SYSTANE®

Lubricant Eye Drops and Lubricant Eye Gel

Clinical Science Compendium

Summary of peer-reviewed clinical
and laboratory research

Medical Affairs North America

Alcon

INTRODUCTION

At Alcon, our ocular health products for dry eye and ocular allergy, such as SYSTANE® lubricant eye drops, are designed, manufactured and marketed with a body of science developed through rigorous bench research and clinical studies. As the body of knowledge behind Alcon's products grows, so does the challenge of making our customers aware of its depth. Our medical affairs organization is thus focused on both high-quality data generation and its communication to the clinical community.

High-quality scientific publications are essential to convey the clinical community's knowledge and experience with new technology. This clinical science compendium provides a consolidated view of peer-reviewed publications for the SYSTANE® family of products,* with a focus on Lubricant Eye Drops (SYSTANE®, SYSTANE® ULTRA, SYSTANE® BALANCE, SYSTANE® HYDRATION, and SYSTANE® COMPLETE) and Lubricant Eye Gel (SYSTANE® Gel Drops).

In addition to exploring this compendium, we encourage you to visit Alcon's Medical Affairs website—AlconScience.com—to learn more about how medical science matters to us. Beyond scientific publications relating to Alcon's portfolio, you will find more information on independent medical educational grants, teaching facility equipment placement, and areas of interest for investigator-initiated trials.

METHODOLOGY

The 46 articles summarized in this compendium were identified using the PubMed and Google Scholar databases incorporating the search terms "Systane", "Systane dry eye", and "hydroxypropyl guar dry eye." Articles were included when they were published between January 1, 2004 and February 10, 2020, and contained research involving the use of a SYSTANE® product for the temporary relief of burning and irritation due to dryness of the eye. Only manuscripts published in peer-reviewed journals and available in English were included in this compendium.

*** SYSTANE® products are indicated for the temporary relief of burning and irritation due to dryness of the eye**

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SYSTANE®

Laboratory Data

Ubels et al. *Curr Eye Res.* 2004;28:437–444

OVERVIEW

STUDY DESIGN

Preclinical study to determine the ability of SYSTANE® to protect ocular surface epithelial cells from desiccation *in vivo* and *in vitro,* and to promote recovery of the damaged corneal epithelial barrier *in vivo*

STUDY SITE(S)

Multiple sites in the United States

PATIENTS

Not applicable; New Zealand white rabbits and immortalized human corneal epithelial (HCE) cell models

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

In vivo experiments: rabbits' eyes were held open for 2 hours while treated with (1) SYSTANE® (PEG/PG/HP-guar), (2) a formulation identical to SYSTANE® but without HP-guar, and (3) a carboxymethylcellulose (CMC) artificial tear with Purite as a preservative (CMC/Purite, Refresh Tears® (Allergan, Inc., Irvine, CA, USA)). *In vitro* experiments: desiccation and cell viability tested in HCE cells treated with SYSTANE®, a second formulation containing hydroxypropylmethylcellulose with 0.01% benzalkonium chloride (BAC) preservative (HPMC/BAC, Visine Tears® (Pfizer, Inc., New York, NY, USA)), and Refresh Tears®

KEY ENDPOINT(S)

Damage due to desiccation, recovery of the corneal epithelium from damage, viability of corneal epithelial cells in culture

ANALYSIS AND CONCLUSIONS

SYSTANE® provided long-term desiccation protection and had no apparent deleterious effects on epithelial cell cultures.

SYSTANE® provided conditions in which a damaged corneal epithelium can recover normal barrier function, and the SYSTANE® formulation appears to provide an effective mucomimetic artificial tear product, suggesting that the product will be effective in providing superior relief for the dry eye sufferer.

STUDY RESULTS

IN VIVO DESICCATION STUDY

- Application of a single drop of SYSTANE® to rabbit corneas prior to 2 hours of desiccation resulted in corneal uptake of methylene blue that was not significantly different than the uptake by naïve corneas
- Neither the PEG/PG formulation without HP-guar, nor the artificial tear with CMC/Purite (Refresh Tears®), were effective in protecting the cornea from desiccation

CARBOXYFLOURESCEIN (CF) UPTAKE

- Treatment of corneas with 0.01% BAC for 5 minutes caused a significant increase in corneal CF uptake to 32.7±1.6 nmoles/g, compared to a control level of 2.6±2.2 nmoles/g
- When corneas were exposed to BAC for 5 minutes, followed by treatment with SYSTANE® for 1.5 hours, corneal uptake of CF was 4.2±2.3 nmol/g which was not significantly different from the 2.4±1.5 nmol/g CF uptake by paired, control corneas P>0.05)
- CF uptake by damaged corneas treated using the product without HP-guar or Refresh Tears® was significantly different from CF uptake by paired control corneas (P<0.05)

DESICCATION AND VIABILITY OF CELLS IN CULTURE STUDY

- After 15 minutes of exposure to SYSTANE®, the tear formulation without HP-guar, and Refresh Tears®, corneal epithelial cells were 77.0±4.5%, 62.5±7.0%, 87.7±6.9% viable, respectively, compared to untreated cells in keratinocyte basal medium (KBM)
- After 10 minutes of desiccation, the viability of cells exposed to the tear product without HP-guar decreased significantly to 55.6±4.1%; the viability of HCE cells treated with SYSTANE® remained at 81.9±5.7%, but decreased to 72.7±7.8% with Refresh Tears®
- Thirty minutes of desiccation reduced the viability of cells exposed to SYSTANE® to 54.9±4.5%, but this remained significantly greater than the 34.2±6.3% viability of cells exposed to the tear product without HP-guar, or the 25.4±12.8% viability of cells treated with Refresh Tears® (P<0.05)
- After 30 minutes of desiccation, the viability of cells treated with Refresh Tears® did not differ from the cells treated with Visine Tears®

Comparison of Ocular Lubricant Osmolalities

Bitton et al. *Optom Vis Sci.* 2017;94:694-699

SYSTANE® | SYSTANE® HYDRATION | SYSTANE® BALANCE | SYSTANE® ULTRA | SYSTANE® Gel Drops | Laboratory Data

OVERVIEW

STUDY DESIGN
Laboratory study to evaluate the osmolality of commercially available ocular tear lubricants.

STUDY SITE(S)
Single site in Canada

PATIENTS
N/A; laboratory study

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Thirty-seven (37) ocular lubricants (including SYSTANE®, SYSTANE® BALANCE, SYSTANE® Gel Drops, SYSTANE® HYDRATION, and SYSTANE® ULTRA) were evaluated for osmolality using a vapor pressure osmometer

KEY ENDPOINT(S)
Osmolality of commercially available ocular tear lubricants by product and key ingredient

ANALYSIS AND CONCLUSIONS

The majority of artificial tears assessed were found to be hypo-osmolar, making them suitable for the management of dry eye disease.

The hydroxypropyl guar lubricants had the lowest average osmolality, whereas the lubricants with hydroxylpropyl methylcellulose had the highest average osmolality; however, there was no statistical difference between carboxymethylcellulose, hydroxylpropyl methylcellulose, hyaluronic acid, and hydroxypropyl guar lubricants.

STUDY RESULTS

INDIVIDUAL TEAR PRODUCTS

- Of the 37 ocular lubricants tested, 35 drops (94.6%) had an osmolality of less than 295 mmol/kg
- Refresh Optive® Fusion (Allergan, Inc., Irvine, CA, USA) had an osmolality between 295 and 308 mmol/kg
- I-Drop PLUS® (I-Med Parma, Inc., Dollard-des-Ormeaux, QC, CAN) had an osmolality of more than 308 mmol/kg
- The lubricant with the lowest osmolality value was Blink Intensive Tears® (Abbott Laboratories, Abbott Park, IL, USA) with 142.7±2.9 mmol/kg

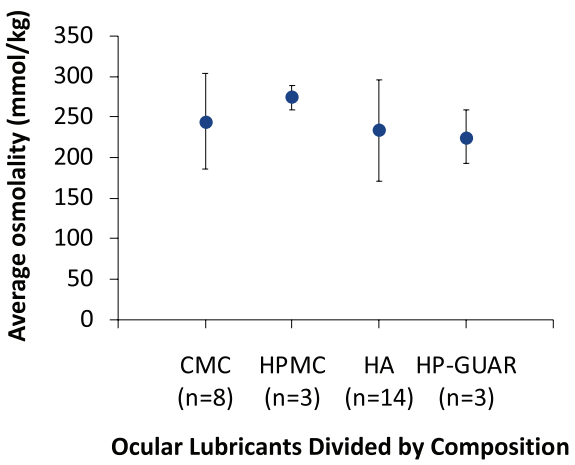
INGREDIENT COMPARISON

- The hydroxypropyl guar lubricants (SYSTANE® artificial tears) had the lowest average osmolality (225±32.4mmol/kg; range, 191 to 255 mmol/kg), whereas the lubricants with hydroxylpropyl methylcellulose had the highest average (273±14.3 mmol/kg; range, 258 to 287 mmol/kg); however, statistical analysis revealed no significant difference between all four groups evaluated (P>0.05) (**Figure 1**)
- The average osmolality and ranges were 245±58.1 mmol/kg (range, 154 to 306 mmol/kg) and 233±61.9 mmol/kg (range, 143 to 323 mmol/kg) for carboxymethylcellulose and hyaluronic acid lubricants, respectively

Table 1. Ocular lubricant osmolality. Adapted from Bitton et al. *Optom Vis Sci.* 2017;94:694-699.

	Average (SD) Osmolality, mmol/kg	Reported Value, mOsm/kg
Blink Gel Tears	154 (3.8)	177
Blink Moisturizing	156 (2.5)	n/a
Blink Intensive	143 (2.9)	n/a
Blink Tears	150 (1.0)	172
Bion Tears	262 (7.0)	240-300
GenTeal Tears	196 (2.0)	205-235
Systane	235 (3.5)	270-330
Systane Balance	230 (8.1)	255-320
Systane Gel Drops	191 (4.4)	255-320
Systane Hydration	240 (2.9)	n/a
Systane Ultra	255 (4.0)	270-300
Tears Naturale	258 (3.5)	n/a
Tears Naturale Forte	287 (4.6)	290-320
Tears Naturale II	274 (4.5)	260-320
Refresh Optive Advanced	259 (2.1)	240-320
Refresh Optive Fusion	306 (1.0)	n/a
Refresh Celluvisc	286 (3.5)	270-350
Refresh Endura	236 (2.9)	220-310
Refresh Liquigel	261 (0.6)	250-330
Refresh Plus	294 (2.0)	270-340
Refresh Tears	239 (1.5)	260-330
Refresh Ultra	186 (6.0)	200-260
Tears Plus	247 (3.6)	260-310
TheraTears (unit dose)	154 (0.6)	170
TheraTears	161 (0.0)	170
Liposic Drops	261 (4.0)	220-260
Moisture Eyes	243 (2.6)	280-320
HYLO	278 (0.6)	240-290
HYLO Gel	277 (2.6)	240-290
HYLO-DUAL	284 (5.5)	n/a
I-Drop	269 (1.5)	250-290
I-Drop Pur	266 (0.0)	n/a
I-Drop PLUS	323 (2.1)	270-350
I-Drop PM	266 (1.0)	250-290
I Drop Pur Gel	279 (2.3)	270-350
Hyabak	184 (1.2)	200
Thealoz	296 (2.6)	202

Figure 1. Ocular lubricant osmolality grouped by composition.



CMC=carboxymethylcellulose and HPMC=hydroxylpropyl methylcellulose, HA=hyaluronic acid, HP-GUAR=hydroxypropyl guar

Clinical Evaluation of an HP-guar Gellable Lubricant Eye Drop for the Relief of Dryness of the Eye

Christensen et al. *Curr Eye Res.* 2004;28:55-62*

SYSTANE®
Clinical Signs
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Safety

OVERVIEW

STUDY DESIGN

Six-week, concurrently controlled, double-masked clinical study to evaluate the efficacy of a lubricant eye drop containing polyethylene glycol 400 and propylene glycol demulcents with hydroxypropyl-guar as a gelling agent (test product: SYSTANE®) to a system with carboxymethylcellulose (control product: Refresh Tears®, Allergan, Inc., Irvine, CA, USA) for reducing dry eye signs and symptoms

STUDY SITE(S)

Seven sites in the US

PATIENTS

Eighty-seven (87) dry eye patients

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Subjects qualifying at the screening visit (Day - 7) were dispensed an aqueous saline solution without polymers, for use in both eyes four times per day for one week. On Day 0 (baseline), subjects were randomized 1:1 to either use SYSTANE® or Refresh Tears® in both eyes four times per day for the duration of the study. Follow-up visits occurred at Days 7, 14, 28 and 42

KEY ENDPOINT(S)

Safety, conjunctival staining, corneal staining, and symptoms

ANALYSIS AND CONCLUSIONS

In this study, SYSTANE® was more effective at reducing both the signs and symptoms of dry eye compared to Refresh Tears®.

Treatment with SYSTANE® was associated with a decrease in the amount of conjunctival and corneal staining.

*Dr. Christensen is an employee of Alcon Laboratories

STUDY RESULTS

SAFETY AND CLINICAL SIGNS

- Both products used four times a day were safe and well tolerated by dry eye subjects
- Treatment with SYSTANE® was associated with a decrease in the amount of conjunctival staining, while the Refresh Tears® treatment was associated with no substantial change; a statistically significant treatment effect was observed with greater conjunctival staining in the Refresh Tears® group compared to SYSTANE® (P=0.025)
- Within each treatment group, a statistically significant decrease from baseline in mean corneal staining was observed at all time points (P< 0.001); the mean decrease in corneal staining from baseline to Day 42 was 52% and 41% for the SYSTANE® and Refresh Tears® groups, respectively (P<0.0001); the change in corneal staining scores from baseline at each of the four study visits revealed decreased staining for all five zones for both treatments
- Investigation of treatment differences by day revealed that the subjects in the SYSTANE® group exhibited statistically greater decreases in temporal corneal staining at Day 14 and Day 42 when compared with the Refresh Tears® group (P<0.05)

PATIENT-REPORTED SYMPTOMS

- A statistically significant difference was observed on the acceptability questionnaire at the exit visit, with subjects in the Refresh Tears® group more likely to agree with the statement “My eyes feel dry in the morning” than those in the SYSTANE® group (mean score 3.4±1.3 vs. 4.0±1.1; P=0.015)
- Statistical significance was observed between treatment groups at exit in agreement with the statement “My eyes feel dry at the end of the day” (P=0.023); subjects in the Refresh Tears® group were more likely to agree with this statement compared to those in the SYSTANE® group (mean score 3.3±1.4 vs. 3.9±0.9)
- Subjects using SYSTANE® were more likely to agree with the statement “My eyes feel refreshed longer than expected when I used the drops” compared those using Refresh Tears® (mean score 3.6±1.2 vs. 3.0±1.1; P=0.037)
- SYSTANE® was associated with a statistically significantly lower frequency of foreign body sensation relative to Refresh Tears® (P=0.033)
- A statistical trend between treatment groups was observed for reduced frequency of dryness with subjects in the SYSTANE® group reporting less frequent dryness than those in the Refresh Tears® group (P=0.057)

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

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Hartstein et al. *Curr Med Res Opin.* 2005;21: 255–260*

OVERVIEW

STUDY DESIGN

Open-label, multi-center, prospective study to evaluate the efficacy of a polymer hydroxypropyl guar (HP-Guar) gellable lubricant eye drop (SYSTANE®) in reducing dry eye signs and symptoms

STUDY SITE(S)

Twenty nine (29) ophthalmology practices in environmentally dry areas

PATIENTS

One hundred and forty-seven (147) patients with a diagnosis of moderate dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Eligible patients were dispensed a run-in drop (Opti-Free® Express Rewetting Drops, Alcon Laboratories, Fort Worth, TX, USA) to use four times daily (QID) for 7 days, and then examined; patients continuing to meet the inclusion criteria were dispensed SYSTANE® to use QID, and re-examined on Day 28

KEY ENDPOINT(S)

Corneal and conjunctival staining, ocular discomfort symptoms, product acceptability rating

ANALYSIS AND CONCLUSIONS

In this study, SYSTANE® relieved signs and symptoms associated with moderate dry eye, with measurable improvements evident in both objective staining and subjective questionnaire measures.

Significant reductions were evident in both corneal and conjunctival staining from Day 0 to Day 28, while subjective measures of symptoms also showed significant improvement.

*This study was financially supported by Alcon

STUDY RESULTS

CLINICAL SIGNS

- At Day 28, a statistically significant reduction in mean corneal staining from Day 0 was seen with use of SYSTANE® for each of the five zones on the National Eye Institute (NEI) grid and for the sum of all zones; the mean decrease from Day 0 (baseline) for the sum of the 5 zones (scale 0–15) was 4.1 (P<0.001), a reduction of 62%
- Corneal staining was reduced for 94% (138), unchanged for 5% (7), and increased in 1% (2) of patients
- Staining was reduced significantly for each of the five corneal zones (P<0.0001 for all)
- A statistically significant decrease in total conjunctival staining from Day 0 (baseline) was seen at Day 28 with SYSTANE®; staining for the aggregate of the six areas decreased 3.1, a change of 59% (P<0.0001)
- Compared to baseline, 78% (115) of the patients showed improvement, 14% (20) were unchanged and 8% (12) had worse aggregate conjunctival staining on Day 28
- In each of the six conjunctival areas, average scores showed significant improvement (all P<0.0001)

SYMPTOMS

- At Day 28 with SYSTANE®, patients were significantly more comfortable for each of the six sensations (Dryness, Burning, Scratching, Foreign body sensation, Grittiness, Stinging) compared to Day 0 (all P<0.0001)
- The total severity rating decreased by 4.5 points from Day 0 to Day 28, and dryness, which was the highest scoring sensation at Day –7 (mean score 2.4), and at Day 0 (mean score 2.0) was rated a mean of 1.1 at Day 28
- A statistically significant difference was observed with the acceptability Likert questions at Day 28 (P<0.0001)
- Compared to Day 0, patients using SYSTANE® were more likely to agree with the self-developed statements 'My eyes feel refreshed longer than expected when I use the drops', 'I frequently forgot my symptoms during use of the drops', 'My eyes feel refreshed when I use the drops', and 'My eyes feel comfortable on the instillation of the drops' and to disagree with the statements 'My eyes feel dry in the morning' and 'My eyes feel dry at the end of the day'

The Effect of Two Novel Lubricant Eye Drops on Tear Film Lipid Layer Thickness in Subjects with Dry Eye Symptoms

Korb et al. *Optom Vis Sci.* 2005;82:594-601

OVERVIEW

STUDY DESIGN

Double-blind, internally paired study to determine if a single eye drop of either Soothe® (Alimera Sciences, Inc., Alpharetta, GA, USA) or SYSTANE® produces a significant increase in lipid layer thickness (LLT) for subjects reporting symptoms indicative of dry eyes

STUDY SITE(S)

United States

PATIENTS

Forty (40) subjects with tear film lipid layer thickness ≤75 nm

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients received a single eye drop of Soothe® in one eye and a single eye drop of SYSTANE® in the contralateral eye

KEY ENDPOINT(S)

Change in LLT at 1 minute, 5 minutes, and 15 minutes post-eye drop instillation

ANALYSIS AND CONCLUSIONS

In this study, administration of one drop of Soothe® artificial tears more than doubled LLT, a 107% mean increase, whereas SYSTANE® increased LLT by 16%.

STUDY RESULTS

LLT CHANGE FROM BASELINE

- A total of 89 individuals with dry eye symptoms were screened for inclusion in the study; of the 89 subjects presenting with dry eye symptoms, 73.0% (n=65) had baseline LLT≤75 nm, indicating that the lipid layer is thin or deficient with the majority of individuals reporting dry eye symptoms
- Post-eye drop instillation, the mean LLT for eyes treated with Soothe® more than doubled from 60.0±1.8 nm to 124.4±4.9 nm (P<0.0001)
- The mean LLT for eyes treated with SYSTANE® increased from 61.5±1.8 nm to 71.3±2.6 nm (P<.0001); the 107% mean increase in LLT with administration of Soothe® was significantly greater than the 16% mean increase with SYSTANE® (P<0.0001)
- There was no instance of a decrease in LLT after the instillation of Soothe®, while a decrease in LLT after instillation of SYSTANE® occurred in 7.5% of the study subjects

A Clinical Evaluation of Systane

Gifford et al. *Cont Lens Anterior Eye.* 2006;29:31-40*

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

OVERVIEW

STUDY DESIGN

Open trial to evaluate the benefits of SYSTANE® in optometric practice

STUDY SITE(S)

Single center in the United Kingdom

PATIENTS

Thirty eight (38) subjects with dry eye were enrolled, with 32 completing the follow-up visit

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Clinical and patient-reported findings were evaluated before and after using SYSTANE® four times a day (QID) for 28-days

KEY ENDPOINT(S)

Tear film break-up, corneal staining, conjunctival staining, tear meniscus height, ocular discomfort severity

ANALYSIS AND CONCLUSIONS

In this study, SYSTANE® proved effective in reducing the symptoms of dry eye. However, induced blur appeared to be a complication for many participants.

The authors suggest that the gelling properties of HP-Guar in SYSTANE® may be influential in promoting ocular surface recovery through improved ocular surface retention of the lubricants.

*This study was financially supported by Alcon

STUDY RESULTS

PATIENT-REPORTED OUTCOMES

- A significant improvement was recorded with SYSTANE® use for all reported sensations from the 'Ocular Discomfort—Severity' questionnaire (P<0.01) except 'burning' (initial mean: 0.34, day 28 mean: 0.22; P=0.157)
- 'Dryness' was the most severely reported symptom both at the initial visit and 28-day follow-up and showed the greatest statistical improvement with SYSTANE® use (initial mean: 1.91, day 28 mean: 1.22; P=0.00004)
- The four most severely reported symptoms (foreign body, gritty, dry, and scratchy) were found to improve to similar degrees over the duration of the trial, while the sensation of stinging improved to a lesser, though still significant degree (P=0.0082)

CLINICAL OUTCOMES

- A significant improvement in conjunctival hyperemia was reported over the duration of the trial (P=0.0047), with the mean grading score improving from 0.47 at the initial visit to 0.22 at the 28-day follow-up
- A significant improvement was seen in the total corneal sodium fluorescein (NaFl) staining score over the duration of the trial (initial score: 4.656, follow up score: 2.813; P≤0.001)
- Analysis of the individual National Eye Institute (NEI) regions of the cornea revealed that all except the superior region showed a significant reduction in staining at follow-up
- Total conjunctival NaFl staining was found to significantly improve over the trial (initial score: 6.813: follow up score: 4.750; P=0.001)
- When considered as individual NEI conjunctival areas, significant improvements were recorded for the superiornasal, nasal, inferior-nasal, and temporal regions
- The tear film analysis tests showed a significant increase in the mean NaFl tear break-up time measurements from 5.7 s to 7.6 s (P=0.00157) over the 28-day trial period; however, the measurements of tear meniscus height showed no significant change

Comparison of Initial Treatment Response to Two Enhanced-Viscosity Artificial Tears

Noecker. *Eye Contact Lens.* 2006;32:148–152

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

OVERVIEW

STUDY DESIGN

Comparison of the effectiveness of 1.0% carboxymethylcellulose (CMC) (Refresh Liquigel®; Allergan, Inc., Irvine, CA, USA) and propylene glycol/polyethylene glycol 400 (PG-HPG) (SYSTANE®) in providing relief of dry eye symptoms and signs

STUDY SITE(S)

Single site in the United States

PATIENTS

Sixty (60) patients who complained of dry eye symptoms and had ocular surface staining at baseline

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were given Refresh Liquigel in one eye and SYSTANE® in the other. Five minutes after the initial drop application, patients were questioned on overall preference and comfort. Patients were then randomized to receive Refresh Liquigel® or SYSTANE® in both eyes for 1 week

KEY ENDPOINT(S)

Patient comfort and preference, corneal staining, conjunctival staining, conjunctival injection

ANALYSIS AND CONCLUSIONS

In this study, patients reported Refresh Liquigel® to be more comfortable than SYSTANE®, when used for 1 week.

After 1 week of use, Refresh Liquigel® provided greater relief of dry eye signs and symptoms than SYSTANE®.

