Long-term visual performance and patient reported outcomes with a trifocal intraocular lens

Investigational Product: AT LISA 839MP

Indication: Cataract Surgery and Refractive Lens Exchange

Study design: Retrospective and cross-sectional observational study

Sponsor: Qvision, Ophthalmology Department, Vithas Virgen del Mar Hospital, Carretera del Mami, s/n, 04120 Almería

Document date: 30-07-2020

Protocol Number: QVI-20-02

Phase Study: Post-market

Study initiation date: 15-9-2020

Study completion date: 27-11-2020

Principal Investigator:

Joaquín Fernández Pérez

QVision, Unidad Oftalmológica, Hospital Virgen del Mar, Carretera del Mami, s/n, 04120 Almería

Study Coordinator:

Manuel Rodríguez Vallejo

QVision, Unidad Oftalmológica, Hospital Virgen del Mar, Carretera del Mami, s/n, 04120 Almería

TABLE OF CONTENTS

LIST OF ABREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BFC	Best Fit Circle
BFCr	Best Fit Circle Radius
BFCi	Best Fit Circle Irregularity
CDVA	Corrected Distance Visual Acuity
CEIm	Ethics Committee of Drugs and Medical Devices
CRF	Case Report Form
DCIVA	Distance Corrected Intermediate Visual Acuity
DCNVA	Distance Corrected Near Visual Acuity
FAUC	Far Area Under the Curve
GCP	Good Clinical Practices
IAUC	Intermediate Area Under the Curve
ICH	International Council for Harmonisation
IOL	Intraocular Lens
IOP	Intraocular Pressure
LDI	Light Distortion Index
MIOL	Multifocal Intraocular Lens
MPMAV	Maximum Positive Maximum Visual Acuity
MTF	Modulation Transfer Function
NAUC	Near Area Under the Curve
NdYAG	Neodynium YAG laser for Posterior Capsulotomy
PCO	Posterior Capsular Opacification
SAE	Serious Adverse Event
TAUC	Total Area Under the Curve
UDVA	Uncorrected Distance Visual Acuity
UIVA	Uncorrected Intermediate Visual Acuity
UNVA	Uncorrected Near Visual Acuity
VA	Visual Acuity

1 SYNOPSIS

Name of Sponsor: Qvision, Ophthalmology Department, Vithas Virgen del Mar Hospital, Carretera del Mami, s/n, 04120 Almería	
Name of Finished Product: AT LISA 839MP	
Title of Study: Long-term visual performance and patient reported outcomes with a trifocal intraocular lens	
Principal Investigator: Joaquín Fernández Pérez	
Study centre(s): Qvision, Ophthalmology Department, Vithas Virgen del Mar Hospital, Carretera del Mami, s/n, 04120 Almería	
Studied period (years): 15-9-2020 to 27-11-2020	Phase of development: Post-market
Objectives: The main aims of this study were to evaluate the patient reported outcomes (PROs), safety and efficacy, after 6-year (66 - 78 months) from the binocular implantation of the 839MP. A secondary aim was to evaluate new metrics such as contrast sensitivity defocus curves and light distortion analysis.	
Methodology: Retrospective cross-sectional study with two stages: • Phone call interview: First stage included patient reported outcomes of visual function, spectacle independence and satisfaction through questionnaires conducted by a phone call in all the patients implanted in our center with AT LISA 839MP from March 2014 to June 2015 (n=92) which accomplished inclusion / exclusion criteria and were able to be contacted by phone (n=62). The incidence of Nd-YAG capsulotomy was retrospectively evaluated through the revision of the medical history, in patients for which capsulotomy was conducted in our center, or a question, for those treated in another center. • Study visit: Second stage included the consecutive invitation of these phone interviewed patients to a visit in our center for a long-term visual performance assessment up to accomplish the required sample size (n=37). Corrected and uncorrected monocular visual acuities were the primary end-points for testing non-inferiority hypothesis in comparison to 12-month follow-up mean results reported in the literature. Secondary variables of assessment were contrast sensitivity defocus curve and light distortion analysis.	

Number of patients (planned and analyzed):

92 for PROs planned and 62 analyzed

37 for visual performance planned and analyzed

Inclusion Criteria:

- Phone call interview:
  - Patients of either sex, 45 years of age or older at the time of surgery and less than 80 years of age at the time of the phone call.
  - Patients implanted bilaterally with the AT LISA 839MP MIOL in the capsular bag.
  - No surgical complications reported in the clinical history that could affect postoperative visual acuity: damage to the capsular bag, intraocular hemorrhage, etc.
  - Operated between 66 months from the first implanted eye and up to 78 months from the surgery of the second eye
  - Patient able to hear, understand and give express consent orally.
- Study visit:
  - To have participated in the first stage of the study corresponding to the phone call interview.
  - Irregular astigmatism in either eye measured with corneal tomography (total high-order corneal aberrations at 4 mm < 0.5 µm).
  - Patient able to read, understand and provide a written informed consent form.
  - Sufficient availability, willingness, skills, and cognitive awareness to comply with follow-up/study procedures and study visits.

