

Prospective, Randomized, Controlled Comparison of SYSTANE UD Eye Drops Versus VISINE INTENSIV 1% EDO Eye Drops for the Treatment of Moderate Dry Eye

Christina Jacobi,¹ Friedrich E. Kruse,¹ and Claus Cursiefen²

Abstract

Purpose: The aim of this prospective, randomized, clinical, single-center study was to compare the safety and efficacy of 2 ocular surface lubricant eye drops: preservative-free hydroxypropyl (HP)-Guar (SYSTANE UD[®]) eye drops versus preservative-free *Tamarindus indica* seed polysaccharide (TSP) 1% (VISINE INTENSIV 1% EDO[®]) eye drops.

Methods: Fifty-six eyes of 28 patients with moderate keratoconjunctivitis sicca (DEWS severity level 2) were enrolled in the trial. Patients were randomized for 2 treatment groups (SYSTANE UD eye drops vs. VISINE INTENSIV 1% EDO eye drops). The eye drops in both groups were applied 5 times per day for 3 months. Statistical analyses were performed using Statistica[™] software (Mann–Whitney U-test and Wilcoxon test). *P*-Values < 0.05 were considered significant.

Results: After 3 months of treatment the patients of both groups had subjective benefit in the relief of symptoms of dry eye disease evaluated by the Ocular Surface Disease Index (OSDI) questionnaire score. Patients treated with HP-Guar and TSP showed improvements in tear film stability measured by tear break-up time (TBUT), which are statistically significant in the HP-Guar group (*P* = 0.02).

Conclusions: The results of this clinical trial show improvements of symptoms and signs in patients with moderate dry eye after the consistent use of preservative-free HP-Guar and TSP lubricant eye drops. Both artificial tear formulations produce amelioration in tear film stability improving eye conditions and patient quality of life. HP-Guar seems to be slightly more effective in improving ocular surface protection by decreasing tear film evaporation.

Introduction

DRY EYE IS defined as 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. Major pathophysiological mechanisms increase osmolarity of the tear film and inflammation of the ocular surface (DEWS 2007).^{1–4} Current management and therapy of dry eye includes the use of artificial tears, anti-inflammatory agents, biological tear substitutes, and the systemic use of antioxidants (omega-3 fatty acids). Recent increases in knowledge and understanding of the pathogenesis of dry eye have led to the development of improvements in artificial tear preparations that are intended to address not only the tear film disorder but also to improve and protect the ocular surface.^{5–9}

Moreover, new artificial tears are able to substitute the mucin layer of the 3-layered tear film. The aim of this study was to compare the safety and efficacy of 2 ocular surface lubricant eye drops: preservative-free hydroxypropyl (HP)-Guar (SYSTANE UD[®]) eye drops versus preservative-free *Tamarindus indica* seed polysaccharide (TSP) 1% (VISINE INTENSIV 1% EDO[®]) eye drops. HP-Guar is suggested to preferentially bind to the more hydrophobic, desiccated or damaged areas of the surface epithelial cells, providing temporary protection for these cells. TSP possesses mucomimetic, mucoadhesive, and pseudoplastic properties.^{10–16} The mucin-like molecular structure of TSP is similar to corneal and conjunctival mucin 1 (MUC1), a transmembrane glycoprotein thought to play an essential role in protecting and wetting the corneal surface.^{12,14,17,18}

¹Department of Ophthalmology, University of Erlangen-Nuremberg, Erlangen, Germany.

²Department of Ophthalmology, University of Cologne, Cologne, Germany.

Methods

This prospective, randomized, clinical single-center study was conducted according to the principles contained in the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the University of Erlangen-Nuremberg. Written consent was obtained from all patients after explanation of the procedures and study requirements. Fifty-six eyes of 28 patients (age 44 ± 8 ; 9 men and 19 women) with moderate keratoconjunctivitis sicca (DEWS dry eye severity level 2)¹ were enrolled in this clinical trial.

