# CROSS-LINKING CORNEALE A GUIDA TERANOSTICA

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SOSi Società Oftalmologica Siciliana

## XLIX Congresso Regionale Società Oftalmologica Siciliana

**Presidente: Prof. Pasquale Aragona**

**Giardini Naxos, 10-12 Aprile 2025**

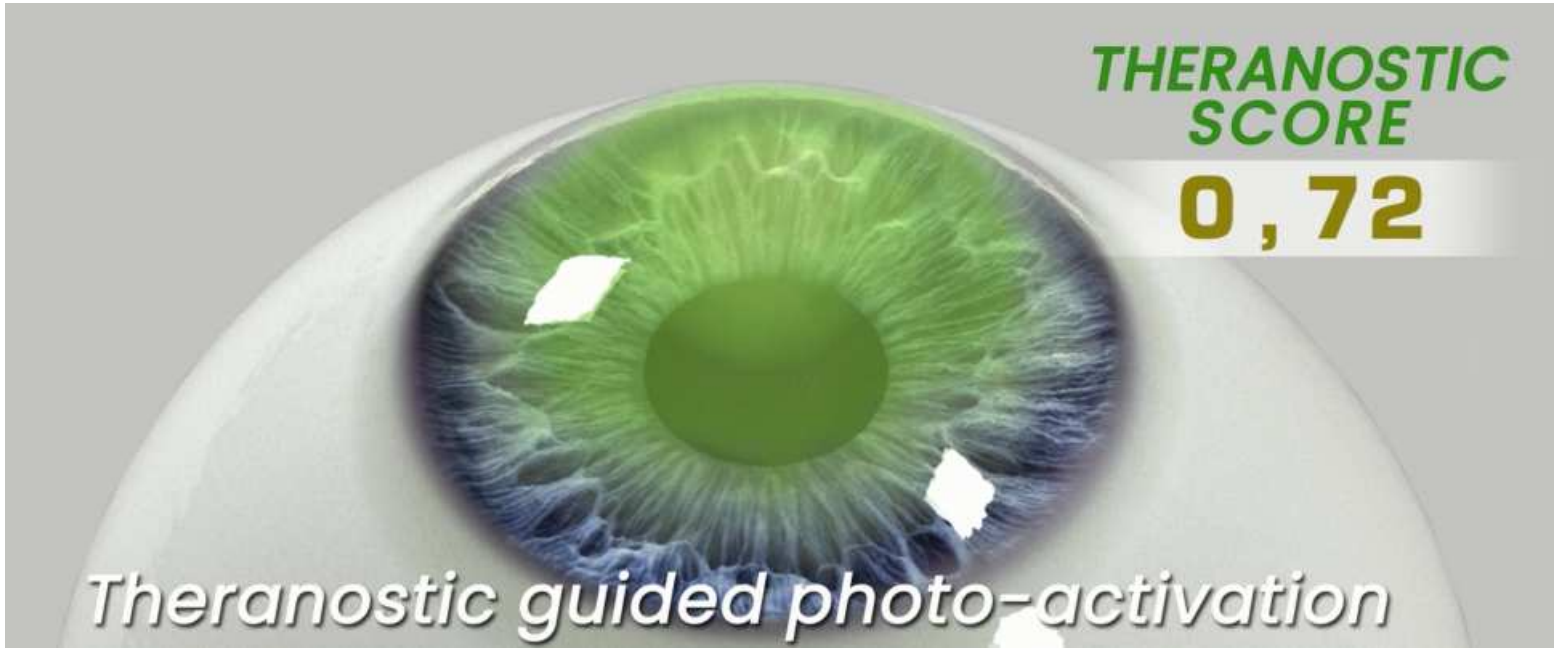
# OUTLINE

1. THERANOSTICS
2. ARGO MULTICENTER RANDOMIZED CLINICAL TRIAL
3. THERANOSTIC-GUIDED CORNEAL THERAPY
4. CLINICAL CASES

*Disclosure*: co-founder and shareholder Regensight srl and Vision Engineering Italy srl

# THERANOSTICS

**Theranostics** combines ***thera***py & diag***nostics***



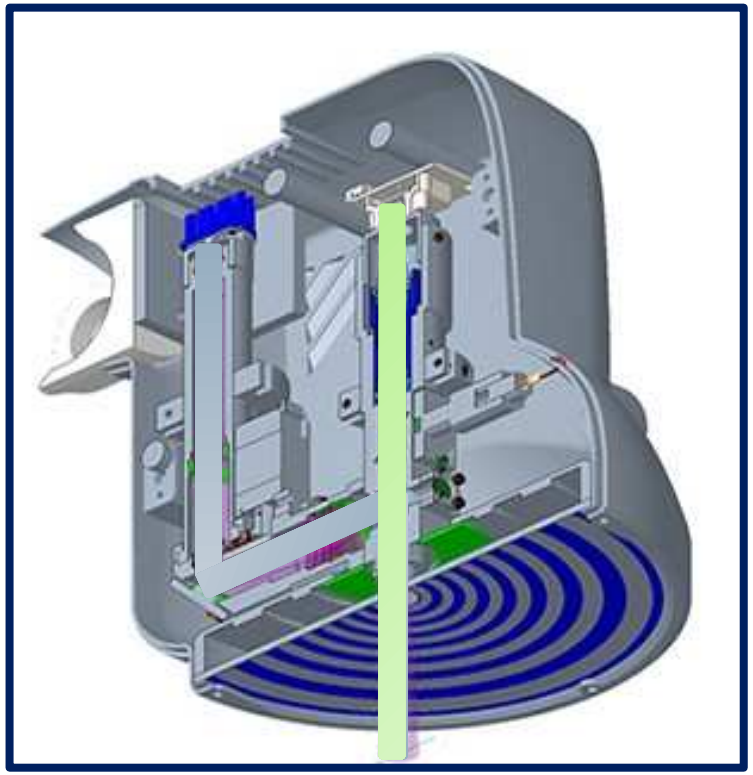

Theranostics is an emerging approach of **personalized**, **precision** and **predictive** medicine.

