Measurement of axial refraction following implantation of LS-313 MF30 Multifocal intraocular lens

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PROTOCOL
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Reliable objective refraction after implantation of LS-313MF30 Multifocal intraocular lens (Oculentis GmbH)

Subject	Determination of the refraction after implantation of the multifocal MICS intraocular lens LS-313 MF30 from Oculentis GmbH in Berlin
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Content

1. BACKGROUND

Since 2012, the asymmetric multifocal posterior chamber lens MICS LS-313 MF30 (Oculentis GmbH, Berlin, Germany) has been implanted in the Department of Ophthalmology Neubrandenburg following cataract surgery in suitable patients.

To determine the refraction after the implantation of an asymmetric multifocal intraocular lens we have used the eye refractometer PR 60 or PR 50 (Rodenstock, Munich). This manual refractometer projects test mark images onto the retina of the eye via a measuring beam path, which are viewed via a coaxial observation beam path and are manually focused.
So far, this is our only objective way to measure the different focal points of the multi-focals lens.

Furthermore, we have the opportunity to determine the distance and near refraction subjectively. The accuracy of this method, however, depends on the cooperation of the patient.

The manual eye refractometers PR 60 and PR 50 (Rodenstock, Munich) work with light cones of 3 mm diameter.
The optic of the LS-313 MF30 intraocular lens has a diameter of 6 mm, half of the optic is used for far vision, half for near vison. Under ideal conditions (pupil becomes maximally dialated; no peripheral capsule opacity or secondary cataract cover the peripheral part of the optic)the Rodenstock refractometer aproides a sharp image on the fundus.
However, usually it is not possible to image the entire light cone of the Rodenstock refractometer on the retina in case of a non-maximally dialated pupil, a peripheral secondary cataract or a peripheral capsule opacification or an anterior capsular phimosis. Therefore, sometimes the separate determination of the axial refraction for the near and the far part is not sufficiently accurate.

The new iTrace device (TraceyTechnologies, Housten, Texas, USA) could provide more accurate measurement results. This wavefront device uses significantly smaller cones of light (about 1mm) that should allow you to determine more accurate readings in multifocal optics.
A reliable objective refraction is required if patients fail to achieve sufficient visual acuity after the implantation of a multifocal IOL.
This study will investigate whether the new iTrace device (Tracey Technologies, Housten, Texas, USA) is suitable for precisely measuring the far and near part of the LS-313 MF30 Intraocular Lens.
Comparative devices are the refractometer PR 50 or PR 60 (Rodenstock, Munich), the determination of the subjective refraction and the determination of the refraction with auto-refractometers, which are available at the Department of Ophthalmology Neubrandenburg.

2. SYNOPSIS

2.1 Study objective

This study protocol is designed to collect postoperative refraction readings follow implantation of a multifocal Intraocular Lens (LS-313 MF30) with the following devices:

- Eye Refractometer PR 60 or PR 50 (Rodenstock, Munich),
- ITrace (Tracey Technologies, Housten, Texas, USA),
- Autorefraktor Mod. ARK-760A (NIDEK CO, LTD, Gamagõri, Japan),
- Autorefractor Mod. ARK-560A (NIDEK CO, LTD, Gamagõri, Japan),
- Autorefractor KR-800s (TOPCON, Willich, Germany),
- Combined keratometer and aberrometer KR-1W (TOPCON, Willich, Germany).

The subjective refraction is additionally determined as a reference method.

The purpose is to find an accurate objective method for measuring refraction in patients with multifocal lenses of the type LS-313 MF30.

2.2 Study population

- 100 eyes should be included in the study

2.1.1 Inclusion criteria for patients

- Patients after cataract surgery with implantation of the MICS-IOL LS-313 MF30 and complete postoperative corneal clearing
- At least 18 years of age
- Signed consent form

2.1.2 Exclusion criteria for patients

- Patients with corneal opacities that interfere with the refraction measurements
- Patients with posterior capsule opacity already developed, which interferes with the refraction measurement, if the patients refuse the removal of the secondary cataract.