Inclusion criteria for moderate dry eye disease were typical symptoms measured by a validated questionnaire: Ocular Surface Disease Index questionnaire Score (OSDI Score) > 40 , a tear break-up time (TBUT) < 10 s, a Schirmer test with anesthesia < 10 mm, and lid-parallel conjunctival folds (LIPCOF) > 2 . OSDI Scores were evaluated prior to and after the treatment.

Exclusion criteria consisted of medical history of trauma or infection, ocular allergies, pregnancy, lactation, history of refractive surgery/ocular surgery/any other surgery within the previous 6 months, immunosuppressive medications, or the use of contact lenses within 14 days prior to ophthalmological examination. Moreover, patients wearing punctum plugs; patients with history or evidence of epithelial keratitis from herpes simplex; recent varicella, corneal, or conjunctival viral disease; acute corneal, conjunctival, or palpebral bacterial infection; or ocular fungal infection were excluded from this clinical trial.

Patients were randomized for 2 treatment groups: HP-Guar group: SYSTANE UD eye drops (Alcon Labs, Inc., Fort Worth, TX) versus TSP group: VISINE INTENSIV 1% EDO eye drops (Johnson and Johnson, New Brunswick, NJ), which were applied 5 times per day for 3 months. No other concurrent ocular therapy was used.

The test measurements were accomplished in the following order in all patients.

OSDI Score questionnaire

The OSDI is a subjective symptom questionnaire that measures the severity of dry eye disease. It includes 12 items regarding visual function, ocular symptoms, and environmental triggers queried for the past week. Possible answers for the questions are as follows: none of the time, some of the time, half of the time, most of the time, and all of the time (0–4). The scoring algorithm published contains scores from 0 to 100 (0 = no disability, 100 = complete disability).¹⁹ The OSDI is used as an outcome measure in randomized controlled trials.⁹

Visual acuity measurements

Visual acuity was evaluated by best spectacle-corrected visual acuity (BSCVA) using the Snellen chart.

LIPCOF (Degree 0–3)

LIPCOF were evaluated by slit-lamp examination. The classification of LIPCOF according to Höh et al.²⁰ was used. With Degree 0, no permanent conjunctival fold exists. Degree 1 describes the permanent presence of an individual fold, which does not exceed the height of the normal tear meniscus. With Degree 2, the LIPCOF disintegrates into 2 or several small parallel folds that are lower than the normal tear

meniscus. If there are several parallel conjunctival folds exceeding the height of the normal tear meniscus, then Degree 3 exists.²⁰

TBUT(s)

For diagnosing tear film stability, a standardized measurement of the tear film break-up time was accomplished. Five microliters of nonpreserved 2% sodium fluorescein was instilled onto the bulbar conjunctiva without inducing reflex tearing by using a micropipette. Then, the patient was instructed to blink normally without squeezing several times to distribute the fluorescein and then refrain from blinking until told otherwise. The slit-lamp magnification was set at $10\times$ and a Wratten 12 yellow filter was used to enhance observation of the tear film over the entire cornea.^{1,21–23} A stopwatch was used to record time between last complete blink and the first disruption of the tear film. After observing the TBUT, the patient was instructed to blink normally again. Three measurements were taken as recommended by the DEWS report 2007,¹ and the average was calculated.⁹

Fluorescein and rose bengal staining

Fluorescein- and rose bengal-impregnated strips (Bio Glo™ Sterile Fluorescein Ophthalmic Strips; Rose Glo™ Sterile Rose Bengal Ophthalmic Strips, Alta Loma, CA) were used. A single drop of sterile, nonpreserved saline was applied to the fluorescein or rose bengal-impregnated strip. The drop was allowed to just saturate the tip of the paper strip, and the excess was shaken off. The lower eyelid was pulled down and the tip of the strip touched gently on the inferior palpebral conjunctiva. Then, the patient was asked to gently close and roll the eyes around to adequately distribute the dye across the ocular surface. The right eye was done first, followed immediately by the left eye. For fluorescein staining, a blue exciter filter was used over a white light source, and the staining pattern and density of staining of the conjunctiva and cornea were observed. A Kodak Wratten 12 barrier filter (Kodak, Rochester, NY) was placed over the slit-lamp objectives to improve the viewing of epithelial staining of the ocular surface.

