CLINICAL INVESTIGATION PLAN (CIP)

Title: ZEISS RESIGHT Disposable Lenses evaluation study

RESIGHT Disposable

Version number: v *1.0* – Date *7/03/2023*

Clinical Investigation number: S67415

Single Identification Number (SIN): *CIV-23-02-042213*

Sponsor

<University Hospitals Leuven (UZ Leuven) or KU Leuven>
Herestraat 49, B-3000 Leuven

Coordinating Investigator

Peter Stalmans

LIST OF PARTICIPATING SITES

(if applicable)

List Of Participating Sites	Principal Investigator
Not applicable (single site UZ Leuven)	

SIGNATURES

Title: ZEISS RESIGHT Disposable Lenses evaluation study

CIP: RESIGHT Disposable

The undersigned confirm that the following CIP has been acknowledged and accepted and that they agree to conduct the Investigation in compliance with the approved CIP (and any subsequent amendments if applicable) and will adhere to the principles outlined in the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., the EU Medical Device Regulation 2017/745 (MDR), EU General Data Protection Regulation 2016/679 (GDPR)) and ISO 14155:2020), the appropriate local legislation(s) and all other applicable legal and regulatory requirements as amended. The most stringent requirements, guidelines or regulations must always be followed.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the Investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Investigation publicly available through publication or other dissemination tools, in accordance with this CIP without any unnecessary delay and that an honest accurate and transparent account of the Investigation will be given; and that any discrepancies from the Investigation as planned in this CIP will be explained.

Coordinating Investigator

Prof. Dr. Peter Stalmans	……	……
Name & Title	Signature	Date

Principal Investigator (Participating Site) (Principal Investigator is the same as Coordinating Investigator in case of a monocentric investigation)

Prof. Dr. Peter Stalmans	……	……
Name & Title	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Annual Progress Report
AR	Adverse Reaction
ASADE	Anticipated Serious Adverse Device Effect
BCVA	Best-corrected visual acuity
CA	Competent Authority
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CM	Concomitant Medication
CRA	Clinical Research Associate
CRF	Case Report Form
DD	Device Deficiency
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EMR	Electronical Medical Record
FAMHP	Federal Agency for Medicines and Health Products
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
IMD	Investigational Medicinal Device
ISF	Investigator Site File
KWS	Klinisch workstation, i.e. the EMR used in the UZ Leuven
Log MAR	Logarithm of the minimal angle of resolution
LPLV	Last Patient Last Visit
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SADE	Serious Adverse Device Effect

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

FUNDING AND SUPPORT

Funder	Type of Financial or Non-Financial Support
Carl Zeiss Meditec AG	Grant

ROLES AND RESPONSIBILITIES

The Principle Investigator (PI) is responsible for the conduct of the Investigation at his/her Participating Site, and for protecting the rights, safety and well-being of the participants. As such the PI must ensure adequate supervision of the Investigation conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Investigation-related duties. The PI will ensure that adequate training is provided and documented for all Investigation staff, prior to conducting assigned Investigation-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g., study progress, communication, CIP training and support of the participating sites, annual reporting, end of Investigation notification(s) and results reporting etc.) of the Investigation. The CI fulfils both Investigator's and Sponsor's responsibilities, as outlined in ISO 14155:2020 and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

CIP SYNOPSIS

Title of clinical Investigation («Investigation»)	Title: ZEISS RESIGHT Disposable Lenses evaluation study
CIP Short Title Acronym	RESIGHT Disposable
Sponsor name	<University Hospitals Leuven (UZ Leuven) or KU Leuven>
Coordinating Investigator	Peter Stalmans
Contact Address CI	UZ Leuven, Herestraat 49, 3000 Leuven
Contact Email CI	peter.stalmans@uzleuven.be
Contact Phone CI	+32 16 34 22 29
SIN number	CIV-23-02-042213
Other public database number	not applicable
Principal Investigators and Participating Sites	not applicable
Medical condition or disease under investigation	-Macular pathology requiring surgery: macular pucker, macular hole, vitreomacular traction -Retinal detachment
Study rationale	See row below
Primary objective	To evaluate the intra-operative efficacy of a new intra-operative viewing device.
Secondary objective(s)	/
Clinical Investigation Design	Investigator-initiated, mono-center, academic, prospective, interventional case study
Endpoints	To determine the effectiveness of the device compared to the reusable RESIGHT lenses and Vitreq contact lens presently used as standard-of-care.
Sample Size	120 eyes in two cohorts (60 in each cohort)
IMD	Disposable RESIGHT lenses
Comparator device(s)	Reusable RESIGHT lenses and Vitreq contact lens
Maximum duration of treatment of a Participant	Total inclusion time of each patient is surgery time (from first incision till removal of vitrectomy cannulas)
Maximum duration of the Investigation	Total inclusion time of each patient is surgery time (from first incision till removal of vitrectomy cannulas)
Anticipate First Patient First Visit (FPFV)	Q1 2023
Anticipate Last Patient Last Visit (LPLV)	Q4 2023
Third Parties	Carl Zeiss Meditec AG, Rudolf-Eber-Straße 11, 73447 Oberkochen, Germany: Grant

STUDY FLOWCHART

Schedule of Events – Study specific Procedures / Assessments

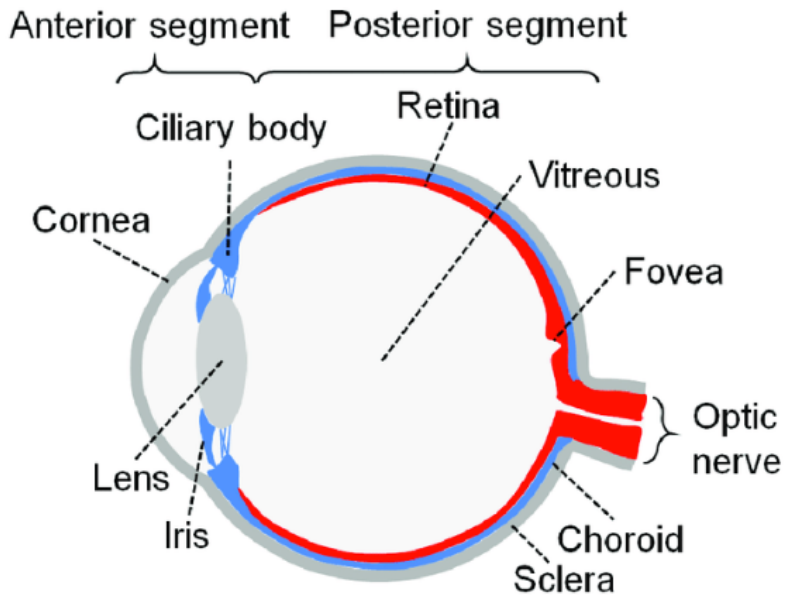
Please indicate in the flowchart with different colors whether a procedure is performed as part of the standard of care or specifically for the Investigation.
Describe the visits and applicable procedures/investigations (with a reference number or letter) in more detail in a footnote below the study flowchart

Procedures/ Assessment	Pre-surgery	Surgery
Timing (weeks)	0	0
Informed consent	X [1]	
Inclusion / Exclusion criteria	X	
Randomisation	X	
Vitrectomy +/- Phaco paramaters		X
Device Deficiences		X
(Serious) Adverse event (S)(AE) assessment		X

1 : Informed Consent process should take place prior to all other study-related procedures at the screening visit

1 Background and Rationale

For several eye disorders, a surgical therapy is required. Depending on the type of surgery, different areas of the eye need to be visualized. For this purpose, a dedicated ophthalmic microscope is used. To view the anterior segment (i.e. the lens and all structures anterior to it), no additional optical attachment is required. To visualize the posterior segment (i.e. all structures posterior from the lens), an additional optical system is required in conjunction with the surgical microscope.