Light-triggered theranostics for keratoconus involves **UV-A light** excitation of photo-activatable **riboflavin**, enabling **simultaneous** controlled corneal therapy and imaging

# THERANOSTICS

**Theranostics** combines ***thera***py & diag***nostics***

*The **same UV-A light source** is used* for **simultaneous** fluorescence **imaging** *to measure the corneal **riboflavin concentration** and for* **targeted photo-polymerization** *to treat the cornea*



# ARGO BACKGROUND


## CONCLUSIONS of COCHRANE META-ANALYSIS STUDY

*"Most effective method for **corneal cross-linking** is not known.*

**CXL efficacy fluctuates between 10% and 90%***

***Theranostic UV-A device** measuring real-time corneal concentration of riboflavin, via acquisition and analysis of fluorescence emitted from riboflavin when illuminated by UV-A light (Marco Lombardo et al.) **to solve it**".*

***ARGO TRIAL Question**: Is CXL effective for halting disease progression?*

***TRIAL Hypothesis**: Is riboflavin concentration the primary factor influencing CXL treatment efficacy?*

Ng SM, Ren M, Lindsley KB, Hawkins BS, Kuo IC. Transepithelial versus epithelium-of corneal crosslinking for progressive keratoconus. Cochrane Database of Systematic Reviews 2021; Issue 3. Art. No: CD013512.

*Chunyu T et al. Sci Rep 2014; 4: 5652.
Li J et al. PLoS One 2015; 10(5): e0127079.
Sykakis E et al. Cochrane Database Syst Rev 2015; 3: CD010621.
Kuo IC et al. Cochrane Systematic Review. Am J Ophthalmol. 2021;229:274-287.
Serrao S et al. Int Ophthalmol 2022; 42(1):337-348.

# PRIMARY OUTCOME

CLINICAL TRIAL NCT05457647

The primary outcome measure was **validation of the combined use of theranostic imaging biomarkers**, ***riboflavin score*** and ***theranostic score***, through measurement of their accuracy and precision to correctly classify eyes and **positively predict a $K_{max}$ flattening at 1 year after treatment**.

# STRATIFICATION

## CLINICAL TRIAL NCT05457647

The study consisted of a study arm, where participants were stratified with allocation ratio 1:1 into either treatment protocol:

- Epithelium-off corneal cross-linking (“**Epi-OFF CXL**”)
- Epithelium-on corneal cross-linking (“**Epi-ON CXL**”)

**Objective:** to validate the predictive ability of theranostics, regardless of the CXL treatment protocol

# INVESTIGATORS

## CLINICAL TRIAL NCT05457647

The ARGO trial has been approved by the Italian Ministry of Health (prot. n. DGDMF/I.5.i.m.2/2021/2024 05/01/2022) in conformity with **art. 62 and Annex XV of the Regulation (EU) 2017/745 MDR**.

- Azienda Ospedaliera Universitaria Careggi, Università di Firenze
  - Prof.ssa Rita Mencucci
- Azienda Ospedaliera Universitaria G. Martino, Università di Messina
  - Prof.ssa Anna Maria Roszskowska
- Policlinico Universitario Mater Domini – Università Magna Graecia di Catanzaro
  - Prof. Vincenzo Scorcia

**Scientific Director Dr. Marco Lombardo**

Approval was granted by the Ethical Committees of Regione Calabria Sezione Area Centro (prot. n. 358 18/11/2021), AOU Gaetano Martino (prot. n. 101 23/11/2021) and Area Vasto Centro (prot. n. 21250_spe 18/01/2022)

# STUDY POPULATION

## CLINICAL TRIAL NCT05457647

| **Patients' demographics and medical history** | |
|---|---|
| **N** | **50** |
| **Gender (Female, %)** | 13 (26%) |
| **Age (years)** | **26 ± 5**<br>Median: 26 (95% CI: 22 - 30) |
| **Positive family history of keratoconus (n, %)** | **12 (24%)** |
| **Concurrent pathologies** | history of allergy: n.4 (8%)<br>hypothyroidism: n.3 (6%)<br>diabetes mellitus: n.1 (2%)<br>systemic lupus erythematosus and ulcerative colitis: n.1 (2%) |

