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Approvals :

Job Title	Approved by	Quality Role	Date	Signature status	Comment
CRA	Ido Klein	Approver	20-Oct-2022	Approved	
CMO	Gilad Litvin	Approver	20-Oct-2022	Approved	
VP QA / RA / CA	Gerry Tal	Approver	20-Oct-2022	Approved	

Change Revision History :

Rev.	Date	Change Description	ECO	Release Date
L	20-Oct-2022	Section 10.11 - Premature Termination or Suspension of the Study was added		
K	23-May-2021	• Section 4.2.3 - Table 1 (CorNeat KPro lens features) - revised per updated IFU • Section 4.2.7 - Implantation procedure - revised to include a description of the removal of flanges procedure and per updated IFU • Section 8.1.5 - Post-operative supportive care - added a requirement to instruct the patient to wear UV-blocking sunglasses after surgery.	ECO-27286	13-Jul-2021
J	06-Jan-2021	• Added section 10.9 - Device Explantation • Added reference to IOP measurements in section 8.1.6 • Added section 8.1.5 - Post operative Supportive Care		

I	01-Oct-2020	Changes were made to section 4.2.2. "Optics" per Health Canada's comments received on 24.9.2020		
H	06-Jul-2020	Safety management was revised to state that SAE reporting to the Sponsor will be done via the EDC system		
G	01-Jul-2020	• Pseudophakia was added as an inclusion criteria • References pertaining IOL implantation during the CorNeat KPro surgical procedure were omitted • Unanticipated Adverse Device-related Event (UADE) definition was added (section 10.5)		
F	11-May-2020	Hospitaization period will be per the PI's discretion (estimated 1 day)		
E	07-May-2020	The word "plan" was replaced with the word "Protocol"		
D	28-Apr-2020	• Added specification for IOP measurement technique • Added a recommendation for hospitalization of 2 days after the surgery		
C	10-Feb-2020	Format correction (PDF was uploaded to QMS)		
B	10-Feb-2020	1. typographical errors correction and minor phrasing improvements were made. 2. Section 2 - Abbreviations were added 3. Section 8.2 – Minor inclusion & exclusion criteria adjustments were made 4. Section 5.2.3 – Two notes were added: 1. Regarding the preference that patients should be pseudophakic at the end of the procedure; 2. Regarding the requirement that an extra CorNeat KPro unit and a corneal graft will be		

		ready in the operating room 5. Section 9.1.3 – Intraoperative evaluation procedure was corrected 6. Section 9.2 – Table of Assessments was corrected according to the actual planned schedule of procedures 7. Section 11.7 – Known Potential Risks section was added. 8. Header and footer were changed to comply with document control format of the QMS		
A	10-Feb-2020	Baseline		

CLINICAL INVESTIGATIONAL PROTOCOL

Study Name:

Prospective, open label, single arm, First in Human (FIH) clinical study to assess Safety and efficacy of the CorNeat Keratoprosthesis for the treatment of corneal blindness

Sponsor:

CorNeat Vision
Email: info@CorNeat.com
4 Hasheizaf St. Raanana, Israel

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

Table of Contents

1 Abbreviations

ICF	Informed Consent Form
FIH	First In Human
OCT	Optical coherence tomography
DSMB	Data-safety-monitoring-board
REB	Research Ethics Board
MedDRA,	Medical Dictionary for Regulatory Activities
EC	Ethics Committee
KPro	Keratoprosthesis
PT	Preferred Term
OD	Right eye
OS	Left eye
SAE	Serious Adverse Events
eCRF	Electronic Case Report Form
BCVA	Best Corrected Visual Acuity
VAS	Visual Analogue Scale
SOC	Standard Of Care
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device-related Events

2 Investigator Agreement

I have read and understand the protocol and agree that it contains all the ethical, legal and scientific information necessary to conduct the Study. I confirm that I am legally and technically qualified to serve as an investigator for this clinical trial and agree to personally conduct and supervise the described study. I agree to conduct the study as detailed herein and in compliance with ISO 14155 and applicable regulatory requirements. I will provide copies of the protocol to all physicians, nurses and other professional personnel who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the investigational device used in the trial, the permitted concurrent medications, the efficacy and safety parameters, the conduct of the study and their roles and responsibilities in the study. Furthermore, I understand that any changes in the protocol must be approved in writing by the Sponsor and subsequently must be approved by the reviewing Ethics Committee/ Research Ethics Board, prior to their implementation; except when necessary to protect the safety, the rights or welfare of subjects.

I agree to allow sponsor monitors and auditors as well as inspectors from regulatory authorities, full access to all source documents, including medical records, at the research facility for subjects screened in the study.

A signed, written informed consent form will be obtained from all subjects or the subject's legally authorized representative and the date that this consent was obtained will be appropriately documented in the subject's medical file.

I further agree to report to the sponsor any adverse experiences in accordance with the terms of this protocol, local regulation, and ISO 14155.

_____

Principal Investigator Name (Print) _____

Principal Investigator (Signature) _____Date _____

Medical Center Name: _____

3 Study Synopsis

Study Name:
Prospective, open label, single arm, First in Human clinical study to assess Safety and efficacy of the CorNeat Keratoprosthesis for the treatment of corneal blindness
Objectives: The objective of this clinical study is to prove the safety of the CorNeat Keratoprosthesis (KPro).

Study endpoints:

Primary Safety Endpoint:

The frequency and severity of all unanticipated adverse device-related events (UADE) or treatment-related adverse events, during and after implantation of the CorNeat KPro and up to 12 months should be less than SOC (as detailed in section Known Potential Risks).

Effectiveness Endpoints:
Primary Endpoint: Retention of implant
Secondary Endpoint: Improved visual acuity

Intended uses: The CorNeat KPro's intended use is to treat corneal blindness, by providing a clear optical media, in patients with an opaque cornea, who are not suitable candidates for Keratoplasty.

Study Population: 10 subjects suffering from unilateral or bi-lateral corneal blindness, not reasonably amenable by transplanting human tissue. The KPro can be implanted in OD or OS (selection is according to PI discretion).
Study Duration: Subjects will be followed up for 12 months following device implantation

Inclusion criteria – (i) Male or female aged ≥ 18 and ≤ 80 years on the day of screening; (ii) Candidates must have the ability and willingness to attend all scheduled visits and comply with all study procedures; (iii) keratoprosthesis surgery is indicated in cases when keratoplasty is not a reasonable option or following a verifiable history of prior failed corneal transplantation. (iv)Indications that fall under poor candidate for keratoplasty include but are not limited to: herpetic keratitis, vascularized corneal scar, Ocular Cicatricial Pemphigoid, alkali burn, Steven Johnson Syndrome, and limbal stem cell deficiency; (v) pseudophakia; (vi) adequate tear film and lid function; (vii) perception of light in all quadrants; (viii) Female patients of childbearing age must have negative pregnancy test at screening and agree to use an effective method of contraception throughout the study.
Exclusion criteria – (i) reasonable chance of success with traditional keratoplasty; (ii) current retinal detachment; (iii) connective tissue diseases; (iv) end stage glaucoma; (v) history or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to planned implantation; (vi) history of ocular or periocular malignancy; (vii) history of extensive keloid formation; (viii) any known intolerance or hypersensitivity to topical anaesthetics, mydriatics, or component of the device; (ix) signs of current infection, including fever and current treatment with antibiotics; (x) severe generalized disease that results in a life expectancy shorter than a year; (xi) any clinical evidence that the investigator feels would place

the subject at increased risk with the placement of the device; (xii) corneal thickness less than 400 or higher than 1,200 microns in any region of the pachymetry map of the eye intended to be operated; (xiii) currently pregnant or breastfeeding; (xiv) participation in any study involving an investigational drug or device within the past 30 days or 5 half-lives of the drug (whichever longer) or ongoing participation in a study with an investigational drug or device and; (xv) intraoperative complication that would preclude implantation of the study device; (xvi) Vulnerable populations

Patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the protocol and implanted with the CorNeat Kpro device.

Visit Schedule:

- Screening:

  Day -14-0, Subjects will sign ICF on screening visit and baseline assessment will be performed.

- Baseline examinations and Implantation:

  Implantation day will be recorded as day 0; enrolment day.

- Follow Up- (up to 12 months) visit schedule: One day post op, one week, one, two three, six, nine- and twelve-months post-surgery.

On each follow-up visit, subjects will be subjected to the following examinations: (i) slit-lamp biomicroscopy, (ii) visual acuity (BCVA), (iii) IOP, (iv) concomitant medications record, (v) Pain assessment and (vi) Adverse events recording. In addition, OCT/UBM imaging will be performed on screening visit, on 1week post-op and every 3 months starting at 3 months post-surgery.

Sample size consideration:
Sample size of 10 patients for FIH study to assess the safety of the application on a non-statistical basis According to FDA guidance document for Keratoprosthesis, a sample size of 20 patients is required for product 510(k) approval Guidance dated March 3, 1999

Sample size justification:
Reference to FDA guidance for Keratoprosthesis 510K where proving safety is the target and 20 subjects with a minimum of 330 days of follow up is needed.

Safety Assessment: A record of UADE, Incidence and nature of serious adverse events (SAE), Incidence and nature of adverse events
will be collected throughout the study starting from implantation visit.
The ten first implanted subjects will comprise the FIH cohort. Once the 10^{th} subject successfully completes the 6^{th} month post-surgery follow-up, an independent data-safety-monitoring-board (DSMB) will review the data and submit its conclusions to the ethics committee/REB and regulatory authority.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).
AE data will be listed individually and summarized by SOC and by PT within a system organ class.
Additional tables will present adverse events by PT, SOC and severity and by relatedness to study device.

Ethics Committee /REB and regulatory authority

The study protocol, IB describing the device, its materials, manufacturing process, verification and validation tests and the ICF, which will be in compliance with the study protocol will be submitted to the ethics committees in the participating clinical sites and the respective governing regulatory authorities. The study can start once ethics committees and regulatory authority approval is granted.

