A 1-month study of efficacy and safety of 0.18% sodium hyaluronate (Vismed®) *vs.* 0.3% carbomer and 0.9% saline in patients with bilateral moderate dry eye syndrome

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Introduction

- According to the recent definition of the Dry Eye Workshop (DEWS) group[1], dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.
- Several authors[2,3] obtained excellent results in the symptomatic treatment of this pathology with solutions containing sodium hyaluronate, when these solutions were used at regular intervals.
- Sodium hyaluronate (SH) was chosen as the active compound in Vismed® because of its unique viscoelastic properties, which lubricate and protect the ocular surface. In addition, SH exhibits water entrapping and mucoadhesive properties, which delay the evaporation of the product from the eye surface.
- Vismed® is a unique formulation that contains ions naturally present in the tear fluid (namely calcium, magnesium, potassium, sodium and chloride) to maintain the physiology of the cornea. It has been formulated to be hypotonic, in order to compensate for the hypertonicity of tears in patient experiencing dry eye syndrome.

Study objective

The aim of this study is to assess the efficacy and safety of 0.18% sodium hyaluronate (Vismed®) *vs.* 0.9% sodium chloride (saline) and 0.3% carbomer solutions in patients with bilateral moderate dry eye syndrome.

Methods

Study design

Randomised (1:1:1), double-masked, parallel-group, controlled, 3-arm, multicentre (5 centres in Hungary), phase II trial, conducted according to GCP. All patients gave their written informed consent for participation in the study.

Main inclusion criteria

- Male and female patients aged 18 years and over,
- With a total score of staining with lissamine green of at least 5/12 and not more than 10/12 for each eye,
- With at least 2 symptoms of dry eye among soreness, scratchiness, dryness, grittiness and burning, each:
  - Occurring at least often and
  - Rated at least 30 mm and not more than 70 mm on the 0 to 100 mm VAS,
- With at least 2 out of the 3 following objective parameters:
  - Schirmer I test ≤ 10 mm wetting/5 min for each eye,
  - Tear film BUT ≤ 10 s for each eye,
  - Staining with fluorescein with a total score ≥ 3/7 for each eye.

Products and treatment

Sodium hyaluronate 0.18% (Vismed®) or sodium chloride 0.9% (saline) or carbomer 0.3% (Lacryvisc®) 1 instillation into each eye 2 to 4 times per day for 28 days.

Statistical analysis

Kruskal-Wallis H-tests and subsequent U-tests according to Wilcoxon Mann Whitney were performed.

Procedures and assessments

Table 1: Study design and schedule of assessments

	Run-in	Baseline	Treatment and follow-up, double-masked
			Vismed® / Carbomer / Saline
Procedures and assessments	**V1 D-16 to D-12**	**V2 D0**	**V3 D28 ± 3D**
Inclusion and exclusion criteria	X	X	
Concomitant medications and medical history	X	X	X
Symptoms intensity and frequency	X	X	X
Repercussion of symptoms on daily life	X	X	X
Comfort of the eye drops (blurred vision)			X
Slit lamp examination	X	X	X
Tear volume (Schirmer I test)	X	X	X
Tear film BUT	X	X	X
Corneal staining with fluorescein	X	X	X
Staining with lissamine green	X	X	X
Global efficacy judgement			X
Adverse event report	X	X	X

Results

Patients

Patient disposition is shown in Table 2 while demographic and baseline characteristics are summarised in Table 3.

