Summary of Experimental Animal and Human Clinical Studies on Diabetic Keratopathy

Corneal epithelium

- Wound healing
- Re-epithelialization
- Corneal opacification
- Corneal sensitivity

Corneal endothelium

- Changes in size and shape
- Maintain corneal hydration

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PRESERVING VISION AND HEARING FOR YOU AND YOUR PETS

Progression of Diabetic Keratopathy

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Diabetic Keratopathy

Hyperglycemia

⇑ A R

⇑ Sorbitol Accumulation

Metabolic Disturbance

Neuropathy → **Decreased Sensitivity**

⇓ Cell turnover → **Epithelial Cell Morphology** → **Defect**

⇑ Cell loss → **Endothelial Cell Morphology** → **Edema**

Advanced

STRESS

Summary of animal studies

Diabetic and Galactosemic Rats

- Observe Delayed Wound Healing Following Limbus to Limbus Scraping of Corneal Epithelium
- Restoration of Corneal Sensitivity

Galactose-fed Dogs

- Specular microscopic studies indicate that the hexagonal shaped corneal endothelial cells change in the size (polymegathism) and shape (pleomorphism) indicative of some endothelial cell death in diabetes and galactosemia -- these changes are reduced by ARIs
- Intervention studies suggest that amelioration of endothelial cell changes requires ARI therapy prior to the advent of endothelial morphologic changes because endothelial cells do not reproduce

Aldose Reductase Inhibitors Prevent Delay in Corneal Wound Healing and Cloudy Appearance Galactosemic Rats

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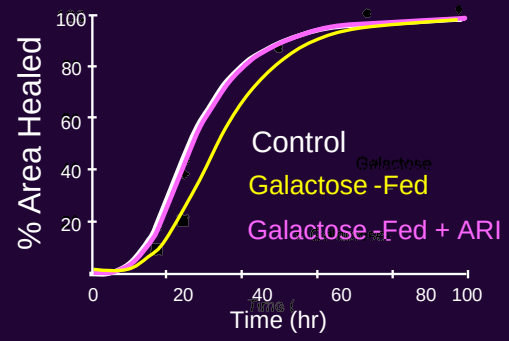
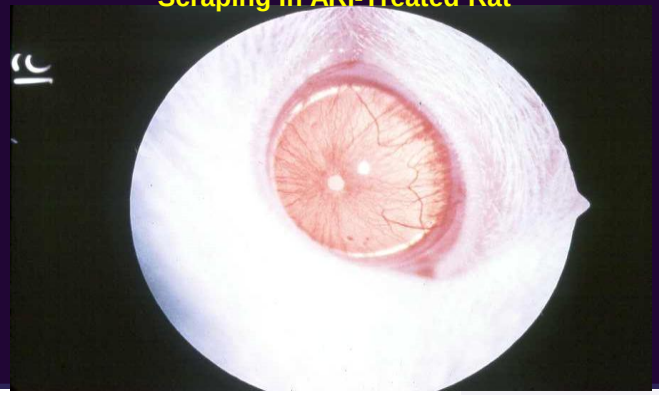
Healed Cornea After Limbus to Limbus Scraping In Normal Control Rat

