CLINICAL INVESTIGATION PLAN

Title: SAFETY AND EFFICACY OF AN INTRACORNEAL PROSTHESIS IN PATIENTS WITH CORNEAL BLINDNESS

Abbreviated title/acronym: Intracorneal Prosthesis for Corneal Blindness / INTRAKER

EUDAMED Number: -

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Sponsor: Fondazione Banca degli Occhi del Veneto ETS (FBOV)

Via Paccagnella n. 11 - 30174 Zelarino Venice (VE)

Manufacturer: Intra-Ker S.r.l. - Viale A. Gramsci, 42 -- 47142 Forlì (FC)

Contract Research Organization: OPIS S.r.l. - Via G. Matteotti, 10 - 20832 Desio (MB)

Clinical investigation sites	**Investigators**	**Study acceptance**
Coordinating center Ophthalmology Unit - Cona Hospital (FE) Azienda Ospedaliero-Universitaria di Ferrara Via A. Moro, 8 - 44124 Ferrara	Principal Investigator Prof. Marco Mura	Signature _____ date _____
Satellite center n.1 Ophthalmology Unit - Villa Igea Hospital Ospedali Privati Forlì Viale A. Gramsci, 42 - 47122 Forlì (FC)	Principal Investigator Dr. Cristina Bovone	Signature _____ date _____
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Legal representative of the Sponsor	**Legal representative of the Manufacturer**
Dr. Diego Ponzin	Prof. Massimo Busin
Signature _____	Signature _____
date _____	date _____

ABBREVIATIONS

BCVA, best corrected visual acuity

CDVA, corrected distance visual acuity

CNVA, corrected near visual acuity

eCRF, electronic case report form

DD, device deficiency

MD, medical device

AE, adverse event

SAE, serious adverse event

ETDRS, early treatment for diabetic retinopathy study

FBOV, Fondazione Banca degli Occhi del Veneto ETS

IB, Investigator's Brochure

IOP, intraocular pressure

logMAR, logarithm of the minimum angle of resolution

CIP, clinical investigation plan

SD, standard deviation

CT, corneal tissue

VA, visual acuity

1. BACKGROUND AND RATIONALE

1.1 The cornea: structure and function

The cornea is a transparent and avascular tissue that continues posteriorly with the sclera forming the outermost tunic of the eye. The cornea acts as a barrier against infections and mechanical damage to the internal structures of the eye; moreover, the cornea and tear film are responsible for approximately 3/4 of the total refractive power of the eye [1].

From outside to inside, the cornea consists of five successive layers: corneal epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The outermost layer is a stratified epithelium composed of 5-6 layers of non-keratinized squamous cells capable of rapidly regenerating and restoring their integrity in case of injury. The epithelium rests on its own basement membrane, in continuity with Bowman's membrane, an acellular disorganized condensation of collagen fibers and proteoglycans. Below Bowman's membrane is the corneal stroma which constitutes 90% of the corneal thickness. It is composed of lamellae of collagen fibers that run parallel within the same lamella and are organized in orthogonal planes to one another. The regular spatial orientation of stromal collagen fibers and the constancy of the interfibrillar distance of collagen fibers are necessary requirements for maintaining tissue transparency. Descemet's membrane is a thin layer of collagen fibrils located between the stroma and endothelium. The endothelium is composed of a single layer of polygonal cells without replicative capacity that perform the function of osmotic pump regulating the degree of hydration of the corneal stroma and, consequently, the maintenance of transparency [1].

1.2 Indications for corneal transplantation and graft failure

Numerous infectious, inflammatory, and degenerative diseases can cause loss of corneal transparency, partially or completely compromising visual function. In these patients, the only effective therapeutic option for visual rehabilitation is the replacement of the diseased cornea with an analogous portion of vital and transparent tissue from a donor cornea (keratoplasty) [2].

However, the presence of neo-vascularization or ocular surface diseases as well as one or more previous corneal transplant procedures are all conditions associated with reduced survival of a transplanted graft either due to immunological rejection reaction or accelerated loss of the endothelial cell population, even in the absence of immunological rejection itself.

In these patients, within 3-10 years of surgery, 70% of transplants fail, despite local or systemic immunosuppressive therapy [3-5]. Any repetition of the transplant is accompanied by further reduced survival, so much so that after 3 failed transplants, most surgeons no longer operate [6].

To date, no safe and long-term effective treatment is yet available for corneal pathologies for which performing or repeating corneal transplantation is not indicated due to the high risk of failure.

