AN OPEN-LABEL MULTICENTER PHASE 2 CLINICAL SAFETY INVESTIGATION OF THE ENDOART® IMPLANTATION IN SUBJECTS WITH CHRONIC CORNEAL EDEMA

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To evaluate the safety of EndoArt® in subjects with chronic corneal edema.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Anterior eye structural change, deposit and degeneration
Study type	Observational non invasive

Summary

ID

NL-OMON52020

Source
ToetsingOnline

Brief title
The EndoArt® implant study

Condition

- Anterior eye structural change, deposit and degeneration

Synonym
chronic corneal edema, swelling of the cornea

Research involving
Human

Sponsors and support

Primary sponsor: EyeYon Medical
Source(s) of monetary or material Support: The sponsor;Eye Yon Medical.

Intervention

Keyword: chronic corneal edema, endothelial prosthesis, safety

Outcome measures

Primary outcome

The frequency and severity of device related adverse events, from patient entry through the 6 month follow-up period. Adverse events will be assessed on a continuous basis and will continue to be collected for 12 months.

Secondary outcome

• Improvement from baseline in central corneal thickness (CCT) at 6 months postoperatively

• Incidence of primary post-surgical detachment of the device.

• Time to and rate of, primary and subsequent rebubbling to facilitate adhesion of the device

• Change in Best Corrected Distance Visual Acuity (BCDVA) from baseline.

• Change in pain score as assessed by a Visual Analogue Scale (VAS) from baseline.

Study description

Background summary

The cornea is a clear, transparent, dome-shaped structure that covers the front portion of the eyes. An adult cornea is about 0.5 millimeters thick at its center. It comprises five major layers, namely, the epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium.
The cornea maintains a fluid equilibrium which ensures optimal light transmission in order to facilitate visual acuity. This is achieved through the active pumping of fluid by the corneal endothelium layer. When endothelial cells are injured, fluid begins to accumulate within the corneal stroma

resulting in corneal edema leading to vision impairment and if left untreated, bullous keratopathy and pain.

Causes of corneal edema include Iatrogenic intraoperative damage to the endothelial layer most commonly due to cataract surgery, Fuchs' dystrophy, corneal infection, glaucoma with significant raised IOP, and trauma.

A primary symptom of corneal edema is blurred vision. The individual with corneal edema may also see halos or rainbows around streetlights, headlights, and other bright lights at night. As corneal edema progresses, it may affect the epithelial corneal layer resulting in bullae. These can rupture and become painful, cause sensitivity to light, and increase the risk for sight-threatening infections.

Corneal blindness is a leading cause of vision loss worldwide, often requiring a corneal transplant (keratoplasty) for treatment. In developed countries, partial thickness corneal transplants have now become the most often performed corneal transplants with endothelial keratoplasty being the most common. Although advances have been made over the past two decades in the field of endothelial keratoplasty there are still several issues that must be overcome. EyeYon medical has developed the EndoArt® (Artificial Endothelial Layer) implant which is a permanent implant. The EndoArt® device is indicated for use as an endothelial keratoprosthesis device and is designed specifically for the replacement of the endothelial cell layer of the cornea that has become dysfunctional. With the development of endothelial keratoplasty techniques, surgeons are now able to remove only the diseased endothelial layer of the cornea and replace the layer with donor tissue, leaving the healthy areas of the cornea intact. The most common types of endothelial keratoplasty procedures are Descemet's Stripping Endothelial Keratoplasty (DSEK) and Descemet's Membrane Endothelial Keratoplasty (DMEK).

The EndoArt® device is attached to the posterior corneal surface thereby impeding the transfer of aqueous humor into the cornea and decreasing chronic corneal edema. The device is designed to serve as an alternative to posterior lamellar keratoplasty (PLK) in providing alleviation of corneal edema and improving corneal clarity. As is done in PLK, a portion of the posterior cornea may be removed prior to insertion of the implant to the tissue as in DSEK or DMEK. EndoArt® is implanted using a single suture for better positioning with or without a Descemetorhexis.