STUDY RESULTS

PATIENT-REPORTED OUTCOMES

- Ocular comfort data 5 minutes after drop application supported a preference for Refresh Liquigel® over SYSTANE® (preferred by 36% and 24% of patients, respectively), although many patients (40%) had no preference
- Only 9% of patients thought that Refresh Liquigel® was stickier or caused more blur compared to 29% (stickier) and 33% (caused more blur), respectively, with SYSTANE®; thirty-five percent (35%) of patients found Refresh Liquigel® more soothing than SYSTANE® (22% of patients)

CLINICAL SIGNS

- After 1 week of use, Refresh Liquigel® produced a statistically significant reduction in corneal inferior staining (P<0.001), while SYSTANE® did not (P=0.185)
  - When comparing mean staining scores at week 1 to baseline, the mean score in the Refresh Liquigel® group (0.73) was statistically significantly lower (P=0.008) than the mean score in the SYSTANE® group (1.04)
  - The mean reduction from baseline in staining was statistically significantly greater with Refresh Liquigel® than with SYSTANE® (P=0.019); with corneal sum staining after 1 week, a trend toward significance was evident in mean staining scores (P=0.053).
  - Refresh Liquigel® produced a statistically significant reduction in sum staining (P=0.004) at week 1, yet there was no significant change with SYSTANE® (P=0.407)
- Mean conjunctival staining scores were significantly lower in the Refresh Liquigel® group than in the SYSTANE® group at week 1 in the temporal region (P=0.005) and in sum staining (P=0.016)
- In terms of conjunctival injection, mean staining scores were statistically significantly lower in the Refresh Liquigel® group than in the SYSTANE® group for temporal (P=0.015) and sum staining (P=0.045) after 1 week of therapy
- There were no significant between-group differences in mean change in conjunctival staining from baseline

An Evaluation of Tear Film Breakup Time Extension and Ocular Protection Index Scores Among Three Marketed Lubricant Eye Drops

Ousler et al. *Cornea.* 2007;26:949-952*

OVERVIEW

STUDY DESIGN

Randomized, double-masked, crossover study to report the performance of an artificial tear containing propylene glycol and polyethylene glycol as active demulcents with hydroxypropyl-guar as a gelling agent (SYSTANE®) and compare it with that of two artificial tears containing carboxymethylcellulose (Refresh Tears® and Refresh Endura®; Allergan, Inc., Irvine, CA, USA)

STUDY SITE(S)

Single site in the United States

PATIENTS

Fifty (50) patients who reported a history of dry eye in both eyes, had used or desired to use artificial tears within the, past year, had a tear film breakup time (TFBUT) of ≤5 seconds in at least 1 eye at baseline, and exhibited a deficient ocular protection index (OPI) (TFBUT < interblink interval (IBI)) at all 3 visits before treatment

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Subjects received SYSTANE®, Refresh Tears®, or Refresh Endura® bilaterally; each subject was randomized to receive all 3 drops throughout the study, at different study visits

KEY ENDPOINT(S)

TFBUT and OPI scores

ANALYSIS AND CONCLUSIONS

In this study, SYSTANE® was more effective than Refresh Tears® at prolonging TFBUT up to 20 minutes after instillation and more effective than Refresh Endura® at prolonging TFBUT up to 30 minutes after instillation.

SYSTANE® was an effective first-line dry eye therapy and a superior ocular surface protector compared with Refresh Endura® and Refresh Tears® in the sample test population.

*This study was financially supported by Alcon

STUDY RESULTS

TEAR FILM BREAKUP TIME

- SYSTANE® extended TFBUT longer than both comparator drops at all time points
- Compared with Refresh Tears®, SYSTANE® statistically significantly lengthened mean baseline-corrected TFBUT at 5, 10, 15, 20, and 60 minutes after drop instillation (all P<0.05)
  - SYSTANE® was numerically, but not statistically, more effective at extending TFBUT than Refresh Tears® at 30 and 45 minutes
- Compared with Refresh Endura®, SYSTANE® statistically significantly lengthened mean baseline-corrected TFBUT at 5, 10, 15, 20, and 30 minutes after drop instillation (all P<0.05)
  - TFBUT extensions with SYSTANE® were numerically, but not statistically, higher than those of Refresh Endura® at 45 and 60 minutes.
- There were no significant differences, with respect to TFBUT, between Refresh Tears® and Refresh Endura® at any time point
- There were no significant changes in blink rate (pre- or post-treatment) for any of the 3 test drops

OCULAR PROTECTION INDEX

- With regard to eyes achieving a positive OPI, SYSTANE® was significantly greater at 15 (P=0.02) and 30 minutes (P=0.03) after drop instillation than eyes treated with Refresh Tears®, with statistical trends shown at 5 and 20 minutes
- The percentage of eyes achieving a positive OPI was significantly greater with SYSTANE® at 5 minutes (P=0.02) than eyes treated with Refresh Endura®
- A statistical trend in favor of SYSTANE® versus Refresh Endura® was shown at 10, 15, 20, and 30 minutes after drop instillation

Corneal Staining Reductions Observed after Treatment with Systane® Lubricant Eye Drops

Christensen. *Adv Ther.* 2008;25:1191-1199*

OVERVIEW

STUDY DESIGN
Analysis of corneal staining reductions in patients using propylene glycol / polyethylene glycol 400-based artificial tear drops (SYSTANE®)

STUDY SITE(S)
One site in the United States

PATIENTS
One hundred and seven (107) patients with dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Analysis was conducted on corneal staining scores, as reported in two previously published, randomized, double-masked, 6-week clinical studies of SYSTANE®. Results were also reviewed for an open-label study that investigated corneal staining over a 5-week period after patients discontinued SYSTANE® therapy

KEY ENDPOINT(S)
Change from baseline in corneal staining

ANALYSIS AND CONCLUSIONS

Composite analysis of Studies 1 and 2 showed that SYSTANE® significantly reduced corneal staining (P<0.0001), suggesting a reduction in the severity of patients' dry eye.

Five weeks after discontinuing treatment with SYSTANE®, the mean sum of corneal staining scores increased by 195.0%.

*This study was financially supported by Alcon

STUDY RESULTS

STUDY 1 AND STUDY 2

- Study 1 demonstrated a reduction in corneal staining of 52.0% after 6 weeks of treatment with SYSTANE®, while Study 2 demonstrated a reduction of 35.2% after the same time period
- Changes from baseline to day 42 in the sum of corneal staining scores were statistically significant in both studies (P<0.0001); the mean sum staining scores were 5.0 and 5.4 in Studies 1 and 2, respectively

COMPOSITE ANALYSIS AND STUDY 3

- The composite analysis of the results from Studies 1 and 2 included 107 patients and showed a decrease in corneal staining after just 1 week of therapy that continued throughout the duration of the trial
- By day 42, the composite reduction in corneal staining from baseline for SYSTANE® was 47.1%; this reduction was statistically significant (P<0.0001)
- Study 3 (open-label) showed that 5 weeks after discontinuing treatment with SYSTANE®, the mean sum of corneal staining scores increased by 195.0%
- The mean change from baseline in corneal staining was significant (P<0.0001)

Impact on Ocular Surface Evaporation of an Artificial Tear Solution Containing Hydroxypropyl (HP) Guar

Uchiyama et al. *Eye Contact Lens.* 2008; 34:331–334*

OVERVIEW

STUDY DESIGN
Randomized, double-blinded, placebo-controlled, 2-period, cross-over clinical trial to determine whether any acute effects on evaporative parameters are produced when using a solution containing hydroxypropyl (HP) guar (SYSTANE®) versus normal saline solution in the eyes of patients with keratoconjunctivitis sicca (KCS)

STUDY SITE(S)
Single site in the United States

PATIENTS
Twelve (12) patients with a clinical diagnosis of KCS

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Patients were randomly assigned to either treatment sequence: 1 (Saline at the first visit, SYSTANE® at the second visit) or 2 (SYSTANE® at the first visit, saline at the second visit); acute effect of single drop applications of each solution on ocular surface evaporation was evaluated at 35%-45% and 25%-35% relative humidity (RH)

KEY ENDPOINT(S)
Tear evaporation rate

ANALYSIS AND CONCLUSIONS

A single drop of SYSTANE® significantly decreased aqueous tear evaporation in both RH conditions at 30 minutes.

These results suggest that HP-Guar has attributes that improve the integrity of the ocular surface tear film in a manner that lessens the rate of evaporation, and this effect may be achieved with SYSTANE® in normal eyes or sub-clinical dry eyes when in low RH environments.

*This study was financially supported by Alcon

STUDY RESULTS

TEAR EVAPORATION

- Eyes evaluated following a single instillation of SYSTANE® had a statistically significantly reduction in mean ocular surface evaporation rate at 30 minutes post-instillation compared to that of pre-instillation under both RH conditions
  - 35%-45% RH: 0.0631±0.0332 µL/cm2/min at baseline, 0.0568±0.0330 µL/cm2/min at 30 minutes (P=0.028)
  - 25%-35% RH: 0.0873±0.0384 µL/cm2/min at baseline, 0.0758±0.0435 µL/cm2/min at 30 minutes (P=0.023)
- The effect of SYSTANE® 60 minutes post-instillation also showed a trend toward causing decreased evaporation rate (35%-45% RH: 0.0585±0.0255 µL/cm2/min; 25%-35% RH: 0.0815±0.0372 µL/cm2/min), but it did not reach statistical significance (P>0.05 vs. baseline)
- A single instillation of saline solution did not produce statistically significant changes on evaporation rate after either 30 minutes or 60 minutes post instillation
  - At 35%-45% RH, evaporation rate was 0.0642±0.0312 µL/cm2/min at baseline, 0.0603±0.0248 µL/cm2/min at 30 minutes, and 0.0675±0.0381 µL/cm2/min at 60 minutes with saline instillation (P>0.05 vs. baseline)
  - At 25%-35% RH, evaporation rate was 0.0856±0.0374 µL/cm2/min at baseline, 0.0822±0.0299 µL/cm2/min at 30 minutes, and 0.0922±0.0498 µL/cm2/min at 60 minutes with saline instillation (P>0.05 vs. baseline)
- Comparisons of the mean evaporative rates between the two treatments at 30 minutes at the lower relative humidity was statistically significant (P=0.044)
- At 35–45% humidity, the mean percentage reduction in evaporative rate from pre-instillation in SYSTANE®-treated eyes was 10% at 30 minutes post-instillation and 7.3% at 60 minutes; eyes treated with saline showed a decrease of 3.3% and an increase of 8.3% 30 and 60 minutes post-instillation, respectively
- When the evaporative rates were determined at 25–35% humidity, the mean percent reduction in SYSTANE®-treated eyes was 13.2% at 30 minutes and 6.6% at 60 minutes post-instillation; the effect on the saline-treated eyes was similar to those obtained at 35–45% humidity

One month use of Systane® improves ocular surface parameters in subjects with moderate symptoms of ocular dryness

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Versura et al. *Clin Ophthalmol*. 2008;2:629–635*

OVERVIEW

STUDY DESIGN

Prospective, open-label, single-center study to evaluate the efficacy of SYSTANE® Lubricating Eye Drops in improving the symptoms of moderate ocular dryness

STUDY SITE(S)

Single site in Italy

PATIENTS

Fifty (50) adults with moderate symptoms of ocular dryness, tear film break-up time (TFBUT) <10 seconds, and reporting ≥1 ocular discomfort symptom

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Saline was used for a washout period of 3–5 days, and subjects were dispensed SYSTANE® for use four times daily and re-examined again after 28 days

KEY ENDPOINT(S)

TFBUT, ocular discomfort symptoms, overall satisfaction

ANALYSIS AND CONCLUSIONS

SYSTANE® effectively relieved the symptoms associated with moderate ocular dryness, with measurable improvement in objective TFBUT, subjective symptoms, and overall satisfaction.

Overall, subjects also reported being satisfied with SYSTANE® after 28 days of use.

*This study was financially supported by Alcon

STUDY RESULTS

TFBUT AND OCULAR DISCOMFORT

- A statistically significant increase was observed in the mean sodium fluorescein TFBUT from 6.9 seconds at the baseline visit to 8.5 seconds on day 28 in the left eye, and from 6.8 seconds to 8.5 seconds in the right eye (P=0.0001)
- A significant improvement was recorded over the 28-day study period for all reported sensations from the Ocular Discomfort – Severity questionnaire
  - Burning sensation was reported as “moderate” by 13/50 and “serious” by 1/50 subjects at baseline visit, and as “moderate” by 4/50 and “serious” by 0/50 subjects on day 28
- Stinging sensation was reported as “moderate” by 7/50 subjects at baseline visit and by 3/50 subjects on day 28

PATIENT SATISFACTION

- A significant difference was observed with the overall satisfaction questions on day 28; compared with baseline visit, most subjects agreed with the statements “My eyes feel refreshed when I use the drops” (44/50), “My eyes feel comfortable upon instillation of the drops” (36/50), and “My eyes feel refreshed longer than expected when I use the drops” (21/50)
- Most subjects responded with “undecided” to the statements “My eyes feel dry at the end of the day” (27/50), “I frequently forget my symptoms during the use of the drops” (27/50), and “My eyes feel dry in the morning” (21/50)

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

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Rolando et al. *J Ocul Pharmacol Ther.* 2009;25:271-277

OVERVIEW

STUDY DESIGN

Prospective, controlled, investigator-masked group study to evaluate the efficacy of a non-Newtonian tear substitute containing 0.4% polyethylene glycol 400 (PEG 400) and 0.3% propylene glycol in an 0.18% hydroxypropyl-guar (HPG) containing vehicle (SYSTANE®) in reducing the signs and symptoms of dry eye, as well as its effect on ocular protection

STUDY SITE(S)

Single site in Italy

PATIENTS

Twenty (20) patients diagnosed with moderate to severe dry eye (17 patients completed the full 28 days of the study, with three patients being lost to follow-up)

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Subjects self-administered SYSTANE® four times daily (QID); after 28 days, the effect of SYSTANE® was evaluated

KEY ENDPOINT(S)

Global Staining Score, inter-blink tear film stability, Ocular Protection Index (OPI), and subjective symptoms

ANALYSIS AND CONCLUSIONS

Improvements in ocular surface staining and dry eye symptoms with SYSTANE® were evident as early as the first follow-up visit (day 7) and continued throughout the 28 days of the study with a concurrent increase in OPI to a level greater than unity.

These results indicate that SYSTANE® is a fast-acting, long-lasting, and effective treatment for dry eye, alleviating the signs and symptoms of dry eye as well as affording improved ocular surface protection.

STUDY RESULTS

CLINICAL SIGNS AND SYMPTOMS

- Over 28 days of SYSTANE® use, Global Staining Score decreased from 16.35 ±2.18 to 2.59 ±1.46, a reduction of 83.91% (P<0.0001)
- The corresponding decrease in the Mean Dry Eye Symptom Score was from 7.25±1.52 to 1.29±0.57, a reduction of 82.09% (P<0.0001)
- The improvement plots for Global Staining Score and Mean Dry Eye Symptom Score showed a decreasing trend at all points and there was a positive trend in the improvement plot for OPI; both the Global Staining Score and the Mean Dry Eye Symptom Score showed statistically significant improvement as early as day 7 (all comparisons P<0.0001 vs. baseline), and over the time periods from day 7 to day 14 and from day 14 to day 28 (P<0.0001 for all)
- The mean OPI value was <1 at baseline (0.91); the value increased to >1 by the 7-day visit (1.05) and remained >1 for the remaining duration of the study (day 14: 1.17; day 28: 1.16) (P<0.01 vs. baseline on days 14 and 28), indicative of a more stable tear film with continued use of the HPG containing ocular lubricant

INDIVIDUALLY SCORED ITEMS

- The total corneal staining score decreased significantly from 7.35 to 1.06 (P < 0.0001), a change of 84.21% over the course of 28 days, and the total conjunctival staining score also decreased from 9.00 to 1.53 (P<0.0001), an 83.02% change over the same time period; the improvement from day 7 to day 14 and from day 14 to day 28 was statistically significant for both of these variables (all P<0.0001); staining was also reduced significantly for each of the five corneal and each of the six conjunctival sectors over the 28-day study period
- Each symptom (foreign body sensation, tiredness, burning / stinging, scratchiness, desire to keep eyes closed) showed a significant reduction in severity over the course of the study (P<0.0001 for all); the improvement from day 7 to day 14 and from day 14 to day 28 was also statistically significant for each symptom

Tear Osmolarity Measurement using the TearLab Osmolarity System in the Assessment of Dry Eye Treatment Effectiveness

Benelli et al. *Cont Lens Anterior Eye.* 2010;33:61-67

OVERVIEW

STUDY DESIGN
Randomized, investigator-masked study to evaluate the efficacy of three commercially available lubricant eye drops for the treatment of mild, dry, irritated eyes

STUDY SITE(S)
Single site in Italy

PATIENTS
Sixty (60) patients with dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Patients were divided evenly into three groups: carboxymethylcellulose sodium (CMC), 0.5% (Cellufresh®, Allergan, Inc. Irvine, CA, USA) (group 1); polyethylene glycol 400, 2.5% and sodium hyaluronate (Blink Intensive Tears®, Abbott Medical Optics, Inc., Santa Ana, CA) (group 2); HP Guar 0.18% (SYSTANE®) (group 3); patients used their assigned artificial tear up to four times per day for 30 days, and testing was performed at baseline and at 30 days

KEY ENDPOINT(S)
Tear osmolarity, wavefront aberrometry, tear break-up time (TBUT), Schirmer tear test, fluorescein staining, and best-corrected visual acuity

ANALYSIS AND CONCLUSIONS

In this study, Blink Intensive Tears® treatment resulted in significantly improvement in tear osmolarity compared with Cellufresh® and SYSTANE® after treatment on day 1 and day 30. All groups demonstrated an improvement with respect to TBUT and Schirmer test

The authors suggest that tear osmolarity testing has the potential to become the gold standard in the diagnosis and management of dry eye disease.

STUDY RESULTS

TEAR OSMOLARITY

- At day 1, there was a statistically significant difference in reduction of osmolarity between Cellufresh® and Blink Intensive Tears® (-5.0±1.9 vs. -9.0±4.2; P=0.0002) and Blink Intensive Tears® and SYSTANE® (-9.0±4.2 vs. -5.0±2.2; P=0.0002)
- The difference between Cellufresh® and SYSTANE® was not statistically significant (P=1.0000)
- At day 30, the difference in reduction of osmolarity was statistically significant between Cellufresh® and Blink Intensive Tears® (-5.6±2.3 vs. -9.9±2.8; P<0.0001) and between Blink Intensive Tears® and SYSTANE® (-9.9±2.8 vs. -4.5±1,8; P<0.0001), but the difference between Cellufresh® and SYSTANE® was not statistically significant (P=0.3111)
- Although there were statistical differences in osmolarity at day 1 and day 30 before and after drop instillation the differences from day 1 to day 30 were not statistically significant (all P>0.4)

ADDITIONAL CLINICAL ENDPOINTS

- There were no statistical differences between the three groups when comparing day 30 wavefront aberrometry with baseline (all P>0.6), although improvements were seen in each group (Cellufresh® -0.25±0.30; Blink Intensive Tears® -0.24±0.29; SYSTANE® -0.16±0.29)
- All groups demonstrated an improvement with respect to TBUT, but there was no significant difference between the three groups
- For the Schirmer test, all groups showed an improvement from baseline to day 30, but there was also no statistically significant difference between the three groups (all P>0.01), and likewise, there were no statistical differences between the three groups with respect to ocular surface staining (all P>0.2)
- There was a slight, but not statistically significant improvement in the Blink Intensive Tears® group from baseline to day 30 when best-corrected visual acuity results were compared (0.02±0.04 vs. 0.01±0.03); in the two other groups, there was no change between the two visits

Effect of Systane and Optive on Aqueous Tear Evaporation in Patients with Dry Eye Disease

Wojtowicz et al. *Eye Contact Lens.* 2010; 36:358–360

OVERVIEW

STUDY DESIGN
Crossover study to compare the effect on aqueous tear evaporation rate of SYSTANE® and Optive® (Allergan, Inc., Irvine, CA, USA) at 30 min post-instillation in patients with dry eye

STUDY SITE(S)
Single site in the United States

PATIENTS
Twenty (20) non–contact lens wearers with dry eye disease

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Aqueous tear evaporation rate measurements of the left eye were taken on each patient with keratoconjunctivitis sicca at two visits (1-week interval between visits); measurements were at baseline and 30 minutes after instillation of 40 µL SYSTANE® or Optive®, per randomization assignment per visit; the same procedure was carried out on the second visit using the opposite study agent

KEY ENDPOINT(S)
Aqueous tear evaporation rate

ANALYSIS AND CONCLUSIONS

In this study, neither SYSTANE® nor Optive® had a significant impact on aqueous tear evaporation at 30 min post-instillation in patients with dry eye.

The authors note that the absence of an effect of either of the study agents on aqueous tear evaporation rate might suggest that these eye drops do not adversely affect the tear film lipid layer.

STUDY RESULTS

EVAPORATION RATE

- The mean rate of evaporation was higher at low relative humidity (RH), regardless of which drop was tested
  - At 25%-35% RH, mean rate of evaporation at baseline and 30 minutes was 0.049±0.023 µL/cm2/min and 0.051±0.025 µL/cm2/min, respectively, for SYSTANE®, and 0.047±0.019 µL/cm2/min 0.052±0.024 µL/cm2/min, respectively, for Optive®
  - At 35%-45% RH, mean rate of evaporation at baseline and 30 minutes was 0.032±0.016 µL/cm2/min and 0.032±0.014 µL/cm2/min, respectively, for SYSTANE®, and 0.031±0.014 µL/cm2/min and 0.034±0.016 µL/cm2/min, respectively, for Optive®
- A decline in RH from 35–45% to 25–35% resulted in an average increase in evaporation rate of 37% in the SYSTANE® group and 35% in the Optive® group
- No significant differences were detected among the groups (P>0.05)

Novel Formulation of Glycerin 1% Artificial Tears Extends Tear Film Break-Up Time Compared with Systane Lubricant Eye Drops

Gensheimer et al. *J Ocul Pharmacol Ther.* 2012;28:473-478

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Safety

OVERVIEW

STUDY DESIGN

Prospective single-center, single visit, randomized, double-masked exploratory trial to evaluate the effectiveness of glycerin 1% formulated with poly (L -lysine)–graft–poly (ethylene glycol) (PLL-g-PEG) (Eyeon Protect™; Eyeon Therapeutics, Inc., Rochester, NY, USA) in extending tear film break-up time (TFBUT) compared with a tear formulation of propylene glycol (0.3%) and polyethylene glycol (0.4%) (SYSTANE®)

STUDY SITE(S)

Single site in the United States

PATIENTS

Sixteen (16) patients with varying levels of dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Noninvasive break-up time (NIBUT) was measured in subjects with asymptomatic to mild (n=5), mild to moderate (n=5), and moderate to severe (n=6) dry eye disease pre-instillation of SYSTANE® or Eyeon Protect™ and again 15, 30, 60, and 120 minutes post-instillation; fluorescein break-up time (FBUT) was measured 120 minutes post-instillation

KEY ENDPOINT(S)

NIBUT at 15, 30, 60, and 120 minutes and FBUT at 120 min; subject responses to questions about the eye drops 5 minutes post-instillation

ANALYSIS AND CONCLUSIONS

In this study, PLL-g-PEG as a polymer excipient in artificial tears (Eyeon Protect™) was found to be effective in improving the performance of demulcents to significantly prolong NIBUT at 15 minutes.

No adverse events were reported during the entire study with either drop.

STUDY RESULTS

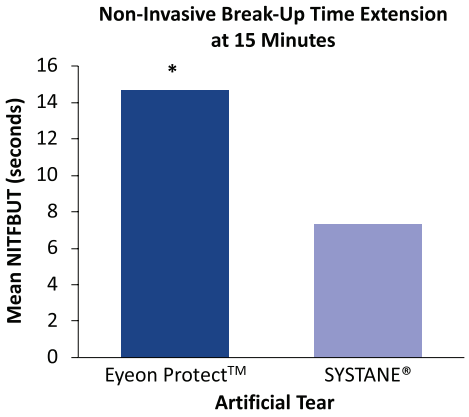
CLINICAL FINDINGS

- Eyeon Protect™ extended mean NIBUT by 14.67 seconds at 15 minutes (P=0.05) compared with pre-instillation NIBUT, while SYSTANE® extended mean NIBUT by 7.40 seconds at the same time point (P=0.34) (**Figure 1**)
- Eyeon Protect™ had a mean FBUT difference from baseline 4.92 seconds longer than SYSTANE® at 120 minutes (P=0.12) (**Figure 2**)
- The area under the curve (AUC) FUBT was numerically superior for Eyeon Protect™ versus SYSTANE® (3,007–1,735 minute-seconds, respectively), but the difference was not statistically significant (P=0.29)
- The return to baseline was superior for Eyeon Protect™ versus SYSTANE® (86–74 minutes, respectively), but the difference was not statistically significant

PATIENT-REPORTED OUTCOMES

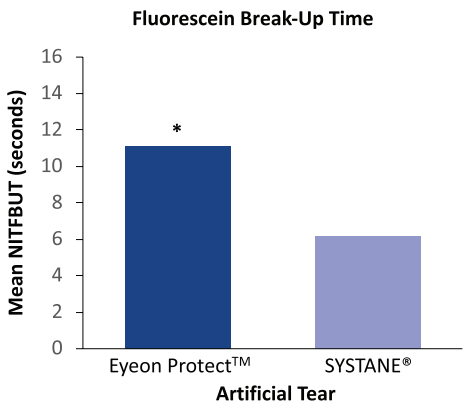
- Four (4) subjects (25%) preferred Eyeon Protect™, five (5) subjects (32%) preferred SYSTANE®, and seven (7) subjects stated there was no difference between the two eye drops
- Two subjects said SYSTANE® led to temporary blurry vision, while no subjects reported visual changes after instillation of Eyeon Protect™

Figure 1. Mean noninvasive break-up time (NIBUT) extension at 15 minutes following artificial tear instillation (N=16).



**Eyeon Protect™ extended mean NIBUT by 14.67 seconds at 15 minutes (P=0.05)*

Figure 2. Mean fluorescein break-up time (FBUT) at 120 minutes following artificial tear instillation (N=16).