1.3 Trans-corneal prostheses

The idea of replacing diseased tissue with an artificial cornea or corneal prosthesis was first introduced in 1789 by the French ophthalmologist Guillaume Pellier de Quengsy. The first surgical case was published in 1853 by Nussbaum who implanted a quartz crystal in the cornea and observed the maintenance of this prosthesis for the following 6 months. Further attempts to perfect a corneal prosthesis have been associated with a high failure rate, with tissue necrosis, aqueous humor loss, infections, and device extrusion. Subsequently, interest in corneal prostheses declined when Zirm successfully performed human corneal transplantation in 1906.

Since then, many corneal prostheses have appeared and subsequently disappeared from the ophthalmological landscape. Currently available prostheses, essentially the Boston keratoprosthesis and the odontokeratoprosthesis, are trans-corneal implants, and therefore represent a conduit between the external environment and the intraocular content: the first (not CE marked) is mainly used in eyes that have maintained adequate lubrication and eyelid function; the second mainly in cases associated with lubrication deficiency or ocular mal-occlusion [7].

There are no comparative studies on the efficacy, in terms of surgical failure, between repeat corneal transplantation and prosthesis implantation [8,9].

The use of trans-corneal prostheses is frequently associated with serious complications such as hypotony, intraocular infection and implant extrusion, as well as retroprosthetic membrane formation and glaucoma. The latter, for example, is reported in over 70% of implanted patients [10].

In addition, only a variable percentage from 50% to 65% of patients who receive a Boston keratoprosthesis maintain visual acuity of 1/10 at 3 years post-implantation [11]. Since FDA approval in 1992, very few studies have described the results of these trans-corneal prostheses with a follow-up exceeding 5 years.

The possibility of implanting the prosthesis within the corneal thickness would maintain it in an intracorneal and therefore extra-ocular position, thereby eliminating all complications arising from the trans-corneal nature of prostheses used until now.

1.4 The Intra-Ker intracorneal prosthesis - Rationale

Intra-Ker is an intracorneal prosthesis made of biocompatible poly-methyl-methacrylate (PMMA) consisting of an optical stem that acts as a lens, with the purpose of allowing light radiation to reach and form a focused image on the retina, equipped with 3 arms that extend outward with the purpose of anchoring the intracorneal prosthesis in the recipient's cornea (IB, Annex 1).

For implantation, the intracorneal prosthesis is (1) inserted between two central portions of corneal stroma derived from the posterior portion of two donor corneas, including Descemet's membrane and without endothelium, for the purpose of isolating the intracorneal prosthesis from contact with the external part of the eye (in the anterior part) and with the anterior chamber of the eye (in the posterior

part), and (2) positioned in the central portion of the recipient patient's cornea, replacing the diseased tissue (IB, chapter 2.7 'Instructions for use', Annex 7).

We believe that the application of Intra-Ker as indicated above, in patients with corneal opacity in whom corneal transplantation has a high risk of failure, can restore and maintain transparency of the central corneal portion over time, allowing light passage to the retina, and therefore vision, and the elimination of susceptibility to rejection phenomena - and the consequent potential implant failure - due to the absence of corneal endothelium.

2. OBJECTIVES and ENDPOINTS

The clinical investigation intends to evaluate the safety and efficacy of Intra-Ker application for visual rehabilitation of patients with monocular or binocular corneal blindness in terms of:

- manifestation of adverse events and intracorneal prosthesis defects (primary objective);
- improvement of visual acuity (secondary objective).

The following variables measured 12 months after prosthesis implantation will be considered:

- incidence of intraocular retroprosthetic inflammatory membrane formation (primary safety variable);
- percentage of patients showing vision improvement of at least one line of visual acuity, starting from the first week after surgery and stability or further improvement until the end of the study period (primary efficacy variable);
- type and frequency of adverse events and Intra-Ker defects.

3. DESIGN AND POPULATION

3.1 Type of clinical investigation

The clinical investigation is experimental, multicenter, prospective, single-arm, with 12-month follow-up observation, aimed at evaluating safety and performance of Intra-Ker, an invasive long-term surgical medical device (MD), classifiable in class IIb (EU Reg. 2017/745, Annex VIII, rule 8), not CE marked and used within the scope of intended use.

3.2 Patients

The study population consists of patients with unilateral or bilateral corneal blindness for whom corneal transplantation performed for the purpose of visual rehabilitation is not indicated due to poor short-to-medium term prognosis ("high-risk transplantation").

3.2.1 Inclusion criteria

1. age ≥ 18 years;
2. presence of light perception;

3. residual visual acuity limited to 1/10 (20/200) or worse;
4. clinical history of at least 2 keratoplasties of any type, performed for any indication and consecutively failed;
5. intraocular pressure ≤ 22 mm Hg;
6. understanding of the purpose and procedures of the clinical investigation and acceptance of participation through acquisition of informed consent.