For rose bengal staining, examination was done at a standard time interval after dye placement (1 min). Each eye was examined in turn, observing the staining pattern and density of staining of the conjunctiva and cornea.¹

For evaluation of both, fluorescein and rose bengal staining, the van Bijsterveld grading system was used.¹

Schirmer test with anesthesia (eyes closed, mm)

After topical anesthesia with 1 drop of oxybuprocaine-HCL (Conjuncain-EDO®), a Schirmer test strip (35×5 mm; Liposic-Schirmer-Test-Streifen, Dr. Mann Pharma, Berlin, Germany) was placed in the lower outer fornix and then the patient was instructed to close his/her eyes. After 5 min, the strip was removed from the eye and the length of wetting was measured.^{1,9}

Intraocular pressure (mmHg)

Intraocular pressure (IOP) was measured with the slit-lamp in combination with the Goldmann applanation tonometer.

Adverse effects

For evaluation of possible adverse effects, patients were examined for acute corneal, conjunctival, or palpebral bacterial infection; ocular fungal infection; ocular allergies; or neovascularization of the cornea. Besides, visual acuity and IOP measurements were performed. The OSDI Score was applied in each patient to assess possible subjective disturbing sensations, for example, burning, blurred vision, or foreign body sensation.

Statistical analysis

Statistical analyses were performed using Statistica™ software for Windows (Mann–Whitney U-test and Wilcoxon matched-pairs signed-ranks test); *P*-values <0.05 were considered significant. The results were expressed as mean ± standard deviation.

Results

At baseline examination, there were no statistically significant differences in all parameters between both groups. Therefore, both treatment groups are comparable. After 3 months of treatment there were improvements of TBUT, Schirmer test, LIPCOF, and OSDI Score in both groups; IOP and BSCVA remained stable. In the HP-Guar group the results of TBUT and OSDI Score showed statistically significant amelioration after 3 months; in the TSP group, only the OSDI Score improved significantly. In the HP-Guar group there was a statistically significant improvement of TBUT after 3 months compared with the TSP group (*P*=0.02).

Evaluation of fluorescein and rose bengal staining showed improvements in the HP-Guar group from 4 (2–6) to 3 (1–6) and from 3 (2–6) to 2 (0–5) but there were no statistically significant differences. In the TSP group there was no improvement in the fluorescein staining but there was amelioration in the rose bengal staining from 3 (1–6) to 2 (1–5). Statistically significant differences could not be detected (Tables 1 and 2). After applying SYSTANE UD eye drops and VISINE INTENSIV 1% EDO eye drops 5 times per day for 3 months, no adverse effects (ocular infections, allergic reactions, or disturbing sensations at application) could be

observed in both treatment groups. Visual acuity and IOP showed rather constant values.

Discussion

In dry eye disease, hyperosmolarity stimulates a cascade of inflammatory events in the epithelial surface cells, involving mitogen-activated protein kinases and nuclear factor-κB signaling pathways and the generation of inflammatory cytokines (interleukin-1α, -1β, and tumor necrosis factor-α) and matrix metalloproteinases at the ocular surface.^{1,5,9,24} Epithelial damage involves cell death by apoptosis, loss of goblet cells, and disturbance of mucin expression. This leads to tear film instability that exacerbates ocular surface hyperosmolarity and completes the vicious circle that is maintained at the ocular surface.^{25–28} It is proven that the stability of the tear film depends on its chemical–physical characteristics interacting with the conjunctival and corneal epithelium via membrane-spanning mucins, for example, MUC-16 and MUC-4. The mucin layer is considered as a surfactant or wetting agent, responsible for lowering the surface tension of the hydrophobic ocular surface. Recently, the tear film has been described as a hydrated mucin gel in which the mucin concentration decreases with distance from the epithelial cell surface.^{1,25,29–31} The mucin in the precorneal tear film is discussed to have a similar protective role as the mucin in the stomach acting as storage vehicle for agents secreted by the main and accessory lacrimal glands and the ocular surface cells.^{1,21,22,25} Our clinical trial was conducted in order to compare 2 preservative-free lubricant eye drops that intend to sustain the mucin layer of the precorneal tear film.

