

# Glaucoma – New Treatments

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# Financial disclosure

- Santen (Speaker honoraria, Consultant)
- Abbvie (Speaker honoraria, Consultant)
- Thea Pharma (Speaker honoraria)

# Glaucoma treatment options

- **IOP lowering**
  - Eye drops
  - Laser
  - Surgery
- **Neuroprotection**
  - Citicoline
  - Nicotinamide

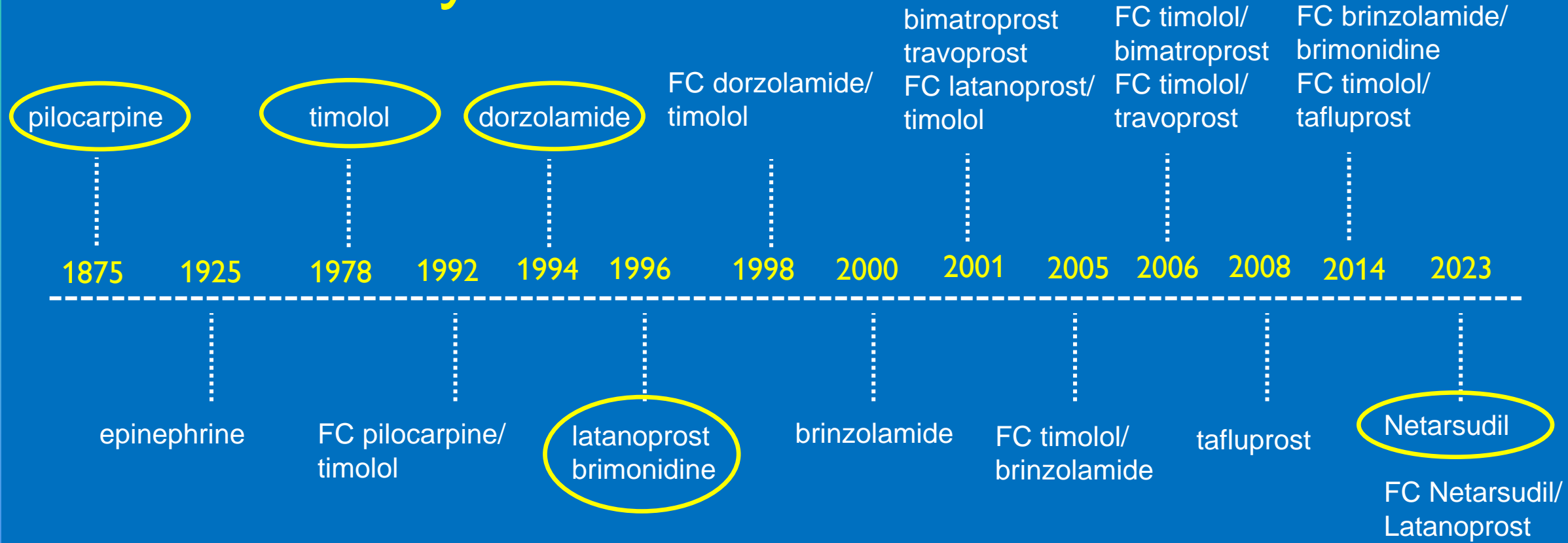
# Glaucoma treatment options

- **IOP lowering**

- Eye drops

- New drug – Rho-kinase (ROCK) inhibitor
- Sustained release drug delivery systems

# Glaucoma Treatment – IOP lowering over the last 150 years



FC = fixed combination



# Glaucoma treatment options

- IOP lowering
  - Eye drops

- New drug – Rho-kinase (ROCK) inhibitor
- Sustained release drug delivery systems

# Netarsudil

Netarsudil (Rhokinsa<sup>®</sup>) – no reimbursement in Sweden

FC Netarsudil / Latanoprost (Roclanda<sup>®</sup>)

