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ORIGINAL RESEARCH

Clinical evaluation of a new multi-purpose disinfecting solution in symptomatic wearers of silicone hydrogel contact lenses

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Background: The purpose of this study was to evaluate the safety and efficacy of a new multi-purpose disinfecting solution containing a diblock copolymer, poly(oxyethylene)-poly(oxybutylene), designed to improve the wetting properties of silicone hydrogel lenses in patients with symptoms of discomfort.

Methods: This 30-day, randomized, concurrently controlled, double-masked, multi-site study involved 589 subjects at 42 investigational sites in the US. Existing symptomatic lens wearers were randomly assigned to either regimen 1 (OPTI-FREE® PureMoist®, Alcon Laboratories Inc,) a newly developed formulation containing the diblock copolymer), or regimen 2 (renu® fresh™ multi-purpose solution Bausch + Lomb, Inc). On days 0, 14 and 30, subjects assessed acceptability and comfort using seven Likert-type questions, rated the intensity of ocular symptoms (comfort, dryness, irritation, scratchiness, burning, stinging) on a visual analog scale (0–100), as well as reported lens wearing time, comfortable lens wearing time, and rewetting drop frequency. The investigators assessed slit-lamp findings (including circumlimbal conjunctival lissamine green staining and corneal fluorescein staining), on-eye lens surface wettability and deposits, visual acuity, and adverse events.

Results: Differences favoring regimen 1 were noted on Day 30 for the primary Likert statement "I can comfortably wear my lenses" ($P = 0.047$) and for comfortable lens wear time ($P = 0.041$). Symptoms of ocular scratchiness, ocular burning, and ocular stinging were all rated lower after 30 days of use by subjects using regimen 1 compared with those using regimen 2 ($P \leq 0.024$). Circumlimbal conjunctival staining (sum score) was significantly lower with regimen 1 ($P < 0.0001$). Other parameters did not show any difference between the two treatment regimens.

Conclusion: This study shows that the new multi-purpose disinfecting solution is safe and effective when used by symptomatic silicone hydrogel contact lens wearers. By improving symptoms of scratchiness, burning, stinging, and comfortable wear time, and decreasing circumlimbal conjunctival staining, the new multi-purpose disinfecting solution enhances the patient's wearing experience and helps maintain optimal lens performance.

Keywords: multi-purpose disinfecting solution; subjective comfort; silicone hydrogel contact lenses

Introduction

Contact lens wearers rate comfort as one of the most important lens attributes,[1] and multiple studies of lapsed contact lens wearers to date have shown that discomfort and dryness are the most commonly cited causes of discontinuation of contact lens usage.[2–8] In the US, nearly three million lens users per year discontinue contact lens wear.[9] Large cross-sectional surveys of patient symptoms as well as clinical trials in the US showed that dryness was the most common symptom of soft contact lens wear,

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with the prevalence of dryness symptoms estimated between 50% and 94%, depending on the test population.[10–14]

Comfort with soft lenses depends on many factors, both patient-related and lens-related. Strategies for managing contact lens-related discomfort in clinical practice and avoiding dropout have traditionally focused on the choice of lens material, design, replacement frequency, or use of rewetting drops.[15] To ameliorate lens-related symptoms, eye care practitioners are increasingly upgrading contact lens wearers from traditional to silicone hydrogel contact lenses.[16] Due to their improved oxygen permeability, silicone hydrogel lenses supply higher oxygen levels to the cornea, reducing complications associated with corneal hypoxia.[17,18] Other characteristics of silicone hydrogel lenses, such as improved surface properties of newer generations of lenses and reduced protein deposition,[19] may contribute to improved on-eye comfort and ease of handling, and decreased conjunctival redness.[20] For instance, a recent large cross-sectional study suggested that, among young adults, 29% of traditional soft lens users reported dryness symptoms that were experienced "always" or "frequently" with contact lens wear, compared with 17% of patients who presented while wearing silicone hydrogel lenses.[21]

However, due to the inclusion of hydrophobic siloxane-containing components, silicone hydrogel contact lens materials have been associated with reduced on-eye wetting.[22] This may result in special challenges for silicone hydrogel lens wearers because complete wetting of the lenses is necessary for full tear-film coverage, minimized tear-film disruption, and smooth tear recovery upon lid closure. One approach to improve success with silicone hydrogel lenses is to create a lens care product that reconditions the silicone hydrogel lenses for a longer-lasting, more wettable surface, and decreased friction between the lens and eyelid. A new multi-purpose disinfecting solution, OPTI-FREE® PureMoist® (Alcon Laboratories Inc, Fort Worth, TX) containing a specifically designed wetting agent, HydraGlyde™ Moisture Matrix, was recently developed. This agent is a proprietary multi-functional linear diblock copolymer composed of poly(oxyethylene)-poly(oxybutylene) (EOBO) in an approximately 4:1 molar ratio, with a molecular weight of about 3000 Da. The poly(oxyethylene) block is hydrophilic, whereas the poly(oxybutylene) block is hydrophobic. EOBO was designed so that poly(oxybutylene) is attracted to hydrophobic contact lens sites which enables the hydrophilic nature of poly(oxyethylene) to attract moisture. Through overnight soaking, EOBO embeds on and within the lens surface, coating the hydrophobic areas of the lens to provide a more hydrophilic surface. X-ray photoelectron spectroscopy and atomic force microscopy provide evidence of nanoscopic surface modifications following treatment of contact lenses with EOBO.[23] This results in improved lubrication and wettability as verified through laboratory techniques, including contact angle measurements, lipophilic dye diffusion assessments, and several microscopic techniques to investigate the surface properties of contact lenses.[23,24]