Exclusion Criteria:

- Phone call interview:
  - Any eye disease documented in the patient's clinical history that may potentially cause a loss of visual acuity or diplopia: Active or recurrent pathology of the anterior segment (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, uncontrolled glaucoma, etc.), retinal or optic nerve pathologies such as diabetic retinopathy, macular degeneration, etc.
  - Eye surgery (including laser refractive surgery) performed before or after the operation with the intraocular lens.
- Study Visit:
  - PCO ≥ 2 according to surgeon criteria that produces a loss of CDVA ≥ 0.2 logMAR
  - Any eye disorder that can potentially cause a loss of visual acuity or diplopia: Active or recurrent pathology of the anterior segment (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, uncontrolled glaucoma, etc.), retinal or optic nerve pathologies such as diabetic retinopathy, macular degeneration, etc.
  - Eye surgery (including laser refractive surgery) performed before or after the operation with the intraocular lens.
  - Use of systemic or ocular medications that may affect vision in the last 6 months.
  - Subjects who participate in any clinical trial or research with drugs or medical devices within 30 days prior to entry into this research and/or during the period of participation in this research.

2 INVESTIGATORS AND STRUCTURE

Investigators are included in Appendix A, main investigator was Joaquín Fernández Pérez (MD, PhD) and study coordinator was Manuel Rodríguez Vallejo (OD, PhD). The main investigator supervised and collaborated, if was required, in all the tasks delegated to research collaborators.

All measurements and data collection were conducted by Noemí Burguera Giménez (OD, PhD) assisted by the clinical area responsible of the center Javier Martínez Peña (OD) who was involved together with the main investigator during the surgeries of the patients recruited in this study (all surgeries conducted by the main investigator).

Collected data on printed CRF paper sheets and codified in an Excel spreadsheet (Microsoft, Redmond, WA) by Noemí Burguera Giménez were monitored by the study coordinator, university trained as Clinical Research Associate. The statistical analysis, study report and medical writing was also conducted by the study coordinator. All the documents send for publication were previously reviewed by David P. Piñero Llorens (OD, PhD).

3 INTRODUCTION

The implantation of multifocal intraocular lens (MIOL) has become a settled method for cataract treatment mainly due to the high rate patient satisfaction ranging from 81.4% to 96.3%.[1] Although there is a lot of clinical evidence that demonstrates the safety and efficacy achieved with MIOLs in the short term period, which explain the high satisfaction rates,[2–10] long-term results still remain poorly investigated. First long-term study with 8-year follow-up was reported for 3M diffractive MIOL which was made of a poly(methyl methacrylate) material, nowadays outdated technology.[11] Most recent bifocal optic and material such as the provided by the Acrysof ReSTOR (SN60D3, Alcon) has also long-term results available.[12] Yoshino et al.[12] reported 5-year follow-up with no differences in distance and near visual acuities in comparison to 1-year, contrast sensitivity function in the normal range and 14.3% of neodymium-YAG (Nd-YAG) capsulotomy rates performed in a mean time of 44.64 months. However, as far as we know, no more long-term studies for bifocal MIOLs have been published, probably because of the decrease on interest by the replace for the current more popular trifocal intraocular lenses (IOLs).

The AT LISA tri 839MP (henceforth 839MP, Carl Zeiss Meditec AG, Germany) was together with the FineVision (Physiol S.A., Liege, Belgium) the first trifocal MIOLs which received the CE mark in 2012 and 2010, respectively.[13] Safety and efficacy for 839MP has been widely reported for short term follow-up periods (1 to 6 month follow-up).[2–10] Long-term studies with 839MP are commonly referred to those which involve 1 or 2 year follow-up period[14–18] and as far as we know there is only one retrospective study for a higher period of 3-4 years follow-up which only covers Nd-YAG rates.[19] 839MP remains one of the most popular and implanted MIOLs and therefore the results for longer periods of time can be considered of great interest.

4 STUDY OBJECTIVES

The main aims of this study were to evaluate the patient reported outcomes (PROs), safety and efficacy, after 6-year from the binocular implantation of the 839MP. A secondary aim was to evaluate new metrics such as contrast sensitivity defocus curves and light distortion analysis.

5 METHODS

5.1 Ethics

5.1.1 Ethics Committee for investigation with medicinal products (CEIm)

The protocol, informed consent forms, recruitment materials and all participant materials were submitted to the CEIm for review and approval. The study was approved on 29/07/2020 by the local ethics committee (Hospital Universitario de Torrecárdenas, calle hermandad de donantes de sangre s/n 04009-Almería) before participant enrrollment. No amendments of the protocol were conducted.

5.1.2 Ethical conduct of the study

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the standards of Good Clinical Practice, as well as European legislation Regulation 536/2014, National Law 14/2007 on Biomedical Research and Autonomous Decree 439/2010, Law on Patient Autonomy 41/2020 and Law 3/2018 on Data Protection and Digital Rights Guarantee.

