Clinical Investigation Title: CT Lucia 601 IOL implantation in the sulcus

The CT Lucia in the sulcus study is a non-commercial (academic with study grant), monocentric, post-interventional observational without use of a study drug.

Clinical Investigation Acronym: CTLucia in the sulcus

Sponsor	*UZ Leuven*
Principal Investigator	*Prof. dr. Peter Stalmans*
Sponsor Reference Number	*S64878*
Version Number and Date	*CLus study Version 3 08022021*

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, regulatory authorities, and members of the Research Ethics Committee.

CLINICAL INVESTIGATION PLAN AUTHORISATION

Principal Investigator Name: Peter Stalmans Title: prof. dr. Signature: Date: Site: UZ Leuven
Statistician Name: Jean-François Fils, Ars Statistica Title: Medical statistician Signature: Date:
Sponsor Name: UZ Leuven Title: Signature: Date:

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This CIP describes the investigation of the CT Lucia 601 IOL implantation in the sulcus. This paper provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the clinical investigation. Problems relating to this clinical investigation should be referred, in the first instance, to the Principal Investigator.

This clinical investigation will adhere to the principles outlined in the ISO 14155:2011. It will be conducted in compliance with the CIP, the Data Protection Act and other regulatory requirements as appropriate.

1. AMENDMENT HISTORY

Amendment No.	CIP Version No.	Date Issued	Author(s) of Changes	Details of Changes

2. LIST OF APPENDICES

Appendix A	Investigator's Brochure
Appendix B	Protocol of the study
Appendix C	Inform Consent Form

3. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BCVA	best-corrected visual acuity
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee (see REC)
GCP	Good Clinical Practise
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IRB	Independent Review Board
Log MAR	logarithm of the minimal angle of resolution
PI	Principle Investigator
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions

4. CLINICAL INVESTIGATION SUMMARY

Title	CT Lucia 601 IOL implantation in the sulcus
Reference Number (Acronym)	CLuS
Clinical phase	Post-marketing study (phase 4)
Objectives	To perform a retrospective investigation of the CT Lucia 601 IOL implantation in the sulcus

Endpoints	Primary endpoint: determine whether the CT Lucia 601 IOL can be used safely in the sulcus
Design	Non-commercial (academic with study grant), monocentric, post-interventional observational without use of a study drug
Data Collection	A single late-postoperative visit, scheduled ≥ 6 months after the vitrectomy *See Study Flow Chart 7.3*
Planned Clinical investigation Period	2019-2020
Clinical investigation population	Patients who had an implantation of the CT Lucia 601 lens
Number of Participants	100

Inclusion/Exclusion Criteria	<u>Inclusion criteria</u>
	• Patients with an implantation of a CT Lucia 601 lens for different reasons:
	  ○ During vitrectomy to treat a complicated cataract surgery and had the implantation of a CT Lucia 601 IOL in the sulcus or patients
	  ○ During phaco surgery with a posterior capsule tear that necessitated the implantation of the implant lens in the sulcus
	  ○ Explantation of an in-the-bag lens and implantation of a CT Lucia 601 as replacement lens (e.g. to treat opacification of the implant lens or intolerance of the implant lens).
	• Age : > 18 years
	• Signed informed consent
	• Preoperative myopia less than 10 diopters
	• Implantation of the CT Lucia IOL at least six months earlier
	
	<u>Exclusion criteria</u>
	• History of uveitis
	• Ocular pathology or history that could influence the biometry of the effective lens position, such as ocular trauma with zonulolysis, congenital iris- or lens defects etc.
	• Any eye condition influencing the lens position (to be specified) according to the investigator

Device Name	CT LUCIA hydrophobic C-loop IOL: CT Lucia® 601P (hydrophobic acrylic with heparin coated surface)

Principle Intended Use	All devices are CE marked and used within their claimed intended use. In general, all devices are intended to be used during ophthalmic surgery.
Manufacturer Name	CT LUCIA 601P

