Running title:

A novel artificial endothelial replacement membrane for the treatment of chronic corneal edema: A first-in-human trial

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Conflicts of Interest and Source of Funding:

OD, ALM, EG and AL are employees at EyeYon Medical. For the remaining authors none were declared.

Keywords:

Keratoprosthesis; Corneal Edema; Endothelial Keratoplasty; Corneal implantation; EndoArt.

Disclosure:

The FIH trial was fully funded by EyeYon Medical, a developer of the EndoArt® implant.

Abstract

Purpose: To report the safety and efficacy results of an artificial lamellar implant for the treatment of chronic corneal edema.

Methods: The EndoArt® (EyeYon Medical, Ness Ziona, Israel), an artificial endothelial replacement membrane designed to treat corneal edema, was implanted in 24 eyes of 24 subjects with low to normal visual potential. We present the safety and efficacy results from a prospective, open-label, single-arm, multi-center study conducted over a 12-month period.

Results: No device-related serious adverse events (SAEs) were reported during the follow-up period. The average central corneal thickness (CCT) was reduced from 759±116 µm at baseline to 613±135 µm at the 12-month follow-up. Best corrected distance visual acuity (BCDVA) improved from an average of 1.88±0.79 logMAR pre-operatively to 1.34±0.57 logMAR at the 12-month follow-up. Sixty percent of the subjects gained at least 3 early treatment diabetic retinopathy study (ETDRS) lines at 12 months. In five subjects, the EndoArt® was removed due to incomplete attachment, and they eventually underwent corneal transplant. No device-related long-term complications, infections, or inflammations were reported. The implants remained transparent throughout the study.

Conclusions: The first-in-human (FIH) results of EndoArt® implantation demonstrated the device's potential to treat patients suffering from corneal edema with a favorable safety profile and effective edema reduction in most patients, with no device-related SAE. The EndoArt® may offer a viable solution in regions with a shortage of donor corneas and for patients who have rejected human tissue.

Introduction

Endothelial keratoplasty (EK) is currently the preferred surgical option for treating refractory corneal edema, with Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) offering good visual acuity and resolution of corneal edema.[1–4] However, these surgeries rely on human donor corneas, which are limited in availability and require carefully calibrated processing, transport, and storage conditions. As a result, millions of people with corneal blindness are left without a viable vision restoration solution.[5–7] Additionally, EK is associated with reduced endothelial cell counts and graft rejections even when performed by experienced cornea specialists.[8–10] A comprehensive retrospective analysis of 30,600 eyes from the Intelligent Research in Sight (IRIS) registry investigating visual acuity (VA) outcomes following EK procedures in the United States revealed that approximately 30% of the eyes did not achieve any visual improvement at the one-year mark after surgery. Moreover, approximately 15% of patients experience decreased VA when using human tissues. Notably, within this extensive cohort, postoperative re-bubbling and repeat keratoplasties were identified as independent factors associated with poorer VA outcomes.[11] The success of human corneal graft transplantation is strongly dependent on the recipient's condition, as comorbidities such as glaucoma, prior trabeculectomy, and anterior chamber intraocular lens (ACIOL) markedly lower graft retention.

A synthetic device[12] that can alleviate corneal edema and serve as an alternative to the donor corneal lamella would benefit patients at high risk for human graft rejection and failure.[13,14] A

synthetic device with a long shelf life is also readily available and may offer an additional option in regions with a shortage of human corneas.

The notion that a synthetic plate can substitute for the corneal endothelium and attenuate corneal edema came from clinical observations and literature reports of aphakic silicone oil-filled eyes, with silicon in the anterior chamber, after retinal detachment repair surgeries, which exhibited a clear cornea despite a low endothelial cell count, suggesting that the barrier mechanism of the silicone could substitute for the function of the corneal endothelium and attenuate corneal edema. After silicone oil removal, the corneas immediately became edematous, demonstrating the blocking function of the plate and its potential for treating patients with corneal edema.[15–18]