Healed Cornea After Limbus to Limbus Scraping In Galactosemic Rat

Rate pf Re-epithelialization in Control and Galactosemic Rats ± ARI



Healed Cornea After Limbus to Limbus Scraping In ARI-Treated Rat



ARIs Increase Corneal Sensitivity (Neuropathy) in 50% Galactose-Fed Rats

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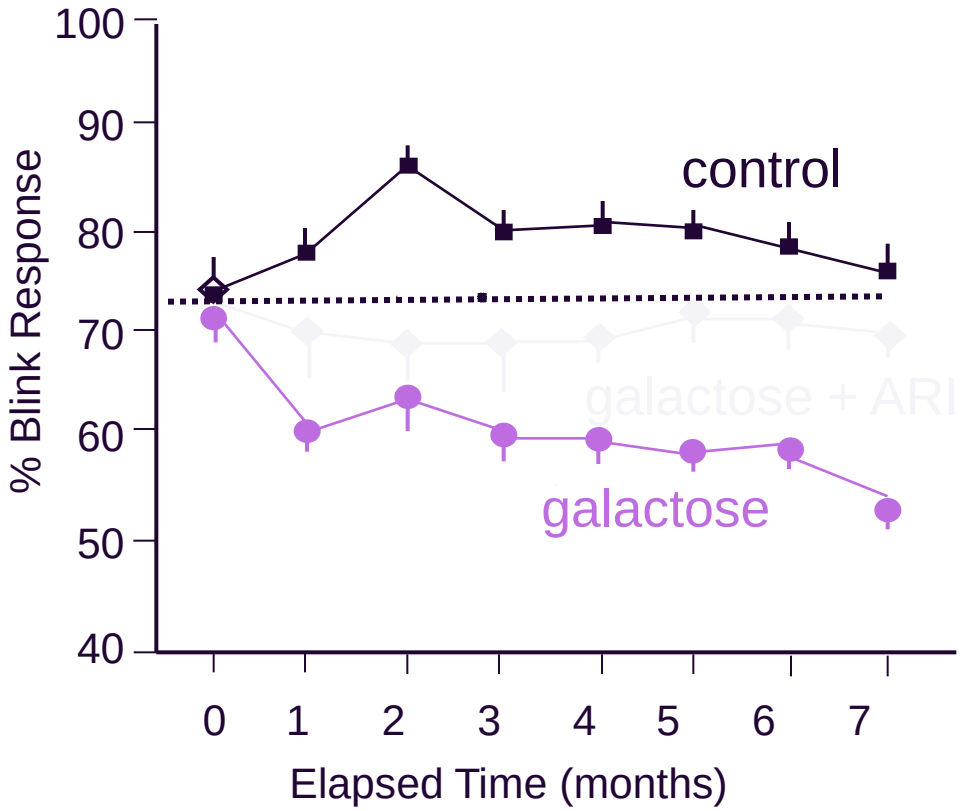
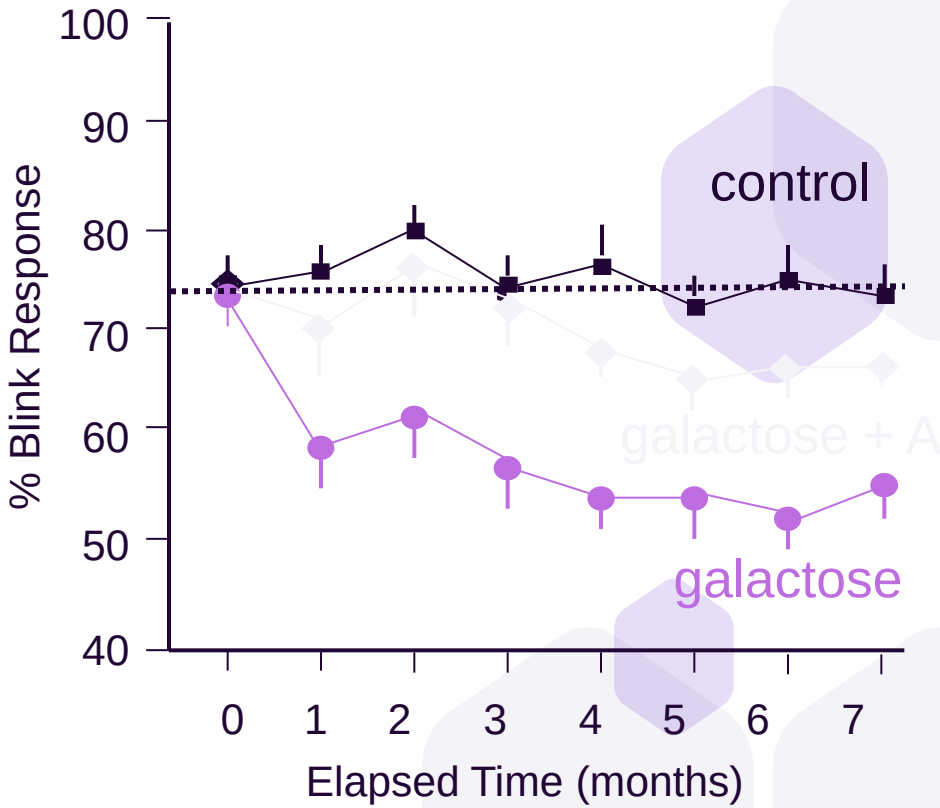
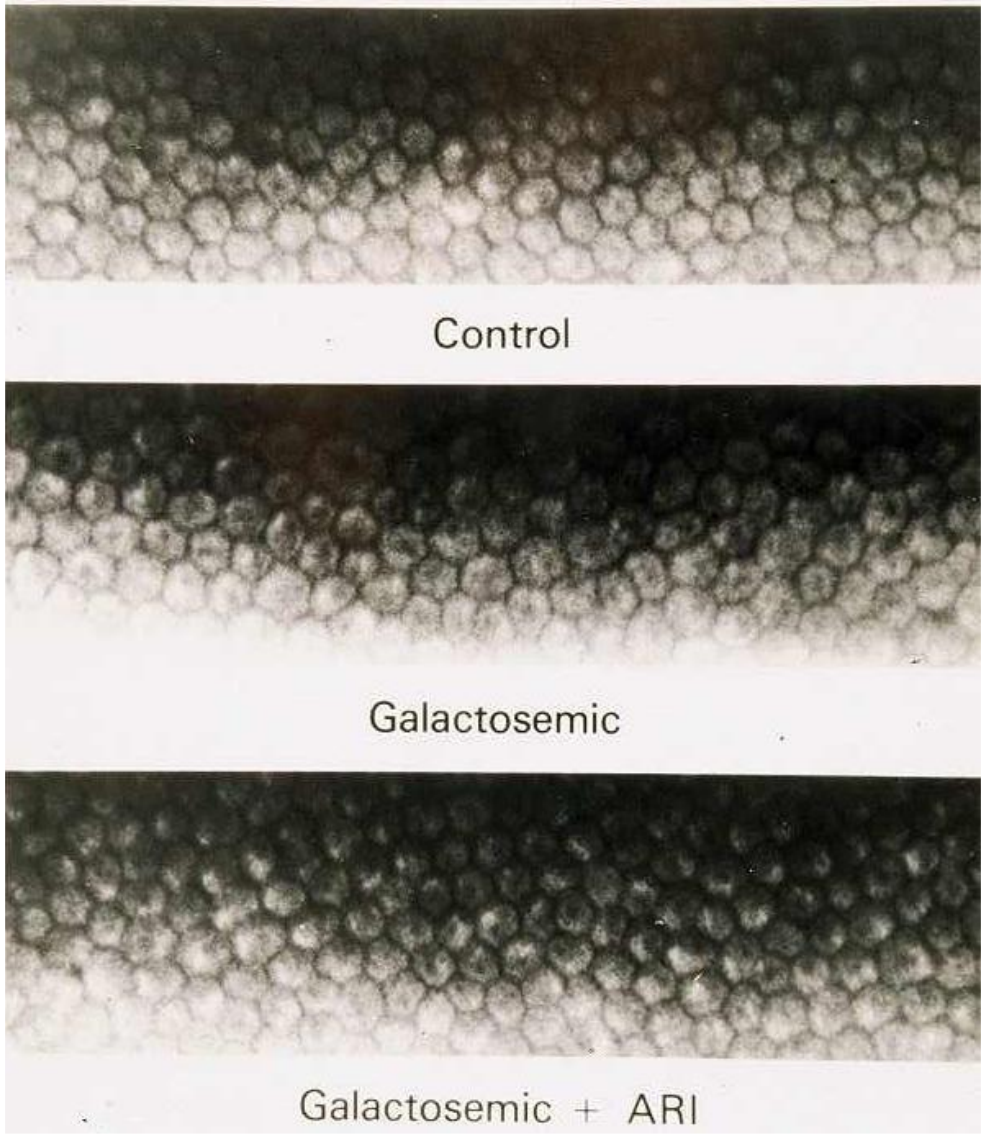
Topical 0.25% CT-112