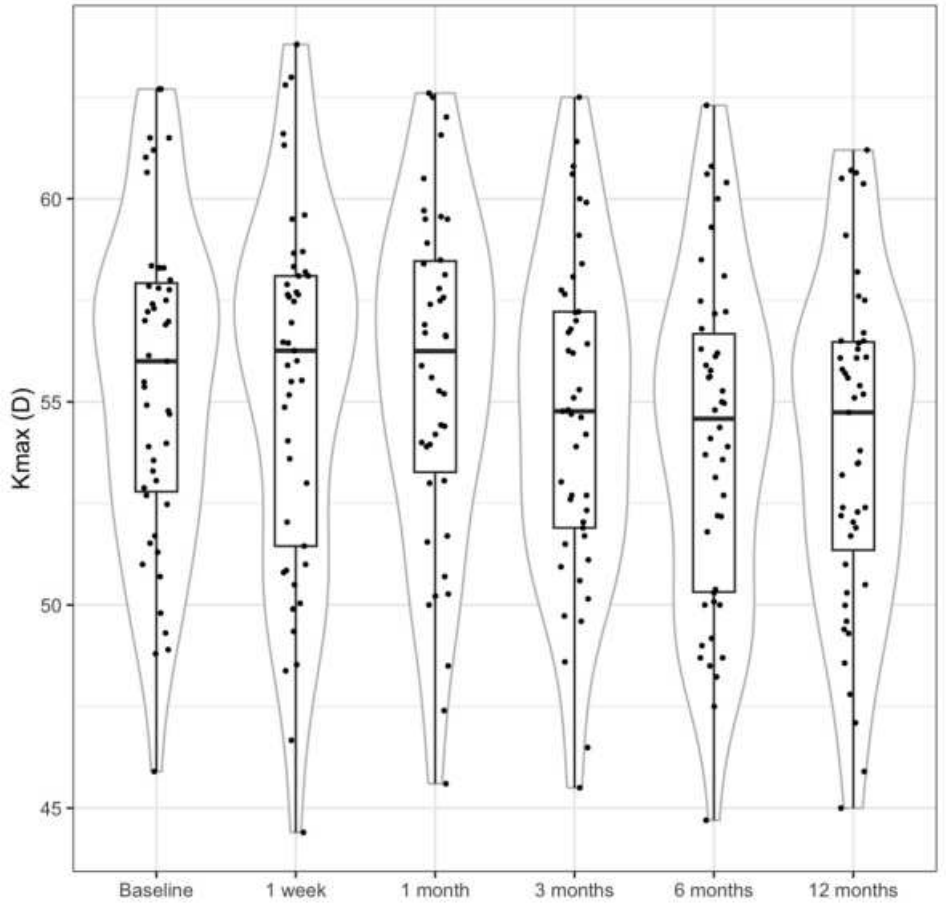
# PRIMARY OUTCOME

## CLINICAL TRIAL NCT05457647

***CUT-OFF VALUES OF THERANOSTIC SCORES WERE <u>NOT KNOWN BY OPERATORS</u>***
*Riboflavin score* >0.40 & *Theranostic score* ≥0.60

**The combined use of *riboflavin score*** and ***theranostic score*** **<u>predicted</u>** the **CXL effect** in **flattening $K_{max}$** at 1 year of follow-up, **regardless of treatment protocol** (**Epi-OFF** or **Epi-ON**) with:

- **<u>91% accuracy</u>**
- **<u>95% precision</u>**



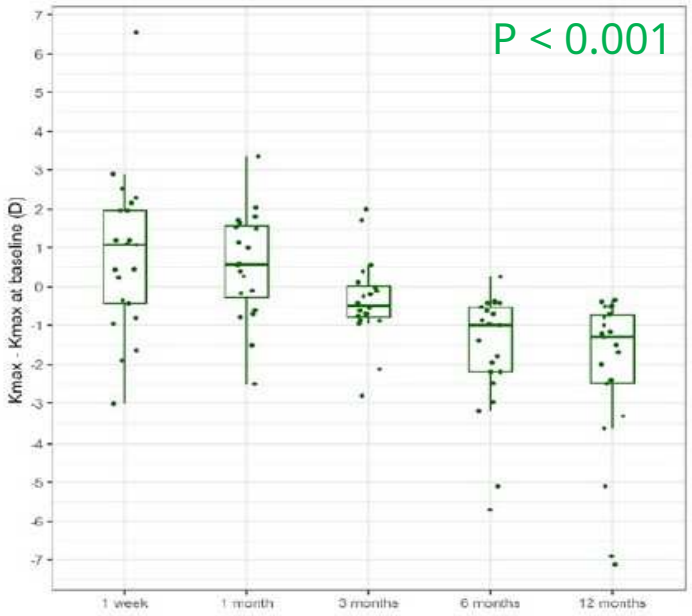
# STRATIFICATION

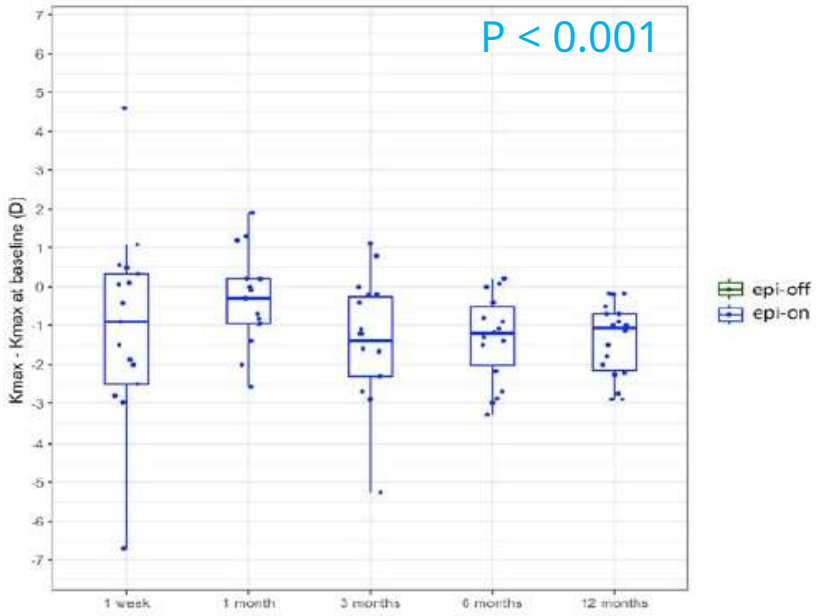
# CLINICAL TRIAL NCT05457647

## $K_{max}$ change in true positives of stratification groups (1 year)

**Thera-CXL epi-off**
$K_{max}$ -2.1 ± 1.9 D

**Thera-CXL epi-on**
$K_{max}$ -1.3 ± 0.9 D




**Vs**

State of the art CXL epi-off
$K_{max}$ -1.3 ± 1.4 D*

**Vs**

State of the art CXL epi-on
$K_{max}$ -0.3 ± 1.5 D*


* References

1. Sykasis E et al. Cochrane Database Syst Rev. 2015;2015(3):CD010621
2. Ng SM et al. Cochrane Database Syst Rev 2021;3(3):CD013512
3. Serrao S et al. Int Ophthalmol 2022; 42(1): 337-348
4. Chunyu T et al. Sci Report 2014; 4: 5652
5. Li J et al. Plos ONE 2015;10(5):e0127079.