A possible explanation for the barrier mechanism is that in a steady state, the relation between the inflow and outflow of fluids into and out of the cornea determines its thickness.[19] This process, governed by passive and active mechanisms, a passive barrier formed by a healthy endothelium and epithelium (tight junctions) which passively limit inflow into the cornea and an active process, the endothelial Na-ATPase pumps that pump fluid out of the cornea, in conjunction with tear film evaporation, to a lesser extent. However, when the endothelial cell count decreases, outflow diminishes, leading to a new relationship between inflow and outflow and creating a new steady state characterized by increased stromal water content and subsequent thickening, known as corneal edema.[20–23] The EndoArt® implant reinforces the passive barrier, by blocking the central portion of the posterior cornea and reducing inflow into the cornea, thus establishing a new steady state, resulting in a thinner cornea and alleviated

corneal edema. The hypothesis suggested that the uncovered peripheral posterior surface of the cornea would facilitate sufficient fluid influx and nutrient transport, ensuring safe corneal physiology without adverse events such as corneal melting or perforation. Furthermore, considering the relatively broad range of corneal thicknesses within which the cornea remains transparent, EndoArt® seeks to reduce corneal thickness to approximately 420-625 µm.[24] This range generally signifies a clear and viable cornea. The implant is composed of a transparent, flexible, water-impermeable, biocompatible synthetic material that can seal a part of the inner corneal surface to relieve corneal edema in the absence of a functioning endothelium (EndoArt®, EyeYon Medical, Ness Ziona, Israel). Prior to human testing, EndoArt® was tested and validated in porcine and leporine eyes with induced corneal edema.[12,25] The synthetic implant provided relief from edema and restored corneal transparency over a 12-month follow-up period, while the control eyes continued to suffer from persistent and severe corneal edema. Additionally, compassionate implantation of the device in subjects who had previously failed multiple corneal transplantations has concluded that implantation of the EndoArt led to rapid corneal deturgescence and CCT restoration, presenting a possible option for patients with chronic corneal edema.[26]

The FIH study, completed in January 2023, focused primarily on evaluating the safety of EndoArt® and refining both the design of the implant and its implantation technique.

Materials and Methods:

A multicenter, international, non-randomized, open-label, prospective trial was conducted in Israel (Soroka Medical Center Beer Sheva, Rambam Medical Center Haifa, Sourasky Medical Center Tel-Aviv, Barzilai Medical Center Ashkelon, and Assuta Medical Center Tel-Aviv), the Netherlands (UMC, Amsterdam), Spain (IMO, Barcelona), Germany (Universitäts-Augenklinik, Heidelberg), and India (LV Prasad Hyderabad), and adhered to the Declaration of Helsinki. The institutional review board of each center approved the study, and subjects who met the eligibility criteria provided informed consent, including consent for the publication of results, before any study-related procedures were performed.

The primary safety endpoint was the frequency and severity of adverse events related to the EndoArt® device documented during and up to 12 months after implantation. Adverse events of particular concern include corneal perforation, corneal melting, uncontrolled inflammation, and severe infection. The secondary efficacy endpoints were CCT and BCDVA.

Subjects:

The participants were required to be older than 40, pseudophakic, and have a stable posterior or anterior intraocular lens (IOL) with chronic corneal edema and a minimal CCT of 650 µm. A VA of 6/30 (0.70 logMAR) or worse was needed, with better VA recorded in the contralateral eye. Patients were excluded if they had any of the following: BCDVA of 6/30 (0.70 logMAR) or worse in the fellow eye, a history of ocular herpes simplex keratitis, a severely scarred cornea unsuitable for regular EK, irregular posterior cornea, current corneal infection, band keratopathy, limbal stem cell deficiency, clinically severe dry eye, phthisis or suspicion of phthisis, ocular hypotension

of less than 6 mmHg or ocular hypertension of more than 25 mmHg, aphakia, significant iris defect that could compromise intraoperative anterior chamber stability, a history of corneal refractive surgery, glaucoma shunts (e.g., Ahmed valve), neurotrophic keratopathy, a history of persistent corneal erosion, difficulties with epithelial growth (re-epithelization), or participation in another investigational study within the past 60 days.