Table 2: Disposition of patients

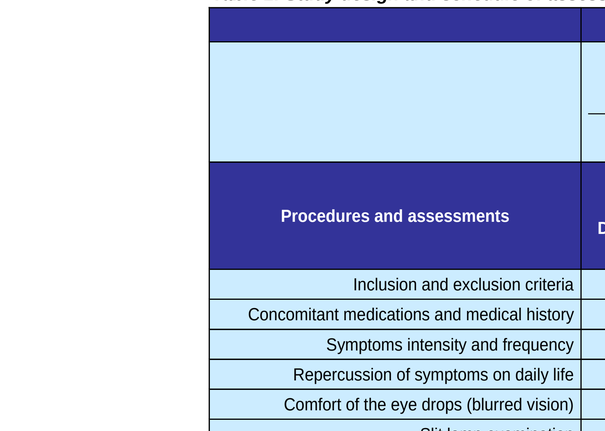


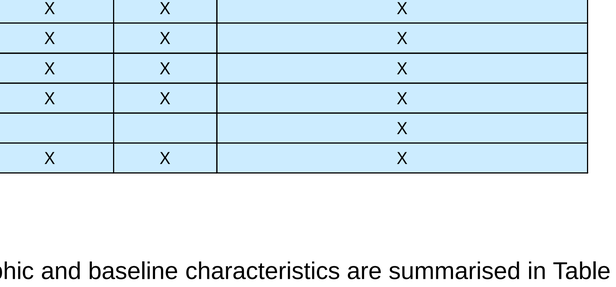
Table 3: Demographic and baseline characteristics, PP population

Characteristics	Vismed® n=36	Saline n=33	Carbomer n=32	p-value
Gender (n) (Female/Male)	30 / 6	29 / 4	27 /5	p < 0.86
Age (years), mean (± std)	**59.12** (11.21)	**62.1** (12.25)	**61.9** (11.15)	p < 0.54
Symptom intensity (mm) mean (± std)	**184.6** (76.0)	**175.4** (70.8)	**183.1** (75.5)	p<0.85
Symptom frequency (score) mean (± std)	**12.1** (2.2)	**12.4** (1.8)	**12.4** (1.9)	p<0.59
Impact on daily life activities (score) mean (± std)	**1.8** (0.7)	**1.8** (0.6)	**1.6** (0.6)	p<0.78
Fluorescein staining (score) mean (± std)	**2.9** (0.8)	**2.9** (1.1)	**3.1** (0.8)	p<0.20
BUT (seconds) mean (± std)	**3.3** (1.1)	**3.3** (1.2)	**3.4** (1.0)	p<0.75
Schirmer I test (mm wetting/5min) mean (± std)	**4.9** (2.8)	**5.0** (3.1)	**5.8** (3.1)	p<0.84

Efficacy

Global symptoms intensity

Vismed® and carbomer showed a significantly greater decrease in symptom intensity compared to saline ($p < 0.0008$ and $p < 0.02$, respectively). There was a strong trend for a greater decrease with Vismed® treatment (-41.4%) compared with the carbomer group (-31.7%), but this difference was not significant ($p < 0.22$) (figure 1).

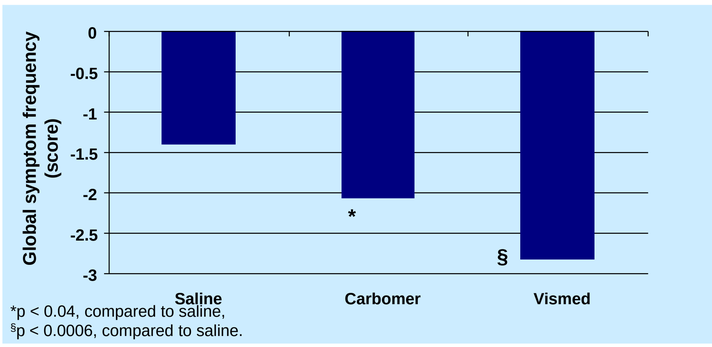


*p < 0.02, compared to saline,
§p < 0.0008, compared to saline.

Figure 1: Global symptom intensity VAS (mm), difference from baseline, mean, PP data set

Global symptoms frequency

Vismed® and carbomer showed a significantly greater decrease in symptom frequency compared to saline ($p < 0.0006$ and $p < 0.04$, respectively). There was a strong trend for a greater decrease with Vismed® treatment (-21.8%) compared with carbomer (-16.5%), with p value close to significance ($p < 0.076$) (figure 2).

