**INFORMATION SHEET AND INFORMED CONSENT FORM FOR PATIENT PARTICIPATION IN A CLINICAL TRIAL**

**Official trial title** SAFETY AND EFFICACY OF AN INTRACORNEAL PROSTHESIS IN PATIENTS WITH CORNEAL BLINDNESS

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**Official trial title in more understandable terms for the patient** USE OF AN ARTIFICIAL CORNEA TO RESTORE VISION

**Structure-context in which the trial will take place**

**Coordinating center and trial coordinator**

Ophthalmology Unit, Cona Hospital - University Hospital of Ferrara (FE)

Trial Coordinator Prof. Marco Mura

**Registry in which the trial has been or will be registered (if applicable) and identification code if available**

Identification code _____

Registry_____

**Principal investigator**

Name _____

Affiliation _____

**Sponsor/Funding entity**

FONDAZIONE BANCA DEGLI OCCHI DEL VENETO ETS

**Ethics committee**

This document consists of the following sections:

A. PREAMBLE

B. INFORMATION SECTION. TRIAL SUMMARY: KEY INFORMATION

C. INFORMATION SECTION. FURTHER DETAILS

D. CONSENT EXPRESSION SECTION

ATTACHMENTS

ADDITIONAL DOCUMENTS

*Dear Sir/Madam, the information contained in the following information sheet is very detailed. We ask you to agree to participate in the trial ONLY after having carefully read this information sheet and having had a THOROUGH DISCUSSION with a member of the trial team who must dedicate the NECESSARY TIME for you to fully understand what is being proposed to you.*

## A. **PREAMBLE**

*Dear Sir/Madam,*

*We propose that you participate in the clinical trial that we will describe below.*

*It is your right to be informed about the purpose and characteristics of the trial so that you can make a conscious and free decision about whether to participate.*

*This document aims to inform you about the nature of the trial, its purpose, what participation will entail for you, including your rights and responsibilities.*

*We invite you to carefully read what is reported below. The researchers involved in this project, indicated at the beginning of this document, are available to answer your questions. No question that comes to mind is trivial: do not be afraid to ask!*

*In addition to us, you can discuss the proposal contained in this document with your family doctor, your family members and other people you trust. Take all the time necessary to decide. You can take home an unsigned copy of this document to think about it or to discuss it with others before making a decision.*

*If you decide not to participate in the trial, you will still receive the best possible care for patients with your condition/disease.*

*Your refusal will not be interpreted in any way as a lack of trust.*

*If you are unable to sign the informed consent, consent can be provided and recorded through appropriate alternative means, such as audio or video recordings, in the presence of at least one impartial witness.*

*Once you have read this form, received answers to any questions and possibly decided to participate in the trial, you will be asked to sign a consent form, of which you will receive a paper copy.*

The Principal Investigator

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## B. **INFORMATION SECTION**

### GENERAL TRIAL SUMMARY: KEY INFORMATION

*This section aims to present in summary form the key aspects of the trial we are proposing you join. The following sections will provide more details in order to give you the opportunity to express or not express fully informed consent to your participation in the trial.*

***- Why am I being asked to participate in this trial?***

*We are asking you to participate in a clinical trial funded by Fondazione Banca degli Occhi del Veneto ETS because you have permanent central corneal opacity in one or both eyes that prevents*

*vision and for this condition a further cornea transplant performed for the purpose of rehabilitating vision is not indicated due to the high risk of failure ("high-risk transplant").*

*A possible alternative therapy to transplantation could be the implantation of a prosthesis made of synthetic material, that is, a transparent medical device that allows light to pass to the retina and enables vision. However, the currently available prostheses cross the entire corneal thickness and penetrate the eye beyond the posterior portion of the cornea, causing a series of early and late unfavorable reactions based on inflammation that lead to the failure of the procedure due to opacification of the prosthesis, ulceration and disintegration of the corneal tissue near the prosthesis, expulsion of the prosthesis.*

*You have been included among those being asked to participate in this trial because you have certain clinical characteristics that will be better specified in section C.*

***- What are the objectives of the trial? How many centers and patients will participate?***

*The trial is being conducted to answer this question: "Is the implantation of the Intra-Ker synthetic material intracorneal prosthesis for visual rehabilitation of patients with corneal blindness safe, in terms of the type and number of adverse events and defects that may occur after it has been implanted in the cornea?"*