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# Assessment of the Predictive Ability of Theranostics for Corneal Cross-linking in Treating Keratoconus

## *A Randomized Clinical Trial*

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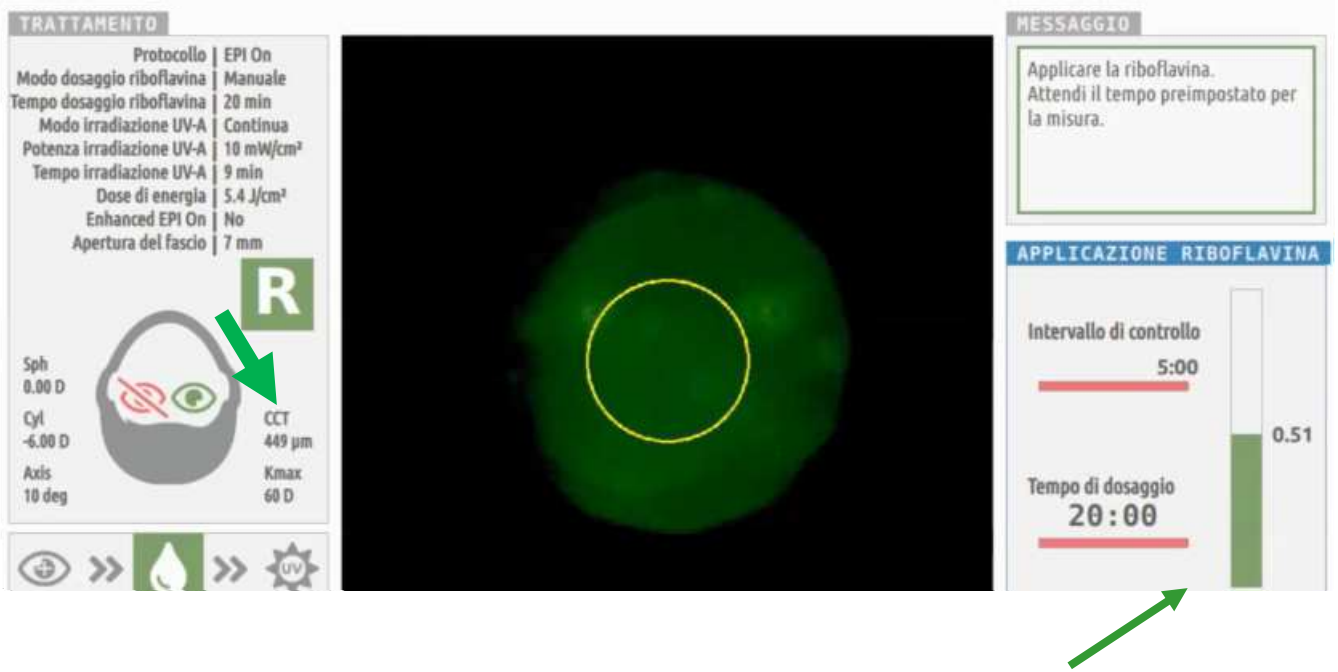
***Ophthalmology 2024; S0161-6420(24)00367-1d***

# OPERATIONAL PROCEDURE

# THERANOSTIC UV DEVICE

## Online monitoring of riboflavin

### ***Riboflavin application phase***

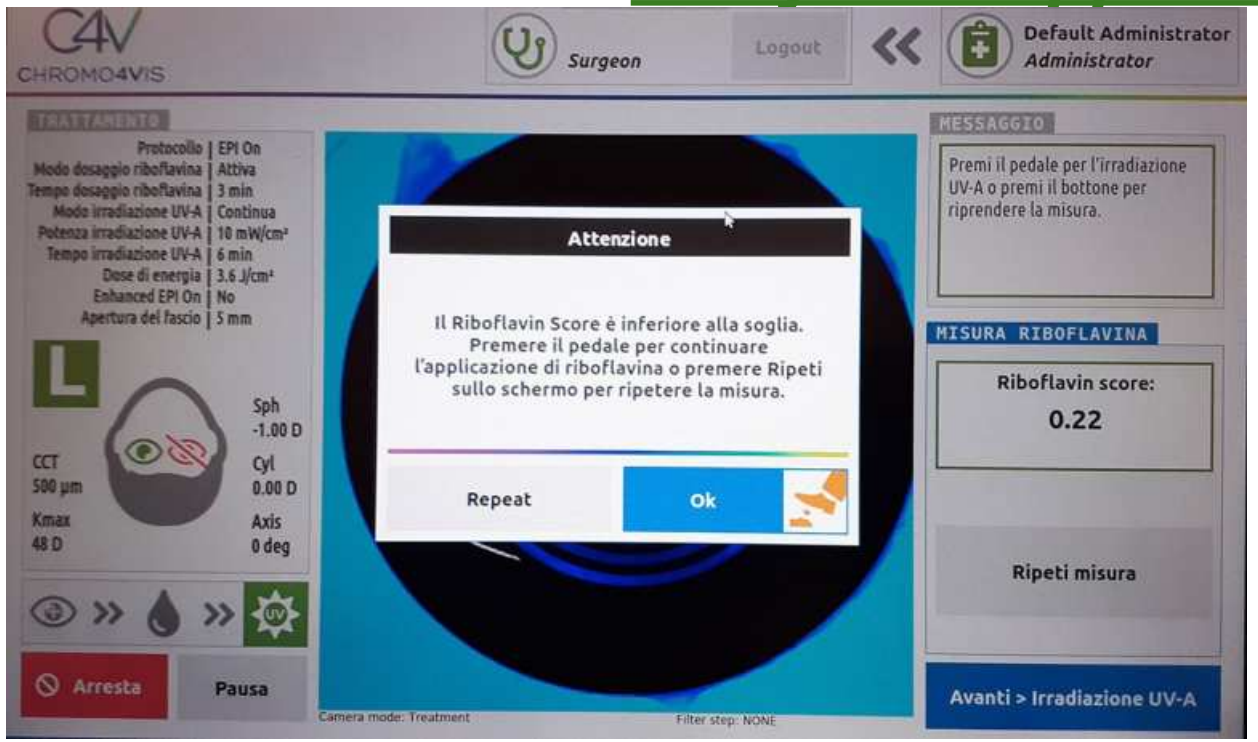



**Riboflavin Score**

*Theranostics makes use of* ***molecular imaging diagnostics*** *to assess* ***corneal riboflavin concentration***