-> IOP lowering due to Rho-kinase inhibition



# ROCK-inhibitor and the trabecular meshwork (TM)

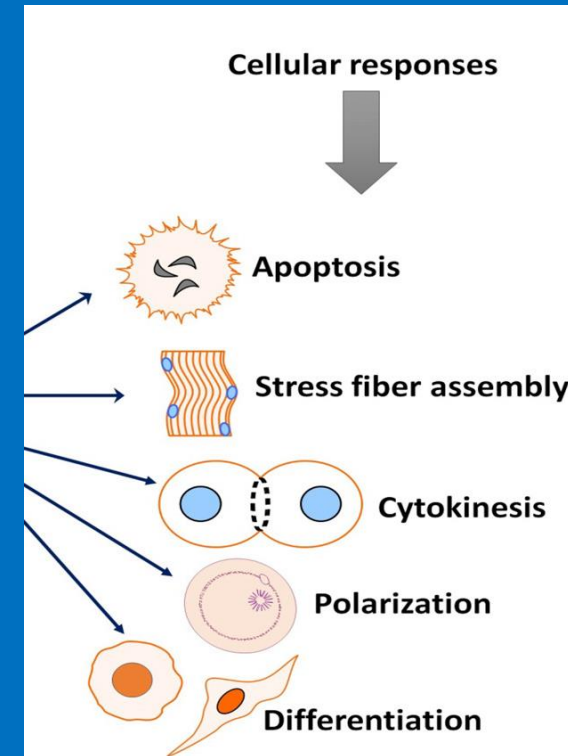
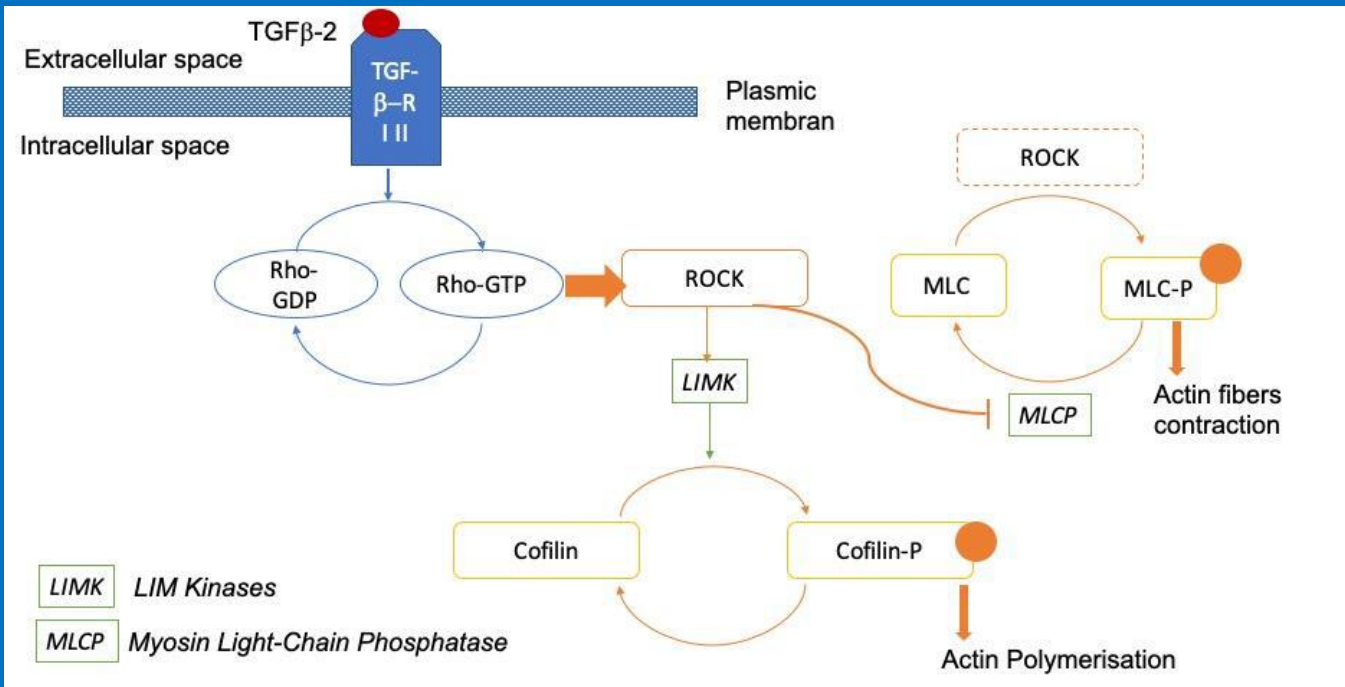


Bild vänster ur: Buffault, J.; Brignole-Baudouin, F.; Reboussin, É.; Kessal, K.; Labbé, A.; Mélik, Parsadaniantz, S.; Baudouin, C. The Dual Effect of Rho-Kinase Inhibition on Trabecular Meshwork Cells Cytoskeleton and Extracellular Matrix in an In Vitro Model of Glaucoma. *J. Clin. Med.* 2022, 11, 1001. License: Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>)

Bild höger modifierat ur: Saadeldin IM, Tukur HA, Aljumaah RS and Sindi RA (2021) Rocking the Boat: The Decisive Roles of Rho Kinases During Oocyte, Blastocyst, and Stem Cell Development. *Front. Cell Dev. Biol.* 8:616762.



