

TULIAISIA ESCRS:STÄ

ON SE JÄNNÄÄ...

KAIHIEN KAUHU, LINSSEJÄ

KAHVIA, TÄRINÄÄ

MARTIN KRONSCHLÄGER

PHARMACOKINETICS OF CAFFEINE IN THE LENS CAPSULE/EPITHELIUM...

PHARMACOKINETICS OF CAFFEINE IN THE LENS CAPSULE/EPITHELIUM

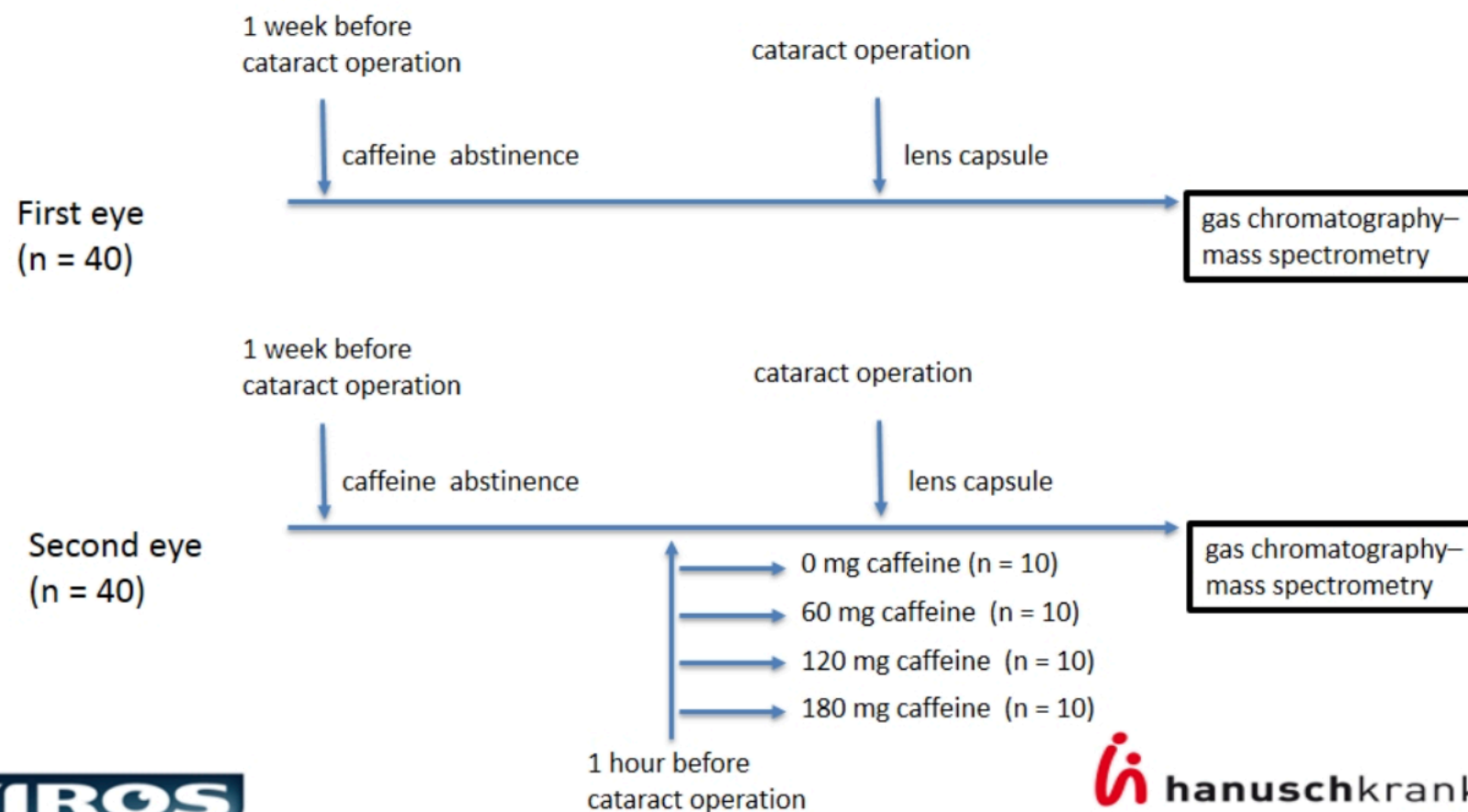
- ▶ “the antioxidant ability of caffeine is similar to glutathione and significantly higher than ascorbic acid”
- ▶ Rottakokeet: UV-säteilyn indusoiman kaihen hidastuminen

Prevention in experimental ultraviolet induced cataract

Substance	Protection Factor	Paper
Vitamin C	1.0	(Mody, 2008)
Vitamin E (α -tocopherol)	1.14	(Söderberg, 2012)
Caffeine	1.23	(Kronschläger, 2013)
Thioltransferase	1.3	(Kronschläger, 2012)

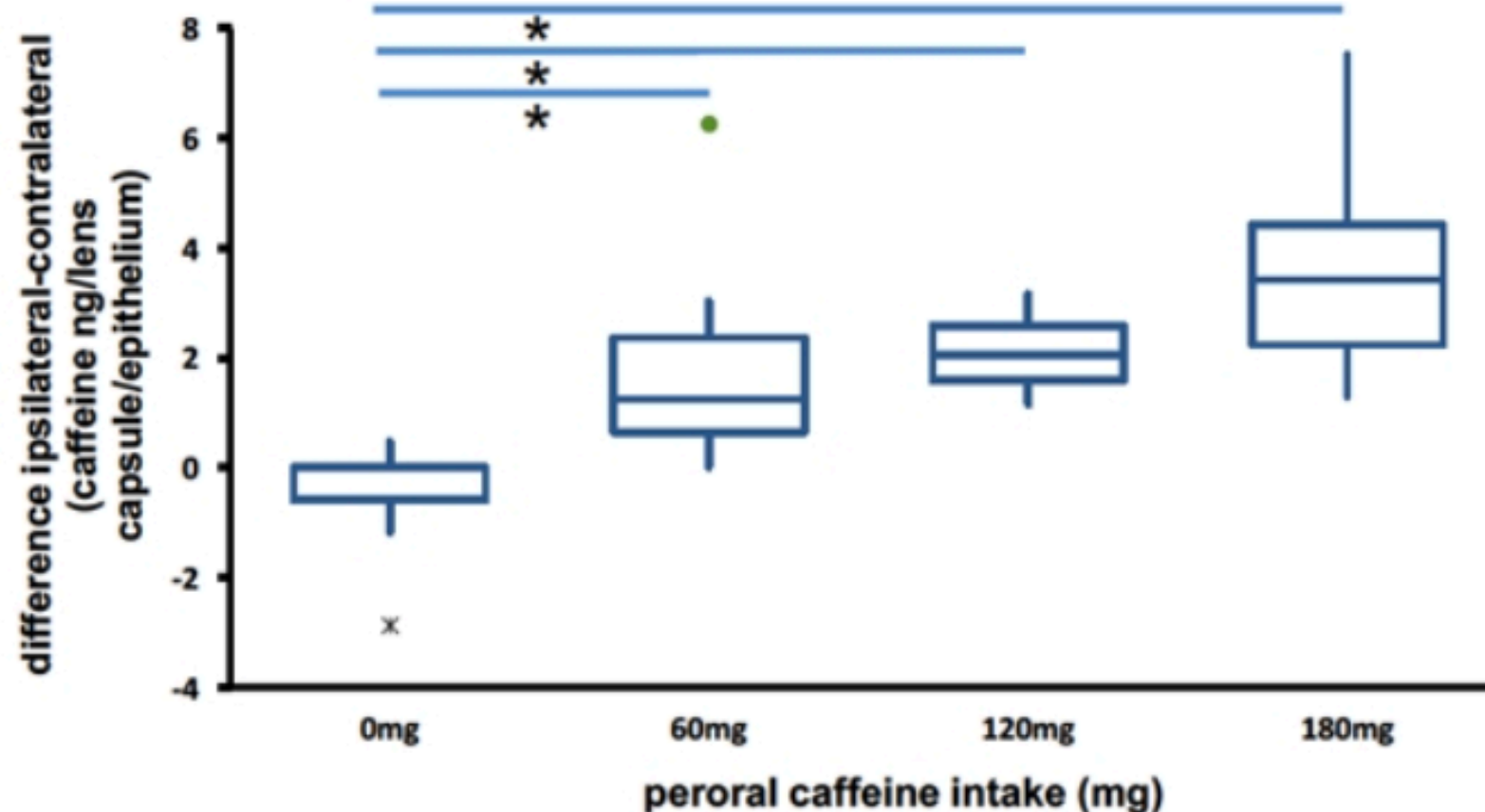
PHARMACOKINETICS OF CAFFEINE IN THE LENS CAPSULE/EPITHELIUM

Methods and Design



PHARMACOKINETICS OF CAFFEINE IN THE LENS CAPSULE/EPITHELIUM

Lens capsule/epithelium caffeine concentration



PHARMACOKINETICS OF CAFFEINE IN THE LENS CAPSULE/EPITHELIUM

Epidemiological Findings

- The incidence of cataract blindness in humans was significantly lower in groups consuming higher amounts of coffee in comparison to the groups with lower coffee intake.

Varma SD, 2016. Effect of coffee (Caffeine) against human cataract blindness. *Clin Ophthalmol*.10:213-220.

- The dietary total antioxidant capacity including coffee of middle-aged and elderly women was inversely associated with the risk of age-dependent cataract.

Rautiainen S, 2014. Total antioxidant capacity of the diet and risk of age-related cataract: a population-based prospective cohort of women. *JAMA Ophthalmol*.132(3):247-52.

Conclusion

- Caffeine accumulates in lens capsule and epithelial cells after oral intake
- Potent candidate to delay the onset of cataract

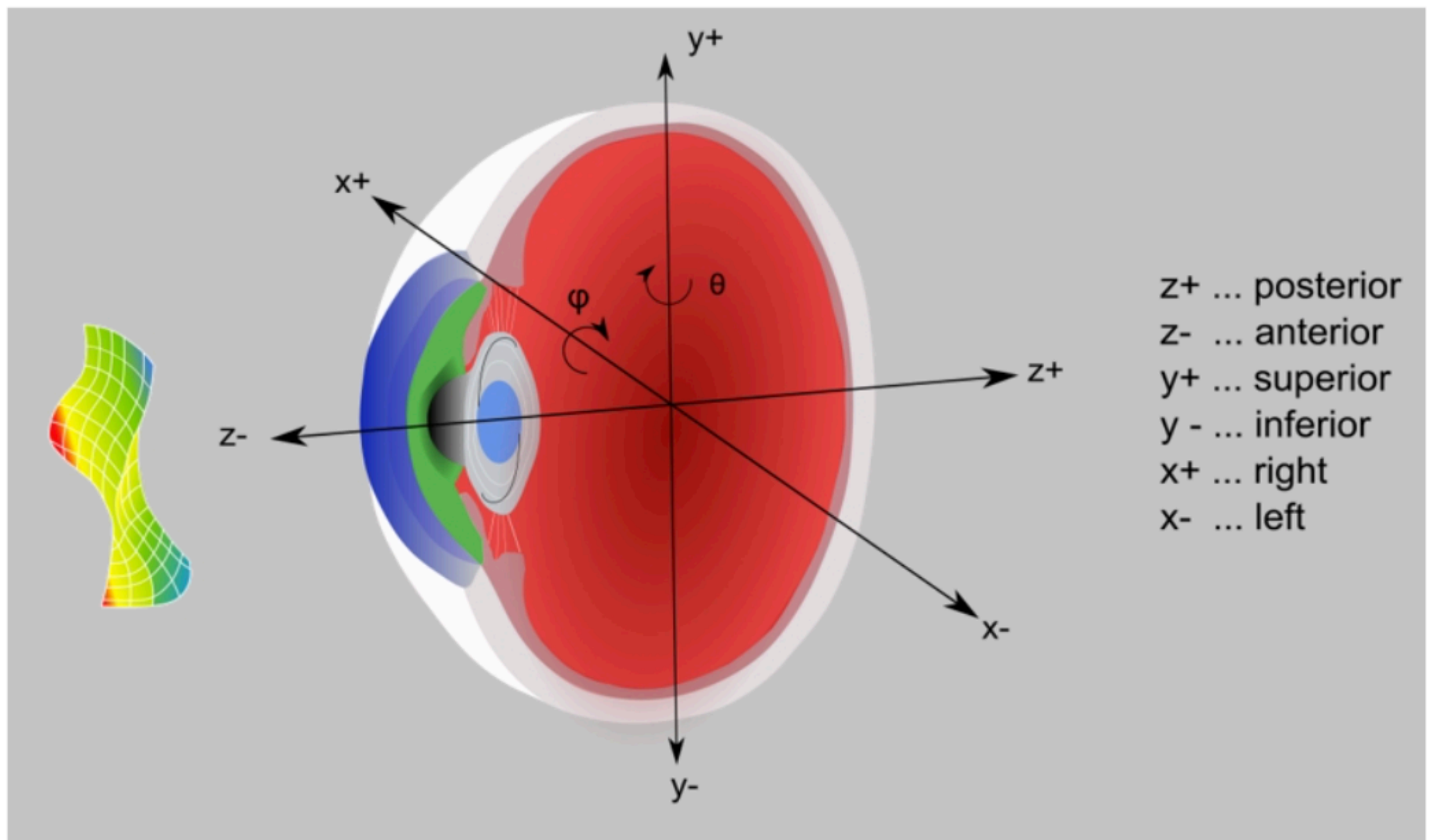


SOPHIE MAEDEL

**DYNAMIC ASESSEMENT AND PREDICTION OF
PSEUDOPHAKODONESIS AFTER UNEVENTFUL
CATARACT SURGERY**

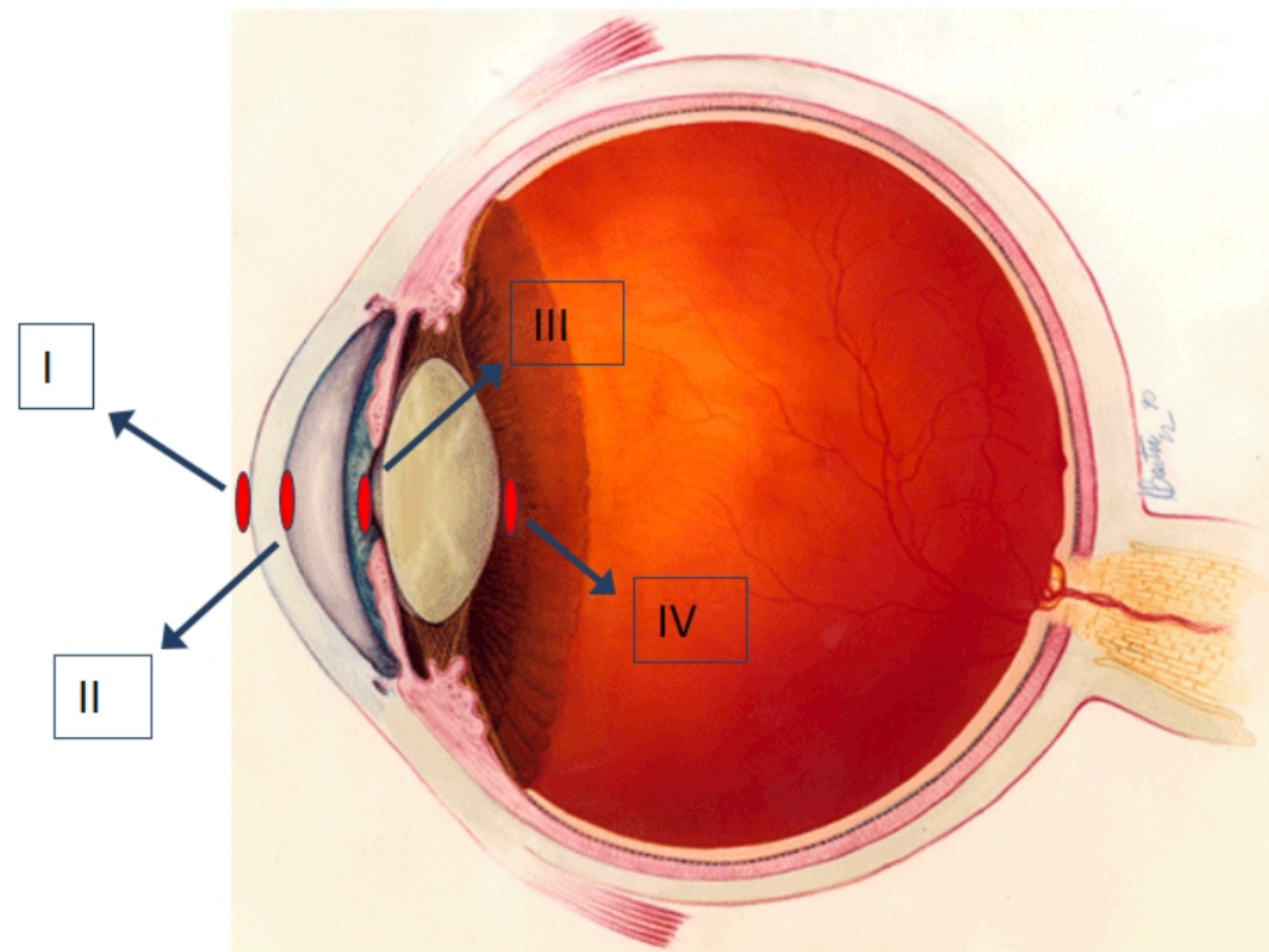
DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

— IOL tilt and decentration



DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

Purkinje reflexes



VIROS

perfectly aligned model eye



PI



Purkinjemeter
(Tabernero et al., Opt.
Express 2006)

PIII



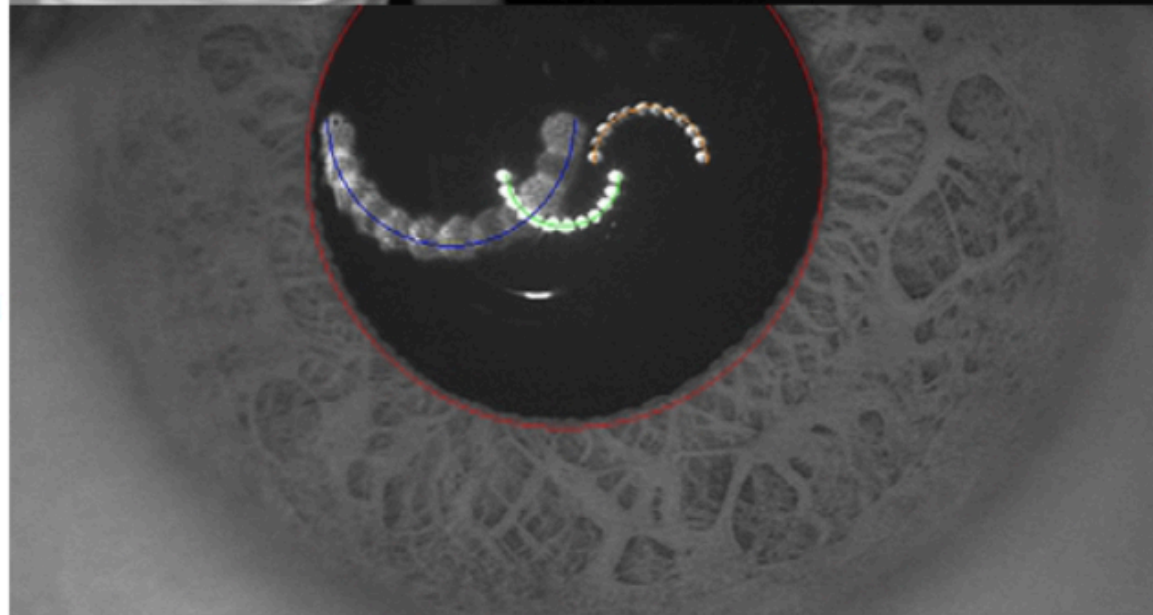
PIIV



DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

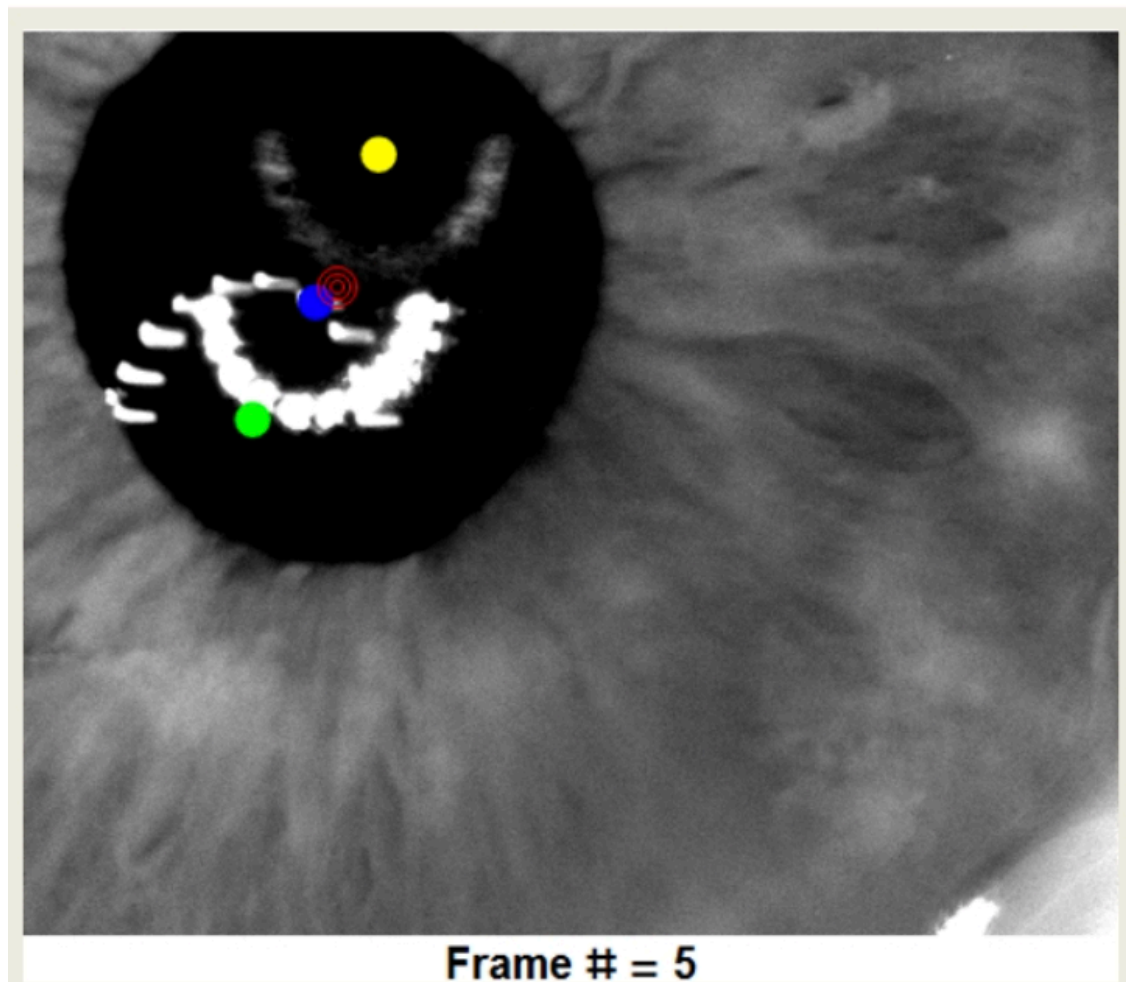


Juan Tabernero, PhD
Pablo Artal, PhD
Laboratorio de Óptica,
Departamento de Física
Universidad de Murcia,
Murcia, Spain



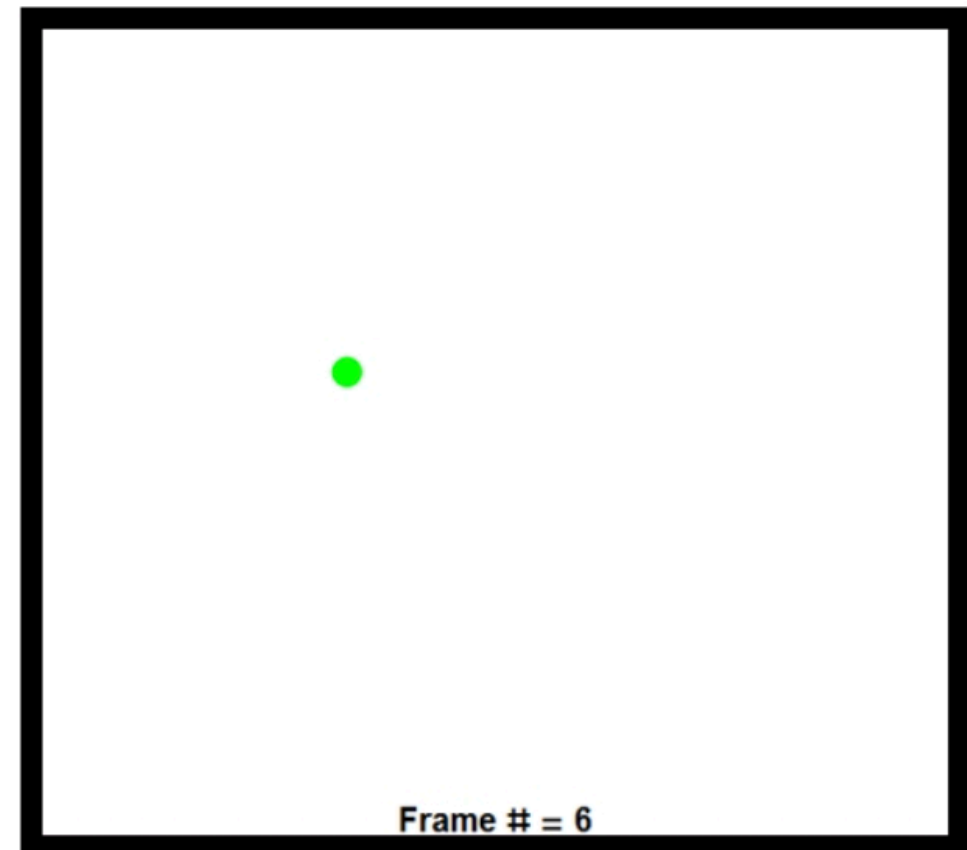
DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

Dynamic Purkinje meter system 1.0



Pseudophakic

- Acquisition of videos of eye movements
 - saccades following alternating LEDs
 - Can detect “wobbling” of capsule and IOL
- ➔ To assess capsular instability



Recording at 28
frames/sec

VIROS

PI

PIV

DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

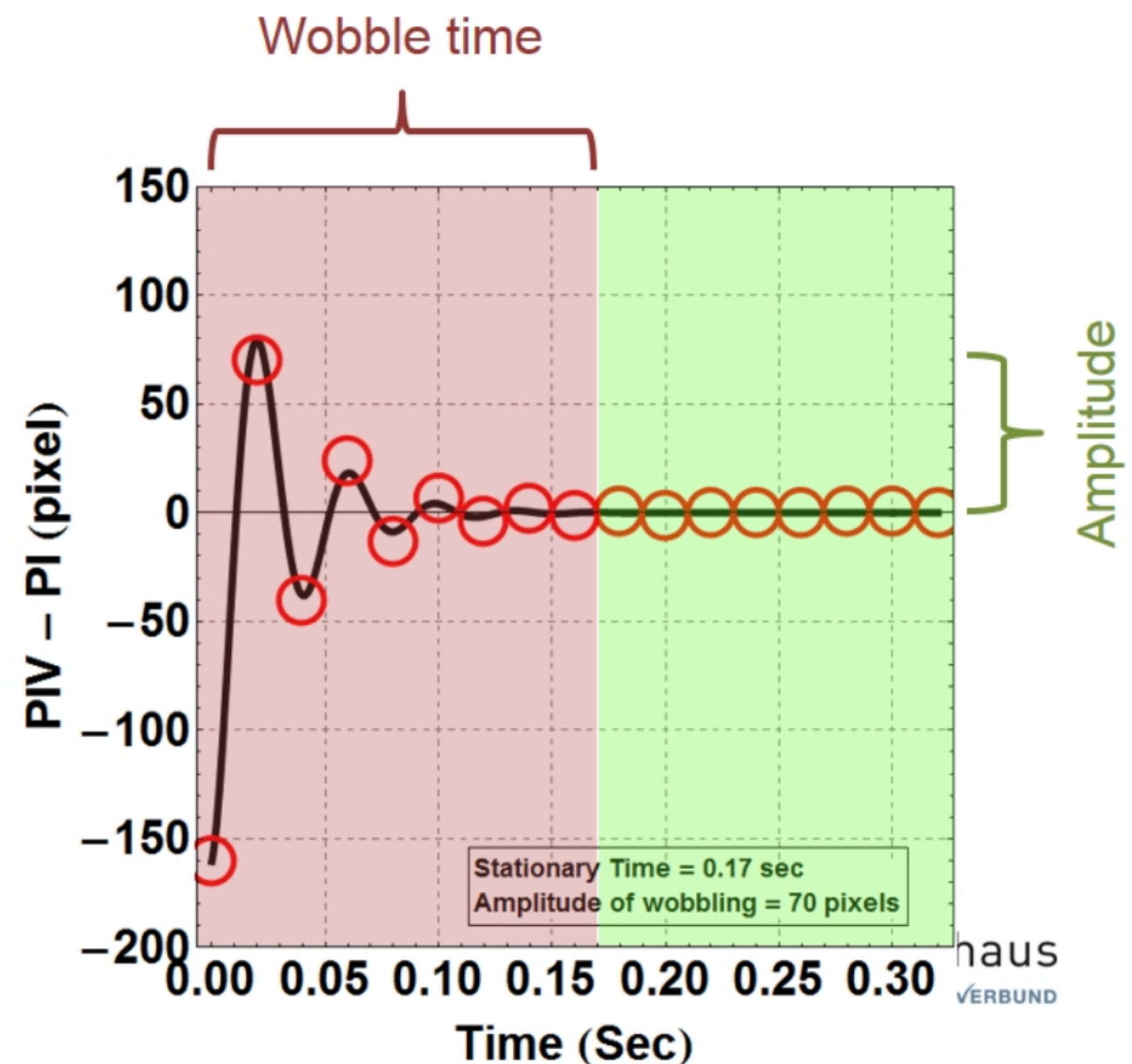
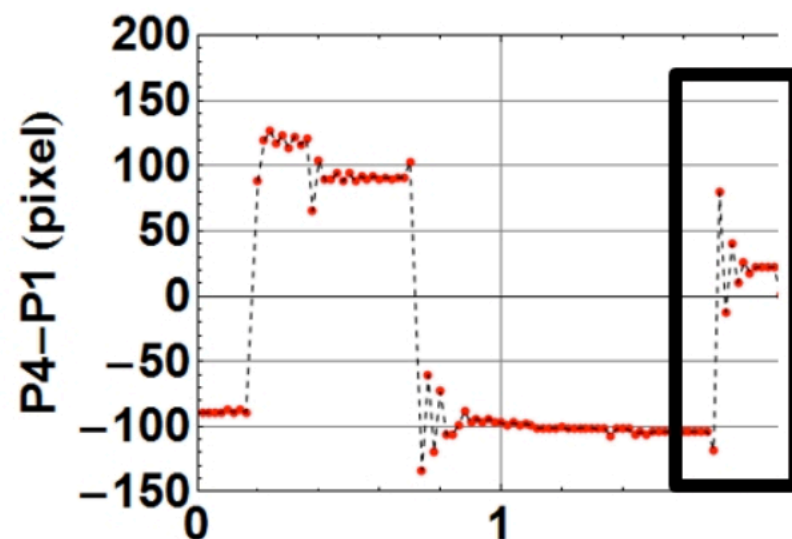
Wobble parameters

Wobble time

No more wobble is detected after this time

Amplitude

Peak with respect to the stationary position.



DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

Study design

prospective, randomized, bilateral comparison trial

- standardized microincision cataract surgery
- one surgeon

→ To compare dynamic capsular bag stability

DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

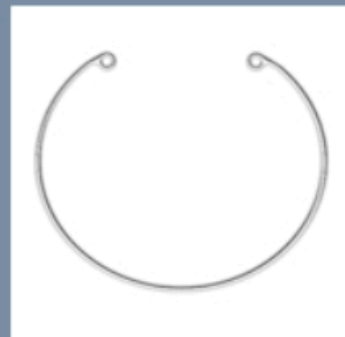
Study design

Tecnis (PCB), Tecnis (ZA9003), Zeiss

Subgroups

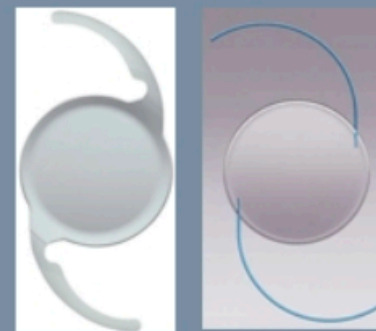
with vs. without CTR

- 20 patients
- 40 eyes



1-piece vs. 3-piece

- 20 patients
- 40 eyes



open-loop vs. plate haptics

- 20 patients
- 40 eyes



PXF

- 10 patients
- 10 eyes



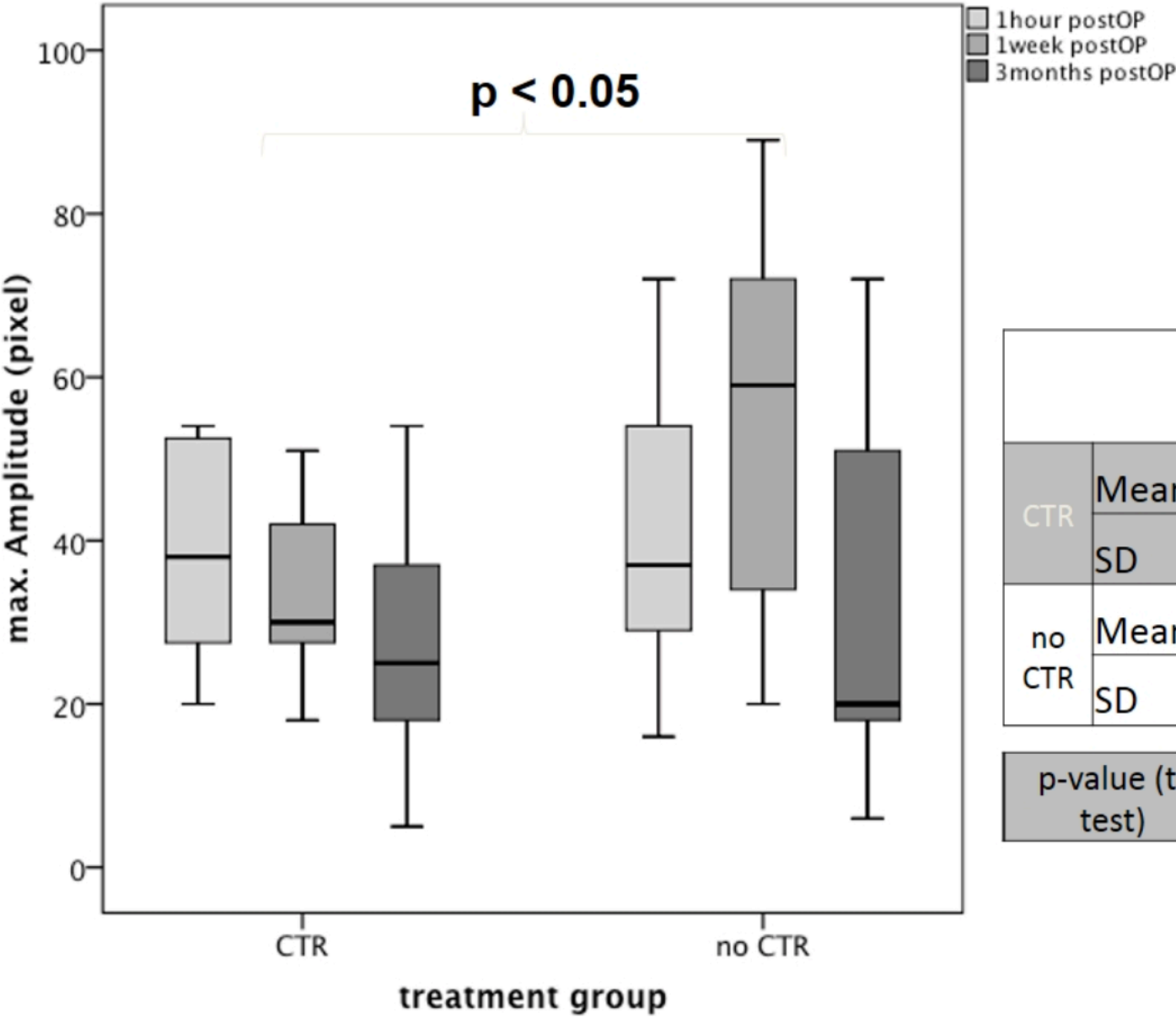
dynamic Purkinje
meter system

- preOP
- 1 hour
- 1 week
- 3 months
postoperativel
y

hanuskrankennaus

DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

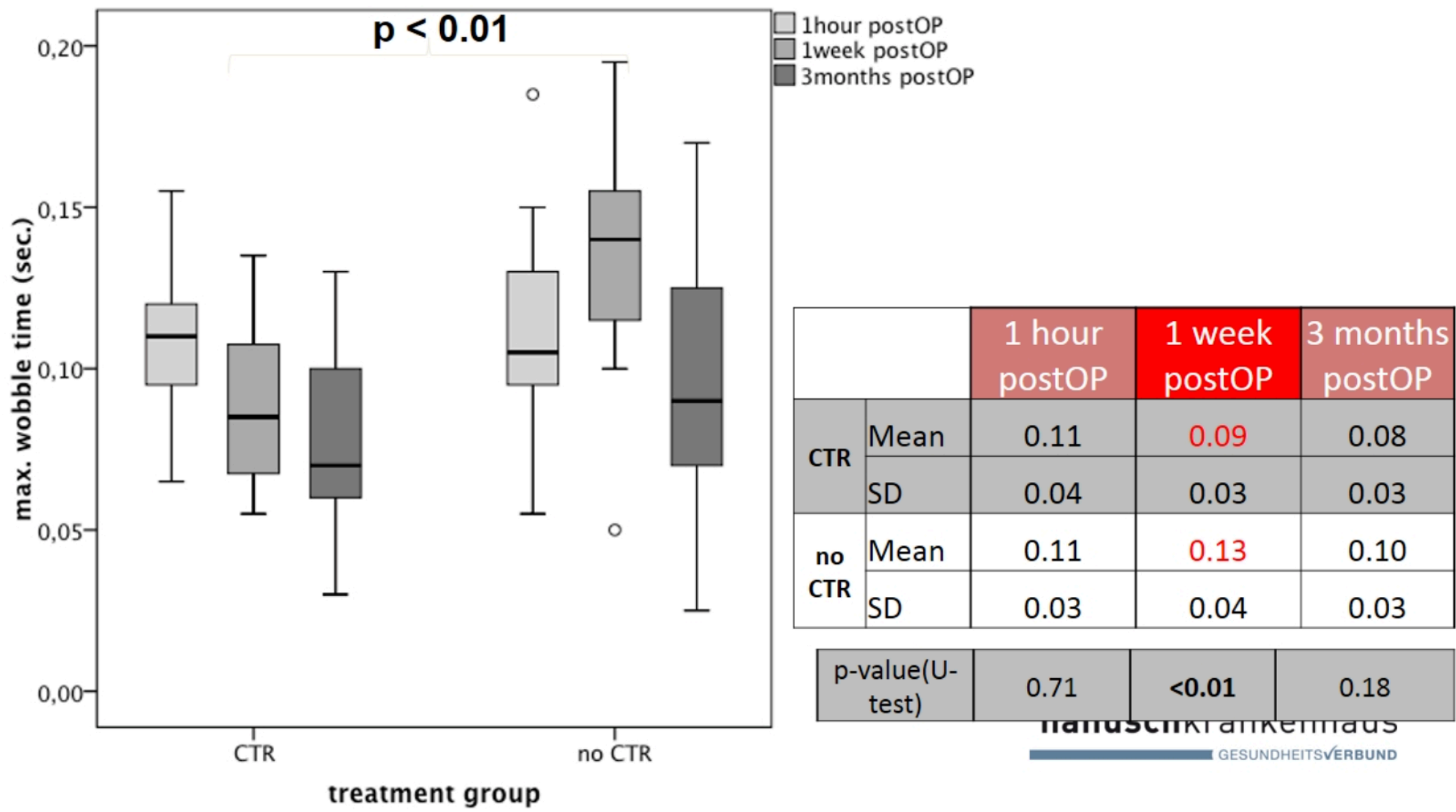
CTR vs. no CTR – Amplitude (pixel)



		1 hour postOP	1 week postOP	3 months postOP
CTR	Mean	36.2	35.6	29.6
	SD	15.3	19.8	15.4
no CTR	Mean	35.9	50.7	29.8
	SD	16.9	22.6	22.6
p-value (t-test)		0.95	<0.05	0.60

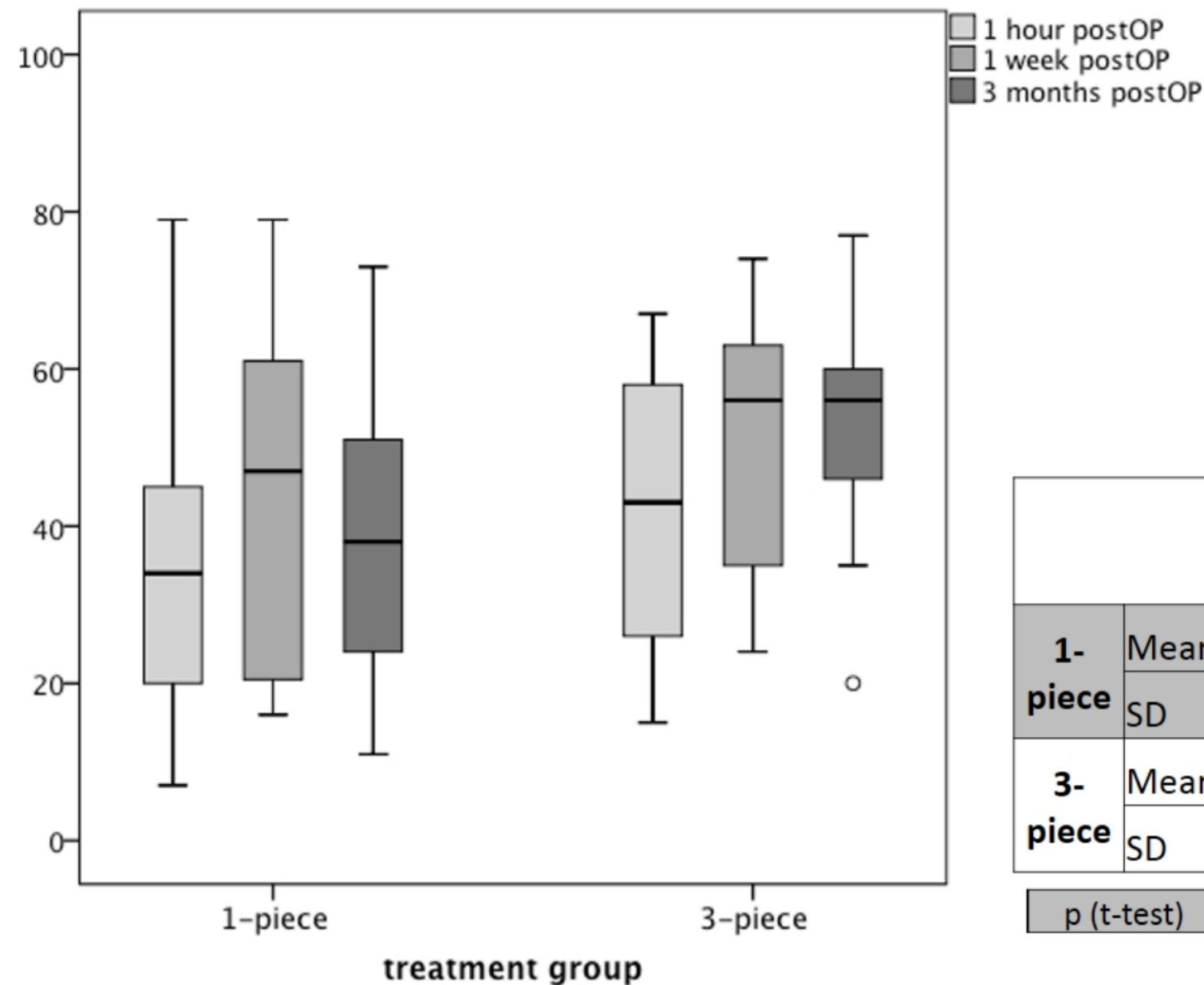
DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

CTR vs. no CTR – Wobble time (sec)



DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

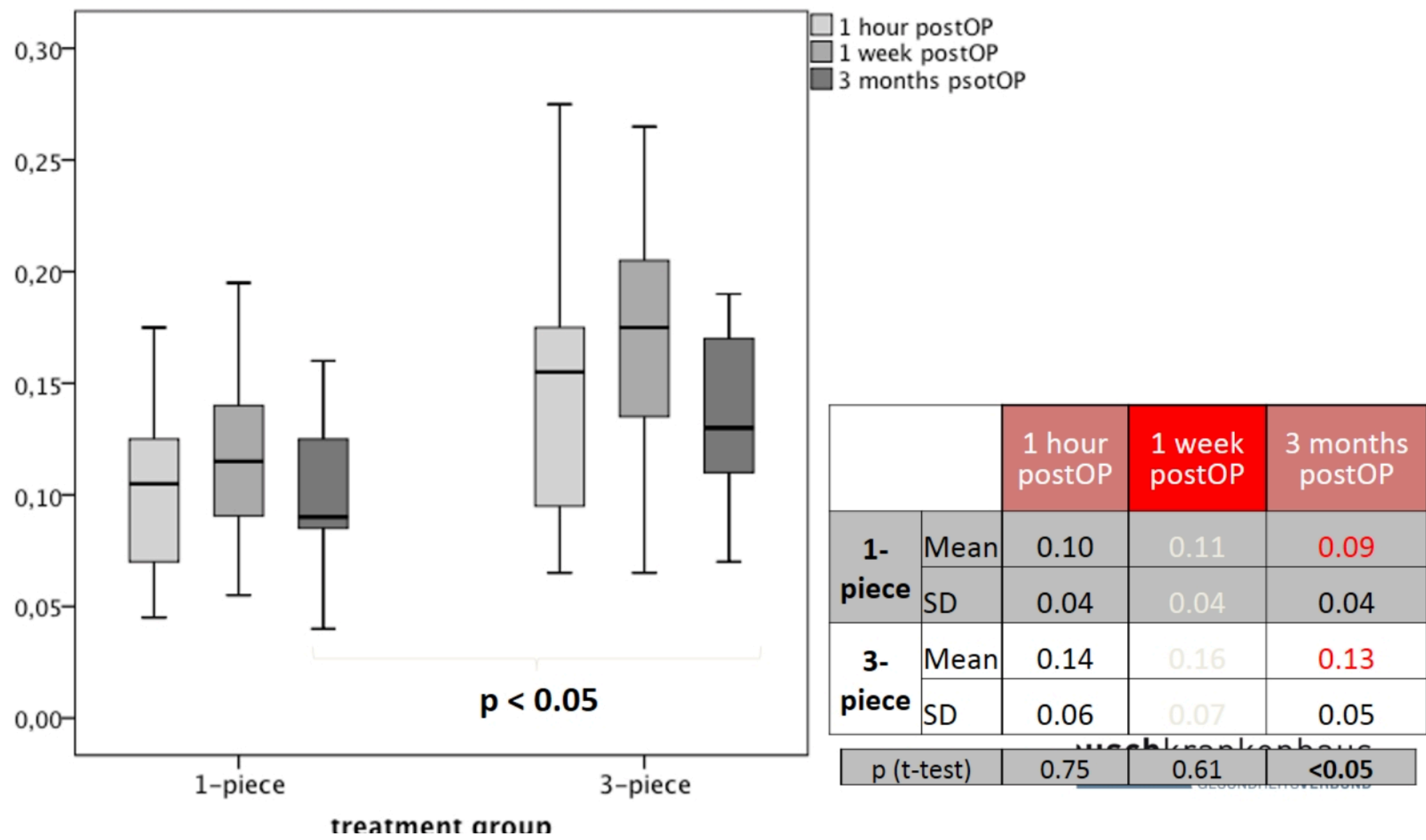
1-piece vs. 3-piece IOL – Amplitude (pixel)



		1 hour postOP	1 week postOP	3 months postOP
1-piece	Mean	34.2	41.7	36.3
	SD	20.2	22.0	18.1
3-piece	Mean	38.0	47.1	44.9
	SD	20.2	18.0	16.3
p (t-test)		0.65	0.52	0.19

DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

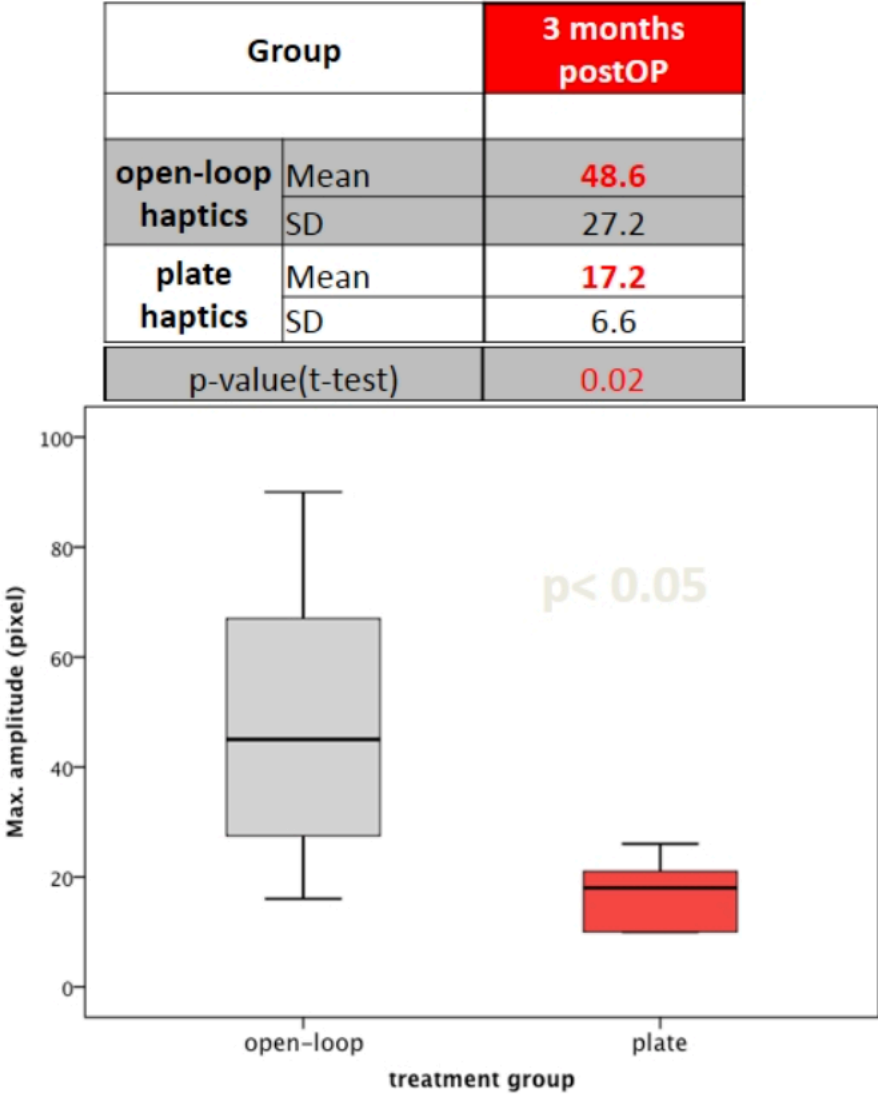
1-piece vs. 3-piece IOL – Wobble time (sec.)



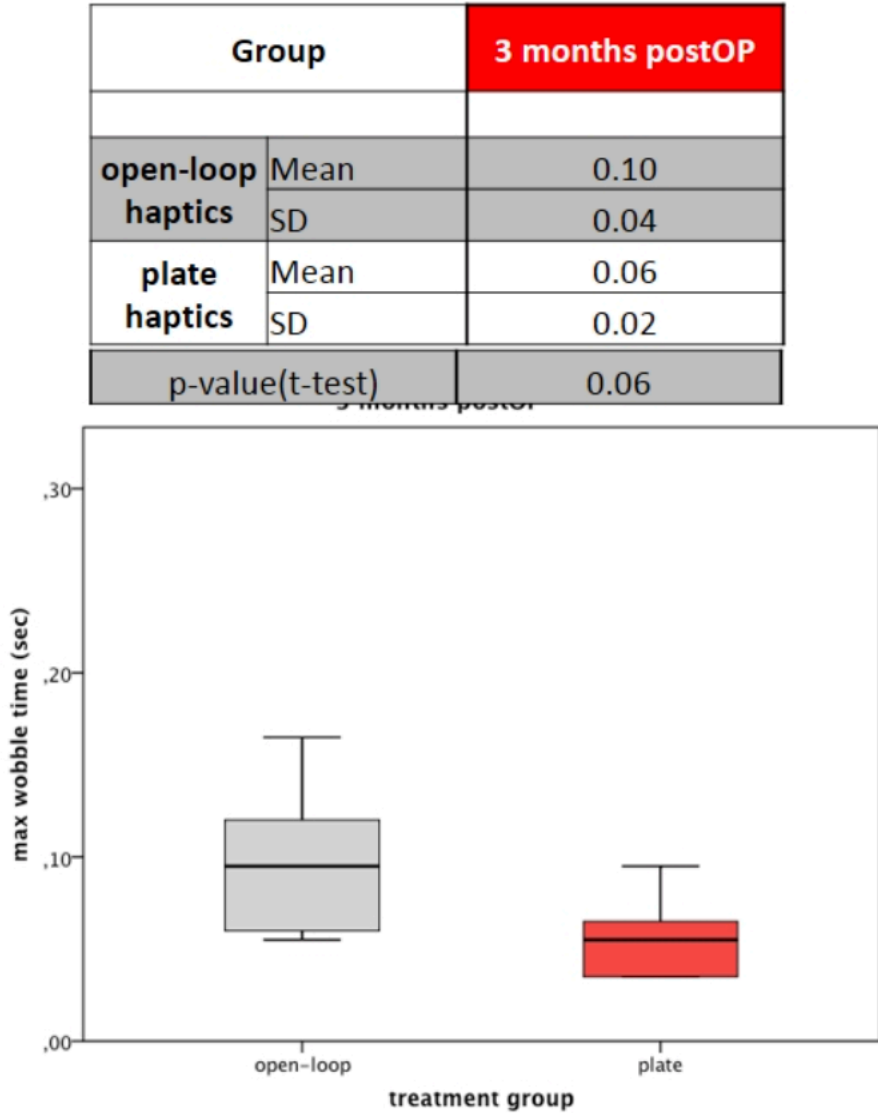
DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

Open-loop vs- plate haptic IOLs Preliminary results (n=14)

Amplitude (pixel)

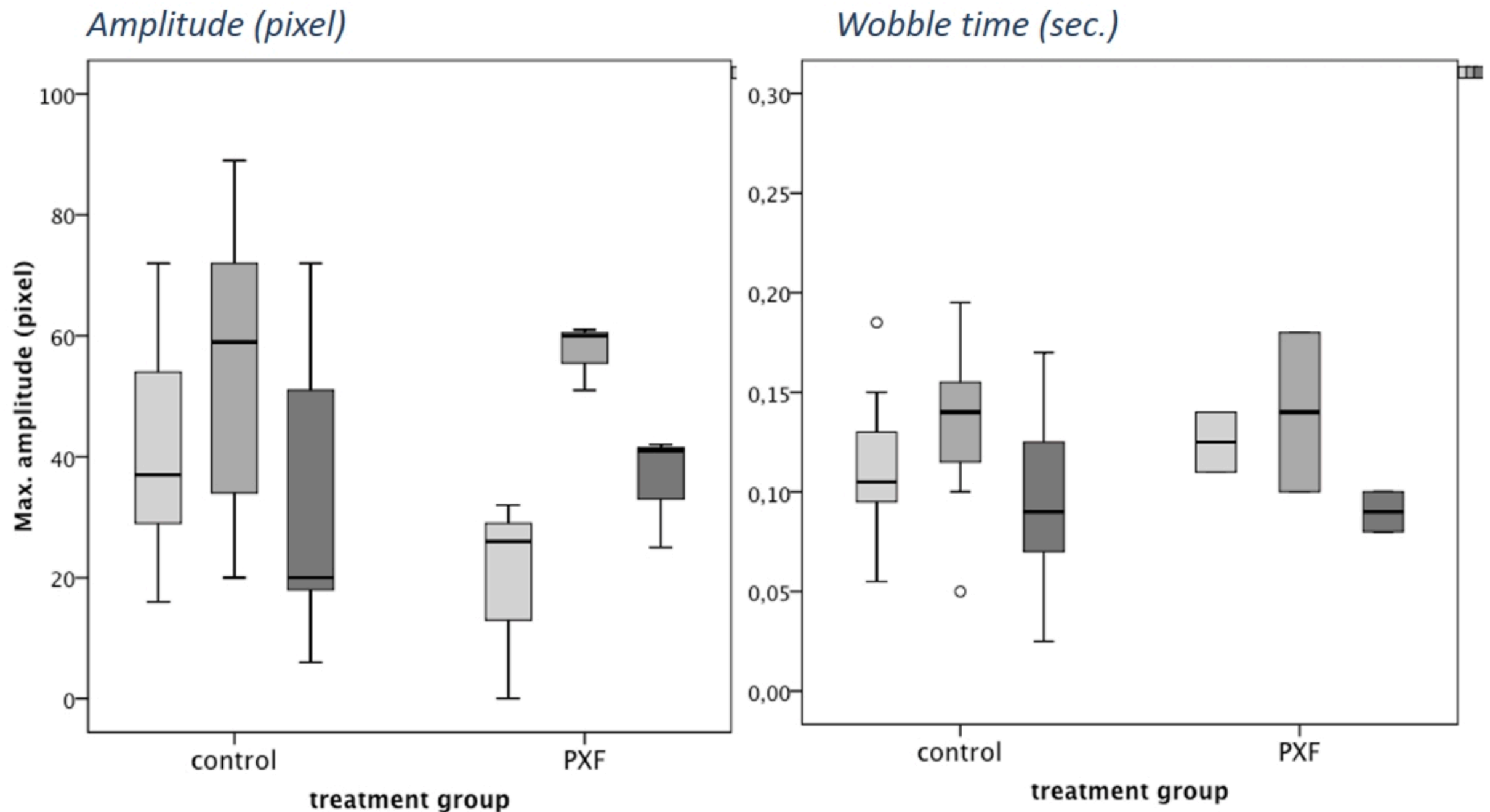


Wobble time (sec.)

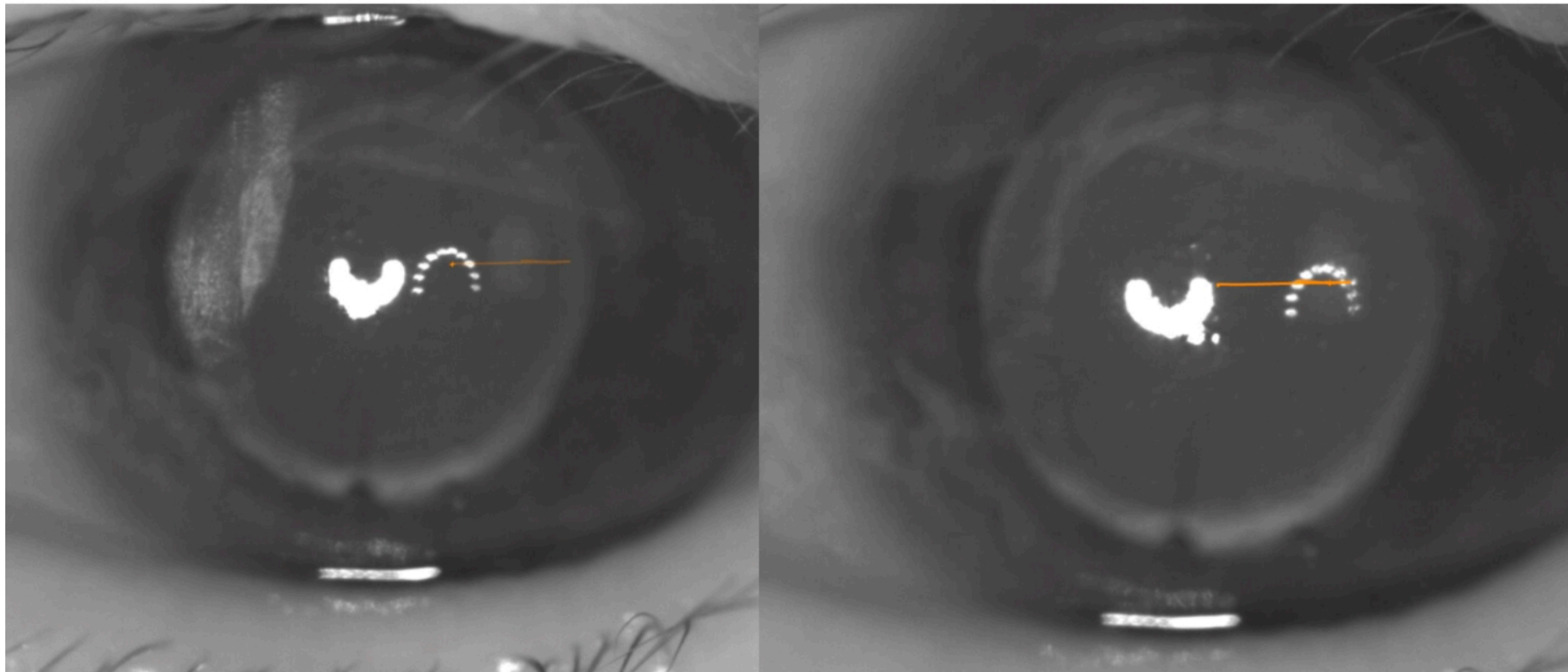


DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

PXF eyes (n=10)

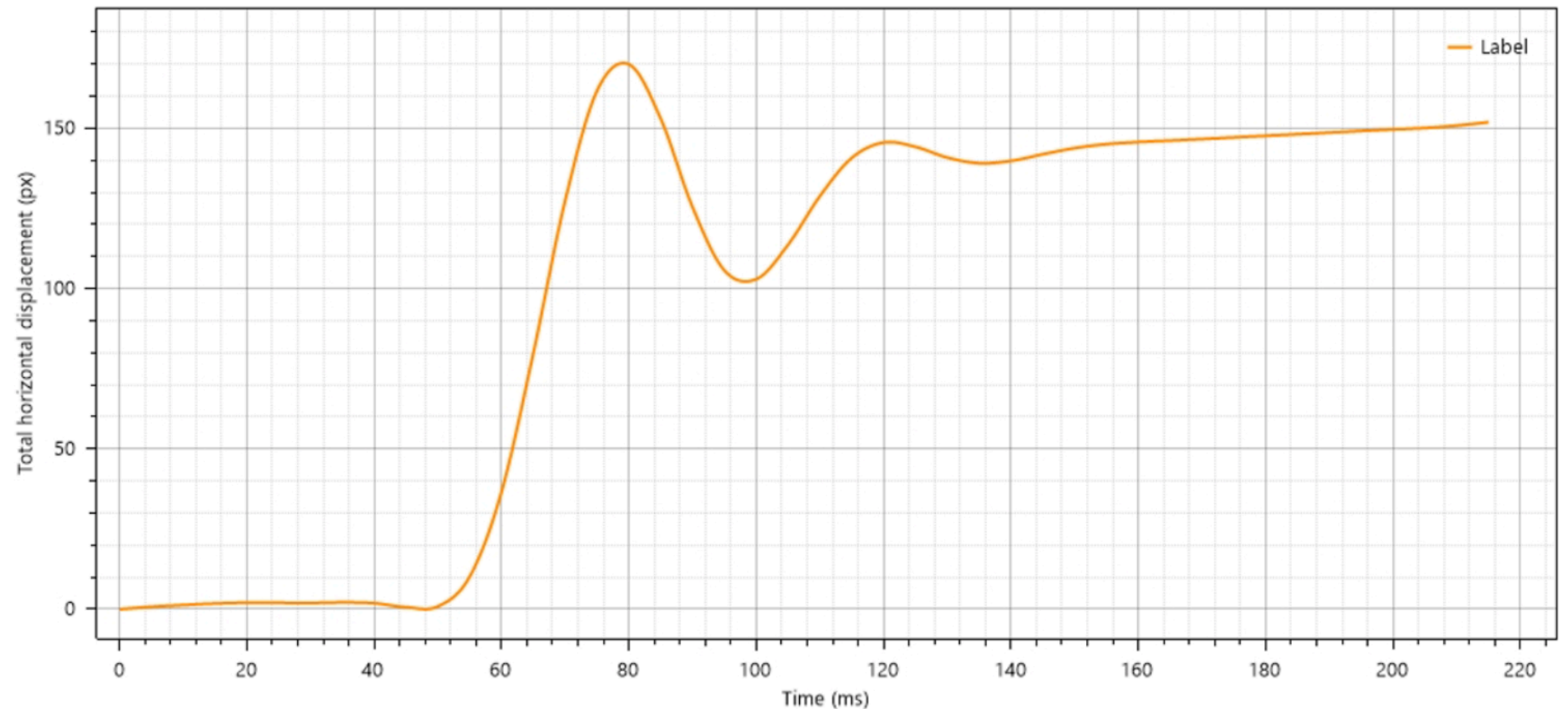


DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...



DYNAMIC ASSESSMENT AND PREDICTION OF PSEUDOPHAKODONESIS...

Total horizontal displacement



HARVEY BURD

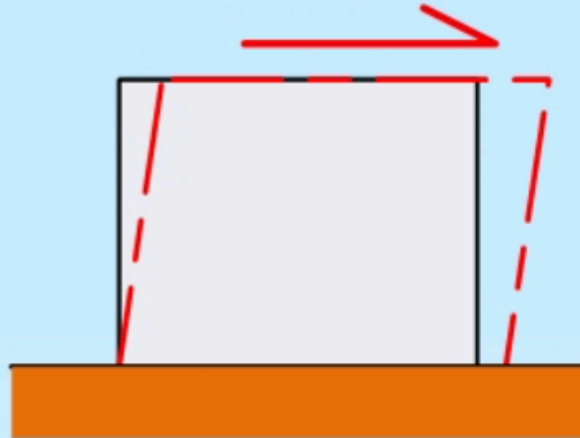
APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Describing material behaviour

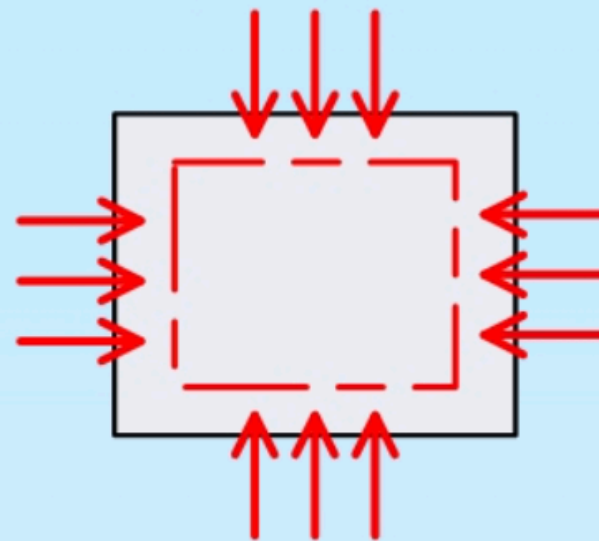
Shear modulus, G

traction



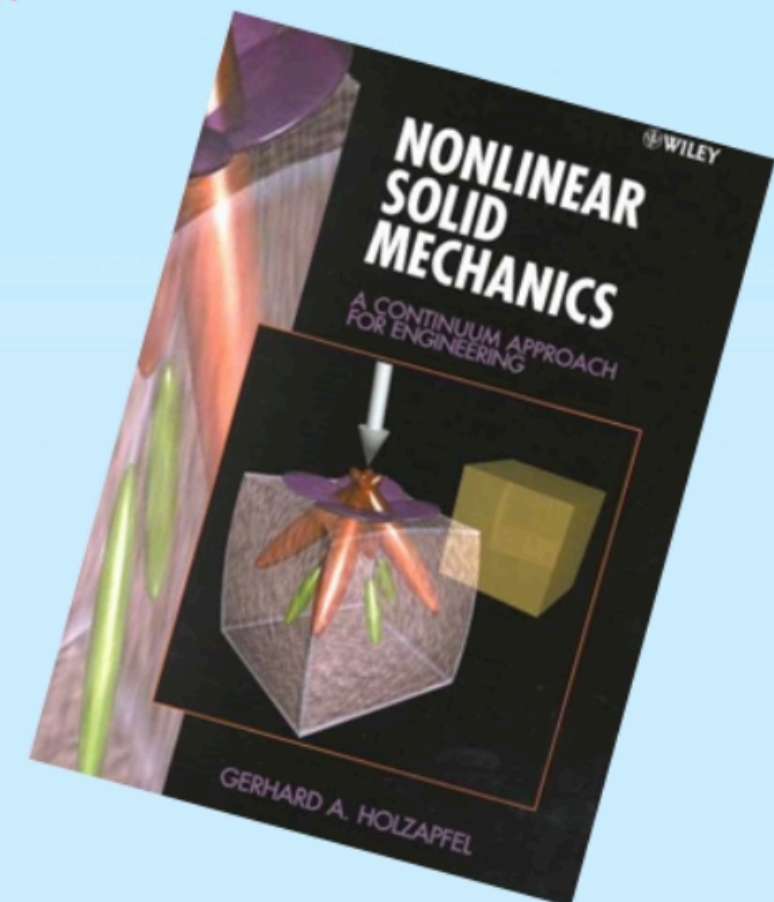
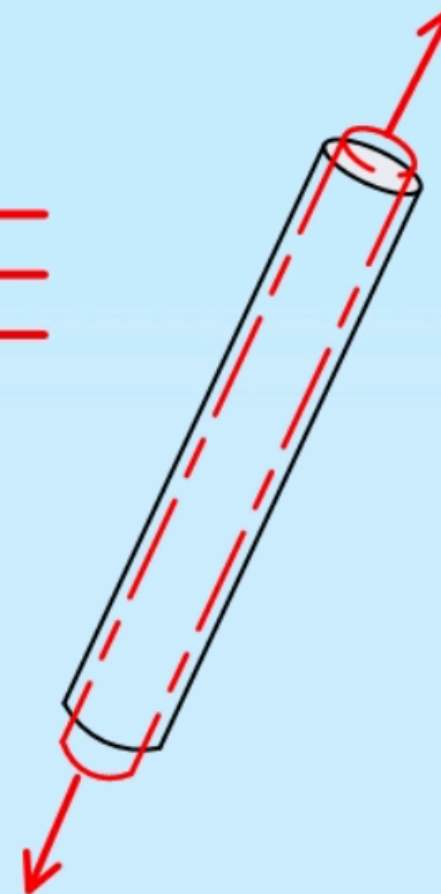
Bulk modulus, K

pressure



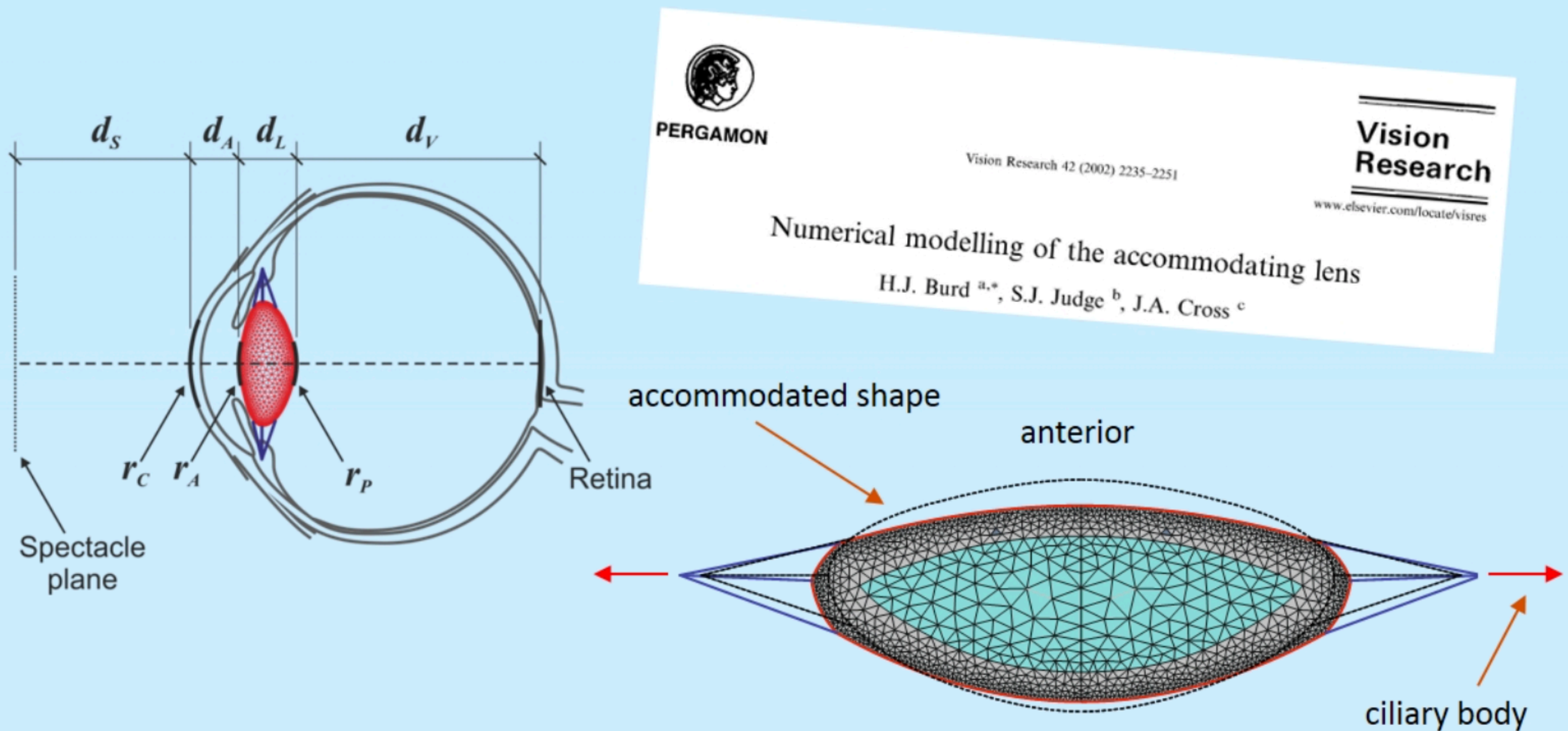
Young's modulus, E

force



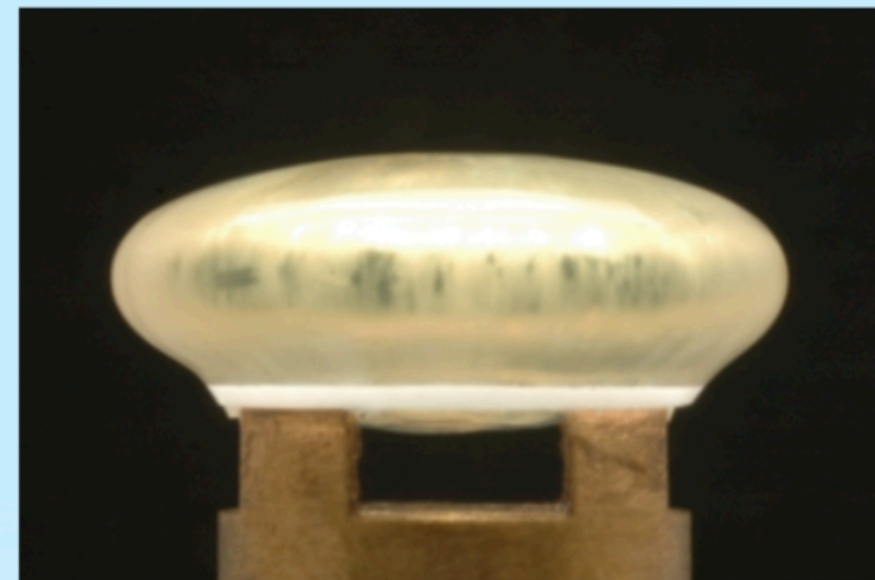
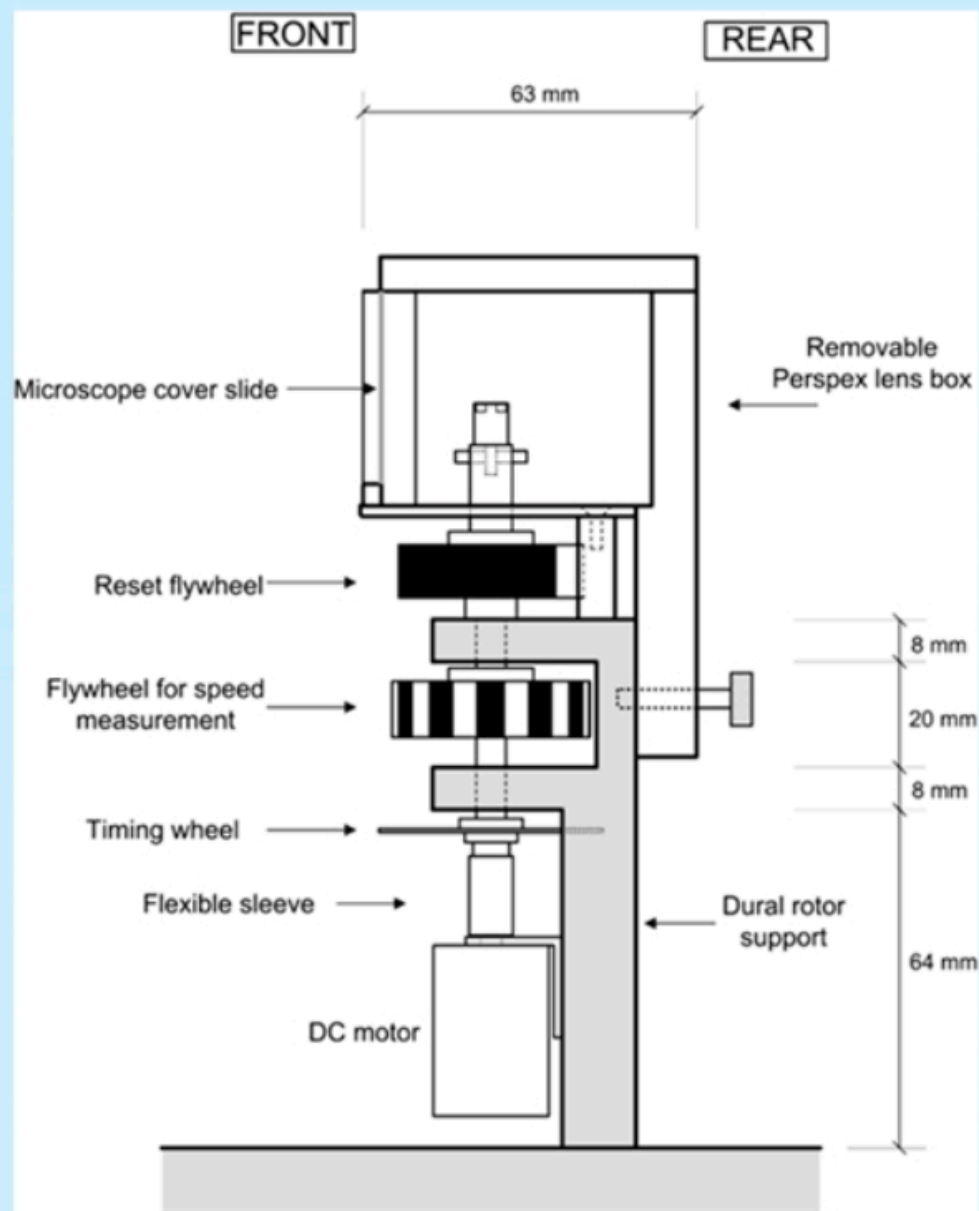
APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Finite element analysis of accommodation



APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Data on lens shear modulus

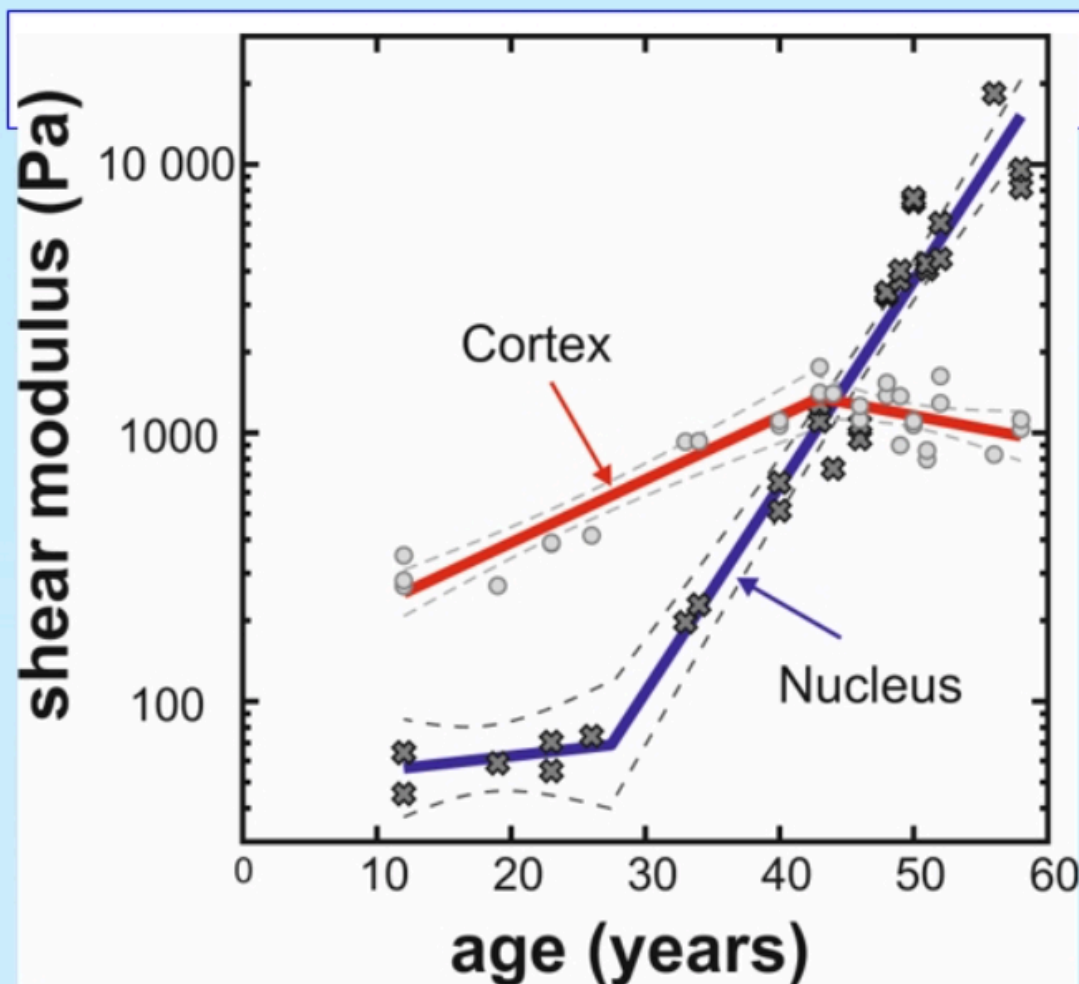


De-capsulated 33-year lens at a rotational speed of 1000 rpm

Wilde, Burd and Judge (2012)
Experimental Eye Research

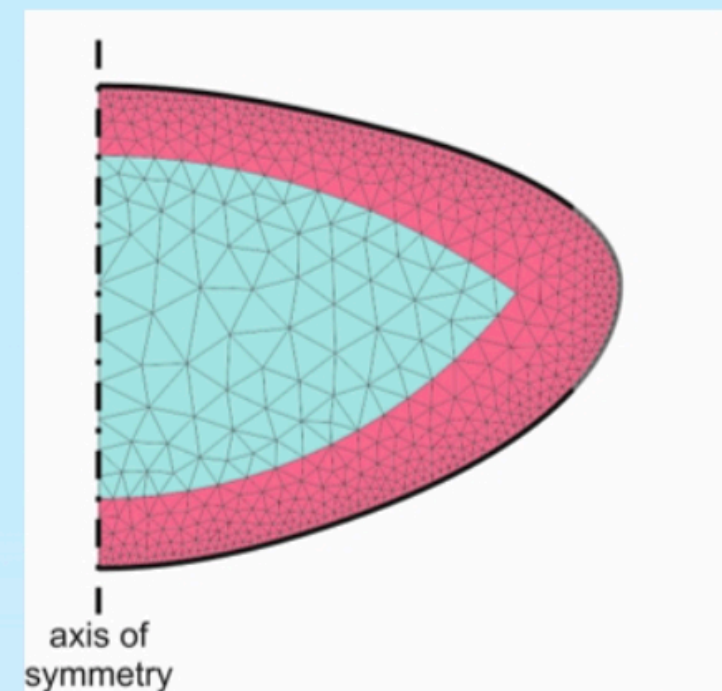
APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Age-related model for lens shear modulus



Shear modulus model

Wilde et al. 2012



Two-compartment model

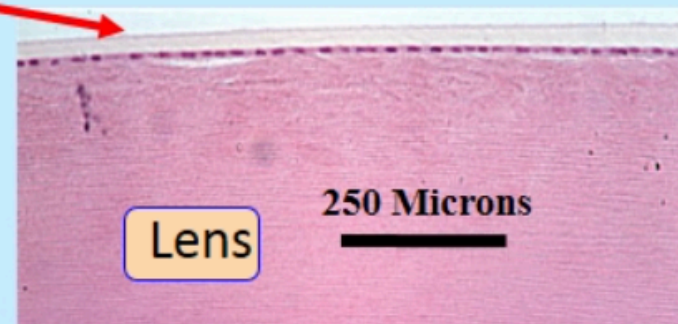
Age (years)	Nucleus	Cortex
29	90	632
45	1500	1300

Shear modulus data (Pa)

APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Assembling the finite element model

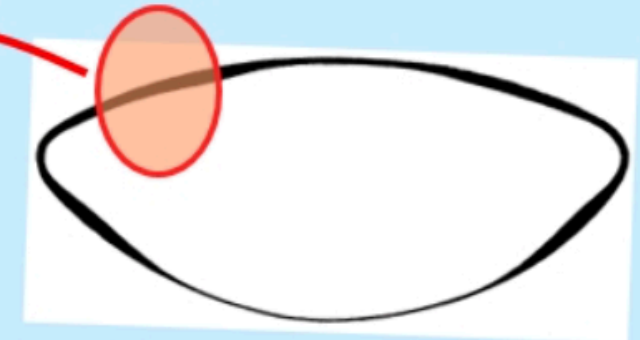
Capsule



250 Microns

Lens

http://www.kumc.edu/instruction/medicine/anatomy/histoweb/eye_ear/eye_ear.htm



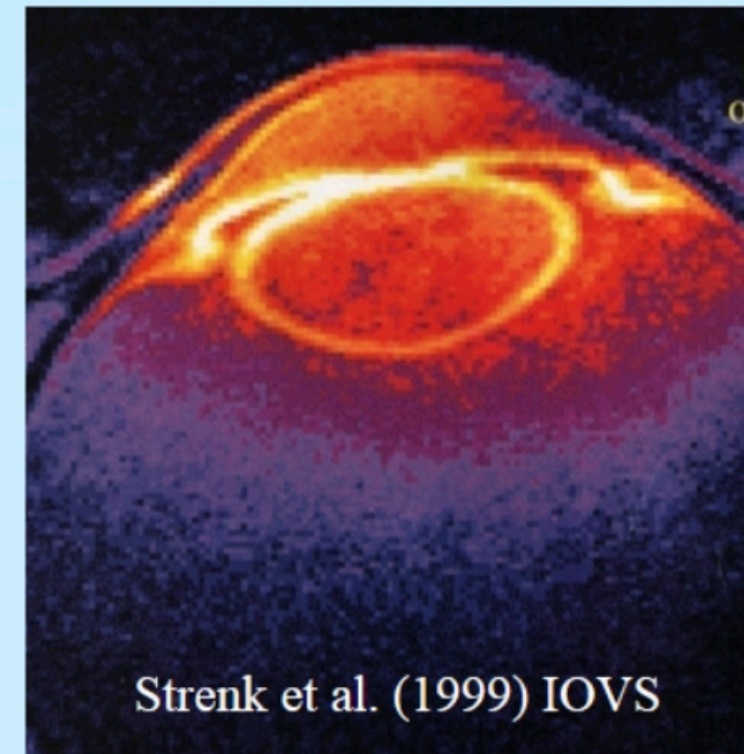
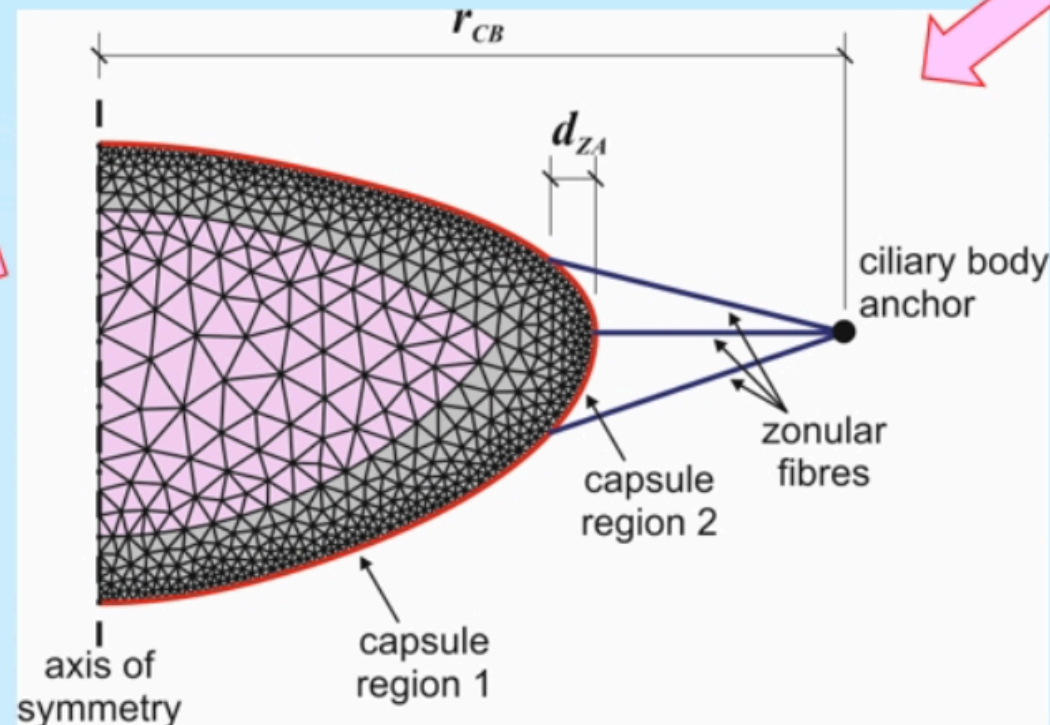
Material properties

Capsule shear modulus

Cortex and nucleus shear modulus

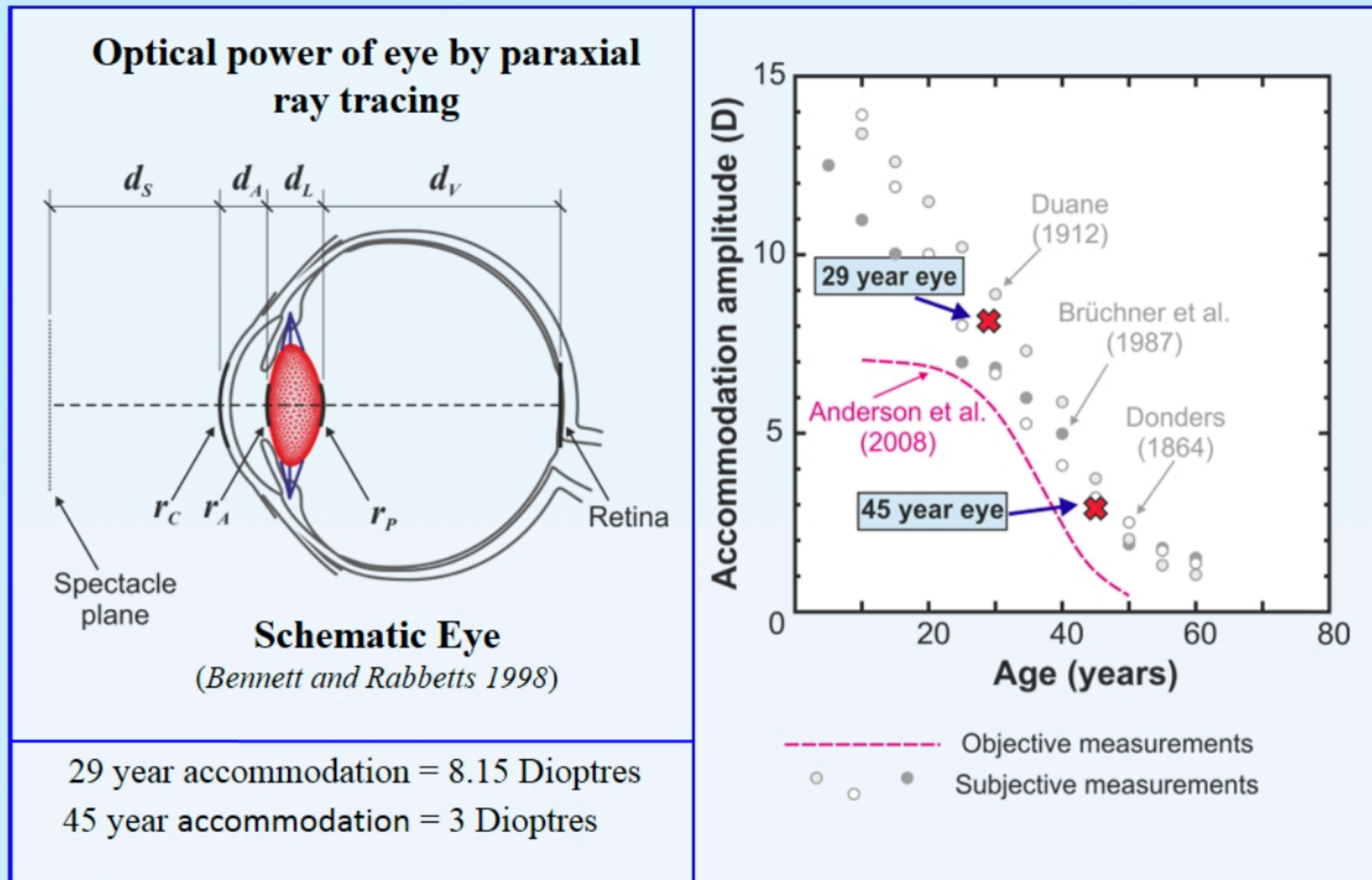
Zonule stiffness

Geometry



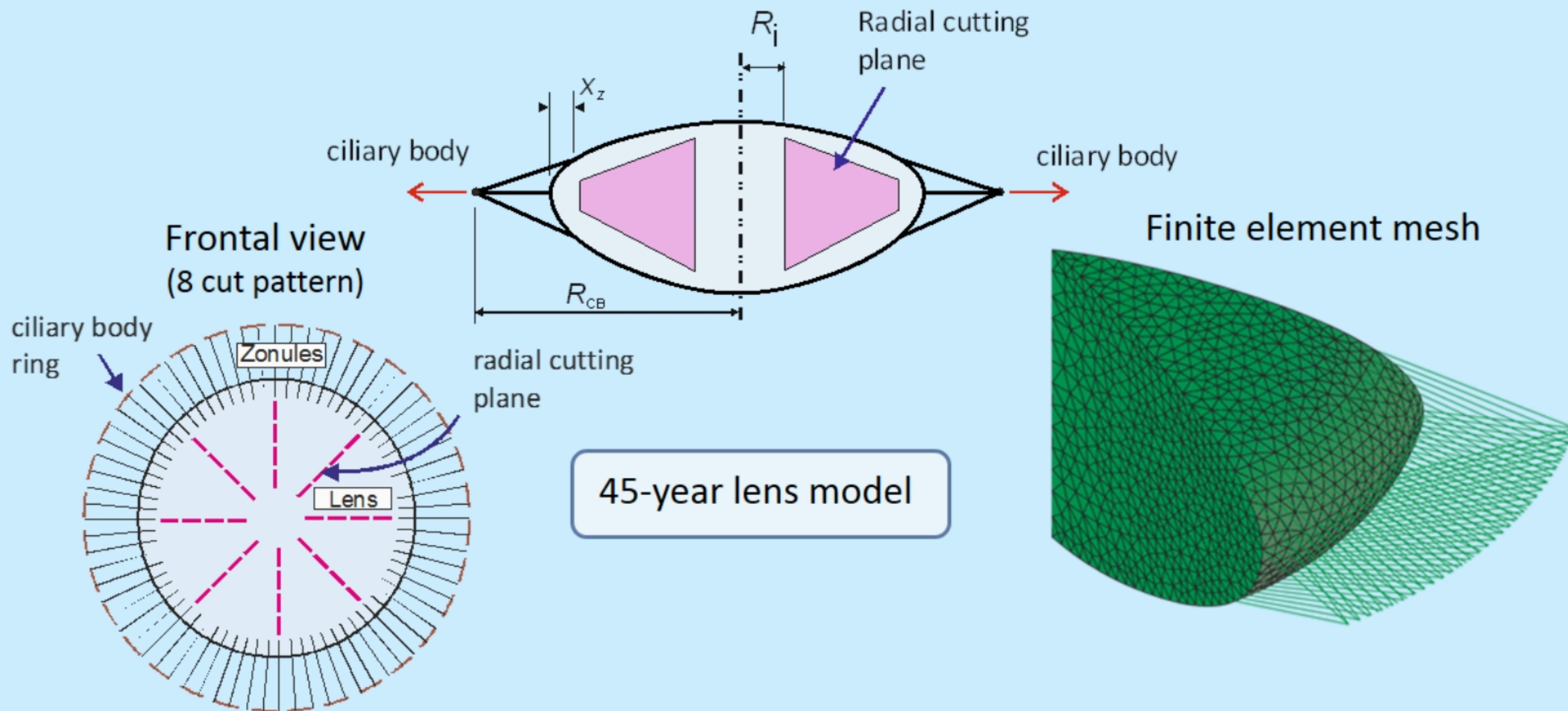
APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Modelling the development of presbyopia



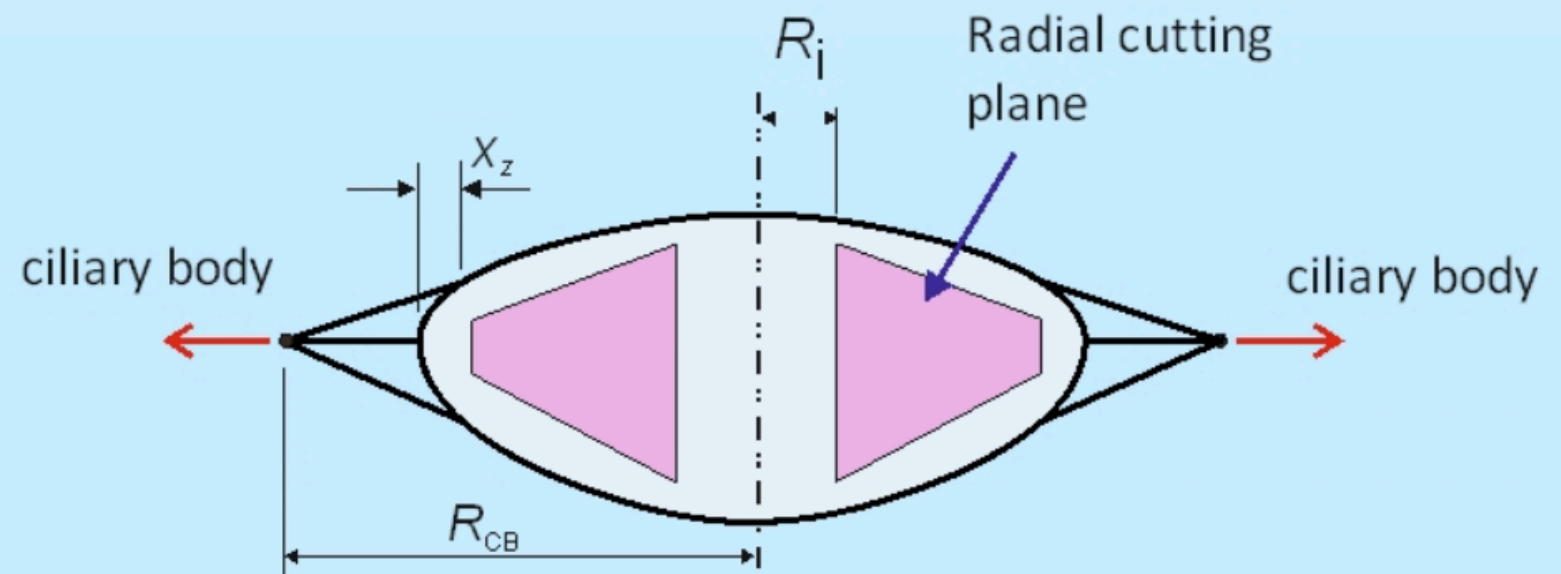
APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Finite element model of lentotomy



APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Radial cutting plane results

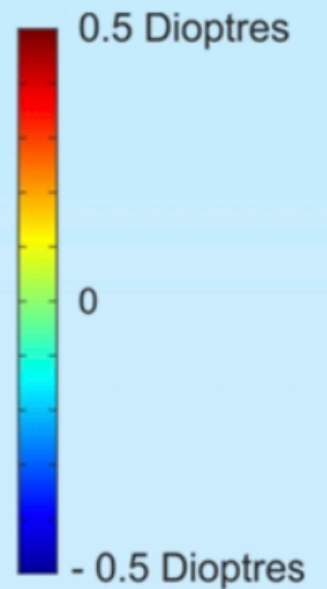
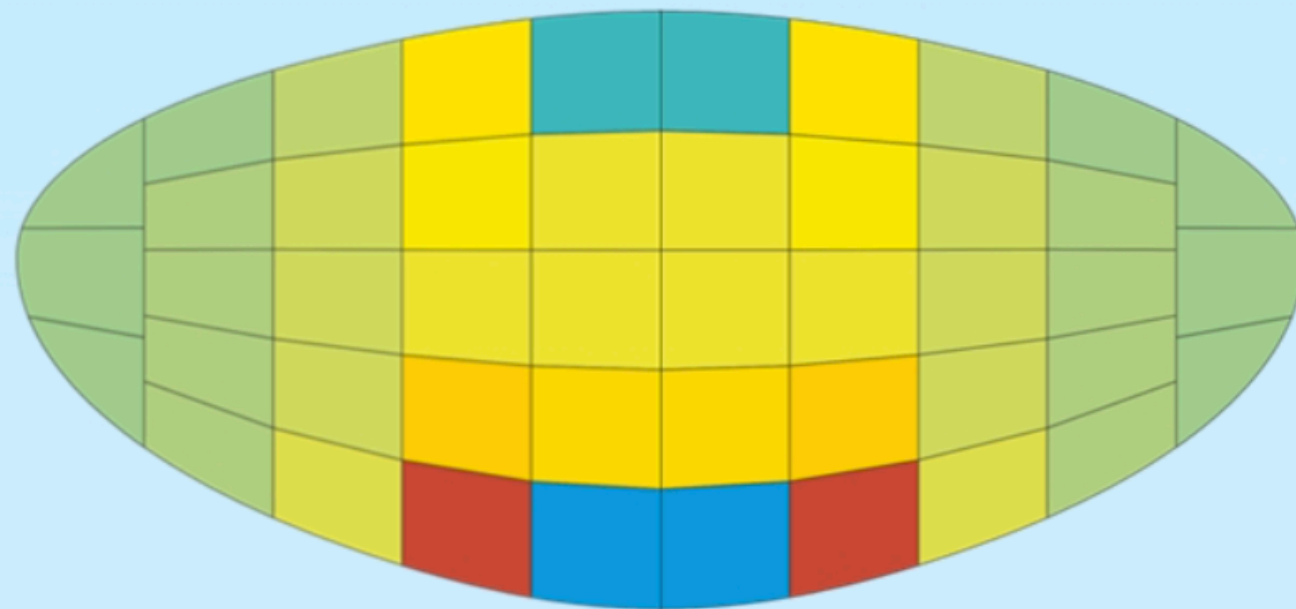
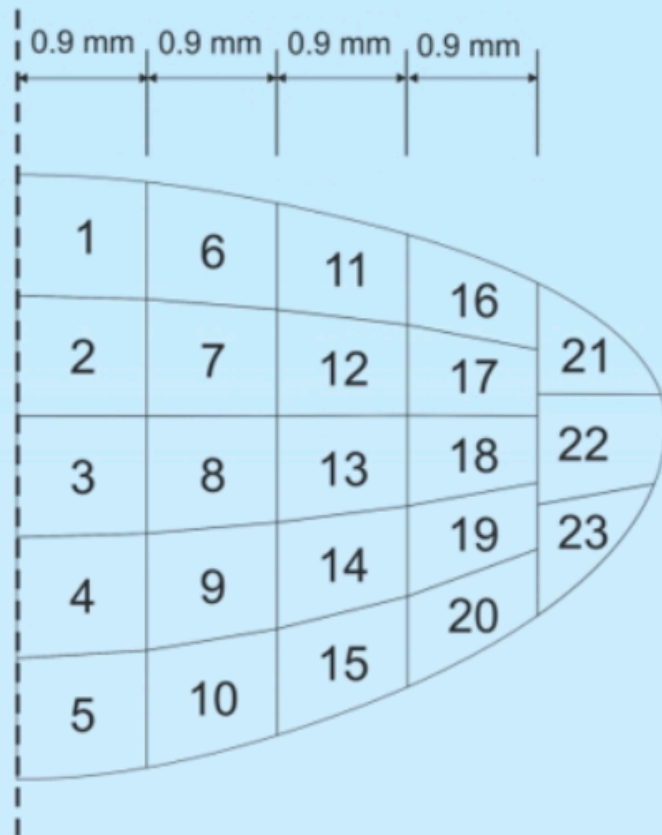


Number of cuts	Internal radius, R_i	Lens accommodation amplitude	Improvement
8	untreated	2.97 D	
8	1.5 mm	3.28 D	0.31D
8	1.0 mm	3.62 D	0.65D
8	0.5 mm	4.03 D	1.06D
8	0 mm	4.77 D	1.8D
32	1.5 mm	3.38 D	0.41D

APPLYING FINITE ELEMENT ENGINEERING CONCEPTS TO ACCOMMODATION

Radial cutting; exploratory patterns

Polar axis



DANIEL GOLDBERG

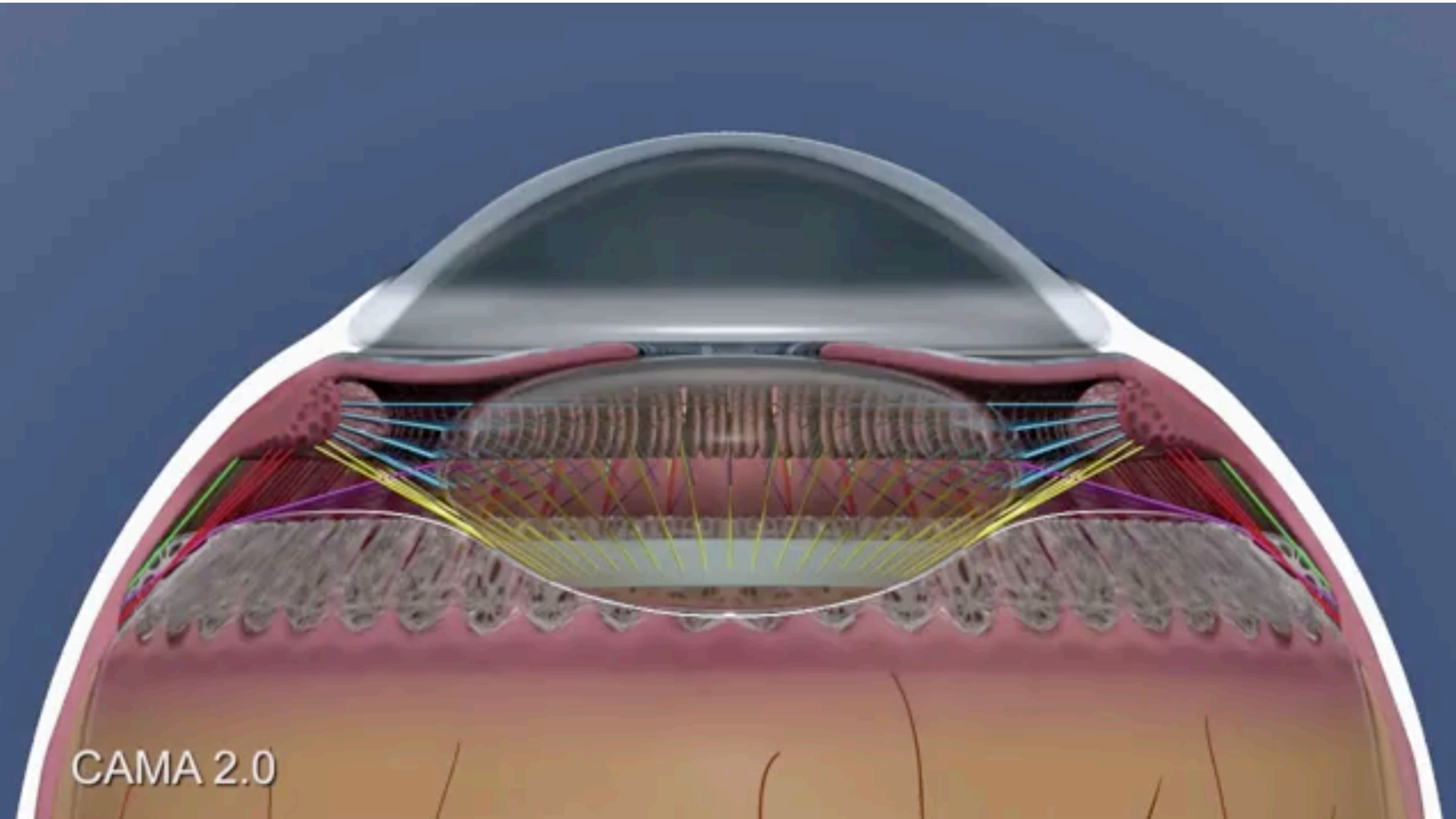
FUNCTIONAL ANATOMY OF THE ZONULE

FUNCTIONAL ANATOMY OF THE ZONULE

Functional anatomy of the zonule

- Function of zonule is to **support the lens and facilitate accommodation and disaccommodation of the lens**
- Zonular fibers composed of fibrillin, elastin and glycoprotein determine tensile strength and viscoelasticity of zonule.
- Mechanism of accommodation: **Reciprocal zonular action**
- **3 divisions of zonule**, including 6 pathways, into Anterior, Crossing, and Posterior zonule based on structure and function
- Crossing zonule and Weiger ligament: cradle and support lens
- Ciliary muscle is engine of accommodation and Bruch's elastic foundation in choroid is engine of disaccommodation

FUNCTIONAL ANATOMY OF THE ZONULE



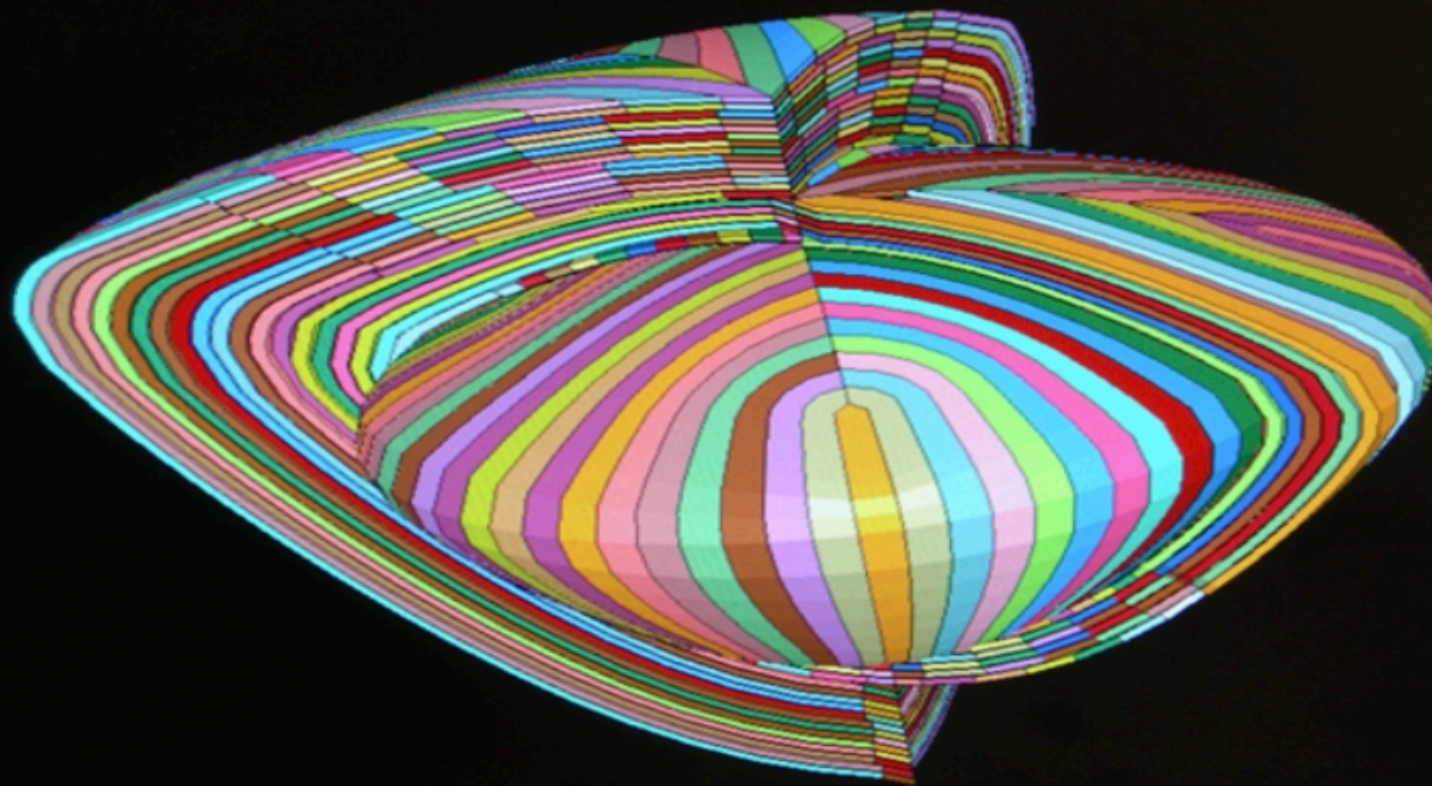
SUNIL SHAH

FEMTO LENTOTOMY AND LASER SCLREAL MICROPORATION

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

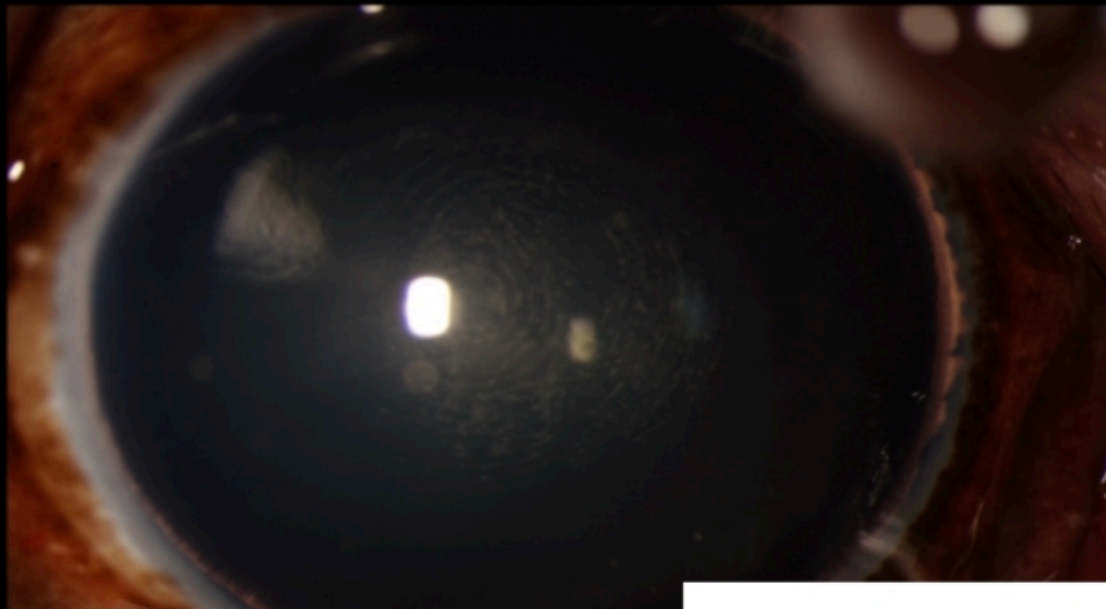
Finite Element Model

Included Overlapping individual Fibers and Suture lines

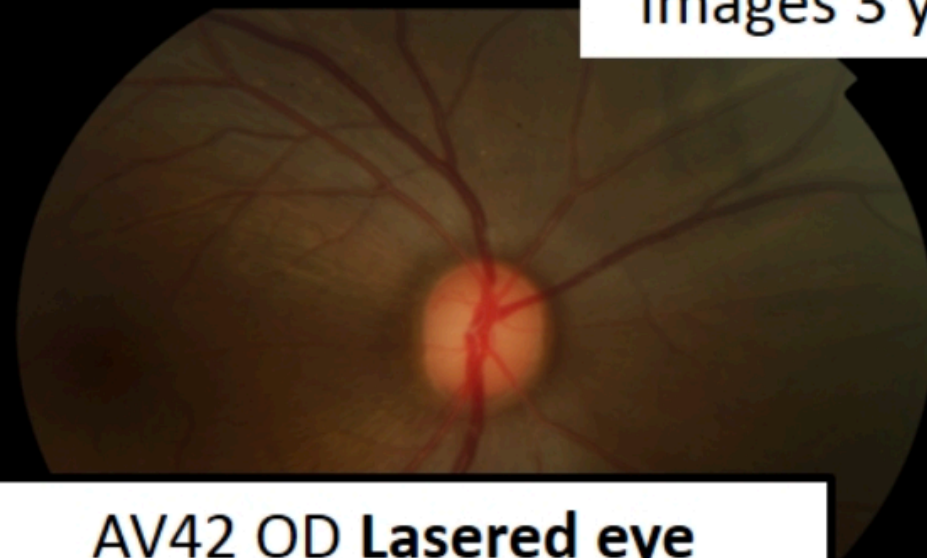


41 Layered Shell Model

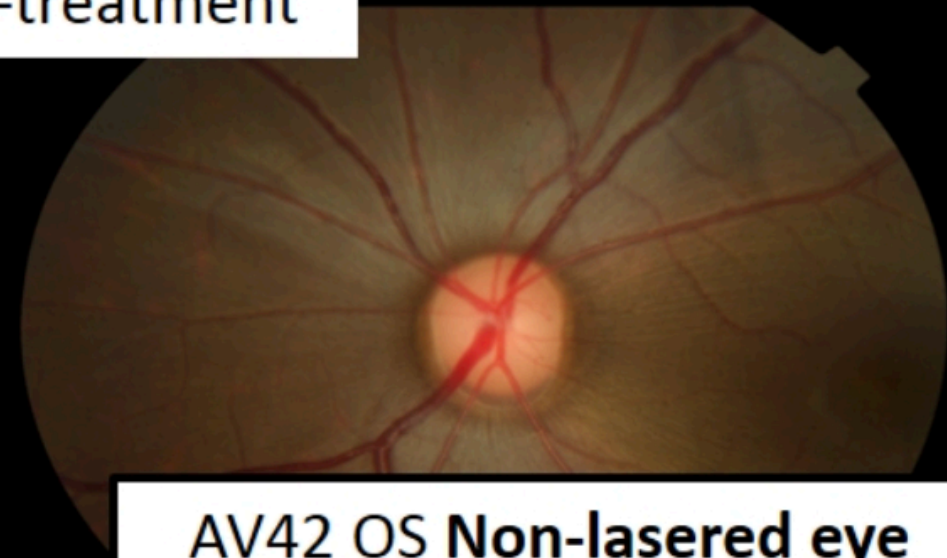
FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION



Images 3 years post-treatment



AV42 OD Lasered eye
11.25 D (CARB)



AV42 OS Non-lasered eye
7.25 D (CARB)

Accommodation Restoration: Primate Studies in 2007

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

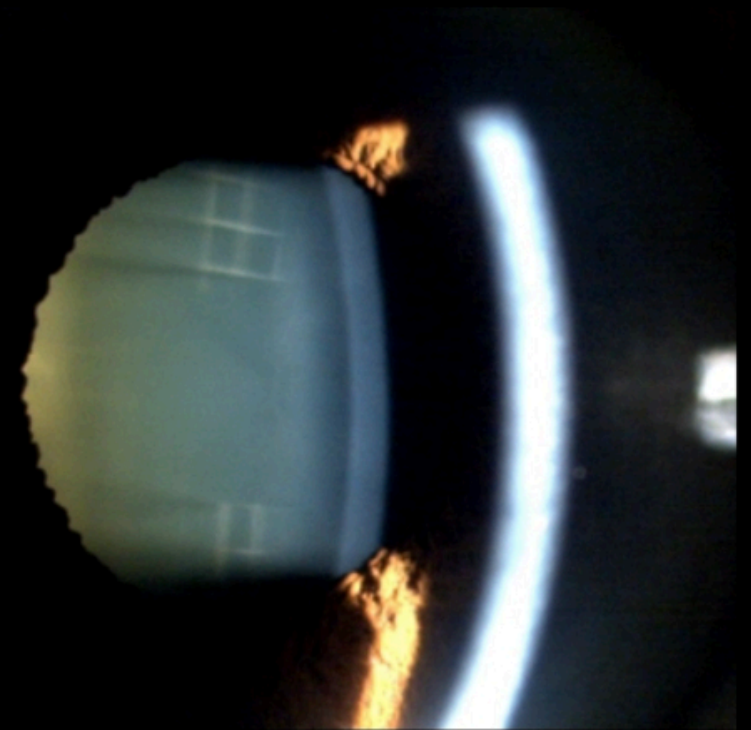
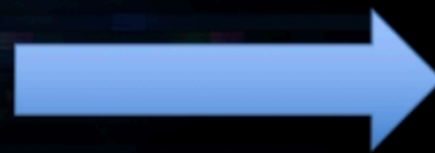
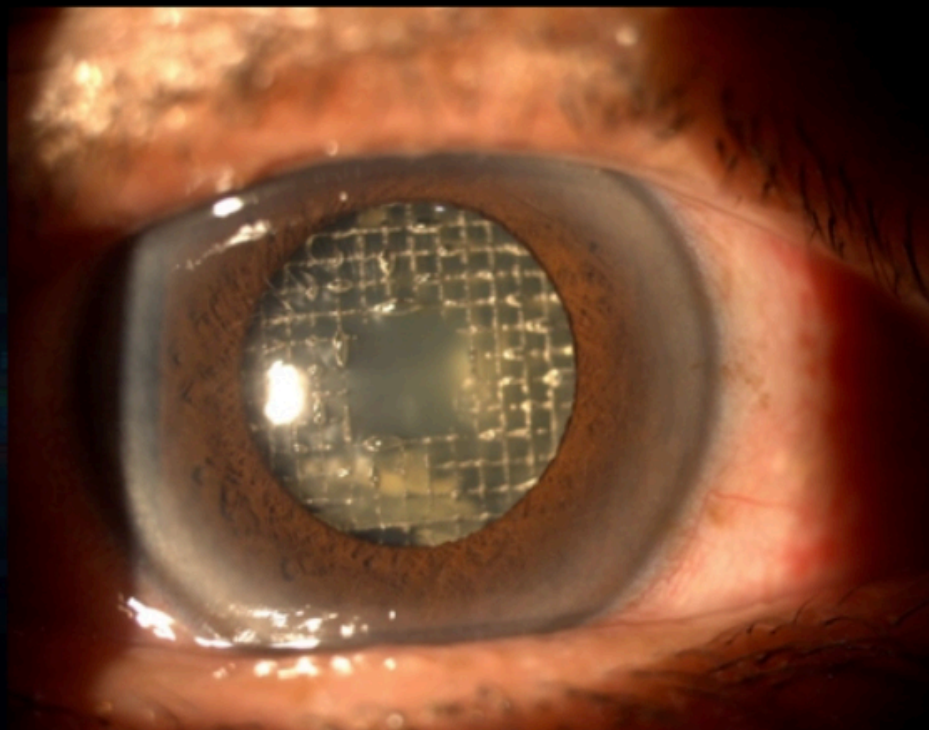
Accommodation Restoration:

- Age: all subjects <55 years of age
- Inclusion:
 - \leq LOCS II Grade 2 Nuclear Cataract
 - Previously elected to have RLE/cataract surgery
 - Agreed to minimum 1 month follow-up prior to lens removal and IOL implantation

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

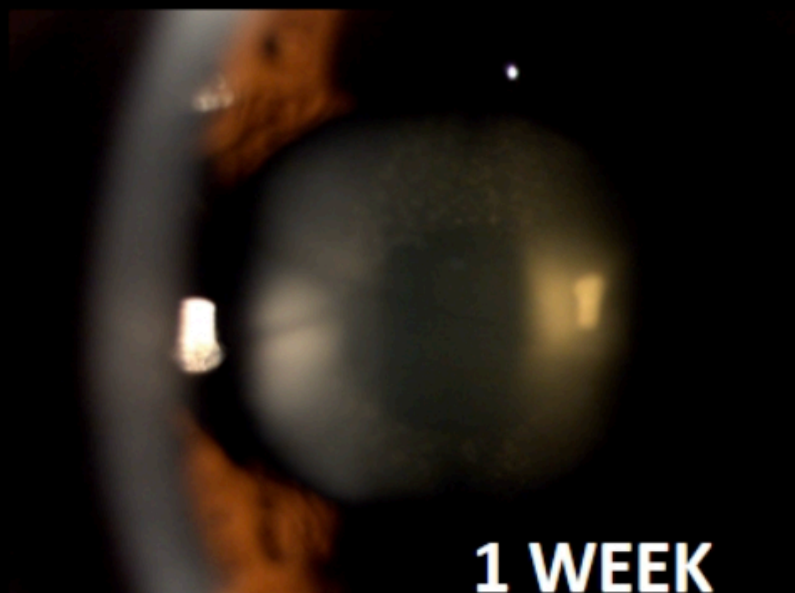
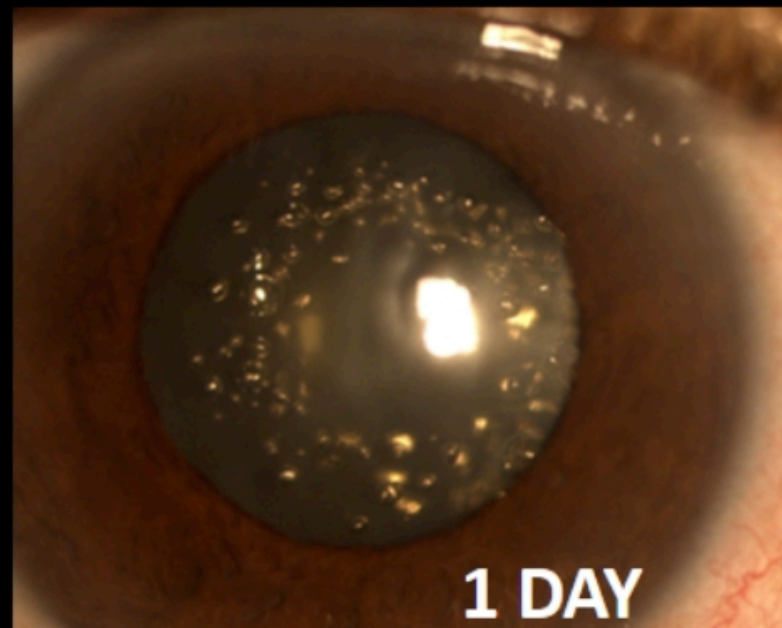
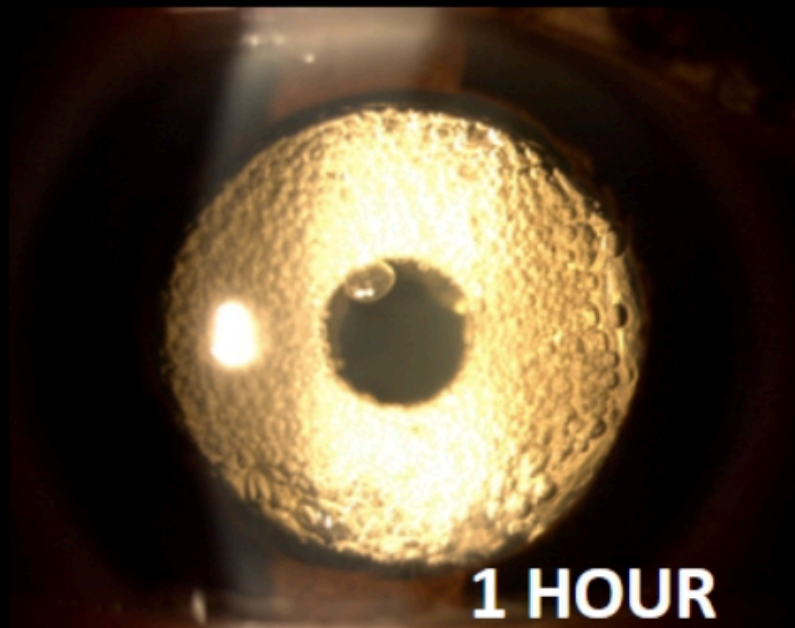
Accommodation Restoration: Prototype & Historical Results (2010)

- 50% showed improvement in subjective accommodation (push down method)
- 33% showed improvement in objective accommodation (Grand Seiko autorefractor)
- 40% showed an increase in BDCNVA



FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

Safety of Laser Pattern with 2 mm Zone of Central Sparing



The early **dense pattern** of bubbles is **not completely resolved within the first 24 hours** but afterwards leaves only a faint, translucent micro-opacity with **no progressive cataract**

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

Accommodation Restoration: Initial Cohort – Preliminary Results

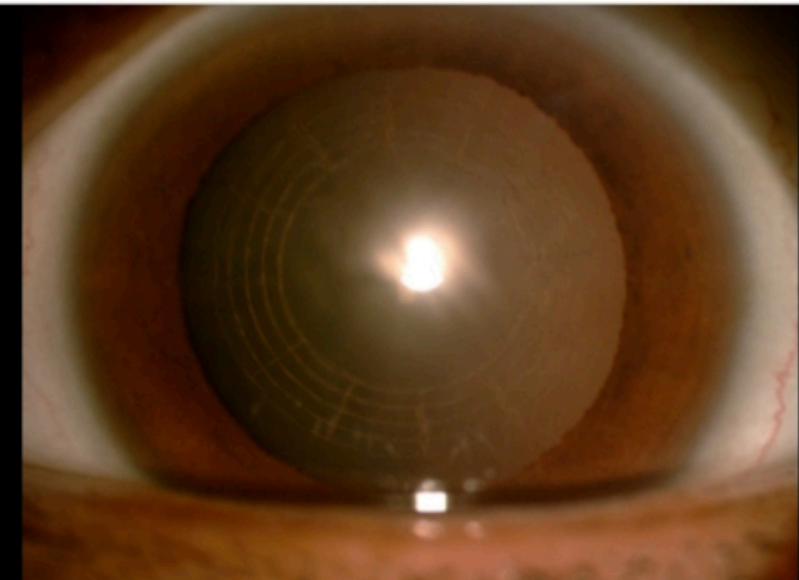
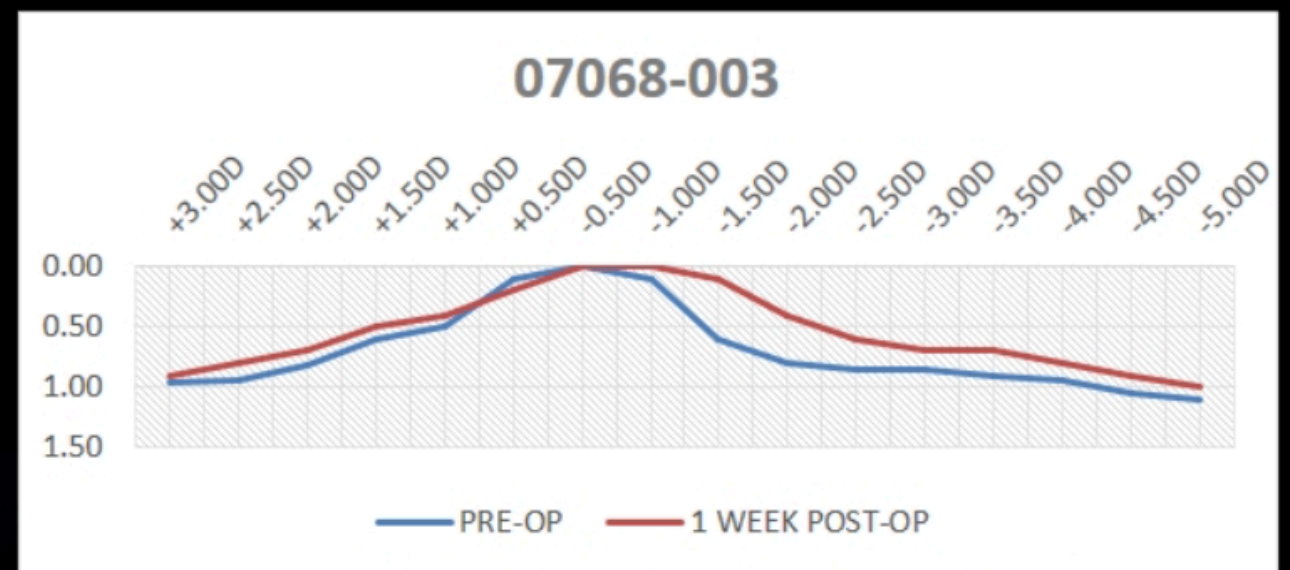
	1 week	
Improvement in UCNVA	94.7%	
Improvement in BDCNVA	88.2%	
Improvement in Defocus Range (>20/40)	84.2%	

	PRE-OP	1 WEEK POST-OP
Mean Patient Preferred Reading Distance (cm)	47.00	41.37
SD	11.96	10.98
Mean logMAR UCNVA	0.51 (20/65)	0.14 (20/27)
SD	0.14	0.09
Improvement in LogMAR BDCNVA	0.234	

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

Accommodation Restoration: Proof of Concept Case Study

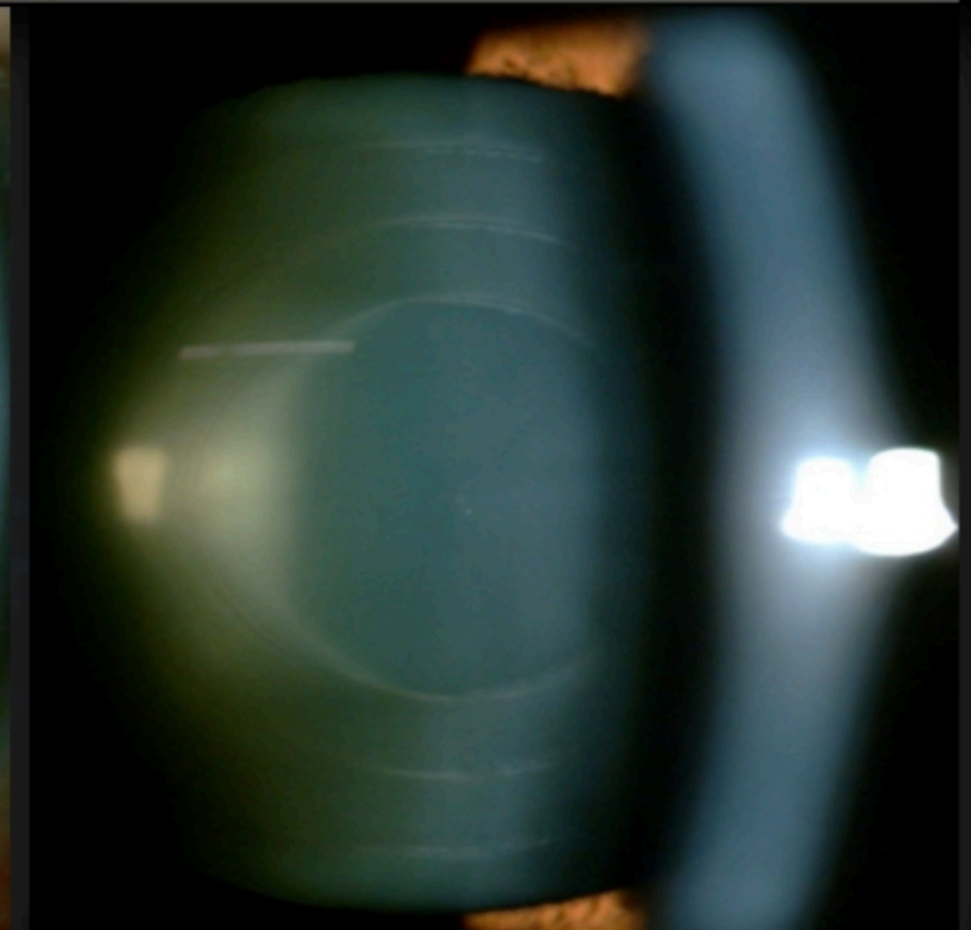
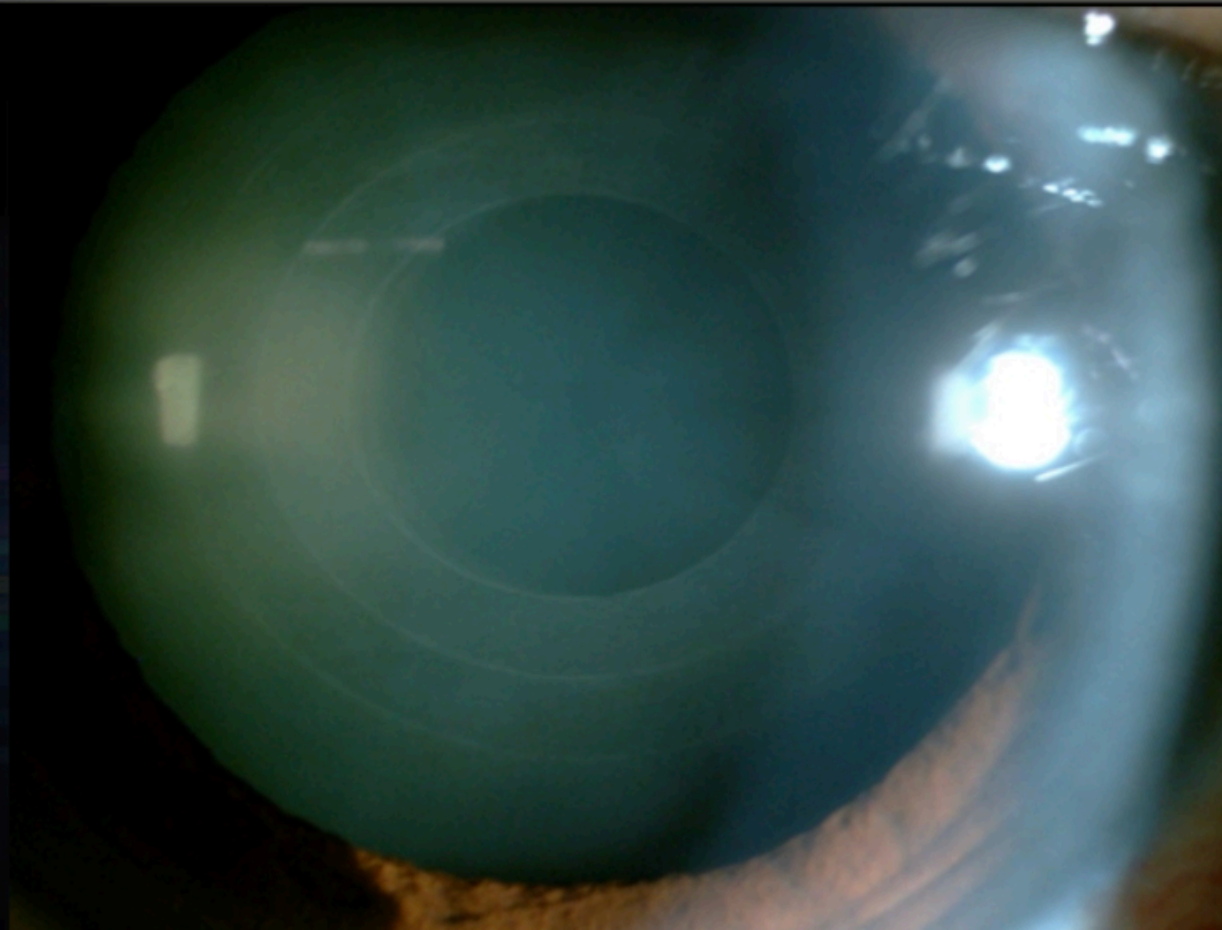
- Pre-op RX: 0.75 sph
- BDCNVA Improvement:
1.0 logMAR to **0.4 logMAR**
(20/200) (20/50)



FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

**Annular Treatment Pattern:
Appearance at 1-day Post-Operative**

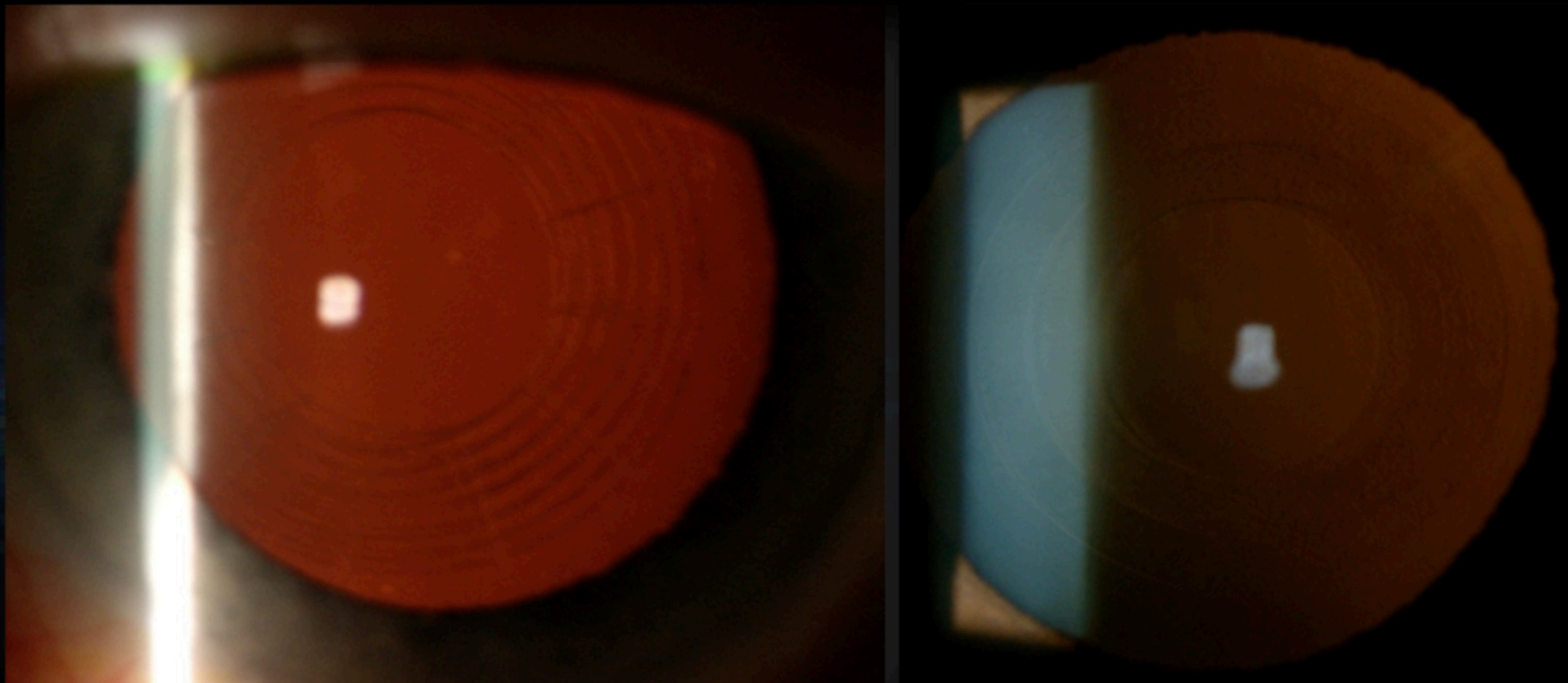
**Uniformly Continuous Pattern and Visual Axis
Spared to Ensure No Light Scattering**



FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

**Annular Treatment Pattern:
Appearance at 1-day Post-Operative**

**Uniformly Continuous Pattern and Visual Axis
Spared to Ensure No Light Scattering**



FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

Femtosecond Laser Accommodation Restoration: Summary

Historical clinical studies in presbyopia show:

- Proof of concept and parameters of safety
- Improved objective accommodation in a small proportion of subjects
- Improved subjective accommodation in a moderate proportion of subjects
- Improved BDCNVA in a moderate proportion of subjects

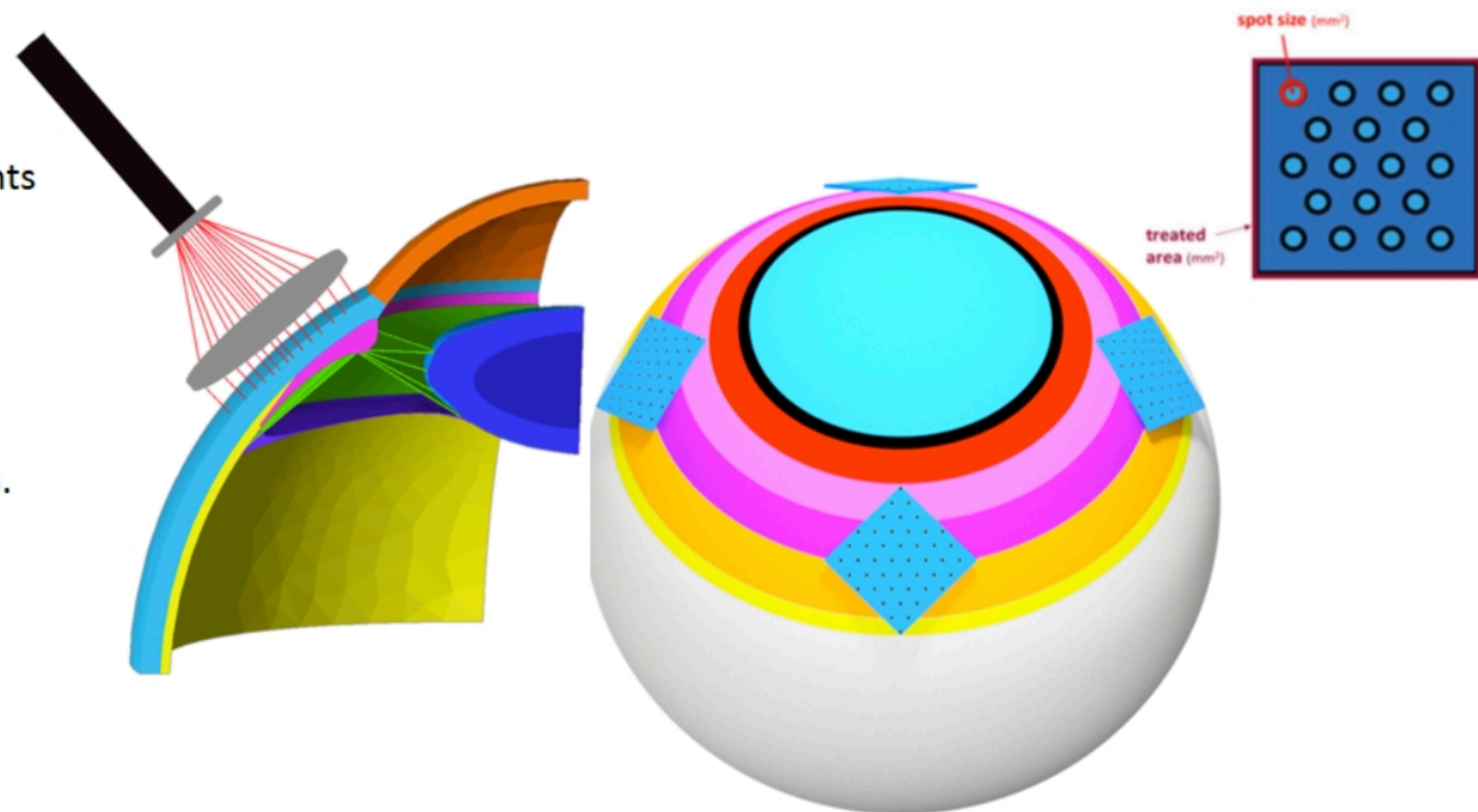
Current studies in investigation:

- Improvement in results through new patterns (commercially sensitive data)
- Enhanced algorithms for enhanced effect
- Factors affecting variable response

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

Laser Scleral Microporation Procedure (LSM)

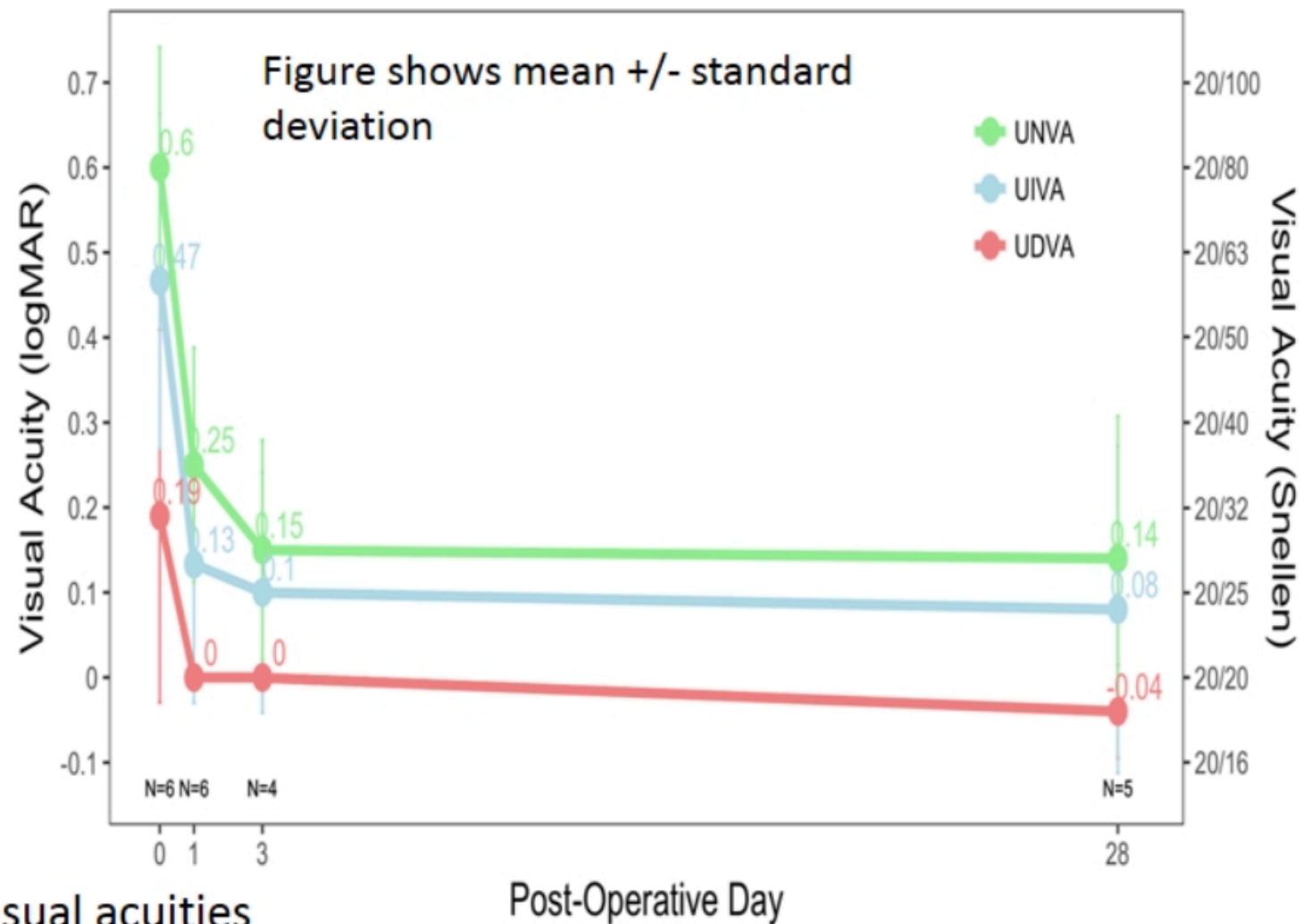
- **Surgical Technique:**
 - Er:Yag laser: 225um spot size, micropores in 4 oblique quadrants
 - Mathematical 3D matrix microporation created over 5 critical zones of ciliary complex
- **Mechanism of Action:**
 - Uncrosslinking: Decrease biomechanical stiffness of sclera.
 - Restore mechanical efficiency accommodation mechanism



FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

LSM Results – Binocular Visual Acuity

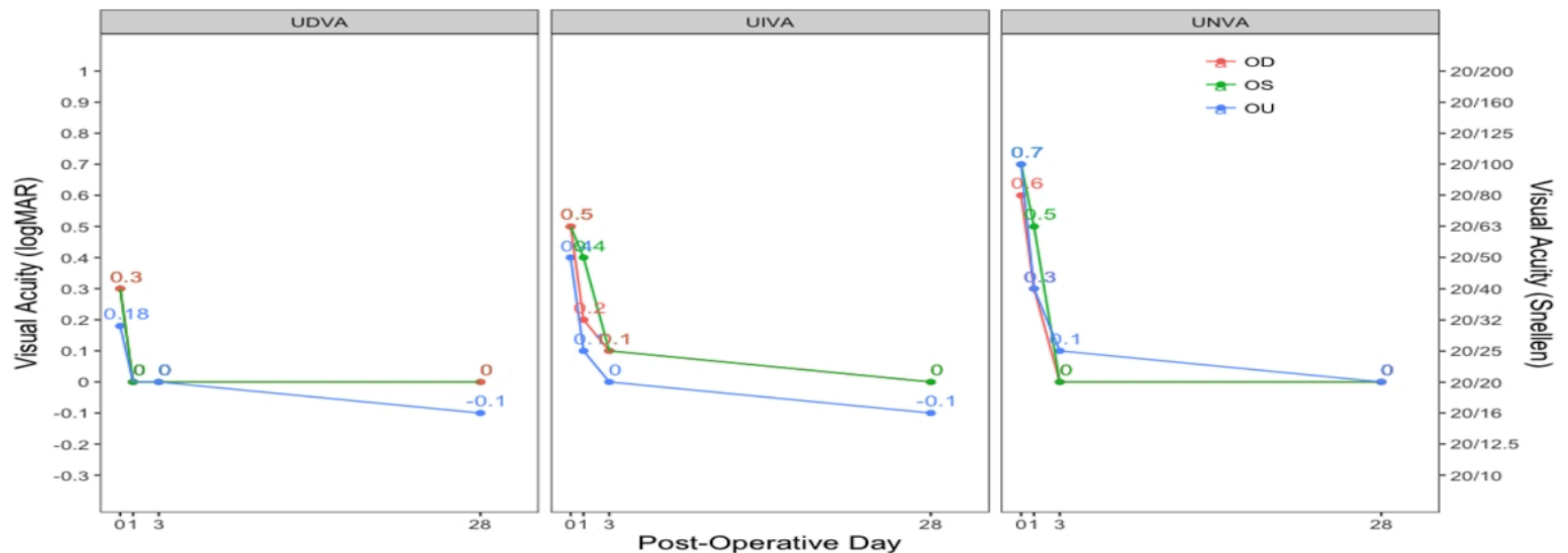
Binocular					
Acuity	Day	N	Mean (logMAR)	Standard Deviation (logMAR)	P-Value
UDVA	0	6	0.19	0.22	-
	1	6	0.00	0.00	0.022
	3	4	0.00	0.00	0.037
	28	5	-0.04	0.055	0.02
UIVA	0	6	0.47	0.20	-
	1	6	0.13	0.16	0.069
	3	4	0.10	0.14	0.021
	28	5	0.08	0.19	0.0087
UNVA	0	6	0.60	0.14	-
	1	6	0.25	0.14	0.0012
	3	4	0.15	0.13	0.00064
	28	5	0.14	0.17	0.0001



- Significantly improved at most time points for all visual acuities
- Median of 4.5 lines of improvement at 1 Month for UIVA and UNVA compared to preoperative
 - Range: 2-8 lines

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LSM Results – Example from one Patient



- Large improvements in UDVA, UIVA, and UNVA
- Binocular UNVA improved by 7 lines 1 month postoperatively
 - 20/100 preoperatively → 20/20 1 month postoperatively

FEMTO LENTOTOMY & LASER SCLERAL MICROPORATION

"We may well have a treatment for presbyopia in the future..."



MICHAEL KORENFELD

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA...

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

A Magical Drug From a Magical Journey (Lipoic Acid Choline Ester)

Presbyopia:

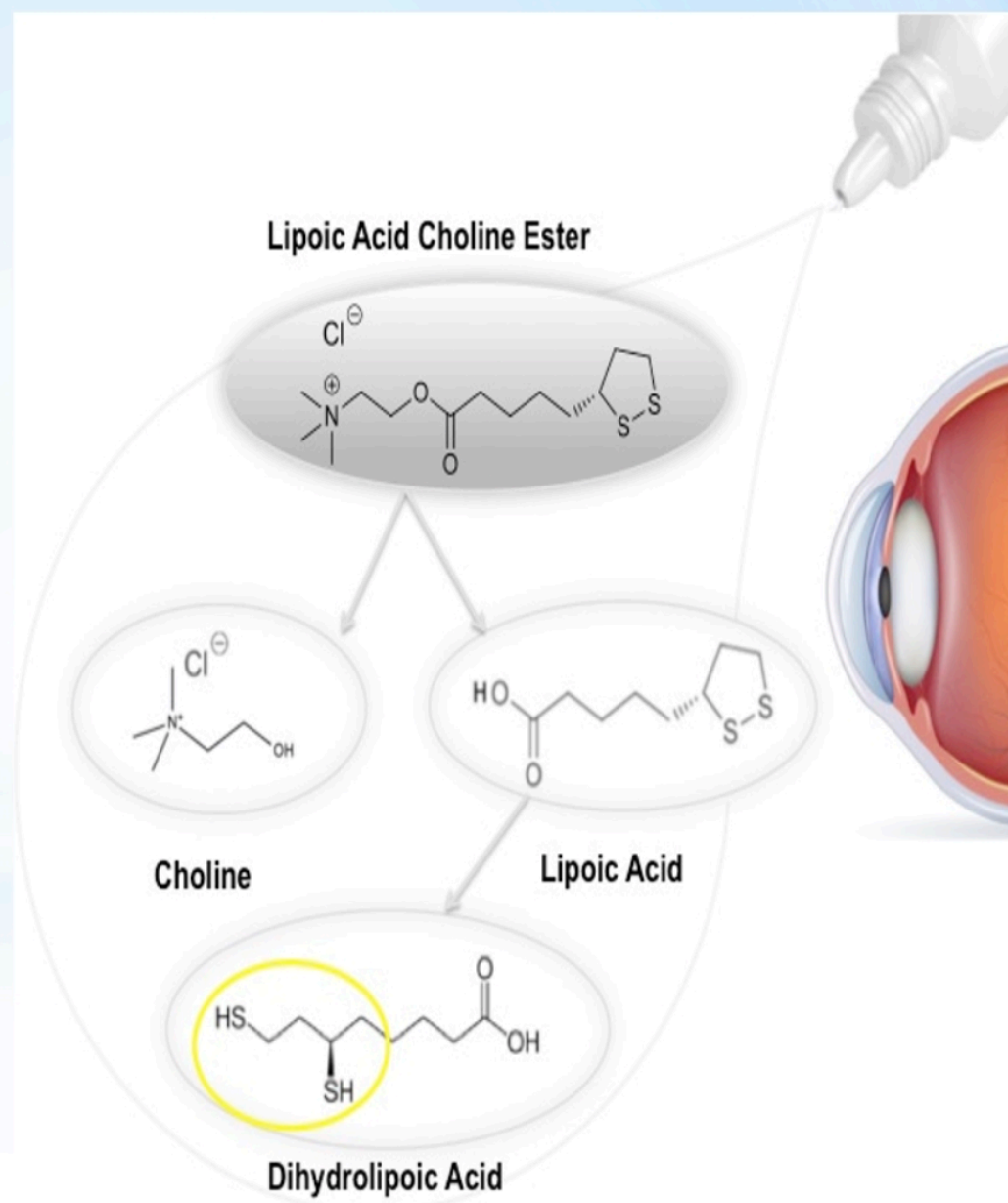
There is a lot happening:

- 1) Lens is enlarging over time (ectoderm)
- 2) The ciliary body is changing (atrophy)
- 3) The viscosity of the vitreous is reducing
- 4) The lens is becoming stiffer (the target)

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

What is EV06 (UNR844)- How Does it Work?

- EV06 (Lipoic Acid Choline Ester) is a prodrug.
- EV06 penetrates cornea and is metabolized into Choline & Lipoic Acid, two naturally occurring substances.
- Enzymes within lens fiber cells chemically reduce Lipoic Acid to active form Dihydrolipoic Acid (DHLA)
- DHLA reduces disulfide bonds between lens proteins – restores lens microfluidics.



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Lipoic Acid Choline Ester

Proof of concept confirmed *in vitro*
with human cadaver lenses and *in*
vivo with rabbits

Concentrations and dosing assessed

Ready for first in human study...
Encore Vision

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

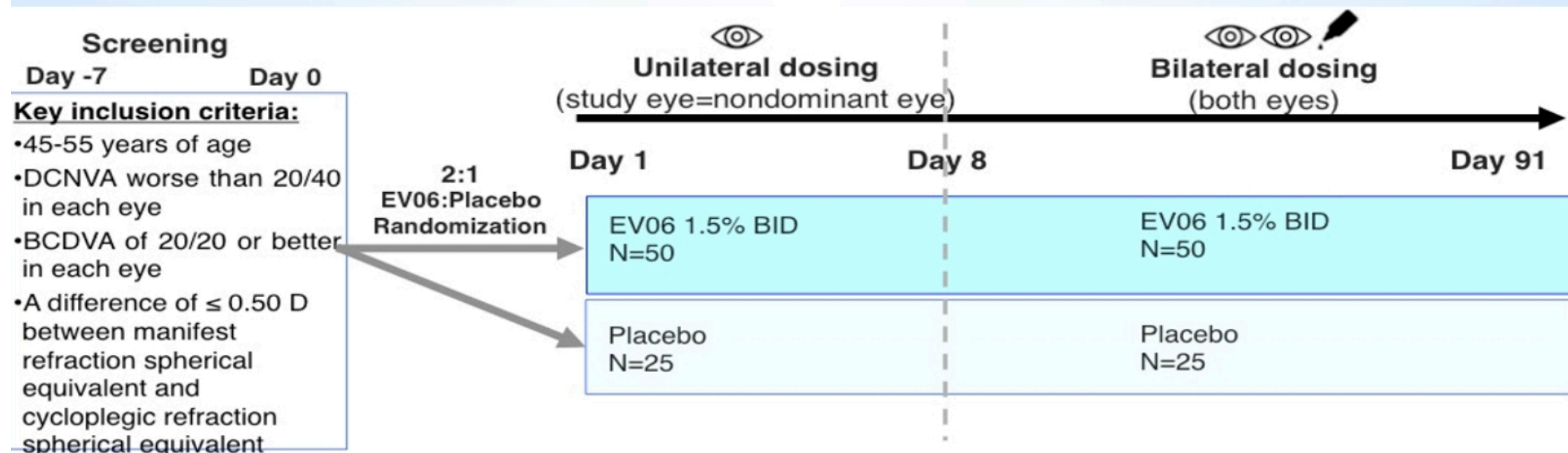
Methods

Objective:

- To evaluate Safety & Efficacy of EV06 Ophthalmic Solution in Improving Distance Corrected Near Visual Acuity (DCNVA) in Subjects with Presbyopia

Study Design:

- Prospective, randomized, double-masked, placebo-controlled multicenter Phase I/II study
- 75 subjects with hyperopia, myopia, or emmetropia and a diagnosis of presbyopia randomized 2:1 (EV06 or Placebo) BID
- Study visits, Days -7, 0, 1, 8, 15, 31, 61, 91
- 4 US Sites



THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Study Outcomes

Safety

- BCDVA
- Pupil Diameter
- IOP
- Slit-lamp findings
- Adverse Events
- **Exploratory Efficacy**
- Mean change in DCNVA
- Proportion of subjects with gain of ≥ 10 letters in DCNVA

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Study Demographics

	Placebo Control	Active EV06
Number of Subjects	25	50
Age (years) \pm SD	51.4 (\pm 3.0)	50.1 (\pm 3.2)
Gender		
Female	80%	66%
Male	20%	33%
Race		
White	72%	70%
Black	28%	30%
Ethnicity		
Hispanic/Latino	20%	32%
Not Hispanic/Latino	80%	68%
Refractive Status		
Myopes	24%	18%
Emmetropes	68%	68%
Hyperopes	8%	14%
Baseline DCNVA (Mean LogMAR \pm SD)		
Study Eye	0.500 (\pm 0.10)	0.507 (\pm 0.11)
Bilateral (OU)	0.408 (\pm 0.12)	0.397 (\pm 0.10)

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Results

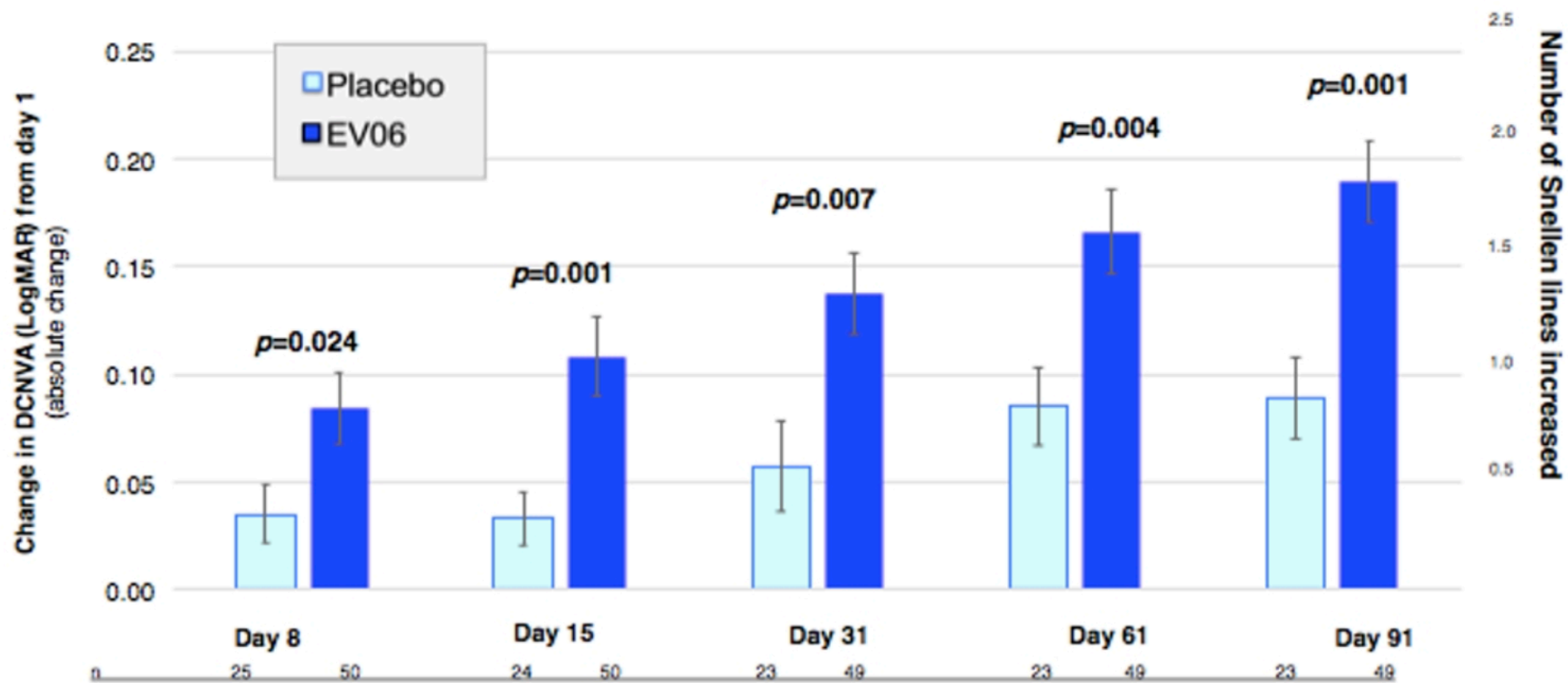
EV06 (UNR844) Is Safe and Well-Tolerated

- No Subjects Discontinued for Adverse Events, Safety Concerns, or Tolerability
- No Serious Treatment-Related AEs; No Sight-Threatening AE's
- No Change in IOP
- Comfortable Upon Instillation
- EV06 Comfort Rating 3.0 vs Placebo Comfort Rating 2.7
 - (Scale 0 – 10; “0” = Very Comfortable; “10” = Uncomfortable)
- No Change in Best Corrected Distance Visual Acuity (BCDVA)
- No Changes in Manifest Refraction Spherical Equivalent or Cycloplegic Refraction
- No Change in Pupil Diameter

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

EV06 (UNR844) Showed Improved Bilateral Near Vision Over Time Mean Change in DCNVA (LogMAR) from Baseline OU