**Eyeon Protect™ had an FBUT 4.92 s longer than SYSTANE® at 120 min (P = 0.12).*

Effects of Lubricating Agents with Different Osmolalities on Tear Osmolarity and Other Tear Function Tests in Patients with Dry Eye

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Comez et al. *Curr Eye Res.* 2013;38:1095-1103

OVERVIEW

STUDY DESIGN

Twelve-week, single-masked, randomized, pilot study to evaluate the effects of different artificial tear eye drops on Ocular Surface Disease Index (OSDI), tear osmolarity, Schirmer's test, and tear break-up time (TBUT) in patients with dry eye disease

STUDY SITE(S)

Single site in Turkey

PATIENTS

Forty three (43) dry eye patients

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomly assigned to receive SYSTANE® for their right eye and Eyestil® (SIFI, Rome, IT) for their left eye (Group A) or to receive Tears Naturale® II (Alcon Laboratories, Inc., Fort Worth, TX, USA) for their right eye and Refresh Tears® (Allergan, Inc., Irvine, CA, USA) for their left eye (Group B); outcomes were assessed at baseline and weeks 2, 4 and 12 after treatment initiation

KEY ENDPOINT(S)

OSDI, tear osmolarity, TBUT, Schirmer's I test

ANALYSIS AND CONCLUSIONS

In this study, all four artificial tear formulations tested were effective in relieving dry eye signs and symptoms.

Although the greatest improvement in two of the objective tests was achieved with treatment with Eyestil®, differences between the four artificial tears tested were not statistically significant.

STUDY RESULTS

TREATMENT GROUP COMPARISONS

- Both the Eyestil® / SYSTANE® groups and the Refresh Tears® / Tears Naturale® II patients demonstrated a significant reduction in mean OSDI scores from baseline to week 12 (Eyestil® / SYSTANE® -26.4±10.5; Refresh Tears® / Tears Naturale® II -27.6±14.7; P< 0.001) (**Table 1**); both groups improved from a mean OSDI rated as severe dry eye at baseline to a mean score rated as mild dry eye by week 12
- The differences in OSDI scores at each visit were not significantly different between groups (all P>0.9) (**Table 1**)
- At week 12, the Eyestil(R and SYSTANE® treated eyes appeared to show greater improvement in Schirmer's I test values (6.7± 3.4 and 6.4±2.9mm, respectively) than did Refresh Tears® and Tears Naturale® II treated eyes (4.7± 2.4 and 4.7± 2.8mm, respectively) but the differences between the groups did not reach statistical significance (P= 0.14)

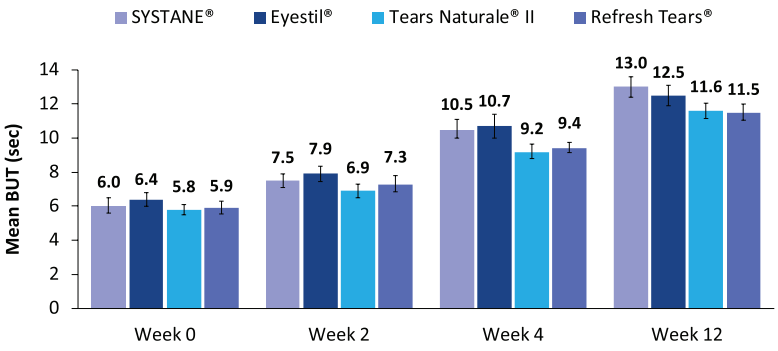
Table 1. Changes from baseline in ocular surface disease index (OSDI) scores between groups across visits

	SYSTANE® / Eyestil® (n=22)	Tears Naturale® II / Refresh Tears® (n=21)	P value
Baseline OSDI Score	41.4±13.9	43.8±17.8	0.92
Difference in Week 2	-6.9±6.4	-7.4±7.3	0.99
Difference in Week 4	-19.1±9.5	-18.1±11.8	0.97
Difference in Week 12	-26.4±10.5	-27.6±14.7	0.99

INDIVIDUAL TEAR COMPARISONS

- Mean tear osmolarity values significantly decreased from baseline with each artificial tear therapy at each visit (p< 0.001 for each of the 4 study drugs across visits); the differences among tear osmolarity values were not significantly different among the four artificial tear therapies at any visit
- Mean Schirmer's test values significantly improved with SYSTANE®, Eyestil®, Tears Naturale® II and Refresh Tears® therapy when compared to baseline values at each visit (P<0.001 for each of the four study drugs across visits); the differences among Schirmers' test values were not significantly different among the four artificial tear therapies at any visit
- Mean TBUT values showed significant improvement from baseline with each artificial tear therapy at each visit, (details in **Figure 1**; P<0.001 for each of the 4 study drugs across visits); for example, the change in TBUT at week 12 was 7.0±3.4 s for SYSTANE®, 6.1±3.3 s with Eyestil®, 5.8±2.3 s with Tears Naturale® II, and 5.6±2.8 s with Refresh Tears®; these TBUT values were not significantly different between the 4 treatments tested at any visit time (all P>0.5)

Figure 1. Tear break-up time (TBUT) results at baseline and at 2nd, 4th and 12th week of treatment.



Efficacy and Safety of Chondroitin Sulfate/Xanthan Gum Versus Polyethylene Glycol/Propylene Glycol/ Hydroxypropyl Guar in Patients with Dry Eye

SYSTANE®

Clinical Signs

Safety

Llamas-Moreno et al. *Clin Ophthalmol.* 2013;7:995-999

OVERVIEW

STUDY DESIGN

Prospective, 2-month-long, randomized, double-blind, single-center, parallel clinical trial to evaluate the efficacy and safety of two ophthalmic solutions in patients with mild to moderate dry eye

STUDY SITE(S)

Single site in Mexico

PATIENTS

Twenty eight (28) patients with mild to moderate dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomly assigned to one of the two treatment groups, study group (chondroitin sulfate and xanthan gum ophthalmic solution (PRO-148; Laboratorios Sophia, SA de CV, Guadalajara, MEX)) or active-control group (SYSTANE®), and received one drop four times a day for two months

KEY ENDPOINT(S)

Tear film break-up time (TBUT) after 2 months of treatment, Ocular Surface Disease Index (OSDI), Schirmer I test, and safety

ANALYSIS AND CONCLUSIONS

In this population of patients with mild to moderate dry eye, treatment with PRO-148 was as effective as treatment with SYSTANE® with regard to TBUT.

Treatment with PRO-148 was also found to be more effective than SYSTANE® at diminishing OSDI in the study population.

STUDY RESULTS

PRIMARY ENDPOINT: TEAR FILM BREAK-UP TIME

- After 2 months of treatment, TBUT was similar in both groups (PRO-148: 6.1±2.5 s; SYSTANE®: 7.3±2.5 s; P=0.088)
- Although there was a mild increase in TBUT in both groups when compared with baseline, this increase was not statistically significant (PRO-148: 5.2±2.3 s vs. 6.1±2.5 s (P=0.222); SYSTANE®: 4.7±2.6 s vs. 7.3±2.5 s (P=0.321)) (**Figure 1**)

ADDITIONAL FINDINGS

- At study conclusion, OSDI was reduced in both groups when compared with baseline, and this reduction was statistically significantly lower in the PRO-148 group compared with the Systane® group (6.7±5.7 reduction vs. 10.8±6.4 reduction; P=0.049) (**Figure 2**)
- There were no differences between groups with regard to Schirmer I and conjunctival, corneal, and global staining scores
- There was a single adverse event present in a patient from the PRO-148 group that was not related to the treatment; no other patient in either group presented any adverse events

Figure 1. Mean change from baseline tear film break up time at each visit (2, 7, 15, 30, and 60 days) between groups.

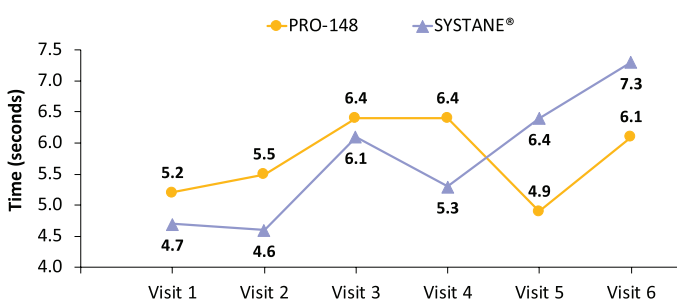
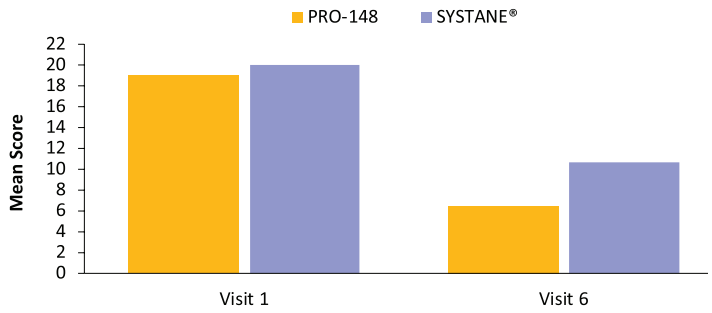


Figure 2. Mean change from baseline in Ocular Surface Disease Index at each visit (2, 7, 15, 30, and 60 days) between groups.



A Randomized Crossover Study Comparing Trehalose/Hyaluronate Eyedrops and Standard Treatment: Patient Satisfaction in the Treatment of Dry Eye Syndrome

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Pinto-Bonilla et al. *Ther Clin Risk Manag.* 2015;11:595-603

OVERVIEW

STUDY DESIGN

Randomized, open-label, crossover trial comparing Thealoz Duo® (Laboratoires Théa, Clermont Ferrand, FR) and SYSTANE®

STUDY SITE(S)

Single site in Spain

PATIENTS

Seventeen (17) adult patients with moderate-to-severe dry eye syndrome

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomized to treatment with Thealoz Duo® (combining trehalose and hyaluronic acid) or SYSTANE® for 7 days

KEY ENDPOINT(S)

Primary efficacy: patient satisfaction evaluated using a 0–100 mm visual analog scale (VAS) on treatment days 0 and 7. Secondary parameters: ocular surface disease index (OSDI), symptoms of dry eye, ocular staining scores (fluorescein and lissamine green), ocular clinical signs, Schirmer test, tear breakup time (TBUT), and global efficacy assessed by the patient and the investigator

ANALYSIS AND CONCLUSIONS

There were no statistically significant advantages for SYSTANE® over Thealoz Duo® for any measured parameter.

Two secondary efficacy parameters (dry eye symptoms and the impact of their symptoms on work) showed statistically significant advantages for Thealoz Duo® over SYSTANE®.

STUDY RESULTS

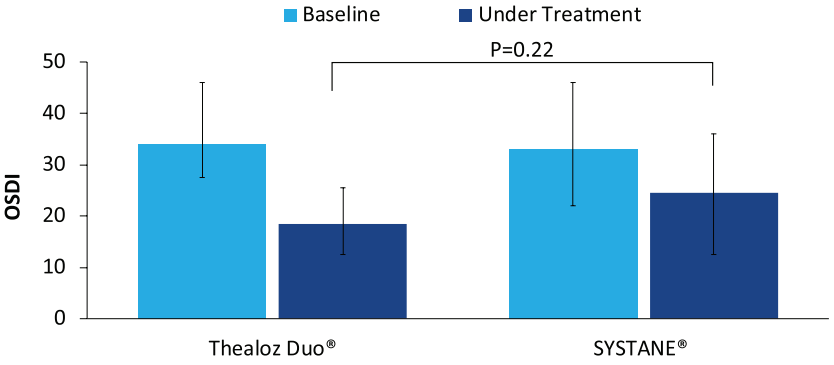
PRIMARY EFFICACY VARIABLE

- Patient satisfaction improved from 44.5±19.0 mm to 70.2±19.2 mm on the VAS during Thealoz Duo® treat¬ment and from 47.2±23 mm to 57. 1 ±19.1 mm during SYSTANE® treatment (P=0.043, mixed-effects analysis of covariance)

SECONDARY EFFICACY VARIABLES

- OSDI fell during treatment with both Thealoz Duo® and SYSTANE® (**Figure 1**); the reduction in OSDI was 15.2±10.9 for Thealoz Duo® and 9.0±11.9 for SYSTANE® (P=0.22)
- Patient dry eye symptoms and impact on daily life, daily activities, impact on work, emotional impact, and ocular comfort were broadly similar between the groups at baseline, and all fell during the study
- Although there were no statistically significant differences between the groups, fluorescein and lissamine green staining improved with both treatments during the study
- The results of the Schirmer and TBUT test both showed a tendency toward improvement during the study without any significant difference between the two treatments
- The global score for effectiveness was slightly higher for Thealoz Duo® (19.9±4.4) than for SYSTANE® (16.7±4.1), whereas the global score for inconvenience was slightly lower for Thealoz Duo® (2.4±1.2) than for SYSTANE® (2.9±1.1); neither difference was statistically significant
- Overall, more patients preferred Thealoz Duo® than SYSTANE® (64.7% vs 11.8%, 23.5% expressed no preference)

Figure 1. Ocular Surface Disease Index (OSDI) scores at baseline after 7 days treatment with Thealoz Duo® or SYSTANE®.



Effects of Artificial Tears on Rabbit Ocular Surface Healing After Exposure to Benzalkonium Chloride

Zhang et al. *Drug Chemical Toxicol.* 2016;39(4):455-460

OVERVIEW

STUDY DESIGN
Animal study to observe the effect of different artificial tears on healing drug-induced keratopathy

STUDY SITE(S)
Single site in China

PATIENTS
Not applicable. Rabbit model (64 healthy adult male New Zealand albino rabbits weighing 2–2.5 kg and aged 3–3.5 months)

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
After benzalkonium chloride (BAK) exposure to induce keratopathy, study animals' eyes were treated 4 times daily with saline solution, Refresh Plus® (Allergan, Inc., Irvine, CA, USA), Hycosan® (Ursapharm, Arzneimittel GmbH, Saarbrücken, DEU), or SYSTANE® ULTRA; surface abnormalities were examined daily; fluorescein staining, histopathological and transmission electron microscopic (TEM) examination were performed at day 0, 2 weeks, and 1 and 2 months

KEY ENDPOINT(S)
Slit-lamp evaluation, fluorescein (FL) test, and histopathological results

ANALYSIS AND CONCLUSIONS

SYSTANE® ULTRA had the greatest effect on improving the condition of BAK-injured corneas.

The authors suggest that eye drops with a nontoxic preservative, such as SYSTANE® ULTRA, are an alternative for drug-induced keratopathy.

STUDY RESULTS

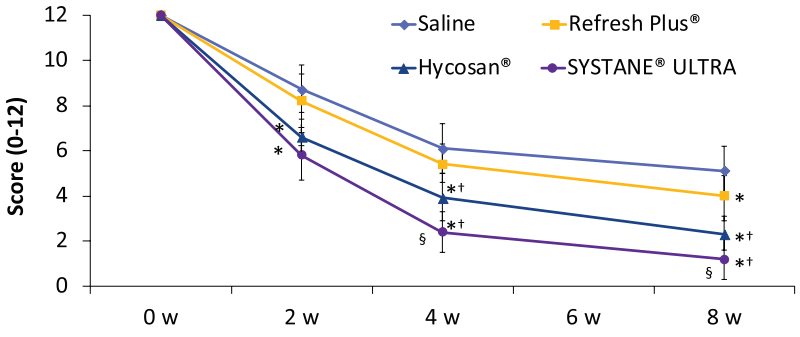
SLIT-LAMP AND FLUORESCEIN STAINING

- At 2 weeks, there was no statistically significant difference in corneal FL staining score between the Refresh Plus® (P=0.2495) and saline groups, while significantly different values were observed in both the SYSTANE® ULTRA (P<0.0001) and Hycosan® groups (P<0.0001) compared with the saline group
  - Comparing FL scores among the three active treatment groups at 2 weeks, the difference was significant between Refresh Plus® and SYSTANE® ULTRA (P<0.0001) and Refresh Plus® and Hycosan® (P=0.0011), but there was no statistically significant difference between Hycosan® and SYSTANE® ULTRA (P=0.0506); the FL of SYSTANE® ULTRA group scores were lower than that of the Hycosan® group (**Figure 1**)
- At 1 month, no statistically significant difference was found between the Refresh Plus® (P=0.0906) and saline groups, but significant differences were shown in both the SYSTANE® ULTRA (P<0.0001) and Hycosan® groups (P<0.0001) compared with the saline group; there was also a statistically significant difference between the Hycosan® and SYSTANE® ULTRA groups (P<0.0005)
- At 2 months, there were similar results as observed at the 1-month endpoint except that the difference was significant between the Refresh Plus® and saline groups (P=0.0150)

HISTOPATHOLOGICAL RESULTS

- Corneal sections of animals treated 2 weeks with saline, Refresh Plus® and Hycosan® showed that the loss of integrity of corneal epithelium had not yet improved, while it nearly returned to normal in the SYSTANE® ULTRA group
- At 2 weeks, the absence of organelles, the broadening of intercellular space and increased numbers of dead cells were observed in the saline group, and the Refresh Plus group additionally showed evidence of edema in the interstitium and dead cells, while edema was observed in the interstitium of the Hycosan® group; the SYSTANE® ULTRA group appeared to be normal
- At 1 month after treatment with saline, Refresh Plus® and Hycosan®, organelles and intercellular space seemed to be normal; however, there were still dead cells observed in the saline and Refresh Plus® groups

Figure 1. Corneal fluorescein staining scores at day 0, week 2, month 1 and month 2.



** P<0.05 vs. Refresh Plus®. † P<0.05 vs. saline. § P<0.05 vs. Hycosan®.*

Efficacy in Patients with Dry Eye After Treatment with a New Lubricant Eye Drop Formulation

Davitt, Bloomenstein, Christensen, Martin. *J Ocul Pharmacol Ther.* 2010;26:347-353*

SYSTANE® ULTRA
Clinical Signs
Patient-Reported Outcomes
Safety

OVERVIEW

STUDY DESIGN

Prospective, double-masked, multisite, parallel-group study of a new formulation of polyethylene glycol 400/propylene glycol-based lubricant eye drops containing hydroxypropyl guar as a gelling agent (SYSTANE® ULTRA) in comparison to Optive® Lubricant Eye Drops (Allergan, Inc., Irvine, CA, USA)

STUDY SITE(S)

Eight (8) sites in the United States

PATIENTS

One hundred thirteen (113) dry eye patients enrolled; the intent-to-treat (ITT) data set included 105 patients

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Following a two-week saline run-in, patients were randomized (1:1) to receive either SYSTANE® ULTRA or Optive® to be administered four times daily (QID) for 6 weeks

KEY ENDPOINT(S)

Ocular staining, symptoms, tear film breakup time, Ocular Surface Disease Index (OSDI), VF-14 questionnaire, treatment satisfaction, safety

ANALYSIS AND CONCLUSIONS

SYSTANE® ULTRA significantly reduced corneal and conjunctival staining compared to baseline, indicating a reduction in disease severity.

SYSTANE® ULTRA was also safe and well tolerated when used QID for 6 weeks by patients with dry eye.

*Dr. Christensen and Anna E. Martin are employees of Alcon Research

STUDY RESULTS

OCULAR STAINING

- Patients in the SYSTANE® ULTRA group had a significantly lower mean corneal staining score than the Optive® group at day 14 (P=0.0009) and at day 42 (P=0.0106)
- The mean reduction from baseline in corneal staining was significantly greater among patients in the SYSTANE® ULTRA group than among patients in the Optive® group at day 14 (mean change: -1.8 vs. -0.8; P=0.0027); a similar trend in favor of SYSTANE® ULTRA was observed at day 42 (mean change: -1.8 vs. -1.1; P=0.0508)
- Patients in the SYSTANE® ULTRA group also exhibited a significantly greater decrease in conjunctival staining compared to patients in the Optive® group at day 28 (P=0.0475) and at day 42 (P=0.0009)

ADDITIONAL PARAMETERS

- After 6 weeks of treatment with SYSTANE® ULTRA, patients reported a significant decrease from baseline in ocular symptoms of dryness, gritty/sandy feeling, and burning (-0.7, -0.8, and -0.5; P<0.0021 for all comparisons relative to baseline); similarly, patients in the Optive® group reported significant decreases in the same 3 ocular symptoms (-0.6, -0.6, and -0.5, respectively; P<0.0006 for all symptoms at day 42 compared to baseline)
- There were no significant differences between or within treatment groups at any assessment time point for the mean tear film breakup time (P≥0.2206 for each comparison)
- At day 42, the mean OSDI score was significantly reduced from baseline among patients in both the SYSTANE® ULTRA (-8.6; P=0.0013) and Optive® (-10.9; P<0.0001) groups
- In the SYSTANE® ULTRA group, 13 patients reported 17 adverse events, 4 of which were related to treatment; in the Optive® group, 6 patients reported 11 adverse events, 7 of which were related to treatment; in all cases, the treatment-related events were mild in severity and resolved without treatment

Lubricant with Gelling Agent in Treating Dry Eye in Adult Chinese Patients

Waduthantri et al. *Optom Vis Sci.* 2012; 89:1647-1653†

SYSTANE® ULTRA

Clinical Signs

Patient-Reported Outcomes

OVERVIEW

STUDY DESIGN

Prospective, randomized, double-masked, double-arm, parallel, interventional study to investigate the efficacy of a lubricant eye drop containing gelling agent in adult Chinese dry eye patients

STUDY SITE(S)

Dry eye clinic in Singapore

PATIENTS

Thirty (30) Chinese patients, aged between 40 and 65 years, diagnosed with dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomized 1:1 to one of two two arms: lubricant eye drops containing hydroxypropyl-guar (HP-guar) gelling agent (SYSTANE® ULTRA) or no gelling agent (Refresh Tears®, Allergan, Inc., Irvine, CA, USA); patients used 1 drop of their assigned treatment, four times a day, for 6 weeks

KEY ENDPOINT(S)

Primary outcome: Symptom Assessment in Dry Eye (SANDE) score (based on severity and frequency of dry eye symptoms on a visual analog scale) at weeks 1, 3, and 6. Secondary outcomes: corneal fluorescein staining, tear break-up time (TBUT), and Schirmer's I test results. Safety outcomes: visual acuity and intraocular pressure, slit lamp biomicroscopy findings, and adverse events

ANALYSIS AND CONCLUSIONS

Both lubricant eye drops, with or without the HP-guar gelling agent, provided dry eye symptom relief.

There was no difference in the efficacy of either lubricant eye drop in terms of symptoms or objective clinical signs of dry eye.

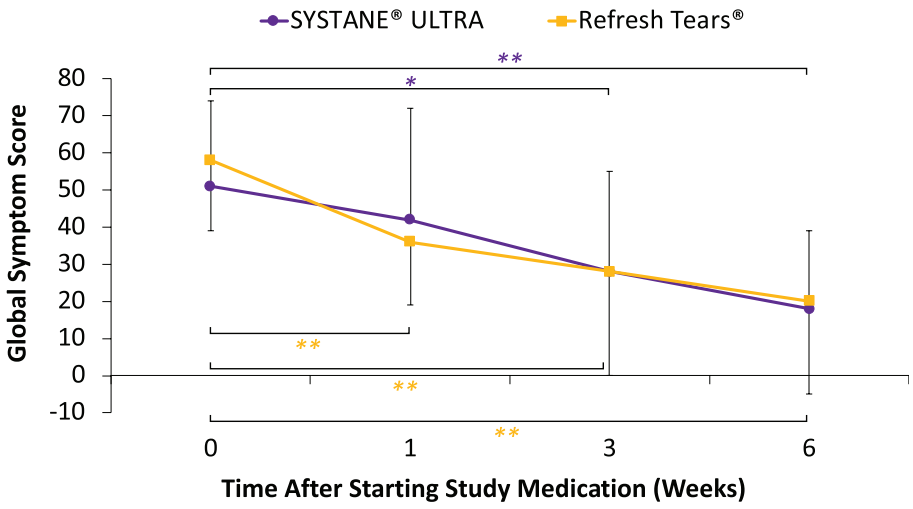
†This study was financially supported by Alcon

STUDY RESULTS

DRY EYE SYMPTOMS

- Symptom scores showed a significant improvement in both treatment groups after 6 weeks of treatment (P<0.001); however, there was no significant difference in SANDE scores between the two groups (P>0.05), with the Refresh Tears® group improving by 37.5±29.4 *(mean±SD) and the SYSTANE® ULTRA group by 33.2±26.6 (**Figure 1** and **Table 1**)
- One patient in the SYSTANE® ULTRA group had a SANDE score that worsened >2 standard deviations (SD of absolute change in the patient's global symptom score between baseline and week 6 = 21.8) from the changes experienced by others

Figure 1. Change in dry eye symptoms (Symptom Assessment in Dry Eye (SANDE) score) among patients using SYSTANE® ULTRA (n=15) and Refresh Tears® (n=15) four times per day, for six weeks.



*P<0.01. **P<0.001.

SECONDARY OUTCOMES

- There was no significant difference in TBUT, Schirmer's test results, or corneal fluorescein staining between the SYSTANE® ULTRA and Refresh Tears® treatment groups at weeks 1, 3, or 6
- No adverse events were seen in either study group after treatment

Table 1. Symptoms of dry eye (Symptom Assessment in Dry Eye (SANDE) score) among patients using SYSTANE® ULTRA (n=15) and Refresh Tears® (n=15) four times per day, for six weeks.