3.2.2 Exclusion criteria

1. clinical history of ocular and/or systemic pathologies that could interfere with the effects of the study treatment or their evaluation (e.g., severe ocular surface diseases, severe optic nerve diseases, central retinal artery or vein occlusion, severe degenerative retinal alterations, retinal detachment, severe amblyopia, phthisis bulbi, etc.);
2. any condition that prevents understanding or communication of informed consent, study requirements and test protocols, including cognitive decline including diagnosed forms of progressive neurological disease, psychiatric illness, deafness;
3. previous implantation of another corneal prosthesis;
4. presence of known allergies to compounds (polymethylmethacrylate, chlorobenzothiazole, and benzoyl peroxide, biocompatible synthetic substances that constitute the prosthesis) and to drugs provided by the protocol;
5. non-acceptance of study evaluations and procedures;
6. (for female subjects) pregnancy, breastfeeding, or intention to plan a pregnancy during the study period;
7. ongoing participation, or within the 30 days preceding recruitment in the study, in any clinical trial with experimental drug or MD in the ophthalmological field;
8. conditions that could limit life to less than 1 year from the time of inclusion.

3.3 Sample size

The primary objective of the clinical investigation is to evaluate the safety of Intra-Ker in terms of percentage of adverse events and device defects applied within the scope of intended use.

In the literature, studies describing results obtained with Boston keratoprosthesis implantation show high incidences of complications. In particular, the trans-corneal nature of prostheses used to date involves intraocular exposure of non-biological material which is responsible for continuous inflammatory stimulation. This mainly translates into a foreign body reaction with formation of intraocular retroprosthetic inflammatory membranes that can compromise drainage pathways from the anterior chamber and pathologically raise intraocular pressure. Regarding the formation of such

membranes, Zerbe et al. report a frequency of 24.8% over an average follow-up period of 8.5 months [12].

The sample size analysis was performed considering the frequency values of retroprosthetic membrane formation reported by Zerbe et al., although the follow-up of this study is shorter than that of our proposed study. Based on the 1-tailed binomial test, estimating a 5% incidence of this complication after Intra-Ker implantation, it will be necessary to treat 27 eyes to obtain an alpha value of 0.025 with a statistical power of 80%. The total number of patients to be included in the study will be increased to 30 to account for a possible 10% drop-out.

4. ORGANIZATION

4.1 Sponsor

The clinical investigation is sponsored by Fondazione Banca degli Occhi del Veneto ETS (FBOV) which assumes responsibility for initiating, managing, and securing funding for the clinical investigation.

Sponsor's contact person for the clinical investigation: Dr. Diego Ponzin, Legal representative
c/o Padiglione G. Rama, Via Paccagnella, 11 -- 30174 Zelarino Venice (VE)
Tel 041 9656400; mob. 348 3111141; diego.ponzin@fbov.it

The Sponsor signs an agreement with each of the entities involved in the clinical investigation (using the forms of the EC Coordinating Center) in which the responsibilities of each party are defined, the commitment to provide the Intra-Ker medical device and all other study-related materials free of charge, coverage of the costs of visits and examinations that will be performed for each patient involved in the clinical investigation, and the stipulation of an RC insurance policy to cover any damages that may occur in relation to the trial.

4.2 Investigation centers

The clinical investigation will be conducted in Italy at three centers:

Coordinating center (identifier: 0-)
Azienda Ospedaliero-Universitaria di Ferrara
Ophthalmology Unit - Cona Hospital (FE) - ITALY
Via A. Moro, 8 - 44124 Ferrara
Principal investigator and study coordinator: Prof. Marco Mura
Tel: 0532 237817; Fax: 0532 237908; E-mail: marco.mura@unife.it

Satellite center n.1 (identifier 1-)
Ospedali Privati Forlì
Corneal Pathophysiology Unit - Villa Igea Hospital

Viale A. Gramsci, 42 - 47122 Forlì (FC) - ITALY
Principal investigator of satellite center n.1: Dr. Cristina Bovone, Ophthalmology specialist
Tel: 0543 419 574; Fax: 0543 419566; E-mail: cristinabovone@yahoo.com
Satellite center n.2 (identifier 2-)
Az. Ospedaliero Universitaria 'Renato Dulbecco' of Catanzaro
Ophthalmology Unit
Viale T. Campanella, 115 - 88100 Catanzaro (CZ) - ITALY
Principal investigator of satellite center n.2: Prof. Vincenzo Scorcia, Ophthalmology specialist
Tel: 0961 364 7135; Fax: 0961 364 7133; E-mail: vscorcia@unicz.it

5. PROCEDURES

5.1 Variations from current clinical practice

The planned procedures do not constitute the standard approach for patients with corneal blindness adopted until now at the Ophthalmology units involved in the clinical investigation.
Patients will be evaluated before surgery (T0) and after 1, 2, 3, 7, 14, 21 days and after 1, 2, 3, 6, 12 months from intracorneal prosthesis implantation.
Data referable to these visits will be collected following acceptance of participation in the clinical investigation and signing of informed consent by patients.