*We are conducting this trial to understand whether the new surgical approach to corneal pathology that consists of replacing the opaque central corneal portion with a prosthesis made of biocompatible synthetic material inserted exclusively within the corneal thickness, so that it is maintained in an intracorneal and therefore extra-ocular position, allows elimination of all the complications of currently available prostheses that penetrate the eye (trans-corneal prostheses).*

*As a secondary objective, we will evaluate the improvement of vision, since the presence of the prosthesis in position at the center of the cornea will allow the passage of light to the retina and therefore vision.*

*The trial is expected to take place in 3 Italian centers and include 30 patients.*

***- What is the routine care approach for treating the disease corneal blindness?***

*The routine care approach is cornea transplantation.*

*In the medical situation in which one or both of your eyes find themselves, having already received 2 or more consecutively failed transplants, a further cornea transplant is not feasible because it would not be able to guarantee corneal transparency due to rejection phenomena or other complications that suggest, in current clinical practice, that such a situation can only be addressed with solutions different from cornea transplantation alone performed with donor corneal tissue.*

*The trial is expected to take place in 3 Italian centers and include 30 patients.*

***- Is deciding whether to participate or not my free choice?***

*You can freely choose whether or not to participate in the trial. Even after accepting, you can change your mind at any time.*

***- If I decide not to give my consent to participate in the trial, what choices do I have?***

*If you decide not to participate in the trial, you can still be followed by the clinical center that is caring for you and will be treated using the best approved (non-experimental) therapeutic methods for your disease.*

*In addition, you may participate in another trial that may be underway.*

***- What happens if I decide to participate in the trial?***

*If you decide to participate in the trial, you will be placed on the surgical programming list that the hospital provides for the study and treated with the procedure provided by the protocol and, within approximately 1-3 months at most, you will receive the implantation of the Intra-Ker corneal prosthesis, a medical device not yet CE certified. After surgery you will be followed for 12 months. The total duration of your participation can therefore reach 15 months.*

*Before taking part in the trial, the doctor asked you to perform some examinations and verified that you have the characteristics required to participate. During the trial, non-invasive ophthalmological instrumental evaluations are planned, which will be detailed below.*

*The entire program of visits and examinations planned during the trial is reported in the next section "What examinations, tests and procedures are planned in the trial?"*

***- What are the risks and benefits if I participate in the trial?***

*Both risks and benefits can result from participation in this trial. It is important to carefully evaluate them before making a decision.*

***Expected benefits***

*By joining the trial, you will have the opportunity to be treated with a medical device, the Intra-Ker intracorneal prosthesis, which could be decisive in terms of the need to regain vision.*

*In addition, by joining the trial you will contribute to the development of corneal prostheses for the treatment of corneal blindness when traditional cornea transplantation is no longer indicated. In the future, you yourself and other patients with your disease could benefit from it.*

*The use of the Intra-Ker keratoprosthesis in a few subjects with your disease (pilot study) has shown that the new treatment/intervention is free of serious side effects and there is very preliminary evidence that some of the patients who were operated on benefited from it. It is therefore possible, but not proven, that the treatment will improve your disease. However, your participation in the trial will allow doctors to acquire useful knowledge to treat future patients.*

***Potential risks***

*We want to make sure that you understand from the outset what some possible risks are: additional information can be found in the next section "What risks can I face if I participate in this trial?"*

*If you decide to take part in this trial there is the risk that the treatment will prove ineffective and it will not be possible to achieve improvement in visual acuity due to the presence of complications related to the prosthesis implantation (formation of intraocular retroprosthetic inflammatory membranes; prosthesis extrusion; ulceration and disintegration of corneal tissue) that require surgical re-intervention.*

*The study provides for careful monitoring of each of these reactions and, if necessary, the performance of additional surgery.*