Anatomy of the eye: anterior and posterior segment

1.1 Surgical microscope device

For this purpose, a modern ophthalmic surgical microscope such as the ARTEVO 800 used in our center, integrates many functions.

1.1.1 Double binocular optical tract.

The ARTEVO 800 digital 3D microscope system.
Left: the microscope mounted on its floor stand, with touchscreen control pane on the microscope arml. Right: the 55" 3D visualization screen.

Since stereopsis is required during surgery, both the main viewer and the assistant viewer have a binocular optical tract.

1.1.2 Red reflex

During cataract surgery, it is required to visualize both the front and rear side of the lens. For this purpose, a co-axial light source is built in the microscope, which generates a red reflex by reflection from the retina in the back of the eye. The balance between red reflex light and environmental light can be controlled by surgeon.

1.1.3 Wide-angle retina viewing system

During posterior segment surgery (vitrectomy), viewing of the retina is required. For that purpose, an

additional optical system below the microscope is required.

These optical systems can be divided into two categories:

1) Contact lens systems

This lens type is placed on the corneal surface with some contact gel in between the cornea and the lens. Different lenses are being used, either with a convex surface for wide-angle viewing or with a flat (or concave) surface for high-magnification viewing. In the former lens type, an image inverter is required to generate an erect retina image for the surgeon.

Examples of contact lenses for intra-operative retina viewing.
Left: wide-angle viewing lens, Right: high-magnification lens

Although the optical quality of these contact lenses is very good, there are several disadvantages:

- The continuous contact with the corneal surface may cause corneal lesions (epithelial defect), orcause corneal edema during prolonged surgery sometimes rendering retinal visualization impossible necessitating to discontinue the surgery.
- The lens must be kept in a horizontal position on the eye, which requires an experienced surgical assistant to stabilize the lens during surgery. In our center, the surgical assistance is performed by residents in training who rotate every 6 weeks. Hence, it is impossible to have a well-trained surgical assistant for this purpose.
- When using a wide-angle viewing lens, although an extreme wide-field angle can be obtained, this field-of view is highly limited be the pupil size. Since vitrectomy surgery is usually performed in patients >65 years of age, the pupil dilation is often limited, restricting the field-of view.

As a result, the use of a contact lens during vitrectomy surgery is only occasionally used during surgery.

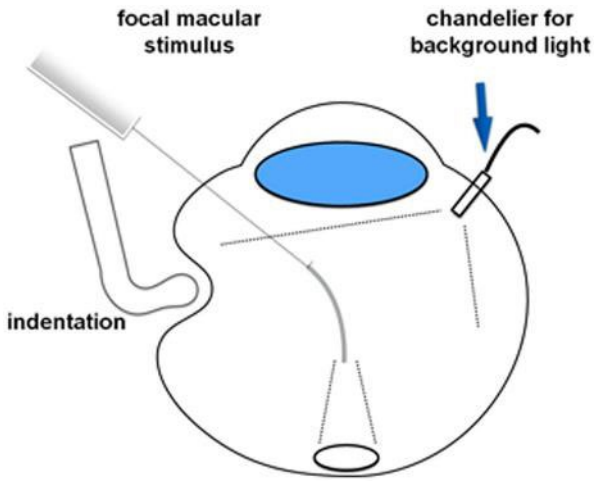
Drawing showing the light tract when performing surgery using a wide-angle contact lens. The size of the pupil determines the field-of-view of the surgeon.

2) Indirect ophthalmoscopy systems

When using an indirect ophthalmoscopy lens system during surgery, a viewing lens is positioned a few millimeters above the cornea.

Since there is no contact between the viewing lens and the cornea, there is no risk of cornea damage or edema. Also, the image generated is less dependent on the pupil size.

A disadvantage is that an indirect ophthalmoscopy system generates an upside-down indirect image of the retina, which implicates that an inverting prism is always required to provide an erect retinal image for the surgeon. Moreover, the field-of-view of the presently available systems is still a little more limited compared to a convex contact lens in combination with a wide pupil. As a result, the surgeon may need to indent the eye during surgery to have a complete view of the retinal periphery.

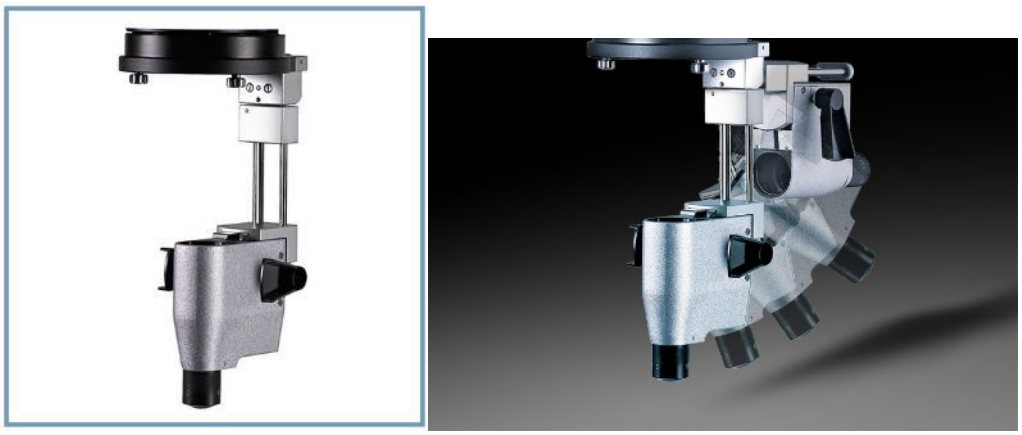


Eye indentation during surgery to see the retinal periphery.

There are several indirect ophthalmoscopy systems available for retinal surgery:

- Haag-Streit Eibos (2) system.

This surgical system was developed by late Prof. Dr. em Luc Missotten, former head of the ophthalmology dept of UZ Leuven. This system was used for more than 20 years on the microscope system used in our old operating theatre in the Sint-Pieter hospital. This system had a built-in inverting prism that omitted the need for an inverting mechanism in the microscope. However, this is a bulky device and is difficult (if not impossible) to clean and sterilize according to present standards.



Haag-Streit Eibos 2 system

- Oculus BIOM system.

This is a popular device that can be mounted under almost any brand of microscope. The ophthalmoscopy lens can be switched hence the surgeon can alternate between high and low magnification viewing. There is nowadays also a disposable version available. A main disadvantage is that when focusing the device, the distance between the ophthalmoscopy lens and the cornea changes, which often results in unwanted touch between the viewing lens and the cornea surface.