Surgeons training for conduct of the clinical trial

- Ophthalmologist training prior to subject enrolment: presentation and wet lab to practice, leveraging a real animal model and where available Human cadaver eyes. The goal of this phase is to train the ophthalmologists who will participate in the study.

Preparation of eCRF and EDC database for data management

The electronic Case Report Form (eCRF) will collect subjects' data during study visits. These include: (i) recording of adverse events; (ii) any concomitant medications if applicable; (iii) demographic data; (iv) medical history; (v) surgical outcome and; (vi) primary and secondary endpoint parameters. The data collected by the eCRF will be accumulated in an Electronic Data Capture (EDC) system database. Data will be entered by study staff during the study and at its conclusion by data management personnel corresponding with the study monitor and site investigators. It will be collected by data improvement through queries, which is automatic using the system's edit checks while data is typed in, and manually following source data verification (performed at monitoring visits). The EDC system will be in compliance with GCP and with Directive 95/46/EC of the European Parliament and of the Council of 24th of October 1995 on the "Protection of individuals with regard to the processing of personal data and on the free movement of such data".

Statistical considerations

Statistical calculations are not required in this FIH study

Conduct of clinical study

Subjects will be screened by the participating clinical sites' clinical team (physician and study staff) during a screening visit. Each subject will sign the ICF (Informed Consent Form) prior to any study activities and will be evaluated for inclusion and exclusion criteria. Only eligible

subjects will be enrolled in the study. Demographic data, medical history and concomitant medication use data will be collected from enrolled subjects. Subjects will be implanted with the CorNeat KPro, and followed-up over a period of 12 months in 8 clinic visits. During follow up visits safety data and use of concomitant medication will be documented. Subjects accrual is planned for a maximum of 12 months and overall first subject in to last subject out is planned for 24 months.
Follow up plan will include complete clinical exam, anterior segment photography and a questionnaire assessing pain and other possible subjective ramifications.

Monitoring of the clinical study
The sponsor will ascertain that the clinical trial is adequately conducted and perform monitoring activities including: sites' initiation, monitoring visits to ensure adherence of sites to the study protocol and GCP, data management activities, sites close out and preparation of final clinical study report. During monitoring visit source data verification will be performed. The CRA will assist in the application submission to the ethics committees and regulatory authorities. The CRA will be responsible for ongoing communication with the ethics committees and regulatory authorities as applicable and as required during the trial.

The CRA will perform its activities following a written and signed delegation of responsibility letter.

Safety management
Any adverse events will be documented and monitored according to the monitoring plan. Reporting of adverse events and serious adverse events will be done as per GCP, ISO 14155:2011 and local regulations. PI will document all serious adverse events (SAE) on the SAE Report Form. SAE will be transmitted to CorNeat Vision via the EDC system. Sponsor's medical monitor will oversee safety management of the study.

4 Introduction

4.1 Background Information

4.1.1 Clinical Context

Corneal pathology is a leading cause of blindness worldwide with 20-30 million patients in need of a remedy and around 2 million new cases/year.[1] The epidemiology of corneal blindness is complex and encompasses injury and a wide variety of infectious, genetic, and inflammatory eye diseases, which cause corneal scarring or opacity and lead to functional blindness. Current solutions for corneal blindness and disease include penetrating keratoplasty (PKP; corneal transplantation), lamellar keratoplasty (DMEK, DALK), and rarely keratoprosthesis (KPro; artificial cornea implantation). Together, keratoplasty and to a much lesser extent KPros

[1] Corneal blindness: a global perspective, John P. Whitcher; M. Srinivasan; Madan P. Upadhyay; Bulletin of the World Health Organization, 2001.

address 5%-10% of global cases.[2] Though a profound cause of distress and disability, transplanting tissue is carried out only around 200,000 times/year worldwide.[3]
In the USA, where there is no shortage in corneal tissue,[2] 51,294 corneal transplantations were performed during 2018, of them the number of PKP grafts was 17,347.[4] Long term graft survival rate following PKP is estimated at 90% after 5 years and 82% at 10 years for first time grafts and 53% and 41% for first re-grafts.[5] These performance rates, plus the fact that some corneal blindness indications are not suitable for keratoplasty, translates to an ever-growing number of patients for whom there is no suitable solution. Moreover, given the fact that visual acuity following PKP depends on the tissue quality, the surgery, the medical indication, and the patient vision potential, many of the patients undergoing PKP are left with poor vision.
Several attempts to develop an artificial cornea have failed in creating robust, scalable and reliable solutions. As such, there exists an unmet need for an efficient, long-lasting and affordable solution to corneal pathology, injury and blindness, which would alleviate this suffering and disability and enable patients to fully exploit their vision potential.

4.1.2 Standard Of Care (SOC)

The transplantation of corneal tissue – keratoplasty – is the method of choice for the replacement of damaged and/or diseased corneal tissue. However, keratoplasty, as a mean for restoring the patient's vision has not effectively resolved all, or even most cases of corneal pathology, due to graft failure, graft retention, and the paucity of harvested, viable, tissue.
In the USA and other countries with mature eye banking, approximately 20% of patients have either failed one or more transplantations or are not a suitable candidate for one. Indications such as recurrent herpes keratitis, ocular cicatricial Pemphigoid, Steven Johnson's syndrome, rejected graft and vascularized cornea are not suitable for keratoplasty and currently have no available solution.
An artificial solution would solve many shortcomings of the Standard of Care (SOC) and therefore alleviate the suffering of scores of affected individuals, predominantly in the developing world. So far, attempts at creating scalable KPros have failed. Whereas previous keratoprostheses (KPros; see Appendix I for comparison to the Boston KPro) have integrated an artificial lens into a biological substrate and was then implanted into the eye, the CorNeat KPro is completely synthetic, involving a microporous skirt and leveraging the subconjunctival space.

[2] Global Survey of Corneal Transplantation and Eye Banking. Gain P1, Jullienne R; He Z; Aldossary M; Acquart S; Cognasse F; Thuret G

[3] The value of corneal transplantation in reducing blindness; Garg P; Krishna PV; Stratis AK; Gopinathan U; Eye (Lond). 2005 Oct;19(10):1106-14.

[4] Eye bank association of America 2018 statistical report.

[5] Long-term graft survival after penetrating keratoplasty, Robert W Thompson Jr.,Marianne O Price, Patrick J Bowers, Francis W Price Jr., Ophthalmology, July 2003, Volume 110, Issue 7.

4.2 Device Description

4.2.1 Product Overview

The CorNeat KPro is a synthetic cornea developed to provide a long-lasting medical solution for corneal blindness, pathology and injury. The solution is designed to provide an accessible, efficient, effective and reliable remedy for people with cornea-related visual impairments.
The CorNeat KPro implant is a patented synthetic cornea that utilizes a novel polymeric bio-integrating skirt to assimilate synthetic optics within resident ocular tissue. Currently available solutions rely either on donor tissue (keratoplasty) or on synthetic implants mounted on biological carrier tissues then attached to the native corneal tissue – a tissue lacking blood vessels and healing capacity. In contrast, the CorNeat KPro integrates seamlessly with the eyewall, underneath the fibroblast-rich and aggressively scarring site of the conjunctiva.
The CorNeat KPro implant (Figure 1) consists of two main components: a lens made of polymethyl methacrylate (PMMA) and a porous integrating skirt surrounding it, made of non-woven and non-degradable medical grade polyurethane mesh.

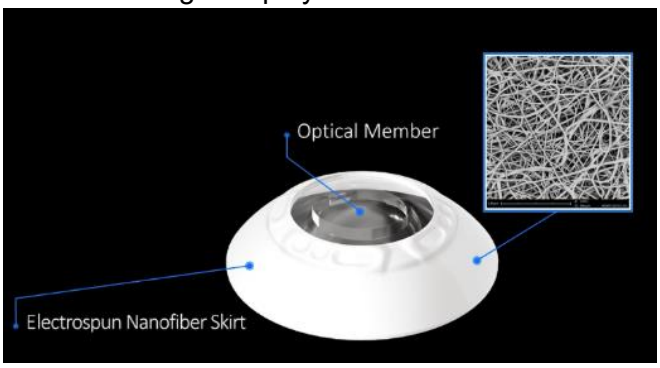


Figure 1: CorNeat KPro main components

The CorNeat KPro is supplied with a set of dedicated implantation tools meant to facilitate a novel and relatively simple surgical procedure, which does not require human tissue and can be performed by most ophthalmic surgeons. The CorNeat KPro implantation kit is depicted in Figure 2. The CorNeat KPro solution, its principles of operation, and corresponding surgical procedure have been proven safe and reliable in multiple preclinical studies and animal implantations. The solution is poised to significantly impact US and global corneal blindness treatment as it is significantly superior to any available alternatives.

Figure 2: The CorNeat KPro implantation kit

4.2.2 Optics

a. The CorNeat KPro's optical element is made of medical-grade PMMA. It provides excellent light transmission as well as UV and hydro stability. The lens is designed to provide a fixed optical power, which is equivalent to that of a normal cornea. The lens, which extends almost the entire way to the limbus (10mm in diameter), provides an effective optical zone approximately 6.5mm in diameter, enabling the patient to benefit from a wide field of view. It also enables the ophthalmologist to examine the patient's eye and perform cataract and retinal surgery post implantation, if necessary. Such surgical procedures can be performed through the 4 access ports located on the rim of the PMMA optics.

   The current optical power of the CorNeat KPro is normalized to 42 D (Figure 3), similar to the naitive cornea and will enable patients to regain sight.. The CorNeat KPro optical design is expected to deliver unprecedented Best Corrected Visual Acuity (BCVA) with no astigmatism.

b. In order to eliminate potential astigmatism due to device malposition/decentration, the CorNeat KPro lens' surfaces are spherical.

c. Any previously implemented IOL was chosen with a dioptric power that has been calculated to enable optimal visual acuity with the patient's native or previously implanted cornea, prior to becoming opaque and requiring Kpro implantation. The range of corneal optical power is not as extensive as that of IOLs. IOL power is mainly influenced by axial length. The residual, post-surgical, optical error is expected to be mild to moderate and one that can be corrected by the aid of spectacles in case of need. The CorNeat KPro can be implanted in any pseudophakic patient and following the implantation the refractive error will be determined and spectacle correction will be prescribed in case of need.
   Patients meeting the inclusion and exclusion criteria suffer from serious vision impairment in one or both eyes. These patients will regain vision but to achieve their full vision potential might need to use spectacles. We believe regaining sight outweighs the surgical and post-surgical risks which are mitigated as far as possible.