Oral Diet 10 mg/kg AL1576



Corneal Endothelial Cells in Galactose-Fed Dogs Include Changes in Size, Shape, and % Hexagonality



Quantitative Effect of ARI Administration on Corneal Endothelial Cell Features in Galactose-Fed Dogs

	Cell Density (cells/mm^2)	Mean Cell Area (μm^2)	Area CV	% Hexagonality
Control n =13	2635 ± 129*	385 ± 22*	0.19 ± 0.02	73 ± 7
Galactose-Fed n = 12	2429 ± 141*	413 ± 141*	0.21 ± 0.03	72 ± 7
Galactose-Fed + Sorbinil n =13	2526 ± 135	392 ± 20	0.20 ± 0.02	72 ± 7

Mean ± SD 1 eye of each dog studied * $p < 0.01$

Intervention Studies

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Endothelial cell analyses in dogs after 38 months of experimental diets wher dogs were fed:

- Normal Control Diet for 38 months
- Galactose diet continuously for 38 months
- Intervention 1* Galactose diet for 24 months followed by 14 months normal diet
- Intervention 2** Galactose diet for 31 months followed by 7 months normal diet

Group	Density (cells/mm^2)	Mean area (μm^2)	Mean perimeter (μm)	Coefficient of variation	Hexagonality (%)	Figure coefficient
control diet	5024 ± 275	199 ± 11	53.40 ± 1.49	0.17 ± 0.01	76 ± 2	0.870 ± 0.000
galactose diet	4500 ± 210‡	223 ± 10‡	56.29 ± 1.29‡	0.17 ± 0.01	78 ± 4	0.875 ± 0.005
intervention 1*	4455 ± 219‡	225 ± 11‡	56.55 ± 1.35‡	0.16 ± 0.01	77 ± 4	0.878 ± 0.004
intervention 2**	4386 ± 212‡	228 ± 11‡	57.08 ± 1.31‡	0.16 ± 0.01	77 ± 4	0.875 ± 0.005

- While significant differences (‡ $p < 0.01$) in endothelial cell size and density were observed between the three groups of galactose-fed dogs and normal, age-matched control dogs but this difference was not reduced by intervention.
- **Amelioration of endothelial cell changes requires therapy prior to the advent of endothelial morphologic changes.**

Diabetic Keratopathy Results From Human Clinical Trial

Limited clinical trials in Japan and compassionate treatments in the United States indicate that both topical and oral administration of ARIs are beneficial in maintaining the corneal epithelium in diabetics

Improvement of Corneal Sensation and Tear Dynamics in Diabetic Patients by the Oral Aldose Reductase Inhibitor, ONO-2235 (Epalrestat) A Preliminary Study

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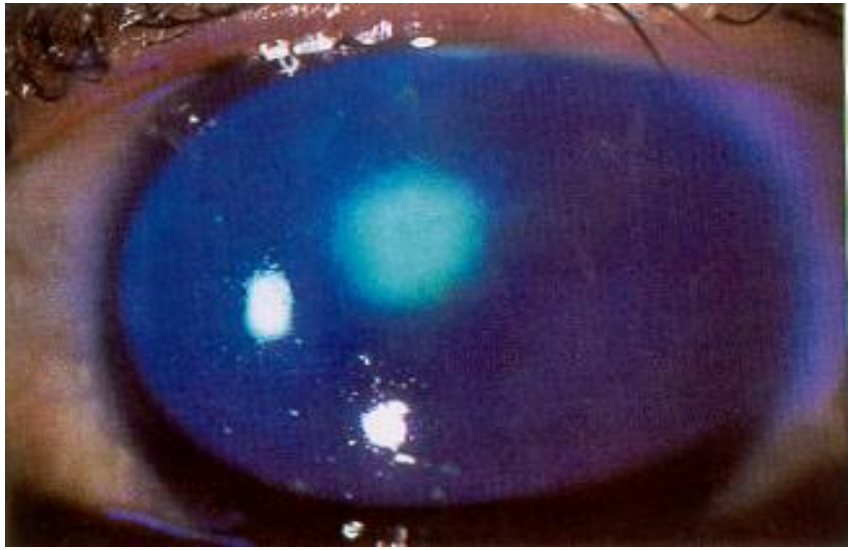
Summary of Preliminary Study

The administration of Epalrestat to patients with diabetic ocular-surface conditions for 3 months led to improvements in tear dynamics and in signs and symptoms of post-cataract extraction keratopathy of patients with diabetes

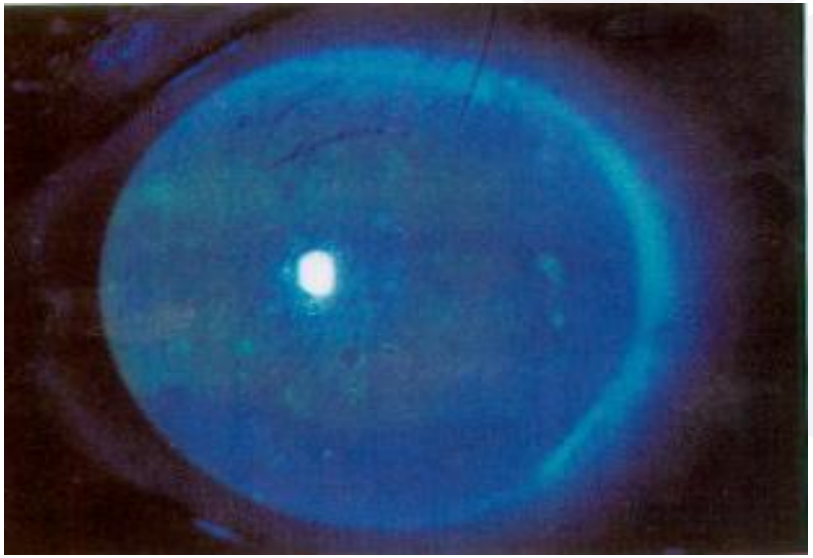
Hiroshi Fujuishima *et al, Cornea* 15(4):368, 1996