	SYSTANE® ULTRA Mean (SD)	Refresh Tears® Mean (SD)	P value
Baseline	50.94 (23.26)	57.64 (18.81)	0.40
Week 1	42.29 (30.16)	36.38 (17.93)	0.52
Week 3	28.26 (26.88)	27.68 (28.20)	0.96
Week 6	17.78 (21.39)	20.17 (25.22)	0.79
Baseline – Week 1	8.64 (22.14)	21.26 (18.84)	0.11
Baseline – Week 3	22.67 (22.11)	29.96 (25.68)	0.42
Baseline – Week 6	33.15 (26.61)	37.47 (29.41)	0.68

Tear Lipid Layer Thickness with Eye Drops in Meibomian Gland Dysfunction

Fogt et al. *Clin Ophthalmol.* 2016;10:2237-2243

OVERVIEW

STUDY DESIGN
Prospective, randomized, open-label, cross-over, examiner masked study of the change in tear lipid layer thickness (LLT) in subjects with meibomian gland dysfunction (MGD) and lipid deficiency following artificial tear instillation

STUDY SITE(S)
Single site in the United States

PATIENTS
Thirty-five (35) subjects aged 30–75 years with tear lipid deficiency and symptomatic dry eye disease

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
A prescreening visit determined the presence of MGD was followed by a screening visit in which baseline LLT was measured, and two study visits to measure the LLT both before instilling a single drop of SYSTANE® ULTRA or emollient, lipid-containing Soothe® XP (Bausch & Lomb, Rochester, NY, USA), and again 15 minutes after instillation; eye drop visits were scheduled on different days to ensure washout

KEY ENDPOINT(S)
Change in LLT from baseline

ANALYSIS AND CONCLUSIONS

In this study of subjects with MGD, the emollient, or lipid containing eye drop (Soothe® XP) increased the LLT of tears when measured 15 minutes after instilling a single drop

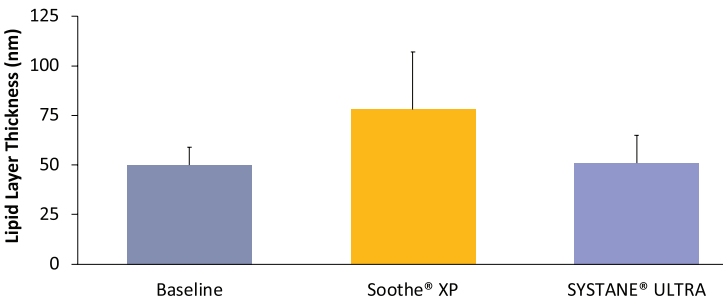
There was no change in the LLT after instillation of the non-lipid-containing eye drop (SYSTANE® ULTRA)

STUDY RESULTS

LIPID LAYER THICKNESS (LLT)

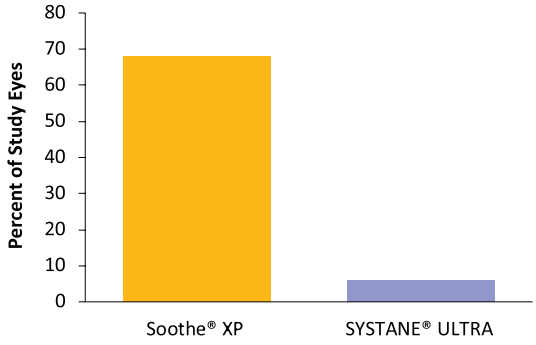
- Instillation of Soothe® XP led to a significant increase in mean (±SD) LLT to 77.5 nm (29.3) at 15 minutes post-instillation. The mean change from baseline was 28.04 nm (27.4); P<0.001 (**Figure 1**)
- Instillation of SYSTANE® ULTRA had no significant impact on LLT 15 minutes following instillation, mean (±SD) LLT was 50.8 nm (14.1) (mean [±SD] CFB of 1.4 nm [10.7]; P=0.6).
- 94% (33/35) of study eyes had an increase of any amount in LLT with Soothe® XP compared to 49% (17/35) with SYSTANE® ULTRA (P<0.001 for the difference in proportions)
- 68% (24/35) of study eyes had a clinically significant increase in LLT following instillation of Soothe® XP, whereas none had a clinically significant decrease in LLT (**Figure 2**)
- 2.9% (1/35) of study eyes had a clinically significant increase and decrease in LLT, respectively, following instillation of SYSTANE® ULTRA
- The difference between treatments in the proportion of study eyes with a clinically significant increase in LLT was statistically significant (P<0.001)

Figure 1. Lipid layer thickness (LLT) prior to and 15 minutes following a single drop of Soothe® XP or SYSTANE® ULTRA in dry eyes with meibomian gland dysfunction (MGD). Data are the mean (± SD) LLT based on stroboscopic video color microscope (SVCM) measurements in study eyes (qualifying eye in subjects with only one qualifying eye, or the eye with the lowest LLT at baseline in subjects with two qualifying eyes).



P<0.001 paired t-test for the change from baseline.

Figure 2. Percentage of study eyes with a clinically significant increase in lipid layer thickness (LLT) 15 minutes following a single drop of Soothe® XP or SYSTANE® ULTRA eye drop in dry eyes with meibomian gland dysfunction (MGD). A clinically significant increase was defined as an increase of ≥15 nm from baseline as determined by stroboscopic video color microscope (SVCM) interferometry.



Evaluation of a New Artificial Tear Formulation for the Management of Tear Film Stability and Visual Function in Patients with Dry Eye

SYSTANE® ULTRA

Clinical Signs

Patient-Reported Outcomes

Torkildsen et al. *Clin Ophthalmol.* 2017;11:1883-1889

OVERVIEW

STUDY DESIGN

Prospective, single-center, open-label, parallel-group study comparing the effects of Rohto® Dry-Aid™ (The Mentholatum Company, Orchard Park, NY, USA) and SYSTANE® ULTRA when used continuously over ~30 days

STUDY SITE(S)

Single center (location not specified)

PATIENTS

Eighty (80) patients with a self-reported history of dry eye for at least 6 months, a history of use or desire to use eye drops for dry eye relief, minimum scores (≥2) in at least one dry eye symptom assessments and one corneal staining measures (2 in at least one region), OSDI score of at least 13, and average tear film break-up time (TFBUT) ≤5 seconds

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Subjects were randomly assigned to one of two test groups (SYSTANE® ULTRA; Rohto® Dry-Aid™) and received treatment twice daily (BID) for a total of 30 days

KEY ENDPOINT(S)

Efficacy, including ocular staining, visual function, and ocular discomfort, evaluated on treatment days 15 and 30

ANALYSIS AND CONCLUSIONS

In this study, Rohto Dry-Aid and SYSTANE® ULTRA elicited comparable effects on the signs and symptoms of DED.

Subjects in the Rohto group experienced superior relief, compared to SYSTANE® ULTRA, from discomfort associated with visual tasking activities and daily diaries, indicating that the Rohto drops may provide a longer duration of symptomatic relief over the course of the day.

STUDY RESULTS

COMFORT ANALYSIS

- Ocular comfort scores confirmed that both products provided an immediate, significant improvement in ocular comfort that was sustained for at least 1 hour after instillation (**Table 1**)
- Subjects in both test groups reported reduced discomfort scores for all symptoms (ocular discomfort, burning, dryness, grittiness, stinging) that were sustained over subsequent study visits
- Subjects in both test groups reported significant improvement (i.e., decreased mean scores) in how much their eyesight "interfered with daily activities" at Visit 3 (30 days) (P=0.014 for Rhoto® group and P=0.036 for SYSTANE® ULTRA)

Table 1. Ocular Comfort Scores among subjects using SYSTANE® ULTRA or Rohto® Dry-Aid™ twice daily, for 30 days.

	Visit 1				Visit 2	Visit 3
	Predose	5 Minutes	20 Minutes	60 Minutes		
Rohto® Dry-Aid™	2.59	1.51	1.77	1.54	2.00	1.85
SYSTANE® ULTRA	2.61	1.41	1.71	1.73	2.29	2.05
P values						
Rohto® vs SYSTANE® ULTRA	0.905	0.683	0.776	0.364	0.135	0.317
Same test agent vs predose	All t-tests significant at P<0.001					

CLINICAL SIGNS ANALYSIS

- Both SYSTANE® ULTRA and Rohto® Dry-Aid™ appeared to yield modest improvement in staining for most regions, particularly at Visit 2 (15 days) (**Table 2**)
- Both test agents elicited increases in TFBUT that were sustained for the 60-minute assessment window at Visit 1; these increases were statistically significant for both test agents at 5 minutes post-instillation (**Table 3**)

Table 2. Mean corneal fluorescein staining by visit among subjects using SYSTANE® ULTRA or Rohto® Dry-Aid™ twice daily, for 30 days.

	Inferior	Superior	Central	Temporal	Nasal
Rohto® Dry-Aid™					
Visit 1	2.04	2.27	0.97	1.92	1.96
Visit 2	2.09	1.86	0.88	1.82	1.86
Visit 3	2.23	2.15	1.14	2.15	2.21
SYSTANE® ULTRA					
Visit 1	1.93	2.01	0.79	1.63	1.80
Visit 2	1.66	1.57	0.59	1.43	1.46
Visit 3	2.07	1.96	0.91	1.88	1.89

Table 3. Tear film break-up time following instillation of SYSTANE® ULTRA or Rohto® Dry-Aid™

	Predose	5 Minutes	20 Minutes	60 Minutes
Rohto® Dry-Aid™	2.44	3.32	3.84	3.27
P value vs baseline		0.011	0.006	0.012
SYSTANE® ULTRA	2.27	3.09	2.87	2.75
P value vs baseline		0.018	0.206	0.442

Comparison of the Efficacy of Carboxymethylcellulose 0.5%, Hydroxypropyl-guar Containing Polyethylene Glycol 400/Propylene Glycol, and Hydroxypropyl Methyl Cellulose 0.3% Tear Substitutes in Improving Ocular Surface Disease Index in Cases of Dry Eye

Maharana et al. *Middle East Afr J Ophthalmol.* 2017;24:202-206

OVERVIEW

STUDY DESIGN

Retrospective evaluation of cases presenting with symptoms of dry eye to compare the efficacy of carboxymethylcellulose 0.5% (CMC), hydroxypropyl-guar containing polyethylene glycol 400/propylene glycol (PEG/PG), and hydroxypropyl methylcellulose 0.3% (HPMC) as tear substitutes

STUDY SITE(S)

Single site in India

PATIENTS

One hundred and twenty (120) patients with Ocular Surface Disease Index (OSDI) score >12 and using topical steroid and topical lubricants

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Medical records of all cases of clinically diagnosed dry eye attending the corneal clinic from July 2014 to June 2015 were reviewed for inclusion; study groups were defined as follows: Group 1 (compounded CMC 0.5%; n=41); Group 2 (PEG/PG (SYSTANE® ULTRA); n=48); Group 3 (HPMC (Genteal®; Alcon Laboratories, Fort Worth, TX, USA); n=31)

KEY ENDPOINT(S)

OSDI, tear film breakup time (TBUT), Schirmer's test (ST), and slit-lamp examination findings

ANALYSIS AND CONCLUSIONS

The results of this study indicate that SYSTANE® ULTRA and Genteal® Eye Drops were better tear substitutes than CMC in patients with dry eye.

The two test formulations (Genteal® and SYSTANE® ULTRA) were comparable with respect to subjective improvement with treatment.

STUDY RESULTS

OCULAR SURFACE DISEASE INDEX

- Patients in the SYSTANE® ULTRA group had a significantly lower mean OSDI score than those in the CMC 0.5% group at week 1 (P<0.0001) and at week 4 (P<0.0001)
- Change from baseline in OSDI at week 1 was 16.32% in the CMC 0.5% group, 35.13% in the SYSTANE® ULTRA group, and 31.5% in the Genteal® group
- Change from baseline in OSDI at week 4 was 29.17% in the CMC 0.5% group, 62.9% in the SYSTANE® ULTRA group, and 57.3% in the Genteal® group
- Patients in the SYSTANE® ULTRA group had a significantly better percentage change in OSDI than those in the CMC 0.5% group at 1 week compared to baseline and at 4 weeks compared to baseline and compared to 1 week (all P<0.0001) (**Table 1**)

TEAR FILM BREAKUP TIME

- Patients in the SYSTANE® ULTRA group had a significant increase in mean TBUT compared to those in the CMC 0.5% group at week 1 (P=0.003) and at week 4 (P=0.001)
- There was no significant difference in improvement in TBUT between the SYSTANE® ULTRA and Genteal® groups at week 1 (P=0.984) or week 4 (P=0.936)
- Patients in the SYSTANE® ULTRA group had a significantly greater percent change in TBUT compared to those in the CMC 0.5% group at week 1 compared to baseline (P= 0.016) and at week 4 compared to baseline (P=0.006) and compared to week 1 (P=0.007)
- Patients in the Genteal® group had a non-significant difference in percent change in TBUT compared to those in the CMC 0.5% group at week 1 compared to baseline (P=0.105), and a significant difference at week 4 compared to baseline (P=0.032) and compared to week 1 (P=0.046) (**Table 2**)

SCHIRMER'S TEST

- Patients in the SYSTANE® ULTRA group exhibited significant improvement in ST in comparison to the CMC 0.5% group at week 1 (P=0.018) and week 4 (P<0.001)
- Treatment with SYSTANE® ULTRA resulted in a significantly greater percent change in ST compared to CMC 0.5% at week 1 compared to baseline (P=0.029) and at week 4 compared to baseline (P=0.002) and compared to week 1 (P=0.008) (**Table 3**)

Table 1. Comparison of percent change in Ocular Surface Disease Index (OSDI) score.

Follow-up Period	Mean Percentage Change in Group 1	Mean Percentage Change in Group 2	Mean Percentage Change in Group 3	P		
				Between Groups 1 and 2	Between Groups 1 and 3	Between Groups 2 and 3
0-1 week	16.32	35.13	31.5	0.000	0.000	0.138
0-4 weeks	29.17	62.9	57.34	0.000	0.000	0.115
1-4 weeks	16.54	42.9	39.41	0.000	0.000	0.450

Table 2. Comparison of percent change in tear film breakup time.

Follow-up Period	Mean Percentage Change in Group 1	Mean Percentage Change in Group 2	Mean Percentage Change in Group 3	P		
				Between Groups 1 and 2	Between Groups 1 and 3	Between Groups 2 and 3
0-1 week	10.971	26.538	27.235	0.016	0.105	0.996
0-4 weeks	18.898	51.148	48.946	0.006	0.032	0.984
1-4 weeks	5.4483	16.566	15.685	0.007	0.046	0.982

Table 3. Comparison of percent change in Schirmer's test.

Follow-up Period	Mean Percentage Change in Group 1	Mean Percentage Change in Group 2	Mean Percentage Change in Group 3	P		
				Between Groups 1 and 2	Between Groups 1 and 3	Between Groups 2 and 3
0-1 week	3.87	19.4	20.0	0.029	0.007	0.997
0-4 weeks	7.01	39.0	48.1	0.002	0.033	0.863
1-4 weeks	2.63	14.5	18.1	0.008	0.120	0.904

CMC = carboxymethylcellulose 0.5%; PEG/PG = polyethylene glycol 400/propylene glycol; HPMC = hydroxypropyl methylcellulose 0.3%

Safety and Efficacy of a Hydroxypropyl Guar/ Polyethylene Glycol/Propylene Glycol-Based Lubricant Eye-Drop in Patients with Dry Eye

Labetoulle et al. *Br J Ophthalmol.* 2017;101:487-492*

OVERVIEW

STUDY DESIGN

Multicenter, randomized, observer-masked, parallel-group study to demonstrate non-inferiority of a hydroxypropyl guar/polyethylene glycol/propylene glycol lubricating eye-drop (HPG/PEG/PG (SYSTANE® ULTRA)) compared with an osmoprotective carboxymethylcellulose/glycerine eye-drop (Optive®, Allergan, Inc., Irvine, CA, USA)

STUDY SITE(S)

Sixteen (16) sites in France and Germany

PATIENTS

Ninety-four (94) adults with dry eye were randomized to treatment (mean±SD patient age: 64.4±13.7 years), and 82 completed the study

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Participants instilled SYSTANE® ULTRA or Optive® 4 times daily for 35 days and then as needed through day 90

KEY ENDPOINT(S)

Primary efficacy endpoint: total ocular surface staining (TOSS) score change from baseline to day 35. Secondary efficacy endpoints: mean treatment effectiveness and treatment inconvenience scores on the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire on day 35; safety (extent of treatment exposure, adverse events (AEs), best corrected visual acuity (BCVA), ocular signs)

ANALYSIS AND CONCLUSIONS

In this study, both SYSTANE® ULTRA and Optive® reduced ocular surface damage, and SYSTANE® ULTRA was shown to be non-inferior to Optive®.

In the patient population studies, both SYSTANE® ULTRA and Optive® were effective, convenient, and well tolerated.

*This study was financially supported by Alcon

STUDY RESULTS

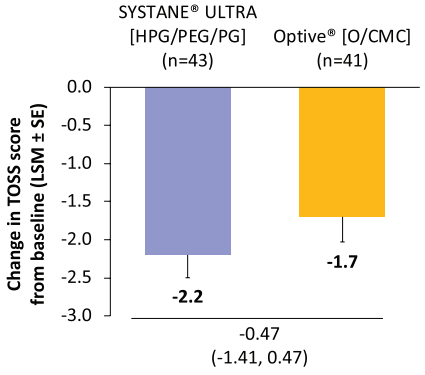
EFFICACY

- TOSS scores at day 35 were 3.5±0.34 points and 3.9±0.35 points in the SYSTANE® ULTRA and Optive® groups, respectively, demonstrating that both treatments reduced ocular surface staining indicative of epithelial damage
- TOSS score change from baseline to day 35 was −2.2±0.33 points with SYSTANE® ULTRA and −1.7±0.34 points with Optive® (treatment difference, −0.47±0.47 points; 95% CI −1.41 to 0.47 points; P=0.318) (**Figure 1**)
- IDEEL scores for treatment inconvenience at day 35 were 69.5±3.0 and 67.1±3.1 with SYSTANE® ULTRA and Optive®, respectively (treatment difference, 2.4±4.4; P=0.586) (**Figure 2**)
- Similar efficacy outcomes were observed in both groups at day 90 (PRN administration) compared with day 35 (four times a day administration)

SAFETY

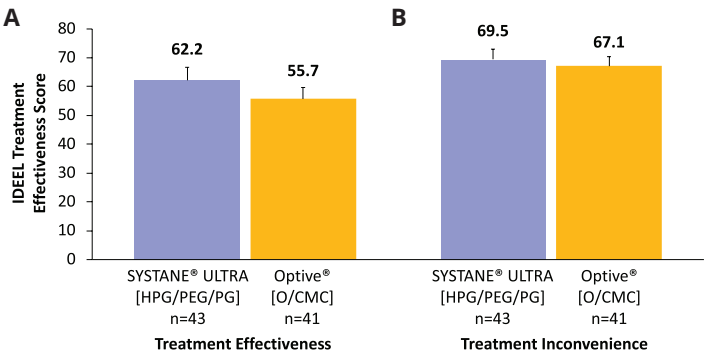
- AEs were reported for 14 patients receiving SYSTANE® ULTRA (35 events) and for 17 patients receiving Optive®; one serious AE (spinal column injury) unrelated to study treatment was reported in the SYSTANE® ULTRA group
- AEs that caused study discontinuation included dry eye, eye irritation, eye pain, eyelid edema and pruritus; most treatment-related AEs were local ocular side effects
- Mean±SD BCVA was similar between groups at baseline (SYSTANE® ULTRA, 82.5±9.1 letters; Optive®, 82.2±14.4 letters) and was similar to baseline at day 35 and day 90; the change from baseline was <2 letters in either group

Figure 1. Mean total ocular surface staining (TOSS) score change from baseline after 35 days treatment with SYSTANE® ULTRA or Optive® eye drops (least squares mean±SE). Mean TOSS scores are indicated within bars. Mean treatment group difference (two-sided 95% CI) is indicated below bars. Lower scores indicate less ocular surface damage.



HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol; O/CMC, osmoprotective carboxymethylcellulose

Figure 2. Mean Impact of Dry Eye on Everyday Life (IDEEL) score after 35 days treatment with SYSTANE® ULTRA or Optive® eye drops (least squares mean±SE). (**A**) Treatment effectiveness, (**B**) treatment inconvenience. Mean IDEEL scores are indicated within bars. Potential IDEEL score range, 0–100. Higher scores indicate improved impact on everyday life.



HPG/PEG/PG, hydroxypropyl guar/polyethylene glycol/propylene glycol; O/CMC, osmoprotective carboxymethylcellulose

Impact of Polyethylene Glycol 400/Propylene Glycol/ Hydroxypropyl-Guar and 0.1% Sodium Hyaluronate on Postoperative Discomfort Following Cataract Extraction Surgery: A Comparative Study

Labiris et al. *Eye Vis (Lond).* 2017;4:13

SYSTANE® ULTRA

Clinical Signs

Patient-Reported Outcomes

Surgical Population

OVERVIEW

STUDY DESIGN

Prospective, clinic-based, randomized trial to explore the impact of two artificial tear preparations on postoperative discomfort following cataract extraction surgery

STUDY SITE(S)

Single site in Greece

PATIENTS

One hundred and eighty (180) patients who underwent cataract extraction surgery

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Cataract surgery patients with no evidence of dry eye disease were randomized to the following postoperative regimes: a) Study group 1 (SG1) received a fixed combination of tobramycin and dexamethasone (FCTD) 4 times daily (QID) for 3 weeks and polyethylene glycol 400/propylene glycol/hydroxypropyl-guar (SYSTANE® ULTRA) QID for 6 weeks; b) Study group 2 (SG2) received FCTD QID for 3 weeks and 0.1% sodium hyaluronate provided in the COMOD® device (Hylocomod®, Farmex, GRE) QID for 6 weeks, and, c) Control Group (CG) received only FCTD QID for 3 weeks

KEY ENDPOINT(S)

Subjective discomfort index (SDI) derived from four direct 10-scale Likert-type questions pertaining foreign body sensation (FBS), blinking discomfort (BD), stinging sensation (SS), and tearing sensation (TS); tear break-up time (TBUT); central corneal thickness (CCT); central corneal sensitivity (CCS)

ANALYSIS AND CONCLUSIONS

In the study population, both SYSTANE® ULTRA and Hylocomod® were equally efficient in alleviating symptoms of ocular surface disease following cataract extraction surgery.

The authors suggest that both SYSTANE® ULTRA and Hylocomod® were equally effective and should be routinely added to the cataract postoperative regime.

STUDY RESULTS

OBJECTIVE CLINICAL SIGNS

- Both SG1 and SG2 demonstrated significantly increased CCT values at the first examination point (1 week) and significantly reduced CCS values at all examination points through week 6 (**Table 1**)
- Non-significant correlations were detected between CCT, CCS and SDI components
- Regarding TBUT, SG 1 and SG 2 demonstrated significantly better (longer) times at all examination points in comparison to CG and to their respective preoperative values (all P<0.05) (**Table 1 and Figure 1**)

DISCOMFORT SCORES

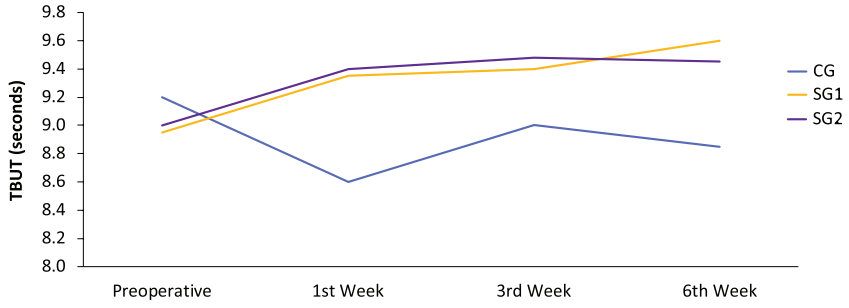
- BD was significantly better in both study groups only at the first week (SG1: 9.24±0.56, SG2: 9.31±0.62; CG: 8.85±1.98, P=0.04) and nonsignificant differences were detected for the rest of SDI components at all examination points
- SG1 and SG2 participants demonstrated significantly better SDI values at the first two postoperative examination visits (until the third week), and borderline better SDI at the last examination visit (**Table 1**)
- Regarding comparisons between study groups, non-significant differences could be detected for all parameters at all examination visits

Table 1. Clinical sign comparison between Study and Control groups, 1st, 3rd, and 6th week. SG1: fixed combination of tobramycin and dexamethasone (FCTD) plus SYSTANE® ULTRA. SG2: FCTD plus Hylocomod. CG: FCTD only.

	1st Week				3rd Week				6th Week			
Parameter	CG	SG1	SG2	P	CG	SG1	SG2	P	CG	SG1	SG2	P
CCT (μm)	550±36*	560±28*	564±41*	0.16	541±32	549±38	555±52	0.42	548±29	550±25	543±31	0.36
CCS (cm)	4.41±0.92*	4.31±1.89*	4.24±1.55*	0.11	4.75±1.14*	4.69±1.2*	4.72±1.41*	0.21	4.82±0.87*	4.77±1.31*	4.79±1.26*	0.26
TBUT (seconds)	8.62±1.45*	9.35±1.34*	9.38±1.11*	0.03	8.98±1.52*	9.41±1.28*	9.47±1.13*	0.01	8.86±1.08*	9.59±1.45*	9.45±1.33*	0.01
FBS	7.74± 1.41	8.92± 1.39	8.99±1.45	0.02	7.92±2.15	9.21±1.89	9.12±1.73	<0.01	8.08±1.23	9.19±1.65	9.21±1.42	0.01
BD	8.85± 1.98	9.24± 0.56	9.31±0.62	0.04	9.05±1.43	9.19±0.74	9.22±0.97	0.12	9.11±0.97	9.21±0.36	9.14±0.47	0.19
SS	9.08± 1.67	9.11± 1.21	9.02±0.87	0.34	9.12±1.47	9.05±0.91	9.09±1.04	0.27	9.02±1.15	9.09±0.64	9.11±0.73	0.22
TS	8.99± 1.22	9.05± 0.88	9.01±0.91	0.23	9.11±0.78	9.06±0.77	9.15±0.94	0.34	9.08±0.85	9.06±0.59	9.13±0.87	0.28
SDI	8.66± 1.57	9.08± 1.01	9.15±1.16	0.04	8.80±1.46	9.12±1.76	9.07±1.52	0.04	8.82±1.05	9.13±0.81	9.17±0.58	0.05

** Significant difference vs. preoperative values CG = control group; SG1 = study group 1; SG2 = study group 2; CCT = Central Corneal Thickness; CCS = Central Corneal Sensitivity; TBUT = Tear Break-up Time; FBS = Foreign Body Sensation; BD = Blinking Discomfort; SS=Stinging Sensation; TS = Tearing Sensation; SDI=Subjective Discomfort Index*

Figure 1. Tear film break-up time (TBUT) in Study and Control groups, 1st, 3rd, and 6th week. SG1: fixed combination of tobramycin and dexamethasone (FCTD) plus SYSTANE® ULTRA). SG2: FCTD plus Hylocomod®. CG: FCTD only.