5.1.3 Patient information and consent

Two informed consents were given depending on the phase of the study:

- For the first stage, the consent was obtained by telephone, the patient was informed about the study and expressed verbal consent for using his/her pseudonymized data in the research. The participant gave the consent orally, the investigator signed the consent form and the date of consent was notified in the patient's medical record. The consent form was stored with the source documents of the study to be provided to the patient to obtain his/her written signature and to receive a copy at the time of his/her visit to the center. This procedure was carried out according to version 12 of June 29, 2020 of the Spanish Agency of Medicines and Healthcare Products' document of instructions for conducting clinical trials in Spain in reference to obtaining consent in COVID-19 studies.

- For the second stage at the clinical center, participants were provided with a patient information sheet with the risks and possible benefits of participating in the study as well

as the sheet corresponding to the first part of the study. The participant signed both informed consent documents before any evaluation or procedure related to study visit. A copy was given to the participants.

The rights and well-being of participants were protected by emphasizing that the quality of their clinical care was not adversely affected if they refused to participate in the study.

5.2 Investigational Plan

5.2.1 Investigational Product

The AT Lisa Tri 839MP is a trifocal intraocular lens with a 6.0 mm biconvex optic (360° posterior square edges) and overall diameter of 11.0 mm including the non-angulated plate haptic. The material consists of a hydrophilic acrylate with a water content of 25% with hydrophobic surface and blocks ultraviolet light according to manufacturer description. The optic structure is diffractive with additions at the IOL plane of +3.33 D for near focus and +1.66 D for intermediate focus and a posterior aspheric surface lead to an induction of negative spherical aberration of -0.18 μm.[13,20]

5.2.2 Overall Study Design

The study design was retrospective and cross-sectional. The study consisted of two stages, the first one with a phone call inverview for collecting the PROs, and a second stage with the consecutive invitation of these patients to a visit at our center to measure the visual performance up to achieve the required sample size. Each stage with some inclusion and exclusion criteria detailed below. The diagram in Figure 1 summarizes the study stages.