SYSTANE UD eye drops consist of the active ingredients polyethylene glycol 400 (0.4%)/propylene glycol (0.3%)–based tear that contains HP-Guar as a gelling agent. The polymer HP-Guar is an *in situ* gelling agent designed to mimic the mucin layer of the tear film providing prolonged contact time. HP-Guar eye drops may also increase the aqueous layer of the precorneal tear film to some degree.^{32–37} Several clinical studies could show that eye drops containing HP-Guar are able to improve tear film stability resulting in less ocular surface staining.^{15,16,33,37–39} In our study there was also a decrease in the fluorescein and rose bengal staining results in the HP-Guar group but no statistically significant

TABLE 1. OCULAR FUNCTION TEST VALUES OBSERVED BEFORE AND AFTER THE TREATMENT WITH SYSTANE UD (HYDROXYPROPYL-GUAR) AND VISINE INTENSIV 1% EDO (TSP) EYE DROPS FOR 3 MONTHS

Function test	HP-Guar group			TSP group		
	Baseline Mean ± SD	3 Months Mean ± SD	Wilcoxon P-value	Baseline Mean ± SD	3 Months Mean ± SD	Wilcoxon P-value
BSCVA	0.9 ± 0.2	0.9 ± 0.21	0.61	0.89 ± 0.19	1.0 ± 0.15	0.36
TBUT	8.5 ± 4.8	14.05 ± 4.93 ^a	0.002	8.21 ± 4.7	10.75 ± 5.77	0.25
Schirmer	11.91 ± 6.09	15.3 ± 8.13	0.33	10.75 ± 8.7	15.1 ± 2.48	0.25
LIPCOF	2.63 ± 1.21	2.45 ± 0.76	0.18	1.75 ± 1.2	2.2 ± 0.77	0.14
OSDI	50.0 ± 19.1	31.3 ± 18.2 ^a	0.01	50.8 ± 12.8	34.1 ± 18.6 ^a	0.03
IOP	12.46 ± 2.45	12.05 ± 1.28	0.78	11.17 ± 2.4	10.95 ± 2.5	0.57
Fluorescein	4 (2–6)	3 (1–6)	0.58	4 (1–5)	4 (0–4)	0.68
Rose bengal	3 (2–6)	2 (0–5)	0.16	3 (1–6)	2 (1–5)	0.22

^a*P* ≤ 0.05, Wilcoxon matched-pairs signed-ranks test: comparison of baseline values with values after 3 months, mean ± SD, fluorescein and rose bengal, mean and I–III. Quartile.

TSP, *Tamarindus indica* seed polysaccharide; HP, hydroxypropyl; SD, standard deviation; BSCVA, best spectacle-corrected visual acuity; TBUT, tear break-up time; LIPCOF, lid-parallel conjunctival folds; OSDI, Ocular Surface Disease Index; IOP, intraocular pressure.

