



**SUNWAY**  
EYE CENTRE

# TREATING DRY EYE DISEASE WITH DIQUAS

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A close-up photograph of a human eye, focusing on the lower eyelid. A large, clear tear is falling from the eye, reflecting light. The eyelashes are dark and long. The background is a soft, out-of-focus light color.

**FINANCIAL DISCLOSURE:**

Honorarium from Santen

**Santen**

*A Clear Vision For Life™*

# DEFINITION

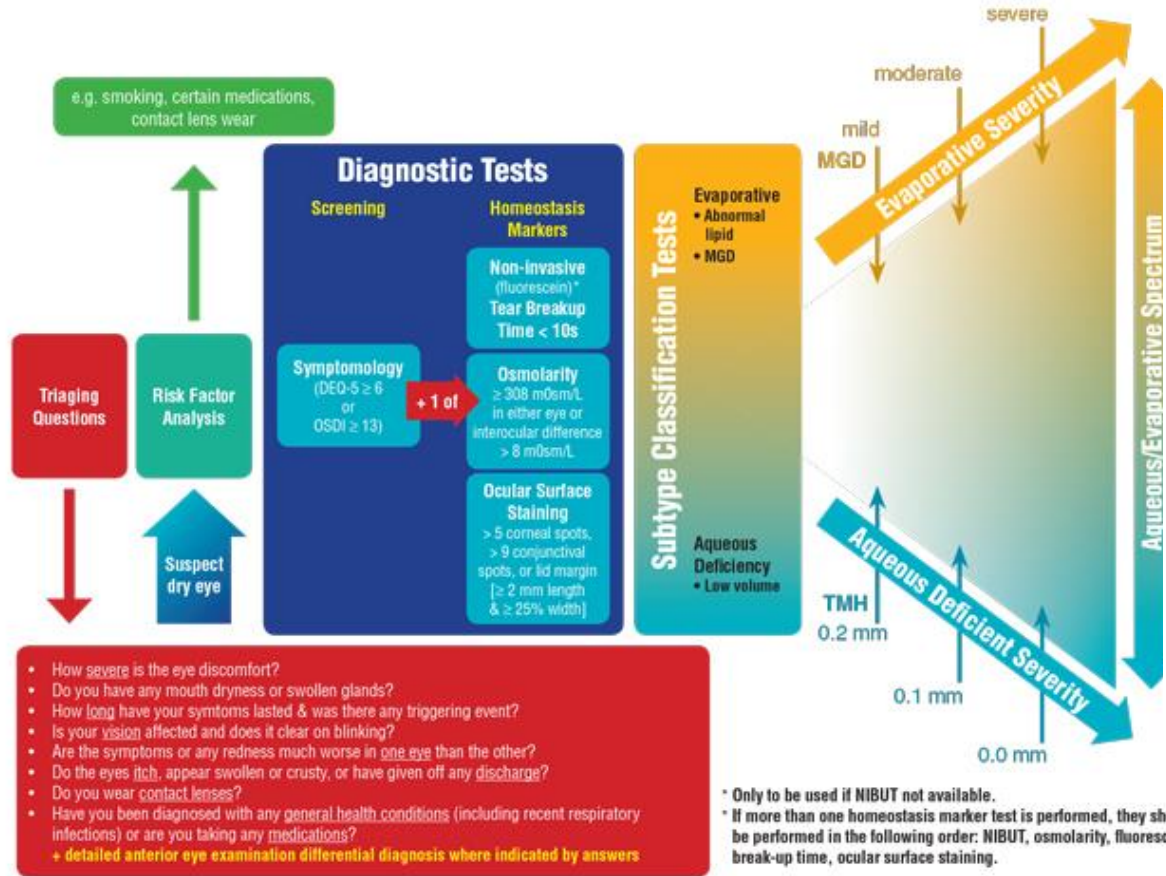
- ▶ Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities play an important role.

Relative to the previous definition, the new definition retains the concept that dry eye is a multifactorial disease. **The most important agreement was that the condition was characterized by an "unstable tear film." It was agreed that the unstable tear film is the *pivotal mechanism of dry eye* causing symptoms and/or visual impairment.**

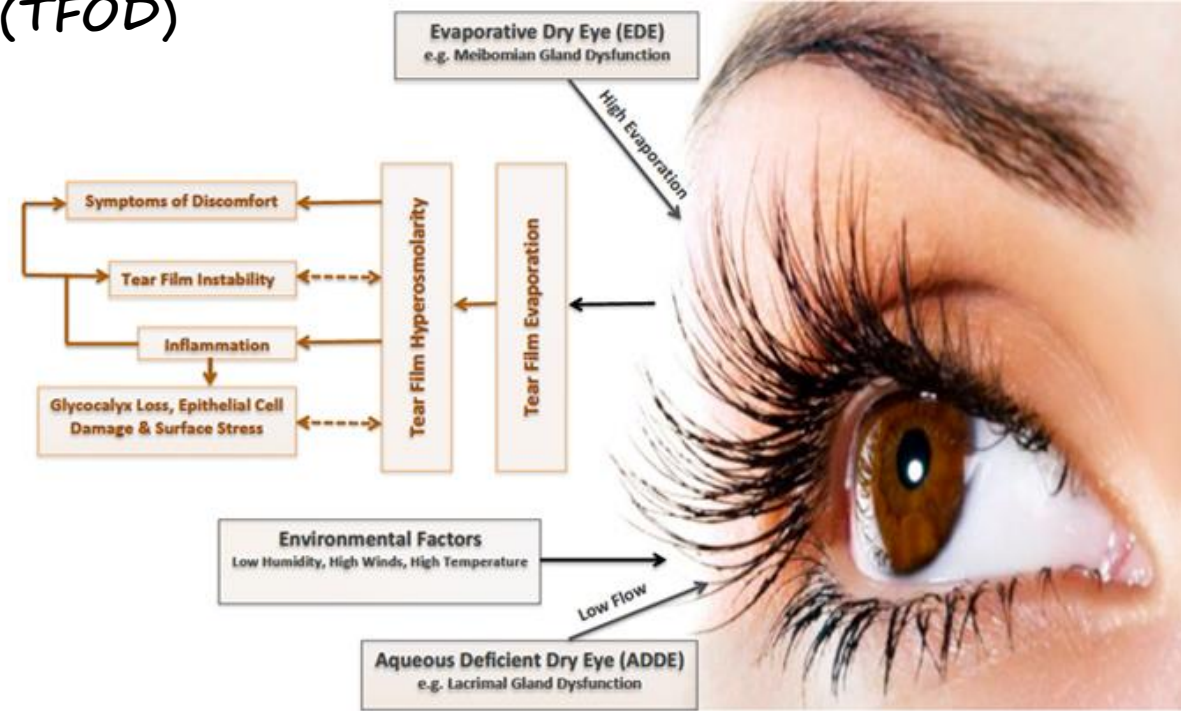
This concept is consistent with the visual impairment in dry eye patients; aberrations due to the unstable tear film comprise an integral feature of the deterioration of vision. This concept also fits well with the corneal neuralgia hypothesis.

Dry eye management- Targeting the ocular surface microenvironment. Xiaobo Zhang, Vimalin Jeyalatha M, Yangluowa Qu, Xin He,Shangkun Ou, Jinghua Bu, Changkai Jia, Junqi Wang, Han Wu, Zuguo Liu, and Wei Li. Int J Mol Sci. 2017 Jul; 18(7): 1398

# Diagnosing dry eyes



## TEAR FILM- ORIENTED DIAGNOSIS (TFOD)



## TEAR FILM- ORIENTED THERAPY (TFOT)

# DED- common features

*Loss of goblet cells (GC)*



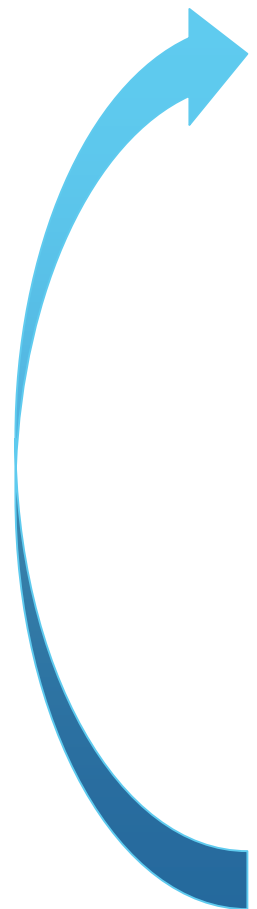
↓ *GC density*



↓ MUC5AC production  
(ocular surface mucin)



↓ TF stability



# MUCIN

- ▶ “heavy molecular glycoprotein”
- ▶ secreted by GCs, LGs and corneal Epi Cells

- ▶ 3 types of ocular surface mucin:

1. Soluble mucin

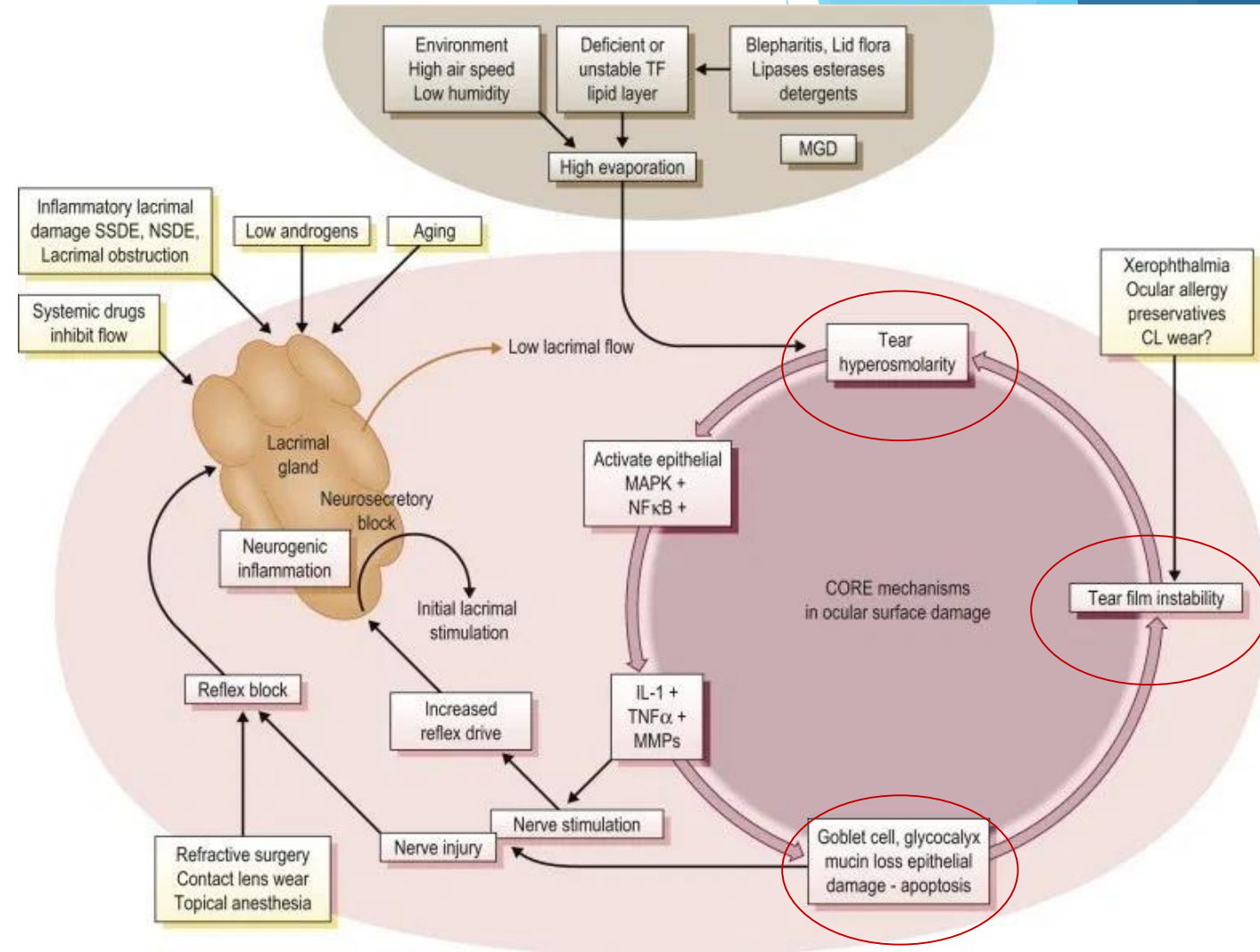
MUC 7

2. Gel- forming mucin

MUC5AC (GC)

3. Membrane- associated mucin

MUCs1, 4, 16 and 20



# IMPORTANCE OF MUC5AC

- ▶ secreted from GC++
- ▶ maintains homeostasis and TF stability of ocular surface
  - ▶ trapping and clearing debris
  - ▶ lubricat and hydrate
  - ▶ smooth optical surface



# The Importance of Ocular Surface Mucin

## 1. Wettability

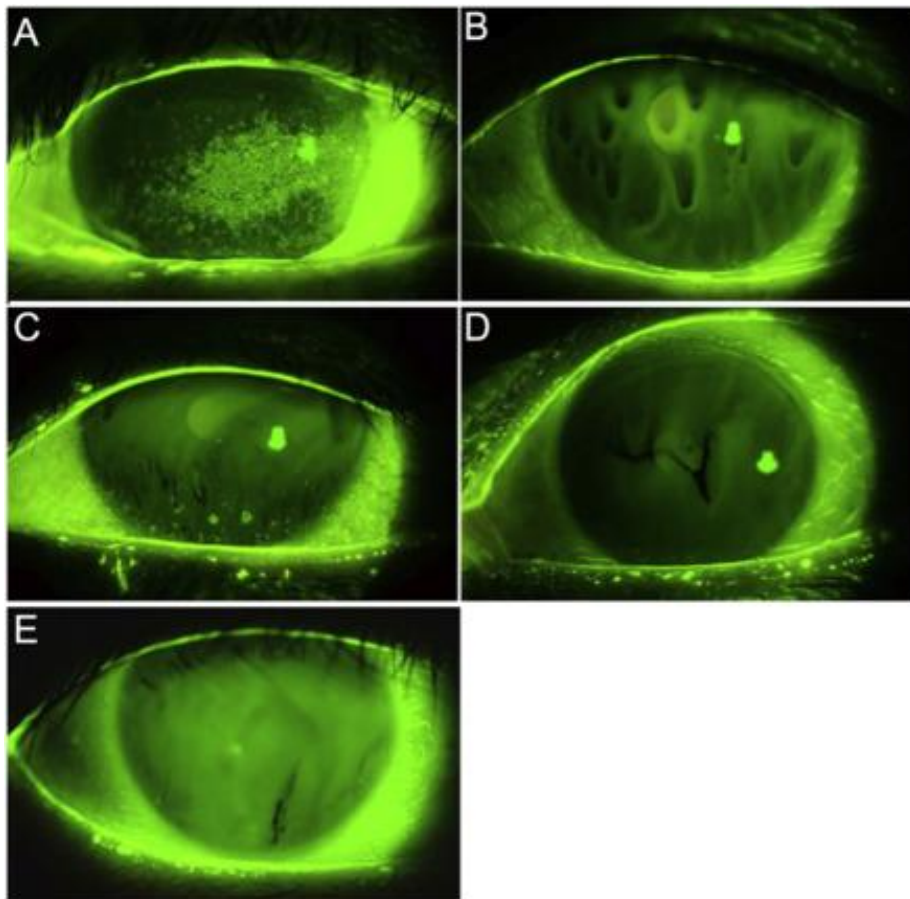
sustain/ 'holding' tear film dynamics, stability, osmolarity, and homeostasis

## 2. Lubrication

facilitates smooth blinking

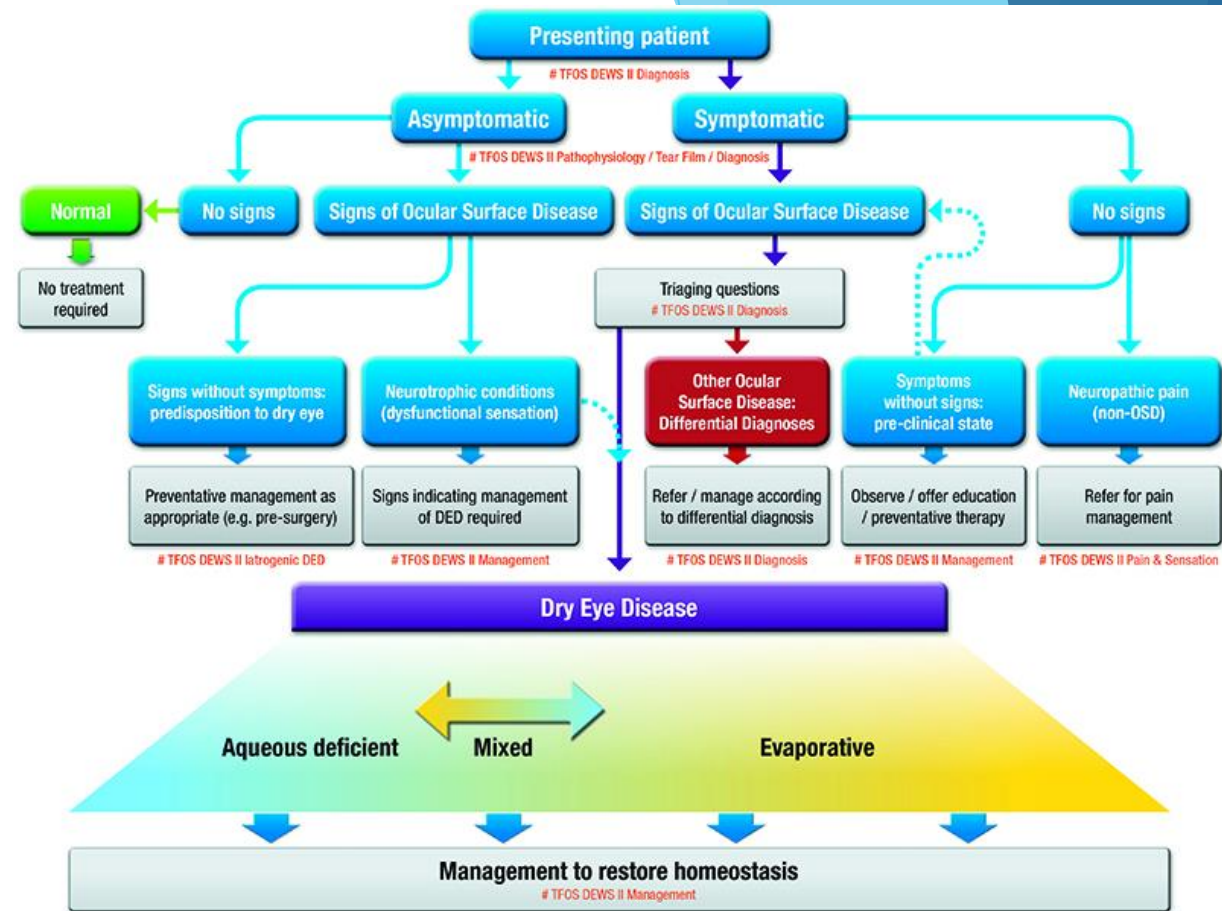
## 3. Barrier function

traps and removed pathogens and debris, pathogen colonization protection



Breakup pattern	When breakup occurs	Suspected abnormality in tear film
A; Area break	Before complete eye opening	Severe aqueous deficiency
B; Spot break	Before complete eye opening or immediately after eye opening	Decreased wettability
C; Line break	During the UMF	Mild to moderate aqueous deficiency
D; Dimple break	During the UMF	Mild to moderate decreased wettability
E, Random break	After the cessation of UMF	Increased evaporation

UMF: upward movement of fluorescein stained aqueous tears



# A therapeutic approach- mucin secretagogue

- ▶ 2007- International Dry Eye Workshop report
- ▶ Future therapy:
  - ▶ diquofosol\*, rebapamide\*, gefarnate, ecabet sodium
- ▶ Aim: promotes mucin MUC5AC secretion from conjunctival GC

\* commercially available

# DIQUAS<sup>®</sup> (diquafosol sodium 3% - BAK free)

potent purinergic P2Y<sub>2</sub> receptor agonist



activate production of inositol triP



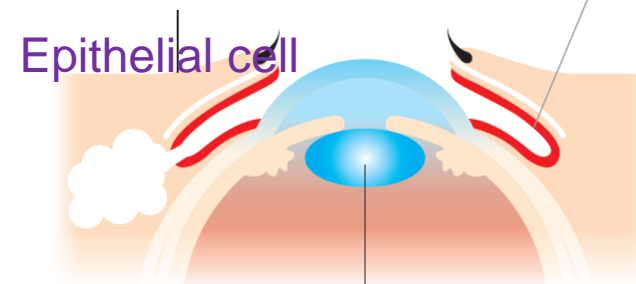
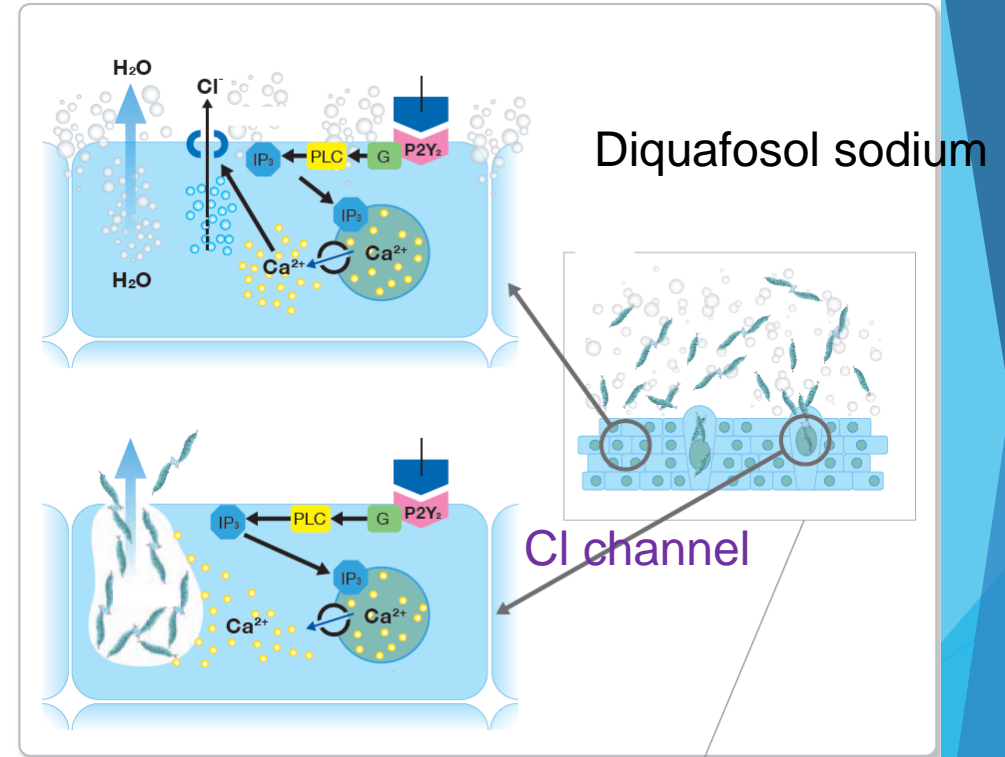
increase release of intracellular Ca<sup>2+</sup>



induces a series of physiologic response



↑ MUC5AC production



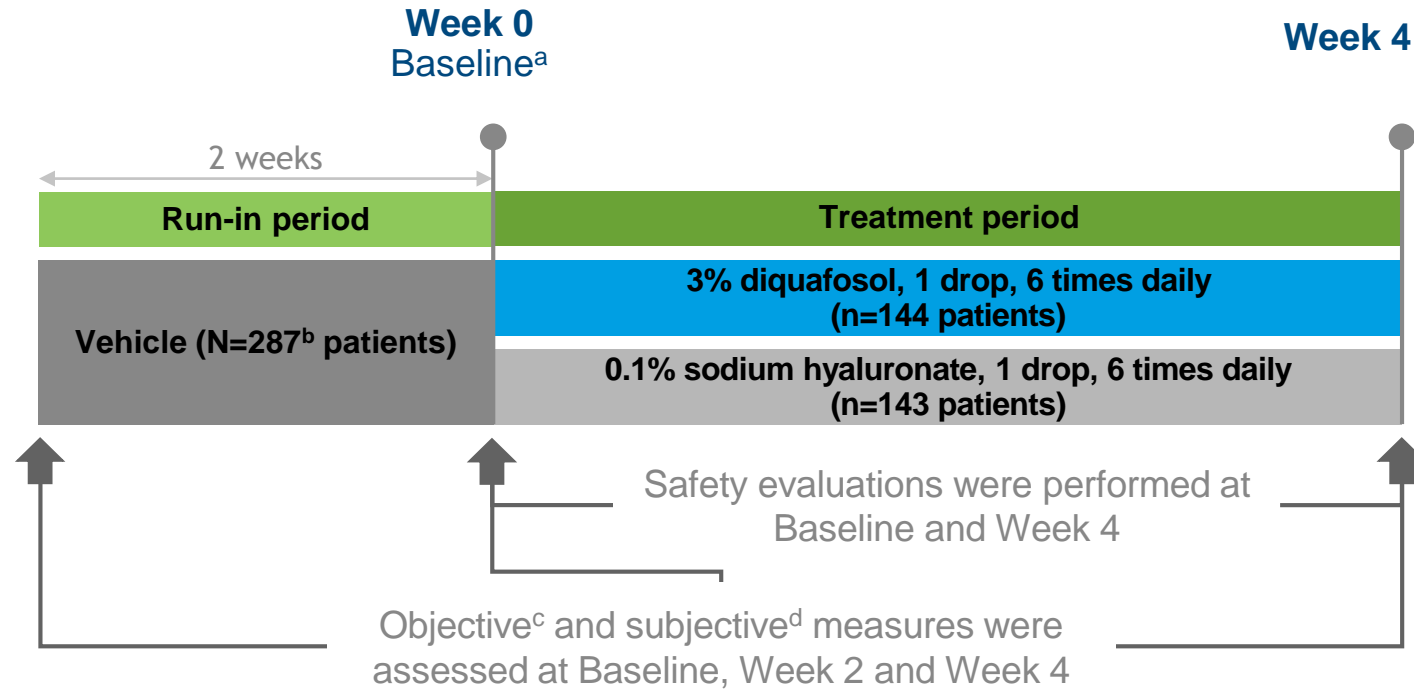
Hori Y, Maeno T. **Effects of diquafosol ophthalmic solutions and rebamipide ophthalmic suspension on tear fluid volume in normal rabbit** [in Japanese]. Atarashii Ganka. 2013; 30: 1007–1010

- *only DQS demonstrate increase MUC5AC level in 15 mins - tear meniscus more in DQS group 30 mins after instillation*

\*DQS- rapidly increase mucin secretion from GC

\*\*Rebapamide- increase GC production

# Efficacy of diquafosol with that of sodium hyaluronate 0.1% in the treatment of patients with dry eye disease



**Primary efficacy endpoints:** change in fluorescein and rose bengal staining scores from Baseline at Week 4  
**Secondary efficacy endpoints:** change in TBUT and symptom score<sup>d</sup> from Baseline at Week 4

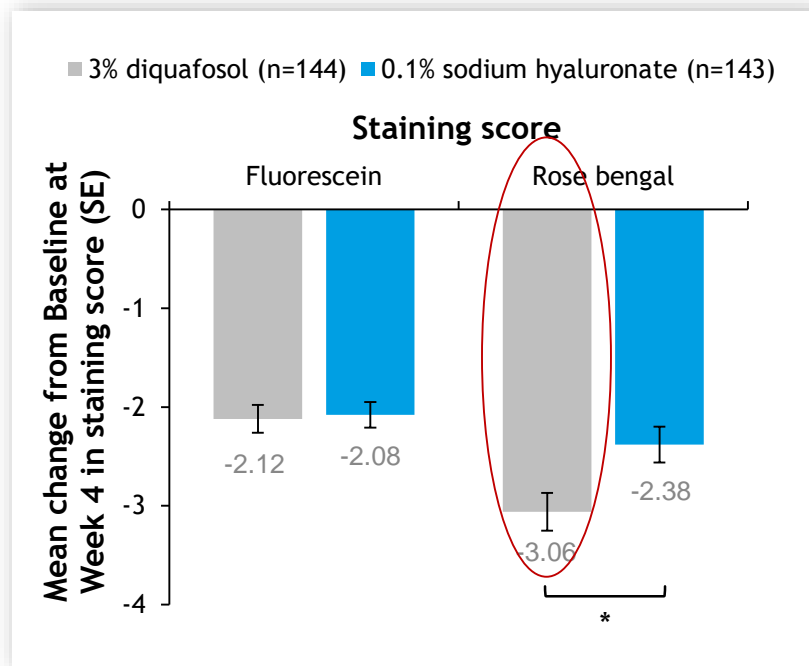
<sup>a</sup>Patients were randomised at Baseline 1:1; <sup>b</sup>number of patients randomised and prescribed study drug, 332 patients were enrolled; <sup>c</sup>corneal and conjunctival rose bengal staining score, corneal fluorescein staining score and TBUT; <sup>d</sup>blurred vision, dryness, eye discharge, eye discomfort, eye fatigue, eye pain, foreign body sensation, heaviness, itching, lacrimation and photophobia  
TBUT, tear break-up time

A 4-week, multicentre, randomised, double-masked, parallel-group comparison study in 287 patients with dry eye disease

# Diquafosol demonstrated superior rose bengal staining score compared with sodium hyaluronate in the treatment of dry eye disease



Diquafosol demonstrated non-inferiority<sup>a</sup> to sodium hyaluronate in fluorescein staining score and superiority<sup>b</sup> in rose bengal staining score in the treatment of dry eye disease



## Ocular staining

- Improvements<sup>c</sup> from baseline were seen in both treatment groups at all timepoints with both rose bengal and fluorescein staining scores
- Significantly greater improvement in rose bengal staining was observed with diquafosol than with sodium hyaluronate

## TBUT

- Improvements<sup>c</sup> from Baseline were seen in both groups at all timepoints
- Change from Baseline was numerically higher with diquafosol than with sodium hyaluronate
- No significant difference was observed between groups

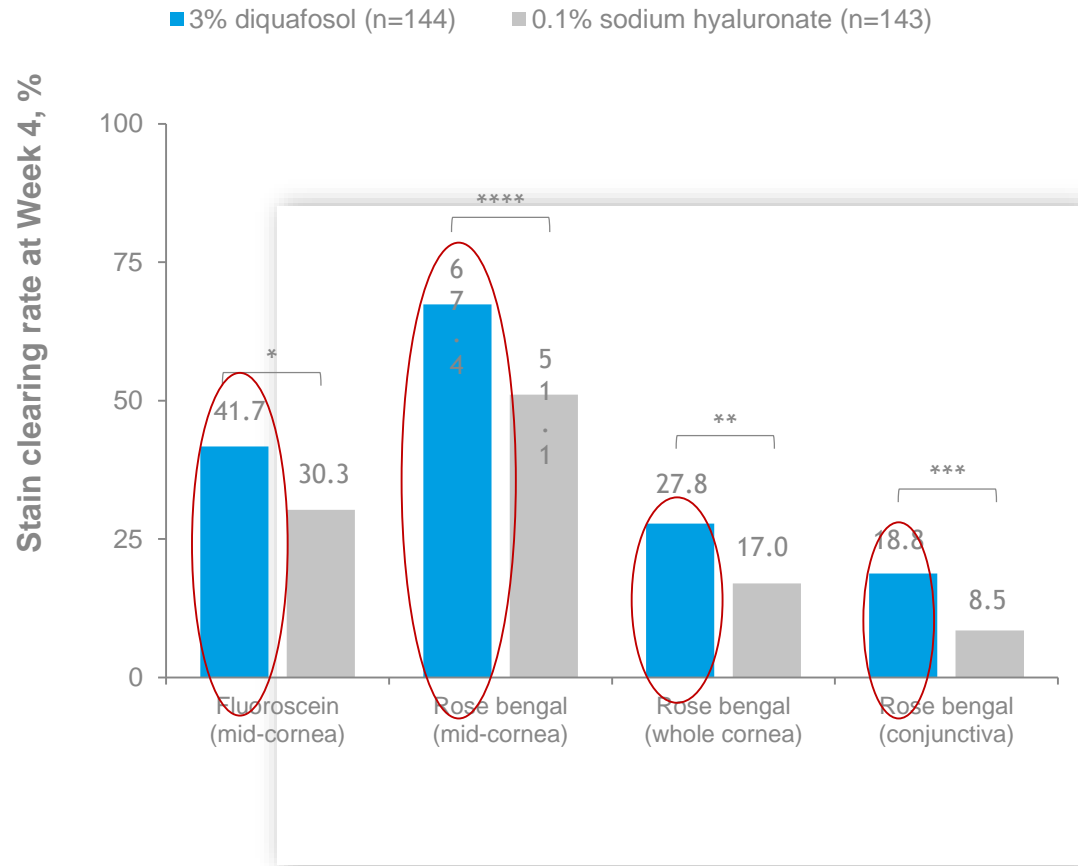
■ \*p=0.01

■ <sup>a</sup>Non-inferiority was determined if the upper limit of the 95% CI of the mean difference in staining did not exceed the non-inferiority limit of 0.34;

■ <sup>b</sup>if non-inferiority was confirmed, then superiority was assessed using the t-test for intergroup comparison of the change at Week 4; <sup>c</sup>no statistical value was given for these improvements

■ CI, confidence interval; SE, standard error; TBUT, tear break-up time

# DQS treatment demonstrated greater stain clearance rates than sodium hyaluronate in patients with dry eye disease



\*p=0.049; \*\*p=0.034; \*\*\*p=0.015; \*\*\*\*p=0.006

<sup>a</sup>Blurred vision, dryness, eye discharge, eye discomfort, eye fatigue, eye pain, foreign body sensation, heaviness, itching, lacrimation and photophobia

## Subjective symptoms<sup>a</sup>

- At Week 4, the diquafosol group demonstrated significantly lower ocular heaviness score compared with the sodium hyaluronate group (p=0.033)
- Compared with Baseline, eye discharge showed no improvement in the diquafosol group, but was improved in the sodium hyaluronate group

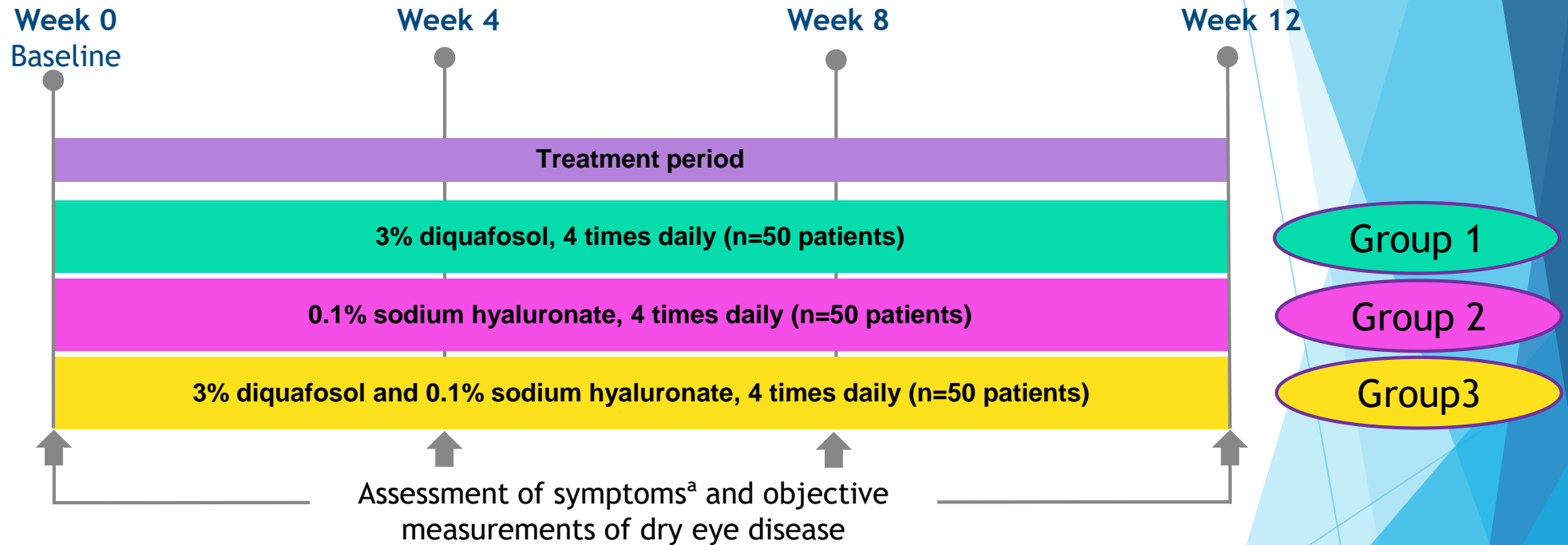
## Other measures

- There were no significant changes from Baseline with either group in clinical laboratory test values, ophthalmologic examinations, intraocular pressure, funduscopy or visual acuity



# Efficacy of diquafosol or SH alone or in combination with sodium hyaluronate

A 12-week, randomised, open-label, parallel-group clinical study in 150 patients with aqueous-deficient dry eye disease



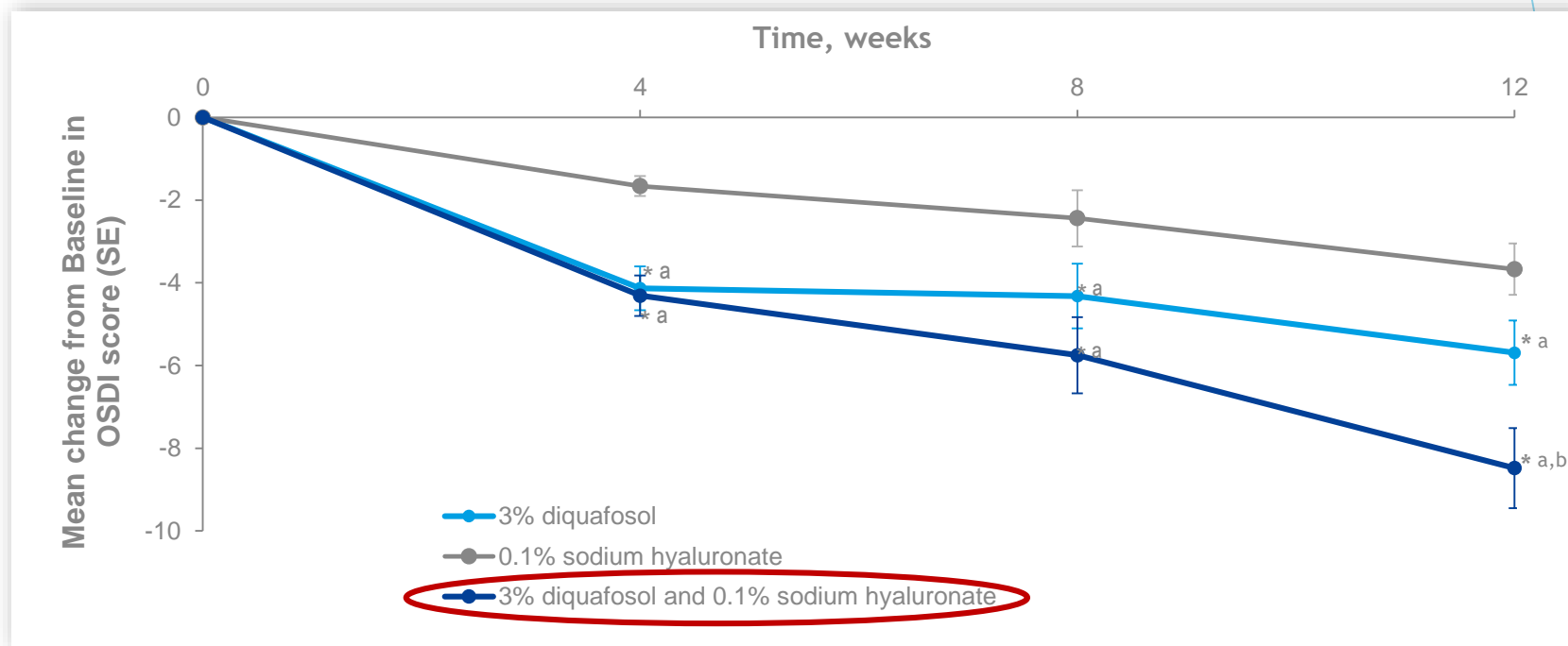
**Efficacy endpoints included:** OSDI score, TBUT, Schirmer's test score, corneal staining score and conjunctival impression cytology

<sup>a</sup>Assessed using OSDI  
OSDI, Ocular Surface Disease Index; TBUT, tear break-up time

# Combination therapy with diquafosol and sodium hyaluronate improved symptoms of dry eye disease



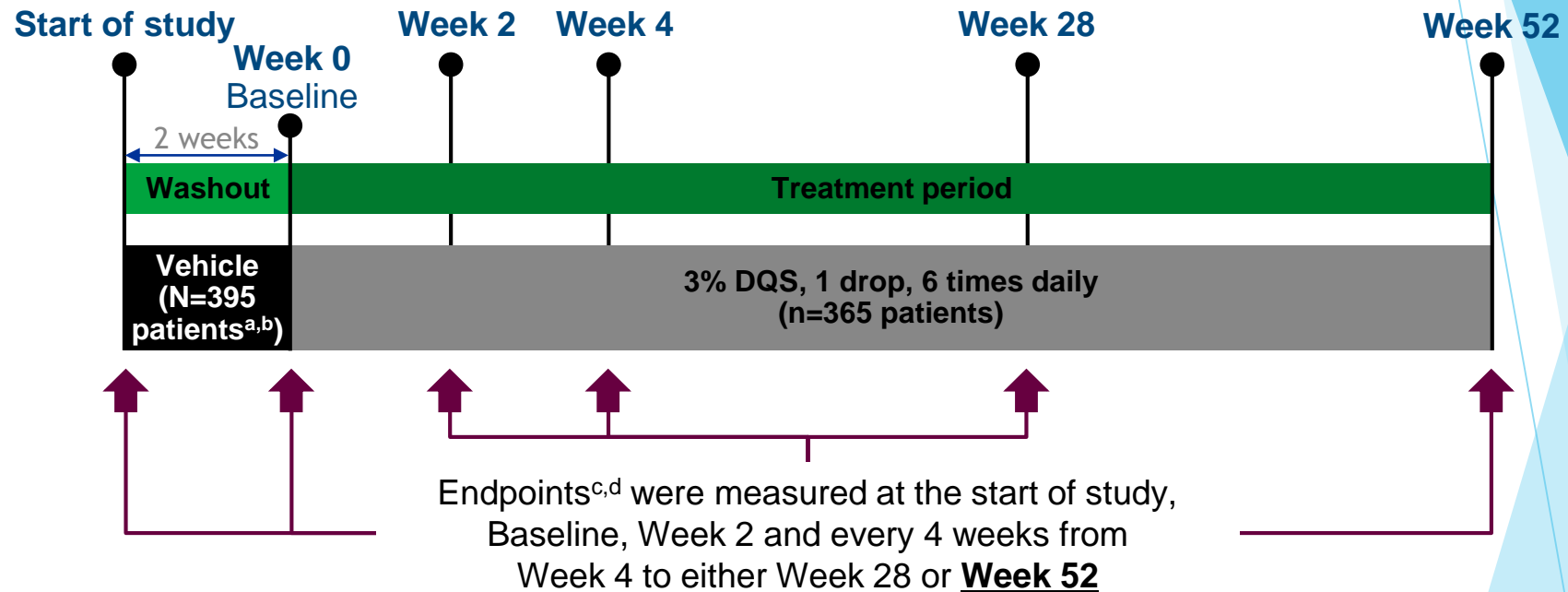
Diquafosol significantly decreased OSDI score *versus* sodium hyaluronate after 4, 8 and 12 weeks of treatment; combination therapy led to a further decrease at Week 12 that was significantly lower than diquafosol



\* $p < 0.05$

<sup>a</sup>*Versus* 0.1% sodium hyaluronate; <sup>b</sup>*versus* 3% diquafosol  
OSDI, Ocular Surface Disease Index; SE, standard error

# Long-term efficacy of diquafosol in the treatment of patients with dry eye disease



**Efficacy endpoints include: changes in fluorescein and rose bengal staining scores, TBUT and subjective symptoms**

<sup>a</sup>30 patients dropped out during the washout period; <sup>b</sup>the eye that showed higher fluorescein staining at Baseline was selected as the study eye;

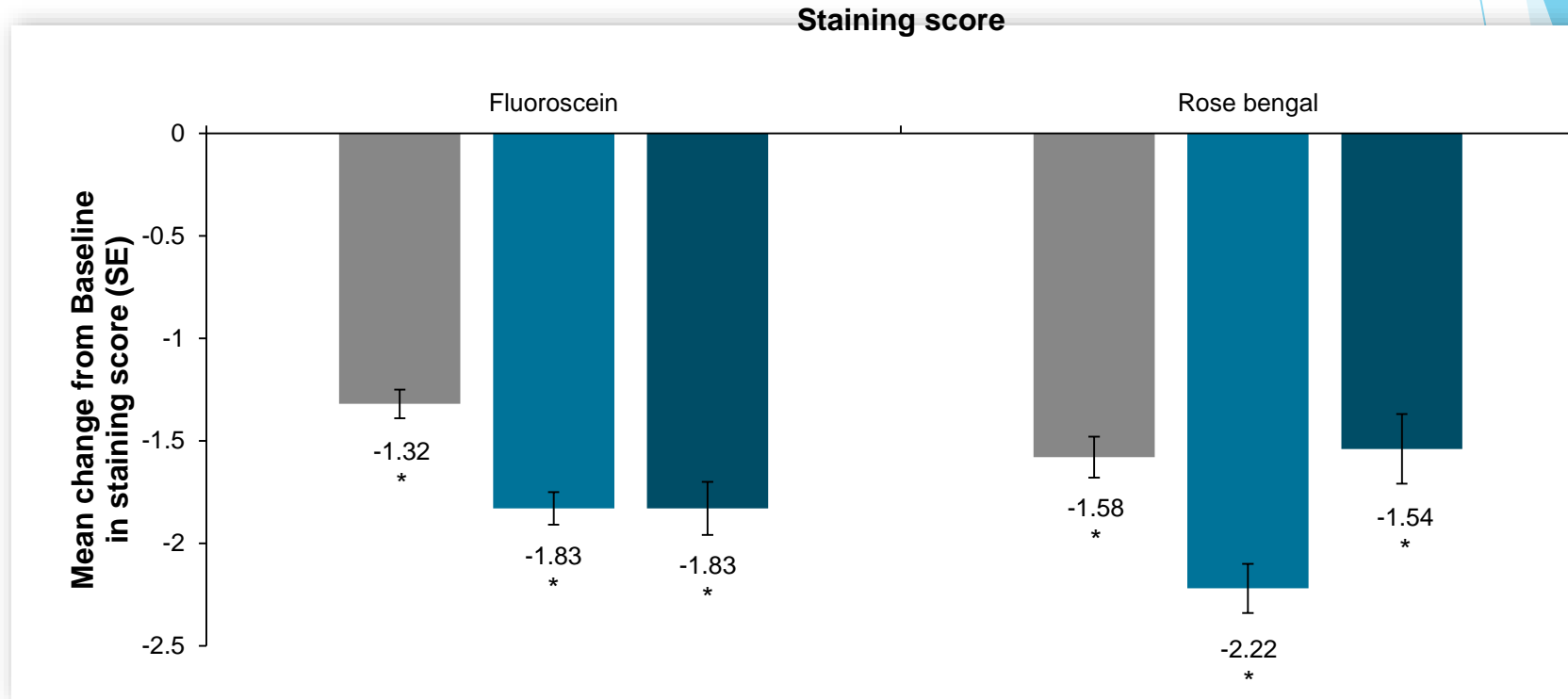
<sup>c</sup>endpoints included changes from Baseline in fluorescein and rose bengal staining scores, TBUT and 11 subjective symptoms (blurred vision, dry eye feeling, eye discharge, eye fatigue, eye pain, foreign body sensation, heavy feeling in eye, itching sensation, lacrimation, ocular discomfort and photophobia); <sup>d</sup>although the primary endpoint of this study was safety, these slides focus on efficacy

TBUT, tear break-up time

# Long-term treatment significantly improved ocular surface staining in patients with dry eye disease

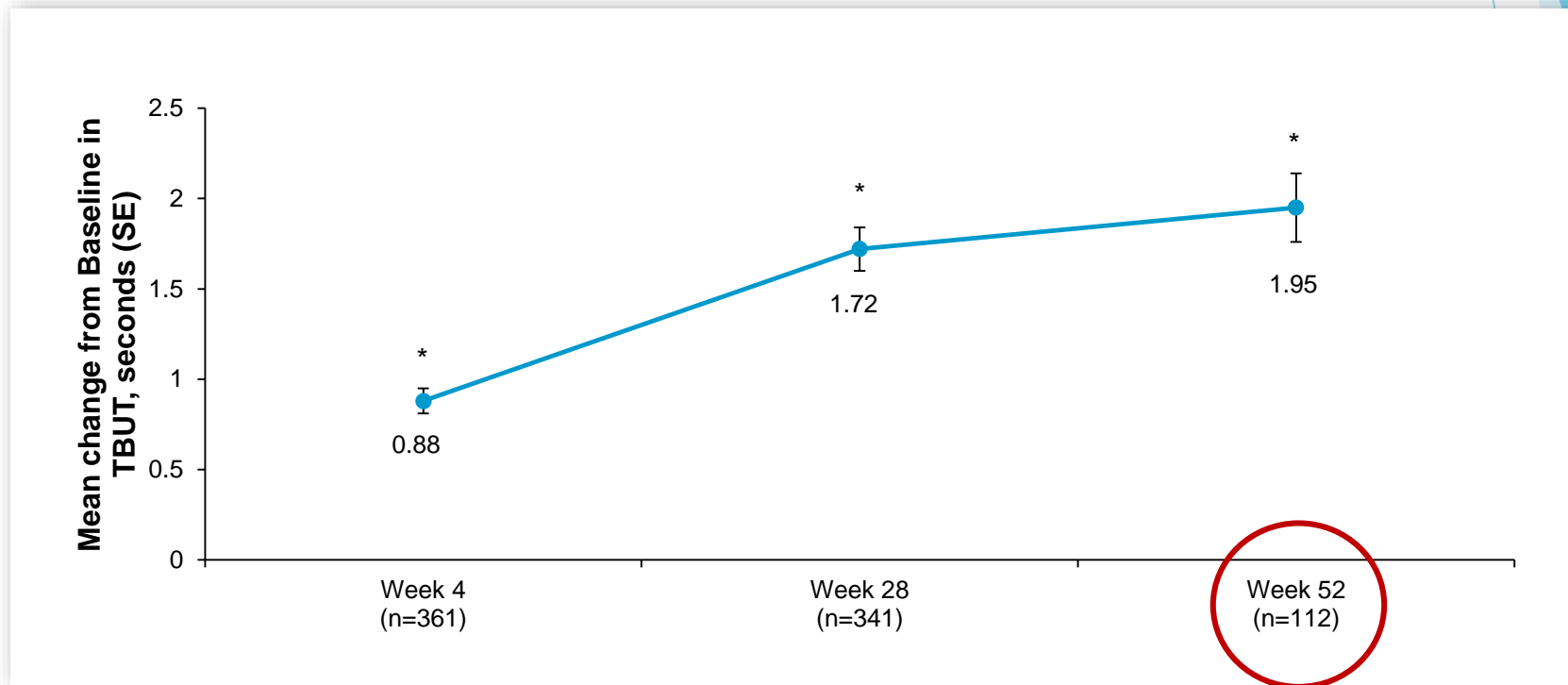


■ Week 4 (n=361) ■ Week 28 (n=341) ■ Week 52 (n=112)



\*p<0.001 compared with Baseline  
SE, standard error

# Long-term treatment significantly improved tear break-up time in patients with dry eye disease



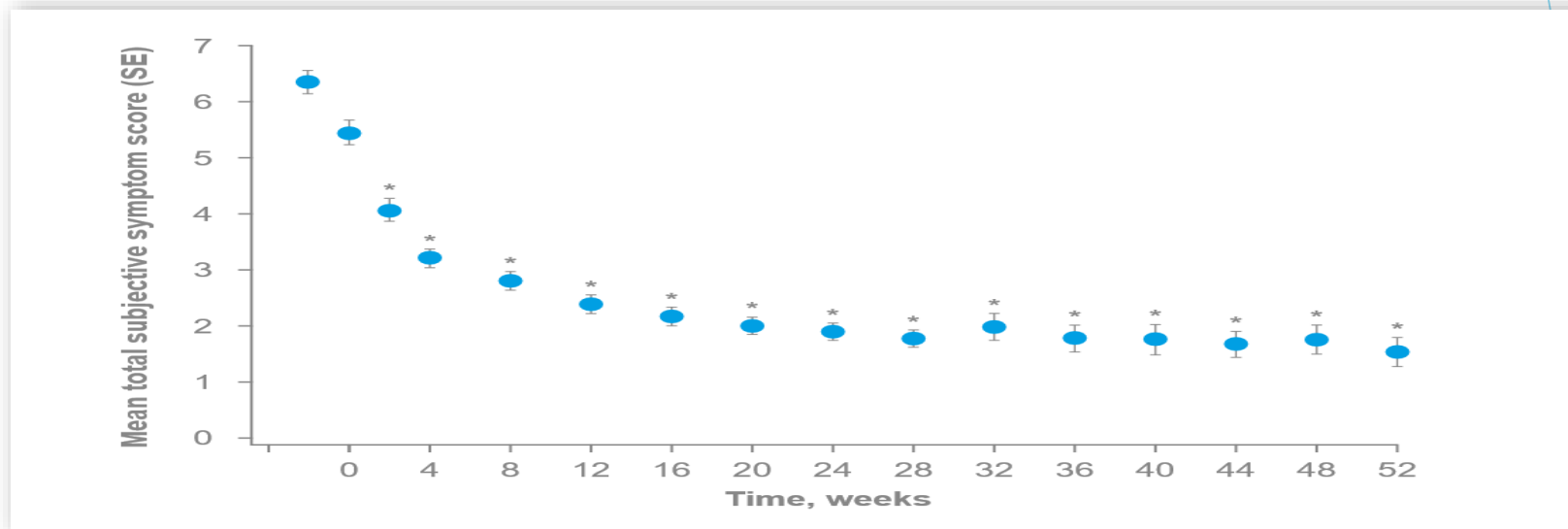
\* $p < 0.001$  compared with Baseline  
SE, standard error; TBUT, tear break-up time

# Long-term treatment significantly improved total subjective symptoms score<sup>a</sup>



Treatment with diquafosol significantly reduced total subjective symptoms score by Week 2 of treatment and maintained this reduction up to Week 52

All symptoms, except eye discharge and lacrimation, significantly improved before Week 4 ( $p < 0.001$ ) and were maintained up to Week 52 ( $p < 0.001$ ); eye discharge and lacrimation did not worsen with long-term treatment



\* $p < 0.001$  compared with Baseline

<sup>a</sup>Total subjective symptoms score includes symptom scores for blurred vision, dry eye feeling, eye discharge, eye fatigue, eye pain, foreign body sensation, heavy feeling in eye, itching sensation, lacrimation, ocular discomfort and photophobia

SE, standard error

# Long-term treatment of dry eye disease with DQS: Tolerability



Most ADRs were mild to allow continuation of the study, and resolved during treatment or after discontinuation of treatment / study completion.

Most of the ADRs, as well as the adverse events, occurred within the initial 4 weeks of treatment, and the incidence did not increase by long-term treatment.

Type	Cases with ADRs	ADR rates (%)
Total ADR	92 / 365	25.2%
ADRs $\geq 1\%$ :		
• Eye discharge	24 / 365	6.6%
• Conjunctival hyperemia	20 / 365	5.5%
• Eye irritation	16 / 365	4.4%
• Eye pain	12 / 365	3.3%
• Itching sensation	10 / 365	2.7%
• Foreign body sensation	9 / 365	2.5%
• Conjunctival hemorrhage	6 / 365	1.6%
• Ocular discomfort	5 / 365	1.4%
• Blurred vision	4 / 365	1.1%

ADR, adverse drug reaction

# LONG TERM EFFICACY AND SAFETY

- ▶ Improvement: 40% Schirmer tests, 80% TBUT
- ▶ 100% improvement: ocular surface staining score (RB, fluorescein, conjunctival staining)
- ▶ Symptoms: 75% improvement
- ▶ Adverse reaction: no severe ADR for DQS 0.5%- 5%

Wu D1, Chen WQ, Li R, Wang Y. **Efficacy and safety of topical diquafosol ophthalmic solution for treatment of dry eye: a systematic review of randomized clinical trials.** Cornea. 2015 Jun;34(6): 644-50

(8 RCTs- 1518 patients- MEDLINE, EMBASE, Cochrane Registry)



# TAKE HOME MESSAGES...

## ▶ Mucin secretagogue:

- (relatively) novel therapy for dry eye disease
- effective and safe (at least 1 year FU)
  - maintain epithelial integrity of ocular surface layer
  - increase mucin secretion
- benefit of adding HA- based AT
- not a typical tear substitute

## ▶ Patient selection

- need to treat concurrent inflammation
- pre-operative DED, aqueous and mucous deficient DED,
- explain re: mild SEs