2.3 Study design

- prospective, monocentric study

2.4 Study investigation plan

- a prospective postoperative examination at the Department of Ophthalmology Neubrandenburg
- retrospective collection of surgical data from the medical record of the Department of Ophthalmology at the Dietrich-Bonhoeffer-Klinikum, Neubrandenburg

3. OBSERVATION PERIOD

The patients participating in the study will be examined once in the Department of Ophthalmology of the Dietrich-Bonhoeffer-Klinikum Neubrandenburg.

4. EXECUTION

4.1 Patient recruitment

Patients who received the multifocal lens LS-313 MF30 in Neubrandenburg at one or both eyes will be asked to participate in this observational study.

4.2 Insurance

A patient and travel insurance is taken out before the start of the study.

4.3 Patient identification

After completion of the data collection, each record will be encrypted.

4.4 Documentation

A data collection form (attachment) is used. The following intraoperative information is collected retrospectively from the electronic patient file of the Dietrich-Bonhoeffer-Klinikum:

- Name and address of the patient
- Date of Birth
- Date of surgery
- Surgeon
- Operated eye (OD/OS)
- Performed cataract surgery with or without femtosecond laser
- Refractive power of the MICS IOL

The following postoperative information will be collected prospectively within the examination date, for the respective patient's eyes treated with the LS-313 MF30 Multifocal Lens:

- postoperative objective refraction values using auto-refractors in miosis
- postoperative objective refraction values using the PR 50 and 60 (Rodenstock, Munich)
- postoperative objective refraction values using the KR-1W (TOPCON, Willich, Germany)
- postoperative objective refraction values, pupillometry, topography and aberrometry with the iTrace in miosis and mydriasis (Tracey Technologies, Housten, Texas, USA)
- postoperative subjective refraction values with and without correction for the determination of the far and near vision
- pupil width in miosis and mydriasis
- corneal condition
- Assessment of vision impairment by the anterior capsule
- Centering of the intraocular lens
- IOL axis according to TABO scheme
- Assessment of the clarity of fundus insight

A data collection sheet serves as documentation and will be transferred into the Excel database (version 14.0.7166.5000/32-Bit, Microsoft, USA) by the study assistants.

4.5 Study investigations

The study will collect the data as follows:

4.5.1 Ophthalmological history

Available data of the general and ophthalmological anamnesis are collected from the existing patient record. This includes general and ophthalmic medication, past medical conditions, past operations, the surgery date, operated eye,pre-op IOL master, surgeon,femto laser if used and refractive power, type and manufacturer of implanted intraocular lenses.

4.5.2 Uncorrected distance and near vision

- ETDRS panel / Snellen panel CAT. NO. 2110 (Precision Vision, Illinois, USA) is used for uncorrected distance vision evaluation. A reading chart is used to test uncorrected reading vision.

4.5.3 Best corrected visual acuity for distance

- ETDRS panel / Snellen panel CAT. NO. 2110 (Precision Vision, Illinois, USA):) is used for corrected distance vision evaluation. A reading chart is used to test corrected reading vision.
A trail frame is used to determine

4.5.4 Refraction determination in miosis using autorefractometers

a) Refractometer/Keratometer, Mod.ARK-760A (NIDEK CO.,LTD, Gamagõri, Japan)
(Location: Cataract center, room B.5.49)

Refraction values will be measured automatically.

b) Auto Kerato Refractometer KR-800s (TOPCON, Willich, Deutschland).
(Location: Functional diagnostics, room B.5.45/46):

Refraction values will be measured automatically. In addition, pupil size will be recorded.

c) Autorefactometer ARK-560A (NIDEK CO,LTD, Gamagõri, Japan)
(Location: Ambulance, room B.6.33.1)

Refraction values will be measured automatically.

4.5.5 Refraction determination in miosis using combined Kerato- and Aberrometer KR-1W (TOPCON, Willich, Germany)

(Location: Functional diagnostics, room B.5.45/46)

Refraction and pupil size will be measured automatically.