TABLE 2. COMPARISON OF THE OCULAR FUNCTION TESTS BETWEEN THE SYSTANE UD (HYDROXYPROPYL-GUAR) GROUP AND VISINE INTENSIV 1% EDO (TSP) GROUP AT BASELINE AND AFTER 3 MONTHS

Function test		HP-Guar group Mean \pm SD	TSP group Mean \pm SD	Mann-Whitney P-value
Baseline	BSCVA	0.9 \pm 0.2	0.89 \pm 0.19	0.17
	TBUT	8.5 \pm 4.8	8.21 \pm 4.7	0.82
	Schirmer	11.91 \pm 6.09	10.75 \pm 8.7	0.19
	LIPCOF	2.63 \pm 1.21	1.75 \pm 1.2	0.20
	OSDI	50.0 \pm 19.1	50.8 \pm 12.8	0.95
	IOP	12.46 \pm 2.45	11.17 \pm 2.4	0.37
	Fluorescein	4 (2–6)	4 (1–5)	0.48
	Rose bengal	3 (2–6)	3 (1–6)	0.52
3 Months	BSCVA	0.9 \pm 0.21	1.0 \pm 0.15	0.34
	TBUT	14.05 \pm 4.93 ^a	10.75 \pm 5.77	0.02
	Schirmer	15.3 \pm 8.13	15.1 \pm 2.48	0.99
	LIPCOF	2.45 \pm 0.76	2.2 \pm 0.77	0.31
	OSDI	31.3 \pm 18.2	34.1 \pm 18.6	0.28
	IOP	12.05 \pm 1.28	10.95 \pm 2.5	0.35
	Fluorescein	3 (1–6)	4 (0–4)	0.08
	Rose bengal	2 (0–5)	2 (1–5)	0.25

^a $P \leq 0.05$, Mann-Whitney U test: comparison between the 2 study groups at baseline and after 3 months, mean \pm SD, fluorescein and rose bengal, mean and I-III. Quartile.

changes. Moreover, clinical trials have demonstrated the ability of HP-Guar eye drops to significantly reduce signs and symptoms of dry eye compared to baseline and to active controls.^{15,16,18,33–35} HP-Guar appears to have a 2-phase pathophysiological mechanism that initially covers the ocular surface and adds volume to the tear film (bulking phase) and then restructures the film to provide durable protection (tear sustaining phase).³⁷ HP-Guar is a derivate of guar gum, a high-molecular-weight branched polymer. In the presence of borate the HP-Guar polymer undergoes a crosslinking/gelling reaction that interacts with cationic lysozyme that represents an important tear film protein. This reaction leads to an increase in viscosity of the tear film, producing a mucin-like coating on the ocular surface.^{15,16,32,39} In our study (Tables 1 and 2) in the HP-Guar group, there were improvements after 3 months in TBUT from 8.5 \pm 4.8 s to 14.05 \pm 4.93 s, in Schirmer test from 11.9 \pm 6.09 mm to 15.3 \pm 8.13 mm, and in OSDI Score from 50.0 \pm 19.1 to 31.3 \pm 18.2, which were statistically significant for TBUT and OSDI Score. The OSDI Score showed mainly improvements in sensitivity to light. Similar results were also demonstrated by other clinical trials of Christensen et al.³⁹ and Ousler et al.²³ showing significant increases in TBUT after instillation of HP-Guar eye drops.³⁷ This may be due to the fact that HP-Guar is supposed to bind to damaged hydrophobic areas of epithelial cells followed by attachment of a protective gel matrix intended to regenerate ocular surface health.³⁷ In our study, there was also a statistically significant difference in the TBUT after 3 months of treatment in the HP-Guar group compared with the TSP group.

TSP possesses mucomimetic, mucoadhesive, and pseudoplastic properties. TSP is a non-ionic, neutral, branched polysaccharide consisting of a cellulose-like backbone carrying xylose and galactoxylose substituents.¹⁴ In animal