Device Description:

The EndoArt® implant is a transparent, foldable, and hydrophilic device composed of a copolymer of hydroxyethyl methacrylate and methyl methacrylate. This material is commonly used in the manufacturing of IOLs. The implants used in this study had a diameter ranging from 5-6.5 mm, a radius of curvature of 6.8 mm, a thickness of 50 µm, and no optical power.

Implantation Procedure:

The implantation of EndoArt® is very similar to that of DSAEK. A peripheral corneal incision of approximately 2.4 mm was made to insert the device. The endothelial cell layer was either left untouched or removed (Descemetorhexis) at the physician's discretion. The folded EndoArt® device was placed into the anterior chamber through a peripheral corneal incision using an off-the-shelf injector or spatula. Once inside the eye, the device was allowed to unfold and was positioned centrally adjacent to the posterior surface of the cornea. To secure the device onto the posterior corneal surface, either an air bubble was introduced, or, through off-label

applications, injections of 20% sulfur hexafluoride (SF6) gas or 10% perfluoropropane (C3F8) gas were made into the anterior chamber, and according to the physician's discretion, a temporary fixating suture was placed at 12 o'clock. Immediately after the procedure, the subject was placed supine and faced up for 2.5-4 hours. The subject was either discharged after the procedure or hospitalized at the physician's discretion.

Visits and procedure:

Each participant underwent a comprehensive baseline evaluation, which included a BCDVA assessment using the ETDRS visual acuity score, pachymetry measurement of CCT by Optical Coherence Tomography (OCT), anterior and posterior segment examination using a slit lamp, endothelial cell count (if feasible), intraocular pressure (IOP) measurement (Goldman applanator), pain assessment using a Visual Analogue Scale (VAS, 0-100) and color photography of the cornea. Corneal clarity was evaluated using a slit lamp and graded as 0 (clear), 1 (clear iris details), 2 (obscured iris details), 3 (pupil barely visible), or 4 (pupil or iris details not visible). Ophthalmic assessments were conducted on days 1, 7, and 14, followed by assessments every 2 weeks for up to 3 months, monthly assessments for the first 6 months, and then every other month for up to 1 year after the procedure. Adverse events were monitored throughout the entire duration of the study period.

Statistical analysis

The Wilcoxon signed rank test was used to determine statistically significant changes from baseline. Calculations were performed using the stats.wilcoxon function in scipy library in Python.

Results:

Twenty-four (24) participants were enrolled, and 17 (71%) completed the one-year follow-up (Table 1). Table 2 summarizes the characteristics of the study population. The mean age of the participants was 69.8±9.6 years, and 41.7% of the participants were female. All subjects had a history of cataract extraction, and five had prior corneal surgeries. More than 30% of the subjects had a posterior segment comorbidity.

TABLE 1 STUDY COMPLETION AND REASONS FOR DROPOUT

Group		Number	Remarks
Enrolled		24	
Completed 1 year of follow up		17	
Dropout	**Implant did not attach**	5	Descemetorhexis was not performed
	Other	2	• Procedural failure; non-device related IOL dislocation. • Subject lost to follow up.

186 TABLE 2 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	
Age (years), Mean ± SD (range)	69.8 ± 9.6 (54 – 86)
Female gender, n (%)	10 (41.7)
Ophthalmic history, n (%)	
Cataract extraction	24 (100.0)
ACIOL	1 (4.2)
Glaucoma	4 (16.7)
Previous glaucoma filtering surgery	2 (8.3)
Previous retinal detachment	3 (12.5)
Vitreal or retinal disease	5 (20.8)
Prior corneal surgery	
DMEK	2 (8.3)
DSAEK	2 (8.3)
DSO	1 (4.2)

ACIOL (Anterior Chamber Intraocular Lens), DSAEK (Descemet Stripping Automated Endothelial Keratoplasty), (DMEK) Descemet Membrane Endothelial Keratoplasty, DSO (Descemet Stripping Only)

Primary Safety Results

Throughout the follow-up period, no serious device-related adverse events were reported (n=24), nor were any chronic inflammatory reactions observed in the treated eyes. No device-related irritation, infection, uncontrolled IOP, or corneal melting was observed. One (1) procedure-related SAE was reported, where the EndoArt® was inverted and required repositioning. One (1) subject demonstrated herpetic epithelial and stromal keratitis, with melting and thinning, which healed with topical acyclovir and systemic steroids without EndoArt® removal. Transient eye pain was reported in 6 patients (25%) mainly due to dry eye or transient bullae. Four patients experienced perioperative IOP elevation, all occurring following gas bubble injection. In three of these patients, paracentesis was necessary for resolution. Transient corneal epithelial defects/ bullae were reported in 4 cases and treated with contact lenses (see Table 3). Increase in lacrimation, dry eye, ptosis and macular oedema were each reported in one subject.