*The important known adverse reactions for the experimental treatment, in addition to those related to the keratoprosthesis reported above, are those related to eye surgery and subsequent post-surgical therapy: allergic reaction to anesthesia, infection, hypotony, hypopyon, hyphema, hemovitreous, expulsive hemorrhage, choroidal hemorrhage, inflammation near a suture requiring surgical therapy, choroidal detachment, retinal tear or detachment, cystoid macular edema, vitreous, retinal, sub-retinal hemorrhage, pupil irregularities associated with structural defects of the iris, infectious endophthalmitis, uveitis, sterile vitreitis, vitreous incarceration, onset or progression of glaucomatous optic neuropathy, adverse events related to drugs and/or interactions with drugs or pre-existing medical conditions.*

***- Is consent final? Can I decide to withdraw from the clinical trial (voluntary withdrawal)?***

*You can decide to withdraw from the trial at any time and for any reason, without having to justify your decision.*

*If you decide to no longer participate, let one of the investigator physicians know as soon as possible: it is important to stop treatment safely. The doctor may consider a final check-up visit/examination appropriate.*

*The doctor will keep you informed of any changes in the trial that may affect your willingness to participate.*

***- Are there reasons why the trial might be stopped not by my choice (early termination)?***

*Yes, the investigator physician may decide to stop your participation in the trial if:*

- *your health conditions should change and participating in the trial would be potentially harmful;*
- *new information becomes available and the trial is no longer in your best interest;*
- *you do not follow the agreed rules for participation in the trial;*
- *for women: you happen to start a pregnancy during the trial;*
- *the trial is stopped by the competent authorities or by the sponsor.*

*In any case, you will be provided with the opportunity to continue the planned follow-up visits in case of consent withdrawal, trial suspension, pregnancy or other.*

## C. *INFORMATION SECTION*. FURTHER DETAILS

1. **What is the purpose of the trial?**

*The trial intends to evaluate the safety and efficacy of the application of the Intra-Ker intracorneal prosthesis for visual rehabilitation of patients with corneal blindness in one or both eyes in terms of:*

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

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

- *presence of formation of intraocular retro-prosthetic inflammatory membrane (primary safety variable);*
- *number of patients showing improvement in vision 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 number of adverse events and defects of Intra-Ker.*

2. **What is the intervention under investigation?**

*The trial is conducted in 3 ophthalmological centers, is prospective, includes only one treatment group (approximately 10 patients treated in each of the 3 centers for a total of 30 patients), with follow-up observation lasting 12 months after surgical implantation of the corneal prosthesis, and is aimed at evaluating the safety and performance of Intra-Ker, a long-term surgical invasive medical device, classifiable in class IIb, (EU Reg. 2017/745, Annex VIII, rule 8), not yet CE certified.*

*The Intra-Ker intracorneal prosthesis is a rigid monoblock device made of biocompatible material (polymethylmethacrylate, PMMA) and includes 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 part composed of 3 fenestrated arms with a width of 1.1 mm that fit into the optical plate and extend outward for about 3 mm with the purpose of anchoring the prosthesis in the recipient's cornea.*

*The trial provides that Intra-Ker be used within the scope of its intended use: "To provide a transparent optical pathway to allow the passage of light through the central portion of the cornea in eyes that have permanent corneal opacity, following failure of any type of cornea transplant for any indication, for which a further transplant is not feasible due to high risk of failure."*

*The planned surgical procedures do not constitute the standard approach for patients with corneal blindness adopted to date at Ophthalmology units, including those involved in the trial.*

*If you agree to participate, you will need to have 12 ophthalmological visits, one before surgery (intracorneal prosthesis implantation) and the following after 1, 2, 3, 7, 14, and 21 days and after 1, 2, 3, 6, 12 months from intracorneal prosthesis implantation.*

*The study population consists of patients with unilateral or bilateral corneal blindness for whom a cornea transplant performed for the purpose of rehabilitating vision is not indicated due to poor short-medium term prognosis ("high-risk transplant"). Patients will be selected based on the following criteria:*

*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.*

*Exclusion criteria*

*1. clinical history of ocular and/or systemic pathologies that could interfere with the effects of the treatment under study or their evaluation (for example: 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 disease, deafness;*

*3. previous implantation of other corneal prosthesis;*

*4. non-acceptance of study evaluations and procedures;*

*5. presence of known allergies to compounds (polymethylmethacrylate, chlorobenzothiazole, and benzoyl peroxide, biocompatible synthetic substances that constitute the prosthesis) and drugs provided by the protocol;*

*6. (for female subjects) pregnancy, breastfeeding or intention to plan a pregnancy during the study period;*