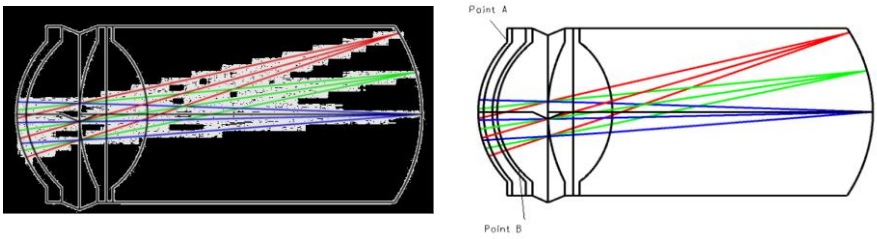


Figure 3: Schematic eye (ZEMAX Ray diagram) with (a, left) natural cornea, and (b, right) KPro cornea.

4.2.3 Properties Relevant to the Clinical Function

The following Figure 4 depicts the CorNeat KPro's anterior and posterior sides. The sections below outline the device features relevant to the clinical function.

Figure 4: CorNeat KPro - anterior and posterior sides

Lens

The CorNeat KPro lens (Figure 5) is made from medical grade PMMA. This material is known to be safe and has been used extensively for manufacturing intra-ocular lenses. PMMA is used also for manufacturing FDA-approved KPros, such as the Boston KPro and Osteo-Odonto KPro. Figure 5 depicts the CorNeat KPro lens Figure 5. Figure 6 and Table *1* outline the CorNeat KPro lens' features relevant to clinical functions.

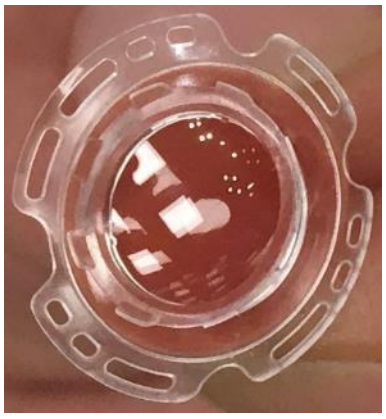


Figure 5: CorNeat KPro Lens

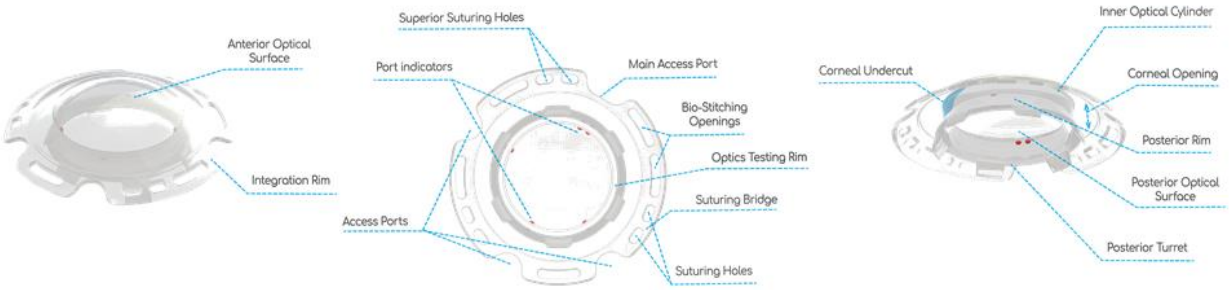


Figure 6: CorNeat KPro lens features

Table 1: CorNeat KPro lens features

Feature		Relevance to clinical function
Corneal undercut/Corneal opening		The lip on the posterior side of the lens hosts the patient's corneal stump. It has a wide opening that can accommodate thick or edematous corneas (up to 1.5mm think). This wide opening also allows for aqueous humor to reach the edge of the cornea, maintain its health and avoid or minimize thinning or melting. In order to keep the eye watertight immediately post-implantation, the undercut wall diameter is slightly larger than the trephination diameter.
Posterior turret		A set of flanges on the posterior side of the lens assist the surgeon with the implant fitting process, and secure the remnant cornea in place. The flanges enable a methodological fitting process as they eliminate the chances of the cornea slipping out of the undercut after being placed into it.
Integration rim	Suturing holes	3 pairs of suturing holes are positioned on the lens' rim, 120 degrees apart. These holes enable suturing the lens to the eye wall at the area of the limbus using non-degradable sutures. The suturing of the device to the eye ensures its centration, retention and bio-integration. It also facilitates the process of fitting the patient's cornea into the KPro corneal undercut.
	Superior Suturing holes	The superior suturing holes are placed at the 12 o'clock position assisting in correct alignment of the device.
	Access ports	4 access ports (openings) on the rim of the PMMA lens positioned around the limbus enable penetrating the anterior chamber with surgical tools . Insertion of surgical instruments into the anterior chamber or vitreous cavity allows intraocular surgical procedures to be performed after CorNeat KPro implantation, if necessary. Ports are positioned in locations consistent with current best practices for cataract and retinal surgery for both right and left eyes.
	Main access port	The main access port, which should be positioned at 11 o'clock, is 2.6mm wide. This port is designed to enable IOL injection following KPro implantation.

	Port indicators	Following implantation, the integration rim, including the access ports, are expected to be covered by conjunctiva. A set of indicators on the optic's edge that are visible under a microscope assist the surgeon in locating the access ports post implantation. The port indicators, which are essentially tiny "bumps" on the surface of the PMMA, are placed on the edge of the central optical zone; one opposite each access port, and two opposite the main access port.
	Integration holes	The integration holes on the rim of the lens are filled with the skirt material. Connective tissue is expected to grow through these holes, practically "biostitching" the PMMA lens onto the sclera. This mechanism further ensures device attachment, mitigating risks of detachment in case the skirt fibers weaken or detaches from the lens.

Integrating skirt

The CorNeat KPro integrating skirt is made from a flexible, durable and non-degradable porous material that stimulates cellular proliferation. The skirt is 250 microns thick and easily placed under the conjunctiva. The skirt extends 6mm from the edge of the lens transparent zone (1cm in diameter) and ends approximately 1mm from the closest insertion of the extraocular muscles (spiral of tillaux).

The skirt dimensions are designed to fit most eyes. Nonetheless, it can be easily cut and adjusted by the surgeon to fit any eye.

4.2.4 Indications for Use

The ultimate intent of CorNeat Vision is to approve the CorNeat KPro as an **alternative to SOC - penetrating, or full thickness, corneal transplantation (Penetrating Keratoplasty, PKP)** where patient tissue is replaced with donor tissue. Section 4.2.6 below outlines PKP indications. Given the commercial and clinical risks involved, CorNeat Vision plans to undertake a stepwise approach, initially seeking approval of the CorNeat KPro device and implantation kit for patients who are poor candidates for PKP. For these indications there is a regulatory precedent as documented in FDA guidance on 510(k) submissions for KPros dated March 3, 1999. These initial indications for use are similar to those that apply to commercially available synthetic corneal implants, such as the Boston KPro. Section 4.2.54.2.5 outlines current indications of use for KPros. The initial intended use for the CorNeat KPro is defined below and is consistent with the FDA's definition of Class II special controls.

Per the FDA guidance for the initial first step, The CorNeat KPro device will be defined as a "keratoprosthesis device implanted permanently to provide a transparent optical pathway through an opacified cornea in an eye that is not a reasonable candidate for a corneal transplant."

As a second step, and once the device safety is validated in a limited clinical study (per the applicable FDA guidance), CorNeat Vision plans to take the necessary steps and initiate additional clinical trial/s and expand the indications for use to also cover those of PKP.

In the treatment of corneal opacities, keratoplasty is the SOC. For some medical indications causing corneal opacities, failure rates of keratoplasty are unacceptable. Patients not suitable

for keratoplasty may attempt keratoprosthesis implantation as a last resort. The following sections outline the major indications for both patient groups.

4.2.5 KPro Indications

- Following corneal transplantation failure
- Vascularized cornea (at least two quadrants)
- Disciform corneal scar due to herpetic keratitis
- Stevens-Johnson syndrome (SJS)
- Ocular cicatricial pemphigoid (OCP)
- Autoimmune diseases
- Ocular burns (acid and alkali) with stem cell deficiency
- Other conditions with poor prognosis with traditional PKP

4.2.6 PKP Indications

- Keratoconus and ectasias
- Corneal degenerations
- Corneal dystrophies including Fuchs endothelial dystrophy
- Ulcerative keratitis infectious and non-infectious
- Post infectious keratitis
- Congenital opacities
- Chemical injuries without stem cell deficiency
- Mechanical trauma
- Refractive indications
- Regraft related to allograft rejection
- Regraft unrelated to allograft rejection

4.2.7 Implantation Procedure

The CorNeat KPro implantation procedure is relatively short (30-45 minutes) and simple when compared to keratoplasty and other KPros. Unlike current practices requiring delicate suturing of transparent donor corneal tissue to the patient's native cornea – a process which is performed by very skilled and well-trained ophthalmic surgeons – the CorNeat KPro snaps into the patient's trephined cornea and is sutured to the eye wall using 3 non-degradable sutures. The provided Marker and Snapper tools enable precise fitting of the device, yielding a well-developed implantation process, which can be taught in a few hours. The process itself minimizes the time the eye is trephined and open (also known as "open sky") to less than one minute, significantly reducing the risk of infection, expulsive hemorrhage, and other complications.

Optional: In cases where the recipient cornea is suspected of being overly stiff, it is recommended to remove two of the posterior rim flanges to facilitate extension of the trephined corneal stump around the posterior turret and insertion into the undercut. If required, place the

KPro on a sterile gauze pad under a microscope, and locate the 2 o'clock and 4 o'clock flanges using the port indicators (note that when viewing the implant from the posterior aspect, the clock positions are anti-clockwise- see Figure 5). Gently hold down the implant using a soft swab and using a needle holder or other tool, grasp the 2 o'clock flange. Bend the flange inward from the posterior turret to completely break it off. The flange stump should be nearly flush with the posterior rim or slightly recessed (see Figure 6). Repeat the procedure with the 4 o'clock flange. Examine the lens for any cracks, residual sharp edges, particles or lens damage before proceeding.