# Online monitoring of riboflavin

## ***Riboflavin application phase***

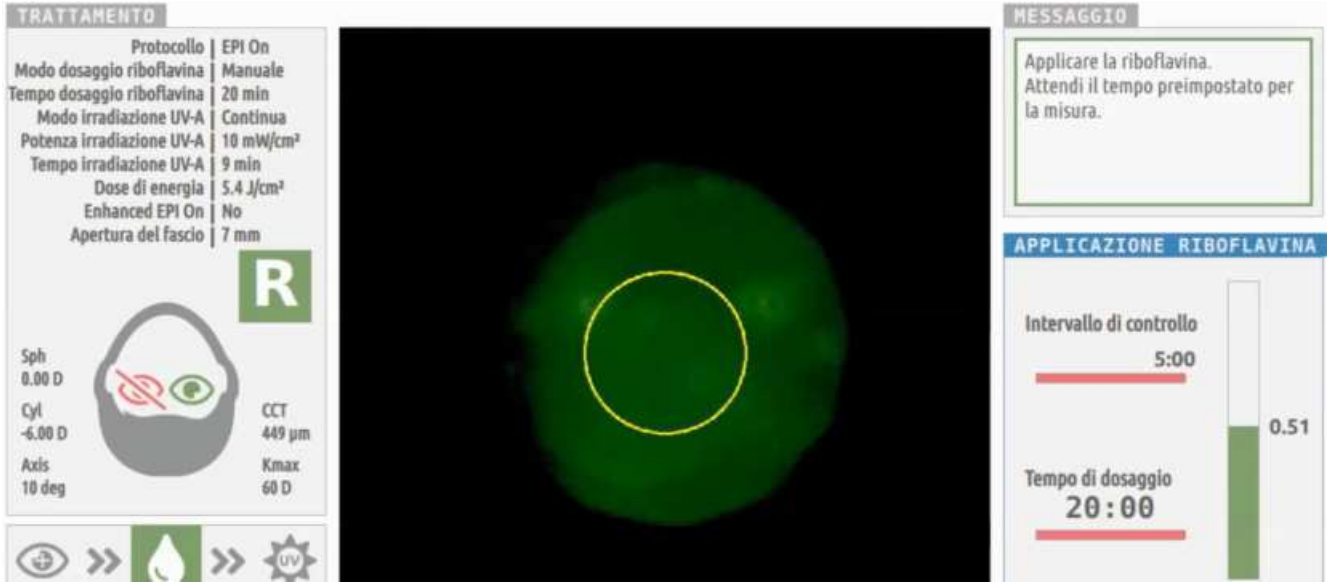



If the ***riboflavin score*** is below the pre-defined threshold of 0.40, the C4V CHROMO4VIS **DOES NOT allow** the operator to proceed to UV-A light irradiation of the cornea

# THERANOSTIC UV DEVICE

## Online monitoring of riboflavin

## ***Riboflavin application phase***





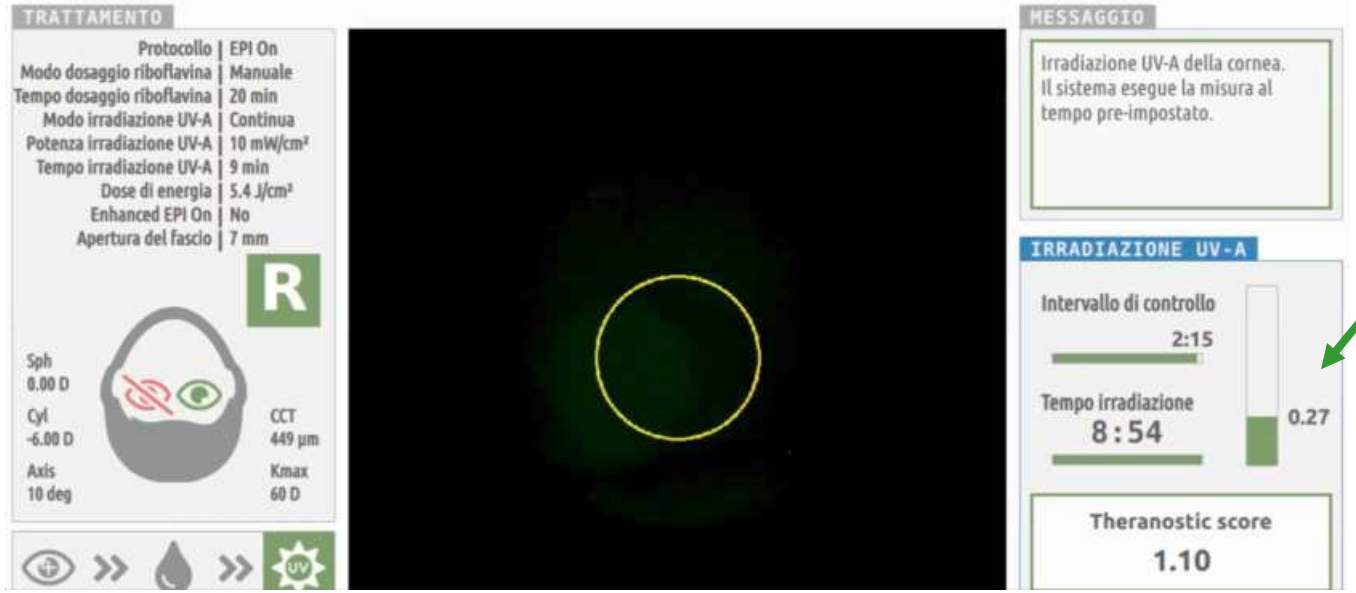
**Riboflavin Score >0.40**

As the ***riboflavin score*** reaches a pre-defined threshold, it **allows the operator to proceed** to UV-A light irradiation of the cornea