Oculus BIOM surgical viewing system: left: reusable, right: disposable

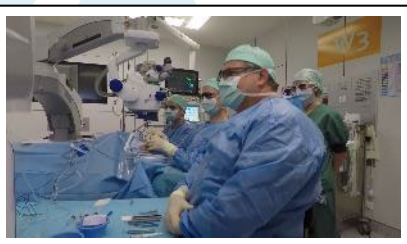
- ZEISS RESIGHT system.

Specifically for the Zeiss microscopes, the RESIGHT system can be used. This device is mounted below the microscope, and allows the surgeon to look through a lens which is held by a swing arm just above the surface of the eye. The RESIGHT system is highly integrated within the ZEISS LUMERA/ARTEVO microscopes, which has several ergonomical advantages. Firstly, the microscope automatically changes several settings (illumination, foot pedal control, inverting system, …) when the RESIGHT is inserted into the field-of-view. Secondly, the focusing can be done with the microscope foot pedal and the system focuses internally whereby the distance between the surgical lens and the cornea remains unchanged.

Since the purchase of our LUMERA 700 (and later on: ARTEVO 800) microscopes, we have been using the RESIGHT system for all our vitrectomy surgeries.

The RESIGHT provides two selectable lenses, the 60D (green one) and the 128D (yellow one).

The yellow lens has lower magnification and more overview to allow good visualization of the periphery. The green lens provides higher magnification for macular surgery but as a consequence offers less overview in the eye. During vitrectomy for macular surgery, the lenses will be switched a few times by dialing the



Click on the thumbnail to view a short video on the practical use of the ReSight system

desired lens in front of the eye. During the vitreous removal and the lasering of the retina, the yellow lens is used. During the macular surgery (e.g. removal of epiretinal membrane or peeling of the inner limiting membrane), the green lens is used.

At present, both RESIGHT lenses are reusable and are cleaned and sterilized (reprocessed) together with the RESIGHT system itself after every surgery. These reusable lenses are validated for 200 reprocessing cycles. We do notice that after a few dozen reprocessing cycles, wear & tear occurs which results in the following observations:

- The lens surface shows scratches from the cleaning process, which deteriorates the surgeons' view.
- The lens surface shows stains, created by leftovers of the cleaning agents used. These stains become permanently "baked" into the lens surface due to the heat from the sterilization process.
- Condensation occurs on the lower surface of the lens (closest to the eye surface), again hindering the surgeon's view.

Picture of RESIGHT wide angle viewing system mounted underneath the ARTEVO microscope.

1.1.4 3D Viewing

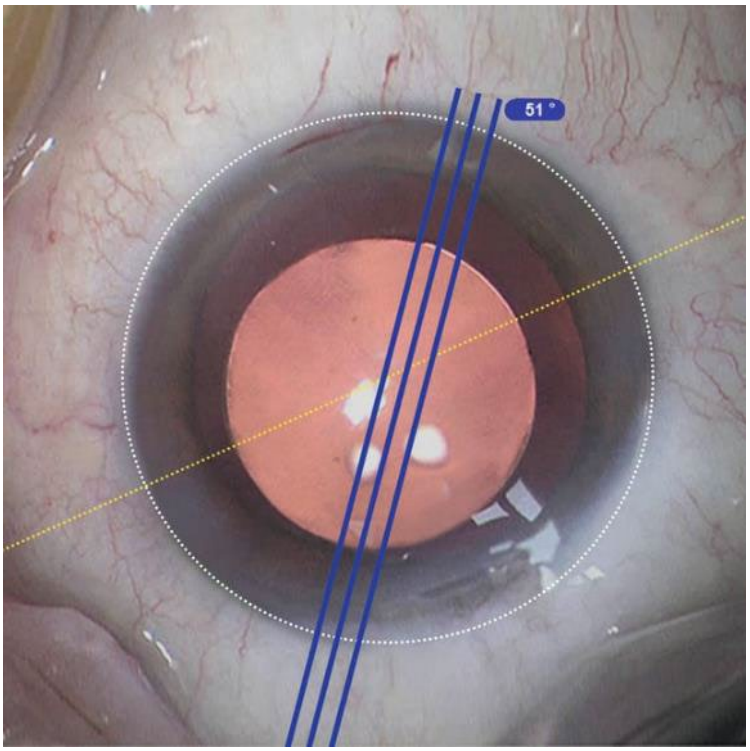
The ARTEVO 800 microscope head has two high-resolution (4K) cameras built-in, that allow the projection of a 3D image on a 55 inch screen. The surgeon can choose to perform the surgery using the screen while wearing (passive) 3D glasses. In this surgical mode, the surgeon is not looking through the microscope, but directly on the 3D screen to perform the surgery. However, for surgeons who prefer not to work on the 3D screen, the microscope can be switched to "hybrid" mode where the surgeon looks through the ocular of the microscope while the other people attending the surgery can view the image on the 3D screen. Even in the middle of a procedure, the surgeon can choose to switch between 3D and hybrid mode by simply flipping a button on the microscope. Because of the high sensitivity of the 4K cameras, less light is required compared to traditional oculars. Mainly during retina surgery using endo-illumination, this makes the surgery safer by reducing the incidence of light-toxicity to the retina. Moreover, a smaller numerical aperture ('diaphragm') can be used for 3D visualization, which increases the depth-of-field compared to viewing through an ocular.

However, a side-effect of the increased depth-of-field is that scratches / stains / condensation on the

RESIGHT lens surface will be more visible. Hence, a clean optical pathway is mandatory for adequate visualization in 3D surgery.

1.1.5 Image layover

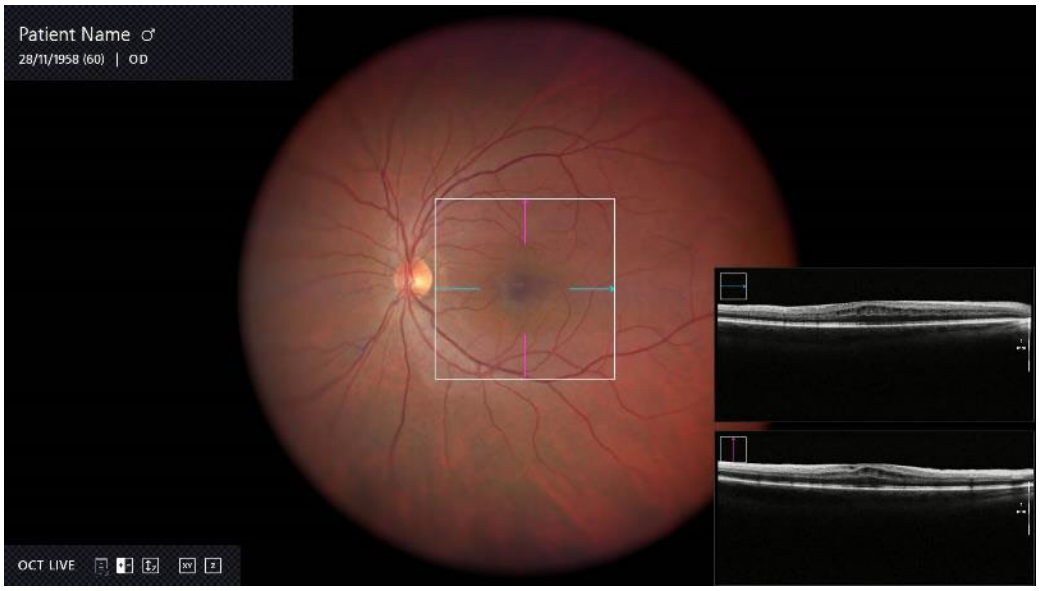
During cataract surgery, a pre-operative photo of the eye (taken with the ZEISS IOLMASTER biometer) can be uploaded in the ARTEVO 800 microscope. Using an image recognition algorithm, the microscope can project additional information on the surgical image. This augmented reality system can show the surgeon the exact incision sites, the correct placement of the capsulorhexis (i.e. the opening that the surgeon makes in the front capsule of the lens), the axis of alignment of a toric implant lens that needs to be rotated in a correct angle in the eye etc.