5.2 Treatment

5.2.1 MD under investigation and intended use

For restoration of visual function, eligible patients who agree to participate in the study will undergo corneal surgery with implantation of the Intra-Ker intracorneal prosthesis, a MD in synthetic material, long-term invasive surgical type, not CE marked, which falls into risk class IIb (EU Reg. 2017/745, Annex VIII, rule 8).
The clinical investigation provides that the MD be used within the scope of **intended use**: To provide a transparent optical pathway to allow light passage through the central portion of the cornea in eyes presenting permanent corneal opacity, following failure of corneal transplantation of any type for any indication, for which further transplantation is not feasible due to high risk of failure.
The Intra-Ker intracorneal prosthesis is a rigid monoblock MD constructed with biocompatible material (polymethylmethacrylate, PMMA) and comprises a central optical plate (diameter 4.3 mm and thickness 0.6 mm) that acts as a lens, with the purpose of transmitting light and forming a focused image on the retina, and a peripheral haptic part composed of 3 fenestrated arms of width 1.1 mm that engage in the optical plate at approximately 120° from each other and extend outward for

approximately 3 mm with the purpose of anchoring the prosthesis in the recipient's cornea for a total width equal to 10 mm (IB, Annex 1).

The implantation of the Intra-Ker prosthesis occurs within a keratoplasty procedure during which the keratoprosthesis is inserted in the central portion of the recipient patient's corneal stroma, replacing the diseased tissue, together with two donor cornea supports obtained from the posterior portion of two donor corneas, including Descemet's membrane and without endothelium, which perform the function of isolating the intracorneal prosthesis from contact with the external part of the eye (in the anterior part) and with the anterior chamber of the eye (in the posterior part).

To request donor cornea supports to be used during Intra-Ker implantation, complete the following table and communicate with:

Dr. Diego Ponzin, tel 041 9656400; mob. 348 3111141; diego.ponzin@fbov.it

Center identifier	
Investigator's surname and name	
Patient identifier	
Date of inclusion in clinical investigation	
Expected date for surgery	
Power of Intra-Ker optical plate (axial length)	

Unused MDs and donor corneal tissues will be collected and disposed of by the Sponsor.

5.2.2 Preparation of corneal stroma sections

The donor cornea supports to be used for Intra-Ker prosthesis implantation are prepared in the FBOV laboratory, following patient inclusion in the clinical investigation and receipt of the supply request from the Investigator.

FBOV is a regional reference center for corneal transplantation authorized for selection, preparation, and preservation of human corneas for transplantation. The activity is performed by specialized personnel according to standardized eye banking techniques (IB, chapter 2.6.2).

The donor cornea supports are made using two donor corneas both subjected to the following processing sequence:

1. hydro-assisted deep lamellar dissection to obtain separation of the deep posterior corneal stroma from the pre-Descemetic layer;
2. partial trephination and removal of the anterior layers of the corneal stroma and reduction of thickness by approximately 50%;

3. removal of a central portion of the deep posterior stroma of the cornea until reaching the pre-Descemetic layer to create the central recess.

This processing makes available two identical donor cornea supports, each intended to: support the intracorneal prosthesis in the posterior corneal part and protect it in the anterior corneal part.

Each support consists of a ring of posterior corneal stromal tissue and pre-Descemetic layer with thickness equal to approximately 250 microns and diameter approximately 11-12 mm (the scleral portion of the donated cornea is also included), surrounding a central recess of approximately 4 mm in diameter consisting of a thin central layer represented precisely by the corneal pre-Descemetic layer.

The complete sequence for cornea processing, quality and safety controls, and shipping conditions to investigation centers are reported in the IB (chapter 2.6.2).

5.2.3 Surgical application of Intra-Ker

Only one eye of each patient will be subject to surgery. In patients with bilateral blindness, Intra-Ker will be implanted in the more compromised eye, while in the case of eyes in the same conditions in the same patient, the right eye will be implanted. Patients will be operated under peri-bulbar anesthesia, unless specifically requested general anesthesia by the patient, obtained through peribulbar injection of 10.0 ml of ropivacaine 0.75% solution.