5. INTRODUCTION

Preface

In Belgium, approximately 120 000 cataract surgeries are performed annually. During this surgery, the lens is removed from its bag, and replaced by an intra-ocular lens (IOL). Older types of IOLs are made from non-foldable PMMA, requiring to make a large incision the eye. Modern types of IOLs are made from foldable acrylic material, allowing the insertion of the IOL through an incision as small as 1.8 mm. Preferably, the IOL is inserted in the lens bag, but in approximately 1 in 500 surgeries, a break of the posterior lens capsule occurs. When this complication occurs, it may not be possible anymore to use an in-the-bag implantation. In this case, the IOL can be inserted in front of the anterior lens bag (and behind the iris), which is named "in-the-sulcus" implantation. If no lens capsule is available, as a last resort the IOL can be clipped on the anterior side of the iris, using a dedicated "irisclaw" IOL. Such complicated surgeries are usually referred to the vitreoretinal department in third-line care centers. In our center, we treat such referred complicated cases weekly.
Another condition where implantation of an IOL in the sulcus may be required is when the implanted IOL (in the bag) opacifies or is not tolerated by the patient (mostly in case of multifocal IOL). In such case, the IOL is usually removed from the bag and replaced by an IOL in the sulcus.

Requirements of sulcus IOLs

For optimal performance and stability, the following properties are preferred for an IOL that is inserted in the sulcus:

- A relatively large optical part of ≥ 6 mm to avoid entrapment of the pupil behind the optic op the IOL
- An angulated IOL design that brings the optic of the IOL backward in order to avoid contact with the posterior side of the iris and also to avoid entrapment of the pupil
- A large IOL total diameter, since the diameter of the sulcus is larger than the lens bag
- A design of the IOL haptics that created a large contact area between the IOL and the sulcus
- A preloaded IOL system to avoid contamination of the IOL before and during insertion that could lead to postoperative infection (endophthalmitis). The use of a preloaded system is nowadays considered as the most effective preventive measure to avoid such serious complication.

Availability of sulcus IOLs

A few older PMMA IOL types are available that are on-label certified for use in the sulcus. However, since the use of these IOLs requires a large incision in the eye and are not preloaded, the use of these lenses is not up to the standard-of-care in modern lens surgery.
In our center, we have been using the IOL "PolyAI" from Physiol, that was certified for use in the sulcus. However, when production of this IOL was discontinued a few years ago, we had to look for a suitable alternative. At that time, a review of the commercially available

IOLs was performed, and it was decided that the IOL "CT Lucia 601" from Zeiss had all the properties that we considered as important for in-the-sulcus implantation, in spite of the lack of an official "in the sulcus" label. Also since we could not find any foldable and preloaded IOL that was officially labeled as "sulcus-IOL", we have implanted this IOL in the sulcus in ~150 patients witch complicated cataract surgery. During the surgery, we found that this IOL had even better handling properties compared to the PolyAI that facilitate the in-the-sulcus positioning. It unfolds very slowly after insertion in the eye, allowing the surgeon to accurately place the IOL haptics in the desired position. Also during the postoperative visits, we assessed a very good centration and positioning of this CT Lucia 601 IOL.
Unfortunately, the IOL manufacturer (Carl Zeiss) decided last year to change the design of the CT Lucia 601, referred to as CT Lucia 611. Although this new design allows easier implantation in the bag, it makes the IOL in our evaluation less suitable for in-the-sulcus implantation. This concern was reported to and discussed with Zeiss. We have suggested to perform a post-implantation analysis study to objectively evaluation the use of the CT Lucia 601 IOL as a sulcus lens. Zeiss has agreed to continue the delivery of the CT Lucia 601 for this purpose.

Study expenses

Besides the examinations collected during the long-term postoperative visit, no additional study examinations are required outside of the normal standard-of-care.
The CT Lucia 601 IOL is registered by the FAGG and reimbursed by the RIZIV/INAMI in the same way as any other IOL, and is already registered in our hospital (CMM), hence there are no additional expenses involved for the patients or for the RIZIV/INAMI that have this IOL implanted. Also, inclusion in the study will be done post-interventionally, hence the vitrectomy surgery itself is not part of the study.