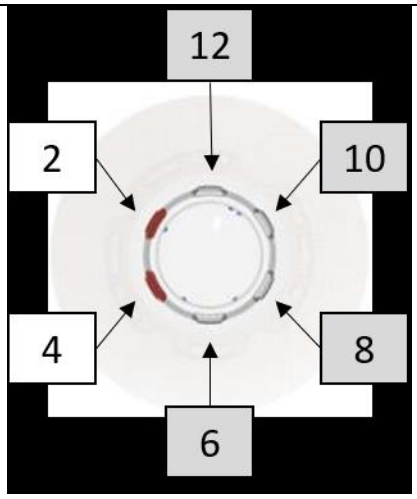


Figure 7 - Note the clock positions of the posterior rim flanges relative to the port indicators.

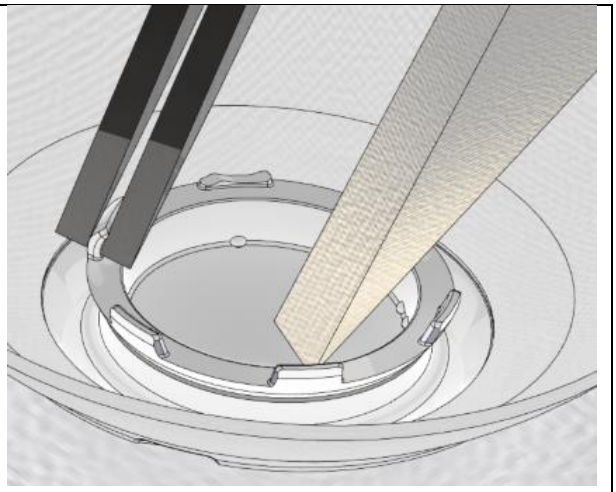
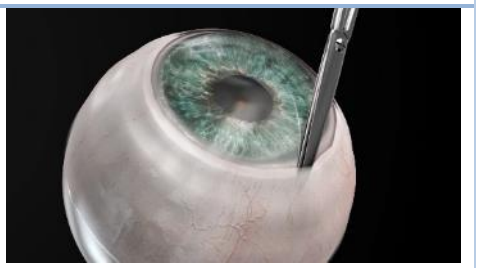
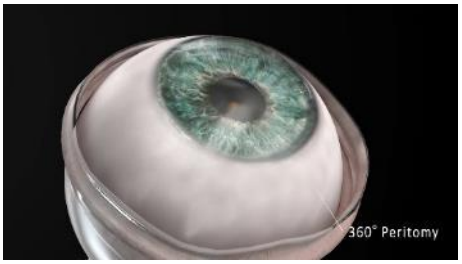
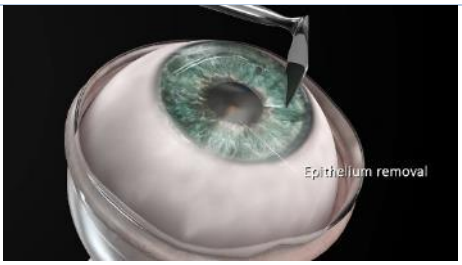
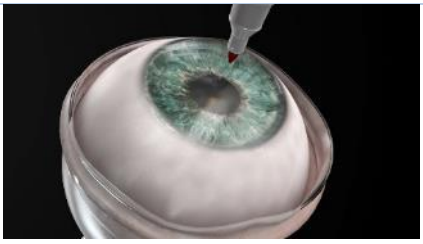
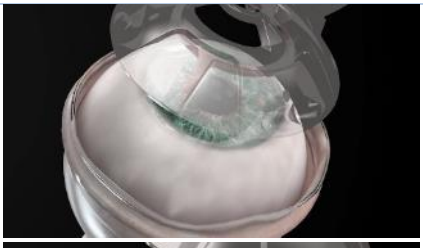
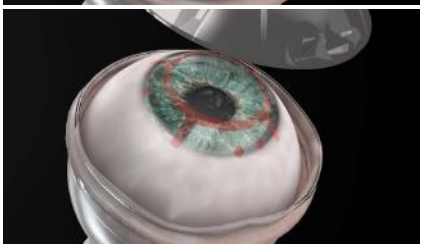
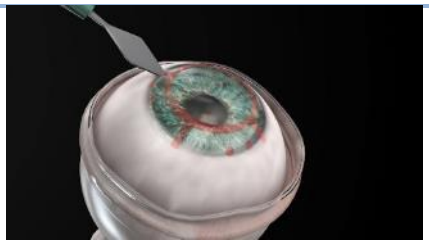
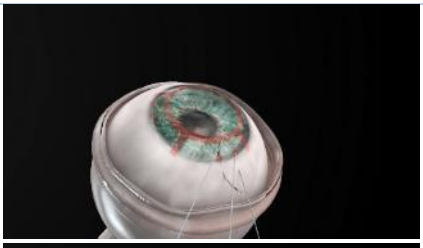
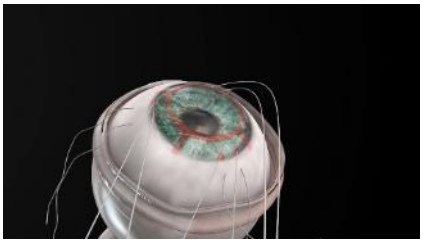
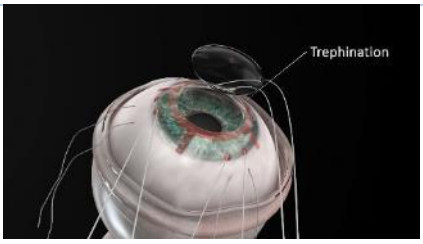
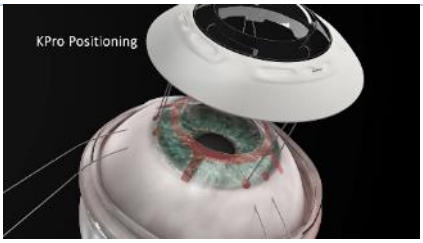
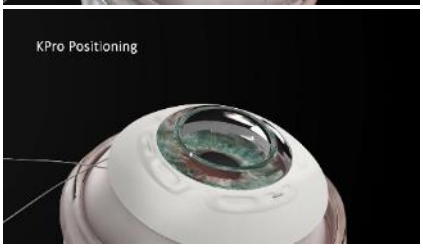
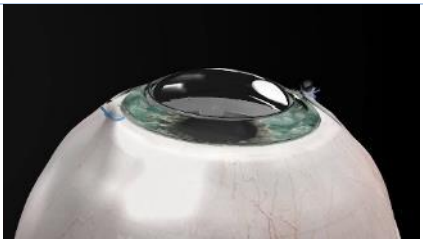


Figure 8 - Illustration of flange removal from the posterior turret

Table 2: CorNeat KPro implantation procedure steps

Step #	Description	Illustration
1.	Perform peritomy 360°, creating a deep pocket.	 
2.	Completely debride the corneal epithelium	
3.	Mark the center of the cornea with a surgical marker. This ensures that subsequent critical procedure steps are aligned.	
4.	Cornea marking. Using the dedicated Marker tool, the cornea surface is marked. The marked pattern includes 3 pairs of suturing marks, 4 potential paracenteses lines, and a trephination edge mark. The marker head is transparent and includes a rounded hole centered on the cornea by aligning it with the central mark. The marker and implant are not symmetrical, and care should be taken to align the superior suturing marks with the corneal 12 o'clock position.	 

Step #	Description	Illustration
5.	Paracenteses + OVD. Two clear corneal incisions are created where indicated by the paracentesis line, and the eye is filled with viscoelastic (OVD).	
6.	Preplace 3 pairs of non-degradable sutures, passing first through dedicated holes on the rim of the KPro's optics, and then through the cornea – entering at the suture hole marks, passing radially through the sclera. Double armed sutures are recommended. Be sure to align the sutures so that they do not cross or become entangled. Inspect the rim of the KPro implant to ensure its integrity before implantation.	 
7.	Once all preparatory steps are completed, trephine the central cornea . Align the trephine crosshairs with the central corneal mark to achieve centration.	
8.	Fasten the implant to the device is fastened to the eye wall by tightening the 3 sutures, and then tying them between the device skirt and the sclera.	 

Step #	Description	Illustration
9.	Using the Snapper, Insert the trephined corneal edge, which is stained for better visualization, into the KPro's posterior (corneal) undercut.	
10.	Exchange the viscoelastic (OVD) with balanced salt solution (BSS).	
11.	Reposition the conjunctiva and suture into place using degradable sutures. The conjunctiva should completely cover the skirt.,Following conjunctival suturing, apply tissue adhesive to ensure tissue approximation during the initial healing period.	

In every implantation procedure, an extra CorNeat KPro unit and a corneal graft will be ready in the operating room and will be used in case of an unexpected intraoperative complication preventing implantation of the dispensed CorNeat KPro unit.
A full animated video of the CorNeat KPro implantation procedure can be found on the CorNeat Vision website here: https://www.CorNeat.com/kpro-animation

Figure 9: CorNeat KPro implantation animation (CTRL+Click to access)

4.2.8 Principles of Operation

The patented design of the CorNeat KPro and the unique implantation procedure include five mechanisms which ensure short- and long-term integration, retention, and water tightness (see Table 3 below). While short-term water tightness is achieved by mechanical means, long-term integration, retention, and water tightness are based on the device's unique skirt, which is implanted subconjunctivally. This porous skirt, made from non-degradable and non-woven fibers, extends near the extraocular muscles' insertions, serving as a scaffold for migration of

fibroblasts from Tenon's capsule (thin membrane enveloping the eyeball from the extraocular muscle insertions to the limbus) and subconjunctival fibrous tissue into the skirt of the CorNeat KPro. This unique integration concept, which has been validated in multiple animal studies, permanently attaches the device to the eye and seals it. Within several weeks, fibroblasts colonize the skirt and sprout collagen within it (Figures 8-11).