CG = control group; SG1 = study group 1; SG2 = study group 2

Efficacy of Polyethylene Glycol–Propylene Glycol-Based Lubricant Eye Drops in Reducing Squamous Metaplasia in Patients with Dry Eye Disease

Aguilar et al. *Clin Ophthalmol.* 2018;12:1237-1243

OVERVIEW

STUDY DESIGN

Phase IV, single-arm, open-label study to evaluate the efficacy of a polyethylene glycol–propylene glycol/hydroxypropyl-guar (PEG-PG/HP-guar) artificial tear formulation (SYSTANE® ULTRA) in reducing squamous metaplasia in patients with dry eye disease (DED), using conjunctival impression cytology (CIC)

STUDY SITE(S)

Single site in Argentina

PATIENTS

Forty-nine (49) patients (n=98 eyes) with active signs and symptoms of dry eye as determined by the study investigator, sodium fluorescein corneal staining sum of ≥3 in either eye, tear film break-up time (TFBUT) of <7 seconds, and Grade I to Grade III CIC

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients with DED instilled one drop of SYSTANE® ULTRA to both eyes, 3 times per day, for a period of 90 days

KEY ENDPOINT(S)

Primary endpoint: change from baseline in goblet cell density (mean CIC) over the 90-day treatment period. Exploratory endpoints: change from baseline in 1) total corneal staining score, 2) total conjunctival staining score, 3) TFBUT at Days 30, 60, and 90, and 4) adverse events (AEs)

ANALYSIS AND CONCLUSIONS

Treatment with PEG-PG/HP-guar artificial tears (SYSTANE® ULTRA) for 90 days decreased CIC score, reduced corneal and conjunctival staining, and increased TFBUT in patients with DED.

The authors suggest that PEG-PG/HP-guar artificial tears (SYSTANE® ULTRA) can help improve ocular surface health and reverse the changes induced by squamous metaplasia in DED.

STUDY RESULTS

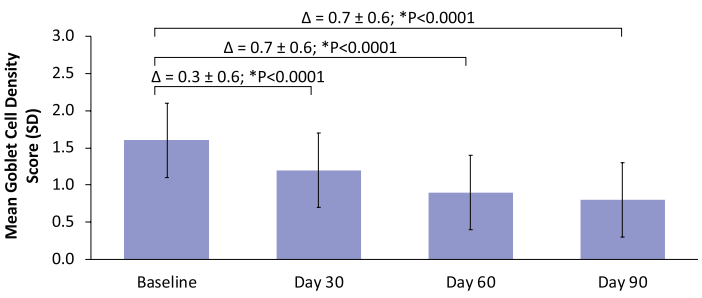
GOBLET CELL DENSITY

- SYSTANE® ULTRA significantly improved CIC score at all follow-up time points compared to baseline (P<0.0001) (**Figure 1**)
- The mean±SD cytology score decreased from 1.6±0.5 units at baseline to 1.2±0.5 units at Day 30, 0.9±0.5 units at Day 60, and 0.8±0.5 units at Day 90
- By Day 90, the severity of squamous metaplasia was reduced in most eyes; 22% of eyes (n=22/98) had improved to Grade 0 (i.e., normal morphology), whereas 64% of eyes (n=63/98) were classified as Grade I; only 3 eyes were classified to have Grade II severity

EXPLORATORY ENDPOINTS

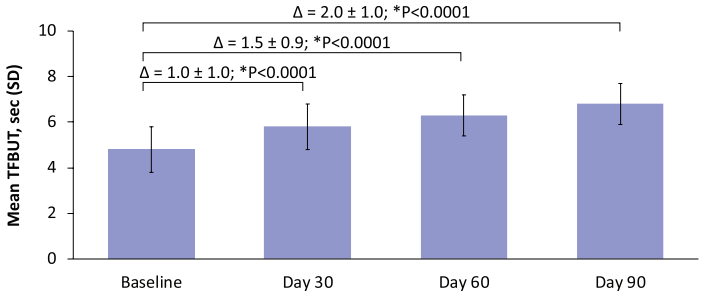
- The mean corneal staining score improved from 5.7±2.8 units (range: 3–11) at baseline to 3.1±2.3 units at Day 30 (range: 0–8), 1.1±0.9 units at Day 60 (range: 0–3), and 0.5±0.6 units (range: 0–2) at Day 90. All eyes demonstrated a total staining sum score <3, with 59% of eyes (n=58/98) having a staining sum score of 0 at Day 90
- Compared with baseline, there was a notable decrease in the mean conjunctival staining score at all follow-up visits (P<0.0001). Mean conjunctival staining scores improved from 5.5±2.1 units (range: 3–11) at baseline to 3.6±2.0 units at Day 30 (range: 0–9), 1.6±1.1 units at Day 60 (range: 0–5), and 0.9±0.9 units (range: 0–3) at Day 90
- At the baseline, the mean TFBUT was 4.8±1.0 s (range: 3–6), and increased to 5.8±1.0 s (range: 3–8) at Day 30 and 6.3±0.9 s (range: 4–8) at Day 60, ending at 6.8±0.9 s (range: 5–9) at Day 90 (P<0.0001 vs baseline at all time points; **Figure 2**). At Day 90, almost 61% of patients reached a TFBUT of ≥7 seconds (vs none at baseline)

Figure 1. Mean±SD conjunctival impression cytology (CIC) scores (i.e., mean goblet cell density) at baseline and Days 30, 60, and 90 after treatment with PEG-PG/HP-guar artificial tears (SYSTANE® ULTRA). Lower scores represent greater improvement.



**P-value for mean change in scores vs baseline.*
SD = standard deviation; PEG-PG/HP-guar = polyethylene glycol–propylene glycol/hydroxypropyl-guar

Figure 2. Mean tear film break-up time (TFBUT) at baseline and Days 30, 60, and 90 after treatment with PEG-PG/HP-guar artificial tears (SYSTANE® ULTRA). Dashed line represents inclusion criterion at baseline.



**P-value for mean change in scores vs baseline.*
SD = standard deviation; PEG-PG/HP-guar = polyethylene glycol–propylene glycol/hydroxypropyl-guar

Clinical Outcomes of Fixed Versus As-Needed Use of Artificial Tears in Dry Eye Disease: a 6-Week, Observer-Masked Phase 4 Clinical Trial

Asbell et al. *Invest Ophthalmol Vis Sci.* 2018;59:2275–2280*

SYSTANE® ULTRA
Clinical Signs
Patient-Reported Outcomes
Safety

OVERVIEW

STUDY DESIGN
Six-week, phase 4, prospective, multicenter, observer masked, active-control, parallel-group clinical trial

STUDY SITE(S)
Eight (8) centers in the United States and Australia

PATIENTS
Ninety-seven (97) patients with dry eye disease (DED) patients having a total ocular surface staining (TOSS) score of ≥ 4 to ≤ 9 on the 15-point Oxford scale and an Impact of Dry Eye on Everyday Life (IDEEL) symptom-bother (SB) score between 16 and 65 at screening and baseline, using benzalkonium chloride (BAK)–free artificial tears on an as-needed basis, once or more a week, for ≥ 3 months prior to the screening visit

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Participants were randomized (1:2 allocation) to receive 1 drop of PEG/PG (SYSTANE® ULTRA) four times daily (QID; n = 34) or as-needed (PRN; n = 63) for 28 days

KEY ENDPOINT(S)
Primary endpoint: change from baseline in TOSS score (according to the Oxford scale) at day 28. Secondary endpoints: change from baseline in IDEEL SB score at day 28, change from baseline in IDEEL treatment satisfaction (TS) scores (treatment effectiveness and treatment-related inconvenience) at day 28

ANALYSIS AND CONCLUSIONS

QID dosing of SYSTANE® ULTRA was not superior to PRN dosing in terms of ocular staining, but the IDEEL symptom-bother score favored QID dosing, suggesting that regular use of artificial tears may provide better symptomatic relief than PRN use.

This clinical trial is the first to investigate the use of regular fixed (QID) dosing versus PRN dosing of an artificial tear product in the management of DED. This is an important factor for clinicians to consider since DED patients tend to seek treatment primarily because of ocular discomfort, and treatment goals are mainly driven toward achieving symptomatic improvement.

*This study was financially supported by Alcon

STUDY RESULTS

OCULAR SURFACE STAINING (TOSS SCORE)

- At day 28, the least squares mean (LSM) change in TOSS score (± standard error [SE]) from baseline was -1.19±0.26 in the QID group and -0.94±0.24 in the PRN group (**Figure 1**)
- Although the treatment difference was numerically in favor of QID treatment (-0.26; CI: -∞ to 0.21; P = 0.184), superiority of QID over PRN dosing was not demonstrated

PATIENT-REPORTED OUTCOMES

- At day 28, the change from baseline in the IDEEL SB score (LSM±SE) was higher in the QID group (-7.0±2.01) than in the PRN group (-2.94±1.85), with a treatment difference (-4.06±2.25, P=0.037) in favor of the QID group (**Figure 2A**)
- A smaller mean (LSM±SE) change from baseline in the IDEEL treatment inconvenience score was observed for the PRN group (-2.77±2.67) than for the QID group (-11.56±2.94) at day 28 (**Figure 2B**)
- The treatment difference (LSM±SE) between the QID and PRN group for the IDEEL treatment inconvenience score was -8.80±3.21 (lower limit of one-sided 95% CI =-14.14; P = 0.996) (**Figure 2C**)

SAFETY

- AEs were reported in 2.9% and 3.2% of participants in the SYSTANE® ULTRA QID and the PRN groups, respectively
- None of the AEs were considered related to the artificial tear treatment

Figure 1. Change in mean total ocular surface staining (TOSS) score from baseline at day 28 (intent-to-treat (ITT) set. The ITT set included all randomized patients who received ≥1 dose of the randomized investigational product (SYSTANE® ULTRA).

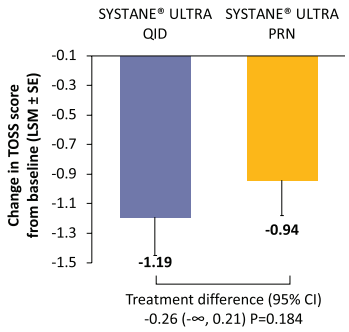
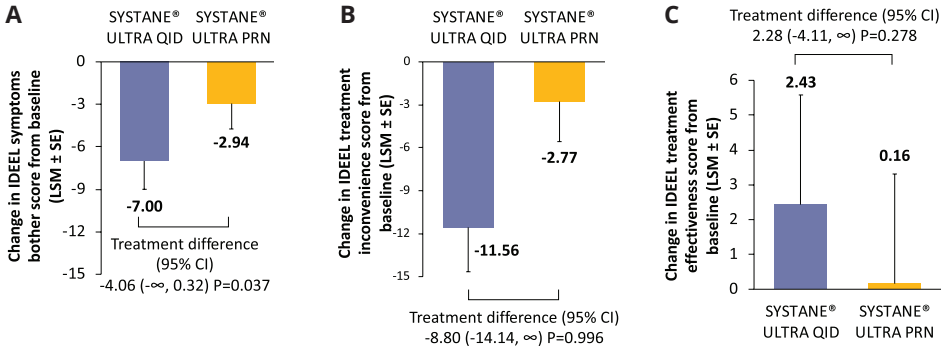


Figure 2. Change in Impact of Dry Eye on Everyday Life (IDEEL) (**A**) symptom-bother (SB), (**B**) treatment inconvenience, and (**C**) treatment effectiveness scores from baseline to day 28 in groups using SYSTANE® ULTRA QID and PRN (intent-to-treat (ITT) set). The ITT set included all randomized patients who received ≥1 dose of the randomized investigational product (SYSTANE® ULTRA).



CI, confidence interval; LSM, least squares mean; PRN, as needed; QID, 4 times daily; SE, standard error.

Does the Temperature of an Artificial Tear Affect Its Comfort?

Bitton et al. *Clin Exp Optom.* 2018;101:641-647

OVERVIEW

STUDY DESIGN

In vitro study to assess temperature, pH and osmolality of a selected artificial tear in ambient and refrigerated conditions, and an open label, cross-over, contralateral eye clinical study to evaluate whether refrigeration enhanced subjective comfort upon instillation

STUDY SITE(S)

Single site in Canada

PATIENTS

Eighteen (18) participants between the ages of 22 and 28 with mild to moderate dry eye (DE) and normal corneal sensitivities

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

SYSTANE® ULTRA was tested at least 24 hours after refrigeration (rAT) or at ambient temperature (aAT). *In vitro* study monitored rate of change in temperature, relative humidity, and pH in 5 minute intervals and assessed osmolality 3 times in 3 different new bottles, all over a 30-minute period. Clinical study participants instilled drops in the morning (at least 30 minutes after waking) and evening; rAT was instilled in the same eye (aAT in contralateral eye) during the first week with a crossover during the second week; the eye receiving first drop was alternated between days

KEY ENDPOINT(S)

In vitro study: changes in artificial tear temperature, pH, and osmolality. Clinical study: subjective comfort for each eye immediately after instillation, on a scale from 1 (poor) to 10 (excellent)

ANALYSIS AND CONCLUSIONS

For patients with mild-to moderate DE, the study results revealed no advantage, with respect to patient perceived comfort, in refrigerating SYSTANE® ULTRA prior to instillation.

Results from the *in vitro* study confirmed that no changes in pH and osmolality of SYSTANE® ULTRA occurred with refrigeration.

STUDY RESULTS

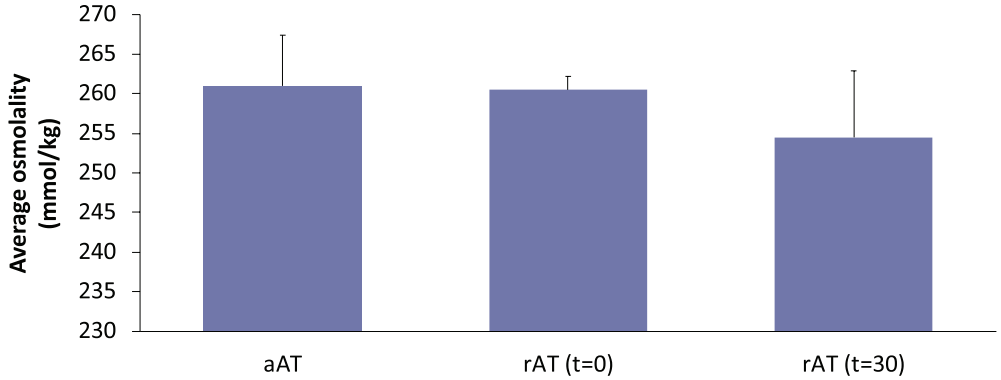
IN VITRO STUDY

- The temperature profile of the aAT remained stable throughout the 30 minute evaluation at 24.2±0.2 °C, while the rAT increased in temperature throughout the 30 minutes as it acclimated to the environment; the rAT took 30 minutes to reach room temperature.
- The pH was measured at 8.0 and remained unchanged for both the aAT and rAT at each time point assessed over a 30-minute period
- The average osmolality was measured at 261.8±6.3 mmol/kg for the aAT, 260.7±1.5 mmol/kg for the rAT immediately after removal from the refrigerator (at t = 0) and 254.3±8.5 mmol/kg for the rAT 30 minutes after retrieval (at t = 30) (**Figure 1**); no significant difference in osmolality was noted between all three conditions

CLINICAL STUDY

- Mean comfort scores (± standard deviation) for the aAT and the rAT were 7.8±0.9 and 7.6±1.4, respectively
- Mean comfort scores (± standard deviation) for AM and PM were 7.7±1.2 and 7.8±1.1, respectively
- A non-parametric Friedman test of differences among repeated measures was conducted and rendered a chi-squared value of 3.74, which was not statistically significant (P=0.29)

Figure 1. Average osmolality (mmol/kg±standard deviation) of the ambient (aAT) and refrigerated (rAT) artificial tears (SYSTANE® ULTRA) immediately after retrieval from the refrigerator (t = 0) and 30 minutes after retrieval (t = 30).



Tear Osmolarity Changes After Use of Hydroxypropyl-Guar-Based Lubricating Eye Drops

Ng et al. *Clin Ophthalmol.* 2018;12:695-700

OVERVIEW

STUDY DESIGN
Prospective, open-label, bilateral eye feasibility study to evaluate tear osmolarity after using a hydroxypropyl-guar (HP-guar)-based lubricating eye drop (SYSTANE® ULTRA) four times daily (QID) for 3 weeks

STUDY SITE(S)
Single site in Canada

PATIENTS
Thirty-one (31) participants with dry eye disease (Ocular Surface Disease Index [OSDI] score ≥20 and tear osmolarity ≥300 mOsm/L in at least one eye) were enrolled and 28 participants completed the study

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
Participants instilled one drop of SYSTANE® ULTRA four times daily (QID) in each eye for 3 weeks; at follow-up, symptoms and ocular surface parameters were assessed, and one drop of SYSTANE® ULTRA drop was instilled on-site, into each eye, and osmolarity was measured after 15 minutes

KEY ENDPOINT(S)
Symptoms (OSDI) and ocular surface parameters (tear osmolarity, non-invasive tear film break-up time (NITBUT)) following three weeks using SYSTANE® ULTRA QID; tear osmolarity 15 minutes after instillation

ANALYSIS AND CONCLUSIONS

In this study, a significant reduction in tear osmolarity and improvements in dry eye symptoms, corneal staining, and NITBUT were observed after 3 weeks of QID SYSTANE® ULTRA use.

After on-site administration of SYSTANE® ULTRA, a decrease in osmolarity was demonstrated 15 minutes after drop instillation.

STUDY RESULTS

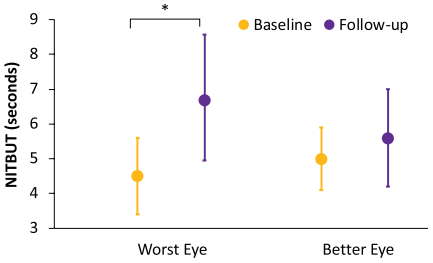
SYMPTOMS AND OCULAR SURFACE PARAMETERS

- At baseline, mean OSDI score was 44.9±15.2, and after 3 weeks of SYSTANE® ULTRA use, the mean OSDI score was significantly reduced to 28.3±17.0 (P<0.01)
- Mean NITBUT at baseline was 4.5±2.9 and 5.0±2.3 seconds (worst eye (WE) and best eye (BE), respectively), and after 3 weeks of drop use improved to 6.7±4.6 and 5.6±3.6 seconds; there was a statistically significant improvement in the WE only (WE P<0.05, BE P=0.46) (**Figure 1**)
- Improvements in corneal staining were observed in all quadrants in both eyes at the follow-up visit; however, a statistically significant improvement was observed only in the central cornea in both eyes (P<0.00001)
- Small reductions in conjunctival staining scores and conjunctival hyperemia in both eyes were observed, but these changes were not statistically significant (P>0.05)

TEAR OSMOLARITY

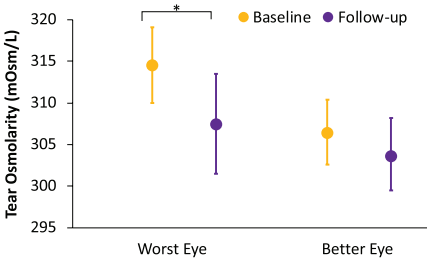
- At baseline, mean osmolarity in the WE was 314.63±11.9 mOsm/L. After 3 weeks of SYSTANE® ULTRA use, mean tear osmolarity was reduced to 307.7±15.7 mOsm/L in the worst eye (P<0.05 vs. baseline) (**Figure 2**)
- In the BE, mean tear osmolarity at baseline was 306.6±10.1 mOsm/L and reduced to 303.9±11.3 mOsm/L after 3 weeks of SYSTANE® ULTRA use (P=0.228 vs. baseline)
- At the follow-up visit, a significant reduction in osmolarity was observed 15 minutes after instilling SYSTANE® ULTRA in the worst eye, from 307.7±15.7 to 299.3±13.4 mOsm/L (P<0.05), and the mean reduction from 303.9±11.3 to 298.2±12.9 mOsm/L in the BE approached significance (P=0.09) (**Figure 3**)

Figure 1. Non-invasive tear break-up time (NITBUT) at baseline and after 3 weeks of SYSTANE® ULTRA Lubricant Eye Drop use.



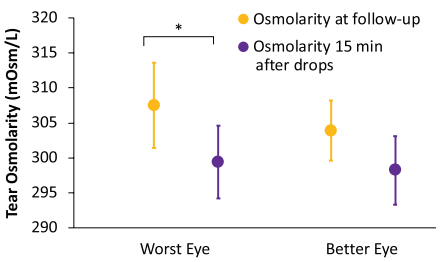
**P<0.05 vs. baseline.*

Figure 2. Tear osmolarity in the worst eye (WE) and best eye (BE) at baseline and after 3 weeks of SYSTANE® ULTRA use (mean and 95% CI shown).



**P<0.05 vs. baseline.*

Figure 3. Tear osmolarity in the worst eye (WE) and best eye (BE) before and 15 minutes after instillation of SYSTANE® ULTRA, determined at the follow-up visit (mean and 95% CI shown).



**P<0.05 vs. baseline.*

Efficacy of an Artificial Tear Emulsion in Patients with Dry Eye Associated with Meibomian Gland Dysfunction

SYSTANE® BALANCE

Clinical Signs

Patient-Reported Outcomes

Sindt and Foulks. *Clin Ophthalmol.* 2013;7:1713-1722‡

OVERVIEW

STUDY DESIGN

Open-label study to assess the efficacy of an artificial tear emulsion for the treatment of dry eye associated with meibomian gland dysfunction (MGD).

STUDY SITE(S)

Five clinical sites in the United States

PATIENTS

Forty-nine (49) patients with a diagnosis of dry eye associated with MGD using artificial tears or cyclosporine ophthalmic emulsion, 0.05% at least two times per day

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients completed 1-week treatment with their habitual topical therapy according to their normal schedule and then 4-week treatment with SYSTANE® BALANCE; an electronic medication monitoring device (Medication Event Monitoring System (MEMS)) was used to track dosing of the habitual and treatment drops

KEY ENDPOINT(S)

Subjective assessments included a preference survey, the Impact of Dry Eye in Everyday Life (IDEEL) questionnaire, and the Work Productivity and Activity Impairment questionnaire; objective assessments included visual acuity, meibomian gland expression and dropout, tear film breakup time, corneal staining, and dosing frequency

ANALYSIS AND CONCLUSIONS

Data from this study reveal that SYSTANE® BALANCE was effective for treating the signs and symptoms of dry eye in MGD patients.

For the primary study endpoint of patients' treatment preference, 61.4% of patients responded that they preferred SYSTANE® BALANCE to their habitual therapy.