Typical Case of Corneal Ulcer Improvement With Aldose Reductase Inhibitor

Patient No. 3 : 57 years old, male, preproliferative retinopathy



Corneal ulcer was seen in the right eye and it remained for one month before treatment with Epalrestat



Cornea was essentially clear
1 month after Epalrestat administration

Hiroshi Fujuishima *et al, Cornea* 15(4):368, 1996

Changes in Ocular Surface Condition and Tear Production After 3-month Treatment With Oral Epalrestat

n=14	Corneal sensation (g/mm^2)	BUT (s)	RB	Fluorescein	Schirmer (mm)	Cotton (mm)
Pretreatment	4.1 ± 4.8	2.5 ± 1.1	1. 9± 1.7	2.9 ± 1.9	7.5 ± 3.8	22.1 ± 6.8
After-treatment	3.0 ± 3.1	3.4 ± 1.0	1.0 ± 1.3	1.6 ± 1.7	8.8 ± 4.5	27.4 ± 7.8
P Value (t test)	0.015	0.003	0.03	0.02	0.03	0.0001

BUT: break-up time, RB: Rose Bengal stain

Hiroshi Fujuishima *et al, Cornea* 15(4):368, 1996

Phase II clinical trials in both Japan and the US confirm the beneficial effects of the aldose reductase inhibitor CT-112 for diabetic keratopathy when administered as a topical ophthalmic suspension

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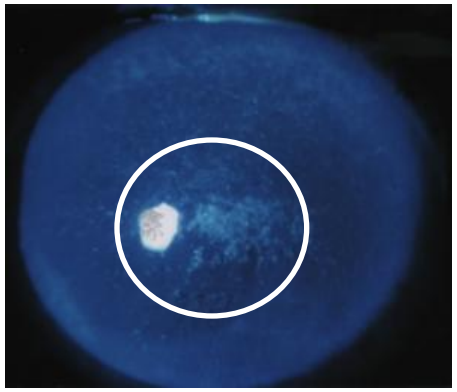
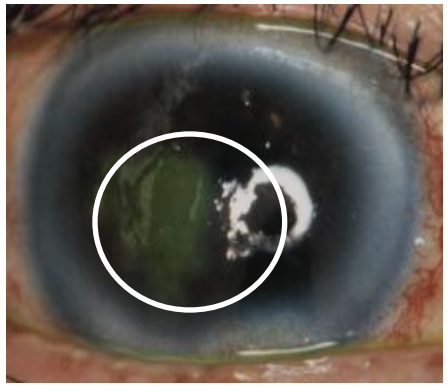
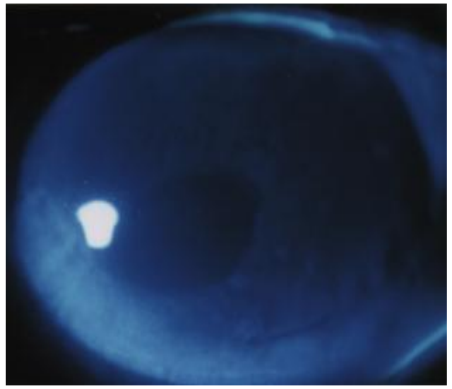
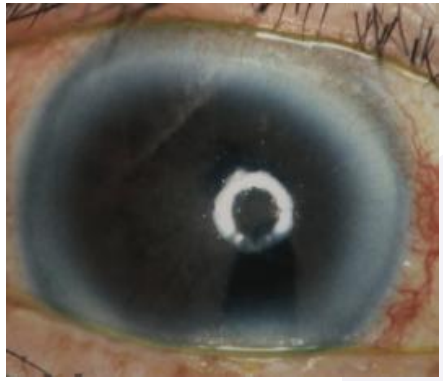
Corneal Wound Healing





Treatment with Topical CT-112





Hosotani *et al*, *Folia Ophthalmol Jpn 1986*

Effect of Aldose Reductase Inhibitor on Corneal Edema After Cataract Surgery

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Corneal thickness before and after cataract surgery

	Before surgery	After surgery	
		day 5	day 14
Non diabetic	531 ± 19	573 ± 40	567 ± 30
Diabetic	539 ± 23	616 ± 38*	597 ± 41*
Diabetic + CT-112	554 ± 17*	596 ± 30	570 ± 27

*$p < 0.01$ vs No diabetes

Awata *et al, Proc Jpn-US AR Workshop* 1990

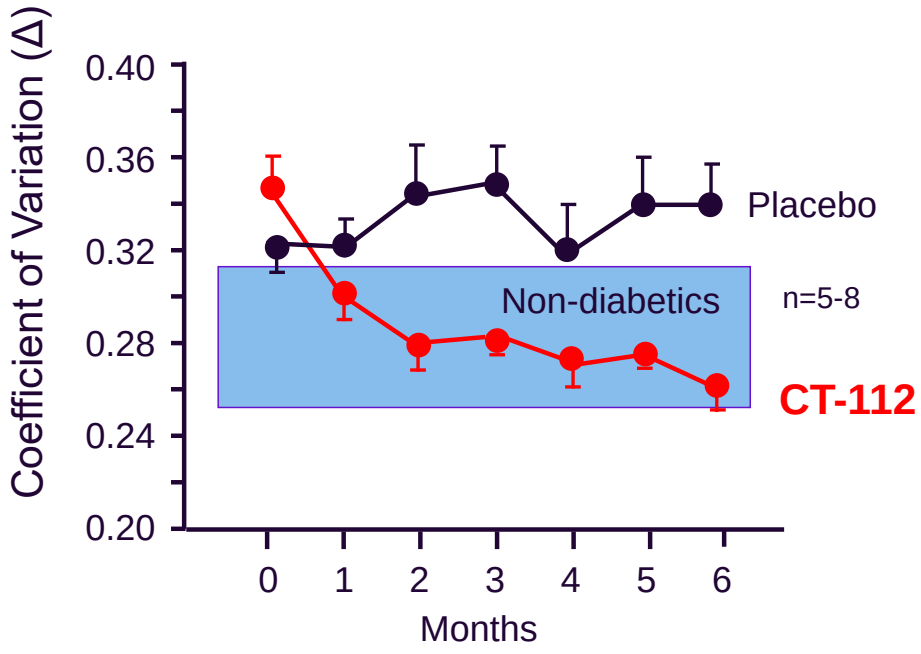
Effect of Aldose Reductase Inhibitor on Corneal Epithelial Morphology

		Placebo Group		CT-112 Group	
		Before	After	Before	After
Cell area (μm^2)	Mean ± S.E.	834 ± 30	812 ± 37	881 ± 37	728 ± 31
	Range	596-1055	557-1218	583-1218	533-1103
	p value		.3776		<.0001

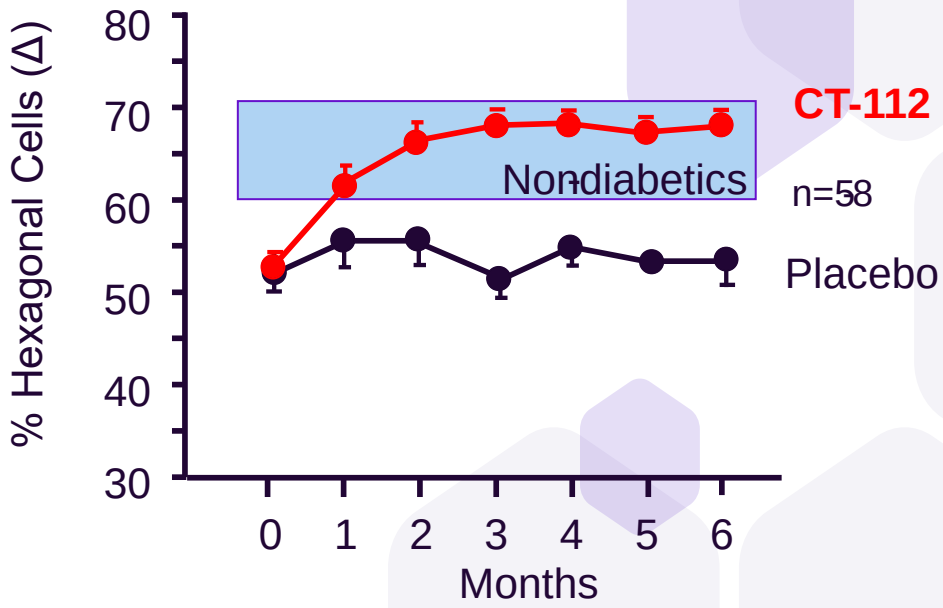
Hosotani *et al*, *Am J Ophthalmol* 1995

Effect of Aldose Reductase Inhibitor on Morphological Changes in Corneal Endothelial Cells

Coefficient of Variation



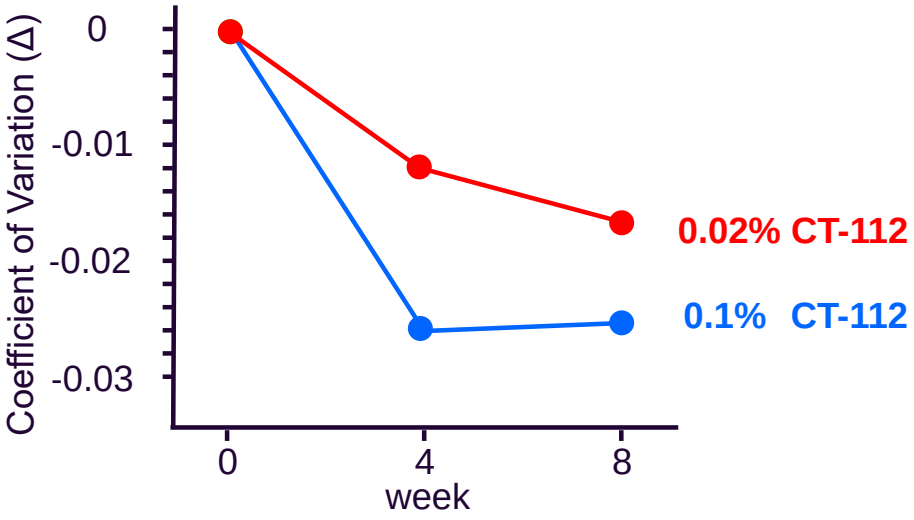
Percent Hexagonality



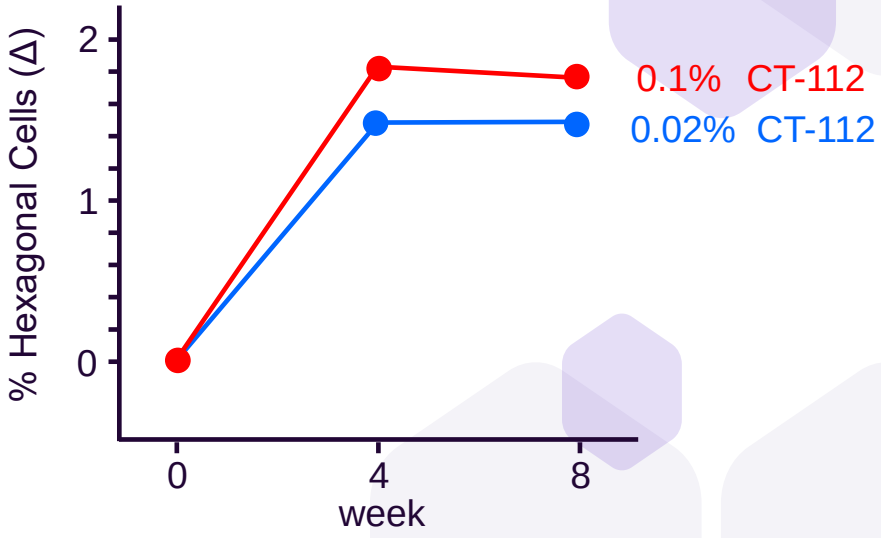
Effect of Aldose Reductase Inhibitor on Morphological Changes in Corneal Endothelial Cells

Phase II Japan, 100 Patients administered 4 times / day for 8 weeks

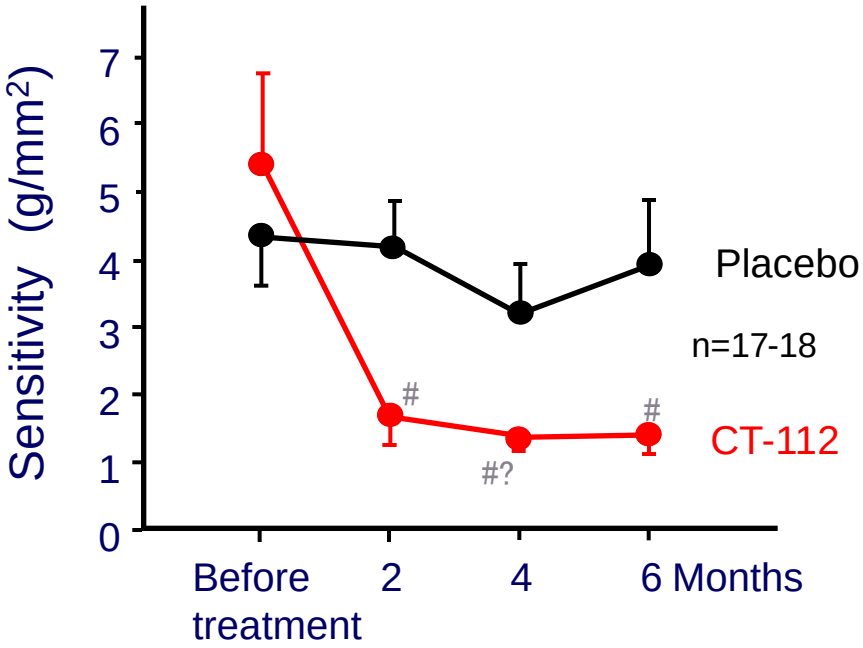
Coefficient of Variation



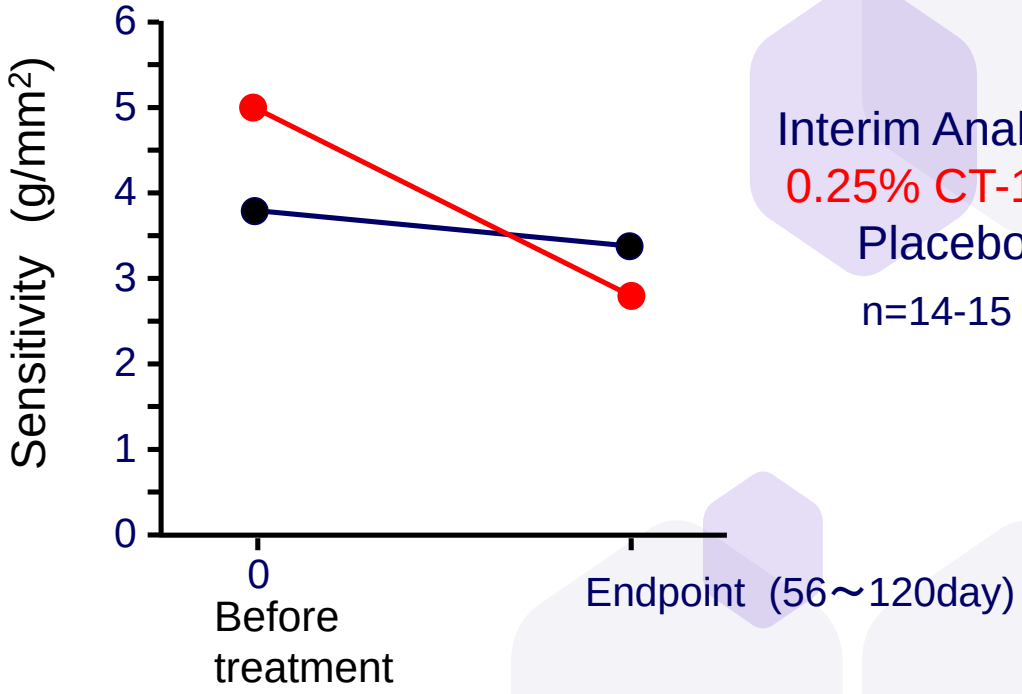
Percent Hexagonality



Effect of Aldose Reductase Inhibitor on Changes n Corneal Sensitivity (Cochet-Bonnet)



Phase II US, 2 X25 Patients
administered 4 times / day for 4 months



Hosotani *et al*, *Am J Ophthalmol* 1995

Limited Clinical Studies Indicate that Aldose Reductase Inhibitors are Effective on Treating Diabetic Keratopathy by Modifying:

1. Epithelial damage (SPK, and epithelial defects)
2. Enlargement of superficial epithelial cell areas
3. Decrease in corneal sensitivity
4. Enlargement of endothelial cell sizes
5. Corneal edema