CALLISTO augmented reality: a live projection of the horizontal axis (yellow) and required positioning of a toric implant lens (blue) is available in overlay on the surgical image.

1.1.6 iOCT

Optical Coherence Tomography (OCT) was first introduced in ophthalmology in the mid-nineties for retinal viewing. Since then, the use of OCT has expanded extensively, and has now become one of the main technologies used for eye imaging, both in the anterior and the posterior segment. This OCT technology is now also available integrated in surgical microscopes (iOCT), and offers real-time visualization of the cornea, the lens and the retina.



ARTEVO intra-operative OCT (iOCT): a vertical transsection of the retina can be viewed during surgery.

1.2 Disposable RESIGHT Lenses

These wear & tear disadvantages can be overcome by using disposable lenses mounted on the RESIGHT system. Such disposable lens system compatible with the RESIGHT is already available from a third-party source (Oculus LenZ), but is not implemented in our center because of the high cost. Moreover, this Oculus LenZ is shaped to replace both the high-magnification 60D RESIGHT lens (green) and the wide-field 128D RESIGHT lens (yellow), but this does not offer the same optical quality compared to each of these two separate lenses.

ZEISS has designed a series of disposable lenses that are compatible with the RESIGHT system.

1. WIDE-ANGLE LENS (Yellow)
2. MACULA LENS (Green)
3. ULTRA WIDE-ANGLE LENS (Purple)

All three lenses are created from the same material:

- Optical part: PMMA (poly-methyl methacrylate = ”plexiglas”)
- Holder arm: ABS20 (acrylonitrile butadiene styrene; same material as Lego bricks)
    - MACULA LENS: color green 509
    - WIDE-ANGLE LENS: color yellow 408
    - ULTRA WIDE-ANGLE LENS: color traffic purple 854

There materials are commonly used for medical applications and can be sterilized in ethylene-oxide without deformation, opacification or leaching.

I had the opportunity to test these prototypes of these lenses on *in vivo* pig eyes in lab conditions. From these preliminary tests, the following conclusions were drawn:

1. The disposable wide-angle lens has the same use as the present reusable yellow lens, but it's improved design makes it possible to use this lens for both peripheral work as well as macula surgery.
2. Macula lens: this lens has the same macula surgical use as the present reusable green lens. However, it's improved resolution provides comparable or even better performance than a flat contact lens.
3. Ultra-Wide angle lens: this newly designed lens provides the same wide-angle view as a convex contact lens, albeit without any contact with the corneal surface. However, this ultra-wide lens must be kept closer to the corneal surface compared to the yellow lens, hence may condensate more easily.

Apart from the optical improvements, the use of disposable RESIGHT lenses is expected to also overcome the issues that we presently encounter when using the reusable lenses:

- No scratches or stains on the lens surface since a brand-new lens is used in every surgery.
- Not more (or minimum) condensation of the lens surface of the disposable lens as compared to the resuable lens since each disposable lens will have an intact coating.

2 Objectives and Design

2.1 Study objectives and hypotheses

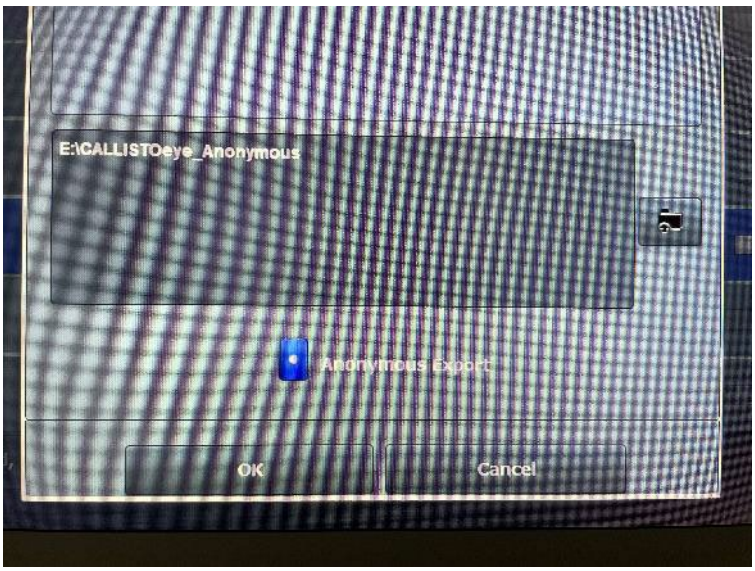
This study is designed to obtain more information on the efficacy of the disposable RESIGHT lenses in routine vitrectomy surgery. This information can lead to adjustments to these surgical lenses to further fine tune a device which can be used by other surgeons.

Theoretically, both the improved lens design and better resistance to fogging should improve the visualization of the retina hence facilitate the surgery, increasing the surgical safety.

During the surgery, a comparison will be done between the present lenses used (reusable RESIGHT lenses and disposable Vitreq contact lens) and the new disposable RESIGHT lenses. For that purpose, both lenses will be mounted on the rotating arm of the RESIGHT allowing the surgeon to toggle between both lenses during surgery. This toggling takes a few seconds, hence the total surgery time may be extended by ~30 seconds. However, this will most likely not impact patient safety since a vitrectomy surgery typically requires one hour time.

To compare the image generated by the present and the new RESIGHT lenses, both still shots and (short) video recordings will be created during the surgery. For this purpose, the internal camera and recording system of the ARTEVO microscope will be used. This will not have any impact on the surgery duration. Since only the retinal image is recorded, there is no risk of patient recognition on the recorded photos and videos.

Moreover, the Artevo microscope has a function that generates anonymous data export which will protect the patients' identity.



Anonymous data export from ARTEVO microscope

Although there is no contact between the lens and the patient, the lens is touched by the surgeons' glove, hence must be sterile. ZEISS will deliver these lenses pre-sterilized according to the present required standards. ZEISS will provide these lenses packaged and labeled according to their specifications.