6. OBJECTIVES

The purpose of the study is to collect data that are parameters of post-IOL implantation safety:

- Questionnaire on subjective quality of vision
- Centration and anteroposterior position of the IOL (using biometry)
- Presence and quantification of any inflammation or pigment present in the anterior chamber (flare meter)
- Refractive outcome, with calculation of customized A-constant of the CT Lucia 601 IOL in-the-sulcus and quantification of higher-order aberrations (HOA)
- General safety-parameters:
    - Visual acuity
    - Intra-ocular pressure
    - Presence of macular edema or retinal nerve fiber layer (RNFL) thinning (SD-OCT)
    - Any adverse ophthalmic events

7. CLINICAL INVESTIGATION DESIGN

Inclusion of the patients will be done post-interventionally: patients that underwent a (usually urgent) vitrectomy to treat a complicated cataract surgery with the implantation of a CT Lucia 601 IOL in the sulcus will be asked to participate in this clinical trial.
For this trial, one additional long-term postoperative visit (at least 6 months after the vitrectomy) will be required besides the standard-of-care visits. During this study visit, besides the standard ophthalmological clinical examination and a questionnaire about subjective vision quality, the following technical examinations will be performed:

1. Biometry (using Zeiss IOLmaster 700 SS-OCT and Oculus Pentacam) to assess the position of the IOL in relation to the cornea (centration and anterior chamber depth).
2. SD-OCT to assess the potential presence of macular edema or retinal nerve fiber layer (RNFL) thinning.
3. Anterior chamber flare to determine the amount of inflammation and pigment dispersion present in the anterior chamber (using Kowa Flare Meter).
4. Quantification of HOA using iDesign Hartmann shack aberrometer

8. CLINICAL INVESTIGATION POPULATION

8.1. Number of participants

A total of 100 patients will be included.

Estimated enrolment time is 12months

8.2. Inclusion criteria

- Patients who had implantation of a CT Lucia 601 lens for different reasons:
  - During vitrectomy to treat a complicated cataract surgery and had the implantation of a CT Lucia 601 IOL in the sulcus or patients
  - During phaco surgery with a posterior capsule tear that necessitated the implantation of the implant lens in the sulcus
  - Explantation of an in-the-bag lens and implantation of a CT Lucia 601 as replacement lens (e.g. to treat opacification of the implant lens or intolerance of the implant lens).
- Age : > 18 years
- Signed informed consent
- Preoperative myopia less than 10 diopters
- Implantation of the CT Lucia IOL at least six months earlier

8.3. Exclusion criteria

- History of uveitis
- Ocular pathology or history that could influence the biometry of the effective lens position,
  such as ocular trauma with zonulolysis, congenital iris- or lens defects etc.
- Any eye condition influencing the lens position (to be specified) according to the investigator

9. PARTICIPANT SELECTION AND ENROLMENT

9.1. Identifying participants

The particiants of the study are patients who had an implantation of a CT Lucia 601 lens at least six months earlier. This could be for different reasons such as a complicated cataract surgery, a posterior capsule tear during vitrectomy or an explantation of an in-the-bag lens with placement of a sulcuslens.

The patients will be contacted by the study nurse to inform them about the study and its purpose. An information brochure and a copy of the informed consent will be sent to the patient after this informative call to allow to read the information through at home. About 1-2 weeks later, after receiving the informed consent form, the patients will receive a second call to ask for final approval or disapproval to be enrolled in the trial and to make one visit in het hospital for some postoperative non-invasive examinations.

9.2. Consenting participants

Patients that had an implantation of the CT Lucia 601 at least 6 months ago, will receive a phone call of the study nurse and will receive an informed consent at home. After 2 weeks the study nurse will make a second call to ask the patients to participate in the clinical trial. Per patient, both eyes will be eligible for inclusion in the study. The contralateral eye without CT Lucia 601 will be used to create a control group.

Following the guidelines of the Ethics Review Committee of the World Health Organisation (WHO ERC), potential participant must personally sign and date the latest approved version of the informed consent form before any clinical investigations are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the clinical investigation; the implications and constraints of the clinical investigation plan; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the clinical investigation. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Coordinating/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the clinical investigation site.