# THERANOSTIC UV DEVICE

**Online monitoring of treatment effect**

## ***UV-A light irradiation phase***

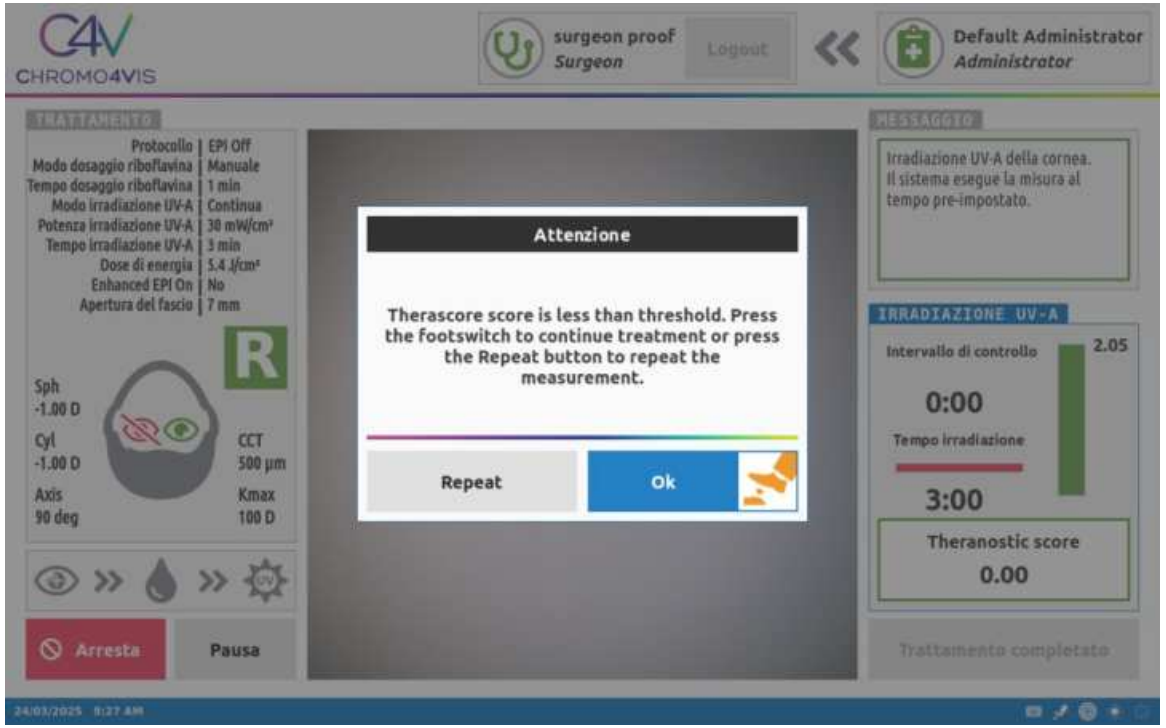



*Theranostics tailor the **exact therapeutic dose of riboflavin and UV-A light** energy to the cornea for predictive tissue strengthening and corneal flattening*