4.5.6 Refraction determination in miosis using Purkinje reflex and different optical WF measurement zones of the iTrace device (Tracey Technologies, Housten, Texas, USA)

The room lighting is darkened and the window blinds closed. The patient is positioned with the chin on the chin rest and the forehead on the forehead rest. Afterwards, the patient's head is turned slightly sideways so that the iTrace measuring head can be moved towards the patient's eye. The eye not to be examined is first covered with an occluder which the patient himself holds in his hand. The patient is asked to look through the iTrace device and fix a distant object. It is important to ensure that nothing blocks the patient's gaze, as this affects the patient's accommodation and may result in unwanted refractive readings.
Now select the single red wavefront icon (manual measurement) in the upper right corner of the screen to start a WF scan. The white target is first positioned on the edge of the entrance pupil, outside the center. At the same time, the iTrace device is moved back and forth to focus the iris details and thus set the most suitable measurement level. The 4 white dots (4 IR points) in the center of the pupil represent the Purkinje reflexes that are used to center the following measurements (center of 4 points). The patient is asked to focus the red light. Now the assistant presses the Enter key to make the red scan points visible. For the first measurement the separate 1 mm scan button (64 points) is selected. The scan pattern is centered on the center of the 4 white dots (Purkinje reflexes). The patient is asked not to move, to blink twice and then open both eyes wide. The fixation light is switched off with F10. Pressing the button on the joystick triggers the measuring process. If all wavefront measurement points are validly evaluable (visible within the pupil), the measurement is saved by confirming the green check mark symbol. Otherwise, the measurement has to be repeated until a valid evaluation is possible.
For the 2nd, 3rd and 4th measurement, the red wavefront symbol is selected again, followed by the Enter key and selecting 2, 3 or 4 in the keypad to move the measurement zone to 2, 3 or 4 mm. At the same time, the iTrace measuring module is held firmly in place with one hand and moved only slightly backwards to remain in the measuring plane. The respective measuring processes for the 2, 3 and 4 mm measuring zones are carried out analogously to the procedure described above for 1 mm measurement, checked for validity and saved.
The data collection for the 4 measurement zones is carried out using the WF Verification Display by selecting the respective WF measurement individually in the patient main menu and confirming with the blue arrow pointing to the right. The refraction value (Sph, Cyl and Axis) is shown in the WF verification display. Furthermore, the SE spot in the RSD (Retinal Spot Diagram) is set as distortion-free as possible by pressing the F1 and F2 keys to determine the focus of the Spherical Equivalent. Care must be taken to ensure that the outermost color ring is used for the evaluation, which ensures a symmetrical setting (orientation rather to the green ring). The indicated defocus value corresponds to the opposite numerical value of the refraction, therefore plus values must be raised with minus values and minus values must be raised with plus values.

4.5.7 Determination of Corneal Topography in Miosis using the iTrace (Tracey Technologies, Housten, Texas, USA)

Immediately after the wavefront measurements, 3 topographic images are taken. Therefore, a bright illumination light is projected onto the patient's cornea by the device. Now the single circular blue topography icon (manual measurement) in the upper right corner of the screen is selected to start a CT scan.
By means of the joystick, the green, central Placido circle will be positioned in the middle of the yellow quadrangular target by horizontal and vertical adjustment.

The picture is accurately centered when the dark green ring turns light green. It should be noted that the laser focus is always situated at the right side of the yellow square target.. The iTrace device is now moved slowly towards the patient until the white laser focus point crosses the center of the green ring and the yellow target. During the approach, the software will automatically start to track the laser focus point (a red cross will appear). The iTrace device will then automatically take the measurement when the bright green ring and the yellow target are exactly centered and the white laser focus points move slowly through the bright green circle. The CT-Verfication Display, which is now automatically displayed, checks whether the measurement is valid (uniformly visible Placido circles and no eyelids in the measurement area). Afterwards the valid measurement is saved by pressing the green tick. A total of 3 valid measurements are collected and saved. Using the Compare function, the 3 measurements are qualitatively compared with each other and the recording with the smallest deviations marked with an * asterisk in the note field.
The topography image with the * asterisk is individually evaluated, without selecting a WF measurement, using the CT-Verification Display (in the patient's main menu, the right-pointing blue arrow) and the SIM-K values K1 and K2 as well as the flat corneal axis by K1 are collected.