# ROCK-inhibitor and the trabecular meshwork (TM)

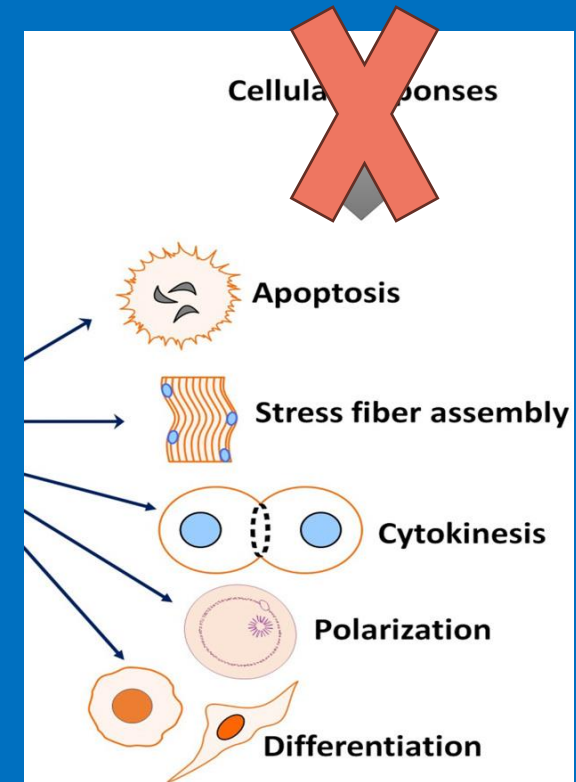
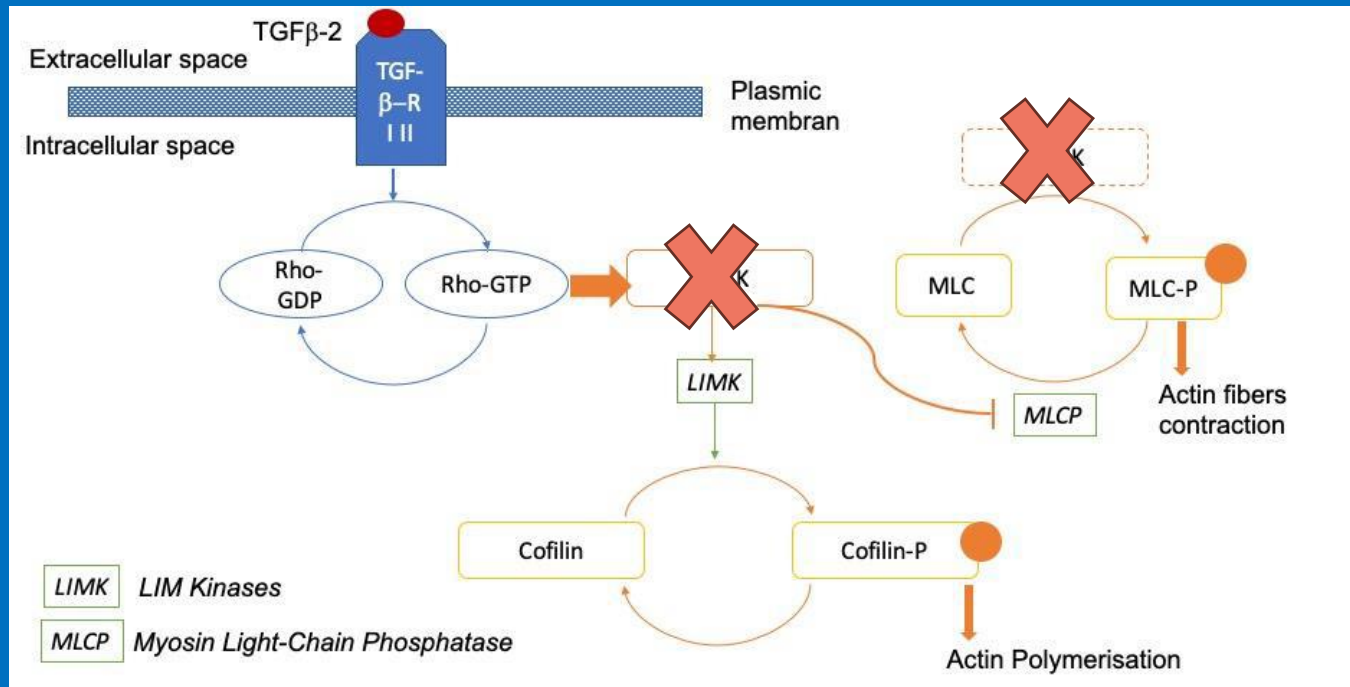
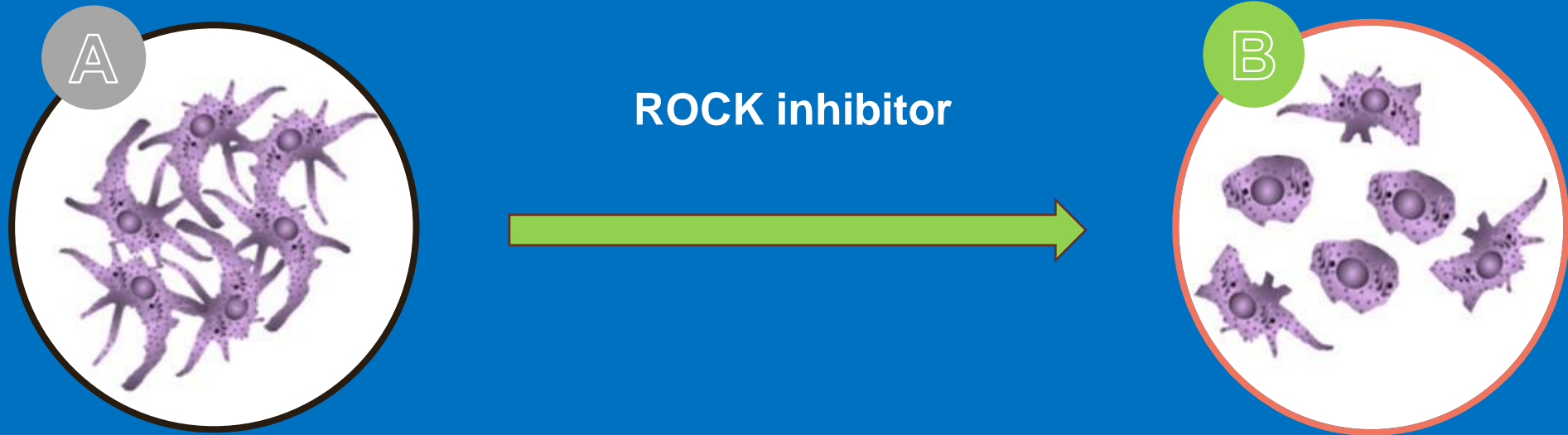