In case of updates of the participant information and Informed consent the participant must personally sign and date the latest approved version of the informed consent form before any further clinical investigation specific procedures are performed.

For this clinical trial, signature for approval from the patient will be obtained at the appointment in the hospital on the date agreed with the study nurse.

9.3. Randomisation

All patients who received a CT Lucia 601 at least 6 months ago will be contacted and asked for participation in our clinical trial. There will be no randomization necessary since we only plan one postoperative non-invasive visit without performing an invasive intervention or using a study drug. All patients will undergo the same technical examinations.

9.4. Withdrawal of participants

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the

presence of any Adverse Event/Adverse Device Effect or Device Deficiency and, if possible, be assessed by an investigator. Adverse Event/Adverse Device Effect should be followed up.

Subjects may be withdrawn from investigation treatment and assessments at any time, at the discretion of the investigator.

Incorrectly enrolled subjects will be withdrawn from further investigation treatment and assessments. A subject may, however, continue the investigation under special circumstances (i.e. if continuation of investigation treatment or follow-up actions are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

10 INVESTIGATIONAL DEVICE

10.1. Investigational device details

CT LUCIA hydrophopic C-loop IOL: CT Lucia® 601P
- Hydrophopic acrylic
- Heparin coated surface
- Preloaded system (avoiding contamination and minimizing risk of endophthalmitis)
- Off-label used for 'in the sulcus' implantation

Easy handling properties:
- unfolds very slowly after insertion in the eye: time for positioning IOL haptics

Perfect 'in the sulcus' design: good centration and positioning postoperative
- large optical part of ≥ 6 mm to avoid entrapment of the pupil behind the optic
- angulated IOL design that brings the optic backward to avoid contact with iris or entrapment of pupil
- IOL haptics make large contact between IOL and the sulcus

10.2. Device manufacturer

Carl Zeiss NV (Department in Belgium: Ikaroslaan 49 1930 Zaventem, Belgium)

10.3. Device accountability

In the hospital, there is a standard procedure for returning faulty products. This procedure will be followed, similar to the standard clinical path.

10.4. Storage conditions

All intra-ocular implant lenses are prepackaged in a sterile way. The CT Lucia 601 comes with a disposable preloaded system and are used before expiration date.

10.5. Concomitant Treatments

Not applicable

11 CLINICAL INVESTIGATION ASSESSMENTS

11.1. Investigation Characteristics

❖ The following post-operative parameters will be collected:

- Indication of the surgery with implantation of the lens in the sulcus
- Refraction: objective and subjective
- Best Corrected Visual Acuity (BCVA)
- Pneumotonometry: intra-ocular pressure
- Biometry (using Zeiss IOLmaster 700 SS-OCT) to assess the position of the IOL in relation to the cornea (anterior chamber depth).
- Oculus Pentacam to determine IOL positioning relative to the iris
- SD-OCT: to assess the potential presence of macular edema and RNFL thinning
- Anterior chamber flare meter (Kowa) to determine the presence and quantification of any inflammation or pigment dispersion present in the anterior chamber
- Aberrometry to quantify HOA caused by IOL tilting/decentration

Note that all of the above investigation are non-contact measurements, hence without any risk of adverse events.

❖ Questionnaire about subjective quality of vision at least 6 months postop

- The patient will be asked to grade the quality of vision, at the time of completion, with a score of one to five according to the score system below:

- The questionnaire will be completed during the study visit

11.2. Surgical procedure

This is a post-interventional observational study without use of a study drug.
There will be no surgical procedure in this study since there is only one single late-postoperative observational visit with technical examinations.

11.3. Safety assessments

The reporting rules under the RD of 15/Jul/1997 and 18/Mar/1999 are not applicable in this post-marketing study.

Medical device incidents will be routinely collected and reported under the national materiovigilance rules at the discretion of the Investigator.

11.4. Adverse events that do not require reporting

Not applicable in this study

12. DATA QUALITY ASSURANCE

12.1. Monitoring, Audit and Inspections

Investigator and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents.

12.2. Training of staff

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff at the site involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

The staff at the investigational site will sign a confirmation document that they are trained.