Table 3: Short and long-term retention features

Time of action Mechanism	Short term retention Water tightness Ease of implantation	Long term retention Globe integrity
Posterior undercut	√	√
Posterior flanges	√	√
3 non-degradable safety sutures	√	√
Bio-integrative porous, polymeric skirt		√
5 Bio-integration grooves		√

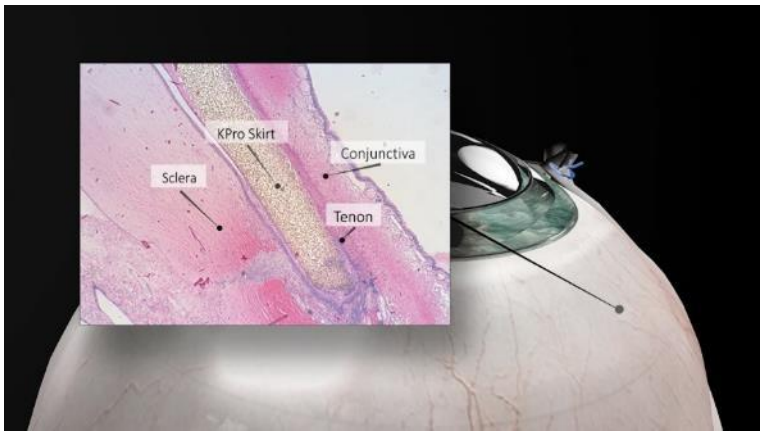


Figure 10: CorNeat KPro skirt laid between the sclera and the conjunctiva
NZW rabbit histopathology slide showing no inflammation/capsule around the skirt 1- month post implantation

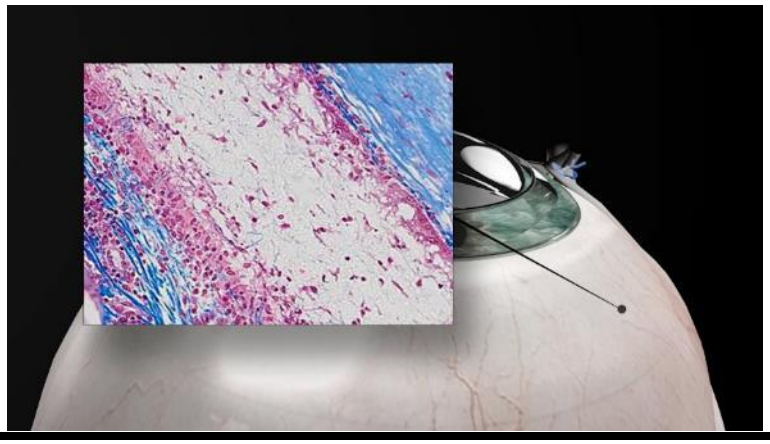


Figure 11: NZW histopathology slide stained with Mason Trichome showing fibroblasts (pink) and collagen (blue) within the device's skirt as it is laid between the sclera and the conjunctiva

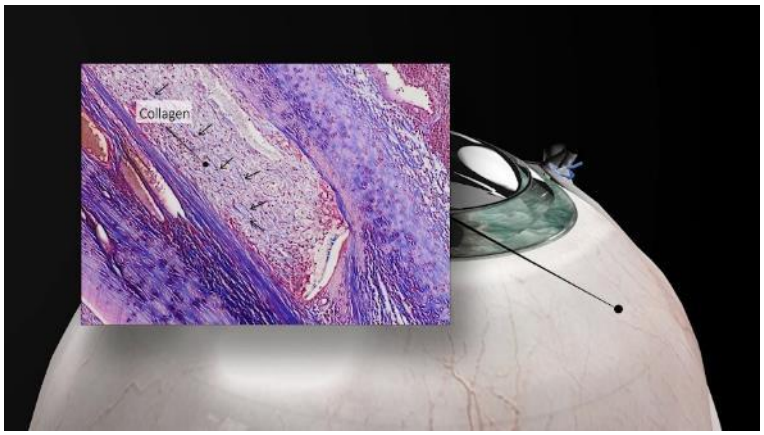


Figure 12: NZW histopathology slide stained with Mason Trichome 6 months post operation. The device's skirt is fully colonized with fibroblasts (pink) and collagen (purple)

Figure 13: CorNeat KPro integration concept proven in an NZW rabbit (6 months post operation)

The mechanisms that hold the device's lens in place and seal the eye in the short term enable the skirt to integrate. These include the device posterior (corneal) undercut, which hosts the recipient corneal stump – a set of flanges on the posterior side mitigating the risk of the stump slipping out of the undercut – and 3 sets of non-degradable sutures securing the lens onto the sclera. This mechanism, which ensures water tightness, was tested in cadaver eyes and validated to withstand an Intra Ocular Pressure (IOP) greater than 3X the upper limit of normal IOP, with no leaks. The mechanism is based on the fact that the central cylinder, which traverses the native cornea, is larger in diameter than the trephination. The native corneal stump, which is pushed against the PMMA cylinder, creates a seal that prevents aqueous humor from leaking out. The short-term mechanisms that secure the device into place reduces the skirt's movements and stabilizes it in a way that enables its biological integration (see Figures 12-15).

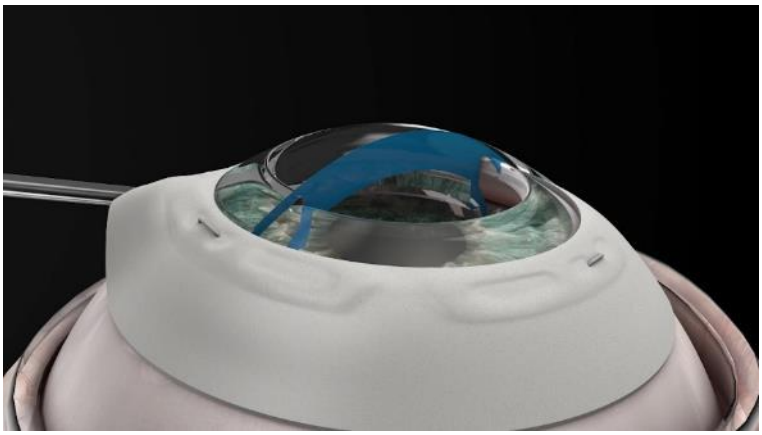


Figure 14: CorNeat KPro illustration showing how short-term water tightness is achieved. The lens' cross section shows how the native corneal stump fits into the device's corneal undercut as well as 2 of the 3 non-degradable sutures securing the device onto the sclera.

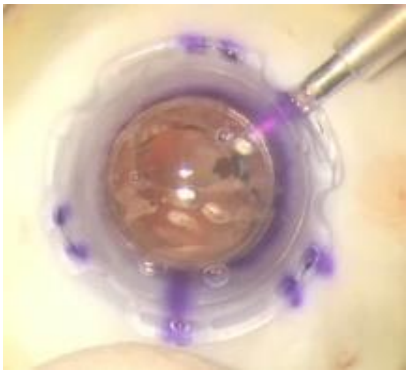


Figure 15: CorNeat Lens water tightness test performed on cadaver eye
Intraocular pressure raised to 3X the normal pressure using BSS infusion

In order to further ensure long term retention, the KPro's PMMA lens is surrounded by a set of curved integration holes. These holes are filled with skirt material, which stimulates cellular growth and colonization. It is expected that connecting tissue will grow through the holes, thus "bio-stitching" the PMMA to the eye wall. This function was validated in animal implantations.

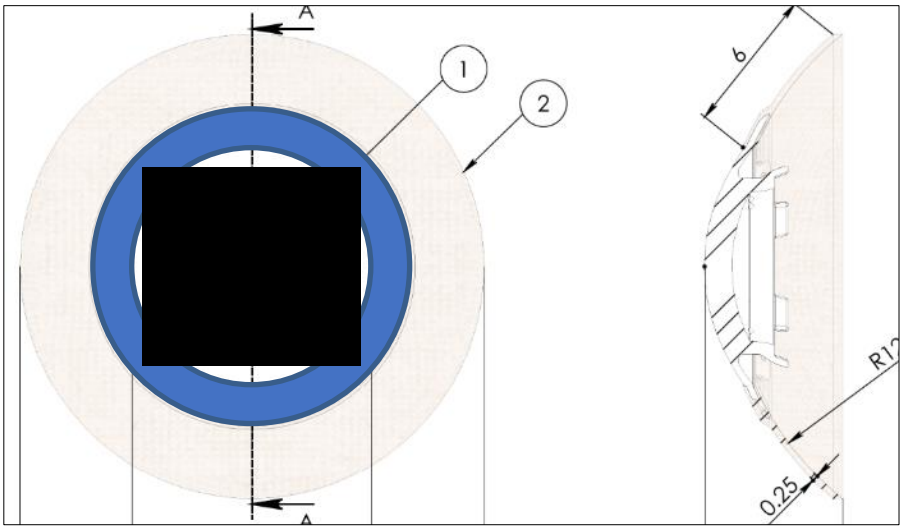


Figure 16 : CorNeat KPro illustration - blue area represents optics integration rim sandwiched by the skirt material

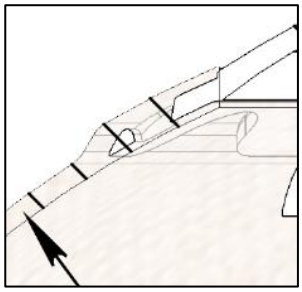


Figure 17: A cross section of the integration rim showing an integration hole filled with the skirt material

4.2.9 Regulatory History

There is no regulatory history for the CorNeat KPro device and respective implantation kit. For the initial indications for use, which are detailed in section 4.2.5, FDA submission will be based on guidance on 510(k) submissions for KPros dated March 3, 1999. Product will be classified as class II special controls.
CorNeat Vision does not have regulatory history as all its products are currently in development phases. Company products are developed and validated in compliance with relevant standards and QMS system is implemented and audited as required.