TABLE 3 ADVERSE EVENTS

Adverse event	Number of subjects, n (%)	Comments

Eye pain	6 (25)	In two cases, the implant was not attached
Intraocular pressure increased	4 (16.7)	Perioperative due to gas bubble
Transient corneal epithelial defect/ bullae	4 (16.7)	
Ocular discomfort	2 (8.3)	
Conjunctivitis	2 (8.3)	

Re-bubbling Procedure

A re-bubbling procedure was performed when a complete or clinically significant partial detachment of the EndoArt® implant was identified. Throughout the trial, an average re-bubbling rate of 2.9 ± 2.0 procedures per subject was documented. During the study, an improved attachment technique was established, including an obligatory Descemetorhexis, a temporary fixation suture, and the utilization of long-lasting gas, resulting in no detachment or the necessity for re-bubbling in the final two patients.

First-In-Human (FIH) Dropout

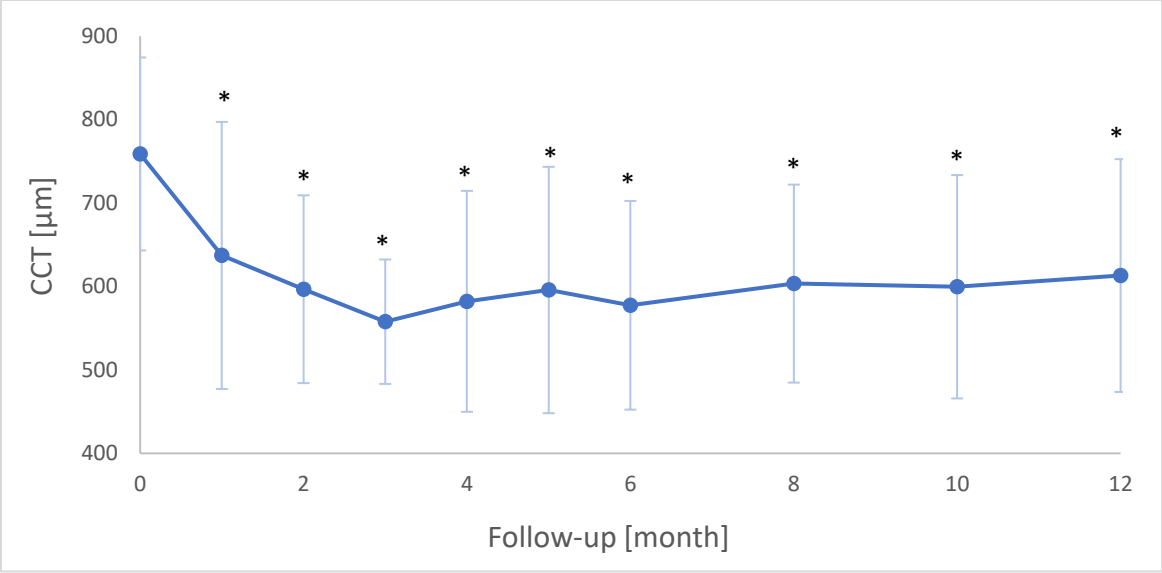
Six (6) EndoArt® implants (25.0%) were explanted. In five (5) patients, the devices were explanted due to attachment failure despite repeated re-bubbling and replaced with DSAEK. In all those patients, Descemetorhexis was not performed. In one (1) patient, the IOL was dislocated during the procedure, which led to an inability to create an effective air bubble and was converted to

Penetrating Keratoplasty (PK). The removal of all devices was straightforward, without any complications.