12.3. Data Management

In this study, an electronic case report form (eCRF) will be used for data capture. As eCRF, the RedCap platform will be used, which is supported by the UZleuven. A new project with dedicated forms will be created. All changes in the eCRF are logged and time-stamped.

All documents will be stored safely in confidential conditions. On all clinical investigation-specific documents, other than the signed consent, the participant will be referred to by the clinical investigation participant number/code, not by name or EMR number.

All clinical investigation documentation will be kept for 10 years from the clinical investigation plan defined end of clinical investigation point. When the minimum

retention period has elapsed, clinical investigation documentation will not be destroyed without permission from the sponsor.

13. STATISTICS

13.1. Description of statistical methods

The results from this clinical investigation will be presented with descriptive statistics. No hypothesis testing is planned for this investigation.

For continuous variables (ex: age)
In case, the data follow of a normal distribution the T-Test will be applied and the data will be reported as the means and standard deviations by group. Otherwise a signed- rank test of Wilcoxon will be performed and the data will be report as the medians and interquartile ranges.

For count data, the Pearson's Chi² test will be applied to compare the groups and the data will be reported by counts and proportions by group.

13.2. The number of participants

Given the exploratory nature of the trial, 100 patients will be recruited by group.

13.3. The level of statistical significance

For all analyses, the level of significance will be 5% two-sided significant level.

13.4. Criteria for the termination of the clinical investigation

There will be only one postoperative visit to examine the patients, the clinical investigation will be terminated after this visit. No statistical interim analysis is planned.

13.5. Procedure for accounting for missing, unused and spurious data

Missing data will be reported with reasons given where available, and the missing data pattern will be examined. We will explore the mechanism of missing data by means of logistic regression models which will explore if missingness (i.e. whether the primary outcome is missing or not) is related to measured baseline variables. Covariates found to be predictive of missingness will, where appropriate, be included as a covariate in the analysis model.

13.6. Procedures for reporting any deviations from the original statistical plan

The final statistical plan will be agreed prior to final data lock and prior to any analyses taking place. Any deviation thereafter will be reported in the final trial report.

13.7. Inclusion in analysis

All patients who received a CT Lucia 601P IOL will be contacted and asked to participate in the trial.

14. Clinical Investigation Management

14.1. Clinical investigation management group and parties involved

The clinical investigation management group consists of the following participants:

Principal Investigator Name: Peter Stalmans Title: Vitreoretinal surgeon Address: UZLeuven Herestraat 49 3000 Leuven Telephone: Email: oogziekten@uzleuven.be
Statistician Name: Mr. Jean-François Fils Title: Bio-Statistician Address:Ars Statistica, Nivelles Telephone: Email:
Clinical investigation Management Name: Ingeborg Vriens Title: Study Nurse Address: UZLeuven Herestraat 49 3000 Leuven Telephone: +32 16 34 22 29 Email: Ingeborg.vriens@uzleuven.be

Clinical investigation Coordination Centre

For general queries, supply of clinical investigation documentation, and collection of data, please contact the Clinical Investigation Coordinator:

Name: Ingeborg Vriens
Address: Herestraat 49, 3000 Leuven
Telephone: +32 16 34 22 29
Email: ingeborg.vriens@uzleuven.be

Clinical Queries

Clinical queries should be directed to oogziekten@uzleuven.be who will direct the query to the appropriate person

Investigation site

Name: UZ Leuven
Address: Herestraat 49, 3000 Leuven
Telephone: +32 16 33 26 60
Email: oogziekten@uzleuven.be

Sponsor

Name: UZ Leuven
Address: Herestraat 49, 3000 Leuven
Telephone: +32 16 33 23 70
Email: oogziekten@uzleuven.be

Funder (application was sent in)

Name: Carl Zeiss NV, Department in Belgium
Address: Ikaroslaan 49, 1930 Zaventem
Telephone: +32 2 719 39 11
Email: info@zeiss.be

14.2. Clinical investigation steering committee

Patients included in this clinical trial follow the standard clinical path, underwent prior surgery using the standard vitrectomy device and using the currently used instruments. During the (single) study visit, all tests are non-contact examinations and performed by an experienced study nurse. Hence, there is no increased safety risk for patients enrolled in this investigation. For this this reason, no steering committee or DMC will be constituted.