*7. ongoing participation or in the 30 days preceding recruitment in the study in any clinical trial with experimental drug or medical device in the ophthalmological field;*

*8. conditions that could limit life to less than 1 year from the time of inclusion.*

*If you complete the trial and have benefited from the new treatment, you will not need to receive additional administrations of the device.*

*If you have not benefited from the treatment, the prosthesis is not expected to be used twice for the same eye.*

*In the event that further investigations relating to the Intra-Ker prosthesis are abandoned for your disease, your treating physician will reassess your treatment options.*

3. **What examinations, tests and procedures are planned if I participate in the trial?**

*If you agree to participate, you will need to have 12 ophthalmological visits (in addition to the day of surgery), the first in which your inclusion in the study will be evaluated and you will be offered participation. If you accept, the surgical procedure (intracorneal prosthesis implantation) will be performed and you will be evaluated in subsequent visits after 1, 2, 3, 7, 14, and 21 days and after 1, 2, 3, 6, 12 months from intracorneal prosthesis implantation.*

*During these visits, each lasting approximately 30 minutes, non-invasive instrumental ophthalmological examinations will be performed that are part of the usual care approach for*

*patients with corneal pathology, all of which are mandatory for the trial, while the surgical implantation of the Intra-Ker intracorneal prosthesis (lasting approximately 1 hour) is not part of the usual care approach.*

*Safety and efficacy evaluations of the prosthesis will include*

- *the initial visit (with measurement of vital parameters, blood pressure, heart rate and body temperature), objective examination of both eyes, quality of life questionnaire;*
- *post-surgery visits include: measurement of vital parameters, current topical and systemic therapies*

*efficacy evaluation (vision measurement, daily activities questionnaire), safety evaluation (ocular examination at the slit lamp, optical coherence tomography of the anterior and posterior segment, evaluation of the occurrence of adverse events and defects of the medical device, color photography of the ocular fundus).*

*The implantation of the intracorneal prosthesis performed*

*The implantation of the Intra-Ker prosthesis occurs as part of a surgical procedure during which the keratoprosthesis is inserted in the central portion of the corneal stroma in replacement of the diseased tissue, together with two healthy cornea supports obtained from the posterior portion of two donor corneas, including the Descemet's membrane and without endothelium, which perform the function of isolating the intracorneal prosthesis from contact with the outside of the eye (in the anterior part) and with the anterior chamber of the eye (in the posterior part). In this way it is ensured that the prosthesis remains intra-corneal.*

4. **What risks can I face if I participate in the trial?**

*The reasonably foreseeable risks, including those related to the medical device under investigation and the treatment modality (corneal surgery) that you may face are the following:*

- *lack of efficacy of the experimental treatment: even if we believe that the new treatment can act on your disease better than those already available, we cannot exclude that it will be ineffective in you;*
- *events dependent on the surgical procedure, necessary for prosthesis implantation, and subsequent therapies that have the purpose of reducing the risk of post-operative infection (which we believe are comparable to those expected for surgical procedures concerning the cornea.*

5. **How will I be informed of any unexpected results following diagnostic investigations?**

*The trial does not include analyses (genetic, radiographic, etc.) from which unexpected results may emerge.*

6. **Is it useful/necessary to inform my family doctor?**

*If you decide to participate in the trial, it is important to inform your general practitioner. To this end, we have prepared a letter that you can deliver to your doctor, in which the trial procedures are explained.*

7. **What will be my commitment and responsibilities if I decide to participate?**

*If you decide to participate in the trial you are asked to commit to:*

- *Scrupulously observe the indications and requests from the healthcare staff following the trial and guarantee attendance at appointments.*
- *Inform the doctor following the trial:*
    - *of any side effects that arise during the trial,*
    - *of any visits or hospital admissions in facilities other than the investigator center,*
    - *of current or past participation in other clinical trials.*

8. **Will I have to face costs for participation in the trial? Will I be reimbursed for any expenses? Will I receive compensation?**

*There are no costs to you resulting from participation in the trial as these are fully covered by the Sponsor.*

*Economic compensation for participation in the trial is also not provided.*

9. **What happens if I suffer damage as a consequence of participation in the trial?**