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# ROCK-inhibitor and the TM



# Netarsudil

**Randomized, double-masked multicenter study comparing netarsudil with timolol**

- NET non-inferior to TIM over 3 months follow-up

## Treatment related adverse events:

- Conjunctival hyperemia (NET 16% vs TIM 3.1%) mostly mild to moderate in both treatment arms
- Cornea verticillata (NET 24.5% vs TIM 0%)
- Eye pruritus (NET 7.8% vs BIM 0.9%)

Clinical Trial > Am J Ophthalmol. 2019 Aug;204:97-104. doi: 10.1016/j.ajo.2019.03.002.

Epub 2019 Mar 9.

## **Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study**

Albert S Khouri <sup>1</sup>, Janet B Serle <sup>2</sup>, Jason Bacharach <sup>3</sup>, Dale W Usner <sup>4</sup>, Richard A Lewis <sup>5</sup>, Puiwah Braswell <sup>6</sup>, Casey C Kopczynski <sup>6</sup>, Theresa Heah <sup>6</sup>; Rocket-4 Study Group



# FC Netarsudil/latanoprost

Randomized, double-masked multicenter study comparing FC netarsudil/latanoprost with FC bimatoprost/timolol

Randomized Controlled Trial > Graefes Arch Clin Exp Ophthalmol. 2024 Jan;262(1):179-190.  
doi: 10.1007/s00417-023-06192-0. Epub 2023 Aug 24.

## MERCURY-3: a randomized comparison of netarsudil/latanoprost and bimatoprost/timolol in open-angle glaucoma and ocular hypertension

Ingeborg Stalmans<sup>1,2</sup>, Kin Sheng Lim<sup>3</sup>, Francesco Oddone<sup>4</sup>, Marek Fichtl<sup>5,6</sup>, Jose I Belda<sup>7,8</sup>, Anton Hommer<sup>9</sup>, Guna Laganovska<sup>10</sup>, Cédric Schweitzer<sup>11,12</sup>, Bogomil Voykov<sup>13</sup>, Tomasz Zarnowski<sup>14</sup>, Gábor Holló<sup>15,16</sup>

- NET/LAT non-inferior to BIM/TIM over 3 months follow-up

### Treatment related adverse events:

- Conjunctival hyperemia (NET/LAT 30.7% vs BIM/TIM 9%) mostly mild to moderate in both treatment arms
- Cornea verticillata (NET/LAT 11% vs BIM/TIM 0%)
- Eye pruritus (NET/LAT 7.8% vs BIM/TIM 0.9%)