2.2 Primary Endpoints

The purpose of this study is to evaluate the intra-operative efficacy of new intra-operative viewing device, more specifically:

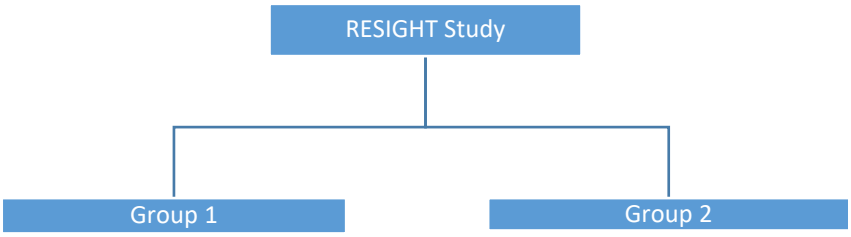
1. To determine whether the performance of the disposable MACULA LENS is comparable or even better than a flat contact lens, due to its improved resolution. For this purpose, the in-house available Vitreq contact lens will be used.
   This parameter will be determined in the macular surgery study arm only.
2. To determine that the disposable ULTRA WIDE-ANGLE LENS does not condensate / condensates to a lesser extent during surgery.
   This parameter will be determined in both study arms.
3. To determine that the disposable ULTRA WIDE-ANGLE LENS allows for imaging up to ora serrata on human eyes, reducing the need for indenting. This parameter will be determined in the retinal detachment surgery study arm only.
4. To evaluate whether both peripheral vitrectomy as well as macula work are possible with the disposable wide-angle lens. This parameter will be determined in the macular surgery study arm only.
5. To evaluate the amount of fogging that occurs when using the disposable wide-angle lens compared to using the reusable yellow lens.
6. To evaluate whether the amount of light to illuminate the retina is reduced when using any of the disposable lenses compared to the reusable yellow/green lenses. This parameter will be

determined in both study arms.

7. To evaluate whether the disposable lenses show a more natural color representation compared to the reusable yellow and green lenses. This parameter will be determined in both study arms.
8. To evaluate whether the iOCT quality recorded with the disposable macula lens is similar to or better than the iOCT recorded using the green reusable lens. This parameter will be determined in the macular surgery study arm only, where iOCT is being recorded as standard-of-care.

2.3 Design of the Clinical Investigation

Investigator-initiated, academic, mono-center, prospective, interventional case study. No randomization will be performed.



Sixty eyes will be enrolled in two study arms:

- Group 1: 60 eyes that undergo primary vitrectomy surgery for retinal detachment
- Group 2: 60 eyes that undergo macular surgery: pucker, vitreomacular traction or macular hole.

The study duration for the participants starts from the moment the patient is informed.

After the surgical procedure, the surgeon will record the parameters that are required to determine the primary outcomes of the study (§6). These parameters will be recorded in a Formasa form specifically designed for this study: see attached document. No information will be collected in this document that can identify the patients, the only clinical information used is the indication of the surgery (since this impacts the primary outcome parameters collected). After all patients (120 eyes) will we included in the trial, a KWS query will be used to export the Formasa forms. Only the content of these forms will be exported for statistical analysis.

In case a device deficiency occurs (any issue that hinders the surgery when using a disposable RESIGHT lens), it will be recorded in the Device Deficiency form (see attachment). Additionally, any (Serious) Adverse Event resulting from such Device Deficiency will be recording in the (S)AE form (see attachment).

2.4 Justification for the design of the Investigation

The design of the study causes minimal influence on the clinical tract of the patient, since no supplementary study visits are required. In case of malfunctioning of the study lenses, minimal effort is required to restore the microscopic viewing system to the standard-of-cure with neglectable impact on the surgery duration.

2.5 Expected Duration of the Investigation

The study duration will be from the start of the surgical procedure till the end of the surgical procedure.

The end of the Investigation will be notified by the investigator within 15 days of the end of the Investigation to the EC/CA.

3 Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Investigation have to meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures
2. Patients that are scheduled for primary vitrectomy surgery to treat retinal detachment or macular disease (pucker, macular hole, vitreomacular traction).
3. Both vitrectomy-only and combined phaco-vitrectomy surgeries
4. General or local anesthesia, or combination
5. Patients aged ≥ 18 years

All participants that are considered for Investigation participation as per the above criteria, will be documented on the Screening Log, including Screen Failures.

3.2 Exclusion criteria

Participants eligible for this Investigation must **not** meet any of the following criteria:

1. Patients aged < 18 years
2. Patient who do not have sufficient command of the Dutch language to read and understand the informed consent form
3. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the CIP.
4. Repeat vitrectomy surgery

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled in the Investigation and will be identified on the Screening Log as Screen Failure.

4 Study Procedures

4.1 Participant consent and withdrawal of consent

The Investigation will be conducted only on the basis of prior informed consent by the participants and/or their legally authorized representative(s). As such, no Investigation-related procedures will be conducted prior to obtaining written informed consent from potential participants.

The process for obtaining and documenting initial and continued informed consent from potential participants will be conducted in accordance with ISO 14155:2020, applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the ISF at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the CIP section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Investigation for any reason at any time. The participant's request to withdraw from the Investigation must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Study data and samples collected before withdrawal can be used in the study. No new study data or samples will be collected after withdrawal of the participant.

4.2 Selection of Participants / Recruitment

In our standard-of-care, patients are proposed to undergo vitrectomy surgery in the outpatient clinic. When

a patient agrees to be scheduled for surgery, he or she will be explained that we have an experimental surgical viewing system available that we'd like to use for the surgery, and that for this purpose, we want to collect the intraoperative data only.

The moment when the informed consent form for the RESIGHT Disposable study is handed to the patient, will be at the same time when the vitrectomy informed consent form is also given to the patient (as is done in standard-of-care in all our patients). In elective surgery (e.g. macular pucker or floaters), the surgery is usually planned on another day than the day of the informed consent. In urgent surgery (e.g. retinal detachment), the surgery is usually performed the same day or the day after. Also in case of urgent surgery, there is a window of several hours between the moment of consent to the surgery and the surgery itself, since these non-scheduled interventions are scheduled only following after the scheduled surgery list. Hence, also in urgent surgery, the patient will have sufficient time to read and sign the informed consent form of the study.

The clinical data that will be used for the study are not different from those obtained in the standard clinical path, which implicates that no extra or specific examinations need to be performed for this trial.

4.3 Randomization Procedure (if applicable)

Not Applicable. Two study arms will be created depending on the surgical indication.

4.4 Premature discontinuation

Participants may voluntarily discontinue from the Investigation treatment and/or prematurely end their participation in the Investigation for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g., via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Investigation, to temporarily interrupt or permanently discontinue the treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, EC or authorized regulatory authority can decide to halt or prematurely terminate the Investigation when new information becomes available whereby the rights, safety and well-being of participants can no longer be assured, when the integrity of the Investigation has been compromised, or when the scientific value of the Investigation becomes obsolete and/or unjustifiable. In case the Sponsor decides to temporary halt or prematurely end the Investigation, or to close a Participating Site in case of major non-compliance and/or critical safety issues, the Sponsor will notify the concerned EC/CA within 15 days of early termination or temporary halt, providing a justification of the event. In the event that the sponsor has temporarily halted or early terminated the Investigation on safety grounds, the Sponsor will inform the EC/CA within 24 hours of the event. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC/CA will be followed.