Secondary efficacy results

Central Corneal Thickness (CCT)

The CCT decreased from an average baseline measurement of 759±116 µm to 613±135 µm (n=17) at 12-months. Significant improvement was noted in the first month after implantation (Figure 1) and remained stable throughout the follow-up. In four (4) patients, the CCT did not show improvement. Among them, three (3) subjects faced insufficient implant attachment, while one subject (1) subject experienced subepithelial fibrosis. Figure 2 illustrates the improvement in CCT once EndoArt® is fully attached using OCT and slit-lamp images of three subjects at baseline and 12-months post-implantation.



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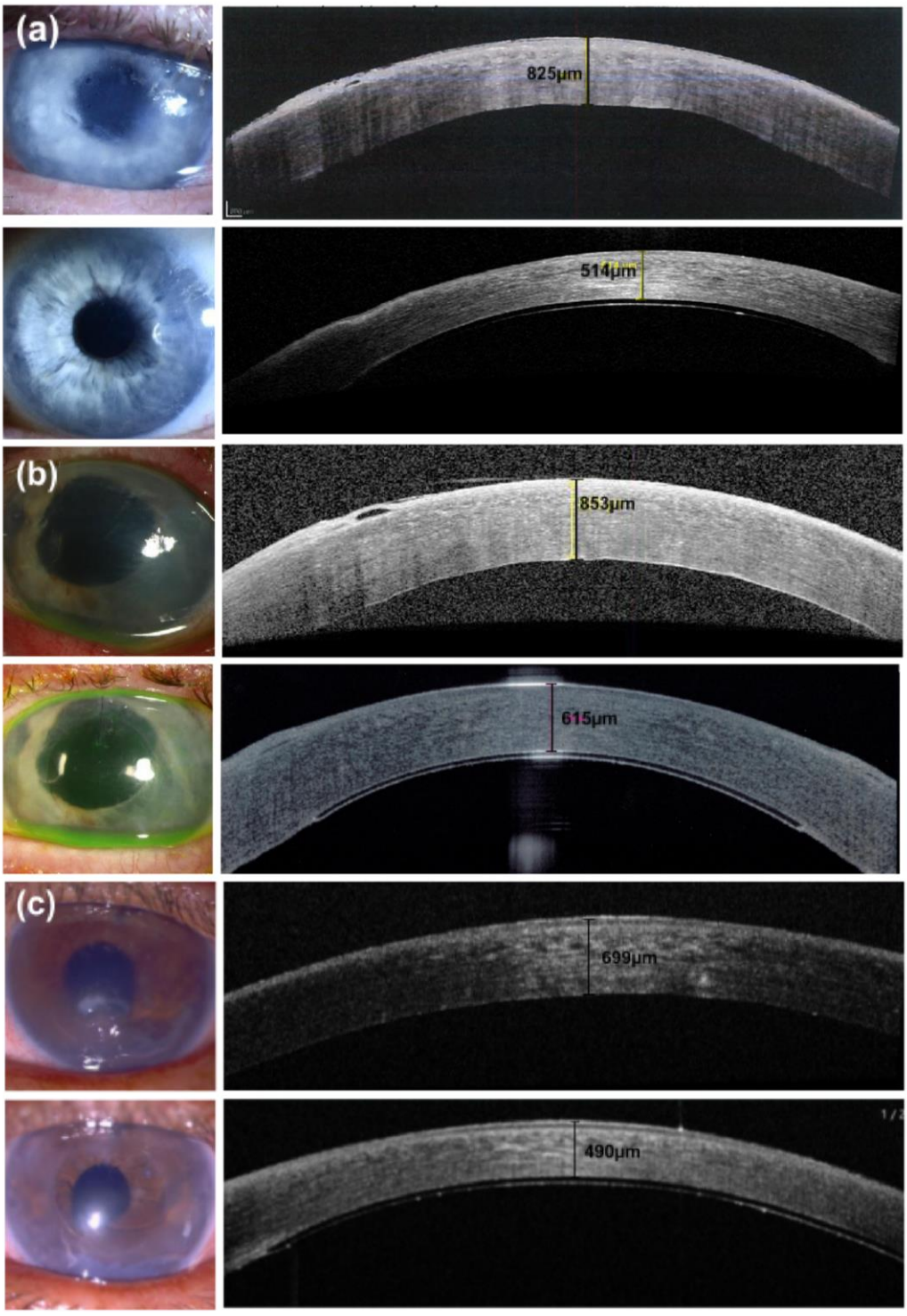
232 Figure 1: Central corneal thickness (CCT) after EndoArt® implantation. The mean ± SD CCT over

