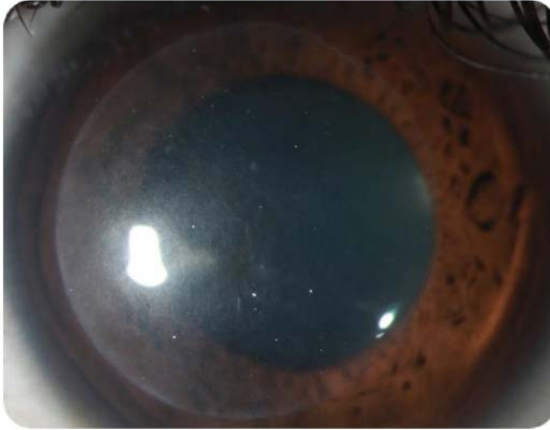


Prospective, Investigator-Initiated Study to Evaluate the Safety and Indicative Effectiveness of Xenia Custom-Made Ocular Implant in Subjects With keratoconus

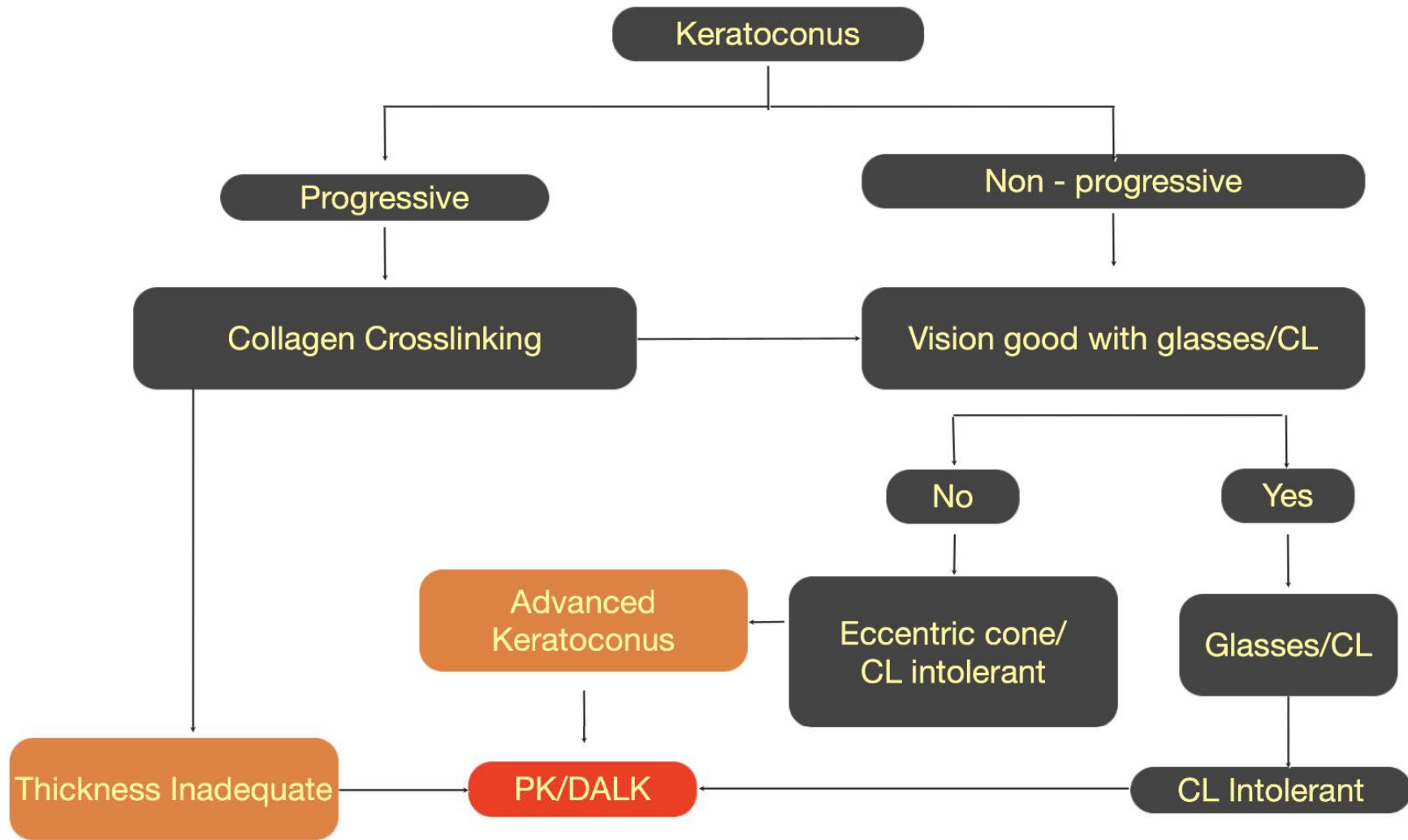


*Pravin K Vaddavalli, MD, Shantilal Shanghvi Cornea Institute
L V Prasad Eye Institute, India*

Financial Disclosure

This study was part of a clinical trial supported by Gebauer Medizintechnik GmbH, Neuhausen, Germany.

Support covered surgical and travel costs for patients and salary for one study optometrist.



Options for advanced keratoconus



Surgical Technique

Midstromal Isolated Bowman Layer Graft for Reduction of Advanced Keratoconus A Technique to Postpone Penetrating or Deep Anterior Lamellar Keratoplasty

Hortens van Dijk, BSc, Jack Parker, MD, C. Maya Tong, MSc, Lorraine Ham, PhD, Jessica T. Lie, PhD, Esther A. Crommeveld-van Baak, MSc, Gerrit R. J. Meides, MD, PhD

Midstromal implant of an isolated Bowman layer graft is a new approach to reduce ectasia in eyes with advanced keratoconus. The procedure should postpone penetrating or deep anterior lamellar keratoplasty. Ten eyes of 9 patients with progressive, advanced keratoconus and contact lens intolerance underwent the procedure with no intraoperative adverse events. Throughout the study period, we observed no complications related to stromal dissection and/or the Bowman layer graft. Maximum corneal power decreased from a mean (SD) of 74.5 (D) dioptries (D) before to 68.3 (5.6) D after surgery ($P = .002$). Hence, implant of an isolated Bowman layer graft may offer a safe and effective new technique to reduce ectasia in eyes with advanced keratoconus, potentially allowing continued long-term contact lens wear. The low risk of complications may render the procedure suitable as a treatment to postpone penetrating or deep anterior lamellar keratoplasty in cases with impending contact lens intolerance and/or corneal scarring (clinicaltrials.gov identifier: NCT02689906).

JAMA Ophthalmol 2016;34(4):405-410.
doi:10.1001/jamaophth.2015.2641
Published online February 23, 2016.

Keratoconus (KC) is regarded as a noninflammatory disorder characterized by progressive ectasia, which is associated with compromised optical function.^{1,2} In the past, early KC stages were managed by hard contact lens wear to obtain a regular anterior optical surface until contact lens intolerance in advanced stages required penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK). Since 2003, UV-A-induced collagen cross-linking became an alternative treatment option for KC. In which the corneal measured at least 400 μm in thickness and preoperative maximum keratometry (Kmax) measured 58 diopters (D) or less.³ Additional developments have enabled treatment of thicker and steeper corneas.⁴ Nevertheless, treatment in cases with more advanced KC may be limited to PK or DALK, which may be complicated by future-related problems, epithelial wound healing abnormalities, and/or corneal curvature changes due to progression of KC in the peripheral host cornea, resulting in a cascade of secondary complications and disappointing visual outcomes.^{5,6}

Because fragmentation of the Bowman layer is a pathognomonic feature in advanced KC,⁷ we hypothesized that a partial restoration of the corneal anatomy might be obtained through a midstromal implant of an isolated Bowman layer graft to remodel the, to flat, ten) the corneal curvature. At the same time, stabilization of the ectasia may be obtained by the Bowman layer split and through the wound-healing reaction between the host stroma and the Bowman layer graft.^{8,9}

In this article, we describe a new surgical approach using a midstromal dissection of a donor-isolated Bowman layer graft to reduce ectasia in eyes with advanced KC (Kmax ≥ 70 D). The procedure should enable continued contact lens wear while avoiding most short- and long-term complications.

Methods

We performed midstromal dissection with implant of an isolated donor Bowman layer graft in the stromal pocket in 10 eyes of 9 patients (3 male and 6 female; age range, 17-71 years) with (indicated) contact lens intolerance owing to progressive end-stage KC, defined as mean keratometry of at least 58 D and steeped Kmax of at least 70 D (Table 1 and Table 2). In all eyes, an unassisted attempt was made to fit a sclera-supported rigid contact lens. All patients signed an informed consent approved by the institutional review board of the Dutch Independent Ethics Committee; the study was conducted according to the Declaration of Helsinki.

Donor Tissue

Donor corneas released for transplant were mounted on an artificial anterior chamber (Vitana [distributed by Rodenand BV]). The epithelial layer was carefully removed using surgical spares. A 360° superficial incision was made using a 30-gauge needle in the clear part of the corneal epithelium with a custom-made stripper (DORC International BV). The Bowman layer was carefully isolated from the anterior stroma over the full 360° toward the central part of the cornea. After complete detachment, subsequent repositioning resulted in a Bowman flap measuring 9.0 to 11.0 mm. Owing to the elastic properties of the Bowman membrane, a Bowman "roll" formed spontaneously which was submerged in 70% ethanol to remove epithelial cells.¹⁰ After rinsing thereof with balanced salt solution (BSS; Bausch & Lomb), it was stored in organ-culture medium (CultivaMax; Eurobio) at 37°C until transplant (Figure 1).

Surgical Technique

We performed manual dissection of a stromal pocket using a technique previously described to create a stromal dissection

Clinical Review & Education



Bowman Layer Transplantation to Reduce and Stabilize Progressive, Advanced Keratoconus

Kerim van Dijk, BSc,^{1,2} Vasilios S. Liavas, MD, PhD,^{1,2} Jack Parker, MD,^{1,2,3} Lorraine Ham, PhD,^{1,2,4,5} Jessica T. Lie, PhD,^{1,2} Esther A. Crommeveld-van Baak, MSc,^{1,4} Gerrit R.J. Meides, MD, PhD^{1,2,4}

Objective: To evaluate the clinical outcome of mid-stromal isolated Bowman layer transplantation, a new surgical technique to reduce and stabilize ectasia in eyes with advanced keratoconus, to postpone penetrating keratoplasty or deep anterior lamellar keratoplasty, and to enable continued daily contact lens wear.

Design: Prospective, nonrandomized cohort study at a tertiary referral center.

Participants: Twenty-two eyes of 19 patients with progressive, advanced keratoconus not eligible for ultraviolet cross-linking.

Interventions: The mid-stroma was manually dissected and an isolated donor Bowman layer was positioned within the stromal pocket.

Main Outcome Measures: Before and up to 36 months after surgery (mean follow-up, 21.17 months), best spectacle-corrected visual acuity (BSCVA), best contact lens-corrected visual acuity (BCLVA), Scheimpflug-based corneal topography measurements, endothelial cell density, biometry, refraction, and intraoperative and postoperative complications were recorded.

Results: Two surgeries were complicated by an intraoperative perforation of Descemet membrane; no other intraoperative or postoperative complications were observed. Maximum keratometry decreased on average from 77.2 ± 6.2 diopters (D) to 68.2 ± 3.7 D ($P < 0.001$) at 1 month after surgery and remained stable thereafter ($P > 0.072$). Mean BSCVA improved from 1.27 ± 0.44 logarithm of the minimum angle of resolution units before surgery to 0.80 ± 0.30 logarithm of the minimum angle of resolution units 12 months after surgery ($P < 0.001$), whereas BCLVA remained stable ($P = 0.105$). Mean thinnest-point pachymetry increased from 332 ± 59 μm before surgery to 360 ± 50 μm at the latest follow-up ($P = 0.012$), and no change in endothelial cell density was found ($P = 0.355$).

Conclusions: With isolated Bowman layer transplantation, reduction and stabilization of corneal ectasia was achieved in eyes with progressive, advanced keratoconus. Given the low risk for complications, the procedure may be performed to postpone penetrating or deep anterior lamellar keratoplasty. *Ophthalmology* 2015;122:909-917 © 2015 by the American Academy of Ophthalmology.

Supplemental material is available at www.aajournal.org.

Keratoconus is a bilateral, noninflammatory, progressive disorder characterized by protrusion and thinning of the cornea, causing compromised optical performance.^{1,2} To obtain heteroptical performance in mild to moderate stages of keratoconus, hard contact lens fitting as well as implantation of intracorneal ring segments may be valuable options.³ In cases of advanced keratoconus, if contact lens intolerance is present or no acceptable vision can be obtained with contact lenses, then deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PK) are common procedures.⁴ However, none of these treatment options stop the progression of keratoconus.

Over the past decade, corneal ultraviolet cross-linking has been introduced to strengthen the stromal collagenous corneal matrix and thereby delay or avoid further keratoconus progression.⁵ As a result, corneal transplantation may be postponed or no longer be required. Ultraviolet cross-

linking currently is indicated for use in keratoconic corneas of at least 400 μm in thickness after removal of the epithelium and in which the preoperative maximum keratometry (K_{max}) value does not exceed 58 diopters (D).⁶ Although techniques are being developed to treat thinner and steeper corneas,⁷ they may be less suitable for more advanced keratoconus. Nevertheless, advanced keratoconus patients may still profit from stabilizing the cornea and halting the progression to preserve visual acuity, while postponing or even preventing DALK or PK and thereby avoiding the inherent complications of these procedures.⁸⁻¹⁰

We recently developed a technique to strengthen and flatten the cornea in cases of advanced keratoconus by means of mid-stromal transplantation of an isolated Bowman layer graft.¹¹ Long-term stabilization of ectasia may be obtained by the Bowman layer itself, as well as through the wound-healing effect between the host stroma

Basic Investigation

OPEN

Corneal Lenticule Allotransplantation After Femtosecond Laser Small Incision Lenticule Extraction in Rabbits

Jing Zhao, MD, PhD, Shen Shen, MD, Mi Tian, MD, Ling Sun, MD, Ph.D, Yu Zhao, MD, Ph.D, Xiaoyu Zhang, MD, Ph.D, and Xingtiao Zhou, MD, PhD

Purpose: To investigate the feasibility of allotransplanting extracted lenticules after femtosecond laser-assisted small incision lenticule extraction (SMILE) in rabbits and the subsequent healing process.

Methods: Fourteen New Zealand white rabbits were divided evenly into 2 groups. The rabbits in group A received SMILE procedures with a ~600-D correction. The lenticules from group A were immediately inserted into a femtosecond laser-created corneal stromal pocket in group B. After surgery, the anterior segment was assessed in vivo by slit-lamp microscopy, corneal topography, optical coherence tomography, and confocal microscopy. All eyes were enucleated for hematoxylin-eosin staining and transmission electron microscopy after the animals were killed.

Results: At postoperative day 1, there was moderate corneal edema in the implanted lenticule stroma. At 6 months, the lenticules were integrated with the surrounding tissue, and the boundary could not be identified through slit-lamp microscopy; regenerated lamellae of the corneal nerves were thicker than at postoperative month 1 as observed through confocal microscopy. The central corneal thickness increased by 58.75 ± 21.58 μm. The lenticules were gradually integrated with the surrounding tissue, and their density was similar to the adjacent tissue according to optical coherence tomography; however, a clear boundary between the lenticule and surrounding tissue was detectable using light microscopy and transmission electron

microscopy, revealing disordered fibers and decreased keratocytes in implanted lenticules.

Conclusions: In this model it is feasible and safe to allotransplant extracted corneal lenticules after SMILE. Healing of implanted lenticules after SMILE is stable at postoperative 6 months, but collagen fiber reorganization requires further investigation.

Key Words: corneal lenticule, allotransplant, femtosecond laser, small incision lenticule extraction

(*JAMA Ophthalmol* 2015;33:221-228)

The femtosecond laser has been applied to laser in situ keratomileusis and refractive lenticule extraction (ReLEx) for the correction of refractive errors.^{1,2} The lenticules created by small incision lenticule extraction (SMILE) are precise and predictable. Our previous study and other reports have confirmed that it is feasible and safe to autologously transplant extracted corneal lenticules from SMILE in animal or human corneas.³⁻⁷ However, autologous transplantation is dependent on the refractive power and corneal thickness. With the development of the SMILE technique and the standardization of lenticule-banking, allogeneic lenticule transplantation could be used to treat hyperopia, because of a broad range of refractive diopters and planar materials. Ganesh et al reported 9 patients with hyperopia successfully receiving transplantation of an allogeneic cryopreserved lenticule extracted from SMILE, but the stromal collagen fibers of the cryopreserved lenticule were damaged because of freezing and thawing.⁸⁻¹¹ In that case, allotransplanting lenticules immediately would be a promising way to solve this issue. In this study, the lenticules from SMILE were transplanted immediately into a femtosecond laser-created stromal pocket to assess the feasibility of allogeneic corneal lenticule transplantation and its subsequent healing process.

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The authors have no funding or conflicts of interest to disclose. Reprints: Jing Zhao, MD, PhD, Key Laboratory of Myopia, Ministry of Health, Department of Ophthalmology, Eye and ENT Hospital, Fudan University, 83 FenYing Rd, Shanghai 200011, China (e-mail: zhaojing@smg.com).

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MATERIALS AND METHODS

Ethics Statement

All experimental and animal-handling procedures were in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were conducted according to the requirements of the Animal Research and Ethics Committee of the Eye and ENT Hospital, Fudan University, Shanghai, China.

Continued on page 223

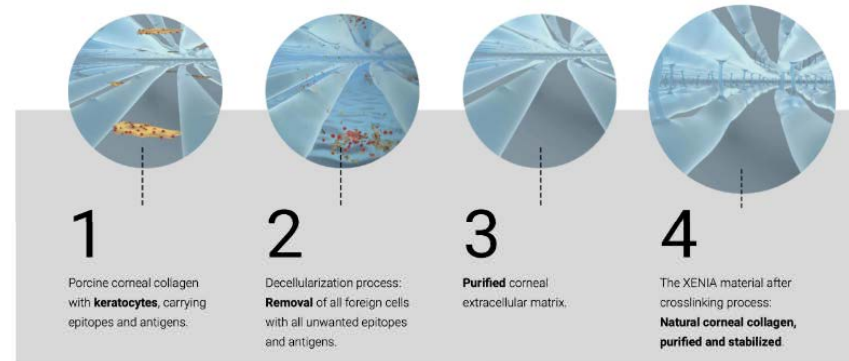
XENIA

Xenia™

- The Xenia™ Lenticule is a **porcine collagen implant**
- Manufactured from **porcine stroma**
- Isolated porcine corneas created with a nano tome followed by a liquid sterilization step
- **Co-planar implant** which is free of cells and their remnants.

Dimensions

- **100 to 300** microns thick
- **7 to 8 mm** diameter
- **Cross-linked** with UV



XENIA - Study

Objectives: To evaluate the **safety** and **indicative effectiveness** of Xenia™ when implanted in subjects with keratoconus

Study Design: Prospective open-label, investigator-initiated clinical study

Number of Subjects & Enrollment: Total of **5 + 3** subjects - 12 month followup

Investigational Site: L V Prasad Eye INSTITUTE, Hyderabad

Outcome measure - Change in keratometry, Measurement Best Corrected Distance Visual Acuity

Inclusion criteria

Diagnosis of **keratoconus**

Visual acuity with CL - **20/40 or better**

No prior **surgery**

Intolerant to contact lens wear

Minimal corneal thickness of **350** microns

No active ocular or systemic illness

Over **18 years** of age.

OCULUS - PENTACAM 4 Maps Refractive

Last Name:
 First Name:
 ID:
 Date of Birth:
 Exam Date: 30/08/2021 Time: 13:14:03
 Exam Info:

Cornea Front

Rf: 5.31 mm K1: 63.6 D
 Rs: 4.75 mm K2: 71.0 D
 Rm: 5.03 mm Km: 67.1 D

QS: **Align** Axis: (flt.) 172.7° Astig: -7.4 D
 Q-val: (8mm) -1.99 Rper: 7.39 mm Rmin: 3.82 mm

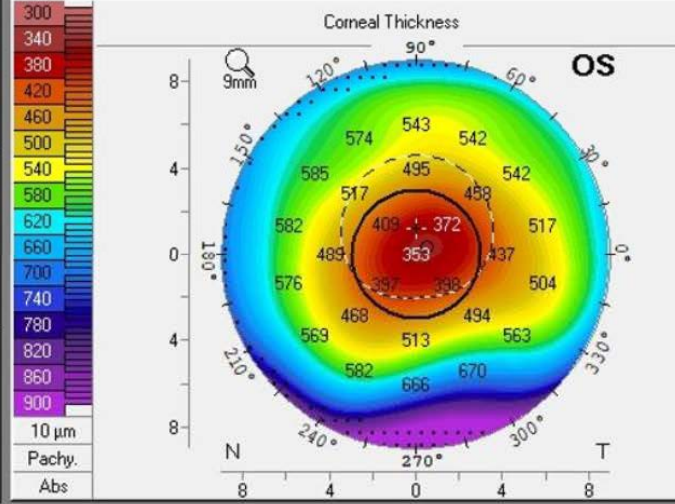
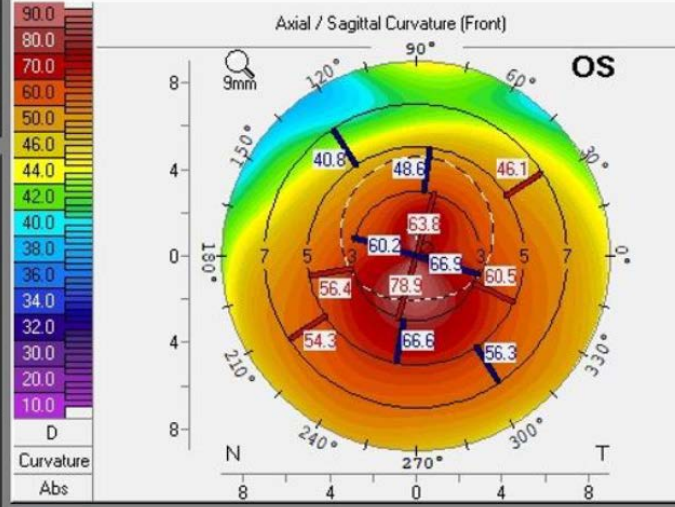
Cornea Back

Rf: 3.96 mm K1: -10.1 D
 Rs: 3.44 mm K2: -11.6 D
 Rm: 3.70 mm Km: -10.8 D

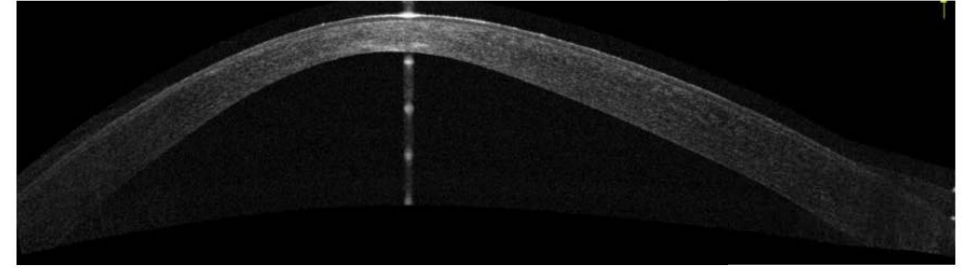
QS: **Align** Axis: (flt.) 8.1° Astig: +1.5 D
 Q-val: (8mm) -1.69 Rper: 6.13 mm Rmin: 2.48 mm

Pupil Center: + 366 μm x(mm) +0.02 y(mm) +0.62
 Pachy Vertex N.: 353 μm 0.00 0.00
 Thinnest Locat.: 349 μm +0.25 +0.19
 K Max. (Front): 88.4 D 0.00 -0.44

Cornea Volume: 60.5 mm³ HWTW: 11.3 mm
 Chamber Volume: 186 mm³ Angle: 31.4°
 A. C. Depth (Int.): 3.96 mm Pupil Dia: 3.44 mm
 Enter IOP IOP(Sum): +7.9 mmHg Lens Th.:
 Axial Length: SNR(Ax.Le) **5.9**



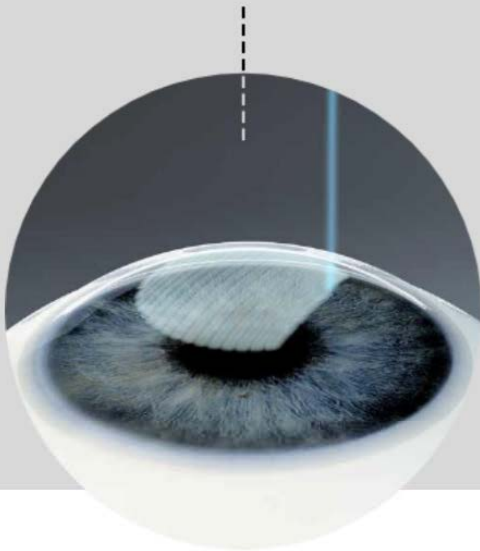
Pre op



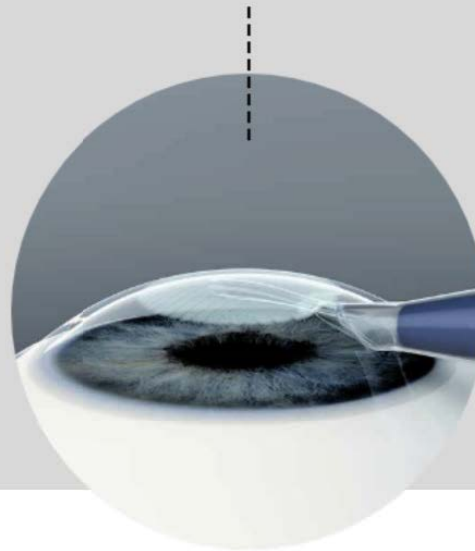
Visual Acuity	Right Eye	Left Eye
UCVA	20/40, N6 at 30cm	CF1meter, <N36, at 30cm
Refraction	Plano/-4.00DC*45°	-11.00DS/-3.25DC*170°
BCVA	20/20P	20/200
Near vision	N6 at 30 cm	N36 at 30 cm

XENIA for Keratoconus

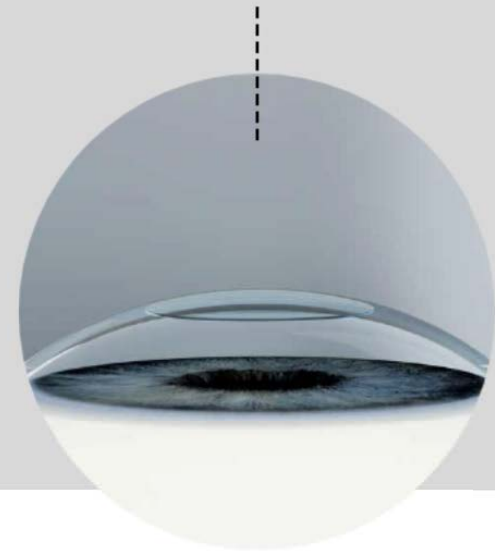
1 For keratoconus patients a **corneal stromal pocket** with a small opening is created.



2 The XENIA implant is **inserted** by means of an injector or forceps.



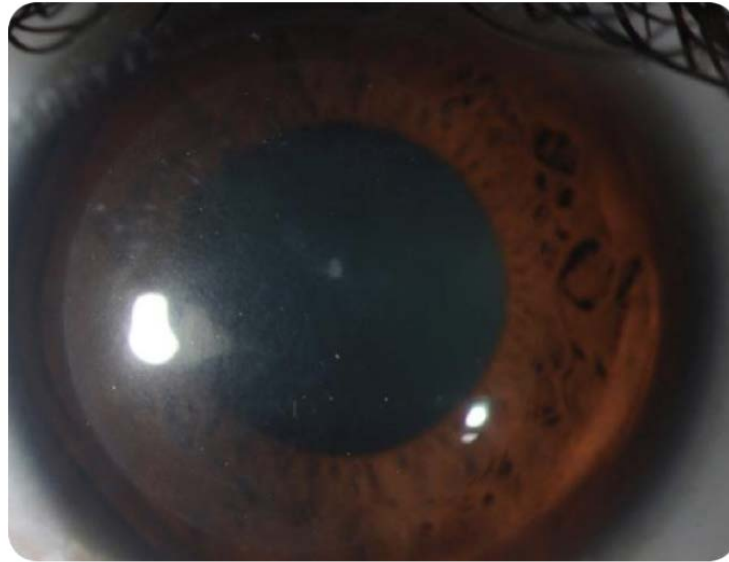
3 After insertion, the XENIA implant is unfolded in the pocket.



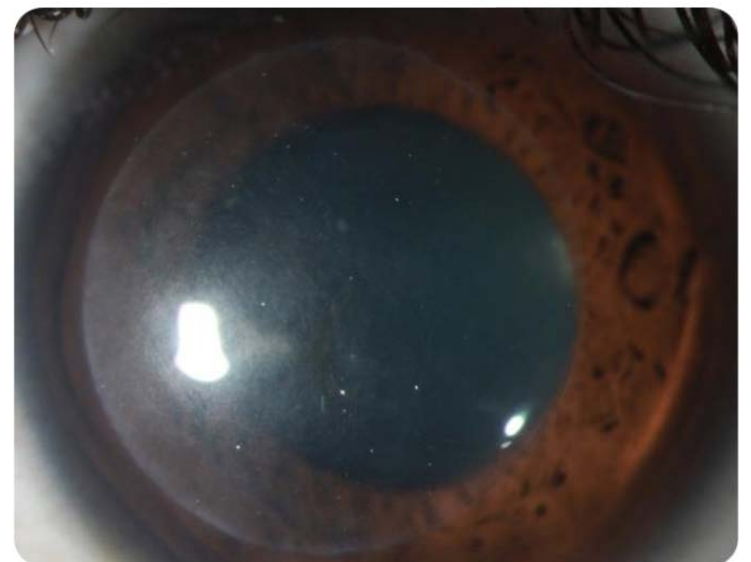
XENIA implant LE



Pre Op

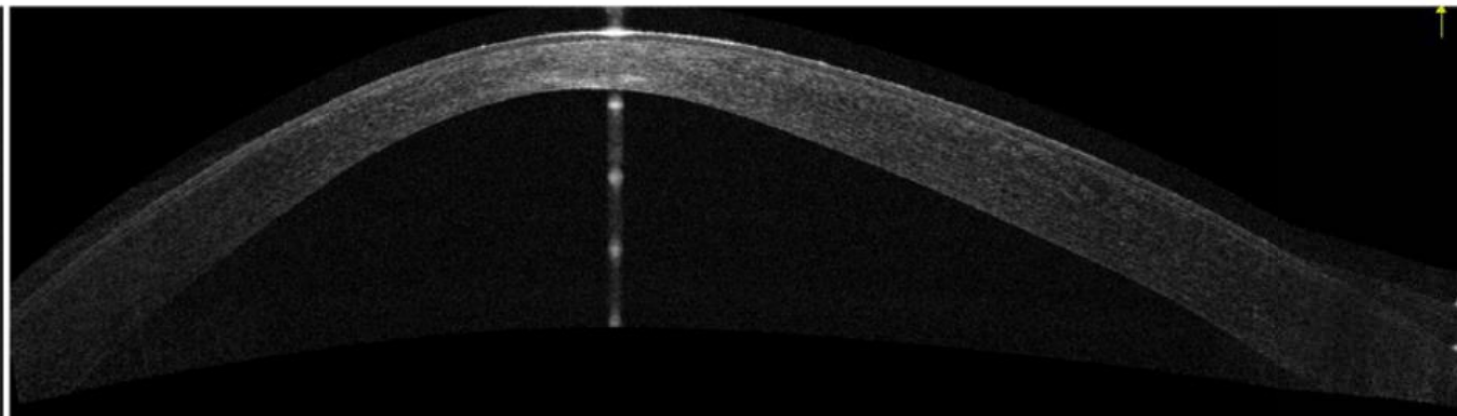
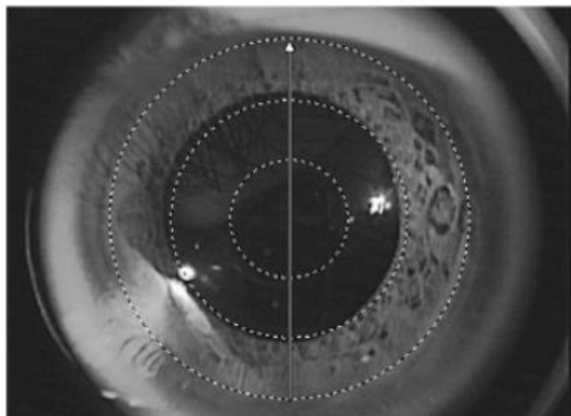


1 month post-op

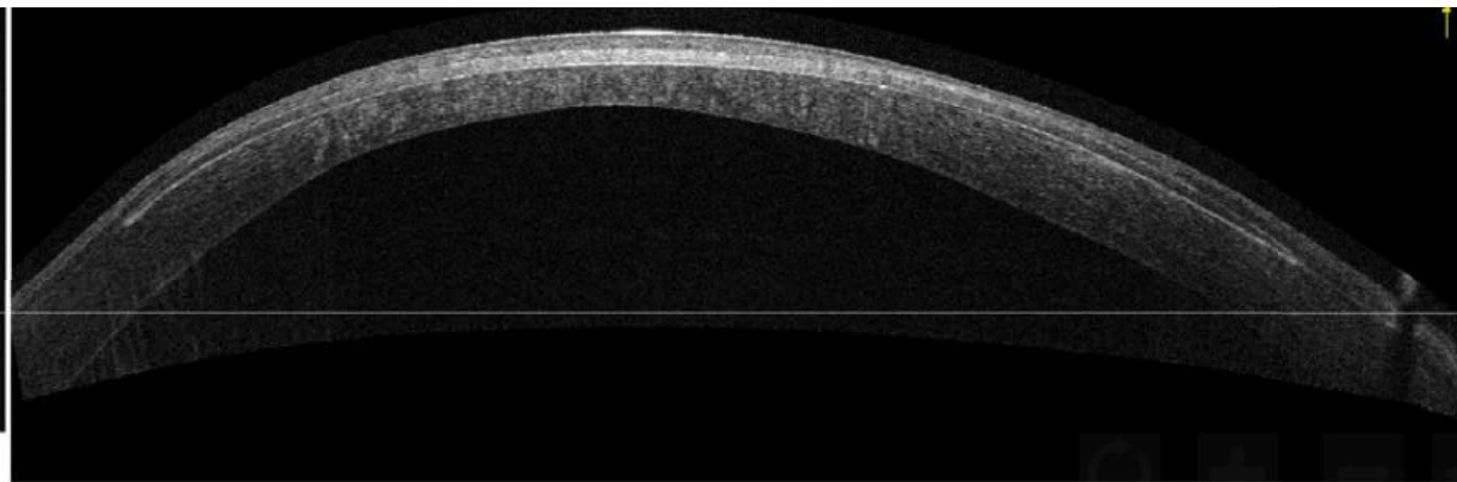
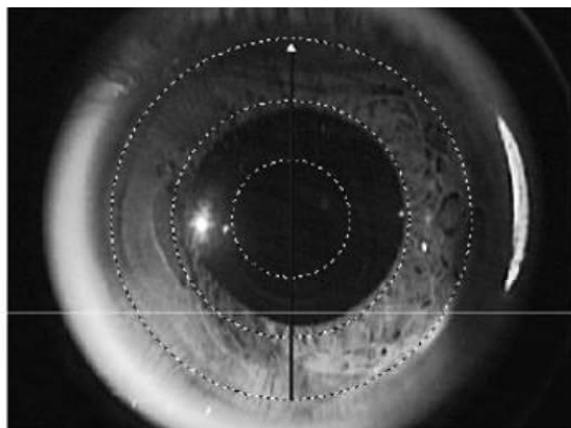


12 month post-op

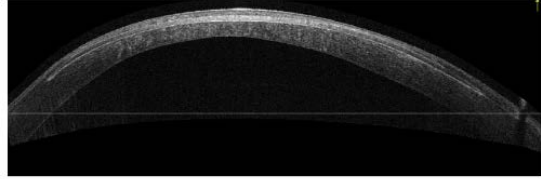
Pre op



Post op

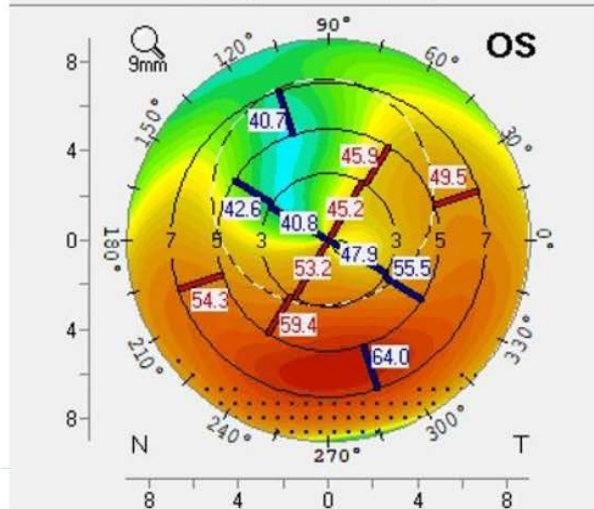


Post op x 12 months

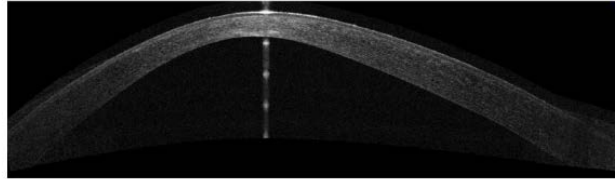


	Pachy:	x[mm]	y[mm]
Pupil Center:	+ 428 μm	-0.13	+1.07
Thinnest Locat.:	○ 368 μm	+0.28	-0.14

Axial / Sagittal Curvature (Front)

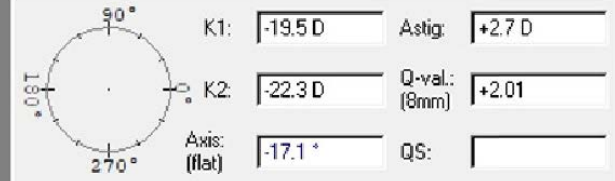
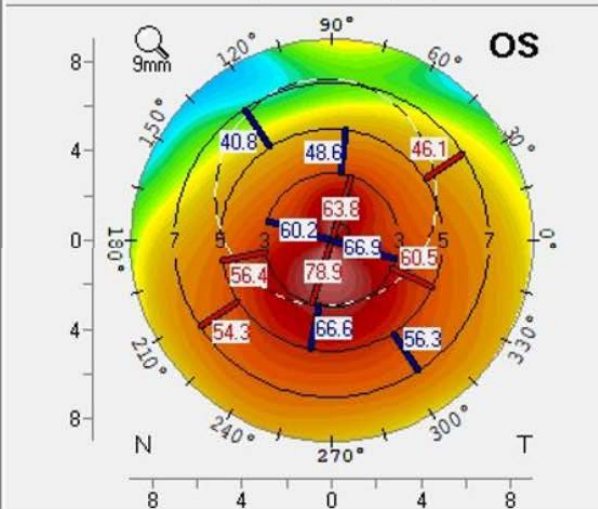


Pre op



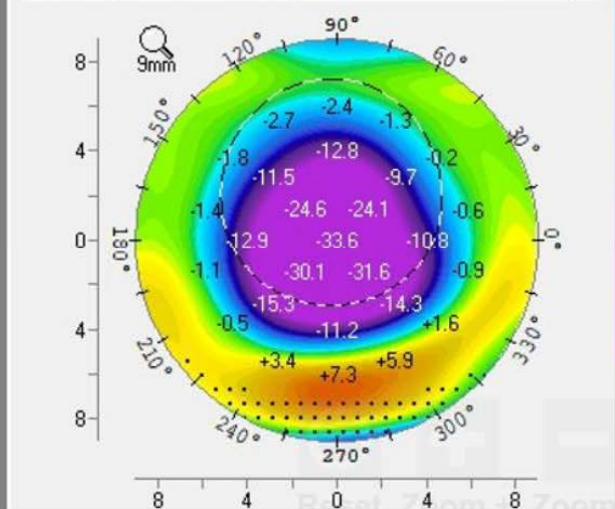
	Pachy:	x[mm]	y[mm]
Pupil Center:	+ 366 μm	+0.02	+0.62
Thinnest Locat.:	○ 349 μm	+0.25	+0.19

Axial / Sagittal Curvature (Front)



	Pachy:	x[mm]	y[mm]
Pupil Center:	+ 62 μm	-0.15	+0.45
Thinnest Locat.:	○ 19 μm	+0.03	-0.33

Axial / Sagittal Curvature (Front)

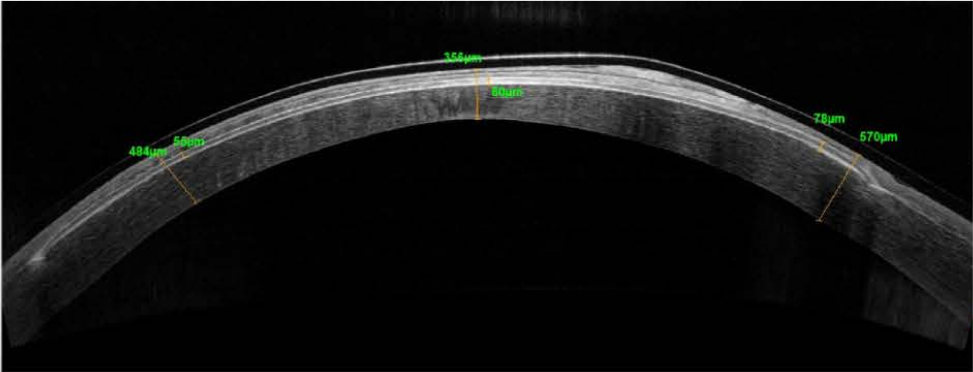
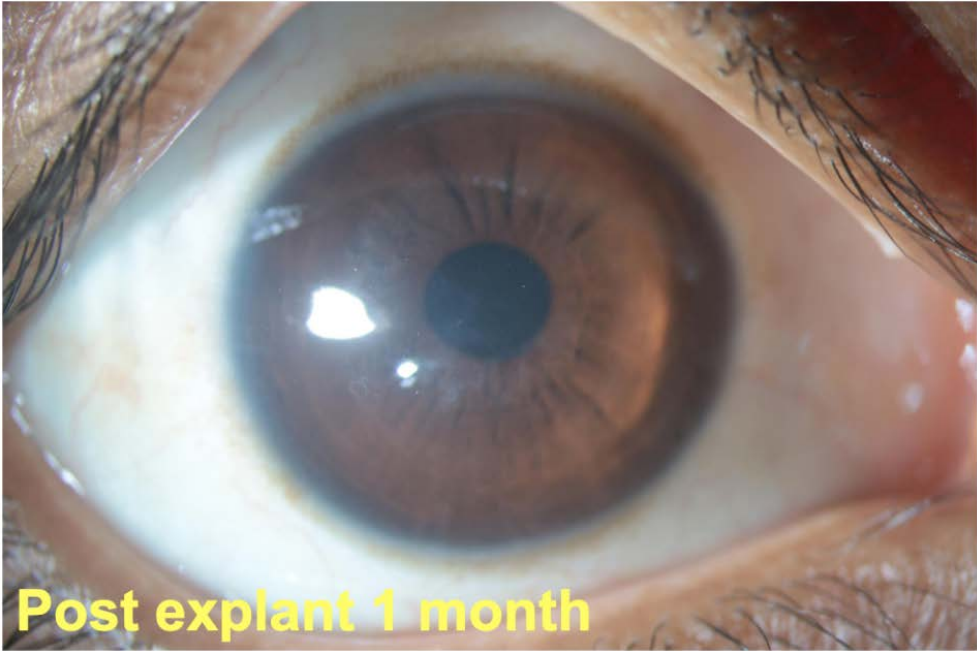


		Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Pre-op	UCVA	CF1mt	20/800	20/250	20/400	20/400
	Ref	-11/-3.00*170	-11/-7.75*70	-2.0/-6.0*140	-3.5/-3.0*150	-5.00
	BCVA	20/200, N36	20/160, N36	20/125p, N18	20/125, N10	20/250, N36
	K1,K2	63.6, 71.0	67.3, 76.2	61.6, 68.6	61.8, 65.0	56.1, 63.3
	CCT	349 μ	359 μ	370 μ	396 μ	348
POP 1m	UCVA	20/250	20/100p	20/80P	20/200	20/125
	Ref	-0.5/-5.00*120	+0.75/-1.00*5	0.0/-2.50*70	-4.0/-2.5*25	0.0/-3.0*160
	BCVA	20/125, N18	20/100, N18	20/50P, N08	20/100, N18	20/100, N24
	K1,K2	41.9, 48.2	47.4, 52.1	39.4, 42.5	54.5, 57.6	39.9, 43.7
	CCT	378 μ	386 μ	405 μ	432 μ	427
POP 3m	UCVA	20/250	20/250	20/100p	20/250	20/100p
	Ref	-2.5/-4.00*140	0.0/-3.00*50	0.0/-4.00*140	0.0/-3.50*20	+3.0/-5.0*160
	BCVA	20/80p N18	20/80, N36	20/50p, N08	20/80, N18	20/80p, N12
	K1,K2	42.7, 47.7	46.4, 51.5	38.1, 40.8	53.2, 55.7	38.4, 42.8
	CCT	383 μ	297 μ	377 μ	413 μ	416

Topography

Subject	K1 Anterior					K2 Anterior					Kmax					Kmean				
	Pre-Op	1m	3m	6m	12m	Pre-Op	1m	3m	6m	12m	Pre-Op	1m	3m	6m	12m	Pre-Op	1m	3m	6m	12m
1	63.6	42	42.7	44.6	44.8	71	48.2	47.7	49.5	48.3	88.4	65.2	65.1	67.4	66.7	67.1	44.8	45.1	46.9	46.5
2	67.3	47	46.4	WD	WD	76.2	52.1	51.5	WD	WD	79.9	77.9	86.3	WD	WD	71.5	49.7	48.8	WD	WD
3	61.6	39	38.1	37.8	36.9	68.6	42.5	40.8	40.6	40.5	71.8	57.9	59.5	59	60.4	64.9	40.9	39.4	39.2	38.6
4	61.8	55	53.2	52.3	WD	65	57.6	55.7	57.7	WD	77.7	67.1	60.6	66.8	WD	63.4	56	54.4	54.9	WD
5	56.1	40	38.4	39.6	40.4	63.3	43.7	42.8	42.1	42.6	70.1	55.9	57.6	58.7	57.5	59.5	41.7	40.4	40.8	41.5
6	57.3	47	46.3	47.5	WD	65	54.3	50.4	51.1	WD	76.2	59.4	59.8	60.8	WD	60.9	50.5	48.3	49.2	WD
7	61.3	51	WD	WD	WD	67.5	53.2	WD	WD	WD	75.4	61.2	WD	WD	WD	64.2	52.1	WD	WD	WD
8	54.6	49	46.7	47.9	NA	61.1	51.5	54.3	55.7	NA	69.8	66.1	67.4	74.1	NA	57.7	50	50.3	51.5	NA

P 007

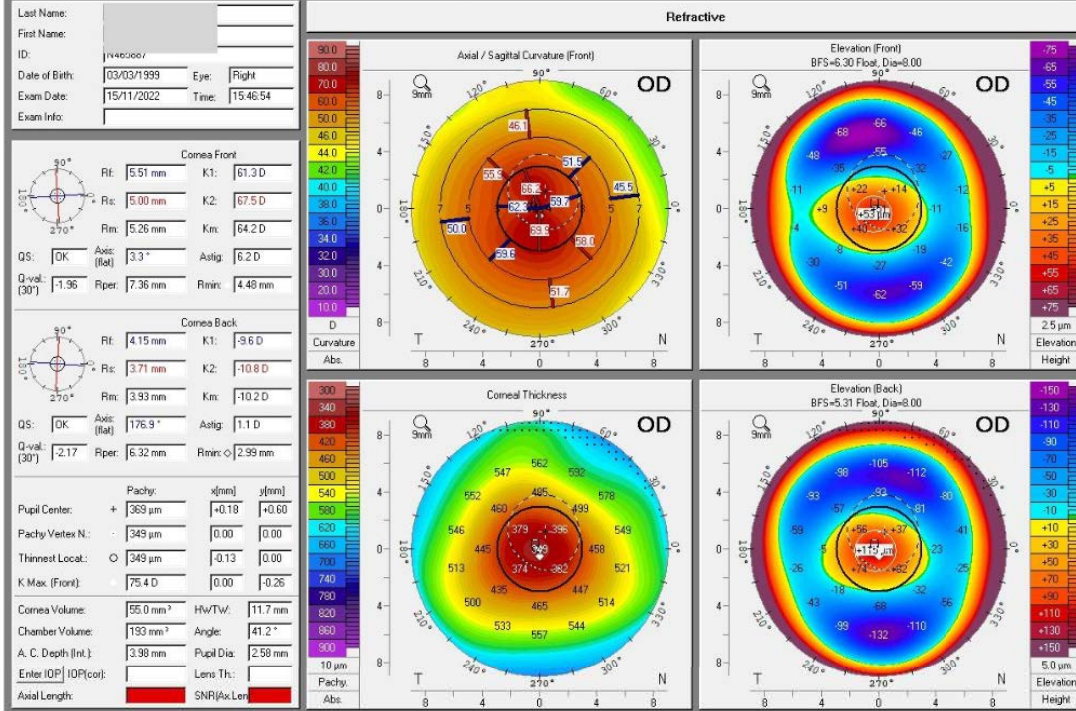


Pre Implant

Post Explant

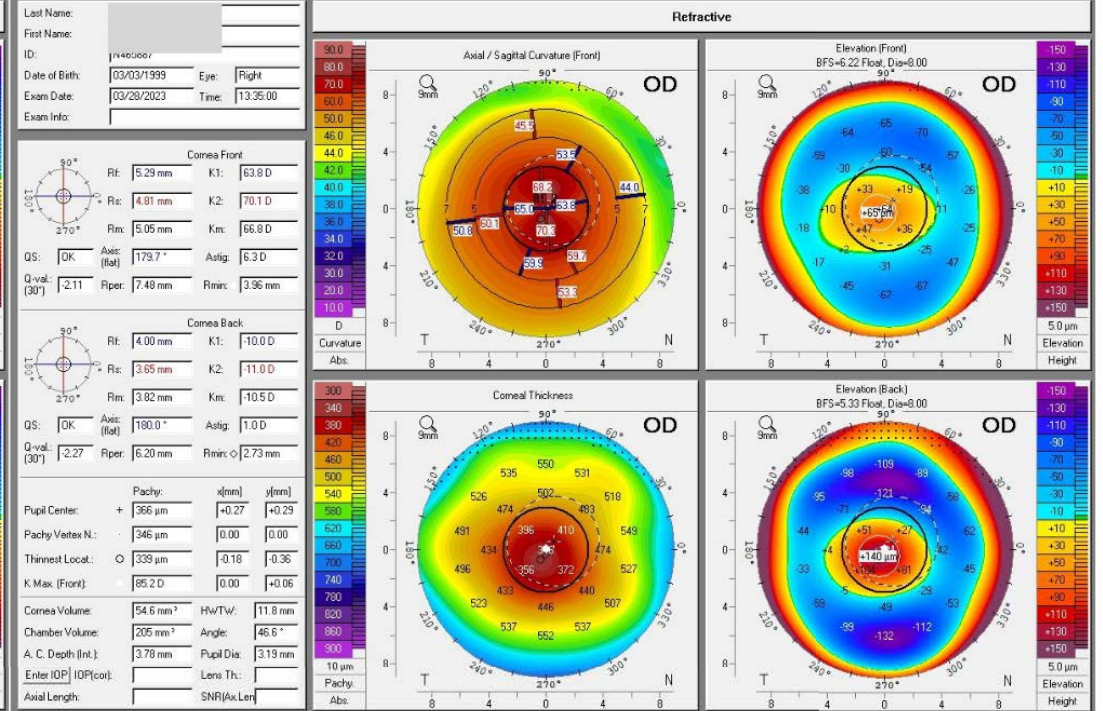
OCULUS - PENTACAM 4 Maps Refractive

1.2712



OCULUS - PENTACAM 4 Maps Refractive

1.2712



Summary

- XENIA stromal lenticule implantation is a viable option for advanced keratoconus
- Improves **corneal curvature** and **visual acuity** and remains stable over a year
- Option for patients **not suitable for collagen cross linking**
- Potential to avoid **need for a corneal transplant**
- Stromal melt and epithelial healing issues might be sorted by **deeper implants**