In addition to providing extended moisture, an ideal multi-purpose disinfecting solution must maintain a high level of disinfection efficacy, provide superior cleaning, and be stable for long-term storage. The new multi-purpose disinfecting solution, OPTI-FREE® PureMoist®, incorporates a dual disinfection system, POLYQUAD® (polyquaternium-1) 0.001% and ALDOX® [myristamidopropyl dimethylamine (AL-6289)] 0.0006% and a borate-buffered saline solution in combination with ultrapure 2-amino-2-methyl-1-propanol (AMP) as the buffering technology.

The new multi-purpose disinfecting formulation containing EOBO was first introduced to contact lens wearers in a large clinical trial involving 573 subjects wearing selected silicone hydrogel or traditional soft lens brands. The study confirmed that this new multi-purpose disinfecting solution was well tolerated by patients and that it offered advantages in terms of subjective assessments key to a positive lens-wearing experience.[25,26] The new multi-purpose disinfecting solution also reduced protein deposition on Group IV traditional hydrogel lenses and maintained corneal integrity while minimizing the potential for adverse ocular effects.

Because patients experiencing discomfort with their lenses are more likely to be sensitive to lenses and lens care solutions that fail to perform, a more critical test might involve enrollment of these symptomatic patients. Therefore, the purpose of the present study was to evaluate the safety and efficacy of the new formulation in symptomatic silicone hydrogel lens wearers and compare its performance with that of a commonly used multi-purpose solution.

Materials and methods

This was a 30-day, randomized, concurrently controlled, double-masked (subject and investigator) multi-site study involving 589 subjects at 42 investigational sites in the US between July 23, 2010 and January 7, 2011. Investigators were located in geographically diverse sites such that the potential effects of environmental and seasonal factors were minimized. The study was approved by a research ethics committee (Sterling Institutional Review Board, Atlanta, GA), conducted according to the ethical principles

of the Declaration of Helsinki, and all subjects gave their written informed consent before commencing the study.

Investigative sites were selected based on their research experience, adequate numbers of potential subjects, and on their practice of prescribing the lens brands selected for this study. To ensure consistency among the 42 investigational centers, training on all aspects of the protocol and for each procedure was provided at an in-person meeting of investigators and study coordinators, and through web-based training for the minority of investigators and site staff unable to attend the live meeting.

Subjects and lenses

Subjects were adult daily contact lens wearers who reported end of the day contact lens-related ocular discomfort. They were screened so that they "strongly disagreed" or "disagreed" with the statement "My contacts are comfortable all day long" and they "agreed" or "strongly agreed" with either of the following statements: "During the day, I take my contacts out earlier than I like because they become uncomfortable" or "Late in the day, my contacts become uncomfortable, but I continue wearing them".

There were no requirements as to subject gender or occupation. Volunteer subjects with healthy eyes (other than correction for refractive error and symptoms as noted above) were to be established wearers for at least 2 weeks of one of the following four spherical or multifocal silicone hydrogel contact lens brands: Acuvue® Oasys™, Air Optix™ Aqua, Biofinity®, or PureVision®. They wore the lenses on a daily wear schedule (minimum of 4 hours per day) and were correctable to 20/30 (Snellen) or better in each eye at distance with study lenses. In order to balance lens brands across study sites, each site was to enroll subjects wearing only two of the four study lens brands, as assigned by the Sponsor.

The start of the study (Day 0) was scheduled to be at the end of each subject's lens wear cycle for their particular brand of lenses. On that day, subjects were dispensed a new pair of study lenses that matched their pre-study brand. Acuvue Oasys lenses were to be replaced on Day 14 while the other lens brands were to be worn for the duration of the 30-day study period without scheduled replacement, consistent with the recommendation in each manufacturer's fitting and patient management guide.

Subjects were required to have used a multi-purpose solution as their care regimen, without any other care products (no daily or enzyme cleaners) for at least one week prior to the baseline visit. Pre-study use of labeled rewetting drops in addition to the multi-purpose solution was acceptable. Subjects with a previously known sensitivity or intolerance to any products with similar ingredients to the study products were excluded. Also excluded were subjects using topical ophthalmic medication within 7 days of baseline, with conjunctival or structural lid abnormalities, with current or a history of ocular or lid infections/severe inflammation within 6 months prior to baseline, ocular surgery within 12 months prior to baseline, or with systemic health problems or medications that might affect contact lens wear. Based on Day 0 slit-lamp examination results, subjects were further excluded from the study if they presented with findings (corneal: edema, neovascularization, staining and infiltrates; injection, tarsal abnormalities, and other complications) rated as either moderate or severe.