Circumstances requiring premature treatment interruption or discontinuation of the Investigation, include but are not limited to:

- Safety concerns related to IMD or unacceptable intolerability
- Investigation participation while in violation of the inclusion and/or exclusion criteria

In any such case of early termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up. It is recommended that follow-up information will be collected as follows:

For participants whose status is unclear because they fail to appear for visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Investigation (e.g., dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

5 Investigational Medical Device (IMD)

Investigational Medical Device Name (& company brand)	**CE mark (Y – N - NA)**	**Used within Indication (Y or N)**	**Manufacturer of the device**
Single-use WIDE-ANGLE LENS from ZEISS	N	Y	Carl Zeiss Meditec AG
Single-use ULTRA WIDE-ANGLE LENS from ZEISS	N	Y	Carl Zeiss Meditec AG
Single-use MACULA LENS from ZEISS	N	Y	Carl Zeiss Meditec AG
Reusable 128D lens from ZEISS (yellow)	Y	Y	Carl Zeiss Meditec AG (ref 30AL128D)
Reusable 60D lens from ZEISS (green)	Y	Y	Carl Zeiss Meditec AG (ref 30AL60DM)
Vitreq disposable contact lens	Y	Y	BVI / Vitreq (ref .VL00.D01)

5.1 Intended use

The device is intended to be used during ophthalmic surgery.

5.2 Identification and description of the IMD

See Investigator Brochure

5.3 Instructions for use

See section IFU in Investigator Brochure

5.4 Device qualification and classification

The device is intended for retinal visualization during vitreoretinal surgery, similar to its already existing reusable counterparts. It is manufactured by Carl Zeiss Meditec AG and delivered pre-packaged and sterilized.

The device is non-active Risk classification is low (Class Is) since there is no physical contact between the device and the patient.

5.5 Device Accountability

After delivery, the IMD will be stored at room-temperature (as prescribed by the manufacturer) and opened from its sterile packaging immediately prior to use.

In the hospital, there is a standard procedure for returning faulty products. This procedure will be followed, similar to the standard clinical path. The IMD (used or un-used) will be returned to the manufacturer after the clinical investigation is completed.

6 Safety reporting

6.1 Definitions

The definitions and reporting requirements adopted in this CIP are based on the MDR 2017/745, ISO 14155:2020 and the MDCG 2020-10/1 European guideline.

6.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device. (MDR Article 2(57))

Note:
1. This definition includes events that are anticipated as well as unanticipated events.
2. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved. For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.

6.1.2. Serious Adverse Event (SAE)

A SAE is any adverse event that led to any of the following:

a) death,

b) serious deterioration in health of the subject, that resulted in any of the following:
- life-threatening illness or injury,
- permanent impairment of a body structure or a body function,
- hospitalisation or prolongation of patient hospitalisation,
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
- chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect. (MDR Article 2(58))

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

6.1.3. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Note 2: This includes any event that is a result of a use error or intentional misuse of the investigational medical device.

6.1.4. Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

6.1.5 Unanticipated Serious Adverse Device Effect (USADE)

An (USADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

6.1.5. Device Deficiency (DD)

A DD is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

For DD reporting, only non-CE marked surgical components described in the investigator brochure are considered as IMD.

Specifically for this study, a faulty production of such lens could obscure the retinal visualization for the surgeon. However, this issue would be noticed by the surgeon at the very beginning of the surgery and the lens would be replaced by another disposable lens sample (or by a reusable lens).

6.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness).
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the ICF.

The following events are commonly observed and are therefore not considered as AEs for the purpose of the Investigation: adverse events that are related to malfunctioning of (an)other surgical device than the surgical microscope or the disposable RESIGHT lenses, e.g. the vitrectomy device.
Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events are not to be considered as SAEs:

- Pre-planned hospitalisations, unless the condition for which the hospitalisation was planned has worsened from the first Investigation-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for CIP therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by the Investigation staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the IMD and/or Investigation procedures
- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**

Not related	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the IMD, or the procedures related to application of the IMD; - the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the SAE can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the IMD used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the IMD or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the IMD or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship	The SAE is associated with the IMD, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with IMD use/application or procedures; - the event involves a body-site or organ that • the IMD or procedures are applied to; • the IMD or procedures have an effect on; - the SAE follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the IMD used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

6.3.2 Timelines for reporting

- After informed consent has been obtained, but prior to first use of the IMD, only AEs caused by an Investigation specific procedure should be reported
- After first use of the IMD, AEs will be reported as follows:
  - All AEs, SAEs, and DDs will be reported until 7 days after last use of the IMD, or until last follow-up visit (whichever occurs first).

All SAEs as defined in the CIP must be reported to the Sponsor within 24 hours of the investigation staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

SAE details will be reported by the Investigator to the Sponsor:

- By completing the SAE form in the (e)CRF

If an authorised Investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the Investigation.

SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of the Investigation (whichever occurs first).

- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the Investigation: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMD or experiment after the subject has ended the Investigation, the Investigator should report this SAE within the same timelines as for SAEs during the Investigation.

6.3.4 Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the Investigation.

6.3.5 Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). The Sponsor will notify all deaths as soon as possible after becoming aware to the EC and provide additional information if requested.

6.4 Recording and reporting of Device Deficiencies

Each DD must be documented by the Investigator in the source documents and reported to the Sponsor on a Device Deficiency form.

If the DD leads to the occurrence of a (S)ADE, the (S)ADE must also be reported by the Investigator to the Sponsor on the appropriate forms and within the specified timelines.

6.5 Reporting requirements to Ethics Committee's (EC's) and Competent Authorities (CA's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs and DDs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, ECs and applicable CA's based on applicable legislation.

6.5.1 Sponsor's reporting of Serious Adverse Events and Device Deficiencies

The Sponsor is responsible to report to the CA's where the Investigation has commenced:

- Any SAE that has a **causal** relationship with the IMD, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
- Any DD that might have led to a SAE if:
  a) Appropriate action had not been taken, or
  b) Intervention had not occurred, or
  c) If circumstances had been less fortunate;
- New findings/update in relation to already reportable events.

These 'reportable events' must be reported within the following timelines:

- A reportable event which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it must be reported immediately, but not later than **2 calendar days** after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event.
- Any other reportable event or a new finding/update to it must be reported immediately, but not later than **7 calendar days** following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.

6.5.2 Annual reporting

The Sponsor has the obligation to, once a year throughout the Investigation (or on request), submit a progress report to the EC's and CA's containing an overview of all SADEs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

6.5.3 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	Sponsor	as defined in CIP
	SAE	SAE form	Sponsor	asap, but no later than 3 calendar days after awareness
	DD	DD form + AE/SAE form (if applicable)	Sponsor	as defined in CIP (exception: within 3 calendar days if considered reportable event)
	Death	SAE form	Sponsor	asap
Sponsor	all reportable events (of all participating sites)	EU SAE report form (excel)[1]	- CA for Belgium -> FAGG: via mail to ct.rd@fagg.be	asap, but no later than 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) 7 calendar days (all other reportable events)
	Death	SAE form + narrative	- EC	asap
	Annual Progress Report	APR template	- EC - CA for Belgium -> FAGG: via Common European Submission Portal (CESP)	annually

[1] The SAE report form in Excel format can be downloaded from the following web page: https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

6.6 Data Safety Monitoring Board (DSMB)

Not applicable

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the study-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical study report.