14.3. Data monitoring committee

N/A, see section 14.2.

14.4. Monitoring plan

The study protocol will be reviewed by the CTC prior to study approval. If the CTC evaluates that the study should be monitored, a monitor will be appointed by the CTC. In this case, the monitor will visit the Investigator site prior to the start of the clinical investigation and during the course of the clinical investigation if required, in accordance with the monitoring plan. Monitoring will be performed according to ISO 14155:2011.
Data will be evaluated for compliance with the clinical investigation plan and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the clinical investigation plan, GCP and the applicable regulatory requirements.

15. GOOD CLINICAL PRACTICE

15.1. Declaration of Helsinki

The Investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

15.2. Guidelines for GCP

The Investigator will ensure that this clinical investigation is conducted in full conformity with relevant regulations and with the International standard for Good Clinical Practice for clinical investigations of medical devices for human subjects (ISO 14155:2011).

15.3. Ethics review

The clinical investigation plan, Investigator's Brochure, Case Report Forms (CRFs), informed consent form, participant information sheet and any other documents needed for review by an appropriate Ethics Committee (EC) or regulatory authority will be submitted to obtain written approval. Any additional requirements imposed by the EC or regulatory authority will be followed, if appropriate.

The Investigator will submit and, where necessary, obtain approval for all amendments to the original approved documents. Furthermore, the clinical investigation will not begin until the required approval/favourable opinion of the EC or regulatory authority has been obtained.

15.4. Patient Information and Consent Form

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the investigation. Subjects must also be notified that they are free to discontinue participation in the investigation at any time. The subject should be given the opportunity to ask questions and time for consideration.

The subject's signed informed consent has to be obtained before conducting any investigation related procedures. The original must be filed by the Principal Investigator. A copy of the Patient Information including the signed Consent Form should be given to the subject. If modifications are made according to local requirements, the new version must be approved by the EC.

15.5. Subject data protection

The clinical investigation staff shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR") and the Belgian Law of July 30 2018 on the protection of natural persons with regard to the processing of personal data)

The clinical investigation staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by clinical investigation staff and authorised personnel. The clinical investigation will comply

with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

15.6. Procedures in case of medical emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

16. CLINICAL INVESTIGATION CONDUCT RESPONSIBILITITES

16.1. Clinical investigation plan amendments

Amendments to the clinical investigation plan must be submitted to the Sponsor for review before submitting to the appropriate EC and Regulatory Authority for approval.

16.2. Clinical investigation plan violations, deviations and serious breaches

The Clinical investigator will not implement any deviation from the clinical investigation plan without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to clinical investigation participants.

In the event that the Clinical investigator needs to deviate from the clinical investigation plan, the nature of and reasons for the deviation will be recorded in the CRF and notified to the Sponsor. If this necessitates a subsequent clinical investigation plan amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and Regulatory Authority for review and approvals as appropriate. It is Sponsor policy that waivers to the clinical investigation plan will not be approved.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately.

16.3. End of clinical investigation

The end of clinical investigation is defined as the last participant's last visit.

The investigator and/or the clinical investigation steering committee have the right at any time to terminate the clinical investigation for clinical or administrative reasons.

The end of the clinical investigation will be reported to the EC and Regulatory Authority within 90 days, or 15 days if the clinical investigation is terminated prematurely. The Investigators will inform participants of the premature clinical investigation closure and ensure that the appropriate follow up is arranged for all participants involved.
A summary report of the clinical investigation will be provided to the EC and Regulatory Authority within 1 year of the end of the clinical investigation.

16.4. Insurance and indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

16.5. Funding

A grant request to support this retrospective clinical trial will be sent to Carl Zeiss.

17. REPORTING, PUBLICATIONS AND NOTIFICATIONS OF RESULTS

17.1. Authorship policy

Ownership of the data arising from this clinical investigation resides with the clinical investigation team. On completion of the clinical investigation, the clinical investigation

data will be analysed and tabulated, and a clinical investigation report will be prepared in accordance with ISO14155:2011.