**Theranostic Score**

## Online monitoring of treatment effect

# ***UV-A light irradiation phase***



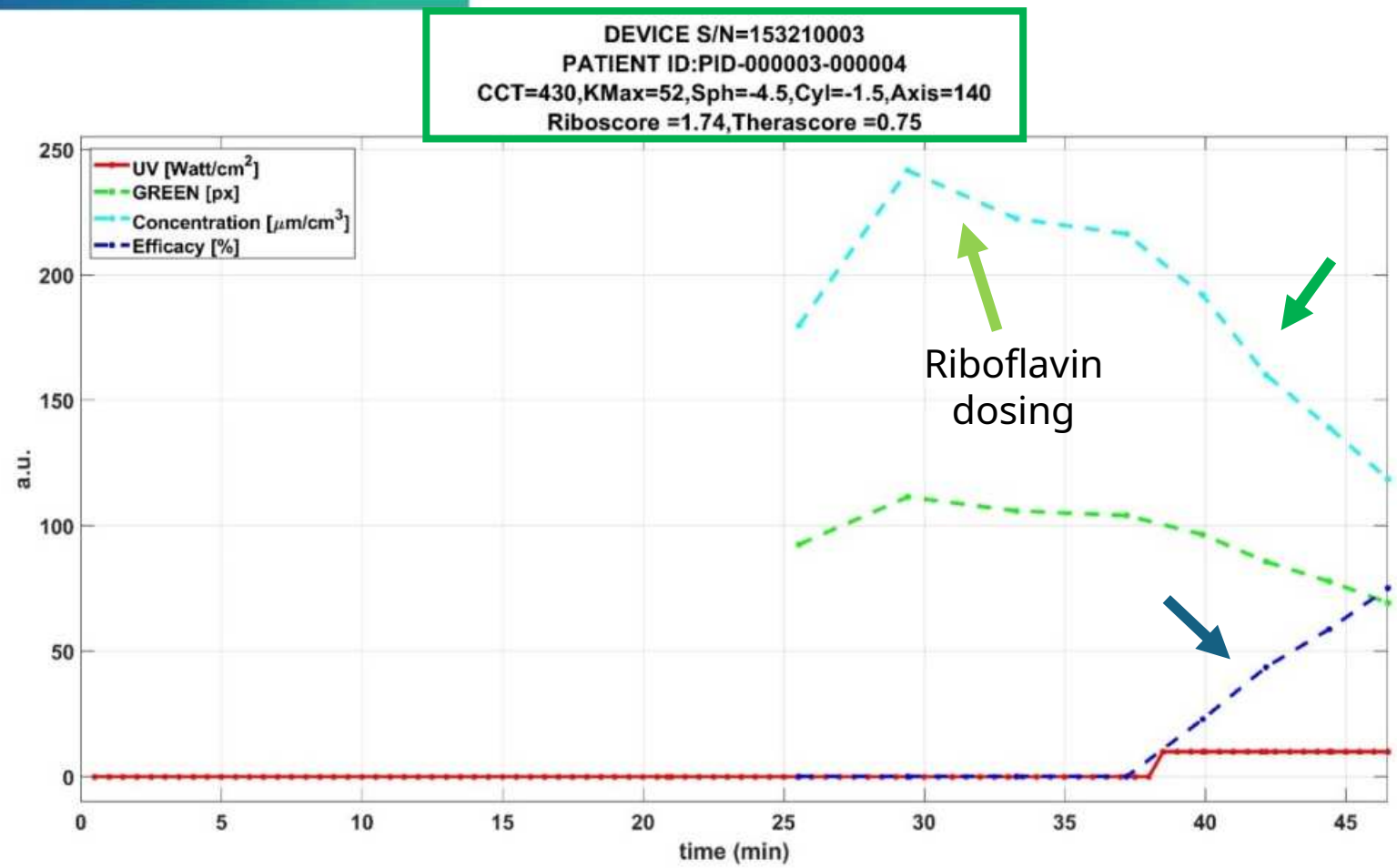

If the system detects a ***theranostic score*** <0.6 at the end of the pre-set UV-A irradiation time, it warns the operator to continue UV-A light irradiation.

**Theranostic Score <0.6**

# ARGO Study Case

## 18 years old patient

**EpiOFF CXL :** 15 min. **RitSight** dosing + 10 mW/cm² UV-A irradiation for 9 min.




*riboflavin score* = 1.74 & *theranostic score* = 0.75

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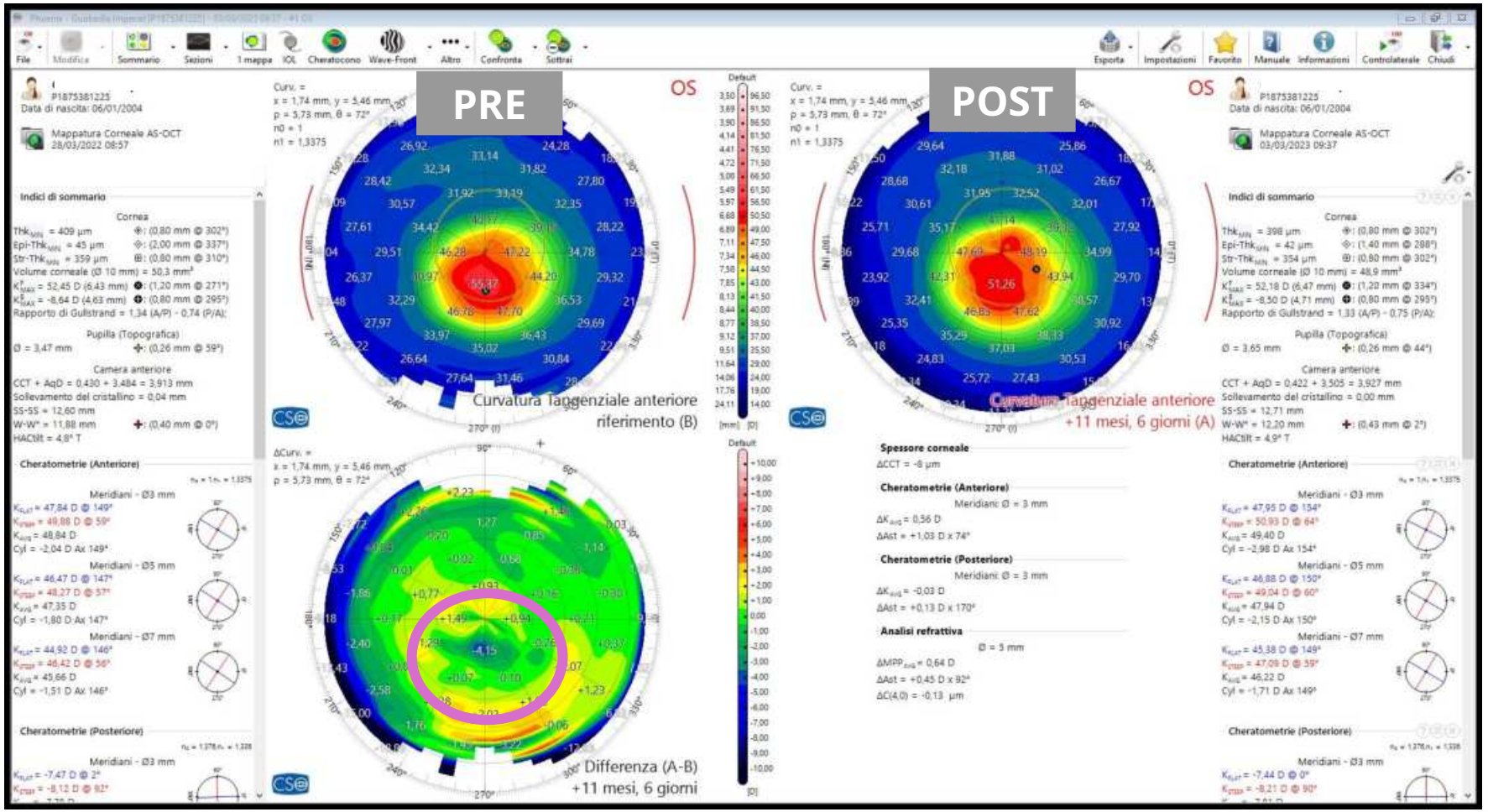
# EpiOFF study case