studies it was shown that TSP, added to eye drops for the topical ocular administration of certain antimicrobial agents, enhanced transcorneal disposition and intra-ocular penetration of these drugs.⁴⁰ The mucin-like molecular structure of TSP is similar to MUC1, a transmembrane glycoprotein thought to play an essential role in protecting and wetting the corneal surface.^{10–14} MUC1 is a membrane spanning mucin, expressed by the epithelium of the conjunctiva and has the function to facilitate the spread of gel-forming mucin. Mucins possess surface activity and the mucin layer provides the corneal epithelium with a hydrophilic surface in order to spread the tear film over the cornea and ocular surface. Mucus deficiency leads to poor contact of the tear film with the eye surface and a loss of film stability.^{10–14} In our study in the TSP group, OSDI Score improved significantly from 50.8 \pm 12.8 to 34.1 \pm 18.6 after 3 months. Especially improvements in blurred vision, burning of the ocular surface, and the feeling of gritty eyes could be found. After 3 months of treatment the patients of both groups had subjective benefit in the relief of symptoms of dry eye disease evaluated by the OSDI Score. In the HP-Guar group there was a relief in the impression of sensitivity to light whereas in the TSP group there was a greater amelioration in blurred vision, burning, and the feeling of gritty eyes. Rolando et al.¹⁴ could also find significant improvement in the subjective symptoms of dry eye disease in patients treated with TSP 1% eye drops between baseline and final visits after 90 days, especially for symptoms relating to trouble blinking, ocular burning, and sensation of foreign body. Further, statistically significant improvements between baseline and final visits were observed under topical therapy with TSP 1% eye drops with respect to tear film break-up time and corneal and conjunctival damage measured by vital stainings.¹⁴ In our clinical trial there was a decrease in the rose bengal staining that was not statistically significant. Moreover, there were no statistically significant differences between the TSP group and the HP-Guar group.

The results of our study show significant differences between the HP-Guar group and the TSP group in the TBUT after 3 months of treatment. The reason for this could be the different viscosities and pH values. The HP-Guar containing SYSTANE UD eye drops has a viscosity of \sim 8–15 mPa \cdot s and a pH of 7.9. HP-Guar is pH sensitive. When it is exposed to the ocular surface pH of dry eye patients (\sim 7.6), the viscosity increases significantly to about 263 mPa \cdot s. HP-Guar adapts its viscosity to the ocular surface pH. The drier the ocular surface, the more viscous HP-Guar becomes with an increased cross-linking resulting in a strong gel-like structure. Therefore, HP-Guar is able to provide an excellent ocular surface protection.^{32,39} TSP 1% eye drops on the other hand have a viscosity of \sim 70–180 mPa \cdot s and a pH value of 7.2. When exposed to the tear film, TSP becomes less viscous and evenly distributes over the ocular surface.^{13,14}

In both treatment groups there was amelioration in tear film stability improving eye conditions and patient quality of life. No adverse effects could be found. HP-Guar seems to be slightly more effective in improving ocular surface protection by decreasing tear film evaporation. Both preservative-free artificial tear formulations were effective and comparable in relieving symptoms and signs of dry eye syndrome in these patients with DEWS dry eye severity level 2.

Acknowledgments

This study was supported by Alcon Labs, Inc., that provided the preservative-free artificial tear formulations for both treatment groups.

Author Disclosure Statement

Competing financial interests of all authors have been appropriately disclosed according to the policy of the Journal. No competing financial interests exist for all authors.