‡This study was financially supported by Alcon

STUDY RESULTS

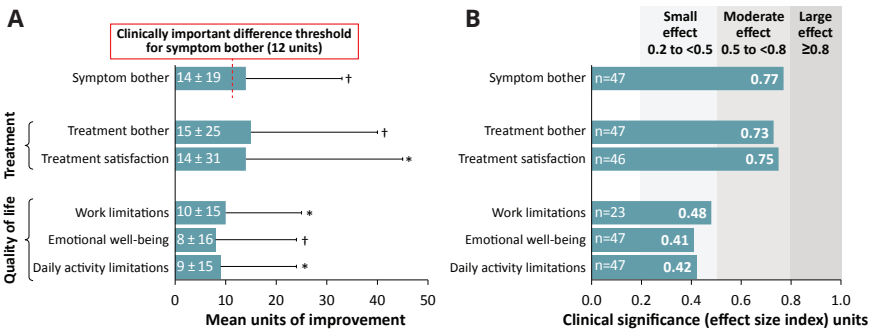
SUBJECTIVE EFFICACY OUTCOMES

- All six of the IDEEL questionnaire subscales indicated that the patients experienced statistically and clinically significant improvements after 4 weeks of SYSTANE® BALANCE use (**Figure 1**)
- For Work Productivity and Activity Impairment questionnaire assessment of impairment to non-work activities, improvement was statistically significant (P=0.006), with a mean magnitude of 11.3%±26.4% alleviation of impairment.
- For the primary study endpoint of patients' treatment preference, 61.4% (n=27/44) of patients responded that they would choose the new study medication (SYSTANE® BALANCE), while 38.6% (n=17/44) responded that they would choose their previous medication.
- Among patients who had any type of "earlier-generation" SYSTANE® product in their prior therapies, the newer-generation SYSTANE® BALANCE study medication was preferred by 70% (n=14/23)
- Among patients who did not have any type of SYSTANE® product in their prior therapies (n=26), SYSTANE® BALANCE was preferred by 54.2% (n=13/26)

OBJECTIVE EFFICACY OUTCOMES

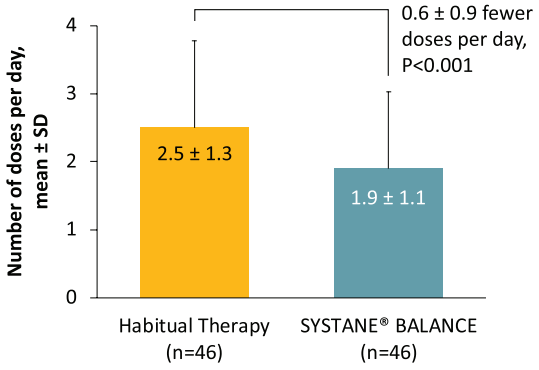
- With habitual therapy, study participants (n=46) self-administered 2.5±1.3 doses per day. With the study medication, that frequency decreased to 1.9±1.1 doses per day; the paired mean decrease in dosing frequency was significant (P<0.001), 0.6±0.9 fewer doses per day (**Figure 2**)
- Values for meibomian gland expression grades were 1.6±0.7 at baseline (n=49 patients) and 1.2±0.6 at visit 4 (n=47 patients); paired change from baseline was −0.4±0.8 grading units, or −17%±36% (n=47 patients; P=0.002)
- At visit 4, 5.6±4.4 glands were missing per eye (n = 47 patients), representing a magnitude of change of 0.1±1.3 glands from baseline; this change was not statistically significant (P= 0.45)
- Changes in tear film breakup time from baseline to visit 4 were clinically modest but statistically significant (0.6±2.1; P<0.05); mean staining left behind after the tear film test was in the mild range for all corneal sectors at baseline and at visit 4
- Improvement in staining was significant for each corneal sector (all sectors P<0.05) and for overall corneal score (P<0.001), with a magnitude of −1.0±1.3 units of overall improvement (on a 16-point scale) per patient
- At visit 4, the per-patient improvement in visual acuity was −0.03±0.11 logMAR units (P=0.08; n=46)

Figure 1. Improvement on the subscale scores of the Impact on Dry Eye in Everyday Life (IDEEL) questionnaire, from baseline (with habitual drops) to visit 4 (after 4 weeks of treatment with study drops (SYSTANE® BALANCE)). (**A**) Mean change per patient; maximum possible change was 100 units. (**B**) Clinical significance of improvement (effect size indices).



*P<0.01. † P<0.001.

Figure 2. Dosing frequency for the 46 study participants whose electronic dosage records were complete at both time points (after 1 week of habitual therapy and after 4 weeks of study medication).



Time Course of Changes in Tear Meniscus Radius and Blink Rate After Instillation of Artificial Tears

SYSTANE® BALANCE

Clinical Signs

Bandlitz et al. *Invest Ophthalmol Vis Sci.* 2014;55:5842-5847

OVERVIEW

STUDY DESIGN

Investigation of the capability of a Portable Digital Meniscometer (PDM) to measure alterations in tear meniscus radius (TMR) after the instillation of artificial tears, and to evaluate any relationships between TMR alterations and changes in blink rate (BR).

STUDY SITE(S)

Single site in Germany

PATIENTS

Twenty-two (22) healthy subjects

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Central TMR and BR were measured at baseline, and 0, 1, 5, 10, and 30 minutes after instillation of an artificial tear containing hydroxypropyl-guar and glycol (SYSTANE® BALANCE) or saline (SAL); a dose of 35 µL was applied in one eye in a randomized order with a washout period between each drop

KEY ENDPOINT(S)

Change from baseline in TMR and BR, tear volume loss (TVL) and tear volume loss rate (TVLR) per blink

ANALYSIS AND CONCLUSIONS

In this study, TMR remained significantly increased up until 5 minutes after application of SYSTANE® BALANCE.

BRs were significantly increased (vs. baseline) upon application of SYSTANE® BALANCE and SAL drops.

STUDY RESULTS

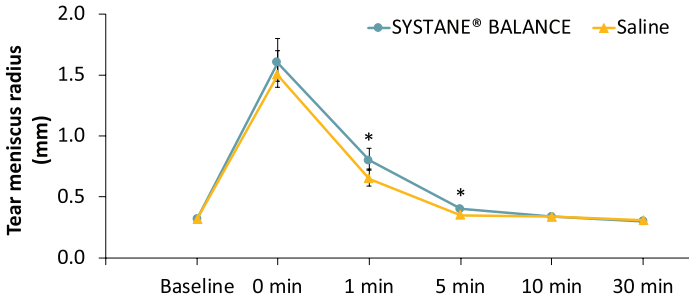
TEAR MENISCUS RADIUS AND BLINK RATE

- Compared to baseline value (0.33±0.08 mm), TMR with SAL was significantly increased upon application of drop (1.55±0.69 mm) and remained significantly greater at 1 minute (0.66±0.36 mm; ANOVA on ranks with Dunnett post hoc test, P<0.05) (**Figure 1**)
- TMR with SYSTANE® BALANCE (baseline, 0.32±0.07 mm) remained significantly increased after application (1.62±0.81 mm), through 1 minute (0.81±0.43 mm) and 5 minutes (0.39±0.08 mm; P<0.05)
- Compared to SAL, TMR with SYSTANE® BALANCE was significantly flatter at 1 minute (0.15±0.32 mm; P=0.044) and 5 minutes (0.05±0.08 mm; P=0.008)
- BRs with SAL (baseline, 14.8±7.7) and SYSTANE® BALANCE (baseline, 14.9±9.4) were significantly increased upon application of drops (22.5±11.8 and 21.3±11.8, respectively; ANOVA on ranks with Dunnett post hoc test, P<0.05), but became similar to baseline after 1 minute (P>0.05)
- There was no significant difference in BR between the two solutions

TEAR VOLUME LOSS AND TEAR VOLUME LOSS RATE PER BLINK

- For both solutions, there was no statistically significant difference in the calculated rate of TVL per blink when comparing:
  - The first time interval 0 to 1 minute (SAL, 1.24±1.16 µL/blink; SYSTANE® BALANCE 1.41±1.72 µL/blink) to the second time interval 1 to 5 minutes (SAL, 0.68±1.03 µL/blink; SYSTANE® BALANCE 0.83±0.79 µL/blink; ANOVA on ranks with Dunnett post hoc test, P<0.05) -
  - The third time interval 5 to 10 minutes (SAL, 0.02±0.11 µL/blink; SYSTANE® BALANCE 0.12±0.12 µL/blink) to the fourth interval 10 to 30 minutes (SAL 0.07±0.17 µL/blink; SYSTANE® BALANCE 0.08±0.23 µL/blink; ANOVA on ranks with Dunnett post hoc test, P<0.05)
- The comparison between all other time intervals showed a statistically significant difference in the rate of TVL per blink (P<0.05)

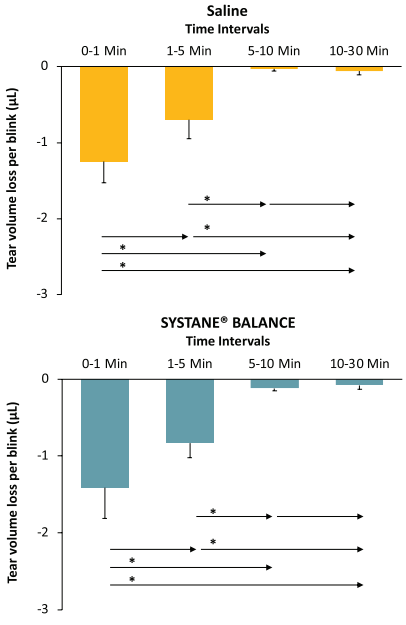
Figure 1. Variations in tear meniscus radius (TMR) after the instillation of SYSTANE® BALANCE artificial tears and saline (SAL) (mean±standard error (SE)).



** P<0.05, paired t-test.*

Figure 2. Calculated tear volume loss (TVL) per blink over the different time intervals after the instillation of a 35 µL drop of saline (SAL) of SYSTANE® BALANCE (mean±standard error (SE)).

**P<0.05, ANOVA on ranks with Dunnett post hoc test.*



The Effect of Tear Supplementation on Ocular Surface Sensations during the Interblink Interval in Patients with Dry Eye

SYSTANE® BALANCE

Clinical Signs

Dienes et al. *PLoS One.* 2015;10: e0135629†

OVERVIEW

STUDY DESIGN

Placebo-controlled investigation of the characteristics of ocular surface sensations and corneal sensitivity during the interblink interval before and after tear supplementation in dry eye patients

STUDY SITE(S)

Academic centers in Hungary and Spain

PATIENTS

Twenty (20) subjects with dry eye symptoms were included in the dry eye group; fourteen (14) subjects without any clinical signs and/or symptoms of dry eye were included in the control group

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Tear film dynamics were assessed by noninvasive tear film breakup time (NI-BUT) in parallel with continuous recordings of ocular sensations during forced blinking; corneal sensitivity to selective stimulation of corneal mechano-, cold, and chemical receptors was assessed using a gas esthesiometer; all measurements were made before and 5 min after instillation of saline and hydroxypropyl-guar (HP-guar) drops (SYSTANE® BALANCE)

KEY ENDPOINT(S)

Ocular surface sensations during forced blinking; effect of tear supplementation on ocular surface sensations during forced blinking, NI-BUT, and corneal sensitivity

ANALYSIS AND CONCLUSIONS

Although tear supplementation improves the protective tear film layer, and thus reduces unpleasant sensory responses, the rapid rise in discomfort is still maintained with blinking and might be responsible for the remaining complaints of dry eye patients despite artificial tear use.

Ocular surface irritation responses due to tear film drying are considerably increased in dry eye patients compared to normal subjects.

†Publication fees of the manuscript were partially covered by the Spes Futuri Research Grant provided by Alcon Hungary Kft (LD)

STUDY RESULTS

IRRITATION SCORES AND NI-BUT

- In the dry eye group, the saline eye drop significantly reduced sensory responses after the first 10 seconds during the interblink interval (P< 0.004) (**Figure 1A**)
  - The application of SYSTANE® BALANCE resulted in a significant reduction of the sensory responses throughout the entire interblink interval (P<0.004)
  - The difference between sensory responses after application of saline drops or SYSTANE® BALANCE was statistically significant at every 5-second time frame during the interblink interval (P<0.004)
- In the control group (no dry eye symptoms), saline eye drop significantly reduced the sensory responses only after the first 30 seconds during the interblink interval (P<0.004) (**Figure 1B**)
  - The application of a SYSTANE® BALANCE resulted in a significant reduction of sensory responses after the first 20 seconds during the interblink interval (P<0.004)
  - The difference between sensory responses after saline or SYSTANE® BALANCE application was statistically significant at every 5-second time frame after the first 20 seconds during the interblink interval (P<0.004)
- Tear supplementation with SYSTANE® BALANCE significantly increased the time to develop tear film breakup and maximum irritation during forced blinking (P=0.01)

TEAR FILM BREAKUP

- Average NI-BUT (8.18±3.28 seconds) increased significantly after application of SYSTANE® BALANCE (10.44±4.44 seconds; P=0.003) but increased only slightly after application of saline (9.86±4.96 seconds; P=0.14)
- The average increase in NI-BUT was 31% after application of SYSTANE® BALANCE and 17% after application of saline drops.
- In the dry eye group, the interblink interval increased from 3.77±2.59 seconds to 4.11±2.13 seconds (P=0.48) after application of saline and to 5.52±2.84 seconds (P=0.01) after application of SYSTANE® BALANCE.
- In the control (no dry eye symptoms) group, the interblink interval increased from 6.23±2.21 seconds to 7.19±2.55 seconds (P=0.11) after application of saline and to 8.13±3.03 seconds (P=0.01) after application of SYSTANE® BALANCE.

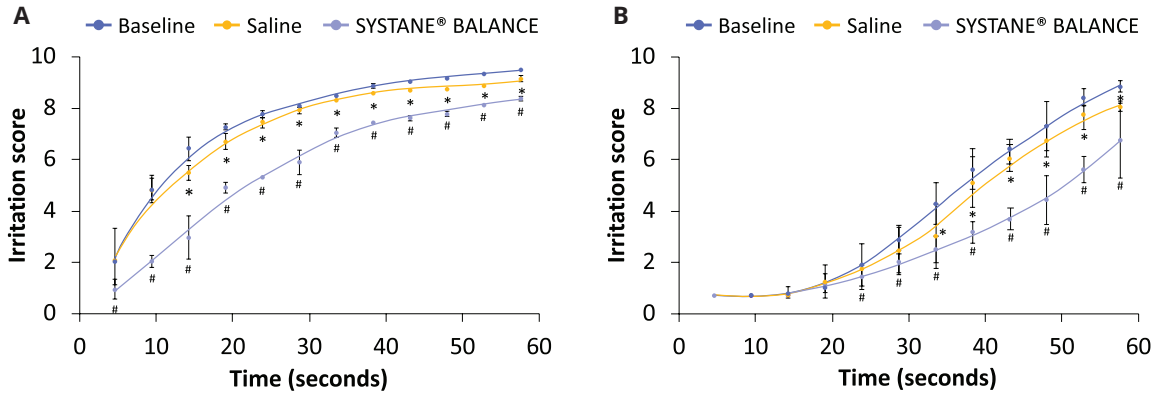


Figure 1. Mean irritation scores as a function of time during forced blinking in dry eye and in normal subjects. Mean values of ocular irritation scores during interblink interval after application of saline or SYSTANE® BALANCE in the (**A**) dry eye group and (**B**) control group

** baseline vs. saline P<0.004; # baseline vs. SYSTANE® BALANCE P<0.004.*

Clinical Evaluation of an Oil-Based Lubricant Eyedrop in Dry Eye Patients with Lipid Deficiency

Baudouin et al. *Eur J Ophthalmol.* 2017;27:122-128*

SYSTANE® BALANCE

Clinical Signs

Patient-Reported Outcomes

Safety

OVERVIEW

STUDY DESIGN

Prospective, multicenter, randomized, single-masked, parallel-group phase 4 clinical study to evaluate and compare the efficacy of a lipid-based lubricant eyedrop formulation (hydroxypropyl guar/propylene glycol/phospholipid [HPG/PG/PL]) with preservative-free saline for the treatment of dry eye

STUDY SITE(S)

Thirty-five (35) sites in France (14), Germany (4), Italy (4), the Netherlands (3), Poland (3), Spain (3), and the United Kingdom (4)

PATIENTS

Two hundred and fourteen (214) patients aged ≥18 years and diagnosed with dry eye ≥6 months before the pre-run-in screening visit; the following dry eye criteria were required to be present in at least 1 eye at the screening visit: meibomian gland dysfunction grade ≤2 for meibum expressibility and meibum quality, tear film breakup time (TFBUT) ≤5 seconds, and unanesthetized Schirmer I test result ≥3 mm

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

During 15-day run-in, patients self-instilled 1 drop of saline in each eye 4 times daily (QID). At post-run-in baseline visit (day 0), eligible patients were randomized 1:1 to receive either SYSTANE® BALANCE or preservative-free saline. During the first treatment phase (through day 35), patients instilled assigned drops in each eye QID. In the second treatment phase (through day 90), patients instilled their assigned drops as needed (PRN)

KEY ENDPOINT(S)

Primary efficacy: change in TFBUT from baseline to day 35 in the study eye (i.e., the eye with the shorter TFBUT at screening). Additional outcomes: changes from baseline to day 35 in total ocular surface staining (TOSS) score and impact of dry eye in everyday life (IDEEL) questionnaire scores; safety (assessed throughout by adverse event (AE) reporting)

ANALYSIS AND CONCLUSIONS

Thirty-five days of QID SYSTANE® BALANCE treatment resulted in a statistically significant improvement in TFBUT and IDEEL treatment effectiveness scores compared with saline but not in TOSS or IDEEL treatment inconvenience scores.

The study data also indicate that SYSTANE® BALANCE was well-tolerated by subjects.

*This study was financially supported by Alcon

STUDY RESULTS

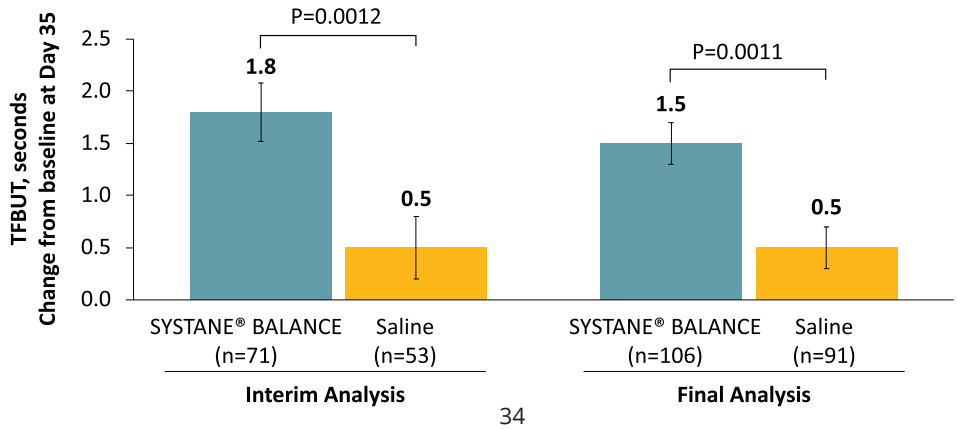
CLINICAL SIGNS AND PATIENT-REPORTED OUTCOMES

- Mean±SE TFBUT change from baseline to day 35 was significantly greater with SYSTANE® BALANCE compared with saline; the between-group difference was 1.3±0.4 seconds (**Figure 1**)
- The between-group difference in mean±SE TFBUT change from baseline to day 35 in the final analysis was 1.0±0.3 seconds (P=0.0011)
- The IDEEL treatment effectiveness score change from baseline to day 35 was 21.5±2.4 in the SYSTANE® BALANCE group and 5.5±2.7 in the saline group; the between-group difference was 16.0±3.6, favoring SYSTANE® BALANCE (P<0.0001)
- The IDEEL treatment inconvenience score changes from baseline to day 35 were 1.3±1.6 and 0.8±1.7 with SYSTANE® BALANCE and saline, respectively; the between-group difference of 0.52±2.3 was not statistically significant (P=0.8211)

SAFETY

- Ocular AEs were reported by 19% of patients receiving SYSTANE® BALANCE and 8% of patients receiving saline through treatment day 90
- Non-ocular AEs were reported for 17% of patients receiving SYSTANE® BALANCE and 16% of patients receiving saline
- Two patients in each treatment group experienced serious AEs; no serious AEs were related to treatment

Figure 1. Mean change from baseline at day 35 in tear film break-up time (TFBUT). SYSTANE® BALANCE was superior to saline at day 35 for prolonging TFBUT in patients with lipid-deficient dry eye at both the interim and final analyses.



Lipid Supplements and Clinical Aspects of Tear Film in Habitual Lens Wearers

Rohit et al. *Optom Vis Sci.* 2017;94:174-182

SYSTANE® BALANCE

Clinical Signs

Patient-Reported Outcomes

Contact Lens Population

OVERVIEW

STUDY DESIGN

Double-masked, randomized, crossover, placebo-controlled intervention study to establish the effect of lipid supplements on the tear lipid layer and their influence on contact lens wear comfort in habitual lens wearers

STUDY SITE(S)

Single site in Australia

PATIENTS

Forty (40) participants with a history of ≥6 months of soft contact lens wear of at least 5 to 6 hours per day for a minimum of 5 days per week were recruited; sixteen (16) recruits were symptomatic and 24 were asymptomatic (as determined by the Contact Lens Dry Eye Questionnaire)

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

An emulsion drop containing phosphatidylglycerine (SYSTANE® BALANCE) and a saline drop as a placebo or a liposomal spray containing phosphatidylcholine (TearsAgain™, BioRevive, Burnley, Victoria, AUS) and a saline spray as a placebo were used three times a day for 2 weeks with 48 hours washout between each intervention

KEY ENDPOINT(S)

Ocular comfort index (OCI), lipid layer distribution patterns (0 = no lipid layer, 5 = color fringes) and noninvasive surface drying time (proxy for tear film stability) with Tearscope, and tear evaporation rate with Vapometer assessed at days 1 and 14

ANALYSIS AND CONCLUSIONS

Irrespective of supplementation, ocular comfort during contact lens wear improved with increased tear film stability and a reduced tear evaporation rate.

The lipid supplements evaluated in this study did not improve contact lens wear discomfort from baseline.

STUDY RESULTS

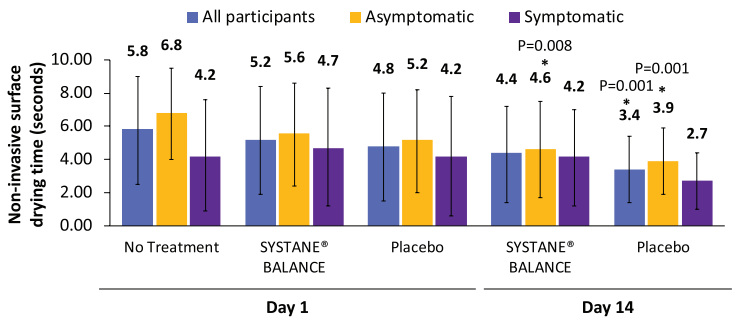
ARTIFICIAL TEAR OUTCOMES

- The OCI measured at day 14 showed that there was no change in ocular comfort either with the lipid drop (SYSTANE® BALANCE) or with the placebo compared to baseline
- By day 14, the noninvasive surface drying time was reduced (3.4±2.0 s, P=0.001) compared to baseline (5.7±3.2 s) with the placebo drop but not with SYSTANE® BALANCE (4.4±2.9 s; P=0.17)
- Symptomatic and asymptomatic wearers did not significantly differ in their noninvasive surface drying time from baseline at day 1; however, by day 14, noninvasive surface drying time of asymptomatic wearers significantly reduced with SYSTANE® BALANCE (4.6 s vs. 5.6 s; P=0.008) and placebo (3.9 s vs. 5.2 s; P=0.001) whereas the noninvasive surface drying time of symptomatic wearers remained unaffected from baseline (P=0.16)
- The placebo drop significantly changed the lipid layer distribution (P=0.03) with a higher percentage of thinner patterns, compared to baseline, whereas no change was seen with SYSTANE® BALANCE
- Tear evaporation rate did not change from baseline either with the SYSTANE® BALANCE or with the placebo at day 1 or at day 14
- Symptomatic status did not have an effect on ocular comfort, lipid layer distribution, and tear evaporation rate after the drop treatment
- Analysis of normalized noninvasive surface drying time and tear evaporation data showed no significant difference with either of the drop interventions at day 1 compared to baseline; however, at day 14, normalized noninvasive surface drying time significantly reduced with placebo drop (P=0.006) but not with SYSTANE® BALANCE (P>0.99) compared to baseline (**Figure 1**)

OPHTHALMIC SPRAY OUTCOMES

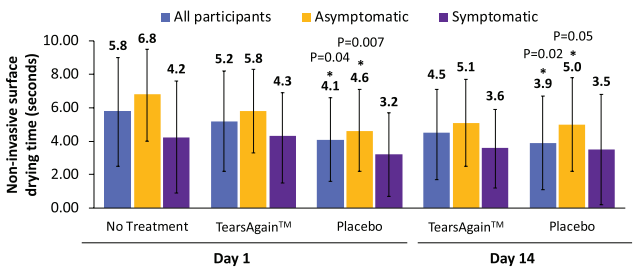
- The OCI measured at day 14 showed no change in ocular comfort either with the lipid spray (TearsAgain™) or with the placebo spray compared to baseline
- The noninvasive surface drying time was significantly reduced with the placebo spray from baseline to day 1 (5.7±3.2 s to 4.1±2.5 s; P=0.04) but not at day 14 (4.4±3.4 s; P=0.09), whereas the lipid spray had no effect on the noninvasive surface drying time either at day 1 (5.2 ±2.6 s; P=0.99) or at day 14 (4.5±2.6 s; P=0.32) compared to baseline
- Symptomatic wearers had shorter noninvasive surface drying time compared to asymptomatic wearers at baseline (P=0.002) with the lipid spray and with the placebo at day 1 and day 14 (all P<0.05); only asymptomatic wearers had a significant reduction in noninvasive surface drying time at day 1 (P=0.008) and day 14 (P=0.03) compared to baseline
- Neither lipid spray nor placebo affected the lipid layer pattern and tear evaporation rate from baseline at day 1 or at day 14
- Symptomatic status did not have an effect on lipid layer distribution and tear evaporation rate after the spray treatment
- Analysis of normalized noninvasive surface drying time and tear evaporation data showed no significant difference with either of the spray interventions at day 1 or at day 14 compared to baseline (**Figure 2**)

Figure 1. Noninvasive surface drying time of symptomatic and asymptomatic contact lens wearers along with all participants after the use of lipid drop (SYSTANE® BALANCE) and saline drop (placebo) at day 1 and day 14. Error bars indicate standard deviation.



** Significant difference vs. baseline (P<0.05).*

Figure 2. Noninvasive surface drying time of symptomatic and asymptomatic contact lens wearers along with all participants after the use of lipid spray (TearsAgain™) and saline spray (placebo) at day 1 and day 14. Error bars indicate standard deviation.