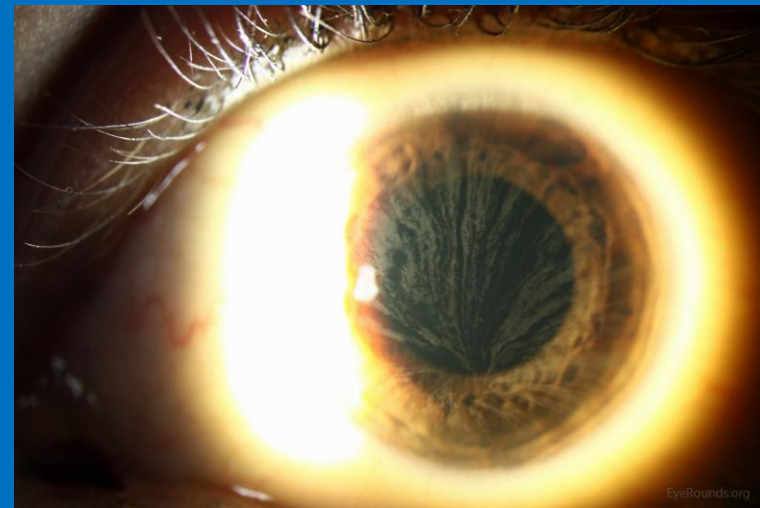
# Netarsudil & FC Netarsudil/latanoprost

## Pros:

- FC without timolol
- additional IOP lowering mechanism

## Cons:

- higher rate of discontinuation with therapy due to side effects
- Cornea verticillata