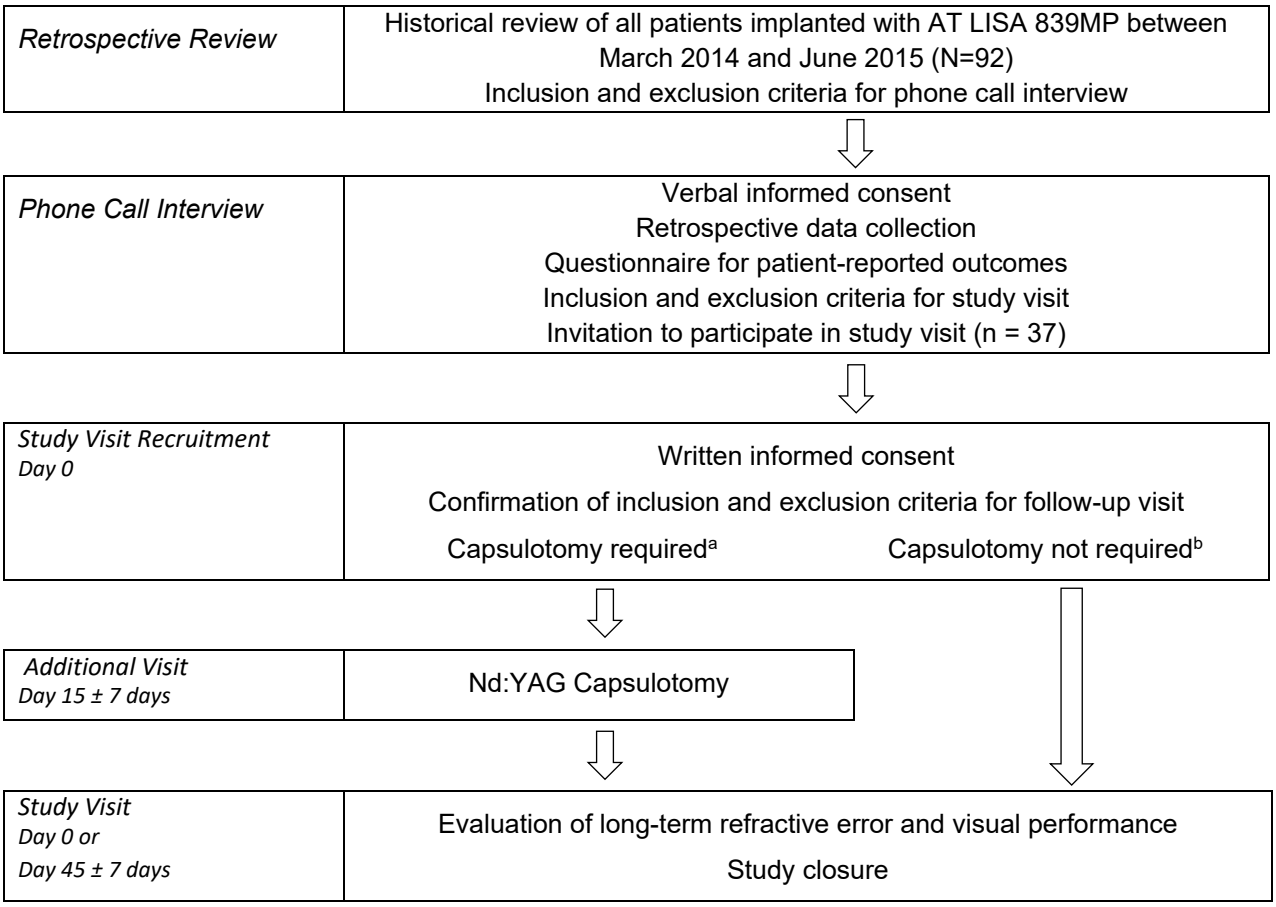

Figure 1. Study design summary

5.3 Selection of study sample

5.3.1 Phone call interview

5.3.1.1 Inclusion criteria

- Patients of either sex, 45 years of age or older at the time of surgery and less than 80 years of age at the time of the phone call.
- Patients implanted bilaterally with the AT LISA 839MP MIOL in the capsular bag.

- No surgical complications reported in the clinical history that could affect postoperative visual acuity: damage to the capsular bag, intraocular hemorrhage, etc.
- Operated between 66 months from the first implanted eye and up to 78 months from the surgery of the second eye.
- Patient able to hear, understand and give express consent orally.

5.3.1.2 Exclusion criteria

- Any eye disease documented in the patient's clinical history that may potentially cause a loss of visual acuity or diplopia: Active or recurrent pathology of the anterior segment (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, uncontrolled glaucoma, etc.), retinal or optic nerve pathologies such as diabetic retinopathy, macular degeneration, etc.
- Eye surgery (including laser refractive surgery) performed before or after the operation with the intraocular lens.

5.3.2 Study visit

5.3.2.1 Inclusion criteria

- To have participated in the first stage of the study corresponding to the Phone Call Interview.
- Irregular astigmatism in either eye measured with corneal tomography (total high-order corneal aberrations at 4 mm < 0.5 μm).
- Patient able to read, understand and provide a written informed consent form.
- Sufficient availability, willingness, skills, and cognitive awareness to comply with follow-up/study procedures and study visits.

5.3.2.2 Exclusion criteria

- PCO ≥ 2 according to surgeon criteria that produces a loss of CDVA ≥ 0.2 logMAR
- Any eye disorder that can potentially cause a loss of visual acuity or diplopia: Active or recurrent pathology of the anterior segment (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, uncontrolled glaucoma, etc.), retinal or optic nerve pathologies such as diabetic retinopathy, macular degeneration, etc.

- Eye surgery (including laser refractive surgery) performed before or after the operation with the intraocular lens.
- Use of systemic or ocular medications that may affect vision in the last 6 months.
- Subjects who participate in any clinical trial or research with drugs or medical devices within 30 days prior to entry into this research and/or during the period of participation in this research.

5.4 Safety Evaluation

5.4.1 Definition of adverse events

An adverse event (AE) was defined as an adverse or unfavorable medical occurrence in a subject, including any abnormal sign (e.g., an abnormal physical examination), symptom, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Some adverse events could happen during the 6 years period between the surgery date and the study visit, some of these adverse events were identified and reported even these could be part from the Exclusion Criteria. In this case, those were reported as a recruitment failure together with the adverse event reason. A list of possible adverse events anticipated can be found in ISO-11979-7:2018.[21]

5.5 Procedures followed and devices used for data collection

A summary of procedures conducted are listed in Appendix B. Phone call interview with collection of PROs was done by one of the research collaborators also in charge of performing the clinical measurements at the center during study visit. The explorations prior to patient recruitment were carried out by an experienced optometrist or physician depending on the required test and the competencies of each professional. For example, the optometrist performed visual acuity and refraction measurements but the physician was responsible of evaluating the PCO, establishing whether the Nd-YAG could lead to improved visual acuity as well as any other tests related to eye health.

5.5.1 Clinical history

- Each patient's medical history was reviewed prior to making the phone call interview.

- This first review aims to explore whether the inclusion/exclusion criteria were met before making the call.

- The variables reviewed in the medical history were:

    - Surgery date

    - Eye and general health

    - Intraocular lens implanted power

    - Adverse events reported in the history during surgery or post-operative follow-up

    - Date of patient's last visit to the clinic

    - Months after surgery on which Nd-YAG capsulotomy was done, if it was the case, and the eye/s

5.5.2 History obtained during the phone call interview

- During the phone call and study visit the patient was consulted about possible diseases and concomitant medications in the 6 months prior to the call or visit.

- The inclusion/exclusion criteria were confirmed through a patient interview for all those issues related to the patient's eye and general health history that might not be found in the medical records.

5.5.3 Patient reported outcomes

- The following questionnaires were carried out during the phone call interview:

    - VF-14 to assess vision-related difficulty in performing everyday tasks.[22]

    - PRSIQ to assess independence of spectacles at far, intermediate and near distances.[23]

    - Additional questions related to satisfaction, dysphotopsia and decision to have the same MIOL procedure (Appendix C).

5.5.4 Slit-lamp evaluation

The slit lamp examination was performed during the study visit. An examination of the eyelids, conjunctiva, cornea, intraocular lens and anterior vitreous was performed.