The statistical analysis for the clinical investigation will be outsourced to a licensed medical statistician (Ars Statistica).

A pseudonymized Excel-export will be generated from the eCRF for statistical analysis.

7.1 Sample Size Determination

120 eyes in 2 cohorts

.

7.2 Statistical Analysis

7.2.1 Efficacy Analysis

All endpoints: For group comparisons, continuous data will be compared by means of T-test/ANOVA when homogeneity of variances, tested with the Bartlett's test, and normality of the residuals, tested with the Shapiro-Wilks test, will be reached and means and standard deviations (means ± StDev) will be reported. When homogeneity of the variance or normality of the residuals will not be proved, Wilcoxon signed rank/Kruskal-Wallis test will be performed on rank data and medians and inter-quartile ranges (median [Q25 – Q75]) will be reported. Next, the dependence between two continuous variables will be studied through Pearson's correlation. Last, for count data, the Pearson Chi-Squared test will be performed to compare proportions.

7.2.2 The level of statistical significance

The statistical significance level will be 5%

7.2.3 Procedure for accounting for missing, unused and spurious data

Missing data
In case of missing values, the underlying missingness process (MCAR, MAR or MNAR) will be investigated and 5 multiple imputations will be performed using the **MICE** R package.
We will test with the statistical test of Jamshidian and Jalal (2010), implemented in the MissMech R Package (Jamshidian, Jalal & Jansen,2014), whether missing data were MCAR. If they were not MCAR, we investigated whether or not the missing mechanism could be explained by baseline characteristics (eg, sociodemographic, medical features) of patients using logistic regression, which would suggest an MAR mechanism. If missing data were not MCAR or MAR, they were considered as MNAR.
A sensitivity analysis will be performed on the primary outcome on the aggregated datasets from the multiple imputation.

7.2.4 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.

7.2.5 Inclusion in analysis

All eyes will be included in the analysis.

7.3 Interim Analysis and Final Database Lock

No interim analysis is planned.

8 Data handling

Data handling and data flows for the Investigation are summarized below.

An eCRF will be created on the RedCap platform, containing the following instruments:

- Surgeons' report on the disposable RESIGHT lens(es) used during surgery: same information as recorded in the Formasa form
- Device Deficiency form
- (Serious) Adverse Event form

This platform provides all required functionality, security and traceability to be compliant with a CRF. To pseudonymize the patient data, a sequential data number will be created as study number not containing a link to any patient identification data using in the hospital. A separate file containing the EMR number of each patient linked to the study number (pseudonymized data) will be kept behind the hospital firewall, only accessible by the study personnel involved in this trial.

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.

All clinical investigation documentation will be kept for 25 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.

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Investigation will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source data will be collected and recorded in the participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Investigation).

It remains the responsibility of the Investigator to check that all data relating to the Investigation, as specified in the CIP, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Investigation data will be transcribed from the source records (i.e., participant's medical file or study-specific source data worksheets) into an (e)CRF by study staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The (e)CRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data, such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g., UZ Leuven EAD number), social security number etc.

8.1.1.2 Data Validation

All data relating to the Investigation must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized study staff.

Proper audit trails must be available to demonstrate the validity of the Investigation data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e., who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Study Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB).

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the study-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Investigation must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular with the GDPR, and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Study staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Investigation disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Investigation as described in this CIP. The collection, processing and disclosure of personal data, such as participant health and medical information, is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each participant, and will maintain a TMF/ISF containing all study documents, as specified in ISO 14155:2020 Annex E entitled "*Essential clinical investigation documents",* and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to study data and documents for the purpose of monitoring, audits and/or inspections by authorized entities, such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such, (e)CRFs, source records and other study related documentation (e.g., ISF, TMF, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with ISO 14155:2020, the Sponsor is responsible for monitoring the Investigation to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the study procedures have been followed as shown in the approved CIP, and that relevant study data have been collected and reported in a manner that assures data integrity. To this end, source data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Investigation will be performed by qualified individuals (independent from the site study staff), as applicable.

UZ Leuven Clinical Trial Center (CTC) performs a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as intermediate risk' as the potential risks associated to study procedures and protocol design are markedly higher to that of standard medical care since the IMD has no CE label.
However:
- The IMD is non-invasive and will not collect other or more parameters than already collected during standard of care practices.
- Safety risks associated with trial participation are lower or equal to standard of care.
- No medical decisions are taken (solely) based on the output of the intervention with the IMD.
- The duration of trial participation for each subject is short (1 examination only).

Based on the above risk assessment and as permitted by ICH-GCP (r2) section 5.0.4, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by ICH-GCP E6(r2) §1.38) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data. Nonetheless, the UZ Leuven study team will take all possible measures to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in ICH-GCP(r2) and ISO:14155.

8.4 Archiving

As specified in ISO 14155:2020 section 8.6, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Clinical Investigation Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Investigation.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Investigation.

The Sponsor and Investigator is responsible for archiving study specific documentation (such as but not limited to the CIP, any amendments thereto, the final Clinical Study Report (CSR) and the study database), according to ISO 14155:2020. Source data and site-specific study documents (such as but not limited to the original signed ICFs) will be archived by the Participating Site(s) according to local practice, and for a period of at least 10 years after the clinical Investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.[1] Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

[1] According to UZ Leuven policy, Study documents will be archived for at least 25 years following termination of Investigation.

9 Ethical and Regulatory Considerations

9.1 Ethics Committee (EC) review & reports

Before the start of the Investigation, this CIP and other related documents (e.g., ICF, advertisements, IB, etc.) will be submitted for review to the EC and to the relevant CA for authorization. The Investigation shall not commence until such approvals have been obtained.

It is the responsibility of the CI to produce the APR and submit to the EC/CA within 30 days of the anniversary date on which favourable opinion to start the Investigation was given, and annually until the Investigation is declared ended.

The CI must notify the EC/CA of the end of the Investigation. This notification must be made within 15 days of the end of the Investigation. For multinational investigations, the concerned CA will be notified when the Investigation ends in its country. The CI will notify the Belgian CA when the Investigation has ended in Belgium and when the Investigation has ended in all participating countries. In absence of EUDAMED, local guidelines with regards to end of investigation notification will be followed. The Sponsor must notify the CA in case of a temporary halt or early termination of the Investigation. This notification must be made within 15 days of the temporary halt or early termination, providing a justification of the event. In the event that the Sponsor has temporarily halted or early terminated the Investigation on safety grounds, the CA must be informed within 24 hours of the event.

The CI will submit a final report with the results of the Investigation, including any publications/abstracts, to the EC/CA within 1 year of Investigation termination, or within 6 months for paediatric Investigations. In case of a temporary halt or early termination this report must be provided within 3 months.

9.2 Peer review

Not applicable

9.3 Regulatory Compliance

The Investigation will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical investigations in the EU, as provided for in the MDR, as applicable, and any subsequent amendments, as well as in compliance with ISO 14155:2020, other GCP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th, 2004 regarding experiments on the human person (as amended), or the Belgian law of December 22nd, 2020 concerning medical devices, as applicable, the Belgian royal decree of May 18th, 2021 concerning clinical investigations of medical devices, and with the GDPR, the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd, 2002 on patient rights, and all other applicable legal and regulatory requirements.