The surgical procedure includes:

1. central partial corneal trephination (diameter 6.5 mm)
2. lamellar keratectomy of the anterior stroma in the central 6.5 mm zone;
3. creation of an intracorneal pocket for 360 degrees, starting from the base of the trephination, extended to the limbus;
4. removal of the remaining part of the cornea within the central 6.5 mm;
5. reduction of the first donor cornea support by punching with diameter 6.5 mm and transplantation of this portion within the central 6.5 mm of the recipient's cornea; fixation by interrupted suture in 10-0 nylon;
6. positioning of Intra-Ker (convexity upward) resting on the donor cornea support and insertion of the fenestrated arms into the corneal pocket prepared as indicated in point 2;
7. reduction of the second donor cornea support by punching with diameter 6.5 mm and transplantation of this portion outside the central 6.5 mm of the recipient's cornea to protect the intracorneal prosthesis in the anterior part of the eye; fixation by interrupted suture in 10-0 nylon.

Patients may remain hospitalized for the first 3 days after surgery.

The complete description of the surgical procedure is reported in the IB (chapter 2.6.3).

5.2.4 Pharmacological therapy

To reduce the risk of intraocular infection, at the end of the Intra-Ker intracorneal prosthesis implantation procedure, triamcinolone acetonide (1 mL, 40mg/mL) and gentamicin sulfate (1 mL, 40mg/mL) are administered by subconjunctival injection.

In the postoperative period, patients should use Betabioptal eye drops (combined ophthalmic solution based on Chloramphenicol 5mg/mL and Betamethasone 2mg/mL) one drop every 2 hours for 14 days reduced to one drop 4 times a day for an additional 14 days.

Subsequently, the medication is discontinued and the patient will use an eye drop based on Chloramphenicol 0.4%, one drop a day for the following 6 months.

5.2.5 Definition of absence of clinical benefit / MD functioning / surgical failure

Absence of clinical benefit is defined as the lack of visual improvement.

The **MD is defined as functional** if transparency of the optical pathway is restored, which regardless of improving the patient's visual acuity allows exploration of intraocular structures by the Investigator.

Surgical failure is defined as lack of improvement/worsening of visual acuity in the presence of complications requiring surgical re-intervention (formation of intraocular retroprosthetic inflammatory membranes; prosthesis extrusion; corneal tissue liquefaction).

5.3 Criteria for participation interruption and exclusion of enrolled patients

Patients who agree to participate in the clinical investigation have the right to discontinue participation at any time they deem appropriate, for any reason and without having to provide justifications. Patients will be guaranteed the best care provided for their condition. The reason for voluntary discontinuation of the clinical investigation must be indicated in the electronic case report form (eCRF).

Patients who do not attend the follow-up visit will be considered 'lost to follow-up'. The Investigator undertakes to contact these patients at least twice and, in case of contact, will verify adherence to the protocol and the patient's willingness to continue the study (this activity is recorded in the eCRF).

In case of adverse events or serious adverse events, the Investigator may evaluate study discontinuation and patient exclusion.

Patients will be followed until event resolution or condition stabilization and possible exclusion dependent on event manifestation.

In all cases, the Investigator will do everything possible to perform the evaluations provided for the end-of-study visit and record the results in the eCRF.

5.4 Safety variables

The following safety variables evaluated at each study visit through objective examination and/or patient reporting will be examined:

- type and number of adverse events (AE) and device deficiencies (DD).

In particular, the formation of intraocular retroprosthetic inflammatory membranes represents the primary endpoint on which the sample size calculation is based.

The safety evaluation and list of possible expected and unexpected AEs and DDs are included in the Risk Management Process (IB, chapter 5) and summarized in this clinical investigation plan at point 8.2.

5.5 Efficacy variables

For measurement of visual functionality (secondary variable), the results of evaluations performed 12 months after intracorneal prosthesis implantation will be considered using the following visual acuity tests:

- ETDRS test for distance
- Jaeger test for near

In the presence of visual acuity below 1/10, the ability to count fingers / perception of hand movement / perception of light will be evaluated.

The results of the above tests will be considered separately.

5.6 Clinical data collected

All data of clinical investigation participants will be recorded and stored by personnel involved in the study at each center in visit reports that must include the description of instrumental examination results and the printout of such examination evaluations (for OCT, Ultrasound, fundus oculi examinations).

Visit reports are archived in each patient's hospital record, images used for instrumental evaluation in the memories of instruments used for examination.

Data useful for the study are subsequently reported on the eCRF for each patient.

5.6.1 Screening visit - **SV**

The study is illustrated to the patient and witness/guardian/legal representative (as needed) who are asked for availability for anamnesis research, objective examination and vital signs evaluation, and performance of a series of examinations, in both eyes, to verify whether study inclusion criteria are met.

During SV, patient eligibility for study participation is determined by evaluating all inclusion and exclusion criteria as specified in section 3.2.

In SV, complete medical history is collected, and signs and symptoms of all significant previous pathologies are documented.