** P<0.05 vs. baseline.*

Effect of Lipid-Based Dry Eye Supplements on the Tear Film in Wearers of Eye Cosmetics

SYSTANE® BALANCE

Clinical Signs

Wang et al. *Cont Lens Anterior Eye.* 2017;40:236-241

OVERVIEW

STUDY DESIGN

Prospective, randomized, paired-eye, investigator-masked trial to compare the effects on tear film parameters and contamination in cosmetic eyeliner wearers, after single application of two lipid-based dry eye treatments

STUDY SITE(S)

Single site in New Zealand

PATIENTS

Fifty (50) participants

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Pencil eyeliner was applied to the upper eyelid periocular skin of both eyes, anterior to the lash line. Baseline tear film quality was assessed fifteen minutes after eyeliner application. A lubricant drop (SYSTANE® BALANCE) was then applied to one eye (randomized) and liposomal spray (Tears Again®; Optima Pharmazeutische GmbH, DEU) to the contralateral eye

KEY ENDPOINT(S)

Tear film contamination, lipid layer grade, non-invasive tear film break-up time, and tear evaporation rate fifteen minutes post-treatment and compared to pre-treatment values

ANALYSIS AND CONCLUSIONS

Administration of both the lipid-containing lubricant eye drop (SYSTANE® BALANCE) and the phospholipid liposomal spray (Tears Again®) resulted in clinically apparent tear film contamination in eyeliner cosmetic wearers.

Although both supplements effected immediate improvements in tear film lipid layer grade, their potential clinical efficacy in improving tear film stability appeared to be compromised when applied concurrently with eye cosmetic products.

STUDY RESULTS

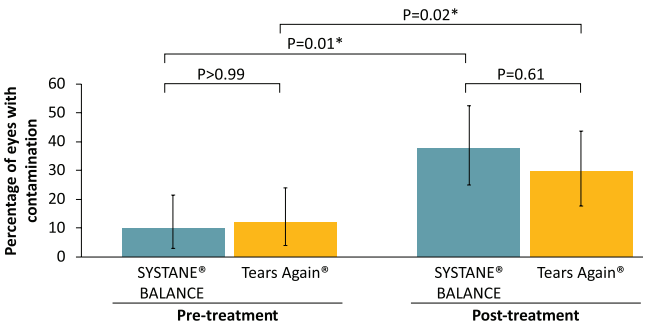
TEAR FILM CONTAMINATION

- Although there were no reports of adverse effects on periocular cosmesis through smudging or tearing, following the application of both lipid-based tear supplements, tear film contamination was observed in a greater proportion of eyes following application of both SYSTANE® BALANCE (P=0.01) and Tears Again® (P=0.02) compared to baseline, although no significant difference was detected between groups (P=0.61) (**Figure 1**)
- There were no significant changes in tear film debris or lid margin foaming following both treatments (all P>0.05), and the two groups did not differ significantly (all P>0.05)

CLINICAL EVALUATION

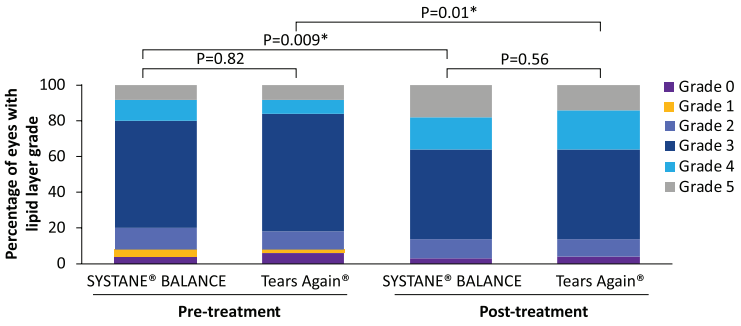
- Tear film lipid layer grade was significantly greater following treatment with both SYSTANE® BALANCE (P=0.009) (**Figure 2**) and Tears Again® (P=0.01); no significant differences were observed in post-treatment lipid layer grade between groups (P=0.56)
- Tear meniscus height increased following SYSTANE® BALANCE application (P=0.04), but not following Tears Again® application (P=0.19); however, the change in tear meniscus height did not vary significantly between groups post-treatment (P=0.31)
- Neither treatment resulted in significant change in non-invasive tear film break-up time (both P>0.05), and no significant differences in break-up time changes were detected between groups (P=0.61)
- Tear evaporation rate did not change following either treatment (both P>0.05), and no significant differences were observed between groups (P=0.23)

Figure 1. Pre-treatment and post-treatment tear film contamination in eyes randomized to lipid-containing lubricant eye drop (SYSTANE® BALANCE) and phospholipid liposomal spray (Tears Again®).



** P<0.05, statistically significant difference*

Figure 2. Pre-treatment and post-treatment tear film lipid layer grade distribution in eyes randomized to lipid-containing lubricant eye drop (SYSTANE® BALANCE) and phospholipid liposomal spray (Tears Again®). Bars represent percentage of eyes within each lipid layer grade. Density of shading corresponds to lipid layer grade.



** P<0.05, statistically significant difference*

Tear Lipid Supplement Prophylaxis Against Dry Eye in Adverse Environments

SYSTANE® BALANCE

SYSTANE® ULTRA

Clinical Signs

Gokul et al. *Cont Lens Anterior Eye.* 2018;41:97-100†

OVERVIEW

STUDY DESIGN

Prospective, randomized, double-masked, paired-eye trial to compare the prophylactic efficacy of single application of lipid and non-lipid containing tear supplements, prior to exposure of symptomatic dry eye subjects to a simulated adverse environment

STUDY SITE(S)

Single center in New Zealand

PATIENTS

Thirty (30) subjects with mild-to-moderate dry eye symptoms

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

A lipomimetic drop (SYSTANE® BALANCE) was applied to one eye (randomized), and a non-lipid containing drop (SYSTANE® ULTRA) applied simultaneously to the contralateral eye; subjects were subsequently exposed to a validated simulated adverse environment model created by a standing fan directed towards the eye, at a distance of 1 m, for 2.5 min

KEY ENDPOINT(S)

Low contrast glare acuity, lipid layer grade (LLG), non-invasive tear break-up time (NIBUT), temperature variation factor (TVF), and tear meniscus height (TMH)

ANALYSIS AND CONCLUSIONS

In this study, a single application of both lipid and non-lipid containing eye drops conferred protective effects against exposure to adverse environmental conditions in subjects with mild-to-moderate dry eye, although the lipomimetic drop (SYSTANE® BALANCE) demonstrated superior prophylactic efficacy.

A higher proportion of subjects reported greater ocular comfort in the eye receiving the lipid-containing drop.

†Alcon donated tear supplements for this study

STUDY RESULTS

LIPID LAYER GRADE

- Repeated measures ANOVA demonstrated statistically significant effects of treatment, time, and treatment-by-time interactions for LLG (all P<0.05) (**Figure 1**)
- SYSTANE® Ultra drop instillation was not associated with a significant rise in LLG (P=0.13) and allowed LLG levels to drop below baseline with adverse environmental conditions (P=0.01)
- Both post-instillation and post-exposure LLGs were greater in the SYSTANE® BALANCE drop group (both P<0.05)

ADDITIONAL FINDINGS

- Significant treatment and time effects were detected for NIBUT (both P<0.05), although the treatment-by-time interaction was non-significant (P=0.17) (**Figure 2**)
- However, both post-instillation and post-exposure NIBUT values were longer in the SYSTANE® BALANCE group (both P<0.05)
- No significant treatment, time, or interaction effects were detected for low contrast glare acuity, TVF, or TMH (all P>0.05)
- A higher proportion of subjects reported greater ocular comfort in the eye receiving the SYSTANE® BALANCE drop (67% versus 17%, P<0.001)

Figure 1. Tear film lipid layer grade (LLG) at baseline and following instillation and simulated adverse environment exposure. Each point represents the tear film LLG of an individual eye. Bars represent the median, and error bars represent the interquartile range.

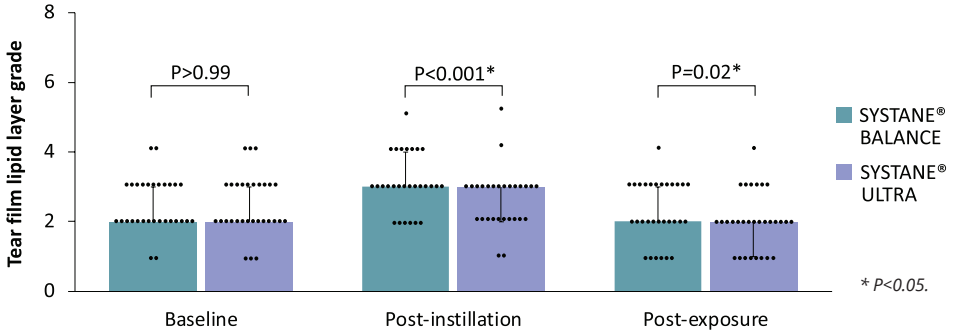
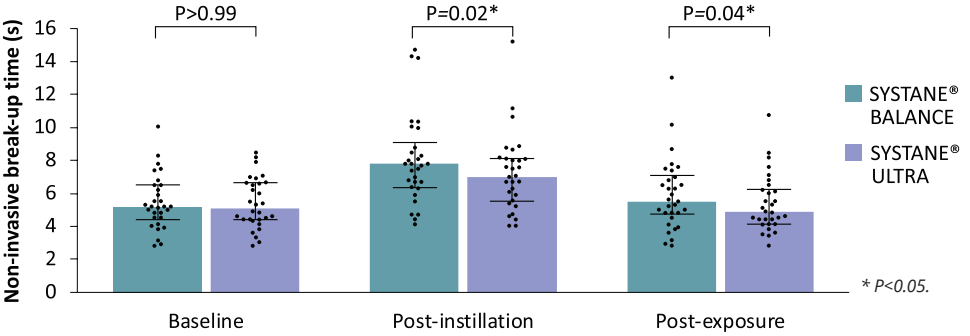


Figure 2. Non-invasive tear film break-up time (NIBUT) at baseline and following instillation and simulated adverse environment exposure. Each point represents NIBUT of an individual eye. Bars represent the median, and error bars represent the interquartile range.



Effect of Tear Supplements on Signs, Symptoms and Inflammatory Markers in Dry Eye

SYSTANE® BALANCE

Clinical Signs

Patient-Reported Outcomes

Martin et al. *Cytokine.* 2018;105:37-44

OVERVIEW

STUDY DESIGN

Masked, randomized, crossover trial to compare the effects of three tear supplements on the signs, symptoms and inflammatory status of subjects with dry eye disease

STUDY SITE(S)

Single site in the United Kingdom

PATIENTS

Eighteen (18) patients with dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Each study subject received all 3 treatments (carboxymethylcelluloseglycerine-castor oil (CGC; Optive Plus™)), hydroxypropyl guar [HPG] [SYSTANE® BALANCE], and carboxymethylcellulose (CMC; Refresh Contacts®) over a 14-week period (four weeks per treatment), with a 1-week washout between each treatment

KEY ENDPOINT(S)

Ocular Surface Disease Index (OSDI) questionnaire, tear osmolarity, non-invasive tear breakup time (NITBUT), tear fluid cytokine analysis, tear evaporation rate (TER), and corneal staining

ANALYSIS AND CONCLUSIONS

All three artificial tears tested in this study were shown to reduce symptoms and improve tear stability when used for 4 weeks.

The CGC treatment resulted in the greatest reduction in ocular biomarkers of inflammation.

STUDY RESULTS

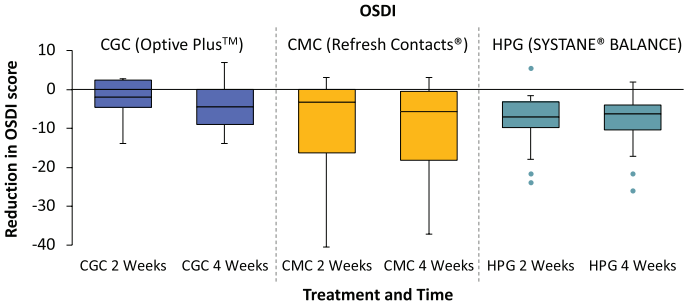
OSDI AND NITBUT

- A significant improvement (decrease) in the OSDI symptom scores was noted after 2 weeks of treatment with both CMC drops (Refresh Contacts®; P=0.004) and SYSTANE® BALANCE (P<0.001) (**Figure 1**)
- Following 4 weeks of treatment, the improvement in OSDI scores was found to be significant for all treatments (Optive Plus™: P=0.008, Refresh Contacts®: P=0.001, SYSTANE® BALANCE: P<0.001); there was no statistically significant difference between the treatments with respect to OSDI outcomes
- There was a significant improvement in NITBUT for all 3 treatments at both 2 weeks and 4 weeks (Optive Plus™ 2 weeks: P<0.001; Refresh Contacts® 2 weeks: P=0.003, Refresh Contacts® 4 weeks: P<0.001; SYSTANE® BALANCE 2 weeks: P<0.001; SYSTANE® BALANCE 4 weeks: P<0.001) (**Figure 2**), and no statistically significant difference between the treatments

TEAR EVAPORATION, OSMOLARITY, AND CORNEAL STAINING

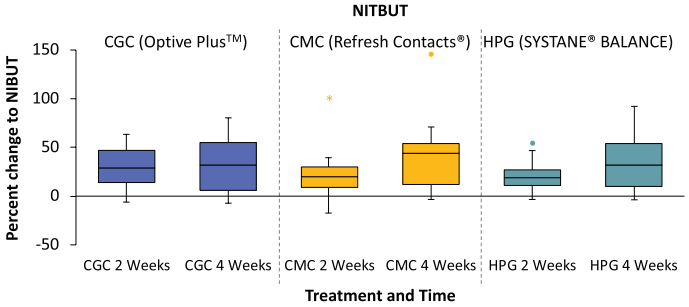
- Measurements of TER, tear osmolarity and corneal staining showed a reduction after 4 weeks for all 3 treatments, however this did not reach statistical significance
- A greater reduction in TER was seen with both the lipid containing-drops (Optive Plus™ and SYSTANE® BALANCE) compared to the non-lipid containing drop (Refresh Tears®); the reduction was greatest with SYSTANE® BALANCE (−11.8 g/m2/h), followed by Optive Plus™ (−9.1 g/m2/h), and Refresh Contacts® (−3.3 g/m2/h)
- A decrease in cytokine concentration (pg/ml) from baseline of >25% was deemed a positive response to therapy
  - After 2 weeks of treatment, the number of subjects exhibiting improvement while using CGC (Optive Plus™) and CMC (Refresh Contacts®) were similar, however fewer subjects showed this benefit when treated with SYSTANE® BALANCE
  - There was no statistically significant difference between the 3 arms of the study when analyzing the percentage change of the biomarkers

Figure 1. Change in Ocular Surface Disease Index (OSDI) score with treatment. Note the zero line is baseline before treatment (probable outliers are represented by the dots).



CGC, carboxymethylcelluloseglycerine-castor oil; CMC, carboxymethylcellulose; HPG, hydroxypropyl guar

Figure 2. Percentage change in non-invasive tear breakup time (NITBUT) with treatment. Note the zero line is baseline before treatment (probable outliers are represented by the asterisk and dots).



CGC, carboxymethylcellulose-glycerine-castor oil; CMC, carboxymethylcellulose; HPG, hydroxypropyl guar

Effects of a Hyaluronic Acid/Hydroxypropyl Guar Artificial Tear Solution on Protection, Recovery, and Lubricity in Models of Corneal Epithelium

Rangarajan, Kraybill, Ogundele, and Ketelson. *J Ocul Pharm Ther.* 2015;31:491-497‡

OVERVIEW

STUDY DESIGN

In vitro study to assess the potential benefits of a lubricant eye drop formulation containing the demulcents propylene glycol and polyethylene glycol and a hyaluronic acid / hydroxypropyl guar (HA/HPG) dual polymer (SYSTANE® HYDRATION) in models of the human corneal epithelium

STUDY SITE(S)

Single site in the United States

PATIENTS

Not applicable

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Cultured human corneal epithelial or corneal-limbal epithelial cells were treated with SYSTANE® HYDRATION or single-polymer formulations containing either HPG or HA. Desiccation protection by cell hydration and surface retention were assessed using cell viability assays. Sodium fluorescein permeability, transepithelial electrical resistance (TEER), and cell viability assays were conducted using pretreated cells exposed to a surfactant / detergent insult. Surface lubricity was assessed in tribological experiments of pericardium–pericardium friction

KEY ENDPOINT(S)

Cell hydration and surface retention, cell and cell barrier protection, surface lubrication

ANALYSIS AND CONCLUSIONS

The HA/HPG artificial tear (SYSTANE® HYDRATION) provided effective hydration and lubrication and demonstrated prolonged retention of effect in cell cultures.

The authors suggest that the HA/HPG formulation of SYSTANE® HYDRATION may potentially promote desiccation protection and retention on the ocular surface.

‡Drs. Rangarajan, Kraybill, Ogundele, and Ketelson are employees of Alcon

STUDY RESULTS

CELL HYDRATION AND SURFACE RETENTION

- Hydration protection against desiccation was significantly greater with the HA/HPG artificial tear (SYSTANE® HYDRATION) compared with media controls, HPG-only or HA-only formulations (P<0.001); protection with the HPG-only formulation was significantly greater compared with the HA-only formulation (P=0.016) (**Figure 1**)
- Cell protection by surface retention of test formulations after removal and rinsing was also significantly greater with SYSTANE® HYDRATION compared with media controls, the HPG-only formulation, and the HA-only formulation (P<0.001), and was also significantly greater with HPG versus HA (P=0.01)

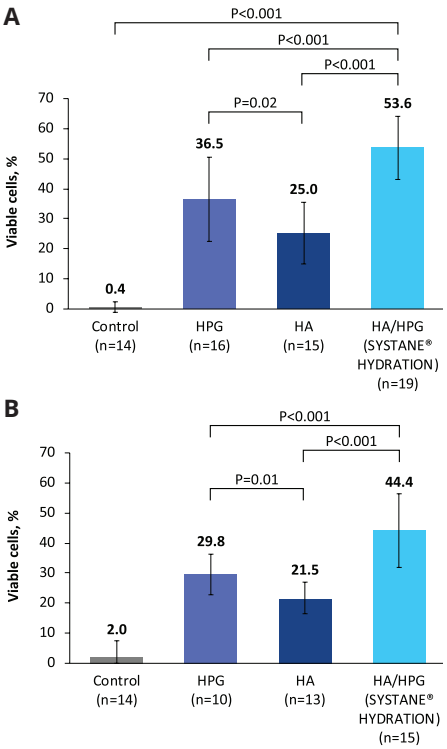
CELL AND CELL BARRIER PROTECTION

- Immediately after insult:
  - Samples pretreated with the HA-only formulation or HA/HPG (SYSTANE® HYDRATION) demonstrated significantly less fluorescein permeability immediately after insult compared with media controls (P<0.001)
  - There were no significant differences between treatments in mean TEER relative to pretreatment resistance
  - Markedly more viable cells were observed with SYSTANE® HYDRATION compared with media controls, the HPG-only formulation, and the HA-only formulation; cell viability was similar between media controls, HPG-treated samples, and HA-treated samples
- After 4 hours of recovery post-insult:
  - Significantly less permeability was evident with HA-only () and SYSTANE® HYDRATION compared with media controls (P=0.02 and P<0.001, respectively) and with SYSTANE® HYDRATION compared with HA (P=0.01)
  - TEER was significantly greater with SYSTANE® HYDRATION (111±6%) compared with media controls (75±10%), the HPG-only formulation (79±8%), and the HA-only formulation (81±7%) (all P<0.001); SYSTANE® HYDRATION-treated cells had an approximately 20% greater resistance after 4 h of recovery compared with immediately after insult

SURFACE LUBRICATION

- One minute after solution application:
  - Friction was significantly reduced in tissues treated with SYSTANE® HYDRATION, the HPG-only formulation, or HA-only formulation, compared with saline (P=0.007, P=0.01, and P=0.01, respectively)
  - Significantly less friction was observed with SYSTANE® HYDRATION compared with HA-only (P=0.02); the mean±SD coefficient of friction was 0.53±0.07 with saline, 0.07±0.01 with SYSTANE® HYDRATION, 0.07±0.01 with HPG-only, and 0.53±0.7 with HA-only (**Figure 2**)
- One minute after solutions were blotted and saline was added to tissue:
  - Friction values remained significantly lower at the first of 6 measurements for the SYSTANE® HYDRATION-treated tissues compared with HA-only-treated tissues (0.08±0.04 vs. 0.45±0.04; P<0.001)

Figure 1. Hydration protection against desiccation (**A**) after pretreatment with test solutions and (**B**) after test solutions were rinsed from the cell surface.



HA, hyaluronic acid; HA/HPG, hyaluronic acid + hydroxypropyl guar dual-polymer formulation; HPG, hydroxypropyl guar

Efficacy and Safety of Dual-Polymer Hydroxypropyl Guar- and Hyaluronic Acid-Containing Lubricant Eyedrops for the Management of Dry-Eye Disease: a Randomized Double-Masked Clinical Study

SYSTANE® HYDRATION

Clinical Signs

Patient-Reported Outcomes

Labetoulle et al. *Clin Ophthalmol.* 2018;12:2499-2508

OVERVIEW

STUDY DESIGN

Prospective, 6-week, multicenter, double-masked, parallel-group, randomized (1:1), noninferiority study to compare the efficacy and safety of an HPG-HA dual-polymer formulation (SYSTANE® HYDRATION) vs. a sodium hyaluronate (SH)-containing artificial-tear formulation (Hyabak® 0.15%; Laboratoires Théa, Clermont-Ferrand, France) in patients with dry eye disease (DED)

STUDY SITE(S)

Ten (10) centers across France, Germany, Spain, and the United Kingdom

PATIENTS

Ninety-nine (99) dry eye patients were randomized to the two treatment groups and 97 completed the study

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomized (1:1) to receive either SYSTANE® HYDRATION or Hyabak® 0.15% four times a day for 42 days

KEY ENDPOINT(S)

Primary endpoint: change from baseline in total ocular surface staining (TOSS) at day 42. Secondary endpoints: change from baseline at day 42 in treatment satisfaction scores (treatment effectiveness and treatment inconvenience) based on the impact of dry eye on everyday life (IDEEL) treatment-satisfaction module, tear film breakup time (TFBUT), and TOSS (test for superiority)

ANALYSIS AND CONCLUSIONS

Data from this clinical study showed that SYSTANE® HYDRATION, used four times per day for 42 days, was noninferior to sodium hyaluronate-containing Hyabak® 0.15% lubricant eyedrops with respect to improvement in ocular surface staining in DED.

SYSTANE® HYDRATION did not show significant improvement versus Hyabak® 0.15% with respect to IDEEL treatment-satisfaction scores or TFBUT. No new safety findings were identified outside of the known profile of the other hydroxypropyl-guar-containing lubricant eyedrops.

STUDY RESULTS

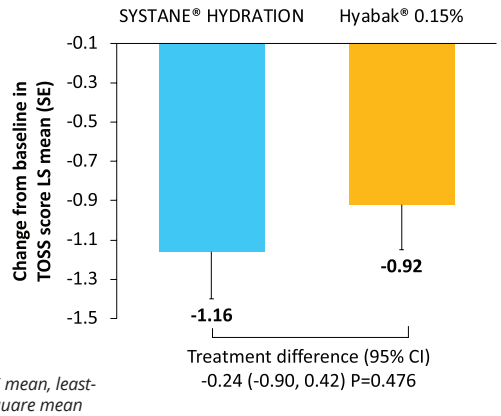
PRIMARY EFFICACY OUTCOME

- Both SYSTANE® HYDRATION and Hyabak® 0.15% led to a reduction in mean TOSS from baseline at day 42
- The least-square (LS) mean±SE change from baseline at day 42 in the TOSS was greater in the SYSTANE® HYDRATION group (−1.16±0.24) than the Hyabak® 0.15% group (−0.92±0.23)
- The LS mean±SE treatment difference was -0.24±0.33, and the upper limit (UL) of the 95% confidence interval was 0.42 (**Figure 1**)
- Noninferiority of SYSTANE® HYDRATION to Hyabak® 0.15% lubricant eyedrops was demonstrated

SECONDARY EFFICACY OUTCOMES

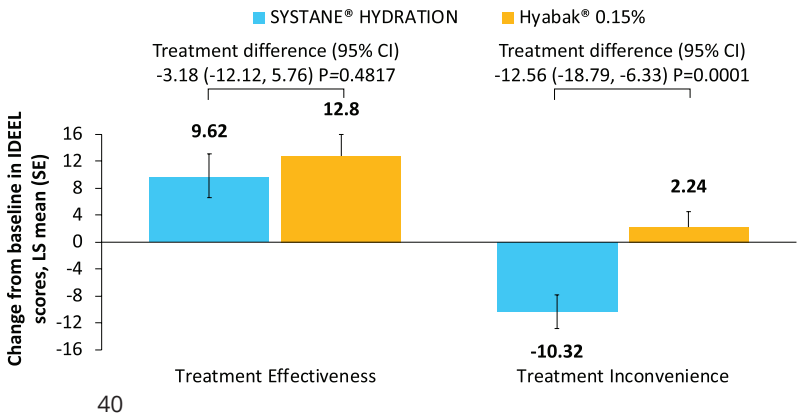
- An increase in mean IDEEL treatment-effectiveness scores from baseline was observed in both treatment groups at day 42
- SYSTANE® HYDRATION did not show improvement over Hyabak® 0.15% for change in IDEEL treatment-effectiveness scores from baseline at day 42 (LS mean difference -3.18 units, P=0.4817) (**Figure 2**)
- IDEEL treatment-inconvenience scores were lower with SYSTANE® HYDRATION than Hyabak® 0.15%, and the difference between the groups was notably in favor of the single-polymer formulation (LS mean difference −12.56 units, P=0.0001)
- SYSTANE® HYDRATION did not show any improvement over Hyabak® 0,15% for mean change from baseline in TFBUT (LS mean difference, −0.30 units; P=0.5789)

Figure 1. Change from baseline at day 42 in total ocular surface staining (TOSS) by treatment group.