9.4 CIP / GCP compliance

The Investigation must be performed in accordance with the CIP, ISO 14155:2020, and applicable regulatory and country-specific requirements. ISO 14155:2020 is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical investigations that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety and well-being of participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible, reliable and reproducible.

The Investigator and study team acknowledge and agree that prospective, planned deviations or waivers to the CIP are not permitted under applicable regulations on clinical investigations. However, should there be an accidental CIP- deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Investigation (e.g., through the ASR, APR, etc.). CIP deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring CIP deviations could potentially be classified as a serious violation of ICH and/or the CIP.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the participants; or

- the scientific validity of the Investigation

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Investigation, even if this action represents a deviation from the CIP. In such cases, the Sponsor should be notified of this action and the EC should be informed according to local procedures and regulations.

9.5 Data protection and participant confidentiality

The Investigation will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR, including the Belgian Privacy Act of July 30th, 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Sponsor, Participating Site and the Investigator shall have and maintain in full force and effect during the term of this Investigation, and for a reasonable period following termination of the Investigation, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

Article 32 of the Belgian Law concerning medical devices dated December 22nd, 2020 applies. Prior to the start of the Investigation, the Sponsor shall enter into an insurance contract in order to adequately cover participants from Belgian Participating Sites in accordance with Article 32 of the said law.

9.7 Amendments

As specified in ISO 14155:2020 section 7.5.1, amendments must not be implemented prior to EC and/or CA review and/or approval, as applicable. Under emergency circumstances, deviations from the CIP to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC/CA as applicable. Such deviations shall be documented and reported to EC/CA as soon as possible.

In accordance with the Belgian law of December 22nd, 2020 concerning medical devices, the Sponsor may develop a non-substantial amendment at any time during the Investigation. If a substantial amendment is introduced to the CIP, or the documents that supported the original application for the clinical Investigation, authorisation is needed, the Sponsor must submit a valid substantial amendment for approval to the EC/CA. The EC/CA will provide a response in accordance with timelines defined by applicable law. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC/CA will be followed.

Amendments to the Investigation are regarded as 'substantial' when they are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

9.8 Post-Study activities

Not applicable

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (most recent version) and European and Belgian regulations require that every research involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study.

In addition, the CI will fulfil its ethical obligation to disseminate and make the research results publicly available. As such, the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

10.1 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 analyzed and tabulated, and a clinical investigation report will be prepared in accordance with ISO14155:2020.

10.2 Publication

The Principal Investigator intends to publish the obtained study data in a specialized journal for retinal surgery. 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 to give feedback on the manuscript within 4 weeks. It is up to the Principal Investigator to decide to make any changes to the manuscript based on this feedback.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Investigation or made in the performance of the CIP ("Inventions") shall vest in the Sponsor. If the Investigation is multicentric, the Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. The Sponsor and the Participating Site have expressly agreed that any and all study data as collected and prepared in the performance of the CIP shall be the sole property of the Sponsor, unless otherwise agreed in the Investigation agreement between the Sponsor and the Participating Site.

12 Joint Commission International (JCI)

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by the Sponsor in its regular activities, and in accordance with JCI standards, the Sponsor shall comply with the following obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Investigation; (b) the Sponsor will ensure that multi-center Investigation reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsor will not grant incentives, other than standard compensations and reimbursement of costs, to participants or to Participating Site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Investigation and will respect the

participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the participants in accordance with all applicable laws.

13 References

Visualization during surgery:

1. Visualization of the retina and vitreous during vitreoretinal surgery: new technologies. Sarah P Read, Jorge A Fortun. Curr Opin Ophthalmol . 2017 May;28(3):238-241.
2. Outcome of primary rhegmatogenous retinal detachment using microincision vitrectomy and sutureless wide-angle viewing systems. Chun-Ting Lai, Wei-Hsun Kung, Chun-Ju Lin, Huan-Sheng Chen, Henry Bair, Jane-Ming Lin, Wen-Lu Chen, Peng-Tai Tien, Yi-Yu Tsai. BMC Ophthalmol. 2019 Nov 19;19(1):230.

Intra-operative adverse events:

3. Pars plana vitrectomy for vitreomacular traction syndrome: a systematic review and metaanalysis of safety and efficacy. Jackson TL, Nicod E, Angelis A, Grimaccia F, Prevost AT, Simpson AR, Kanavos P. Retina. 2013 Nov-Dec;33(10):2012-7
4. United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery Report 3, Retinal Detachment. Timothy L. Jackson, PhD, FRCOphth, Paul H.J. Donachie, MSc, Ahmed Sallam, PhD, FRCOphth, John M. Sparrow, DPhil, FRCOphth, Robert L. Johnston, FRCOphth. Ophthalmology 2014;121:643-648
5. The Royal College of Ophthalmologists' National Ophthalmology Database Study of Vitreoretinal Surgery Report 6, Diabetic Vitrectomy. Timothy L. Jackson, PhD, FRCOphth; Robert L. Johnston, FRCOphth; Paul H. J. Donachie, MSc; TomH. Williamson, MD, FRCOphth; John M. Sparrow, DPhil, FRCOphth; David H.W. Steel, FRCOphth. JAMA Ophthalmol. 2016;134(1):79-85. doi:10.100
6. United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery: Report 2, Macular Hole. Timothy L. Jackson, PhD, FRCOphth, Paul H. J. Donachie, MSc, John M. Sparrow, DPhil, FRCOphth, Robert L. Johnston, FRCOphth. Ophthalmology 2013;120:629–634
7. The Royal College of Ophthalmologists' National Ophthalmology database study of vitreoretinal surgery report 4, epiretinal membrane. Timothy l. Jackson, phd, frcophth, Paul h.j. Donachie, msc, Tom h. Williamson, md, frcophth, John m. Sparrow, dphil, frcophth, Robert l. Johnston, frcophth. Retina 35:1615–1621, 2015

Surgical technique of (phaco)vitrectomy:

8. Stalmans P, A Comparative Study of 23-Gauge and 27-Gauge Vitrectomy for Puckers or Floaters, Including Evaluation of the Effect of Combined Phaco-Vitrectomy Surgery on Postoperative Outcome. Ophthalmologica, Ophthalmologica. 2021;244(3):245-249.

Appendices

Appendix 1: Clinical Investigation Plan history

Original CTP version:	1.0 dated 7/03/2023

Amendment #1:	<CIP version number> dated 7/03/2023
Modifications made / Reason for amendment:	
<CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>

Amendment #2:	<CIP version number> dated 7/03/2023
Modifications made / Reason for amendment:	
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>

Appendix 2: Data Processing Annex (DPA) between Sponsor and Participating Site(s)

Not applicable: single site study UZLeuven

Appendix 3: Hyperlink to RESIGHT video

Click on the thumbnail to view a short video on the practical use of the ReSight system

Appendix 4: Case Report Form in RedCAP

PDF export from RedCap eCRF

Appendix 5: Device Deficiency Form in RedCAP

PDF export from RedCap eCRF

Appendix 6: Adverse Event Form in RedCAP

PDF export from RedCap eCRF