233 time is displayed. A significant improvement from the baseline CCT was observed at the 1-month

234 follow-up, and the CCT remained stable throughout the 12-month follow-up (n=17). *p<0.05



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236 Figure 2: Changes in Clarity and Central Corneal Thickness (CCT). Slit-lamp color photography and

237 optical coherence tomography (OCT) images at baseline (upper images) and 12 months (lower

images) after EndoArt® implantation into the eye of (a) a 67-year-old male, pseudophakic, myopic, after failed DSO; (b) an 80-year-old male, pseudophakic, after glaucoma filtering surgery; and (c) a 60-year-old male, pseudophakic (ACIOL), with a macular scar.

Corneal Clarity

A significant improvement in central corneal clarity was observed within two weeks of surgery, and the degree of improvement remained stable during the 12-month follow-up period. The average clarity improved from 3.2±0.6 at baseline to 1.1±1.1 at the 12-month follow-up.

Best Corrected Distance Visual Acuity (BCDVA)

Of the 17 subjects who reached the 12-month follow-up assessment, two (2) had no vision due to optic neuropathy and were therefore not assessed for visual acuity throughout the study.

Despite low visual potential in 10 of the remaining 15 subjects, attributed to ocular conditions such as retinal detachment, macular scarring, amblyopia, and cystoid macular edema, there was a significant improvement in average visual acuity (VA). VA improved from a baseline LogMAR score of 1.88±0.79 to 1.34±0.57 at 12-month follow-up (Figure 3). Notably, 60% of the patients (9 out of 15) improved at least three lines of ETDRS. The most remarkable improvement in VA was from FC to 0.6 logMAR (6/24).

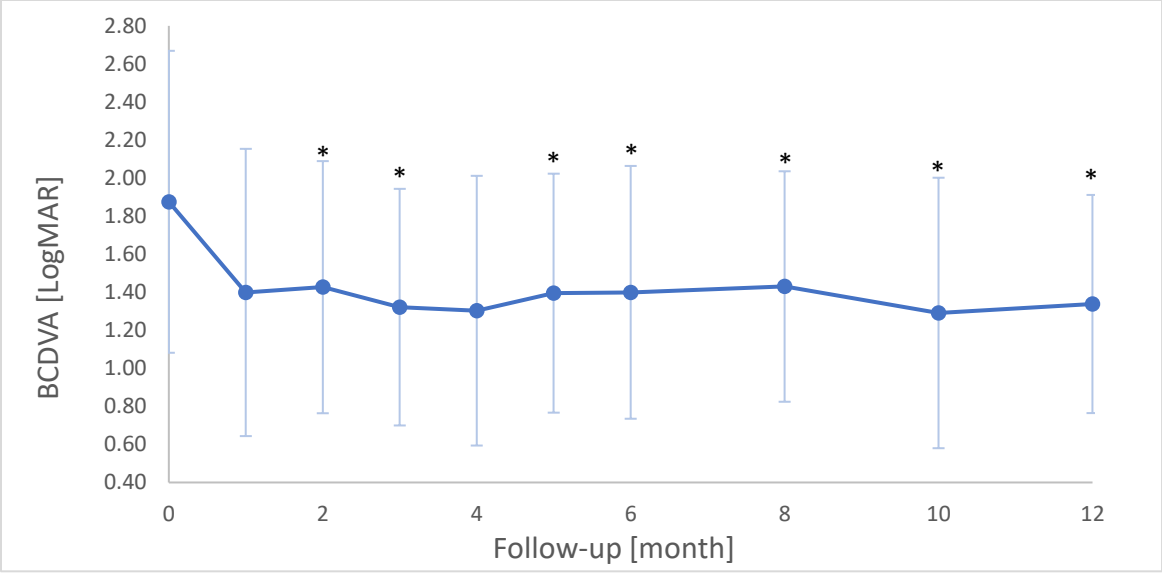

Figure 3: Best-Corrected Distance Visual Acuity (BCDVA) after EndoArt® implantation in subjects with low to normal visual potential. The mean ± SD BCDVA over time after EndoArt® implantation is displayed. A clinically significant improvement from baseline was observed (n=15). *p<0.05