Medical history includes alcohol consumption and smoking habit. In addition, demographic data are collected which will include year of birth, sex, and ethnicity.

Current medical conditions found at this visit are considered concomitant diseases.

Diseases that manifest or are detected for the first time during the study and/or worsening of a concomitant disease during the study are instead documented in the hospital record and reported in the eCRF as AE (see point 8.2).

EVALUATIONS AT SV (ophthalmological instrumental examinations are performed in both eyes)

- Inclusion and exclusion criteria
- Clinical history
- Demographic data
- Current topical and systemic therapies
- Vital parameters (body temperature, blood pressure, heart rate)
- Objective examination in both eyes
- Visual acuity measurement (ETDRS optotype)
- Slit lamp ocular examination
- Digital ocular pressure
- Optical coherence tomography (OCT) of the anterior segment
- B-scan and A-scan ocular ultrasound
- NEI VFQ-25 daily activities questionnaire, compatible with the patient's visual condition (text in Annex)

Images of slit lamp observation must remain archived in the memory of the instrument used for evaluation; the description of the examination result must be reported in the visit report, archived in the patient's hospital record.

OCT and ultrasound images must remain archived in the memory of the instrument used for evaluation; the description of the examination result must be reported in the visit report, archived in the patient's hospital record together with the printout of the examination result.

Color images of the ocular fundus must remain archived in the memory of the instrument used for evaluation; the description of the examination result must be reported in the visit report, archived in the patient's hospital record together with the printout of the examination result.

If the evaluations performed in SV are favorable, and in case of acceptance of participation, the patient and witness/guardian/legal representative (as needed) are asked to sign the informed consent.

Patients presenting bilateral disease condition are illustrated the criterion that determines the choice to implant the Intra-Ker intracorneal prosthesis in one of the two eyes: the worse eye or the right eye in case of equal severity between the two eyes.

5.6.2 Study start visit - **V1** (day of surgery)

EVALUATIONS AT V1 (instrumental examinations are performed in both eyes):

- Vital parameters: body temperature, blood pressure, heart rate
- Documentation of adverse events
- Current topical and systemic therapies
- Slit lamp evaluation

5.6.3 Follow-up visits after 1, 2, 3, 7, 14, and 21 days and 1, 2, 3, 6 and 12 months from surgery (**V2-V12**)

EVALUATIONS DURING FOLLOW-UP (instrumental examinations are performed in both eyes)

- Vital parameters: body temperature, blood pressure, heart rate
- Protocol adherence
- Current topical and systemic therapies
- Efficacy evaluation
    - CDVA measurement at 4 meters (ETDRS optotype)
    - CNVA measurement (Jaeger optotype)
    - NEI VFQ-25 daily activities questionnaire (only at V5 and V12)
- Safety evaluation
    - Slit lamp ocular examination
    - Optical coherence tomography (OCT) of anterior and posterior segment (macula and optic nerve for ocular health evaluation and identification of significant changes in ocular structures.
    - Evaluation of adverse events manifestation and MD defects
- Color photography of ocular fundus to evaluate the ability to visualize ocular fundus details using a scale from 0 to 4: *0 -- Not readable. Disc and macula region are not visualized 1 -- Optic disc is visualized. Other retinal details are poorly visualized. 2 -- Optic disc, macula, major retinal vessels are visualized. Second-order or higher-order retinal vessels are not visualized. 3 -- Optic disc, macula, major retinal vessels are visualized. Second-order or higher-order retinal vessels are poorly visualized. 4 -- Optic disc, macula, major retinal vessels are visualized. Second-order or higher-order retinal vessels are well visualized.*

5.6.4 Study conclusion

With Visit 12 after 12 months from Intra-Ker implantation, the study period ends.

The Investigator provides the patient with a visit report regarding clinical condition and indicates the most appropriate therapy, possible prescription of contact lens or glasses, or the need for further interventions.

The Investigator completes the "Study conclusion" form present in the eCRF.

5.6.5 Supplementary visits

1. If during one of the follow-up visits there is evidence of worsening of the operated eye condition (for example detectable following vision worsening) underlying an AE/DD, the patient must be adequately treated and monitored at intervals of no more than 7 days until complete resolution of the clinical picture.
2. If the patient reports disturbances or abnormalities during any phase of the study, the Investigator must perform at least biomicroscopy examination of the ocular surface and subjective refraction measurement, records the supplementary and/or emergency visit in the hospital record, and reports the recorded data in the appropriate "Emergency visit / Unscheduled visit" form present in the eCRF.

5.6.6 Criteria for participation interruption and exclusion of enrolled patients

Patients who have agreed to participate in the study have the right to discontinue participation at any time they deem appropriate, for any reason and without having to provide justifications. Patients will be guaranteed the best care provided for their condition. The reason for voluntary study discontinuation must be indicated in the "Study conclusion" form present in the eCRF.