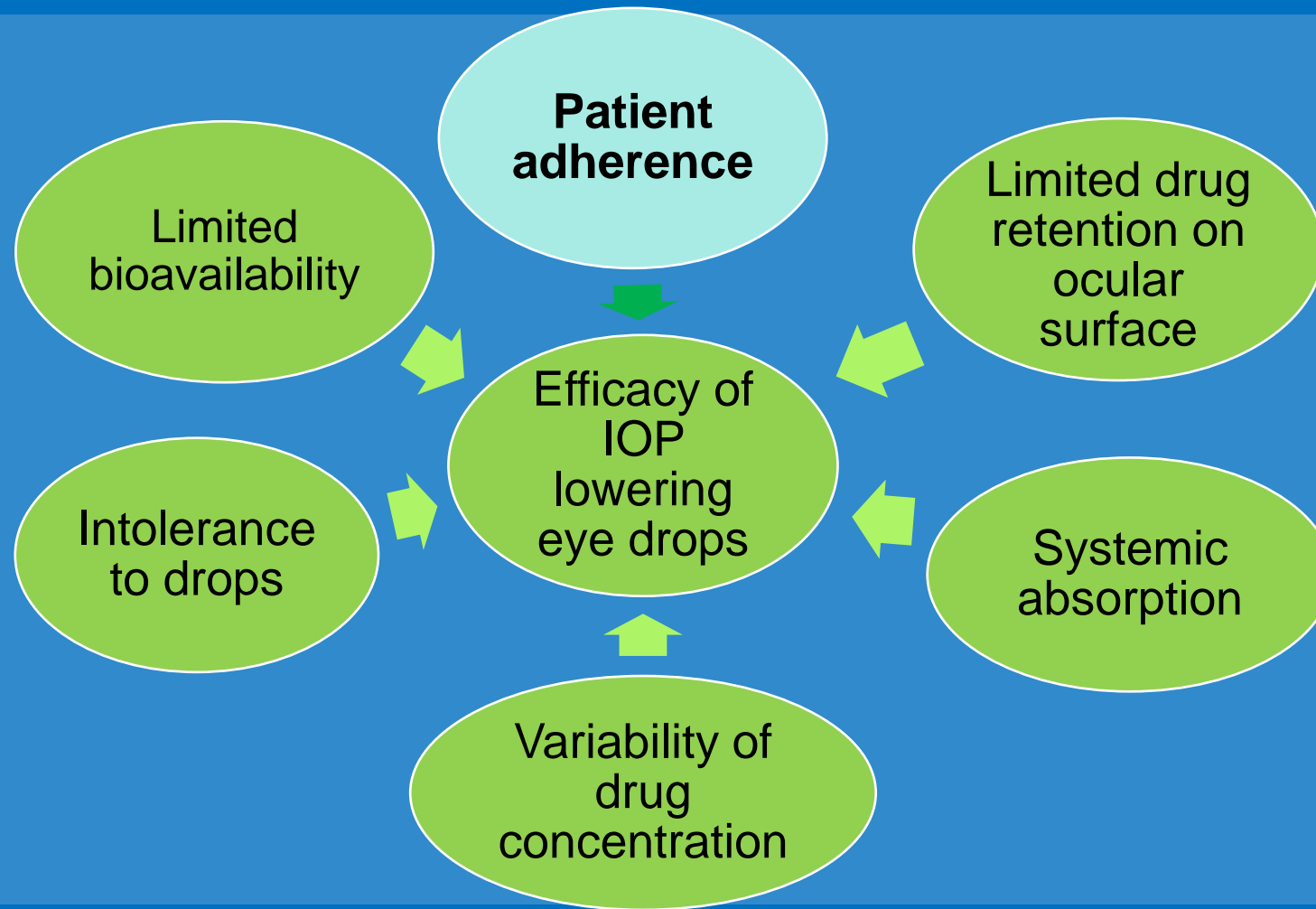


Photography by Brice Critser. Ophthalmic Atlas Images by [EyeRounds.org](https://www.eyeforall.org/), [The University of Iowa](https://www.uniowa.edu/) are licensed under a [Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License](https://creativecommons.org/licenses/by-nc-nd/3.0/).

# Glaucoma treatment options

- IOP lowering
  - Eye drops
    - New drug – Rho-kinasinhibitor
    - Sustained release drug delivery systems

# Sustained release drug delivery systems – Why?



# Sustained release drug delivery systems

- non-degradable devices
- degradable devices



# Degradable device –

## Durysta™ – Bimatoprost SR (AbbVie Inc. North Chicago, Illinois, U.S.A.)

**Design:** intracameral pellet implant within a biodegradable NOVADUR solid copolymer PLGA matrix platform

- Administered into the anterior chamber with an injector

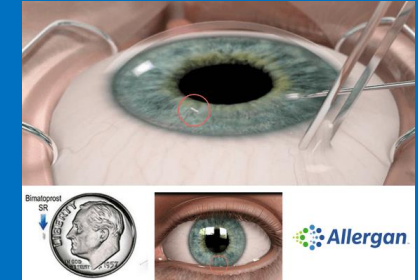
Targeted duration: 6 months\*



\* FDA: 30% IOP reduction over 12- weeks + non-inferior to Timolol

# Degradable device –

## Durysta™ – Bimatoprost SR (AbbVie Inc. North Chicago, Illinois, U.S.A.)



### Pros

- IOP lowering effect over months
- biodegradable
- low levels in off-target extraocular tissue (-> lower risk for orbital fat atrophy)

### Cons

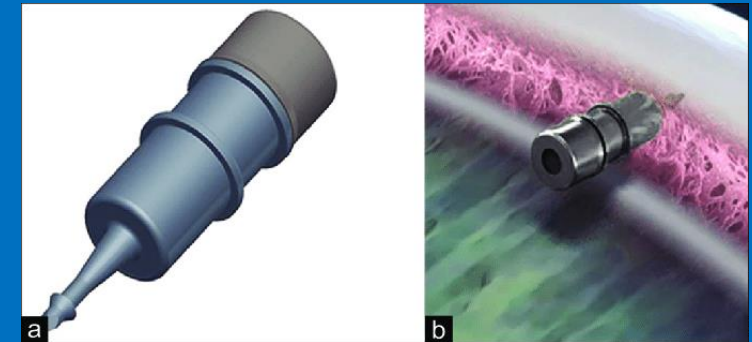
- Invasive
- Risk for endophthalmitis
- Risk of migration
- Conjunctival hyperaemia
- Risk of corneal endothelial cell loss
- Approved for single usage in each patient

# Non-degradable device – iDose<sup>®</sup> TR Travoprost intracameral implant (Glaukos, San Clemente, CA, USA)

**Design:** Titanium implant filled with a travoprost solution covered with a membran

- Intracameral delivery system
- Placed through a small corneal incision
- Anchored to the trabecular meshwork

Targeted duration: 6-12 months\*

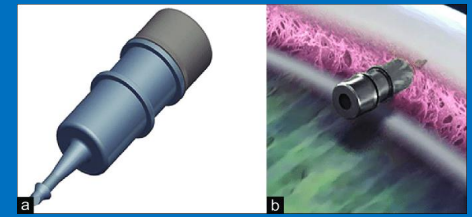


\* FDA: non-inferior to Timolol over first 3 months! 81% without eye drops after 12 months.

# Non-degradable device –

## iDose<sup>®</sup> TR Travoprost intracameral implant

(Glaukos, San Clemente, CA, USA)



### Pros

- IOP lowering effect over months
- no clinically significant corneal endothelial cell loss (36-month Phase 2 data)
- No hyperemia

### Cons

- Invasive
- Side effects
  - increased pigmentation of the iris / iritis
  - dry eye
  - increase in IOP
- Risk for endophthalmitis
- Risk of migration/ device dislocation
- Non-degradable – must be surgically removed when depleted



# Glaucoma treatment options

- **IOP lowering**
  - Eye drops
  - Laser
  - Surgery
  
- **Neuroprotection**
  - Citicoline
  - Nicotinamide

# Neuroprotection

- Citicoline
- Nicotinamide



# Citicoline

Randomized Controlled Trial > J Glaucoma. 2020 Jul;29(7):513-520.

doi: 10.1097/IJG.0000000000001565.

## Can Treatment With Citicoline Eyedrops Reduce Progression in Glaucoma? The Results of a Randomized Placebo-controlled Clinical Trial

Luca Rossetti <sup>1</sup>, Michele Iester <sup>2 3</sup>, Laura Tranchina <sup>1</sup>, Laura Ottobelli <sup>1</sup>, Giulia Coco <sup>4</sup>, Elisabetta Calcatelli <sup>4</sup>, Chiara Ancona <sup>2 3</sup>, Paola Cirafici <sup>2 3</sup>, Gianluca Manni <sup>4 5</sup>

## Randomized double-masked placebo-controlled trial

- Citicoline eye drops
- follow-up: 3 years
- indication of less visual field progression when treated with Citicoline

Randomized Controlled Trial

> Graefes Arch Clin Exp Ophthalmol. 2023 Jun;261(6):1659-1668.

doi: 10.1007/s00417-022-05947-5. Epub 2023 Jan 14.

## The effect of citicoline oral solution on quality of life in patients with glaucoma: the results of an international, multicenter, randomized, placebo-controlled cross-over trial

Luca Rossetti <sup>1</sup>, Francisco Goni <sup>2</sup>, Giovanni Montesano <sup>3</sup>, Ingeborg Stalmans <sup>4</sup>, Fotis Topouzis <sup>5</sup>, Dario Romano <sup>6</sup>, Eleonora Galantin <sup>6</sup>, Noemi Delgado-Gonzales <sup>2</sup>, Sara Giammaria <sup>7</sup>, Giulia Coco <sup>8</sup>, Evelien Vandewalle <sup>4</sup>, Sophie Lemmens <sup>4</sup>, Dimitrios Giannoulis <sup>5</sup>, Theofanis Pappas <sup>5</sup>, Gianluca Manni <sup>8</sup>

## Randomized double-masked placebo-controlled cross-over study

- Citicoline oral solution
- follow-up: 9 months
- slight indication of improved Quality of life when treated with Citicoline

# Citicoline

BUT...

> PLoS One. 2023 Sep 28;18(9):e0291836. doi: 10.1371/journal.pone.0291836. eCollection 2023.

## Efficacy of citicoline as a supplement in glaucoma patients: A systematic review

Julia Prinz <sup>1 2</sup>, Verena Prokosch <sup>2</sup>, Hanhan Liu <sup>2</sup>, Peter Walter <sup>1</sup>, Matthias Fuest <sup>1</sup>,  
Filippo Migliorini <sup>3 4</sup>

## Systematic review

- 5 RCT + 5 retrospective studies
- differences in follow-up, IOP-lowering treatment, citicoline therapy regim

## Conclusion:

Lack of evidence that citicoline had any significant impact on:

- IOP reduction
- Visual field preservation
- Retinal function
- RGC preservation



# Nicotinamide (NAM)

> Invest Ophthalmol Vis Sci. 2019 Jun 3;60(7):2509-2514. doi: 10.1167/iovs.19-27099.

## Nicotinamide Deficiency in Primary Open-Angle Glaucoma

Judith Kouassi Nzoughet<sup>1</sup>, Juan Manuel Chao de la Barca<sup>1 2</sup>, Khadidja Guehlouz<sup>3</sup>, Stéphanie Leruez<sup>3</sup>, Laurent Coulbault<sup>4</sup>, Stéphane Allouche<sup>4</sup>, Cinzia Bocca<sup>1</sup>, Jeanne Muller<sup>3</sup>, Patrizia Amati-Bonneau<sup>1 2</sup>, Philippe Gohier<sup>3</sup>, Dominique Bonneau<sup>1 2</sup>, Gilles Simard<sup>2</sup>, Dan Milea<sup>5</sup>, Guy Lenaers<sup>1</sup>, Vincent Procaccio<sup>1 2</sup>, Pascal Reynier<sup>1 2</sup>

## Cohort study

- 34 POAG and 30 control patients
- lower plasmatic NAM levels in POAG compared to controls

Randomized Controlled Trial > Clin Exp Ophthalmol. 2020 Sep;48(7):903-914.

doi: 10.1111/ceo.13818. Epub 2020 Jul 28.