EndoArt® is intended to treat vision loss related to corneal decompensation secondary to endothelial damage and dysfunction. Furthermore, the technology is designed to treat intractable corneal edema in a more effective manner than the current standard of care (*SOC*), which involves the use of donor tissue.

The rationale for blocking the posterior surface of the cornea came from clinical observation and sporadic literature data demonstrating that corneas of eyes with silicone oil in the anterior chamber are usually transparent, despite very low endothelial count. In addition to these observations, in 1967 Dolman C conducted a successful clinical study in 22 patients with chronic corneal edema. In this study, the endothelium was replaced with an alloplastic material (silicon layer) and attached with sutures to address the intractable corneal edema. However, sutures were found to be very challenging in adhering to

corneal implants.
According to a JAMA report, there are approximately 13 million people in the world currently waiting for corneal tissue. The process of harvesting the tissue and processing it to fit endothelial keratoplasty is complicated. The harvested tissue needs to be prepared and stored in special conditions and needs to be implanted within14 days. The EndoArt® as a synthetic, non-immunogenic device, has a longer shelf life than donor tissue and will not require special storage or transportation conditions. Thus, the treatment will be readily available to patients without waiting for donor tissue. The estimated waiting time is 6.5 months in countries that are considered self-sufficient. For the other countries with an imbalance between supply and demand for corneal transplants, most patients never receive a graft, thus preventing a calculation of waiting time.9 In addition, EndoArt® eliminates the inherent variability, as well as the susceptibility of native tissue to damage or deterioration during harvesting and transfer. A synthetic product may improve effectiveness both by expanding the population who can be effectively treated and by providing a reproducible, stable product that is not subject to degradation in transport prior to implantation.
EndoArt®, a synthetic implant, has the potential to substantially reduce or eliminate the implant rejection rate and simplify the post-operative follow-up care required, compared to both endothelial grafting and full-thickness corneal transplant. According to several reports, 10-30% of DMEK cases result in detachment of the graft in the early postoperative phase. In addition, in case of 2-3 times, donor endothelium rejection additional implantation is most likely to fail again. EndoArt®, as a synthetic device, can be reattached with a minor anterior chamber re-bubbling procedure and in the event of failure for any reason the implant is relatively uncomplicated to remove. Furthermore, if desired, replacement with a new device can be achieved at any time the surgeon feels replacement should occur.
One of the most disruptive aspects of EndoArt® is its off-the-shelf availability since it is a synthetic, non-immunogenic device. It has a 5-year shelf life and does not require special storage or transportation conditions. Moreover, the EndoArt® is implanted in a manner familiar to the majority of ophthalmic surgeons (i.e., small incision cataract surgery) and utilizes a relatively non-complicated procedure to explant and replace should the need arise.
The above potential benefits justify the proposed investigation focusing on the clinical safety and efficacy of the EndoArt®. The EndoArt® implant, as an alternative to the dysfunctional human corneal endothelium, represents a major advance ineffectiveness for the treatment of resultant corneal edema.
This post-market study is designed to collect and evaluate data based on the use of the EndoArt® with the aim of confirming the safety and performance, including the clinical benefit, of the EndoArt® throughout its expected lifetime; identifying unknown side-effects and monitor the identified side-effects and contraindications, and ensuring the continued acceptability of the benefit-risk ratio.
Bibliography in paragraph 17 of the CIP.

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Evaluation of the Results of Preclinical Testing

The EndoArt® has undergone pre-clinical testing in order to assure the performance of the device according to published standards and guidelines where available. These tests include mechanical evaluation of the device, biocompatibility, and optical testing. The device passed these tests successfully. The tests performed on the EndoArt® are described in detail in the Investigator*s Brochure accompanying this clinical investigational plan.