17.2. Publication

The Principal Investigator will decide to publish the obtained study data. The statistician will provide a study report, which will be used as source data to write the results section of the manuscript. The publication will also cover authorship, acknowledgements (mentioning the grant provider of the trial), and an overview of relevant scientific publications.
Before submitting for publication, the manuscript will be sent to the grant provider, allowing the grant provider give feedback on the manuscript within 2 weeks. It is up to the Principal Investigator to decide to make any changes to the manuscript based on this feedback.

18. REFERENCES

1. Intraocular Lens Implantation in The Ciliary Sulcus: Challenges And Risks. Mehta R, Aref AA. Clin Ophthalmol. 2019 Nov 27;13:2317-2323.
2. Observational study of intraocular lens tilt in sutureless intrascleral fixation versus standard transscleral suture fixation determined by ultrasound biomicroscopy. Marianelli BF, Mendes TS, de Almeida Manzano RP, Garcia PN, Teixeira IC. Int J Retina Vitreous. 2019 Jul 29;5:33.
3. Uveitis-Glaucoma-Hyphaema Syndrome. General review. Zemba M, Camburu G. Rom J Ophthalmol. 2017 Jan-Mar;61(1):11-17.
4. Stability and safety of MA50 intraocular lens placed in the sulcus. Kemp PS, Oetting TA. Eye (Lond). 2015 Nov;29(11):1438-41.

19. SAFETY REPORTING

19.1. Definitions

Device Deficiency (DD)

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

Note:

- Device Deficiencies include malfunctions, use errors, and inadequate labelling.

All Device Deficiencies that might have led to a Serious Adverse Device Effect shall be reported in accordance with Serious Adverse Event reporting procedures, as specified below.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device.

Note:

- This definition includes events related to the investigational device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational devices.

Adverse Device Effect (ADE)
Adverse Event related to the use of an investigational device.

Note:

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event (SAE)
Adverse Event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
    1) a life-threatening illness or injury,
    2) permanent impairment of a body structure or a body function,
    3) hospitalization or prolongation of patient hospitalization,
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
    5) chronic disease
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note:
Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)
Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

19.2. Procedures for reporting SAE /SADE or DD that could have led to a SADE

All SAEs/SADEs that occurs during the Clinical Investigation shall be reported, whether or not they are considered causally related to the investigational device.

Device Deficiencies that might have led to SADE must be reported as a SADE if either
a) suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate

The investigator is responsible for informing the EC/IRB and/or the Competent Authority of the SAE/SADE as per local requirements. For this reason, medical device incidents will be routinely collected and reported under the national materiovigilance rules at the discretion of the Investigator.

19.3. Procedures for Device Deficiency reporting

Device Deficiencies will be routinely collected and reported to the corresponding manufacturer(s) as soon as possible, without unjustified delay (i.e. on the same working day). If the Device Deficiency might have led to a SADE the reporting requirements for SADE described above must be followed.

19.4. Causality Assessment

The relationship between the use of the investigational device and the occurrence of each AE/SAE shall be assessed by the investigator and the manufacturer and classified as investigational device related or not related to investigational device.

19.5. Recording of safety information

All safety issues occurring during the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the clinical investigation plan.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship to the device will be assessed by a medically qualified investigator or the sponsor and will be followed up until resolution or the event is considered stable.

All ADE that result in a participant's withdrawal from the clinical investigation or are present at the end of the clinical investigation, should be followed up until a satisfactory resolution occurs.

Where relevant, any pregnancy occurring during the clinical investigation and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect.

19.6. Reporting procedure for all SAEs/SADEs

Reporting to the local national competent authority and the manufacturer will be done by the Principal Investigator.

- The principal investigator has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) after a link is established between the event and the device, but no more than:2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

Device Deficiencies, including SAEs/SADEs will be reported to the corresponding manufacturer(s) as soon as possible, without unjustified delay (i.e. on the same working day).

19.7. Annual reports

In addition to the expedited reporting above, the Principal Investigator shall submit once a year throughout the clinical investigation or on request a Safety Report to the Competent Authority and Ethics Committee