References

- Lemp, M.A., Baudouin, C., Baum, J., et al. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international dry eye workshop. *Ocul. Surf.* 5:75–92, 2007.
- Jacobi, C., Dietrich, T., Cursiefen, C., et al. The dry eye. Current concepts on classification, diagnostics, and pathogenesis. *Ophthalmologie.* 103:9–17, 2006.
- Jacobi, C., Wenkel, H., Jacobi, A., et al. Hepatitis C and ocular surface disease. *Am. J. Ophthalmol.* 144:705–711, 2007.
- Baudouin, C. The pathology of dry eye. *Surv. Ophthalmol.* 45: 211–220, 2001.
- Stern, M.E., and Pflugfelder, S.C. Inflammation in dry eye. *Ocul. Surf.* 2:124–130, 2004.
- Khanal, S., Tomlinson, A., and Diaper, C.J. Tear physiology of aqueous deficiency and evaporative dry eye. *Optom. Vis. Sci.* 86:1235–1240, 2009.
- Lemp, M.A. Evaluation and differential diagnosis of keratoconjunctivitis sicca. *J. Rheumatol. Suppl.* 61:11–14, 2000.
- Barabino, S., Montaldo, E., Solignani, F., et al. Immune response in the conjunctival epithelium of patients with dry eye. *Exp. Eye Res.* 91:524–529, 2010.
- Jacobi, C., Jacobi, A., Kruse, F.E., et al. Tear film osmolarity measurements in dry eye disease using electrical impedance technology. *Cornea.* 30:1289–1292, 2011.
- Gidley, M.J., Lillford, P.J., Rowlands, D.W., et al. Structure and solution properties of tamarind-seed polysaccharide. *Carbohydr. Res.* 214:299–314, 1991.
- Burgalassi, S., Raimondi, L., Pirisino, R., et al. Effect of xyloglucan (tamarind seed polysaccharide) on conjunctival cell adhesion to laminin and on corneal epithelium wound healing. *Eur. J. Ophthalmol.* 10:71–76, 2000.
- Komutarin, T., Azadi, S., Butterworth, L., et al. Extract of the seed coat of *Tamarindus indica* inhibits nitric oxide production by murine macrophages *in vitro* and *in vivo*. *Food Chem. Toxicol.* 42:649–658, 2004.
- Uccello-Barretta, G., Nazzi, S., Balzano, F., et al. Enhanced affinity of ketotifen toward tamarind seed polysaccharide in comparison with hydroxyethylcellulose and hyaluronic acid: a nuclear magnetic resonance investigation. *Bioorg. Med. Chem.* 16:7371–7376, 2008.
- Rolando, M., and Valente, C. Establishing the tolerability and performance of tamarind seed polysaccharide (TSP) in treating dry eye syndrome: results of a clinical study. *BMC Ophthalmol.* 7:5, 2007.
- Wang, T.J., Wang, I.J., Ho, J.D., et al. Comparison of the clinical effects of carbomer-based lipid-containing gel and hydroxypropyl-guar gel artificial tear formulations in patients with dry eye syndrome: a 4-week, prospective, open-label, randomized, parallel-group, noninferiority study. *Clin. Ther.* 32:44–52, 2010.
- Rolando, M., Autori, S., Badino, F., et al. Protecting the ocular surface and improving the quality of life of dry eye patients: a study of the efficacy of an HP-guar containing ocular lubricant in a population of dry eye patients. *J. Ocul. Pharmacol. Ther.* 25:271–278, 2009.
- Uccello-Barretta, G., Nazzi, S., Zambito, Y., et al. Synergistic interaction between TS-polysaccharide and hyaluronic acid: implications in the formulation of eye drops. *Int. J. Pharm.* 395:122–131, 2010.
- Petricek, I., Berta, A., Higazy, M.T., et al. Hydroxypropyl-guar gellable lubricant eye drops for dry eye treatment. *Expert Opin. Pharmacother.* 9:1431–1436, 2008.
- Schiffman, R.M., Christianson, M.D., Jacobsen, G., et al. Reliability and validity of the Ocular Surface Disease Index. *Arch. Ophthalmol.* 118:615–621, 2000.
- Höh, H., Schirra, F., Kienecker, C., et al. Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye. *Ophthalmologie.* 92:802–808, 1995.
- Tomlinson, A., and Khanal, S. Assessment of tear film dynamics: quantification approach. *Ocul. Surf.* 3:81–95, 2005.
- Lemp, M.A., and Hamil, J.R., Jr. Factors affecting tear film breakup in normal eyes. *Arch. Ophthalmol.* 89:103–105, 1973.
- Ousler, G.W., Michaelson, C., and Christensen, M.T. An evaluation of tear film breakup time extension and ocular protection index scores among three marketed lubricant eye drops. *Cornea.* 26:949–952, 2007.
- Chen, Z., Tong, L., Li, Z., et al. Hyperosmolarity-induced cornification of human corneal epithelial cells is regulated by JNK MAPK. *Invest. Ophthalmol. Vis. Sci.* 49:539–549, 2008.
- Kinoshita, S., Kiorpes, T.C., Friend, J., et al. Goblet cell density in ocular surface disease: a better indicator than tear mucin. *Arch. Ophthalmol.* 101:1284–1287, 1983.
- Tsubota, K., and Yamada, M. Tear evaporation from the ocular surface. *Invest. Ophthalmol. Vis. Sci.* 33:2942–2950, 1992.
- Pflugfelder, S.C., Tseng, S.C., Sanabria, O., et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea.* 17:38–56, 1998.
- Goto, E., Endo, K., Suzuki, A., et al. Tear evaporation dynamics in normal subjects and subjects with obstructive meibomian gland dysfunction. *Invest. Ophthalmol. Vis. Sci.* 44:533–539, 2003.
- Bron, A.J., Tiffany, J.M., Gouveia, S.M., et al. Functional aspects of the tear film lipid layer. *Exp. Eye Res.* 78:347–360, 2004.
- Goto, E., Yagi, Y., Matsumoto, Y., et al. Impaired functional visual acuity of patients with dry eye. *Am. J. Ophthalmol.* 133:181–186, 2002.
- Yokoi, N., and Komuro, A. Non-invasive methods of assessing the tear film. *Exp. Eye Res.* 78:399–407, 2004.
- Guzey, M., Satici, A., Karaman, S.K., et al. The effect of lubricating eye drop containing hydroxypropyl guar on perimetry results of patients with glaucoma and trichomatous dry eye. *Ophthalmologica.* 224:109–115, 2010.
- Uchiyama, E., Di Pascuale, M.A., Butovich, I.A. et al. Impact on ocular surface evaporation of an artificial tear solution containing hydroxypropyl guar. *Eye Contact Lens.* 34:331–334, 2008.
- Versura, P., Profazio, V., and Campos, E.C. One month use of Systane improves ocular surface parameters in subjects with moderate symptoms of ocular dryness. *Clin. Ophthalmol.* 2:629–635, 2008.
- Sánchez, M.A., Arriola-Villalobos, P., et al. The effect of preservative-free HP-Guar on dry eye after phacoemulsification: a flow cytometric study. *Eye.* 24:1331–1337, 2010.