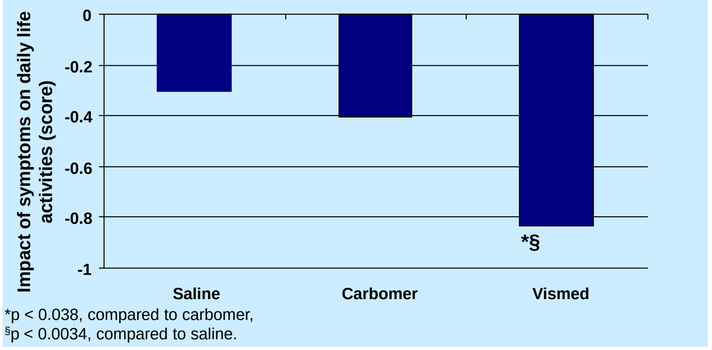


*p < 0.04, compared to saline,
§p < 0.0006, compared to saline.

Figure 2: Global symptom frequency (score), difference from baseline, mean, PP data set

Repercussion of symptoms on activities of daily life

Patients in the Vismed® group showed a significantly greater decrease in repercussion of symptoms on activities of daily life (-46.8%) than those in the saline (-17.7%, $p < 0.0034$) and carbomer groups (-18.7%, $p < 0.038$). No significant difference was found between the carbomer and saline groups ($p < 0.039$) (figure 3).

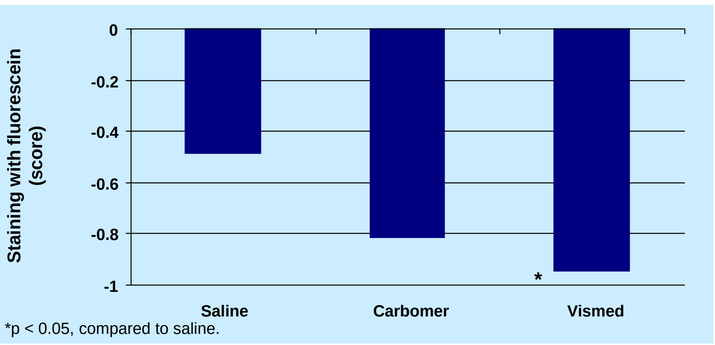


*p < 0.038, compared to carbomer,
§p < 0.0034, compared to saline.

Figure 3: Impact on daily life activities (score), difference from baseline, mean, PP data set

Corneal staining with fluorescein

There was a significantly ($p < 0.05$) greater improvement of fluorescein staining in the Vismed® group (-31.2%), compared to the saline group (-19.1%). A trend in favour of Vismed® was observed between the Vismed® and carbomer (-29.0%) treatments ($p < 0.48$) (figure 4).



*p < 0.05, compared to saline.

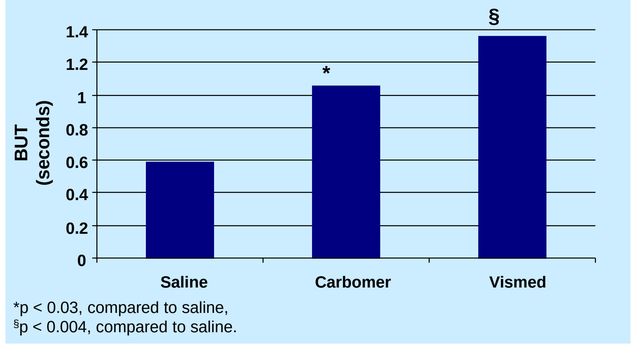
Figure 4: Corneal staining with fluorescein (total score), difference from baseline, mean, target eye, PP data set

BUT in the target eye

There was a significantly greater improvement of BUT in the Vismed® (+46.1%, $p < 0.004$) and carbomer (+40.2%, $p < 0.03$) groups compared to the saline group (+22.5%). Although there was no significant difference between the Vismed® and carbomer groups ($p < 0.45$) a trend in favour of Vismed® was observed (figure 5).