Pain Score

The average VAS (0-100) score significantly decreased from 32±30 at baseline to 2±8 12 months after EndoArt® implantation (Figure 4). All subjects who complained of pain (VAS≠0) at baseline (11 out of 17) experienced pain relief.

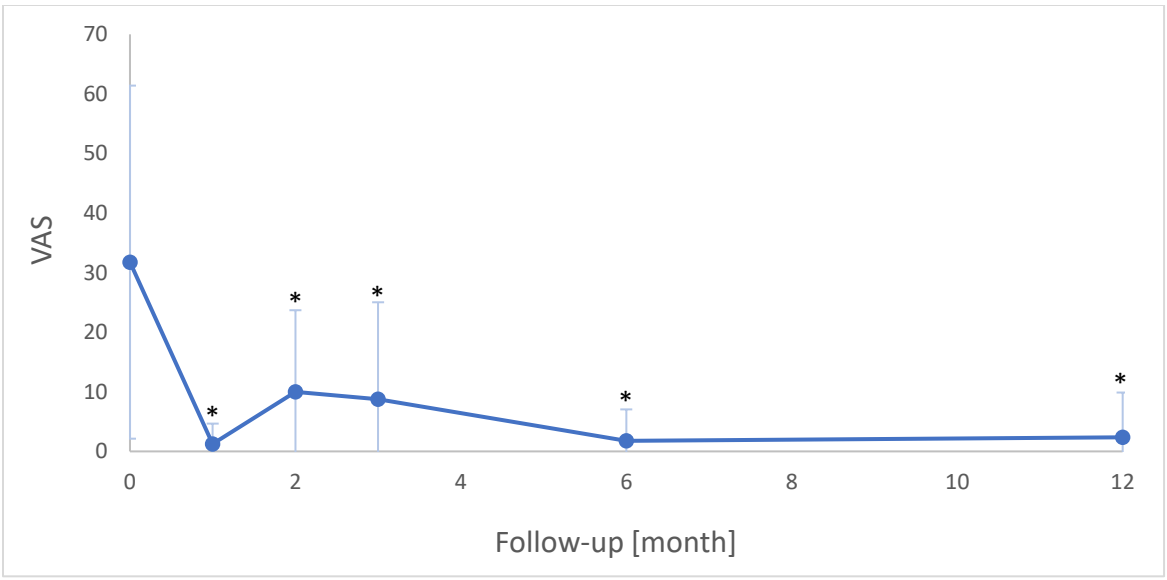

Figure 4: Pain score in Visual Analogue Scale (VAS) after EndoArt® implantation. The mean ± SD pain score was measured using a visual analogue scale. Significant pain relief was noted at all time points (n=17). *p<0.05

Discussion:

The FIH study proved the concept of reducing corneal edema through a barrier mechanism rather than solely relying on endothelial function. As the study progressed, it became apparent that the performance of EndoArt® was closely tied to its attachment quality to the posterior cornea. Factors influencing this attachment, such as the omission of Descemetorhexis, were scrutinized during the study. Indeed, in five (5) cases where Descemetorhexis was not performed, the implant could not achieve attachment and had to be explanted. Surgical steps promoting attachment were identified and consolidated into a protocol. This protocol included a 7.0-7.5 mm Descemetorhexis, a single fixation suture, and 10% C_3F_8 gas for all implantations. Integrating these steps into the EndoArt® implantation technique showed a trend toward minimizing the need for re-bubbling, ultimately resulting in successful attachment in the last two patients without requiring additional re-bubbling. Further details on implementing this modified implantation technique will be provided in upcoming publications of a more extensive cohort study.