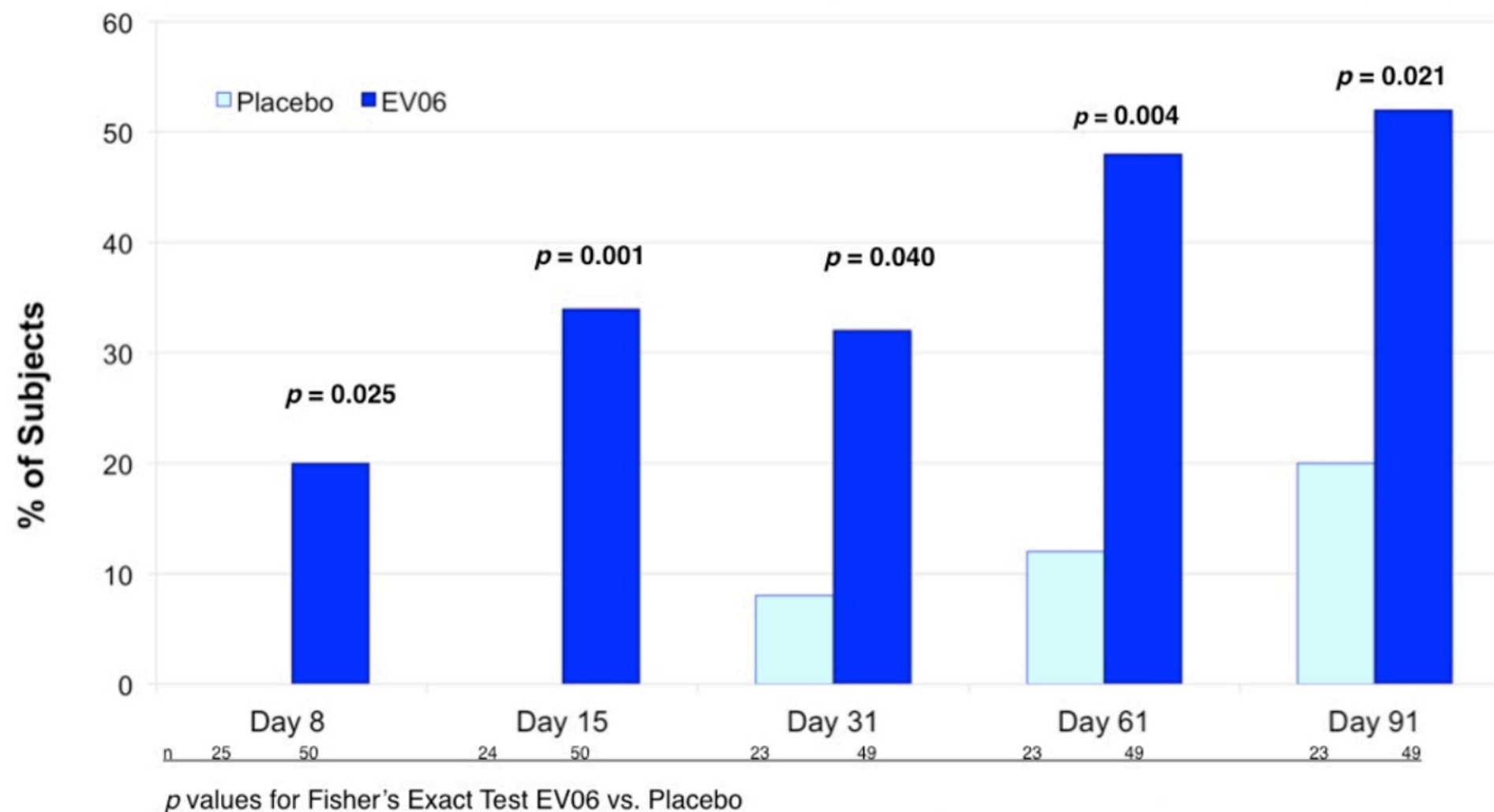


P-values two-sample t-test, EV06 vs. Placebo. Error bars represent SEM

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

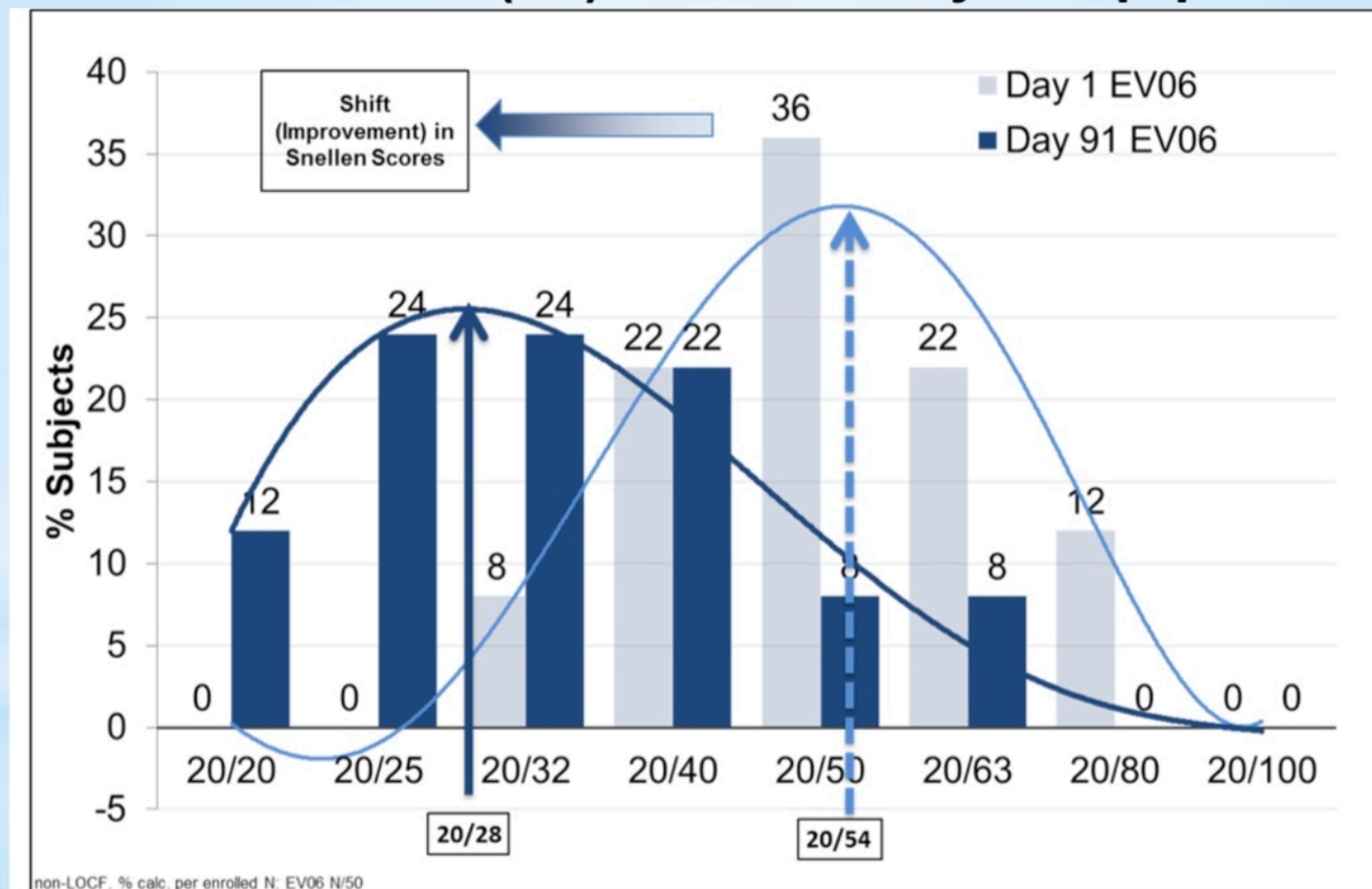
EV06 (UNR844) Improved Percent of Subjects with Gains in Bilateral Near Vision Percent Subjects Showing a *Gain of ≥ 10 letters in DCNVA (OU)*



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Results Continued

**EV06 (UNR844) Showed Improved Bilateral Near Vision Over Time
DCNVA Snellen Scores (OU) Baseline vs Day 91: A population shift**



This figure illustrates the bilateral Snellen distance corrected near visual acuity (DCNVA) for the 50 EV06 subjects on Day 1 (baseline) compared to Day 91 (final visit). The results indicate that there was a clinically significant shift in the DCNVA in this cohort of subjects. The mean Snellen values of 20/28 (Day 91) and 20/54 (Day 1) are approximations.

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

EV06 (UNR844) Improved Near Vision

ETDRS Lines Changed (DCNVA, OU), Baseline vs Day 91

	Placebo Control*		Active EV06*		
Subjects with:	n = 23		n = 49		
Improvement in DCNVA	n	%	n	%	
1 line (≥ 0.10 LogMAR)	12	52%	41	84%	<i>p=0.009</i>
2 lines (≥ 0.20 LogMAR)	5	22%	26	53%	<i>p=0.021</i>
3 lines (≥ 0.30 LogMAR)	0	0%	11	22%	<i>p=0.013</i>
4 lines (≥ 0.40 LogMAR)	0	0%	6	12%	<i>p=0.167</i>
Any Loss in DCNVA (≥ 0.10)	1	4%	1	2%	<i>p=0.540</i>
No Change in DCNVA (-0.09 to 0.09)	10	44%	7	14%	<i>p=0.015</i>
*non-LOCF, % calc based on n per day					p values for Fisher's Exact Test EV06 vs. Placebo

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Summary and Conclusions

- EV06 (UNR844) Ophthalmic Solution, 1.5% improved near vision as measured by clinically and statistically significant improvements in DCNVA compared to Placebo measured by LogMAR and Snellen line changes.
 - Statistically significant improvements in DCNVA were observed in each eye (unilateral vision) following topical ocular use of EV06 (UNR844). Improvements in DCNVA were most pronounced when subjects employed bilateral (OU) vision.
 - 84% of subjects completed the study with 20/40 bilateral vision or greater treated with EV06 (UNR844) versus 52% in Placebo.
 - 53% of subjects completed the study with ≥ 0.2 LogMAR change in bilateral vision treated with EV06 (UNR844) versus 22% in Placebo.
- Treatment with EV06 (UNR844) Ophthalmic Solution, 1.5%, BID for three months was not associated with an increase in Adverse Events, slit-lamp findings, fundus findings or IOP compared to Placebo.
- There were no changes in pupil diameter, BCDVA, Manifest Refraction or Cycloplegic Refraction in the EV06 (UNR844) group compared to Placebo.
- This study was funded by Encore Vision Inc, a privately held eye care company at the time the study was planned, conducted and analyzed. Encore Vision was acquired by Novartis in January 2017.
- EV06 is now identified as **UNR844** by Novartis.

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Purpose

- Few pharmacological options are in development for the treatment of presbyopia, and the durability of these options is not well known. A recent clinical study (NCT02516306) in presbyopic subjects demonstrated statistically and clinically significant improvement in distance corrected near visual acuity (DCNVA) following BID dosing with lipoic acid choline ester eye drops (EV06 Ophthalmic Solution, 1.5%) compared to vehicle control (Placebo).
- The current study followed a cohort of the original study's population for 7 months after cessation of their assigned treatment to assess the long term effects of the investigational product.
- Encore was acquired by Novartis in January, 2017, and the compound is now referred to as UNR844.

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

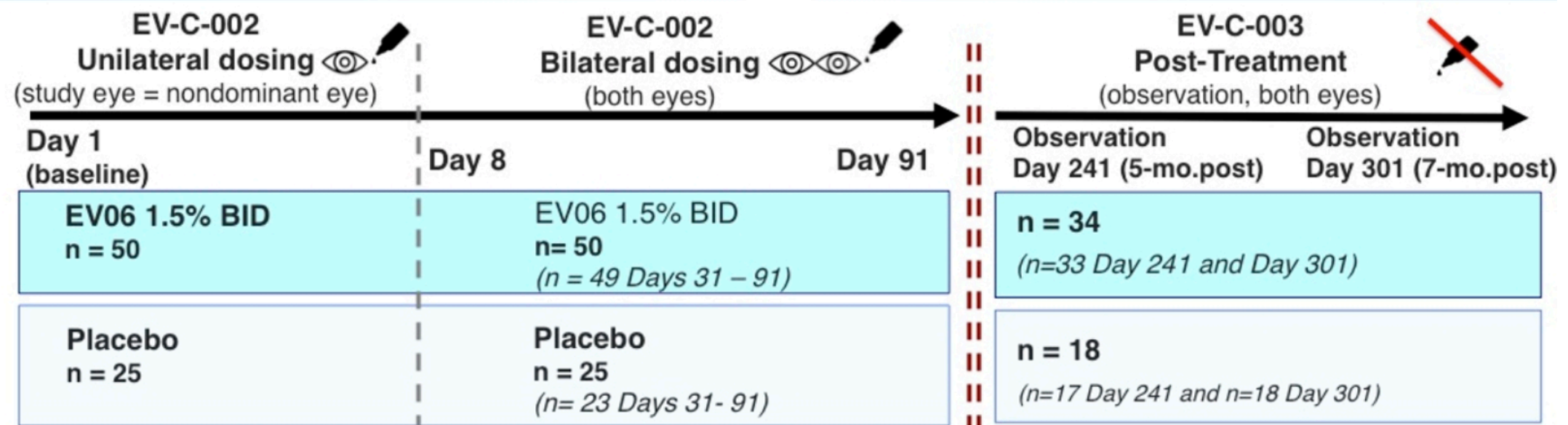
Methods

Objective:

- To evaluate Safety & Efficacy in a subset of subjects who successfully completed the 90-day randomized, double-masked, controlled study of EV06 vs. Placebo, for long term effects beyond the 90 day dosing period.

Study Design:

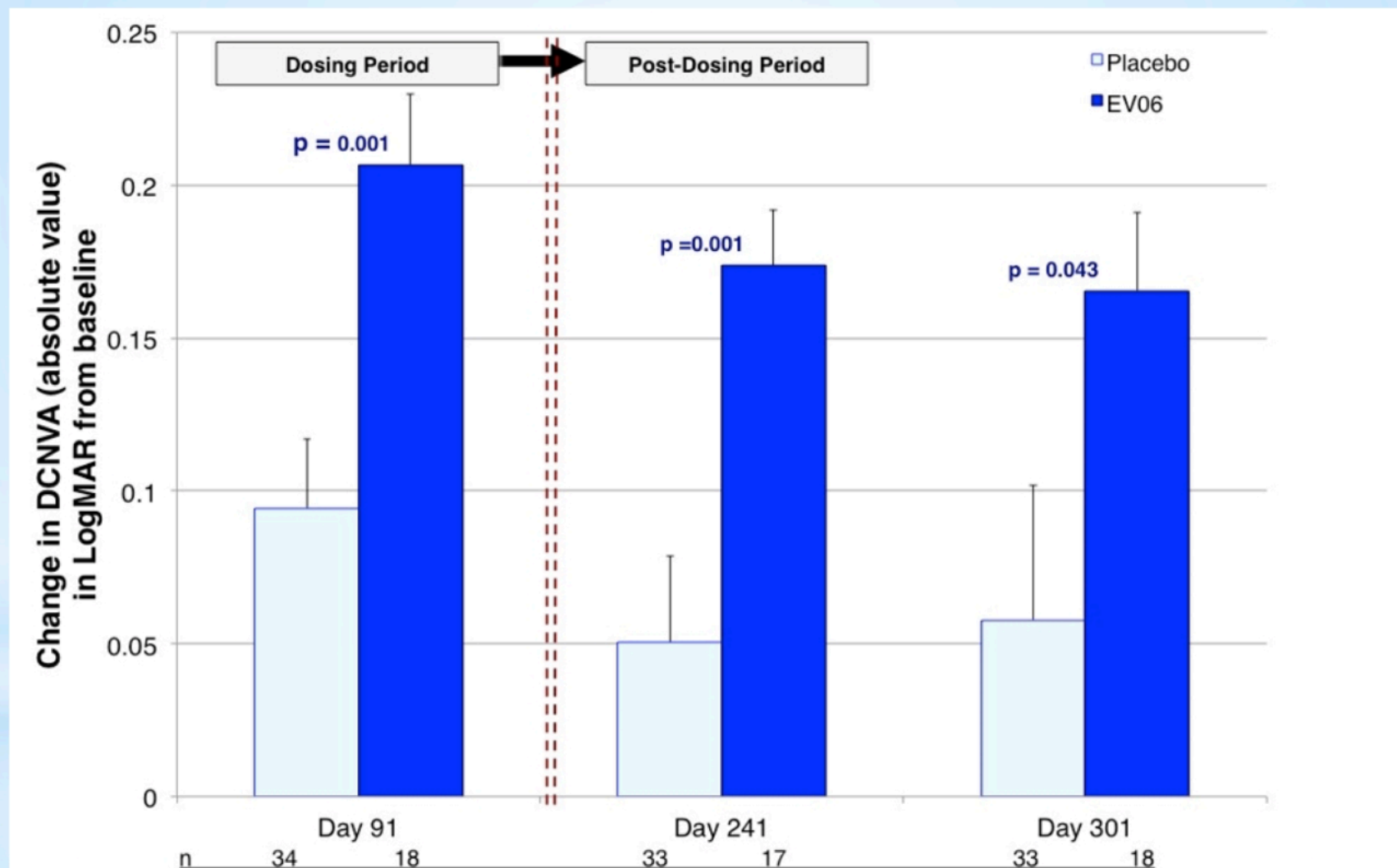
- Subjects remained masked and were observed 150 and 210 days following their last treatment to assess long-term effects on Distance Corrected Near Visual Acuity (DCNVA), Best Corrected Distance Visual Acuity (BCDVA), and Manifest Refraction Spherical Equivalent (MRSE) relative to study Day 1 and Day 91. Biomicroscopic slit-lamp and IOP evaluations were performed for safety. assessment.



THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

Change in DCNVA (LogMAR) from Baseline, Bilateral Vision



Treatment: Subset of subjects in EV-C-002 who continued in EV-C-003; non-LOCF. Mean calculated by n per Day \pm SEM.

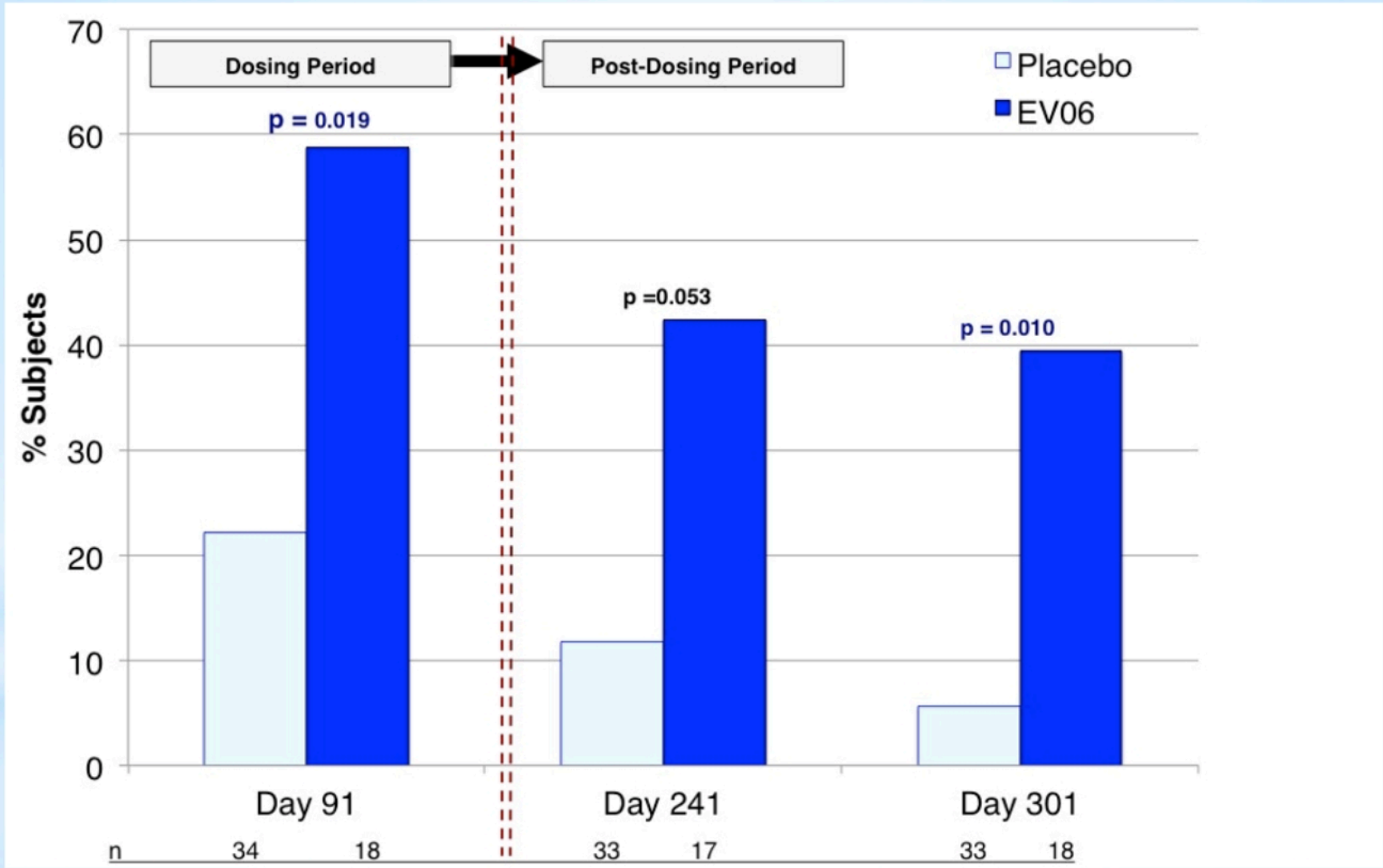
Post-Treatment: observation for 150 days to Day 241 and observation for 210 days to Day 301.

(Note: E- Missing 1 subject on Day 241 and 1 subject on Day 301. P- Missing 1 subject on Day 241)

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

Percent of Subjects with *Gains of ≥ 10 letters in DCNVA (LogMAR) from Baseline, Bilateral Vision*



Treatment: Subset of subjects in EV-C-002 who continued in EV-C-003; non-LOCF. Mean calculated by n per Day \pm SEM.

Post-Treatment: observation for 150 days to Day 241 and observation for 210 days to Day 301.

(Note: E- Missing 1 subject on Day 241 and 1 subject on Day 301. P- Missing 1 subject on Day 241)

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Results Continued

ETDRS Lines Changed (DCNVA), Bilateral Vision
Baseline vs Day 91, Day 241, and Day 301

	Day 1 vs. Day 91			Day 1 vs. Day 241			Day 1 vs. Day 301		
Subjects with:	Placebo n = 18	EV06 n=34		Placebo n = 17 [^]	EV06 n=33 [^]		Placebo n = 18	EV06 n=33 ^{^^}	
Improvement in DCNVA	%	%	p-value	%	%	p-value	%	%	p-value
1 line (≥ 0.10 LogMAR)	56%	88%	0.014	41%	82%	0.009	50%	67%	0.369
2 lines (≥ 0.20 LogMAR)	22%	59%	0.019	12%	42%	0.053	6%	39%	0.010
3 lines (≥ 0.30 LogMAR)	0%	24%	0.040	0%	9%	0.542	0%	21%	0.043
4 lines (≥ 0.40 LogMAR)	0%	18%	0.081	0%	3%	1.000	0%	12%	0.284
Any Loss in DCNVA (≥ 0.1)	6%	0%	0.346	6%	0%	0.340	6%	3%	1.000
No Change in DCNVA	39%	12%	0.034	53%	18%	0.021	44%	30%	0.367

p values for Fisher's Exact Test EV06 vs. Placebo

Day 1 & Day 91: Subset of subjects in EV-C-002 who continued in EV-C-003. Non-LOCF. Cumulative Analysis.

Day 241= Day 150 post-treatment; Day 301= Day 210 post-treatment.

[^]Missing 1 subject on Day 241 and ^{^^}1 subject on Day 301

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Summary and Conclusions

- Subjects that had been treated with EV06 (UNR844) Ophthalmic Solution, 1.5% continued to show significantly greater improvement in bilateral near vision (both eyes simultaneously viewing target) versus Placebo measured by LogMAR change up to 7 months **after** dosing had ceased.
 - 39% of subjects treated with EV06 (UNR844) maintained a ≥ 0.2 LogMAR change in bilateral near vision 7 months after dosing ceased, compared to 6% in Placebo.
 - There were no safety concerns identified.
-
- This study was funded by Encore Vision Inc, a privately held eye care company at the time the study was planned, conducted and analyzed. Encore Vision was acquired by Novartis in January 2017.
 - EV06 is now identified as **UNR844** by Novartis.

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

Novartis now owns this drug UNR844

- * Clinical trials are being planned
- * Drug formulation is being refined (stability)
- * A dispenser that can handle the drug's special needs is being developed.
- * Look for progress in late 2018 and early 2019

THE PHARMACEUTICAL REVERSAL OF PRESBYOPIA WITH A TOPICALLY APPLIED REDUCING AGENT

The Magic Drug: UNR844

- * I believe that nuclear sclerotic cataract is what the continued progression of presbyopia results in.
- * This reducing agent, used chronically or intermittently could plausibly prevent or delay nuclear sclerotic cataract.
- * The use of this drug early enough in life could plausibly prevent both presbyopia and nuclear sclerotic cataracts.

The widespread use of this drug stands to radically alter the visual performance of humans within our lifetimes.

ANJA TUULONEN, MARKO KATAJA

LOMAUTUKSET JA IRTISANOMISET KAIHIKLINIKASSA...?