Evaluation of the Animal Studies

The company has also conducted in-vivo testing in animals to further characterize the safety and performance of EndoArt®.

Up to date, 17 animals (rabbits and pigs) have been implanted with EndoArt® for different follow-up periods (up to 12 months). The procedure in all cases was successful with no procedure-related adverse event.

The adverse events that occurred during the follow-up period were either non-device related or following re-bubbling probably due to animal model limitation. It can be concluded that the EndoArt® is safe following implantation onto the cornea of rabbits or pigs. Safety was demonstrated by the absence of inflammatory reaction or other tissue response to the implanted device at both clinical and histopathological examinations. There was no major adverse event.

Detailed studies results are presented in the accompanied IB.

Evaluation of Interim Clinical Study Results

Up to date, the EndoArt® was implanted during a worldwide multisite clinical study in 24 subjects (20 under the FIH study, 1 under the FIH study in India, and 3 under compassionate treatment).

Procedure Results

In all 24 subjects implanted with EndoArt®, the procedure was completed smoothly with no complications. According to participated physicians, the EndoArt® implantation procedure is easier than the DSAEK procedure; there were no issues of graft handling or concern about endothelial cell damage.

In all cases, the device was inserted through a 2-3 mm incision in the cornea. The endothelial cell layer was left untouched in 5 cases and removed in the other 19 cases. The device was then attached with an injected air bubble of SF6 gas 20% or C3F8 10%. In 10 cases, the device was sutured. Fixation suture was found to be beneficial in reducing the re-bubbling rate.

On average, patients underwent 3 re-bubbling procedures up to 2 months following implantation. Most of the re-bubbling was done mainly in the first-month post-op. In most cases, the re-bubbling procedure has produced stable attachment with minimal risk.

Based on the significantly improved attachment results using the suture technique and the advantage of minimal or no need for re-bubbling, it was decided to use the suture technique in all future cases.

Results:

Twenty-four (24) subjects were implanted with the EndoArt® with a follow-up of

0.5-24 months (13 subjects with at least 6 months follow-up). No device-related nor procedure-related serious adverse events (SAE) have been reported to date. In all cases, no inflammatory reaction was observed in any of the treated eyes at any of the post-surgical examination time points. All implanted eyes are quiet, with no evidence of haze, flare, fibrin, cells, or iris neovascularization. Based on these findings, EndoArt® is demonstrating clinical parameters supporting its design as a sterile, inert, and biocompatible polymer implant.
Clinical Results:
In summary, this initial data demonstrates that EndoArt® provides a treatment option for patients with limited or no other treatment options. Benefits have been observed even in very challenging cases. Several patients, despite low visual potential, demonstrated marked reduction in corneal thickness (n=13), decrease in ocular pain (n=8), and visual improvement (n=7).

Study objective

To evaluate the safety of EndoArt® in subjects with chronic corneal edema.

Study design

Prospective, multicenter, open label, phase 2 clinical safety investigation of the EndoArt® implantation in subjects with chronic corneal edema assessing safety of EndoArt.

Study burden and risks

RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION
Anticipated Clinical Benefit
The purpose of this clinical investigation is to evaluate the safety of implanting EndoArt® in subjects with corneal edema.
The EndoArt® device is indicated for use as an endothelial keratoprosthesis device and is designed specifically for replacement of the endothelial cell layer of the cornea that has become dysfunctional.
The EndoArt® has several advantages in treating corneal edema:
• Rejection of the donor tissue is one of the most serious complication after a corneal transplant and occurs in 5 - 30 % of patients. EndoArt® eliminates the need for long term immunosuppression medications to avoid rejection since the material is inert and non-immunogenic; it thereby eliminates one source of clinical failure (rejection).
• The corneal incision performed in this procedure is smaller and either suture-less or requires minimal sutures.
• Decrease the risk of infection as it is sterile as opposed to human tissue that can*t be sterilized.
• EndoArt® once implanted, is non degradable, while human tissue implantation and manipulation is associated with cell loss.