Patients who do not attend the follow-up visit will be considered 'lost to follow-up'. The Principal Investigator undertakes to contact these patients at least twice and, in case of contact, will verify adherence to the protocol and the patient's willingness to continue the study (this activity is recorded in the eCRF).

The Investigator may decide to discontinue the study and exclude the patient in case of adverse events or serious adverse events manifestation (for example prosthesis extrusion and/or need for further surgery). In such case, the patient will be followed until event resolution or condition stabilization, and possible exclusion will be considered dependent on event manifestation (as indicated in chapter 8.2).

In case it is necessary to explant the Intra-Ker prosthesis, the patient will be followed for at least 6 months following this occurrence to evaluate possible onset of adverse events following the explant procedure. The results of such evaluations are recorded and also reported in the eCRF.

In all cases, the Principal Investigator will do everything possible to perform the evaluations provided for the study conclusion visit and record the results in the eCRF.

6. CLINICAL INVESTIGATION CHART

Evaluation	**SV**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
	-	T0	1 d	2 d	3 d	7 d	14 d	21 d	1 m	2 m	3 m	6 m	12 m
Demographic data	x												
Inclusion / exclusion	x												
Medical history	x												
Vital parameters	x	x	x	x	x	x	x	x	x	x	x	x	x
Current therapies	x	x	x	x	x	x	x	x	x	x	x	x	x
Slit lamp	x	x	x	x	x	x	x	x	x	x	x	x	x
CDVA (ETDRS)	x		x	x	x	x	x	x	x	x	x	x	x
CNVA (Jaeger)			x	x	x	x	x	x	x	x	x	x	x
Ocular pressure	x		x	x	x	x	x	x	x	x	x	x	x
OCT anterior segment	x		x	x	x	x	x	x	x	x	x	x	x
OCT posterior segment			x	x	x	x	x	x	x	x	x	x	x
B-scan and A-scan ultrasound	x												
NEI VFQ-25 questionnaire	x					x							x
Fundus evaluation			x	x	x	x	x	x	x	x	x	x	x
Adverse events (AE)		x	x	x	x	x	x	x	x	x	x	x	x
Device deficiencies (DD)		x	x	x	x	x	x	x	x	x	x	x	x

7. CONCOMITANT TREATMENTS AND TREATMENT MODIFICATIONS

7.1 During the study, it will be possible to use topical or systemic anti-inflammatory and immunosuppressive therapy.

7.2 In case it is necessary to visit the patient at different times than the visit schedule provided in the protocol, the results of such visits are reported on the "Emergency visit / Unscheduled visit" form of the eCRF.

7.3 In case of events and clinical conditions dependent on the intracorneal prosthesis (for example intra and extra ocular infection; prosthesis extrusion, tissue liquefaction) that put the integrity of the ocular globe at risk, the intracorneal prosthesis may be explanted and the eye subjected to another type of surgery (for example total conjunctival coverage).

Re-implantation of Intra-Ker is not provided in case explantation is necessary or the prosthesis is extruded.

7.4 In case of expected or unexpected adverse events occurrence, the Investigator may decide to modify the treatment provided by the protocol based on their clinical judgment, in terms of variation of follow-up visit frequency, use of topical and systemic drugs, secondary surgical interventions.

7.5 In case of absence of clinical benefit, the study will still be continued without modifications to the treatment and follow-up provided by the protocol.

8. ADVERSE EVENTS AND MEDICAL DEVICE DEFICIENCIES

8.1 Definition of adverse event (AE), serious adverse event (SAE) and device deficiency (DD)

For the definition of event types, reference is made to Article 2 of Regulation (EU) 2017/745 integrated by "MDCG 2020-10/1 safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745".

AE is any undesirable clinical manifestation that occurs in a subject participating in a clinical trial. The manifestation of an AE does not imply that there is a relationship between the AE and the medical device and/or procedure under study.

SAE is any unfavorable medical event that results in death, or serious deterioration of health (life-threatening illness or injury; persistent or significant disability or incapacity; hospitalization or prolongation of existing hospitalization; medical or surgical intervention to prevent permanent damage to a body structure or function, chronic pathology).

DD is any deficiency at the level of identity, quality, durability, reliability, safety or performance of the investigational device, including malfunction, use errors, inadequacy of information provided by the manufacturer.

8.2 Expected and unexpected AEs

The risk analysis of the Intra-Ker MD (IB, chapter 5) has shown that, in general, the implantation of the intracorneal prosthesis as indicated in the Instructions for use and provided in the study, includes expected risks analogous to those highlighted for trans-corneal prostheses, and to those correlatable to the type of surgery and corneal transplantation.