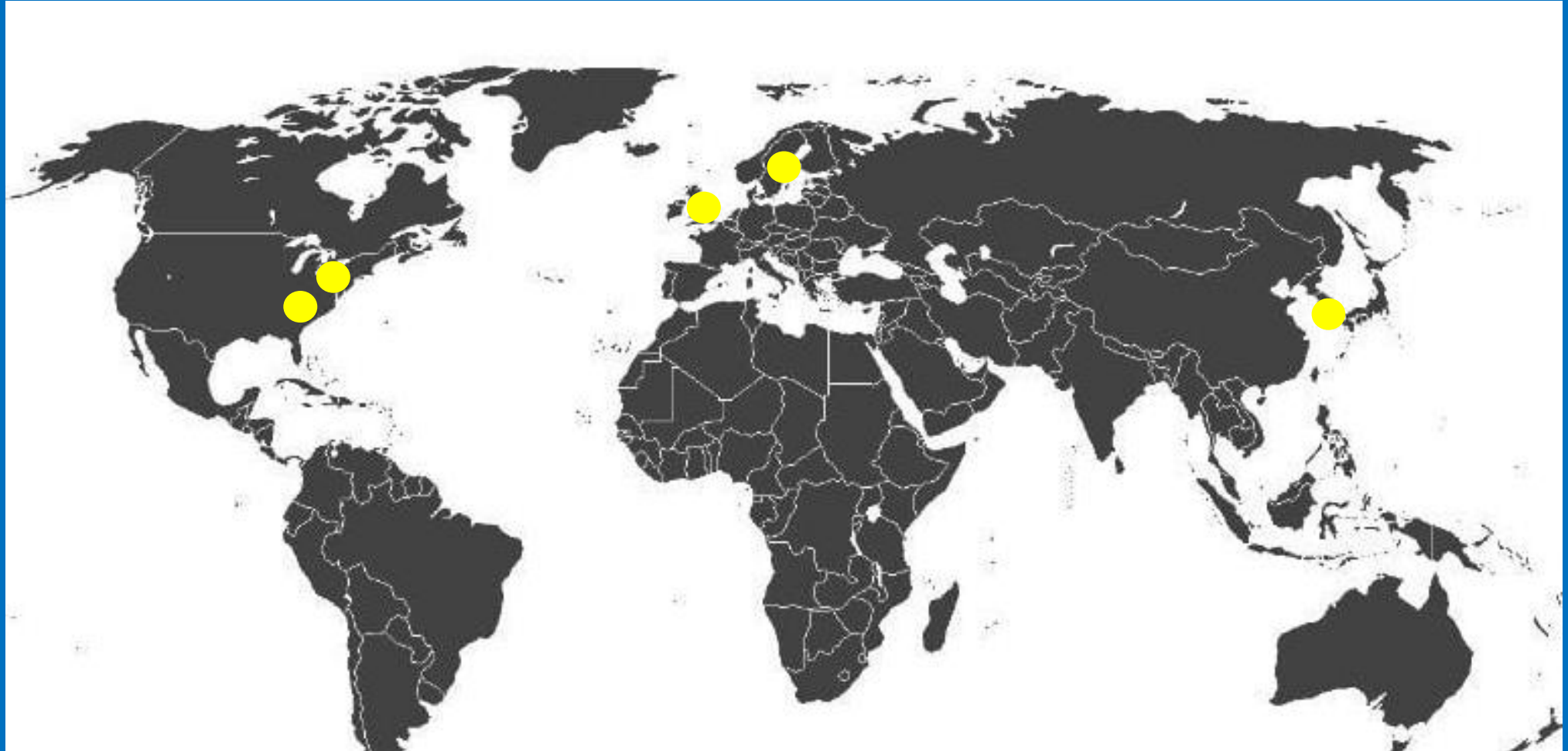
## Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: A crossover randomized clinical trial

Flora Hui<sup>1</sup>, Jessica Tang<sup>1 2</sup>, Pete A Williams<sup>3</sup>, Myra B McGuinness<sup>1</sup>, Xavier Hadoux<sup>1</sup>, Robert J Casson<sup>4</sup>, Michael Coote<sup>1 2</sup>, Ian A Trounce<sup>1 2</sup>, Keith R Martin<sup>1 2 5</sup>, Peter van Wijngaarden<sup>1 2</sup>, Jonathan G Crowston<sup>1 2 6 7</sup>

## Cross-over double-masked randomized clinical trial:

- follow up: 3 months
- NAM additional to IOP-lowering treatment
- Improvement in RGC function (ERG)

# Nicotinamide (NAM) – Ongoing research



Picture from skolbilder.com

# Take home messages

- very few new IOP lowering eye drugs during the last 25 years
- sustained release drug delivery systems
  - non-degradable devices
    - travoprost filled TM implant
  - degradable devices
    - intracameral pellet implant (Bimatoprost)
- Neuroprotection – a possible new/ additional treatment for glaucoma



**THANK YOU!**



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