4.5.8 Determination of pupillometry in Miosis using the iTrace (TraceyTechnologies, Housten, Texas, USA)

The pupillometry is obtained from the performed WF and CT scans. Therefore, the WF image with 3 mm measurement zone and the specified CT image with the * asterisk are selected simultaneously in the main patient menu. Angle K/A (Cataract Evaluation menu) displays the pupil size and decentence distance, as well as the axis of the Kappa angle and Alpha angle.

4.5.9 Determination of HOA (Higher Order Aberrations) in Miosis using the iTrace (TraceyTechnologies, Housten, Texas, USA)

The evaluation of Higher Order Aberrations (HOA) is also recorded with the WF image of the 3 mm measurement zone and the simultaneously selected CT measurement with * asterisks. The right-pointing blue arrow in the main patient menu has to be clicked on, which opens the WF and CT Summery Display. Chang Analysis is selected subsequently and by clicking the right mouse button and selecting the combined display the individual displays of the total, internal and corneal aberrations are opened. For the total eye, internal (calculated value of the implanted IOL) and cornea, the displayed aberration value for HO Total, Spherical Aberration and Astigmatism is documented respectively.

For all further examinations, the pupils are artificially dilated with neosynephrine-POS 10% eye drops and Mydrum eye drops.

4.5.10 Visus determination in Mydriasis using Autorefractometers:

For all three autorefractometers, following the standard miosis measurement, it is tested whether reliable refraction readings can be obtained for the far and near parts of the IOL by focusing on the lense's upper and lower halves of the dilated pupil.

20 to 30 minutes after drug dilatation of the pupils (depending on the reaction of the patient's eye), the procedures listed under 4.5.4.a, b and c are repeated. By contrast, this measurement should initially focus on the upper half of the lens, as far as possible. When the device has triggered and the measured values have been

collected, the data is transferred to the electronic patient record in FIDUS and saved. Subsequently, the process for the lower part of the lens is repeated.

If values scatter too high in 5 to 10 measurements this test procedure is completely stopped and carried on with point 4.5.6.

Pupil width in mydriasis is carried out with the Auto Kerato Refractometer KR-800s (TOPCON, Willich, Germany). This is achieved by pressing the "corneal diameter" button (description under 4.5.4.b)). A measurement window with two positioning bars appears. Moving the bars to the right and left of the eye using the displayed control keys will display the width of the pupil.

4.5.11 Determination of the focal point in the far and near part of the intraocular lens in Mydriasis using the eye refractometer PR60 or PR50 (Rodenstock,Munich)

(Location: PR50 Cataract center, room B.5.50, Ambulance, room B.6.31+32
PR60 Ambulance, room B.6.35)

The doctor ensures that the scale of the observer eyepiece is set to 0, or that his own ametropia is correctly taken into account. It is important that the patient's pupils are sufficiently dilated, since the visible annular illumination zone must be placed completely or at least for the most part in the patient's pupil plane. The doctor looks at the test mark images on the retina on the observation beam path and focuses them. The measured value is then read from a scale in diopters. This measuring process is carried out for the far part as well as for the near part of the IOL. For this purpose, the investigator tries to irradiate most of the annular illumination beam path through the far or near part of the IOL.

4.5.12 Determination of the focal point in the far and near part of the intraocular lens in Mydriasis using the iTrace (TraceyTechnologies, Housten, Texas, USA)

(Location: functional diagnostics)