## 18 years old patient

**EpiOFF CXL :** 15 min. **RitSight** dosing + 10 mW/cm² UV-A irradiation for 9 min.




**$K_{max}$ at 1 year postop:**

**$K_{max}$ -4.1 D**

**Visual Acuity**

Pre-op: **20/25**

-4.50=-1.50@140

1-year post-op: **20/20**

-4.00=-3.50@170

*riboflavin score* = 1.74 & *theranostic score* = 0.75

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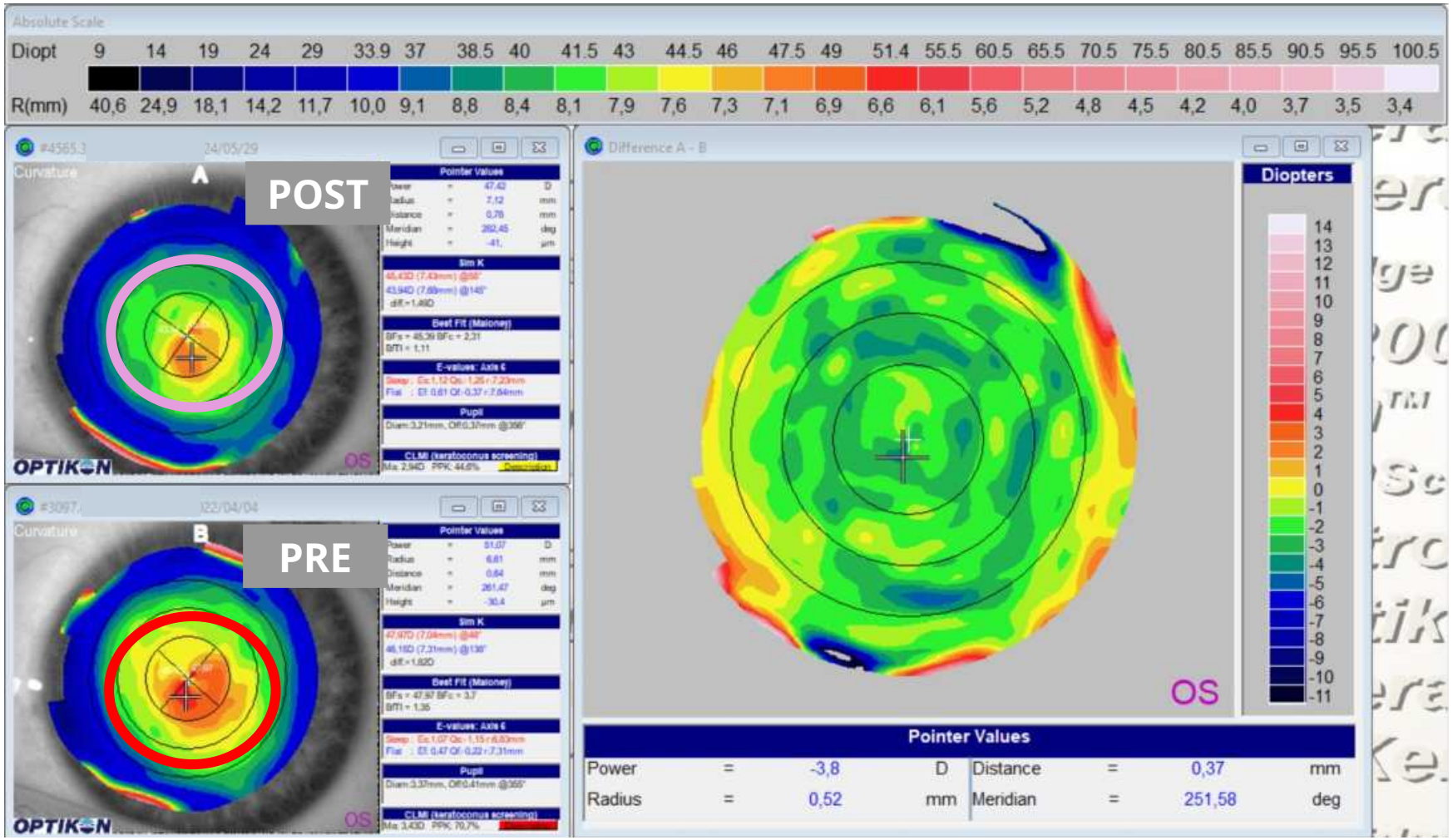
# EpiON study case

## 25 years old patient

**EpiON CXL :** 20 min. **RitSight** dosing + 10 mW/cm² UV-A irradiation for 9 min.




**$K_{max}$ at 2 years postop:**

**$K_{max}$ -3.8 D**

**Visual Acuity**

Pre-op: **16/20**

-0.75=-1.50@140

1-year post-op: **20/20**

-1.50@120

*riboflavin score* = 0.80 & *theranostic score* = 1.05

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# TAKE HOME MESSAGE

## CLINICAL TRIAL NCT05457647

***ARGO CLINICAL TRIAL QUESTION***

*Can we demonstrate definitely that CXL effectively halts progression of keratoconus?*

***ANSWER FROM ARGO CLINICAL TRIAL DATA OUTCOMES***

*Yes, **theranostics** now provides the opportunity to assess CXL treatment efficacy in real-time, **accurately predicting** its therapeutic benefit with **high accuracy** and **precision**.*

# TAKE HOME MESSAGE

## CLINICAL TRIAL NCT05457647

***ARGO CLINICAL TRIAL HYPOTHESIS***

*Is riboflavin concentration the primary factor influencing CXL treatment efficacy?*

***ANSWER FROM ARGO CLINICAL TRIAL DATA OUTCOMES***

*Yes, the key factor determining the CXL therapeutic efficacy is the* ***real-time monitoring of riboflavin concentration*** *within the cornea prior to UV-A light photo-therapy and its efficient* ***UV-A light mediated photo-activation****.*

# THANKS FOR YOUR ATTENTION

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