5 Study Objectives And Endpoints

5.1 Objective

The objective of this clinical trial is to prove the safety and efficacy of the CorNeat KPro device intra and post-operatively.

5.2 Endpoints

5.2.1 Primary Safety Endpoint

The frequency and severity of all unanticipated adverse device-related events (UADE) or treatment-related adverse events, during and after implantation of the CorNeat KPro device up to 12 months should be less than SOC (as detailed in section Known Potential Risks).

5.2.2 Effectiveness Endpoints:

Primary Effectiveness Endpoint: Device retention
Secondary Effectiveness Endpoint: Improvement in visual acuity

6 Study Design

Prospective, open label, single arm, FIH clinical study to assess Safety and efficacy of the CorNeat Keratoprosthesis for the treatment of corneal blindness
Subjects will be screened by the participating clinical site's clinical team (physician and study staff) during a screening visit. Each subject will sign the ICF (Informed Consent Form) prior to any study activities and will be evaluated for inclusion and exclusion criteria. Only eligible subjects will be enrolled in the study. Demographic data, medical history and concomitant medication use data will be collected from enrolled subjects. Subjects will be implanted with the CorNeat KPro, and followed-up for Ocular wall integrity at the implantation site (primary endpoint) and absence of conjunctival irritation at implantation site (secondary endpoint) for 12 months in 8 clinic visits. During follow up visits safety data and use of concomitant medication will be documented. Subjects successfully completing 12 months of follow-up will be monitored for device retention and other safety issues during 3 clinic visits spanning an additional 12 months (not included in the scope of this trial). Subjects accrual is planned for 12 months and overall first subject in to last subject out is planned for 24 months.
Follow up plan will include complete clinical exam, anterior segment photography and a questionnaire assessing pain and other possible subjective ramifications.

7 Study Population and Subject Selection

7.1 Study Population

10 subjects suffering from unilateral or bi-lateral corneal blindness not reasonably amenable by transplanting human tissue. The KPro can be implanted in OD or OS (selection is according to PI discretion).

7.2 Subject Selection

7.2.1 Inclusion Criteria

7.2.1.1 Male or female aged ≥ 18 and ≤ 80 years on the day of screening

7.2.1.2 Candidates must have the ability and willingness to attend all scheduled visits and comply with all study procedures

7.2.1.3 Keratoprosthesis surgery is indicated in cases when keratoplasty is not a reasonable option or following a verifiable history of prior failed corneal transplantation.

7.2.1.4 Indications that fall under poor candidate for keratoplasty include but are not limited to: herpetic keratitis, vascularized corneal scar, Ocular Cicatricial Pemphigoid, alkali burn, Steven Johnson Syndrome, and limbal stem cell deficiency;

7.2.1.5 Pseudophakia

7.2.1.6 Adequate tear film and lid function

7.2.1.7 Perception of light in all quadrants

7.2.1.8 Female patients of childbearing age must have negative pregnancy test at screening and agree to use an effective method of contraception throughout the study

7.2.2 Exclusion Criteria

7.2.2.1 Reasonable chance of success with traditional keratoplasty

7.2.2.2 Current retinal detachment

7.2.2.3 Connective tissue diseases

7.2.2.4 End stage glaucoma

7.2.2.5 History or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to planned implantation

7.2.2.6 History of ocular or periocular malignancy

7.2.2.7 History of extensive keloid formation

7.2.2.8 Any known intolerance or hypersensitivity to topical anaesthetics, mydriatics, or component of the device

7.2.2.9 Signs of current infection, including fever and current treatment with antibiotics

7.2.2.10 Severe generalized disease that results in a life expectancy shorter than a year

7.2.2.11 Any clinical evidence that the investigator feels would place the subject at increased risk with the placement of the device

7.2.2.12 Corneal thickness less than 400 or higher than 1,200 microns in any region of the pachymetry map of the eye intended to be operated

7.2.2.13 Currently pregnant or breastfeeding

7.2.2.14 Participation in any study involving an investigational drug or device within the past 30 days or 5 half-lives of the drug (whichever longer) or ongoing participation in a study with an investigational drug or device

7.2.2.15 Intraoperative complication that would preclude implantation of the study device.

7.2.2.16 Vulnerable populations.

Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the protocol study and implanted with the CorNeat KPro device.

7.3 Informed Consent

Written informed consent must be obtained for each study subject prior to the commencement of the study. The written informed consent (approved by the Institutional Ethics Committee/ REB) must be signed and dated by the investigator. A copy of the signed informed consent form will be given to the subject. The signed informed consent will be retained with the study records at the site. The investigator is responsible for assuring that informed consent is obtained regarding each subject in accordance with local guidelines and ISO14155 standard.

7.4 Replacement of Dropouts

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Subjects, who have not completed the 6-month follow-up visit and drop out of the study for any reason, may be replaced. Dropouts will be evaluated in the Intent to Treat (ITT) Cohort. A separate cohort will exclude these subjects. Every effort will be made to determine the reason for the subject dropping out of the study. Where possible, subjects will be followed for safety and encouraged to return for follow-up visits for any unresolved safety events.

8 Trial Procedures

8.1 Visit Schedule

8.1.1 Screening and Consent

Potential participants will be provided with written information about the study describing the study, advising them of the study requirements, and possible risks. Study investigators must

ensure that potential participants understand the information provided, and review requirements and potential risks. Individuals agreeing to participate in the study must sign the informed consent form according to local regulations. Upon verification of eligibility and execution of informed consent, subjects will be assigned a study code.
Screening visit will be performed up to 2 weeks before surgery and will include:

- Best Corrected Visual Acuity (BCVA)
- Slit Lamp Examination
- IOP – will be measured either by tactile evaluation or using an appropriate tonometry technique
- OCT/UBM imaging
- Pain assessment with visual analogue scale (VAS)
- Concomitant medications
- Women of child-bearing potential must provide a negative pregnancy urine test.
- Subject demographic and medical information acquired from subject's medical file.

8.1.2 Implantation

Implantation day will be recorded as day 0; enrolment day
Safety data will be collected upon enrolment.

Patients will be hospitalized as decided by the surgeon, estimated 1 hospitalization day will be required. Patients will be informed that they have the right to contact the PI or designee per their discretion

8.1.3 Operative Evaluation

During the procedure of each eye, most essential safety parameters, such as collapse and/or bleeding of the anterior chamber, iris or lens damage and unusual surgical problems will be recorded. Additionally, proper placement of the device's components (i.e. optic and skirt) will be confirmed and recorded.

8.1.4 Procedural Failures

Failure to perform study device procedure will be recorded in the CRF as an operative failure.

8.1.5 Post-Operative Supportive Care

Patients will be prescribed with prophylactic antibiotics and anti-inflammatory medications post implantation. Regimen for each medication and/or the addition of medications such as hypertension prophylaxis will be decided on a case by case basis and per the investigator’s discretion.

The following options of treatment may be considered:

- A flouroquinolone, preferably 4th generation, should be applied for the first month QID(4Xd)

If antibiotics are unavailable, 1% povidone iodine 2 to 4 times daily can be used for the short-term.

- To control inflammation after KPro implantation, prednisolone 1% drops 2-4x per day for the first month are recommended either with or without additional non-steroidal anti-inflammatory drugs (NSAID) such as Tromethamine.

Patients will be advised to avoid eye rubbing since infectious or toxic debris may be pushed into the eye and will be instructed to wear sunglasses or UV-blocking contact lenses to protect against UV induced eye damage.

8.1.6 Follow Up

Follow Up- (up to 12 months) visit schedule: One day post op, one week (±2 days) one month (±7 days), two months (±14 days) three months (±14 days), six months (±14 days), nine months (±14 days) and twelve-months (±14 days) post-surgery.

On each follow-up visit, subjects will be subjected to the following examinations: (i) slit-lamp biomicroscopy, (ii) visual acuity (BCVA), (iii) IOP, (iv) concomitant medications record, (v) Pain assessment and (vi) Adverse events recording.

In every follow up visit, IOP will be measured by tactile assessment as follows: Digital palpation of the globe will be performed with the patient gently looking down. Palpation directly over a glaucoma drainage device plate should be avoided in patients with tubes who should be instructed to look in an alternate direction. The eye should then be very gently balloted between the surgeon's two index fingers, as his or her other fingers rest against the face and orbital rim.

In addition, OCT/UBM imaging will be performed on screening visit, on 1-week post-op and every 3 months starting at 3 months post-surgery.

During all study period only safety data (i.e. possibly related or related AEs, SAEs, UADE) will be collected in the eCRF for visits performed outside of protocol visits timetable.

8.2 Table Of Assessment

Assessments/Procedures	Screening	Procedure	Follow-up (time post surgery)							
Time in study	**-14 to -0**	**0**	**1 day**	**1 week ±2 days**	**1 month ±1 week**	**2 months ±2 weeks**	**3 months ±2 weeks**	**6 Months ±2 weeks**	**9 Months ±2 weeks**	**12 months ±2 weeks**
Informed consent	X									
Inclusion /exclusion criteria	X									
Medical history, Demographic, pregnancy test (women of child-bearing potential only)	X									
CorNeat KPro device implantation		X								
Slit Lamp Examination, BCVA, IOP	X	X	X	X	X	X	X	X	X	X
OCT/UBM imaging	X (Anterior)			X (RNFL)			X (RNFL)	X (RNFL)	X (RNFL)	X (RNFL)
Pain Assessment (Visual analogue scale-VAS)	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X
AE/SAE/UADE		X	X	X	X	X	X	X	X	X

Only safety data will be collected in CRF for Post hospitalization period and visits performed between protocol scheduled visits (i.e., related or possibly related AE, SAEs, UADE)

9 Training

CorNeat KPro implantation will be performed only by ophthalmic surgeons which are well trained in corneal surgery specifically keratoprosthesis implantations. Each ophthalmologist will be trained by implanting the CorNeat KPro implant in ex-vivo animal eyes prior to subject enrollment. Prior to the wet lab training, a presentation outlining the procedural step with an in-depth discussion on the unique aspects of the device and procedure will be conducted. The Investigator formal training will be performed by the study sponsor prior to subject enrolment at the study center. Training certificate will be issued to investigators who successfully passed the wet lab.