- Eye lids: Normal / Non-Normal
- Conjuntive:
    - Hyperemia (Normal / Mild / Moderate / Severe)
    - Oedema (Normal / Mild / Moderate / Severe)
- Cornea: Oedema (Normal / Mild / Moderate / Severe)
- Staining: Anterior chamber cells and flare.[24]
- Anterior Capsular Opacification:[25] From 0 to 4 grading
- Posterior Capsular Opacification (PCO):[26] From 0 to 4 grading density
- Intraocular lens centration: [27] From 0 to 4 grading
- Vitreous:[28] From 0 to 4 grading
- IOL calcification:[29] (None / primary / secondary)

5.5.5 Pentacam AXL

A measurement was performed with Pentacam AXL (corneal tomograph with Scheimpflug technology and ocular biometer, Oculus, Germany) to evaluate that the patient met the inclusion criteria in reference to irregular corneal astigmatism and to collect the necessary ocular demographic data for the results report. The following variables were collected with the Pentacam AXL:

- Irregular astigmatism at 4 mm (µm): For Total Cornea (anterior and posterior corneal surfaces combination).
- Anterior lens position (mm): Distance from anterior corneal vertex to anterior intraocular lens.
- Regular astigmatism (D): For Total Cornea.

- Corneal spherical aberration for mesopic pupil size (µm): Recalculated for the mesopic pupil diameter and the Total Cornea.

5.5.6 IOL Master 500

A measurement was performed with IOL Master 500 to obtain:

- Axial length (mm)
- Mean corneal anterior keratometry (D). Average from the steep and flat axis measured for the anterior cornea.

5.5.7 Keratograph 5M

A measurement was carried out for collecting the following variables:

- Photopic pupil diameter (mm)
- Mesopic pupil diameter (mm)

5.5.8 Subjective Refraction

Subjective refraction was performed with a trial frame following our specific protocol for MIOLs.

- The optotype used to carry out the refraction (ETDRS) was placed at a distance of 4 m with a background luminance of 85 cd/m2 (VisionC ETDRS chart, test-eye.com).
- Based on the patient's spectacle refraction (if used), the objective refraction with auto-refractometer, and the corneal astigmatism obtained with Pentacam, the starting sphere and cylinder were selected.
- A 1.00 D myopization with positive spherical lenses was performed in order to shift the defocus curve enough to avoid refraction at a distance over the near focus.
- After reaching the maximum positive maximum visual acuity (MPMVA), patient was myopized with +0.50 D and the axis and magnitude of the cylinder was fitted with a cross cylinder of +/- 0.50 D.

- The procedure was completed by returning to the MPMVA and adding -0.25D on the sphere to obtain the equivalent refraction in infinity considering the proximal distance induced myopia (1/-0.25 = 4m).

- The procedure was completed with a confirmation of +/- 2.50 D so that the negative lens slightly decreases visual acuity (2 lines) and the positive lens significantly decreases visual acuity. This procedure served as confirmation that the refraction was carried out at the focus corresponding to distant vision.

5.5.9 Visual acuity

- Measured in monocular vision with and without the best correction obtained in the subjective refraction.

- Measured in binocular vision without correction.

- Measurements conducted at three distances:

    - Infinity: 4 m with distance vergence correction (+0.25 D)

    - Intermediate: 67 cm

    - Near: 40 cm

- The procedure for measuring visual acuity was carried out with the ETDRS optotype chart (VisionC ETDRS chart, test-eye.com), selecting different sets of letters for each eye and distance in order to avoid a possible bias due to the effect of memorizing letters.

- The procedure for determining the visual acuity threshold was carried out as follows:

    - Read only the first letter from the left and go down.
    - At the first failure, stayed on the previous line and read the whole line.
    - If correct answers were ≥ 3/5 advanced to the next line.
    - If correct answers were < 3/5 read the previous line.
    - Visual acuity was the last with correct answers ≥ 3/5.

5.5.10 Contrast sensitivity defocus curve

- The Multifocal Lens Analyzer App (defocuscurve.com) was used to evaluate the Contrast Sensitivity Defocus Curve in monocular vision (one eye selected at random).

- Patient sitting 4 m from the iPad with +0.25 D vergence correction lens on trial frame over the best correction at infinity.

- The automated procedure varies the contrast for a 0.3 logMAR Snellen optotype equivalent size in steps of 0.1 logCS and uses a staircase psychophysical method to determine the contrast sensitivity threshold.

- The procedure is repeated for each defocus lens until a range of 11 lenses is completed from +1.00 D to -4.00 D in steps of -0.50 D.

- Areas Under the Curve (AUCs) were computed along the total range (Total Area Under the Curve (TAUC), +1.00 to −4.00 D) and for the ranges of Far (Far Area Under the Curve (FAUC), +0.50 to −0.50 D), (Intermediate Area Under the Curve (IAUC), −0.50 to −2.00 D) and Near vision (Near Area Under the Curve (NAUC), −2.00 to −4.00 D).