Expected AEs manifest as:

1. Retroprosthetic membrane formation (*)
2. Ocular infection
3. Hypotony
4. Hypopyon
5. Hyphema

6. Vitreous hemorrhage
7. Expulsive hemorrhage
8. Choroidal hemorrhage
9. Inflammation near a suture requiring surgical therapy
10. Choroidal detachment
11. Retinal rupture or detachment
12. Cystoid macular edema
13. Vitreous, retinal, subretinal hemorrhage
14. Pupil irregularity associated with structural iris defects
15. Opacification, loss, extrusion or intrusion of the MD (*)
16. Infectious endophthalmitis
17. Uveitis, sterile vitritis, vitreous incarceration
18. AE from drugs and/or interactions with drugs or pre-existing medical conditions
19. Allergic reaction to anesthesia
20. Loss of ability to perceive light (*)
21. Corneal ulceration and melting (*)
22. Onset or progression of glaucomatous optic neuropathy

(*) AEs associated with Intra-Ker medical device implantation

Diseases that manifest or are detected for the first time during the study and/or worsening of a concomitant disease during the study are documented in the eCRF as AE.

Detection of health status worsening not previously considered in the Risk Analysis will be considered an unexpected AE.

8.3 Recording, reporting, follow-up of AEs and DDs

The occurrence of AEs and DDs in the period between V1 and V12 must be recorded in the patient's hospital record and reported in the eCRF by the Principal Investigator together with date and time of onset, date and time of disappearance, duration, detected at study visits according to the schema reported in chapter 6. Intensity, relationship with treatment, actions taken and therapies administered must also be reported.

Although female patients who are pregnant or planning a pregnancy during the study times are excluded from being recruited, in the case of female patients who discover they are pregnant during the study, pregnancy details will be collected and reported and patients withdrawn from the study.

The Investigator must report the pregnancy to the study Sponsor within 24 hours of becoming aware by sending the paper "Reportable event form" to: all_phv@opisresearch.com.

The Principal Investigator ensures that subjects in the study receive adequate medical care in case of SAE until complete event resolution.

The manifestation of SAE and DD that could have caused an SAE if appropriate measures had not been taken, intervention had not occurred or circumstances had been less fortunate, must be promptly communicated by the Investigator to the study Sponsor through appropriate paper "Reportable event form" to email address all_phv@opisresearch.com immediately and no later than 3 calendar days from the date of knowledge.

Follow-up information is sent in the same way as the original Report. Any recurrence, complication or progression of the original event must be reported as follow-up of that event, regardless of when it occurs. Follow-up information must describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from participation in the clinical investigation.

The Sponsor communicates as soon as possible to the Competent Authority and the Territorial Ethics Committee of each center, but no later than 2 calendar days from the date of knowledge (in case of imminent risk of death, serious injury or serious illness requiring timely corrective action for other patients/subjects, users or other persons or new evidence) or 7 calendar days from the date of knowledge (in case of any other reportable events or new finding/update of the same) regarding points a), b) and c):

a) any SAE that has a causal relationship with the investigational device, comparator or investigation procedure, or in case such relationship is reasonably possible;

b) any DD that could have led to an SAE if appropriate action had not been taken, the device had not been used, circumstances had been less fortunate;

c) any new evidence in relation to any of the events in a) and b).

The study Sponsor informs the Principal Investigators of other centers regarding all reportable SAEs and DDs of which it has received notification (ISO 14155:2020).

Pending availability of the Electronic System for clinical investigations (Regulation (EU) 2017/745 Art 73), communication will occur using the indications reported in the document "MDCG 2020/10-1 safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 October 2022" using the "Clinical Investigation Summary Safety Reporting Form".

9. STATISTICAL CONSIDERATIONS

Data will be collected during evaluations and clinical examinations regularly scheduled according to the study protocol. Subject demographic data, clinical history, risk factors, preoperative, procedural

and postoperative data will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation) and frequencies or proportions for discrete variables.

Estimates of primary and secondary endpoints will be reported together with related 95% confidence intervals. The one-tailed binomial test will be used to compare the frequency of retroprosthetic membrane occurrence (primary endpoint) after Intra-Ker implantation with that reported in the literature after Boston keratoprosthesis implantation [12]. Kaplan-Meier analysis will be used to determine AE rates over the follow-up duration provided by the study protocol.

Analysis of data collected with the NEI-VF25 questionnaire will follow the method indicated by the authors [13].

10. CLINICAL INVESTIGATION DURATION

Patient recruitment: 6 months

Patient permanence in clinical investigation: 12 months from surgery date

Data analysis: 1 month

Reporting: 1 month

Total duration: 20 months

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