10 Safety Parameter

10.1 Adverse Event Definition

An adverse event is any undesirable or unintentional event that occurs during the course of the study, whether or not considered related to the device. Regardless of severity or relationship to the investigational device, all adverse events occurring during the study must be recorded in the subject's CRF

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

AE data will be listed individually and summarized by SOC and by PT within a system organ class.

Additional tables will present adverse events by PT, SOC and severity and by relatedness to study device.

10.2 Severity of an Adverse Event

Mild Adverse Event

A mild adverse event is one that its symptoms are barely noticeable to the subject. It does not influence performance, require drug treatment or prevent the subject from carrying on with normal life activities.

Moderate Adverse Event

A moderate adverse event is one that its symptoms make the subject uncomfortable and causes some impairment to normal life activities. Treatment for the symptom(s) may be required.

Severe Adverse Event

A severe event is one in which the symptoms cause severe discomfort to the subject and limits the subject's normal life activities. Treatment for the symptom(s) may be required.

10.3 Relationship to Study Device

The following definitions will be used to assess the relationship between an adverse event and the investigational device.

Not Related

The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.

Possibly Related

The event has a reasonable temporal relationship to the use of the investigational device and follows a known response pattern to the investigational device. However, a potential alternate etiology may be responsible for the event. The effect of device withdrawal is unclear. Re-challenge information is unclear or lacking.

Related

The event follows a temporal sequence from the time of use of the device and follows a known response pattern to the investigational device and either occurs immediately following investigational device use, or improves on stopping the use of the device, or reappears on repeat exposure to the device.

10.4 Serious Adverse Event Definition

A serious adverse event is an event that is: (a) fatal, (b) life-threatening (c) results in persistent or significant disability/incapacity (d) requires or prolongs in subject hospitalization or (e) leads to a congenital anomaly or birth defect.

Life threatening is defined as an event in which the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.

Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions.

An unexpected adverse event is one that has not been previously observed or one that is a specificity or severity not consistent with the current investigator brochure.

All pre-existing medical conditions will be recorded on medical history or physical exam case report forms.

Hospitalization or prolonged hospitalization for diagnostic or elective procedures for pre-existing conditions will not be considered as SAE. Exceptions of adverse device effects are changes related to the underlying disease or medical conditions that are consistent with expected disease progression and will not be considered adverse device effects in this study.

10.5 Unanticipated Adverse Device-related Event Definition

An unanticipated adverse device-related event is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in section Known Potential Risks.

10.6 Adverse Event Reporting

When an adverse event occurs, the following information and assessments in the adverse event section of the CRF will be recorded:

- The signs, symptoms or diagnosis of the event
- The date and time of onset and termination of the event (24-hours clock format where midnight is 00:00 and noon is 12:00)
- The adverse event severity using the criteria outlined above
- The relationship of the event to the investigational device as outlined above
- A description of any action taken regarding study device disposition
- A list of any required therapy, medication, treatment or diagnostic procedure
- Clinical behavior prior to the event, such as nutrition, medicine, physical activity etc.
- Any additional data which might be relevant to the event

The investigator is responsible for the appropriate medical management of all adverse events and for the personal safety and well-being of the subjects.

10.7 Serious Adverse Events Reporting and Unanticipated Adverse Device-Related Events (UADE)

Any serious and/or unexpected and/or device related adverse event must be reported to the sponsor- CorNeat Vision and the Clinical Study Monitor via the EDC system. Full details of the event, treatment, and an assessment of the relationship between the investigational device must be provided in the report. The report shall be prepared by the principal investigator.
Reports relating to the subject's subsequent medical course must be submitted to the sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.
CorNeat Vision will notify all investigators in writing of severe/serious or unexpected adverse events when this information is of global importance to subject safety and welfare.
Reporting to the EC/REB will be done according to local regulation.

10.8 Known Potential Risks

Known risks from usage of similar artificial corneas are:

- Postoperative Corneal Melt - is one of the most severe complications that can occur after keratoprosthesis surgery with incidence of up to 30%[6,7,8]. It may lead to scarring, irregular astigmatism, photophobia, decreased vision, and even endophthalmitis.
- Lack of graft retention - Corneal grafts tissue artificial integration is limited and with time the bond between the implant and eye weakens. E.g. Boston KPro's retention rates decreases over time with incidence of lack of retention of 6, 11 and 25% after 1, 2- and 5-years post-op, respectively[9,10].
- Post-operative Glaucoma - is the most important threat to long-term preservation of vision following Boston KPro surgery with elevation of intraocular pressure in 19–38 % of patients postoperatively and progression of pre-operative glaucoma in 7–14 % of patients. Development of glaucoma de novo following Kpro placement has been reported in 2-28% of KPro recipients [11,12,13,14,15].
- Poor post-operative visual quality - Eyes with current KPros have very limited visual field and poor visual function. About 50% of patients implanted with Boston KPro maintain 20/200 CDVA after 8 years from surgery [16,17].

[6] Bouhout, S., Robert, M.C., Deli, S. and Harissi-Dagher, M., 2018. Corneal melt after Boston keratoprosthesis: Clinical presentation, management, outcomes and risk factor analysis. Ocular immunology and inflammation, 26(5), pp.693-699.

[7] Schaub, F., Bachmann, B.O., Seyeddain, O., Moussa, S., Reitsamer, H.A. and Cursiefen, C., 2017. Mid-and longterm experiences with the Boston-keratoprosthesis. The Cologne and Salzburg Perspective. Klinische Monatsblatter fur Augenheilkunde, 234(6), p.770.

[8] Jin, B. and Zhu, X., 2017. The pathogenesis and prevention of corneal graft melting after keratoplasty. J Clin Ophthalmol, 1(1), p.10.

[9] Ciolino, J.B., Belin, M.W., Todani, A., Al-Arfaj, K., Rudnisky, C.J. and Boston Keratoprosthesis Type 1 Study Group, 2013. Retention of the Boston keratoprosthesis type 1: multicenter study results. Ophthalmology, 120(6), pp.1195-1200.

[10] Kang, K.B., Karas, F.I., Rai, R., Hallak, J.A., Kang, J.J., de la Cruz, J. and Cortina, M.S., 2018. Five year outcomes of Boston type I keratoprosthesis as primary versus secondary penetrating corneal procedure in a matched case control study. PloS one, 13(2).

[11] Vora, G.K. and Colby, K.A., 2012. Management of glaucoma following Boston keratoprosthesis. Eur Ophthal Rev, 6, pp.214-217.

[12] Chew, H.F., Ayres, B.D., Hammersmith, K.M., Rapuano, C.J., Laibson, P.R., Myers, J.S., Jin, Y.P. and Cohen, E.J., 2009. Boston keratoprosthesis outcomes and complications. Cornea, 28(9), pp.989-996.

[13] Netland, P.A., Terada, H. and Dohlman, C.H., 1998. Glaucoma associated with keratoprosthesis. Ophthalmology, 105(4), pp.751-757.

[14] Greiner, M.A., Li, J.Y. and Mannis, M.J., 2011. Longer-term vision outcomes and complications with the Boston type 1 keratoprosthesis at the University of California, Davis. Ophthalmology, 118(8), pp.1543-1550.

[15] Sayegh, R.R., Ang, L.P., Foster, C.S. and Dohlman, C.H., 2008. The boston keratoprosthesis in Stevens-Johnson syndrome. American journal of ophthalmology, 145(3), pp.438-444.

[16] Aravena, C., Yu, F. and Aldave, A.J., 2018. Long-term visual outcomes, complications, and retention of the Boston type I keratoprosthesis. Cornea, 37(1), pp.3-10.

[17] Lee, R., Khoueir, Z., Tsikata, E., Chodosh, J., Dohlman, C.H. and Chen, T.C., 2017. Long-term visual outcomes and complications of Boston keratoprosthesis type II implantation. Ophthalmology, 124(1), pp.27-35.

Additionally, in eyes with Boston KPro, the visual field is estimated at approximately 40-45° of half-luminance field which is usually used to estimate the visual field through a device[18].

- Intra-operative suprachoroidal hemorrhage and vitreous prolapse - Conventional penetrating keratoplasty (PK) and current KPro procedures are performed after the cornea has been removed from the eye – aka “open-sky”. Open sky procedures entail high risk of expulsive suprachoroidal hemorrhage and vitreous prolapse[19].
- Retro-KPro membranes (RPM) formation- are the most common complication in KPro implanted patients, with an incidence of 27-47.6%.

  RPM is usually treated with Nd:YAG membranotomy which can cause retinal detachment in 26.7%[20].
- Endophthalmitis - The incidence of endophthalmitis in KPro patients is relatively high (1.2-11.4%) even in patients with prophylactic antibiotic topical treatment[20].

Other risks include:

- Transient inflammatory reaction around the eye
- Vitreous hemorrhage- bleeding inside the eye
- Vitritis- sterile inflammation inside the eye
- Retinal Detachment- separation of the retina from the wall of the eye resulting in loss of vision
- Ptosis- a droopy eyelid
- Foreign body sensation

10.9 Device Explantation

10.9.1 Potential Clinical Scenarios Resulting in Device Explantation

Potential clinical scenarios resulting in the removal of the CorNeat KPro can be attributed to the following three pathological processes:

- Severe retroprosthetic membrane (RPM) formation - Most RPMs are typically treated with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser membranotomy or by surgical membranectomy. However, when an aperture cannot be created in the membrane with either method, the keratoprosthesis should be replaced.
- Infection – may occur due to bacterial, viral, fungal or parasitic pathogens that entered the eye. This will be prevented using prophylactic use of antibiotics and intra-surgical antiseptic technique. In the case of an active infection in the eye, the ophthalmologist will opt for urgent intervention to retrieve a specimen for cultures and to inject potent

[18] Sayegh, R.R., Diaz, L.A., Vargas-Martín, F., Webb, R.H., Dohlman, C.H. and Peli, E., 2010. Optical functional properties of the Boston keratoprosthesis. Investigative ophthalmology & visual science, 51(2), pp.857-863.
[19] Chen, W., 2015. Innovative Method to Avoid the Open-Sky Condition in Penetrating Keratoplasty and the Triple Procedure: Securing the Anterior Chamber. Cornea, 34, p.S113.
[20] Cortina, M.S. and de la Cruz, J., 2015. Keratoprostheses and Artificial Corneas. Fundamentals and Surgical Applications, p.2015.

antibiotics intravitreally. Endophthalmitis patients may also require an urgent surgery (pars plana vitrectomy), and evisceration may be necessary to remove a severe and intractable infection which could result in a blind and painful eye.