5.5.11 Light Distortion Analyzer

- Measurement with the Light Distortion Analyzer (CEORLab, University of Minho, Braga, Portugal) were performed under monocular conditions (one eye randomly selected) with the subjective refraction at distance and uncorrected binocular vision or with the usual correction used by the patient.
- The Light Distortion Analyzer was used to psychophysically measure the light effects perceived by the patient around light sources such as car headlights, streetlights, etc.
- The test consists of a central LED and peripheral LEDs with a luminance ratio of 100/1 so that the central LED generates the light distortion and the peripheral LEDs are activated in an automated way by scanning the visual field through the random inspection of each semi-meridian and 3 repeated measurements in each semi-meridian.
- The scanning protocol is called "in-out 30°" in which the peripheral points around the central source are presented from the inside to the outside of the evaluated field in random

time intervals between 500 and 750 milliseconds. The peripheral LEDs turn on and off sequentially in the same semimeridian from the center to the periphery, the scanning of the different semimeridians were randomized by the device.

- The measurement was carried out at 2 m with +0.50 D to correct the vergence produced by the presentation distance with the lighting of the room in mesopic conditions.

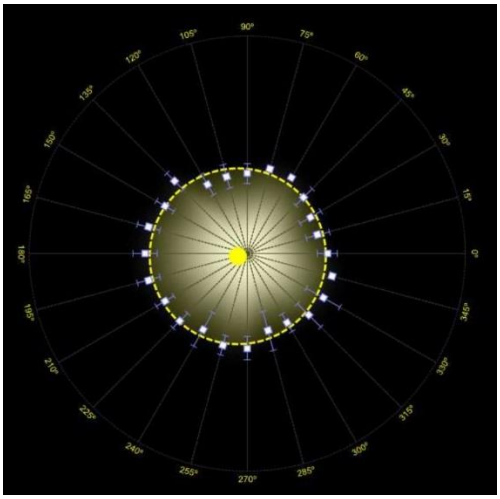

Figure 2. Example of a measurement with the Light Distortion Analyzer.

Figure 2 shows and example of the field explored described by three main variables:

- BFC Irregularity (mm): Average distance from disturbance to Best Fit Circle (BFC) along each semi meridian.
- BFC Radius (mm): radius of the circle that best fits the distortion area.
- Disturbance Index (%): percentage of the area over the Total Tested Area.

5.6 Statistical analysis plan

- Statistical analysis was performed with SPSS 24

- Standardized descriptive graphics were represented with the Refractive Analysis Toolbox library (version 1.0.5) for MATLAB (https://www.test-eye.com/en/refractive-analysis)

5.6.1 Hypothesis and sample size calculation

5.6.1.1 Main hypothesis (non-inferiority)

The primary objective was to assess long-term efficacy by measuring monocular visual acuity with and without correction at distance (CDVA and UDVA), intermediate (DCIVA and UIVA) and near (DCNVA and UNVA). The mean monocular visual acuity and the standard deviations taken as reference were obtained from previous literature.[15] Visual acuity was measured on a logMAR scale so that the smaller the variable, the higher the visual acuity.

A contrast of non-inferiority hypotheses with unilateral significance was carried out, rejection of null hypothesis means than non-inferiority was accomplished:

$H_o = \mu_a \geq \delta + \mu_b$

$H_A = \mu_a < \delta + \mu_b$

H_o = Visual acuity at 6 years was higher or equal (poorer) than at 12 months plus a margin δ

H_A = Visual acuity at 6 years was lower (better) than at 12 months plus a margin δ

μ_a = Mean monocular visual acuity obtained after 6 years of follow-up

μ_b = Mean monocular visual acuity reported in a previous clinical study with 12 months of follow-up.[15]

δ = 0.1 logMAR or 0.02 logMAR

5.6.1.2 Study power

The statistical test planned in the protocol for testing the hypothesis was the one-sided one-sample t-test but the one-sided one-sample Wilcoxon Signed test was finally used due to non-normal distribution of the variables. The margin (δ) selected in the protocol was 0.1 logMAR but the hypothesis was finally also confirmed with a margin of 0.02 logMAR. The software G-Power 3.9.1.2 (Universität Düsseldorf) for an alpha level of 0.05 was used to calculated the power considering the standard deviation obtained in our study.

Table 1. Sample size confirmation

Variables	μ_a	μ_b	Power $\delta = 0.1$	Power $\delta = 0.02$
UDVA	0.06 ± 0.12	0.03 ± 0.13	0.96	0.12
	0.1 [0.1]	0 [-]		
CDVA	-0.05 ± 0.07	0.01 ± 0.11	1	0.99
	-0.1 [0.1]	0 [-]		
UIVA	0.07 ± 0.09	0.12 ± 0.13	1	0.99
	0.0 [0.1]	0.1 [-]		
DCIVA	0.08 ± 0.09	0.11 ± 0.12	1	0.94
	0.1 [0.1]	0.1 [-]		
UNVA	0.08 ± 0.10	0.27 ± 0.15	1	1
	0.1 [0.1]	0.2 [-]		
DCNVA	0.05 ± 0.06	0.25 ± 0.14	1	1
	0 [0.1]	0.2 [-]		

5.6.2 Statistical analysis methods

- Normal distributions were tested with the Shapiro-Wilk test
- Wilcoxon-signed rank test one sample was finally selected for testing the hypothesis for median differences because of the non-normal distribution of the variables.
- Correlations were assessed with the Spearman rho or Multiple Linear Regression for multiple correlations and a single dependent variable.
- Descriptive statistics are detailed in the results section as mean ± standard deviation [median (interquartile-range)].
- A survival analysis was performed for the assessment of Nd:YAG rates.
- SPSS version 24 software (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis.