*Participation in a trial may involve inconveniences and risks that cannot be determined in advance. For this reason, the trial provides insurance coverage to protect your participation.*

*In compliance with current laws, insurance is provided to cover any damage suffered due to participation in the trial, for the entire duration of the trial, covering the civil liability of the investigator and the sponsor.*

[INDICATE THE INSURANCE COMPANY, POLICY NUMBER, MAXIMUM FOR PARTICIPANT, AGGREGATE MAXIMUM *the details of which you will find attached*]

*Under Ministerial Decree of July 14, 2009, the insurance policy does not cover the amount exceeding the maximum and is exclusively operative for damages for which a claim for compensation has been submitted no later than the period provided in the policy* ([30 MONTHS]). *This limitation does not however affect your right to obtain compensation from the party responsible for any damage (to protect the trial subject).*

10. **How will my health data be processed and who will have access to it, including identifying data, during the trial?**

*Your data, in particular personal data and health data and only to the extent that they are indispensable in relation to the objective of the trial and for pharmacovigilance purposes, will be processed in compliance with EU Regulation 2016/679, known as GDPR (General Data Protection Regulation) and Legislative Decree August 10, 2018, no. 101. In practical terms, documents relating to the participant will be kept in a secure place and will not show your name in clear text, known only to the researchers, but an identification code.*

*The data, made anonymous, may be subject to control by regulatory bodies and used for scientific publications (journals, conferences).*

*Your clinical data collected for the purposes of the trial, as well as the results of the examinations performed, will be kept for the times provided by the regulations and subsequently destroyed. They*

*will not be destroyed only if a) it is no longer possible to trace them back to your identity, because they were anonymized during the trial itself; b) in the presence of your specific informed consent.*

*If personal data are transferred to a third country or an international organization, all the guarantees provided by article 46 of GDPR 679/2016 relating to the transfer will be adopted.*

*Further information is included in the attached data processing authorization form.*

11. **How will my biological samples taken for the purposes of the trial be processed and who will have access to them?**

*The trial does not involve the collection and storage of biological samples.*

12. **How can I have access to the results of the trial?**

*Once the trial is concluded and all the resulting data have been collected, they will be analyzed to draw conclusions. The investigators and the sponsor undertake to make them available to the scientific community.*

*The regulation provides for the possibility of access by participants to the trial results. Therefore, you may ask the investigator physician to communicate the general results of the trial to you.*

13. **Has the trial been approved by the Ethics Committee?**

*The protocol of the trial that has been proposed to you has been examined and approved by the Ethics Committee ..... The Ethics Committee has among other things verified the compliance of the trial with Good Clinical Practice Standards and the ethical principles expressed in the Declaration of Helsinki and that safety, rights and your well-being have been protected.*

14. **Who can I contact to obtain more information about the clinical trial I am invited to participate in?**

*For further information, you can contact:*

[INDICATE NAMES AND REFERENCES OF THE INVESTIGATOR CENTER STAFF TO WHOM THE PARTICIPANT CAN TURN]

Dr. [SPECIFY NAME], [SPECIFY PHONE NUMBER, EMAIL]

[INDICATE WHO TO CONTACT ON HOLIDAYS AND ANY AVAILABLE CONTACTS]

15. **If I join the trial, who can I contact in case of need?**

*For any doubts and unplannable or unplanned events during the trial (doubts relating to the ongoing treatment, side effects, decision to abandon the trial, etc.), you can contact:*

[INDICATE NAMES AND REFERENCES OF THE INVESTIGATOR CENTER STAFF TO WHOM THE PARTICIPANT CAN TURN]

Dr. [SPECIFY NAME], [SPECIFY PHONE NUMBER, EMAIL].

[INDICATE WHO TO CONTACT ON HOLIDAYS AND ANY AVAILABLE CONTACTS]

*If you consider it appropriate to report events or facts relating to the trial you have joined to subjects not directly involved in the trial itself, you may refer to the Ethics Committee that approved the trial (INDICATE), to the Health Management of the Trial Center (INDICATE), to the competent authority (AIFA).*

_____ ___/___/_____ _____
_____

Full name of the physician Date Time Signature

who delivered the information

**Attachments**

- Insurance policy
- Consent form for processing of personal data

**Additional documents:**

- Letter for the physician