• EndoArt® also avoids the possibility of primary donor failure due to damage to donor tissue during harvesting, storage, insertion or unfolding. Use of a synthetic material removes the risk of disease transmission from the donor to the host.
• The procedure can be performed in a much shorter duration than traditional corneal transplant surgery.
• The waiting list for a donor tissue in most countries is long. Using EndoArt® will enable availability to everyone in need.
• EndoArt® can be implanted in complex eyes where tissue implantation is not possible or extremely challenging

Anticipated or Potential Adverse Events
Risks that may be associated with implantation of EndoArt® are similar in nature to those encountered with other Endothelial keratoplasty e.g. DSEK (Descemet stripping endothelial keratoplasty) or DMEK (Descemet membrane endothelial keratoplasty).
The following are possible risks the subject may experience from participation in this research:
EndoArt® related
• Cornea abrasion, opacity, haze
• Device Detachment and further surgical manipulation
• Worsening of corneal edema
• Cornea thinning and perforation
Operative related
• Anterior or posterior synechiae
• IOP elevation due to procedure or steroids
• Infection
• Inflammation
• Retinal detachment
In the event of complication, the subject will be treated as deemed necessary by the investigator. This may include DSEK or DMEK procedure.
All adverse events will be collected during the enrollment phase and throughout the subject participation in the study.

Possible Interactions with Concomitant Medical Treatments
This study protocol includes a careful review of relevant medications taken retrospectively by the subject to identify any medications that might reasonably impact the outcome of the procedure. Medications such as topical antibiotics, NSAID*s and steroids are standard therapies for patients following ocular implant surgery. All medications subjects are taking prior to surgery and those administered during the study, will be captured and documented in the eDC.

Risk Analysis and Risk Mitigation
A risk analysis has been conducted, in accordance with ISO 14971 *Application of risk management to medical devices.* The risks associated with this investigational device have been identified and been shown to be minimized

through appropriate design control, by bench testing and by pre-clinical animal testing presented in the Clinical Investigator*s Brochure.
The warnings and actions to minimize the risk for the patients include (but not limited to):
• EndoArt® is designed to replace the endothelial cell layer of the cornea that has become dysfunctional. Preclinical testing has verified that the device is bio-compatible, minimizing the risk of damage to cornea or any other adverse tissue response.
• EndoArt® is designed, intended, and distributed for single use only.
• A site qualification will be conducted to ensure the investigators and the site staff are adequately experienced, an ophthalmology team is in place and the necessary infrastructure is available.
• Only investigators who are experienced and skilled in ophthalmological procedures and in corneal/cataract surgery will be selected.
• To ensure adequate EndoArt® implantation the Sponsor or designee will demonstrate the procedure in a formal training session to the physicians and site personnel involved in the study. In addition, specific instructions for use (IFU) will be provided to all study personnel to make sure that handling of the device and the procedure are perfectly clear.
• Warnings and precautions in the instructions for use including reference to sterility issues.
• Clearly defined inclusion/exclusion criteria so that only appropriate subjects are enrolled to the study.
• Ensuring that the treatment and follow-up of the subjects are consistent with current medical practices.
• Thorough ophthalmic clinical assessment of each subject peri-procedurally.
• Frequent monitoring visits to investigational sites will be conducted.

Risk to Benefit Rationale
The risk analysis for the EndoArt® implant has been performed at the stage of CE approval in EU and IFU finalization. All applicable risks were identified and evaluated, and the applicable mitigations defined. The overall residual risk has been evaluated by the company management and considered acceptable. Two (2) risks are in AFAP region that are related to the clinical aspects and are covered by the information supplied to the user in the IFU.
Thereby the company believes that the benefit of the EndoArt® implant to cure corneal edema was verified through the FIH study interim results and was found to be safe and effective. Since the EndoArt® is the only solution available today to treat corneal edema with an artificial implant, the company assesses that its overall benefit outweighs the risk associated with use of the product. EndoArt® implantation is designed to replace the need for donor corneal tissue removing the risk of tissue rejection and disease transmission from the donor to the host.
Furthermore, EndoArt® fulfils a global unmet need in that the device is readily available removing the burden associated with a lack of donor tissue.