- The Refractive Analysis toolbox for MATLAB (R2019; MathWorks, Natick, MA, USA) was used for conducting the standard plots.[30]

6 REFERENCES

1. Fernández J, Rodríguez-Vallejo M, Martínez J, Tauste A, Piñero DP. Standard Clinical Outcomes With a New Low Addition Trifocal Intraocular Lens. *J Refract Surg*. 2019;35(4):214-221.

2. Mendicute J, Kapp A, Lévy P, et al. Evaluation of visual outcomes and patient satisfaction after implantation of a diffractive trifocal intraocular lens. *J Cataract Refract Surg*. 2016;42(2):203-210. doi:10.1016/j.jcrs.2015.11.037

3. Mojzis P, Peña-García P, Liehneova I, Ziak P, Alió JL. Outcomes of a new diffractive trifocal intraocular lens. *J Cataract Refract Surg*. 2014;40(1):60-69. doi:10.1016/j.jcrs.2013.06.025

4. Law EM, Aggarwal RK, Kasaby H. Clinical outcomes with a new trifocal intraocular lens. *Eur J Ophthalmol*. 2013;24(4):501-508. doi:10.5301/ejo.5000407

5. Marques EF, Ferreira TB. Comparison of visual outcomes of 2 diffractive trifocal intraocular lenses. *J Cataract Refract Surg*. 2015;41(2):354-363.

6. Kretz FTA, Breyer D, Diakonis VF, et al. Clinical Outcomes after Binocular Implantation of a New Trifocal Diffractive Intraocular Lens. *J Ophthalmol*. 2015;2015(962891):1-6. doi:10.1155/2015/962891

7. Kohnen T, Titke C, Böhm M. Trifocal Intraocular Lens Implantation to Treat Visual Demands in Various Distances Following Lens Removal. *Am J Ophthalmol*. 2016;161:71-77.e1. doi:10.1016/j.ajo.2015.09.030

8. Alfonso JF, Cueto LFV, Belda-Salmerón L, Montés-Micó R, Fernández-Vega L. Visual function after implantation of a diffractive aspheric trifocal intraocular lens. *Eur J Ophthalmol*. 2016;26(5):405-411. doi:10.5301/ejo.5000741

9. Plaza-Puche AB, Alio JL. Analysis of defocus curves of different modern multifocal intraocular lenses. *Eur J Ophthalmol*. 2016;26(5):412-417. doi:10.5301/ejo.5000780

10. Plaza-Puche AB, Alio JL, Sala E, Mojzis P. Impact of low mesopic contrast sensitivity outcomes in different types of modern multifocal intraocular lenses. *Eur J Ophthalmol*. 2016;26(6):612-617. doi:10.5301/ejo.5000777

11. Slagsvold JE. 3M diffractive multifocal intraocular lens: Eight year follow-up. *J Cataract Refract Surg*. 2000;26(3):402-407. doi:10.1016/S0886-3350(99)00437-X

12. Yoshino M, Bissen-Miyajima H, Minami K, Taira Y. Five-year postoperative outcomes of apodized diffractive multifocal intraocular lens implantation. *Jpn J Ophthalmol*. 2013;57(6):510-513. doi:10.1007/s10384-013-0277-1

13. Sudhir RR, Dey A, Bhattacharrya S, Bahulayan A. Acrysof IQ panoptix intraocular lens versus extended depth of focus intraocular lens and trifocal intraocular lens: A clinical overview. *Asia-Pacific J Ophthalmol*. 2019;8(4):335-349. doi:10.1097/APO.0000000000000253

14. Brito P, Salgado-Borges J, Neves H, Gonzalez-Meijome J, Monteiro M. Light-distortion analysis as a possible indicator of visual quality after refractive lens exchange with diffractive multifocal intraocular lenses. *J Cataract Refract Surg*. 2015;41(3):613-622. doi:10.1016/j.jcrs.2014.07.033

15. Mojzis P, Majerova K, Hrckova L, Piñero DP. Implantation of a diffractive trifocal intraocular lens: One-year follow-up. *J Cataract Refract Surg*. 2015;41(8):1623-1630.