36. Springs, C.L. Novel hydroxypropyl-guar gellable lubricant eye drops for treatment of dry eye. *Adv. Ther.* 27:681–690, 2010.
37. Christensen, M.T. Corneal staining reductions observed after treatment with Systane lubricant eye drops. *Adv. Ther.* 25:1191–1199, 2008.
38. Hartsein, I., Khwarg, S., and Przydryga, J. An open-label evaluation of HP-Guar gellable lubricant eye drops for the improvement of dry eye signs and symptoms in a moderate dry eye adult population. *Curr. Med. Res. Opin.* 21:255–260, 2005.
39. Christensen, M.T., Cohen, S., Rinehart, J., et al. Clinical evaluation of an HP-guar gellable lubricant eye drop for the relief of dryness of the eye. *Curr. Eye Res.* 28:55–62, 2004.
40. Di Colo, G., Zambito, Y., Zaino, C., et al. Selected polysaccharides at comparison for their mucoadhesiveness and effect on precorneal residence of different drugs in the rabbit model. *Drug Dev. Ind. Pharm.* 35:941–949, 2009.

Received: April 2, 2012
Accepted: June 18, 2012

Address correspondence to:
Dr. Christina Jacobi
Department of Ophthalmology
University of Erlangen-Nuremberg
Schwabachanlage 6
Erlangen 91054
Germany

E-mail: christina.jacobi@uk-erlangen.de