- Tissue necrosis - can result in corneal perforation, hypotony, and / or instability, leading to extrusion of the device. Based on the severity and specific circumstances of each case, the surgeon may decide either to replace the CorNeat KPro with another artificial cornea, seal the eye with a donor cornea or perform an evisceration or enucleation procedures.

10.9.2 Device Explantation Procedure

Upon reaching the decision to remove the device, the surgeon may choose one of the following surgical approaches according to the specific ocular condition and per his/her discretion:

1) Releasing the skirt component from under the overlying conjunctiva using sharp dissection.
2) Removal of only the optic component of the CorNeat KPro while the skirt component remains under the overlying conjunctiva. This will be performed by cutting the skirt around the optic componenet with an appropriate blade or scissors throughout the entire circumference.

The eye will be implanted with either a replacement CorNeat KPro, tectonic corneal graft or an alternative artificial cornea.

It should be noted that in severe cases of the above-mentioned complications, evisceration or enucleation might be the only options remaining.

10.10 DSMB

The ten first implanted subjects will comprise the first-in-human cohort. Once the 10th subject successfully completes the 6th month post-surgery follow-up, an independent data-safety-monitoring-board (DSMB) will review the data and submit its conclusions to the study sponsor. Copies will be forwarded to the REB and to the Ministry of Health.
In order to manage the FIH cohort for DSMB submission participating sites will inform sponsor upon subject screening via subject screening log.

10.11 Premature Termination or Suspension of the Study

The trial will be stopped if severe side effects or infections, resulting in device removal and related with the investigational device, are diagnosed in three patients.

In case of premature termination of the study, the PIs will decide regarding the required future follow up for each patient on a case by case basis.

The trial may be temporarily suspended if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of poor efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

If the study is suspended, the PIs will promptly inform the EC and will provide the reason(s) for the suspension. Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, EC, and /or respective regulatory agency.

11 Insurance

The sponsor will appropriately ensure the study; trial will be covered in accordance to medical centers requirements and local regulation.

12 Data Collection, Processing and Statistical Analysis

12.1 Data Collection and Processing

12.1.1 Subject Data Protection

Investigators are responsible for keeping a list of all subjects, including subject numbers, full names and last known addresses, identification log. Throughout the study, all collected data will be identified by subject number only and kept in accordance with local data protection requirements and with regulation (EU) 2016/679 of the European parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation) GDPR.

12.2 Statistical Analysis and Sample Size

12.2.1 Sample Size Consideration

The rationale for the sample size of 10 subjects for this FIH trial is based on regulatory requirements set down by the FDA in the Keratoprosthesis 510K guidance document and on a clinical trial for corneal blindness using a KPro- trial number NCT03126903 running currently (A Clinical Study to Evaluate the KeraKlear Keratoprosthesis in Patients With Corneal Opacity). In the KearKlear FIH trial 15 patients were included and followed up for 7-21 months.[21] The FDA 510k demands 20 patients followed up for approximately one year. (press here for the FDA protocol)

7 A new epidescemetic keratoprosthesis: pilot investigation and proof of concept of a new alternative solution for corneal blindness.Br J Ophthalmol. 2015 Nov;99(11):1483-7. doi: 10.1136/bjophthalmol-2014-306264. Epub 2015 Apr 13.Alio JL, Abdelghany AA, Abu-Mustafa SK, Zein G.

12.2.2 Sample Size Justification

Reference to FDA guidance for Keratoprosthesis 510K where proving safety is the target and 20 subjects with a minimum of 330 days of follow up is needed.

12.2.3 Statistical Analysis

There is not a separate Statistical Analysis Plan (SAP) document in use for the trial since no statistical methods are applied in this study.
The safety analysis set will consist of all patients who were enrolled into the study. Individual listings of adverse events including adverse events (reported term), duration, relationship to the study device, severity and the adverse events outcome will be provided for the total population, where applicable. AEs will be summarized using frequency counts and percentages.

12.3 Monitoring Procedures

The investigational site will be monitored periodically to assure satisfactory subject enrollment, data recording, and protocol adherence. Study monitoring functions will be performed by CorNeat Vision in compliance with recognized Good Clinical Practices (GCP), ISO 14155 standard. In addition to ensuring adequate communication between the investigators and the sponsor, the monitor's duties include on-site visits, participation in the initial implantations and follow up visits of the device, and review of the study documents and results. The monitor, as well as inspectors and auditors, must have direct access to all relevant source documents. The investigator and staff are expected to cooperate with the study monitor and provide to the study monitor all relevant study documentation. It is essential that the investigator and study coordinator set aside a sufficient amount of time for these visits to permit an adequate review of the study's progress and of completed case report forms.

12.3.1 On-Site Monitoring

On-site monitoring visits include a pre-study visit, periodic visits during the course of the investigation, and a final "close-out" visit at the conclusion of the study. The frequency of monitoring may vary depending on enrollment rate and the quantity of data collection. At the pre-study visit, the monitor will meet with the Principal Investigator and discuss the protocol's contents, study requirements and related staff requirements. The monitor will also evaluate the suitability of the premises for record keeping, regulatory requirements, logistic procedures, availability of suitable source documentation forms, etc. At the pre-study visit, the monitor will specifically verify that the investigator:
Has appropriate training, facilities, subject load, time, and willingness to comply with study requirements;

- Has all study documentation and required records on site; and
- Assumes responsibility for the investigation at his/her center.

Subsequent to the pre-study visit, the monitor will continue to conduct on-site visits to monitor the study's progress. These periodic visits are intended to assess the investigator's adherence

to the Investigational Protocol, maintenance of records, reports, and investigational devices, and review of source documents for accuracy, completeness, and legibility. During these periodic visits, the monitor is required to assess the progress of the study toward meeting its objectives, and to identify any concerns from observations of device performance and/or review of the investigator's subject records, study management documents, and informed consent documents, and to ensure accountability of all subjects that have been treated under the study. The monitor's final on-site visit at the completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the investigator and his/her staff members.
Reports of the on-site visits will be made by the monitor and will include resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, the monitor will prepare a final report according to local regulation. Upon Ethics committee /REB approval of the Final Report, a close-out visit will be performed to ensure that all relevant documentation is filed and archived according to regulations under the investigator's responsibility and unused study device returns to sponsor.

12.4 Study Site Initiation

An initiation meeting will take place at which all procedures will be explained to all staff involved in the study to ensure understanding of the study requirements prior to initiation of study procedures.

12.5 Protocol Changes or Amendments

The principal investigator agrees not to make any changes to the investigational study protocol or its conduct except when necessary to eliminate immediate hazards to human life.
Changes in the investigational study protocol may be made only by written amendment by CorNeat Vision. Protocol amendments must be approved by the EC/REB prior to implementation. Documentation of approval for such amendments must be kept on file by the investigator and forwarded to CorNeat Vision.

12.6 Case Report Forms (CRF)

The data collected by the eCRF will be accumulated in an Electronic Data Capture (EDC) system database. Data will be entered by study staff during the study and at its conclusion by data management personnel corresponding with the study monitor and site investigators. It will be collected by data improvement through queries, which is automatic using the system's edit checks while data is typed in, and manually following source data verification (performed at monitoring visits). The EDC system will be in compliance with GCP and with Directive 95/46/EC of the European Parliament and of the Council of 24th of October 1995 on the "Protection of individuals with regard to the processing of personal data and on the free movement of such data".

12.7 Maintenance of Study File

Study records including subject source documents, case report forms, all test results and signed informed consent forms must be kept on file by the investigator. All Ethics Committee correspondence including notification of protocol and consent form approval and all annual reports along with the final report to the Ethics Committee must be retained. Other documents pertaining to the conduct of the study including laboratory normal values, laboratory certification, monitor correspondence and all other relevant written correspondence must also be kept as part of the permanent record. Records must be retained for at least 15 years and in accordance to local regulation.
Should storage no longer be available to archive source document or must be move to an alternative location, the research staff should notify the key sponsor contact prior to document shipping.

12.8 Device Accountability

On site study device will be kept in a secure location with restricted access. The study devices will be handled by trained personnel. The Investigator will not supply the study device to any individual not involved in the investigation. The study device will be inventoried at regular intervals during the study, and all unused devices will be returned to the CorNeat Vision when study enrolment is closed.

12.9 On-Site Audits

Authorities may request access to all study records, including source documents for inspection. The principal investigator and staff are requested to cooperate with all such audits. The principal investigator must notify CorNeat Vision of any audit as soon as possible. A representative or designee of CorNeat Vision's clinical or regulatory department may also conduct similar auditing procedures and may be present during any outside audit or Inspection.

12.10 Reports

Periodic status reports will be submitted at least yearly or according to local regulation to the EC/REB and according to local regulation. Within 6 months after completion or termination of the study, a final report must be submitted to the EC/REB. The investigator must maintain an accurate and complete record of all submissions made to the EC/REB.

12.11 Disclosure and Publication of Information

All proprietary information including; CorNeat Vision's operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information provided to the investigator or the methodologies used in this study, as well as proprietary information obtained during the course of the study are confidential and will remain the sole property of CorNeat

Vision. The investigator agrees not to disclose any proprietary information supplied by CorNeat Vision in any way without prior written permission.
Individual subject data obtained during this study are confidential and will not be disclosed to third parties with the following exceptions: when the data is needed by the subject's personal physician or other medical personnel responsible for the subject's welfare. For data inspection and verification by CorNeat Vision or designate, regulatory authority auditors or by the Institutional EC.