16. Gundersen KG, Potvin R. Comparison of visual outcomes and subjective visual quality after bilateral implantation of a diffractive trifocal intraocular lens and blended implantation of apodized diffractive bifocal intraocular lenses. *Clin Ophthalmol*. 2016;10:805-811. doi:10.2147/OPTH.S107162

17. Ganesh S, Brar S, Pawar A. Long-term visual outcomes and patient satisfaction following bilateral implantation of trifocal intraocular lenses. *Clin Ophthalmol*. 2017;11:1453-1459. doi:10.2147/OPTH.S125921

18. Kaymak H, Breyer D, Alió JL, Coche B. Visual performance with bifocal and trifocal diffractive intraocular lenses: A prospective three-Armed randomized multicenter clinical

trial. *J Refract Surg*. 2017;33(10):655-662. doi:10.3928/1081597X-20170504-04

19. Bilbao-Calabuig R, Llovet-Osuna F, González-López F, Beltrán J. Nd:YAG Capsulotomy Rates With Two Trifocal Intraocular Lenses. *J Refract Surg*. 2016;32(11):748-752. doi:10.3928/1081597X-20160803-02

20. Hill W, Carson D, Hong X, Karakelle M. Optical bench performance of Acrysof® IQ reSTOR® , AT LISA® tri, and FineVision® intraocular lenses. *Clin Ophthalmol*. 2014;8:2105–2113. doi:10.2147/OPTH.S66760

21. ISO-11979-7:2018. Ophthalmic implants - Intraocular lenses - Part 7: Clinical investigations. 2018.

22. Riusala A, Sarna S, Immonen I. Visual function index (VF-14) in exudative age-related macular degeneration of long duration. *Am J Ophthalmol*. 2003;135(2):206-212. doi:10.1016/S0002-9394(02)01832-9

23. Morlock R, Wirth RJ, Tally SR, Garufis C, Heichel CWD. Patient-Reported Spectacle Independence Questionnaire (PRSIQ): Development and Validation. *Am J Ophthalmol*. 2017;178:101-114. doi:10.1016/j.ajo.2017.03.018

24. Mcneil B. Grading of ocular inflammation in uveitis: an overview. *Eyenews*. 2016;22(5).

25. Mendicute J, Úbeda M. Opacificación y contracción de la cápsula anterior. In: Ramón Lorente JM, ed. *Cirugía Del Cristalino*. Sociedad Española de Oftalmología (SEO); 2008:1695.

26. Tetz MR, Auffarth GU, Sperker M, Blum M, Volcker HE. Photographic image analysis system of posterior capsule opacification. *J Cataract Refract Surg*. 1997;23(10):1515-1520. doi:10.1016/S0886-3350(97)80022-3

27. Fernández J, Rodríguez-Vallejo M, Martínez J, Tauste A, Piñero DP. Patient selection to optimize near vision performance with a low-addition trifocal lens. *J Optom*. 2020;13(1):50-58. doi:10.1016/j.optom.2019.06.003

28. Jabs DA, Nussenblatt RB, Rosenbaum JT, et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509-516. doi:10.1016/j.ajo.2005.03.057

29. Neuhann IM, Kleinmann G, Apple DJ. A New Classification of Calcification of Intraocular Lenses. *Ophthalmology*. 2008;115(1):73-79. doi:10.1016/j.ophtha.2007.02.016

30. Rodríguez-Vallejo M. Refractive Analysis. 1.0.5. A Matlab toolbox for the analysis of refractive results in anterior segment surgery. http://test-eye.com/index.php/en/refractive-analysis. Published 2020. Accessed October 25, 2020.

7 APPENDIX B: SUMMARY OF VISITS AND CONDUCTED TESTS

Procedures	**Phone Call Interview**	**Study Visit (Day 0 or Day 45 ± 7)**
Phone Call Eligibility	X	
Verbal Consent	X	
Medical History / Adverse Events	X	X
VF-14 Questionnaire	X	
PRSIQ Questionnaire	X	
Additional Questions	X	
Study Visit Eligibility		X
Written Consent		X
Implanted IOL Power		R
Slit Lamp		RE / LE
Subjective Refraction		RE / LE
UDVA		RE / LE / Bino
CDVA		RE / LE
UIVA		RE / LE / Bino
DCIVA		RE / LE
UNVA		RE / LE / Bino
DCNVA		RE / LE
CSDC		R
Light Distortion Analyzer		R
PENTACAM		
Irregular astigmatism 4 mm		R
Total regular astigmatism		R
Spherical aberration for mesopic pupil		R
Intraocular Lens Position		R
IOL MASTER		
Axial length		R
Mean Corneal Power		R
KERATOGRAPH 5M		
Photopic pupil diameter		R
Mesopic pupila diameter		R

RE: Right eye measurement
LE: Left eye measurement

Bino: Binocular vision conditions

R: A single eye RE or LE randomly selected at the Study Visit

8 APPENDIX C: ADDITIONAL QUESTIONS

Original questions were conducted in Spanish. Translation has not been validated.

How satisfied are you nowadays with your vision without spectacles in ...

	Very Unsatisfied	Unsatisfied	Neutral	Satisfied	Very Satisfied
Far (1.5 meters or more)	☐	☐	☐	☐	☐
Intermediate (Between 1.5 meters and 45 cm)	☐	☐	☐	☐	☐
Near (Menos de 45 cm)	☐	☐	☐	☐	☐

	Nothing bothering	A Little Bit bothering	Neutral	Bothering	Very Bothering
How bothering are the light effects around the lights at night? For example, streetlights, headlights or taillights of cars	☐	☐	☐	☐	☐

	Very unlikely	Unlikely	Neutral	Likely	Very likely
If you were operated on again, is it likely that you would decide to be implanted with the same intraocular lens?	☐	☐	☐	☐	☐