

Oculentis GmbH, Berlin

PROTOCOL Version A

Study to determine the PCO (Posterior Capsule Opacification) rate of the MICS –(Micro InCiSion) intraocular lens L-313

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Study to determine the PCO (Posterior Capsule Opacification) rate of the MICS –(Micro InCiSion) intraocular lens L-313

Title	Determination of the PCO rate after the implantation of the MICS intraocular lens L-313 of the company Oculentis GmbH in Berlin
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1. BACKGROUND

In recent years scientific researches showed that the PCO rate of MICS intraocular lenses may be higher than the PCO rates known from conventional intraocular lenses (IOLs). Until now, from our own studies, 5 MICS intraocular lenses showed significantly higher PCO rates.

Since September 2008, the intraocular posterior chamber MICS lens L-313 from OSD Medical GmbH, Berlin, Germany, has been used in the Department of Ophthalmology, Dietrich-Bonhoeffer-Klinikum, Neubrandenburg following cataract surgery.

Months or years after this surgery, opacification of the posterior lens capsule with corresponding visual impairment may occur. With the help of a Nd:YAG laser, this so-called secondary cataract, can usually be eliminated quickly and painlessly.

2. SYNOPSIS

2.1 Aim of the study

This study protocol is designed to collect surgical and postoperative information to determine the PCO rate and PCO dynamics of the MICS L-313 intraocular lens. Depending on the result, these findings may influence the further development of the intraocular lens L-313.

2.2 Population

- Up to 3000 patient's eyes should be recruited
- Patients after cataract surgery with implantation of MICS-IOL L-313

2.1.1 Inclusion criteria for the patients

- Willingness to give written consent
- Patients after cataract surgery with implantation of the MICS IOL L-313
- Age of 18 years or older

2.1.2 Exclusion criteria for the patients

- Patients having their residence outside the area of our referring ophthalmologists of Neubrandenburg
- Patients who die within the observation period

2.3 Study-design

- retro-/prospective, monocentral study

2.4 Study-investigation-plan

- intraoperative und postoperative data gathering from the medical records
- Filing a questionnaire to the patients, asking for diagnosis and treatment of PCO (if necessary, a postoperative examination in the Department of Ophthalmology Neubrandenburg in order to determine the PCO, if no PCO was documented or if not known)

2.5 Safety-related results

- Occurrence of intraoperative and postoperative adverse events

3. DURATION OF THE STUDY

The patients participating in the study had undergone cataract surgery at the Department of Ophthalmology in Neubrandenburg. Thus, the date of the operation is known.

The duration of the observation is dependent on the duration of the postoperative period to the diagnosis of the PCO or until the exclusion of the PCO due to the information provided by the patient or by the treating ophthalmologist for each individual patient. The observation period and thus also the study period therefore varies with each patient.

The period for data collection started with the first implantation of the intraocular lens L313 in September 2008 and is scheduled to end in December 2016.

4. IMPLEMENTATION

4.1 Screening

The selection of patients is carried out by the documentation books kept in the operating rooms of the Department of Ophthalmology and the respective surgical reports. Once a patient meets the inclusion criteria, the patient is contacted and asked to participate in the study.

4.2 Patients recruitment

For statistical evaluation, the number of cases is determined using the following formula * before patient recruitment.

$$n = 16 \times \frac{\delta^2}{d^2}$$

n=Subjects number
δ=Standard deviation
d= relevant difference

$$n = 16 \times \frac{0,492^{2**}}{0,1^2} = 387,88 \approx 388 \text{ Patients}$$

80% of the patients eligible for the study underwent surgery 3 to 5 years ago. At a follow-up period of 3 to 4 years, the response rate is 13.9% ***.

This results in:

$$n = \frac{388}{0,139} = 2.791,37 \approx 2.792 \text{ Patients}$$

Due to the relatively high average age (at the time of the operation) of 74.73 years, an even lower response rate is to be expected. For this reason, up to 3000 patients will be contacted.

The patient receives the patient's study information sheet, the declaration of consent as well as an informative sheet for the patients regarding PCO. While retaining one copy of these documents, the patient is required to return the other copy and the completed data collection form to the eye clinic. Only when the signed declaration of consent is present, the patient participates in the study.

*Kutschmann M et al. Aspekte der Fallzahlkalkulation und Powerberechnung anhand von Beispielen aus der rehabilitationswissenschaftlichen Forschung. Rehabilitation 2006;45:377-384

** Zur Vergleichsbasis sind 2 Publikationen mit dem Thema der nachstarquote herangezogen worden:

1. Peterman K, Wildgrube M „A-Konstante und Nachstarquote der Intraokularlinse Akreos™ AO MI-60“, Oktober 2009,
2. Spyridaki M, Höh H „Vergleich von 4 MICS-Intraokularlinsen (ThinLens, AcriSmart, CareFlex, und Acriflex) im Hinblick auf ihre Neodym:YAG-Laser-Kapsulotomieraten“ April 2009

***Renquist K, Jeng G, Mason EE Calculating Follow-up Rates. Obes Surg. 1992; 2(4):361-367

4.3 Patients identification

Upon completion of the data collection, each patient / patient eye will be provided with a unique patient identification code. This code is used for study purposes only. During and also after completion of the study, the patient can only be identified by the study doctor or the head of study center.

4.4 Documentation

The data is collected via the Excel program (Version 14.0.7166.5000/32-Bit, Microsoft, USA). The intraoperative information is taken from the surgical books and the respective surgical reports. The following data is recorded.

- Operation Date
- Name and address of the patient
- Date of birth
- Which eye (right/left)
- Anesthesia
- Power of the MICS-IOL
- Surgeon
- Intraoperative parameters (Phaco time, Phaco machine, Hardness of the lens, etc.)
- Intraoperative special features/complications

The postoperative documentation is taken from the charts or the questionnaire filled in by the patient. Here, the patient should indicate (if possible with a date) whether a Nd:YAG laser treatment has already been performed on the operated eye. If a patient does not provide clear information due to ignorance, then the respective registered ophthalmologist will be contacted.

In patients without a previously diagnosed or treated PCO (in the hospital or at the ophthalmologist), the information date is documented instead of the laser date. If necessary, the patient will be brought to the hospital once in order to assess the present capsule opacity.

4.5 Postoperative Examination

Only if the planned number of 388 eyes is not reached by sending a questionnaire to the patients, the patients, who could not provide information because of uncertainty, are brought to the Eye Hospital Neubrandenburg for the assessment of the postoperative PCO. In this case, a proband study insurance and a travel insurance will subsequently be paid.

As part of the study, the following investigations are then carried out:

- a) General and ophthalmological patient's history
 - Questionnaire on general and ophthalmological medication
 - General pre-existing conditions
 - Previous operations
- b) Best corrected visual acuity
 - ETDRS Panel / Snellen Panel: Letters on panels with decreasing size from top to bottom to determine the visual acuity
- c) Slit lamp examination
 - Eye examination with the help of a microscope to observe the eye under high magnification to assess the anterior, middle and posterior structures of the eye
- d) Assessment of posterior capsule (possibly with dilated pupil)

The newly obtained findings are then supplemented in the data collection table.

5. STATISTICAL ANALYSIS

For data protection reasons, all data of the patient are immediately pseudonymized after collection. The head of the study center ensures that it is no longer possible to draw any conclusions about the respective patient from the data collected.

The data are evaluated with the computer program STATISTICA (Version 10, StatSoft GmbH, Hamburg, Germany) using the Kaplan-Meyer analysis.

The main question is the determination of the PCO rate after implantation of the MICS intraocular lens L-313 under the conditions prevailing in Neubrandenburg.

6. ETHICAL ASPECTS

Prior to the start of the study, a documented approval from the Greifswald Ethics Committee and the relevant regulatory authority will be obtained in accordance with local laws, regulations and authorities. If necessary, an extension, renewal or supplement to the permit must be obtained and forwarded to the sponsor.

7. SAFETY

For any adverse events that have occurred or may have occurred, the local laws and regulations as well as the reporting system of the manufacturer must be considered and followed.

7.1 Adverse events

An adverse event (AE) is an adverse medical event, accidental illness or injury, or adverse clinical sign in a study subject during the observation period, with or without association with the MICS L-313 intraocular lens.

All study eye AEs must be recorded in the data collection table. Each AE must be classified according to the degree of damage to the patient, as well as with respect to the IOL or its implantation procedure.

AEs are classified as follows:

- MILD: Complaints without interruption of the daily routine
- MODERATE: Complaints that reduce or affect daily routines
- SEVERE: Disability with inability to work or to cope with normal daily routine

Changes in a chronic condition or illness are not considered to be AEs.

Cataract surgery-related AEs to be expected are listed here:

- Anterior capsular tear
- Posterior capsular rupture
- Vitreous humor in the anterior chamber
- Intraoperativ hyphema
- Loss of vitreous humor
- Choroid bleeding, effusion or detachment
- Iris injury or trauma
- Corneal damage
- Zonular dialysis
- Fibrin reaction
- Persistent Hyphema
- Corneal clouding, corneal edema
- Retinal complications
- eye movement disorders

7.2 Severe adverse events

An AE is classified as severe without considering the relationship with the IOL when:

- If it leads to death
- If it leads to a significant deterioration of health
 - life-threatening illness
 - permanent impairment of a body part / body function
 - inpatient treatment or extension of inpatient stay is necessary
 - surgical intervention necessary

All serious adverse events (SAEs) must be reported to the sponsor within one week of the occurrence of the event.

8. INVESTIGATOR'S SIGNATURE

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

Prof. Dr. med. H. Hüh
• Chefarzt der Augenklinik •

Name of Investigator in block letters:

Michael Hüh *15-September-2015*

Signature of Investigator:

Date:

Name of the sponsor of the clinical trial in block letters:

A. Hüh *15.09.2015*

Signature of the sponsor of the clinical trial:

Date:

CONFIDENTIAL

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