The room lighting is darkened and the window blinds closed. The patient is positioned with the chin on the chin and forehead on the appropriate rests. Afterwards, the patient's head is turned slightly sideways so that the iTrace measuring head can be moved towards the patient's eye. The patient is asked to look through the iTrace and focus on a distant object. It is important to ensure that nothing blocks the patient's gaze, as this affects the patient's accommodation and may result in unwanted refractive readings.
The following measurements are taken in manual mode by selecting the single red wavefront icon in the upper right corner of the screen. The white target is first positioned on the edge of the entrance pupil, outside the center. At the same time, the iTrace is moved back and forth to focus on the iris details and thus set the most suitable measurement plane. The patient is asked to focus on the red light. Pressing the Enter key makes the red scan points visible. For the following measurements the separate 1 mm scan button (64 points) is selected. The scan pattern is centered on the optic center of the implanted multifocal lens. It is important to ensure that the scan pattern is located exactly between the two lens markings of the optics. The patient is asked not to move, to blink twice and then open both eyes wide. The fixation light is switched off with F10. Pressing the button on the joystick triggers the measuring process. If the wavefront measurement points are validly evaluable (visible within the pupil), the measurement is confirmed and saved by selecting the green check mark symbol. Otherwise, the measurement is repeated until a valid evaluation is possible.
Subsequently, a decentered measurement is carried out, 1.5 mm away from the optical center of the multifocal lens in the IOL far and near part, respectively. It is decentered at right angles to the apparent IOL markers and the 1 mm scan pattern is moved from the IOL center 1.5 mm (estimated based on the presented

1 mm grid) into the far or near part of the multifocal lens. In the decentered measurements, care is taken to measure the entire 1mm scan pattern within the pupil and not be affected by iris margins. The measurement in the far part of the multifocal lens is recorded as data point 1.5 mm upwards. The measurement in the near portion of the multifocal lens is recorded as a data point 1.5 mm downwards.
The data collection for the central measurement and the two 1.5 mm decentered measurements are carried out with the WF Verification Display. For this purpose, the respective WF measurement is selected individually without CT measurement in the patient main menu and confirmed with the blue arrow pointing to the right. The refraction value (Sph, Cyl and Axis) is shown in the displayed WF verification window. Furthermore, the SE spot in the RSD (Retinal Spot Diagram) is set as distortion-free as possible by pressing the F1 and F2 keys to determine the focus of the Spherical Equivalent. Care must be taken to ensure that the outermost color ring is used for the evaluation, which guarantees a symmetrical setting (oriented more towards the green ring). The indicated defocus value corresponds to the opposite numerical value of the refraction, plus values must be raised with minus values and minus values must be raised with plus.

4.5.13 Objective determination of the IOL position in the capsular bag based on Sirius Scheimpflug images (Bon-Optik, Lübeck)

(Location: Functional diagnostics)

The patient is asked to look straight ahead at the red light spot. The study assistant sees the patient's anterior segment of the eye after starting the program. By moving the joystick back and forth, the operator now adjusts the cornea and pupil center to the displayed areas on the screen. The patient is asked to blink again and then leave the eye wide open. If the patient can not do this alone, the upper lid is stopped with a cotton swab. Pressing the start button on the joystick starts the recording. The Scheimpflug camera now takes 36 pictures, while the camera rotates around the patient's eye. It is important that the patient keeps looking straight ahead until the recording is completed. The program automatically saves this recording for each eye. The employee then finds the most vertical (measurement at 180°) and the most horizontal (measurement at 90°) image out of all recorded images. These study-relevant images are transmitted by the established transfer function in the electronic medical record in FIDUS. In order to calculate the tilt position of the IOL accurately, the stored images are anonymized and forwarded to the company Oculentis.

4.5.14 Slit lamp microscopy in Mydriasis

(Location: Ambulance, room B.6.31, B.6.32, B.6.35)

The investigator carries out the ophthalmological examination via a microscope. It is used to observe the eye under high magnification to assess the anterior, middle and posterior structures of the eye and to document any abnormalities or anomalies.
After disinfection of the chin and forehead rest, the patient places his head in the appropriate device. With the aid of various enlargements, the examining doctor has the opportunity to observe the anterior section of the eye in diffuse light first. These include the eyelids, the cornea, the conjunctiva, the anterior chamber, the iris and the pupil. The light is then limited to a slit of about 0.5 mm. This is done by a controller that can individually set the slit size. Now, the front structures are shown by pivoting the slitter from different sides in different light incidence angles of the slit light in section.
Subsequently, the assessment of the multifocal intraocular lens is performed. The investigator examines the IOL through the slit for translucency, both in progressive and in regressive light, assesses the anterior capsule and determines

the diameter of the rhexis. Furthermore, it is checked whether the lens sits in the middle of the rhexis or whether it may have come to a decentration. By rotating the slit, the axis position of the multifocal IOL can now be examined. The narrow slit is turned so that it runs parallel to the visible axis of the IOL. Then the investigator can read the axis position on the slit lamp according to the TABO scheme.
For the assessment of the posterior structures of the eye – vitreous, optic nerve and retina or macula – the investigator additionally requires a 90-dpt magnifying glass. The investigator manually places the magnifying glass about 3 cm in front of the patient's eye with progressive light.
Finally, after completion of all examinations, the examiner documents the findings in the data collection sheet as well as the electronic patient file in FIDUS.

5. STATISTICAL EVALUATION

The data to be documented are transferred from the electronic patient record and the data collection sheet into an Excel spreadsheet by the study assistants. The patient's name, first name, date of birth, and address are not transferred. The personal data will be replaced by a serial number. Due to this serial number, it can no longer be associated with any particular individual.

The data is then transferred to the program STATISTICA (StatSoft, Inc., Hamburg, Germany) and evaluated.

Main question: Which of the refraction measurement methods allows an accurate and reproducible refraction determination after implantation of a multi-focal intraocular lens LS-313 MF30? The reference method is the determination of the subjective refraction.

6. ETHICAL ASPECTS

Prior to commencement of studies, the local laws, regulations and official guidelines require approval from the Greifswald Ethics Committee and the responsible regulatory authority.

7. DATA PROTECTION

The identification of the patients participating in the study and the patient-related information will be treated confidentially. The protection of the data of the patient is always guaranteed. All personal data of the patient will be pseudonymised (see above).

The patient data determined during the study are first documented on the data collection form. Each patient is assigned a sequential identification number. The data is transferred to the Excel data table with this identification number. In a separate patient list, which is stored in the study folder, the identification numbers are assigned to the patient. Only the study team has access to this study folder. The study assistant ensures that it is no longer possible to draw any conclusion from the data stored in Excel to the respective patient.

In the case of publication of the study results no personal data may be used. The medical staff responsible for the transfer of the data from the patient record must be informed about their data protection responsibility.

Upon completion of the study, the investigator will be required to archive the identification list and documentation of the data collected in the study for at least 15 years in paper format.

8. SAFETY

The risk of an adverse event is low in this study because only measurements are taken on different devices and no eye surgery is performed.

Adverse events related to the necessary investigations that are to be expected are listed here:

- in Mydriasis (dilation of the pupil)
  - glare sensitivity
  - allergic reaction
  - continuous dilation over 2 to 3 days

- Accident on the way to the investigations

To safeguard the patients, study and travel insurance are taken out.

9. COMPENSATION

The sponsor pays to the principal investigator an amount of € 3,500.00 for the preparation of the study protocol after the invoice has been issued. For each collected and usable dataset, the sponsor pays a study fee of € 250.00 to the account of the Dietrich-Bonhoeffer-Klinikum, Neubrandenburg. The sponsor pays the head of the clinical trial or his representative a fee of approximately € 2,000.00 for the statistical evaluation after the invoice has been issued.

10. SIGNATURES

I have read the study procedures described in this protocol and I agree to comply with them.

Prof. Dr. med. H. Höh
- Chefarzt der Augenklinik -

Name of the Principal Investigator of the clinical trial (in block letters)

Signature of the Principal Investigator of the clinical trial

Neubrandenburg 02-MAR-2017

Place, date

KLISHKO, VITALIY

Name of the Sub Investigator (in block letters)

Klishko

Signature of the Sub Investigator

Neubrandenburg, 02-MAR-2017

Place, date

CONFIDENTIAL

This protocol contains confidential proprietary information about clinical products of Oculentis GmbH Berlin. I agree to treat this information confidentially and not disclose it to third parties as of the date of this Agreement or until such information becomes public knowledge.