• Designed to improve safety by:

o Avoiding implant rejection since the material is inert and non-immunogenic removing the risk of chronic pharmacological immunosuppressive prophylaxis.
o Avoiding the possibility of primary donor failure due to damage to donor tissue during harvesting, storage, insertion or unfolding.
o Reduced risk of postoperative infection.
• Improved effectiveness by:
o Simplifying the surgical procedure and avoiding the possibility of primary donor failure.
o Removing the risk of rejection and disease transmission from the donor to the host
o The procedure can be performed in a much shorter duration than traditional corneal transplant surgery.
o Reduce the long waiting list for donor tissue in most countries.
o Enables implantation in complex eyes.
Pre-clinical animal studies provided significant data demonstrating the safety and performance of EndoArt® implantation. Consistent with the preclinical findings, the initial clinical experience with EndoArt® has demonstrated efficacy with no significant safety issues.
The EndoArt® implantable device provides potential to treat patients that are not suitable due to poor prognosis for conventional corneal transplant.
Given these benefits, there is sufficient justification supporting a prospective investigation focusing on safety and clinical performance of EndoArt®.
It is reasonable expectation from the current clinical experience, that the benefits of this therapy will outweigh the risks. This study will collect clinical information to further confirm the favourable risk-benefit ratio.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Individuals must meet the following requirements at screening visit:
1. Male or Female subjects 40-85 years of age.
2. Have chronic corneal edema (for a minimum of 3 months) secondary to endothelial dysfunction.
3. Have corneal thickness >600µm by OCT.
4. Have best corrected distance visual acuity 6/19 (20/63) or worse (equivalent ETDRS = 60 letters) with subjective symptoms of impaired visual function
5. Subject with posterior pseudophakia and stable IOL.
6. Willing and able to understand and sign informed consent prior to any study related procedure.
7. Willing and able to follow study instructions (e.g., to lay on one*s back for 4 hours post op.), able to self-administer or have caregiver available to administer eyedrops as required by the protocol for the duration of the study, and able to attend study visits/assessments for the duration of the study.

Exclusion criteria

1. History of ocular Herpetic keratitis.
2. Scarred cornea resulting in visual impairment with intact endothelium (cell density >= 1500).
3. History of posterior vitrectomy.
4. Post PKP
5. Have an irregular posterior cornea (e.g., post trauma)
6. Have a current infection of the cornea.
7. Have band keratopathy and/or limbal stem cell deficiency.
8. Have clinically severe dry eye disease which needs more than 4 drops of lubricant per day.

9. Phthisis bulbi or subject is at risk of developing phthisis.
10. Subject with medically uncontrolled high intra ocular pressure.
11. Aphakia.
12. Anterior chamber IOL or fixated anterior chamber IOL.
13. Pseudophakodonesis.
14. Have large iris defect which could compromise intraoperative air bubble formation
15. Have undergone corneal refractive surgery.
16. History of neurotrophic cornea.
17. History of recurrent corneal erosion or persistent epithelial defect.
18. IridoCorneal Endothelial (ICE) Syndrome or any rare disease/ syndrome creating anatomical or physiological anomalies of the anterior chamber (e.g., corectopia).
19. Recurrent posterior, intermediate or anterior uveitis.
20. Subject receiving regular intravitreal injection.
21. Currently participating or have participated in an investigational study, other than this study, within the past 60 days.

Study design

Design

Study phase:	4
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	EndoArt
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	26-07-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05139771
CCMO	NL78929.018.21