The main concerns surrounding potential adverse events associated with keratoprostheses were corneal melting and perforation, both consequences of insufficient corneal nutrition, however, none of the 24 implanted subjects presented any signs of corneal nutrients depletion. Concerns regarding uncontrolled inflammation and severe infection were also refuted, as none of the subjects exhibited a prolonged inflammatory response. No serious device-related adverse events were reported during the 12-months follow-up. The main adverse events involved ocular pain and discomfort, all resolving during the follow-up period, as well as elevated IOP resulting from

gas bubble injection. The latter required paracentesis to relieve the high IOP in 3 cases. To mitigate the risk of post-operative pupillary block, iridectomy was introduced as a mandatory procedural step.

Over the 12-month follow-up period, a clinically significant decrease in the average CCT was observed in the 17 subjects who completed the study. This decrease in CCT correlated with improved central corneal clarity, as anticipated. As corneal clarity improved, VA enhanced, even among subjects deemed to have low visual potential due to comorbidities. Notably, despite most patients having low visual potential, 60% of all patients exhibited improvements of at least 3 lines in visual acuity at the 12-month follow-up, with the best 12-month VA reaching 0.6 logMAR (6/24).

Similar results were reported in another case series[27] involving five (5) patients with prior EK failures who were implanted with EndoArt®. Corneal clarity and VA showed improvement, with the most significant 6-month improvement in VA recorded from 1.3 logMAR at baseline to 0.2 logMAR (6/9.5). Furthermore, all subjects who reported pain at baseline experienced substantial pain relief after EndoArt® implantation. Importantly, no significant complications, such as corneal melting, chronic inflammation, or related infections, were observed during the follow-up period.

It is important to acknowledge the study's limitations, including the evolving method of EndoArt® implantation over the trial period and difficulties with the early learning curve. In the future, the results of a more extended follow-up period should be reported.

This FIH study provides evidence supporting the concept that EndoArt® may act as a passive barrier, effectively reducing corneal edema and enhancing vision while demonstrating a relatively

safe profile with no device-related SAEs. The reported outcomes highlight its potential utility in treating chronic corneal edema, particularly in high-risk patients with a history of graft rejection, for which the non-rejection nature of EndoArt® is a key feature. Furthermore, EndoArt® may be an available, ready-to-use option in geographic regions with a limited supply of donor corneas. The observed detachment rate, possibly due to the initial learning curve, requires attention for improvement. A more extensive follow-up period and larger cohort are essential to ascertain the precise role of EndoArt® as a therapeutic tool in managing patients with corneal edema.

Data availability:

The datasets analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

OD is the inventor of EndoArt® and co-founder of EyeYon Medical. OD, EG, AL, and MD analyzed and interpreted the EndoArt® FIH trial outcomes and wrote the manuscript. ALM is the co-founder of EyeYon Medical. ALM contributed to the writing of the manuscript. RGL and GUA participated in the EndoArt® FIH trial and contributed significantly to developing the implantation technique. All authors have read and approved the final manuscript.

Acknowledgments:

The FIH trial was fully funded by EyeYon Medical, a developer of the EndoArt® implant. The authors thank Yishai Friedlander, StatistX, for his statistical expertise and valuable contributions to the analysis of the data. The authors gratefully acknowledge Prof. Boris Knaizer, Dr. Sunita

Chaurasia, Dr. Jose Luis Guell, Prof. Igor Kaiserman, Dr. Modi Naftali, Dr. Shmuel Graffi, and Dr. David Varssano for participating.

List of Abbreviations:

SAE	Serious Adverse Event
CCT	Central Corneal Thickness
BCDVA	Best-Corrected Distance Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
FIH	First-In-Human
EK	Endothelial Keratoplasty
DSAEK	Descemet Stripping Automated Endothelial Keratoplasty
DMEK	Descemet Membrane Endothelial Keratoplasty
IRIS	Intelligent Research in Sight
VA	Visual Acuity
ACIOL	Anterior Chamber Intraocular Lens
IOL	Intraocular Lens
OCT	Optical Coherence Tomography
IOP	Intraocular Pressure
VAS	Visual Analogue Scale
DSO	Descemet Stripping Only
PK	Penetrating Keratoplasty

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List of Figures: