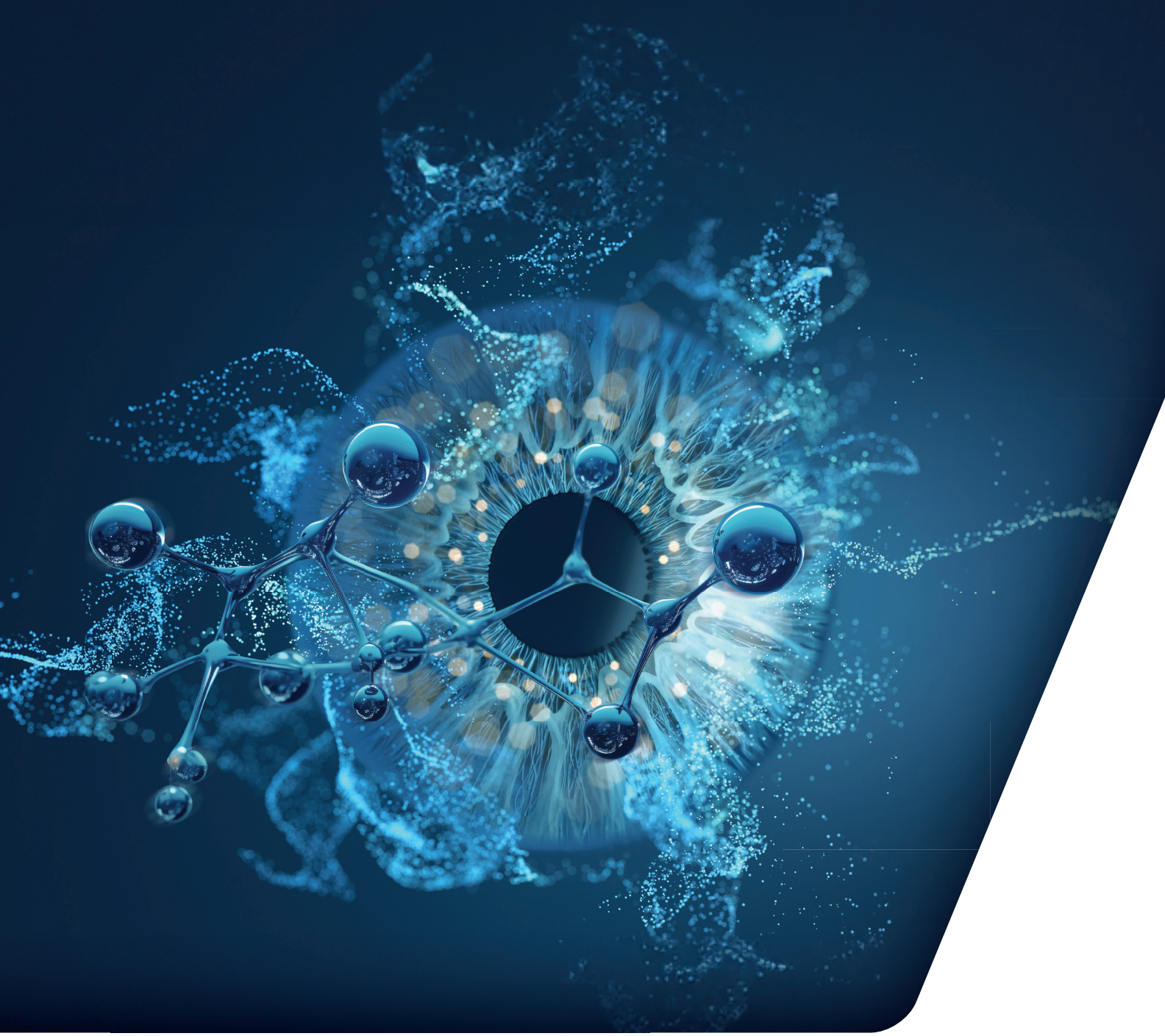

The benefits of high molecular weight Hyaluronic Acid in Ophthalmology

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With over 30 years of Clinical Use, Hyaluronic Acid (HA) has proven to be an Enduring Element of Dry Eye Disease Treatment[1]

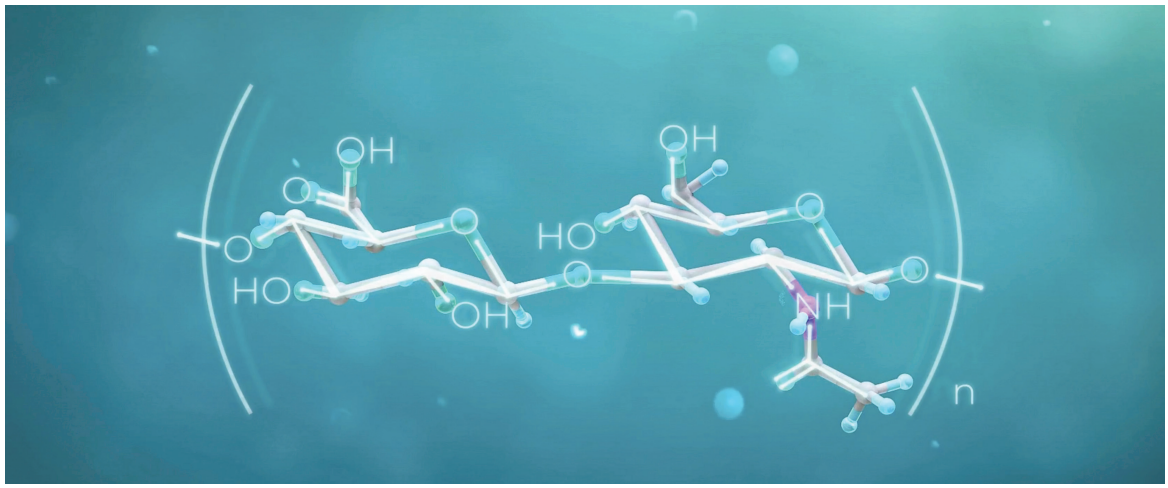


Fig. 1: Hyaluronic acid – a polysaccharide (glycosaminoglycan) consisting of repeating units of D-glucuronic acid and N-acetylglycosamine

HA is a strongly hydrophilic (water-loving) ingredient. It is a naturally occurring substance in the body, with an excellent safety profile[2]

- High water-binding capacity: One gram of hyaluronic acid can bind up to six litres of water.
- Well tolerated: Hyaluronic acid is a substance found naturally in the body, e. g. in the vitreous body of the eye, in connective tissue, in joint fluid and in cartilage.
- Hardly any allergies or side effects: Hyaluronic acid is not perceived by the body as a foreign substance, which means there are rarely allergic reactions or other side effects.

In clinical studies on dry eye patients Hyaluronic Acid has been proven to:[1]

- Improve patient symptoms
- Improve objective measures of dry eye, such as tear break-up time and ocular surface staining, when compared to baseline and to placebo (saline or vehicle)

Not all hyaluronic acid is the same[3-6]

Hyaluronic acid differs in terms of the possible crosslinking, its chain lengths and ultimately the molecular weight. Chain length and molecular weight determine the properties and intended uses.

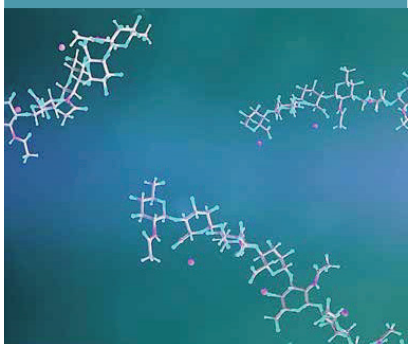
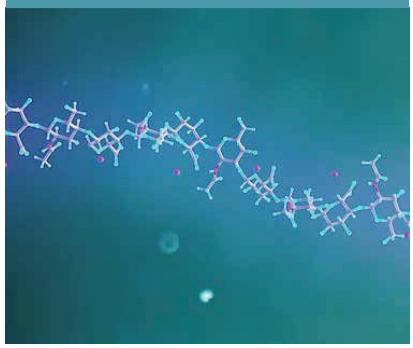
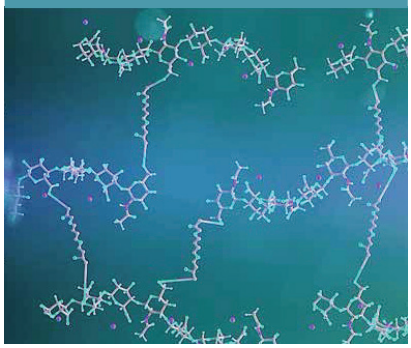
The specific HA chain lengths used in different fields of medicine may vary to provide the most effective treatment for each condition[3]

For Dermatology: Short-chain Hyaluronic Acid that penetrates into deep skin layers and is stored there

For Ophthalmology: Long-chain Hyaluronic Acid with a high molecular weight that moisturises the surface of the eye for a long time

For Orthopaedic: Cross-linked Hyaluronic Acid, which acts as a lubricant and 'shock absorber' in joints

Relevance to dry eye disease[2]

Short-chain Hyaluronic Acid	Long-chain Hyaluronic Acid	Cross-linked Hyaluronic Acid
		
■ Short-chain Hyaluronic Acid is not as viscous, nor can it hold as much water	■ Ideal for dry eye disease	■ Cross-linked Hyaluronic Acid has reduced mucoadhesive strength

Dry eyes benefit particularly from long-chain HA, as it has a high viscosity and therefore a long residence time on the eye without affecting visual acuity[1]

Short-chain and crosslinked hyaluronic acid, on the other hand, are more suitable in other specialties.

The Benefits of Long-Chain High Molecular Weight HA:

1. Long-lasting lubrication:[7,8]

- Superior hydration
- Longer retention time on ocular surface
- Moves like a natural tear

2. Long-lasting protection:[6, 9-13]

- Exhibits anti-inflammatory properties[9-12]
- Reduces and repairs damage to the cornea[13]
- Improves vision stability, discomfort and pain[6,13]

3. Long-lasting replenishment:[1,2,6,13]

- Compensates for lack of secretory mucins[2]
- Potential to increase mucin expression[2]
- Binds to mucins[6]

The clinical performance of eye drops containing very high molecular weight HA is entirely different from that of eye drops containing low to medium molecular weight HA.[3]

Results of clinical research on HA eye drops are not comparable without this parameter.[3]

Long lasting lubrication with high molecular weight HA

The higher the HA molecular weight, the higher the water-binding capacity[3], as there are more side chains to bind more water and hold them at the ocular surface.

- High molecular weight HA has a high viscosity and therefore a long residence time on the eye without affecting visual acuity.[1]
- Eye drops with long chain high molecular weight HA have high viscoelasticity properties which allows them to be non-newtonian. **Non-Newtonian HA eye drops** are perceived **as more comfortable, cause less blurring**, have a **longer residence time**, provide **superior hydration**, and reduce surface friction.[8]

High viscoelasticity: Rapid change of viscosity for non-Newtonian fluids which means:

- **Rapid decrease in viscosity when blinking** ('shear thinning')

This forms a thin film on the surface of the eye that spreads evenly. Visual impairment is avoided due to the reduced viscosity.

- **Rapid change back to high viscosity with the eye open** ('pre blink'/'post blink')

This ensures a long residence time on the surface of the eye. In addition, the high viscosity contributes to the stability of the (artificial) tear film.

High molecular weight HA allows eye drops to mimic the movement of natural tears

> The greater the difference between the viscosity before blinking and the viscosity during blinking under the effect of shear forces, the more viscoelastic the tear substitute (fig. 2) and the better this ensures high tear stability, low friction and good distribution of the eye drops during blinking. [8,14]

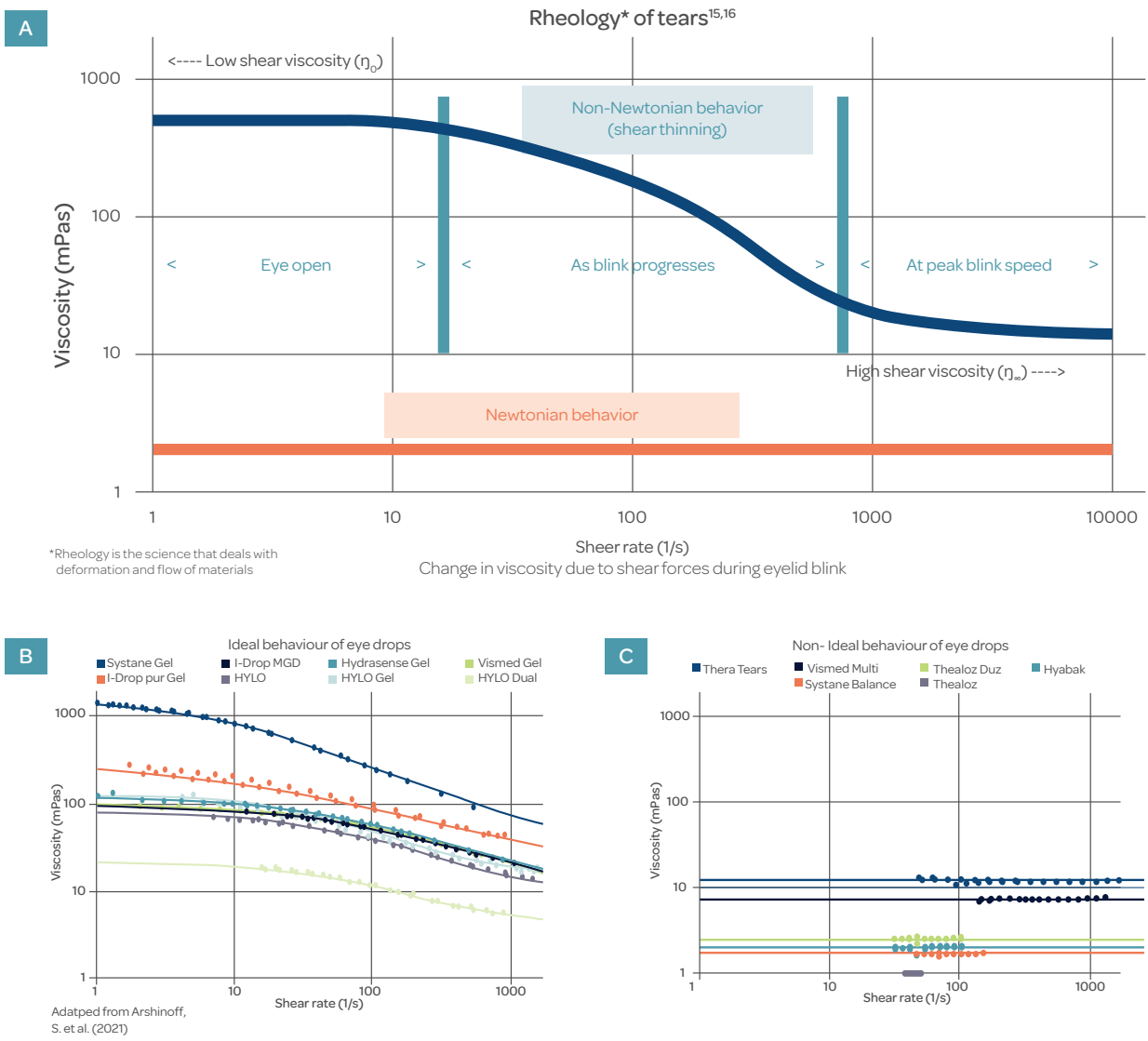


Fig. 2: **A.** Change in viscosity due to shear forces during eyelid blink[8]; **B.** Comparison of different eye drops with ideal behaviour[14] **C.** Comparison of different eye drops with non-ideal behaviour[14]

Long lasting protection with high molecular weight HA

High molecular weight HA offers much more than simply moisturisation – it promotes many positive clinical effects on the eye.

Anti-inflammatory effect

In contrast to short-chain hyaluronic acid, long-chain hyaluronic acid decreases the inflammatory process **by forming a blocking mechanism to prevent the inflammatory response**[11] This process helps to avoid further damage and break the cycle of DED.[12]

High molecular weight Hyaluronic Acid (HA) may help to repair corneal damage[15-17]

HA is known to promote corneal wound healing by **triggering corneal epithelial cell proliferation and migration**. This has been observed in both laboratory and real-world studies.

Promotes the regeneration of corneal nerve cells [13]

Damage to the corneal nerve cells results in the corneal epithelium no longer being properly nourished and can be a pathomechanism for more severe ocular surface disease (Fig. 3). Long-chain hyaluronic acid triggers a **significant increase in nerve fibre length**.

Reduces pain in the eye [18-19]

Long-chain hyaluronic acid blocks the activity of nociceptive nerves in the ocular surface, **relieving pain caused by friction**.

Reduces apoptosis [20-21]

Long-chain hyaluronic acid stabilises human corneal cells and makes them **more resistant** to apoptosis induced, for example, by **preservatives** such as **benzalkonium chloride**, UV-B radiation, burns, etc

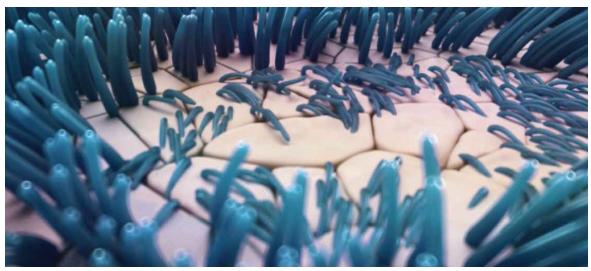


Fig. 3: Damage to the corneal epithelial cells due to changes in the composition of the tear fluid

Superior Protection against Preservative Damage with High Molecular Weight HA [20-23]*

Corneal damage may occur during treatment for DED. e.g. due to drops that contain the preservative Benzalkonium chloride (BAK)[22]

BAK has been associated with:

- Destabilisation of the tear film
- Ocular inflammation
- Damage to corneal nerves [20-21]

Recent research has demonstrated that the application of high molecular weight HA can offer significant protection against and effectively reduces the effects caused by BAK [22]

Research suggests that high molecular weight HA has a protective effect, mitigating the potential harmful impact of BAK in eye drops.

* (vs placebo or LMH HA) to corneal epithelial cells exposed to BAK, in particular reducing oxidative stress and apoptosis.

Long lasting replenishment of the mucoaqueous layer with high molecular weight HA

High molecular weight HA compensates for the lack of secretory mucins.

A deficiency in mucins is an underestimated contributing factor in DED, and is often due to damaged goblet cells.[24]

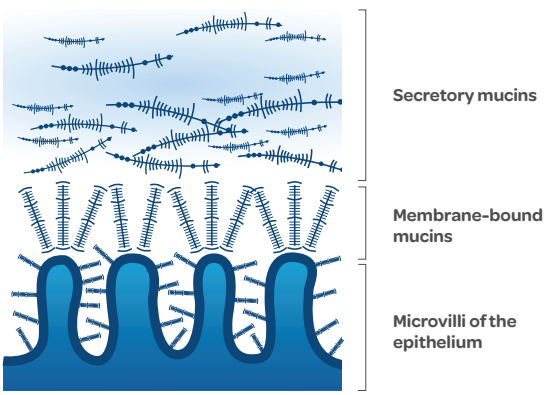
Changes in mucins are not only present in advanced disease; but can be the first signal of ocular surface disease.[25]

MUC5AC levels appear in lower concentrations in the tears of patients with DED.[3,26]

MUC5AC is a secretory mucin and is a gel-forming mucin that affects how much water can be retained in the tear film.[27,28]

Thanks to its unique structure, long-chain high molecular weight (HA) can serve as a substitute for secretory mucins, such as MUC5AC.

The tear film mucoaqueous layer



High molecular weight HA may stabilise the mucin and aqueous layers through its mucoadhesion, helping to provide hydration and break the vicious cycle.[6]

- It has been found that high molecular weight HA exhibited binding with the mucin Muc2, while low molecular weight HA did not.
- It is also hypothesised that high molecular weight HA compensates for reduced MUC5AC levels in DED by forming entanglements with the remaining MUC5AC, further enhancing its mucoadhesive properties and stabilising the tear film.

The mucoadhesive index increases with higher molecular weight of HA.[6]

Comparing the Effectiveness of Low Molecular Weight HA and High Molecular Weight HA

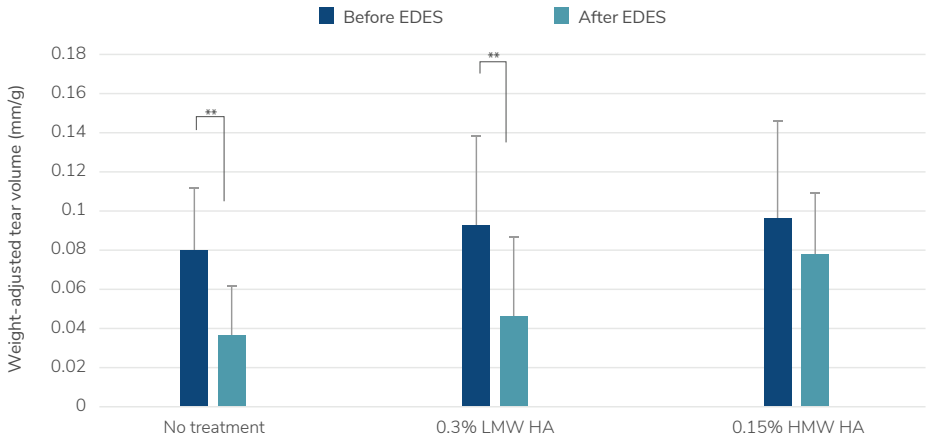
Study 1:

> **A study comparing the effects of low vs high molecular weight HA in dry eye treatment, following environmental dry eye stress (EDES) to mimic an office environment, found:[1]**

Treatment with high molecular weight HA was associated with:

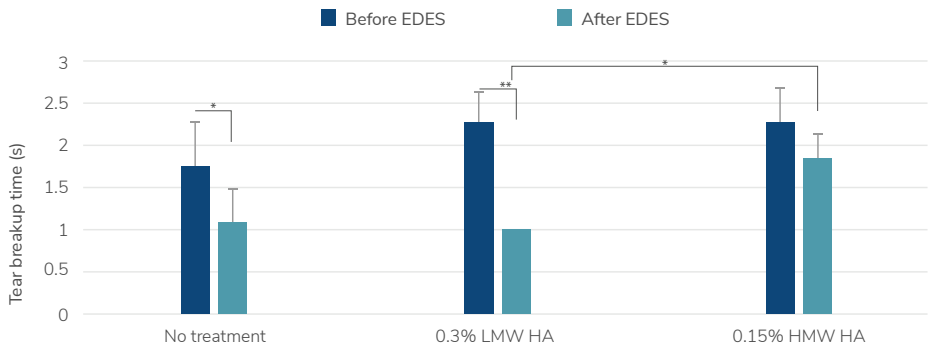
- Greater tear volume – indicating better resistance to drying by retention of water
- Significantly longer tear break-up time – indicating better retention and stabilization of the tear film
- Less staining (fluorescein and lissamine green)

Effect on tear volume: HMW HA resists the effect of drying as no significant decrease in tear volume



EDES: environmental dry eye stress; HMW HA: high molecular weight Hyaluronic Acid; LMW HA: low molecular weight Hyaluronic Acid
** $p < 0.01$

Effect on TBUT: HMW HA maintains tear stability in drying conditions



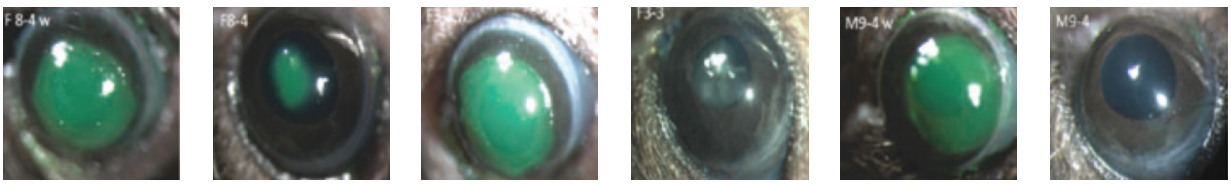
EDES: environmental dry eye stress; HMW HA: high molecular weight Hyaluronic Acid; LMW HA: low molecular weight Hyaluronic Acid
TBUT: Tear Break Up Time
* $p < 0.05$ ** $p < 0.01$

Adapted from Kojima, T. et al. (2020)

Study 2:

Impact of Hyaluronic Acid-Containing Artificial Tear Products on Reepithelialization in an In Vivo Corneal Wound Model using different molecular weights of HA

LMW HA (248 kDa)	MMW HA (918 kDa)	HMW HA (2026 kDa)
6.3% re-epithelized corneas	26.7% re-epithelized corneas	43.75% re-epithelized corneas



0 hour* 24 hour* 0 hour* 24 hour* 0 hour* 24 hour*

*Hours post-treatment following epithelium debridement. Adapted from Carlson, E., Kao, W.W.Y., & Ogundele, A. (2018) and Aragona, P., Papa, V., Micali, A., et al. (2002).

Reduction in staining shown in this study suggests that the **corneas treated with high molecular weight HA had a better recovery and regrowth of the outer layer of cells**[15]

LMW HA Drop (0.15% HA; Hyabak, Thea Pharmaceuticals Limited, United Kingdom); MMW HA Drop (0.18% HA; Vismed, TRB Chemedica International S.A., Switzerland); HMW HA (0.1% HA; Hylo Tear, URSAPHARM Arzneimittel GmbH, Germany)

Study 3:

Application frequency – key indicator for the efficiency of severe dry eye disease treatment – evidence for the importance of molecular weight of hyaluronan in lubricating agents[29]

When treating severe DED, the DF (drop application frequency) can be significantly reduced by using very high Mw HA lubricant eye drops, which better alleviate DED symptoms and decrease the OSDI scores. These drops not only provide an attractive and comfortable alternative for patients with severe DED but also offer the possibility of reducing the disease's socioeconomic burden, both for affected individuals and society as a whole.

Summary

Hyaluronic Acid (HA) has proven to be an enduring element of Dry Eye Disease treatment[1]

- A substance produced naturally in the body, it has a very high water-binding capacity by nature and is very well tolerated[2]

However, not all hyaluronic acid is the same[3-6]

Differing in molecular weight, which is dependent on chain length, the rule is: **Longer chain length = higher molecular weight = higher viscosity, providing Long-Lasting Lubrication**

Long-chain hyaluronic acid is best suited for use in ophthalmology as only high molecular weight hyaluronic acid has the properties that offer these clinical benefits for the eye:

1. Long-lasting lubrication:[7-8]

- Superior hydration
- Longer retention time on ocular surface
- Moves like a natural tear

2. Long-lasting protection:[6, 9-13]

- Exhibits anti-inflammatory properties[9-12]
- Reduces and repairs damage to the cornea[13]
- Improves vision stability, discomfort and pain[6-13]

3. Long-lasting replenishment:[1,2,6,13]

- Compensates for lack of secretory mucins[2]
- Increasing mucin expression[2]
- Binds to mucins[6]

Advantages of high molecular hyaluronic acid at a glance:

- Improvement of symptoms and relief of pain through long-lasting moistening of the surface of the eye
- No visual impairment due to imitating the properties of the natural tear film
- Fewer drops needed subsequently due to extended residence time on the surface of the eye
- Protection of the cornea and conjunctiva

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