LS mean, least-square mean

Figure 2. Change from baseline at day 42 in impact of dry eye on everyday living (IDEEL) treatment-satisfaction scores (effectiveness and inconvenience) by treatment group.



Preclinical Evaluation of a New Hydroxypropyl-Guar Phospholipid Nanoemulsion-Based Artificial Tear Formulation in Models of Corneal Epithelium

SYSTANE® COMPLETE

SYSTANE® BALANCE

Laboratory Data

Rangarajan and Ketelson. *J Ocul Pharmacol Ther.* 2019;35:32-37†

OVERVIEW

STUDY DESIGN

Laboratory study to evaluate the effect of hydroxypropyl-guar anionic phospholipid nanoemulsion (HP-guar nanoemulsion) artificial tear formulation for treatment of dry eye disease (DED), in corneal epithelium models

STUDY SITE(S)

Single site in the US

PATIENTS

N/A. Preclinical study examining cultured human corneal epithelial (HCE) cells, rabbit eyes, and bovine pericardium tissue

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

In vitro cultured HCE cell model was used to assess (1) hydration protection and hydration retention protection against desiccation, and (2) cell recovery after benzalkonium chloride (BAC) damage. Corneal epithelium permeability was measured by 5,6-carboxyfluorescein (CF) uptake in intact rabbit eyes. Lubricity was determined using simulated blinking in bovine pericardium–pericardium tribological experiments; elastic filament strength was measured using an extensional rheometer. Experiments compared the HP-Guar nanoemulsion (SYSTANE® COMPLETE), a microemulsion artificial tear formulation (SYSTANE® BALANCE), and vehicle.

KEY ENDPOINT(S)

Cell hydration retention and hydration protection, cell and cell barrier protection, fluorescein permeability, surface lubrication, elastic filament strength

ANALYSIS AND CONCLUSIONS

The HP-guar nanoemulsion formulation (SYSTANE® COMPLETE) demonstrated significantly greater hydration retention, faster cell recovery after damage, cell barrier protection, and surface lubricity than vehicle in cell cultures.

These laboratory data suggest that SYSTANE® COMPLETE provides longer moisture retention and hydration effect than SYSTANE® BALANCE.

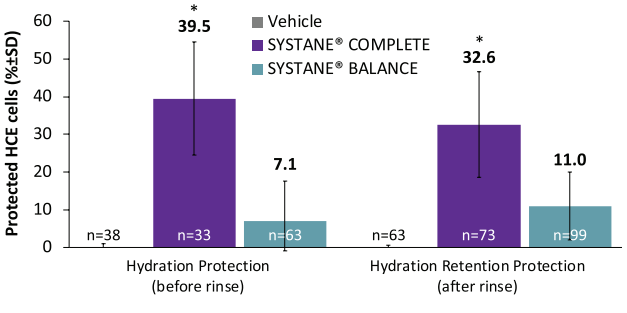
†Drs. Rangarajan and Ketelson are employees of Novartis Pharmaceuticals Corporation.

STUDY RESULTS

HYDRATION RETENTION AND PROTECTION

- SYSTANE® COMPLETE demonstrated significantly greater hydration protection after desiccation compared with vehicle
- The % cell viability (mean±SD) after desiccation in cultured HCE cells pretreated with test formulations was 39.5±14.6 with SYSTANE® COMPLETE, 7.1±10.0 with SYSTANE® BALANCE, and -0.1±0.9 with vehicle (**Figure 1**)
- Protection by hydration retention against desiccation after rinsing of formulations was significantly greater with SYSTANE® COMPLETE compared with vehicle (P<0.05) (**Figure 1**)
- The % cell viability after rinse was 32.6±13.6, 11.0±8.5, and -1.2±0.6 in samples pretreated with HP-guar nanoemulsion, SYSTANE® BALANCE, and vehicle, respectively

Figure 1. Hydration protection (%) in human corneal epithelial (HCE) cells against desiccation before and after rinsing the test formulations from the cell surface.

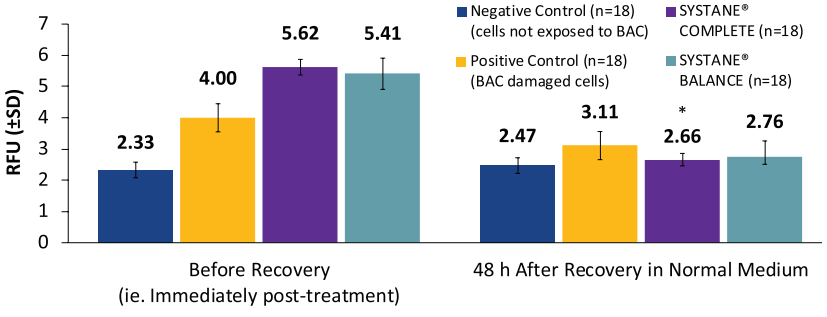


* P<0.05 vs. vehicle.

CELL AND CELL BARRIER PROTECTION

- Cell recovery from BAC exposure was significantly greater in samples treated with SYSTANE® COMPLETE and SYSTANE® BALANCE than cells exposed to BAC alone (P<0.05)
- After 48-h recovery in culture media, the mean fluorescein permeability (RFU– SD) was 2.66±0.2 with SYSTANE® COMPLETE, 2.76±0.2 with SYSB, and 3.11±0.4 for cells exposed to BAC alone (**Figure 2**)
- After 48 h in normal medium, barrier function of BAC-exposed cells treated with the SYSTANE® COMPLETE and SYSTANE® BALANCE returned to that of negative control (**Figure 2**)
- The surface friction in pericardial samples was significantly lower with SYSTANE® COMPLETE and SYSTANE® BALANCE compared with vehicle, during treatment, and after removal of treatment (P<0.05)
- Post-treatment, the friction observed with SYSTANE® COMPLETE-treated samples was significantly less compared with SYSTANE® BALANCE-treated samples (P<0.05)

Figure 2. Fluorescein permeability of human corneal epithelial (HCE) cells treated with test formulations, immediately after benzalkonium chloride (BAC) exposure and after 48 h of recovery.



* P<0.05 vs. vehicle. *RFU, relative fluorescence units; SD, standard deviation*

Comparison of Nanoemulsion and Non-Emollient Artificial Tears on Tear Lipid Layer Thickness and Symptoms

SYSTANE® COMPLETE
SYSTANE® ULTRA
Clinical Signs
Patient-Reported Outcomes

Weisenberger et al. *J Optom.* 2020. Epub ahead of print*

OVERVIEW

STUDY DESIGN
Part 1: cross-over comparison of a nanoemulsion (SYSTANE® COMPLETE) and a non-emollient eye drop (SYSTANE® ULTRA). Part 2: 1-month observational study assessing lipid layer thickness (LLT) and symptoms after 30 days of SYSTANE® COMPLETE use

STUDY SITE(S)
Single site in the United States

PATIENTS
Twenty (20) subjects with dry eye

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED
In Part 1, LLT and dry eye symptoms were measured at baseline and at 15 min, 1 h, 2 h, 4 h and 6 h after instillation of each treatment. In Part 2, LLT and symptoms were assessed after use of SYSTANE® COMPLETE four times daily, for thirty days

KEY ENDPOINT(S)
LLT, dry eye symptoms (Ocular Surface Disease Index (OSDI), visual analog scale (VAS) symptom survey covering ocular dryness, light sensitivity, eye fatigue, blurred vision, and discomfort)

ANALYSIS AND CONCLUSIONS

SYSTANE® COMPLETE use increased average LLT in subjects with low baseline LLT. Statistically and clinically significant improvement in symptoms were found on symptom surveys after QID (four times / day) SYSTANE® COMPLETE use.

These results suggest that SYSTANE® COMPLETE can benefit subjects with dry eye symptoms.

*This study was financially supported by Alcon

STUDY RESULTS

CROSSOVER STUDY

- Analysis of the entire study cohort (baseline LLT <75 nm (n=20)) showed no significant increases in LLT at any timepoint following single-drop instillation of either of the tested eye drops (SYSTANE® COMPLETE: 4.89 ±15.57 nm; SYSTANE® ULTRA: -1.03±7.92 nm; both P>0.05)
- In the cohort of subjects with a baseline LLT <50 nm (n=15), there was a significant increase in the mean LLT 15 minutes after SYSTANE® COMPLETE instillation in both the overall (8.51±13.95 nm; P=0.03) and inferior third (9.15±14.60 nm; P=0.03) of the measured area; for the same cohort, the mean change in LLT 15 minutes after instillation of SYSTANE® ULTRA in the overall (−1.34±5.35 nm; P=0.4) and inferior third (−1.79±7.32 nm: P=0.4) was not statistically significant (**Table 1**)
- In subjects with a baseline LLT ≥50 nm (n=5), no significant changes in mean LLT occurred with use of SYSTANE® COMPLETE or SYSTANE® ULTRA at any time point following single-drop instillation
- Analysis of VAS surveys for all subjects showed significant improvements in many symptoms following instillation of both SYSTANE® COMPLETE and SYSTANE® ULTRA
  - The change in VAS scores revealed significant improvement in average dryness up to 6 hours following instillation of both SYSTANE® COMPLETE (8.6±16.7 mm; P=0.03) and SYSTANE® ULTRA (9.8±19.9 mm: P=0.02)
  - There was also an improvement in average eye fatigue up to 4 hours following instillation of SYSTANE® COMPLETE (8.4±14.0 mm; P=0.01), and significant improvement in average light sensitivity up to 6 hours (10.3±20.5 mm; P=0.02) and average ocular discomfort up to 15 minutes (8.6±18.0 mm; P=0.045) following instillation of SYSTANE® ULTRA

ONE-MONTH STUDY

- There was no significant difference when comparing the initial LLT measured at baseline to the LLT measurement taken after 1 month of QID use of SYSTANE® COMPLETE
- Mean OSDI calculated score at the baseline visit was 17.7±16.0 and the mean OSDI score after using the eye drops QID for 1 month was 12.4±14.2; this decrease of 5.3 in the mean OSDI score from baseline to 1 month post eye drop use was statistically significant (P=0.03)
- The average VAS dryness score decreased by 10.2±21.2 (P=0.045) from baseline (26.3) to 1 month (16.1)

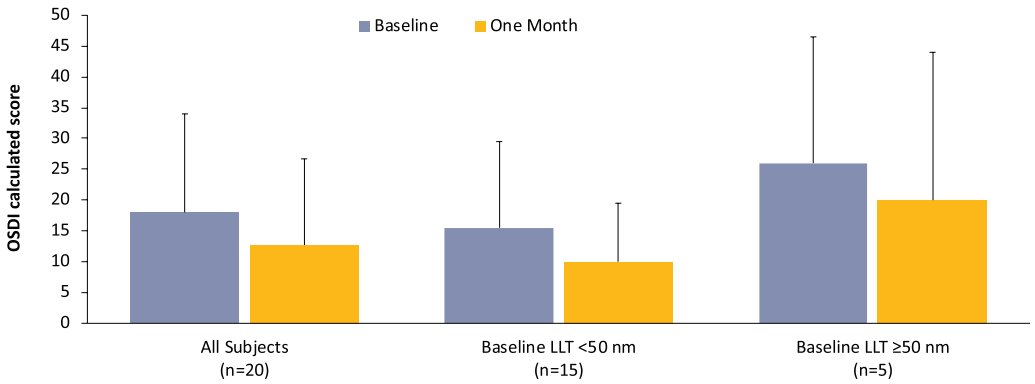


Figure 1. Calculated Ocular Surface Disease Index (OSDI) scores (mean±SD) for each study cohort at baseline and at 1-month follow-up after QID (four times daily) use of SYSTANE® COMPLETE. The observed change in OSDI for all subjects (n=20) exhibited statistical significance (P=0.03). No significant differences in OSDI score were found for either the low (<50 nm lipid layer thickness (LLT) at baseline) or high (≥50 nm LLT at baseline) cohorts.

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

SYSTANE®

Clinical Signs

Patient-Reported Outcomes

Safety

Wang et al. *Clin Ther.* 2010;32:44-52

OVERVIEW

STUDY DESIGN

Prospective, open-label, randomized, comparative, non-inferiority study to compare the efficacy, safety, and local tolerance of artificial tears containing carbomer-based lipids or hydroxypropyl (HP)-guar gel in patients with dry eye syndrome

STUDY SITE(S)

Single site in Taiwan

PATIENTS

Thirty (30) patients with dry eye syndrome

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomly assigned to 1 of 2 treatment groups: the carbomer-based lipid-containing (CBLC) gel group (Liposic® Ophthalmic Liquid Gel; Bausch & Lomb, Rochester, NY, USA) and the HP-guar gel group (SYSTANE®)

KEY ENDPOINT(S)

Primary endpoint: global assessment of study treatment by the patients at weeks 2 and 4. Additional outcomes measured at baseline and 2 and 4 weeks included Schirmer's test values, tear breakup time (TBUT), and a patient subjective assessment of symptoms. Safety: adverse events (AEs) and slit lamp examination

ANALYSIS AND CONCLUSIONS

Both artificial tear formulations used in this study relieved signs and symptoms of dry eye syndrome.

The efficacy of, and patient-reported tolerance to, Liposic® was comparable to SYSTANE®.

STUDY RESULTS

CLINICAL SIGNS

- There was a statistically significant difference in increase in Schirmer's test values from baseline for the right eye in the Liposic® group compared with the SYSTANE® group (3.67 vs 0.73 mm, respectively; P<0.05); the same pattern was also found for the left eye (4.20 vs 1.40 mm; P<0.05)
- At 4 weeks, an increase from baseline in Schirmer's test values was observed in both groups; corresponding mean values in the right eye increased to 5.57 mm from baseline in the Liposic® group and 2.53 mm in the SYSTANE® group; mean left eye values were 5.79 mm for the Liposic® group and 2.33 mm for the SYSTANE® group
- The increase from baseline at 4 weeks was statistically significant in the Liposic® group compared with the SYSTANE® group (both P<0.05)
- At 2 weeks, the mean TBUT values increased to 8.27 (1.94) seconds for the right eye and 7.80 (2.31) seconds for the left eye in the Liposic® group; in the SYSTANE® group, the mean values increased to 8.00 (1.69) seconds for the right eye and 7.40 (2.03) seconds for the left eye there were no statistically significant between-group differences
- After treatment for 4 weeks, the mean values further increased to 9.43 (1.74) seconds for the right eye and 8.73 (2.49) seconds for the left eye in the Liposic® group, while the mean values further increased to 9.29 (2.05) seconds for the right eye and 8.13 (1.88) seconds for the left eye in the SYSTANE® group
- The increase in TBUT values at 4 weeks was observed in both groups; however, there was no significant between-group difference

PATIENT EVALUATIONS

- At the initial assessment during treatment (week 2), most patients in both groups reported a good response (n=9 and n=8 patients, respectively); n=5 patients in each group reported a fair response
- At 4 weeks, an excellent response was reported by n=4 patients (26.7%) who received Liposic® treatment and n=2 patients (13.3%) who received SYSTANE®
- A good response was reported by more patients at 4 weeks in the Liposic® group than in the SYSTANE® group (n=11 (73.3%) vs. n=5 (33.3%), respectively; P=0.004, $\chi 2$ test); a majority of the patients (n=8 (53.3%)) treated with SYSTANE® artificial tears reported a fair response to treatment at 4 weeks

SAFETY PROFILE

- No clinically important changes from baseline were observed in any of the safety parameters; slit-lamp examination did not reveal increases in the cornea, anterior chamber, iris, or lens after treatment
- No serious AEs were reported during this study
  - One patient in the SYSTANE® group complained about mild blurred vision at week 2; this symptom was not observed after further treatment at week 4
  - No subject in the Liposic® group experienced an ocular AE related to treatment

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

SYSTANE® UD

Clinical Signs

Safety

Jacobi et al. *J Ocul Pharmacol Ther.* 2012;28:598-603

OVERVIEW

STUDY DESIGN

Prospective, randomized, clinical, single-center study 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®; Johnson and Johnson, New Brunswick, NJ, USA) eye drops

STUDY SITE(S)

Single site in Germany

PATIENTS

Fifty-six (56) eyes of 28 patients with moderate keratoconjunctivitis sicca

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomized to SYSTANE® UD or Visine Intensiv 1% EDO®; eye drops in both groups were applied 5 times per day for 3 months

KEY ENDPOINT(S)

Tear breakup time (TBUT), Schirmer test, lid-parallel conjunctival folds (LIPCOF), and Ocular Surface Disease Index (OSDI) Score

ANALYSIS AND CONCLUSIONS

Improvements of symptoms and signs in patients with moderate dry eye were shown after consistent use of SYSTANE® UD and Visine Intensiv 1% EDO®.

Both artificial tear formulations produced amelioration in tear film stability.

STUDY RESULTS

CLINICAL SIGNS

- After 3 months of treatment, there were improvements in TBUT, Schirmer test, LIPCOF, and OSDI Score in both groups (details in **Table 1**); in the SYSTANE® UD group, the results for TBUT (8.5±4.8 s to 14.05±4.93 s; P=0.002) and OSDI Score (50.0±19.1 to 31.3±18.2; P=0.01) showed statistically significant amelioration after 3 months; in the Visine Intensiv group, only the OSDI Score improved significantly (50.8±12.8 to 34.1±18.6; P=0.03)
- In the SYSTANE® UD group, there was a statistically significant improvement of TBUT after 3 months compared with the Visine Intensiv group (P=0.02) (**Table 1**)
- Evaluation of fluorescein and rose bengal staining showed improvements in the SYSTANE® UD group from 4 (range: 2–6) to 3 (range: 1–6) and from 3 (range: 2–6) to 2 (range: 0–5) but there were no statistically significant differences vs. baseline
- In the Visine Intensiv group there was no improvement in the fluorescein staining but there was amelioration in the rose bengal staining from 3 (range: 1–6) to 2 (range: 1–5) vs. baseline; no statistically significant differences were detected

VISUAL ACUITY AND SAFETY

- No adverse effects (ocular infections, allergic reactions, or disturbing sensations at application) could be observed in either treatment group
- Visual acuity and IOP showed rather constant values

Table 1. Comparison of the ocular function tests between the SYSTANE® UD group and Visine Intensiv group at baseline and after 3 months of 5 times daily use.

	Functional Test	SYSTANE® UD Group Mean±SD	Visine Intensiv Group Mean±SD	Mann-Whitney P value
Baseline	BSCVA	0.9±0.2	0.89±0.19	0.17
	TBUT	8.5±4.8	8.21±4.7	0.82
	Schirmer	11.91±6.09	10.75±8.7	0.19
	LIPCOF	2.63±1.21	1.75±1.2	0.20
	OSDI	50.0±19.1	50.8±12.8	0.95
	IOP	12.46±2.45	11.17±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±0.21	1.0±0.15	0.34
	TBUT	14.05±4.93*	10.75±5.77	0.02
	Schirmer	15.3±8.13	15.1±2.48	0.99
	LIPCOF	2.45±0.76	2.2±0.77	0.31
	OSDI	31.3±18.2	34.1±18.6	0.28
	IOP	12.05±1.28	10.95±2.5	0.35
	Fluorescein	3 (1-6)	4 (0-4)	0.08
	Rose bengal	2 (0-5)	2 (1-5)	0.25

**P<0.05 vs. Visine Intensiv*
BSCVA, best spectacle-corrected visual acuity; TBUT, tear breakup time; LIPCOF, lid-parallel conjunctival folds; OSDI, Ocular Surface Disease Index Score: IOP, intraocular pressure

Evaluation of Clinical Outcomes in Patients with Dry Eye Disease Using Lubricant Eye Drops Containing Polyethylene Glycol or Carboxymethylcellulose

SYSTANE® Gel Drops

Clinical Signs

Patient-Reported Outcomes

Safety

Cohen et al. *Clin Ophthalmol.* 2014;8:157-164*

OVERVIEW

STUDY DESIGN

Randomized, parallel-group, multicenter, double-blind, 6-week clinical trial to compare changes in corneal staining in patients with dry eye after 6 weeks of treatment with SYSTANE® Gel Drops or Refresh Liquigel® lubricant eye drops (Allergan, Inc., Irvine, CA, USA)

STUDY SITE(S)

Ten (10) study sites in the United States

PATIENTS

One hundred forty seven (147) dry eye patients with sodium fluorescein (NaFL) corneal staining sum score >3 in either eye and who were already using a lubricant eye gel or ointment at least once weekly over the previous month

METHODOLOGY AND ARTIFICAL TEAR(S) TESTED

Patients were randomized to four times daily SYSTANE® Gel Drops (polyethylene glycol 400 0.4% and propylene glycol 0.3%) or Refresh LiquiGel® Drops (carboxymethylcellulose sodium 1%) for 6 weeks

KEY ENDPOINT(S)

Primary efficacy outcome: mean change from baseline to week 6 in NaFl corneal staining. Supportive efficacy outcomes: conjunctival staining, tear film break-up time (TFBUT), Patient Global Assessment of Improvement, Impact of Dry Eye on Everyday Life (IDEEL) Treatment Satisfaction/Treatment Bother Questionnaire, Single Symptom Comfort Scale, and Ocular Symptoms Questionnaire. Safety outcome: adverse events

ANALYSIS AND CONCLUSIONS

SYSTANE® Gel Drops were associated with significantly better corneal staining scores versus Refresh Liquigel® Drops in patients with dry eye.

Supportive efficacy outcomes were not significantly different between groups.

*This study was financially supported by Alcon

STUDY RESULTS

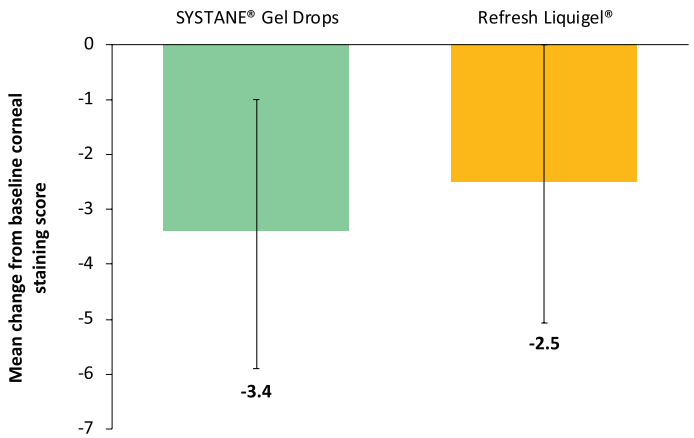
CORNEAL STAINING

- At baseline, mean±SD corneal staining scores were 6.9±2.5 units in the SYSTANE® Gel Drops group and 6.4±2.2 units in the Refresh Liquigel® group
- At every post-baseline visit, mean corneal staining scores were slightly lower in the SYSTANE® Gel Drops group than in the Refresh Liquigel® group (no statistically significant differences)
- At week 6, mean corneal staining scores were 3.3±2.4 units with SYSTANE® Gel Drops (n=67) and 4.0±2.6 units with Refresh Liquigel® Drops (n=70)
- Corneal staining was significantly reduced from baseline to week 6 for both the SYSTANE® Gel Drops (−3.4±2.5 units, P<0.0001, 49% reduction) and Refresh Liquigel® (−2.5±2.6 units, P<0.0001, 39% reduction) groups (**Figure 1**)
- SYSTANE® Gel Drops showed a significantly greater decrease (improvement) in mean sum of corneal staining from baseline than Refresh Liquigel® (P=0.0294)

SUPPORTIVE EFFICACY OUTCOMES

- At baseline, mean lissamine green conjunctival staining scores were 2.8±1.3 units in the SYSTANE® Gel Drops group and 2.9±1.4 units in the Refresh Liquigel® group
- At each visit, differences in mean conjunctival staining scores were ≤0.2 units between groups; no significant differences between groups were observed in mean scores or in change from baseline scores at any visit
- At baseline, mean TFBUT was 4.6±2.8 seconds in the SYSTANE® Gel Drops group and 4.6±3.1 seconds with Refresh Liquigel®
- At each visit, differences in mean TFBUT were ≤0.4 seconds between groups; no significant differences were observed between treatment groups in mean scores or in change from baseline scores
- At week 6, the percentages of patients reporting improvement on the Patient Global Assessment of Improvement was 85% in the SYSTANE® Gel Drops group and 74% in the Refresh Liquigel® group (P=0.1383)
- Mean change from baseline to week 6 on the Single Symptom Comfort Scale was −2.1±2.0 for the SYSTANE® Gel Drops group and −1.6±1.9 for the Refresh Liquigel® group; there were no statistically significant between-group differences at any visit for mean score or change from baseline scores

Figure 1. Mean±standard deviation change in sodium fluorescein (NaFl) corneal staining scores from baseline to the week 6 visit.



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Notes

Notes

See product instructions for complete wear, care and safety information. Rx only

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