALYSIS PLAN

9.1. Analysis Data Sets

Efficacy analyses will be performed based on data from those subjects who complete all testing in the 3-month study visit. A safety analysis will also be performed.

9.2. Statistical Methodology

A summary of the data will be prepared for all subjects and categorized by the lens implanted and the orientation of the preoperative anterior corneal astigmatism.

For variables measured on a continuous scale, these summaries will include the sample size, as well as the mean, standard deviation, median, minimum, and maximum. For variables measured on a categorical scale, summaries will provide the number and percentage of subjects who provided each score.

Preliminary considerations of the data will include the investigation as to whether any transformation (*e.g.,* logarithmic) should be applied prior to the statistical analyses. For categorical data, the sparseness of the data across categories will be considered, and the combination of categories prior to statistical analysis will be applied where deemed appropriate.

For variables measured on a continuous scale, the statistical significance of between-treatment differences will be investigated using an Analysis of Variance (ANOVA) with appropriate post-hoc testing. For variables measured on an ordinal categorical scale, the Kruskal-Wallis signed-rank test or other appropriate non-parametric test will be employed.

9.3. General Statistical Considerations

The statistical analyses will be performed using Statistica, version 12 or higher. All statistical tests of hypotheses will employ a level of significance of alpha=0.05. Subjects will be randomized to one of the two groups (T0 or T2). If surgery is performed on both eyes, the same lens will be implanted in both eyes. At the time of analysis one eye will be randomly selected to be included. If surgery is performed on only one eye (or only one eye meets the inclusion/exclusion criteria), that eye will be included in the analysis.

10. SAMPLE SIZE JUSTIFICATION

Sample size calculation:

- The following parameters are assumed for the sample size calculation:

- Unpaired t-test
- Confidence level of 95%
- Power of 80%
- SD of 0.1 logMAR (data based on a similar previous study [1])
- A mean difference between both groups of 0.06 (data based on a similar previous study [1])

With these parameters, the suggested sample size is 45 eyes per group. To account for potential dropouts, a sample size of 52 subjects per group will be targeted in this study (in total, 104 subjects).

Note that subjects that are enrolled but are found ineligible based on the biometry inclusion criteria on the day of surgery will not be counted against this total.

Statistical Analysis:

- Normality of each variable will be tested with the Shapiro-Wilks normality tests.
- To compare the 2 means of both groups, paired t-tests will be performed, alternatively, if the normality test fails, non-parametric tests (i.e., Wilcoxon Signed-Rank test will be performed).

11. QUALITY COMPLAINTS AND ADVERSE EVENTS

All quality complaints and adverse events that occur during the course of the study will be appropriately documented and reported.

12. GCP, ICH and ETHICAL CONSIDERATIONS

This study will be conducted in compliance with Good Clinical Practices (GCPs), including International Harmonization (ICH) Guidelines, and in general, consistent with the 1996 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements will be adhered to.

This study is to be conducted in accordance with Institutional Review Board regulations. The investigator will obtain appropriate IRB/ethics committee approval prior to initiating the study.

Abstracts will be prepared and presented at: ESCRS, ASCRS

REFERENCES

1. Gundersen KG, Potvin R. Comparing Visual Acuity, Low Contrast Acuity and Refractive Error After Implantation of a Low Cylinder Power Toric Intraocular Lens or a Non-Toric Intraocular Lens. Clin Ophthalmol. 2020 Oct 30;14:3661-3666.