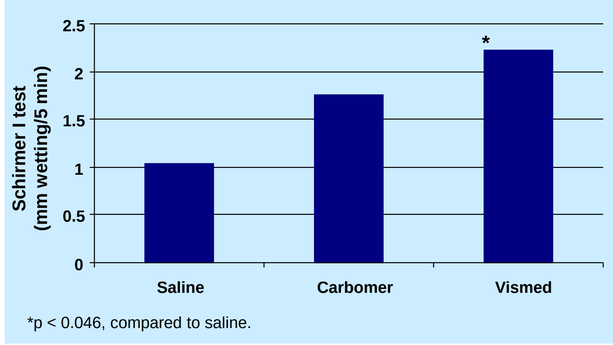
Schirmer I test in the target eye

There was a significantly greater improvement ($p < 0.046$) of Schirmer I test in the Vismed® group (+89.3%) compared to the saline group (+39.3%). Although there was no significant difference between the Vismed® and carbomer (+44.5%) groups ($p > 0.05$) a trend in favour of Vismed® was observed (figure 6).



*p < 0.03, compared to saline,
§p < 0.004, compared to saline.

Figure 5: BUT (seconds) in the target eye, difference from baseline, mean, PP data set



*p < 0.046, compared to saline.

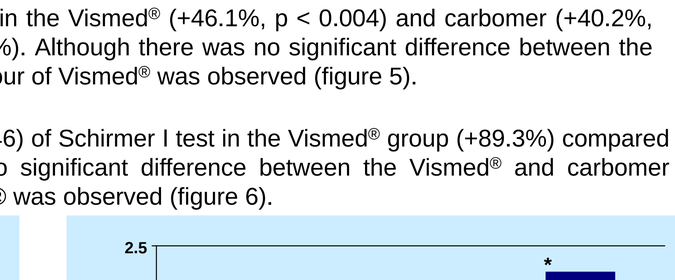
Figure 6: Schirmer I test (mm wetting/5min), difference from baseline, mean, PP data set

Safety

The results for each of the measures used to assess safety and tolerability (BCVA, examination of ocular adnexa, impairment of symptoms) indicate that Vismed® had a similar profile to that of saline and carbomer over 28 days.

Comfort of the eye drops: presence of blurred vision

There was a significantly ($p < 0.008$) higher number of patients experiencing blurred vision following instillation in the carbomer group (56.2%) compared with the saline group (24.2%). No significant difference was observed between the Vismed® and saline eye drops ($p < 0.078$) (figure 7).



*p < 0.008, compared to saline.

Figure 7: Blurred vision, percentage of patients at V3, PP data set

Conclusions

- Results showed that Vismed®, saline and carbomer were well tolerated and effective in reducing subjective symptoms and objective signs in patients with moderate dry eye.
- Vismed® was significantly better than saline and not significantly different from carbomer in improving symptoms intensity and frequency, corneal staining with fluorescein and for global evaluation of efficacy.
- Vismed® was significantly superior to both saline and carbomer in reducing the impact of dry eye symptoms on daily life activities.
- Carbomer was significantly less comfortable in the eye (*i.e.* blurred vision) than saline, whereas no significant difference was observed between Vismed® and saline for this parameter.
- No significant differences were observed between the 3 groups for BCVA, slit lamp examination, lissamine green staining and number of daily instillations of the eye drops.

References

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2. Brignole F, Dupas B, Baeyens V, Baudouin C. Reduction in keratitis and CD44 expression in patients with dry eye treated with a unique 0.18% sodium hyaluronate solution. Invest Ophthalmol 2001; 42(4):S32.
3. Aragona P, Papa V, Micali A, Santocono M, Milazzo G. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. Br J Ophthalmol 2002; 86(2):181-4.