Assessments at baseline and on-study visits

Subjects who met all inclusion/exclusion criteria were randomly assigned to one of two treatment regimens (Day 0) and scheduled for follow-up visits on Days 14 and 30. Visits on Day 14 and Day 30 were to occur at the same time of day, within 2 hours of the time of the baseline visit time, and subjects were required to wear the lenses for at least 4 hours prior to each visit.

At all visits, subjects were asked to respond to the following seven Likert-style statements, that used a five-point scale (from 1 = strongly disagree to 5 = strongly agree) to describe their comfort and satisfaction with their multi-purpose solution: "When I use this solution: 1. I can comfortably wear my lenses; 2. My lenses feel less dry; 3. My lenses feel moist from morning until evening; 4. My lenses are comfortable from morning until evening; 5. My vision is clear at the end of the day; 6. I forget I am wearing my lenses; 7. My lenses feel like new". They also rated comfort and ocular symptoms (dryness, irritation, scratchiness, burning, stinging) on a visual analog scale of 0–100, where higher scores indicate improved comfort and symptoms of dryness while lower scores indicate improvement of the other four symptoms. They reported lens wear time (on day of visit, daily average over the last 3 days prior to the visit, and comfortable wear time average over the last 3 days); and rewetting drop frequency (average times per day rewetting drops were used over the last 3 days).

Each visit also included slit-lamp examination without lenses and two staining evaluations, ie, corneal fluorescein staining and circumlimbal conjunctival lissamine green staining. The investigators also assessed tear film breakup time (baseline only) and Snellen visual acuity. Front lens surface

wettability (from 0 = smooth uniform reflecting surface to 4 = nonwettable lens surface), film deposits (from 0 = no deposit clean surface, to 4 = severe, deposits occupying > 25% of lens front surface), and discrete deposits (from 0 = no deposit, clean surface to 4 = one or more jelly bumps) were also assessed. Adverse events were recorded at all study visits.

To evaluate the cleaning effectiveness of each regimen quantitatively, investigators collected the worn contact lenses on Day 30, and sent them for laboratory analysis of *ex vivo* lipid deposition by high-performance liquid chromatography to OTG Research and Consultancy (London, UK). Laboratory technicians were blinded to the treatment regimen used for each lens. Lipids including cholesterol esters, phospholipids/triglycerides, fatty acids/diglycerides/monoglycerides, cholesterol, and total lipids were quantified. Throughout the study, an interactive voice response system (IVRS) was utilized to facilitate randomization, and to track subject status and visit dates.

Choice of comparative regimen and masking

The comparator chosen for this study (regimen 2) was renu® fresh™ multi-purpose solution (Bausch + Lomb Inc, Rochester, NY). This was the latest formulation of this widely used multi-purpose solution available at the time the study was conducted. Both products were to be used in a rub and rinse regimen. The characteristics and instructions for use of the two solutions are presented in Table 1.

The comparator product was used in the original container but relabeled to minimize bias. Likewise the investigational product was packaged in a non-logo-bearing bottle and generic neck wrapper. The rewetting drops provided with both regimens (Bausch + Lomb® Sensitive Eyes® drops) were also relabeled "rewetting drops" and were optional, to be used on an as-needed basis. Study personnel did not provide any information to subjects regarding the identity of the assigned regimen. No study assessments were made by the site coordinator who dispensed the study solutions and reviewed the study regimen with the subjects. Double-masking of investigators and subjects was maintained throughout the study, and only when the data had been verified and validated, and the database locked was treatment assignment unmasked.

Procedure for slit-lamp examination and corneal staining

Slit-lamp findings (corneal: edema, neovascularization, staining and infiltrates; injection, tarsal abnormalities, and other complications) were graded according to US Food and Drug Administration guidelines[27] using a scale of 0–4 (0, none; 1, trace; 2, mild; 3, moderate; 4, severe) with gradings for corneal edema, neovascularization, and staining further subdivided using a provided scale (A–C).

For the corneal staining evaluation, one drop of fresh nonpreserved sterile saline (UNISOL® 4 preservative free saline solution) was applied to the impregnated paper tip (FUL-GLO® fluorescein sodium sterile ophthalmic strip, 0.6 mg, Akorn Inc, Buffalo Grove, IL) and allowed to drip off the strip without shaking. The strip was then gently touched to the superior temporal bulbar conjunctiva for 1–2 seconds. Staining was viewed and graded 2–3 minutes later using the cobalt illumination light of the slit-lamp and a yellow filter (Wratten No 12).[28–30]

Procedure for circumlimbal conjunctival staining

For evaluation of the bulbar conjunctiva, a lissamine green strip (Lissamine Green Ophthalmic Strips,1.5 mg, HUB

Table 1 Two formulations tested and their recommended regimens

	regimen 1	regimen 2
MPS		
Cleaners	TETRONIC® 1304	HYDRANATE® (hydroxyalkyl phosphonate)
Lubricant/wetting agent	TETRONIC® 1304 and HydraGlyde™ moisture matrix (EOBO 41™)	None
Antimicrobials	POLYQUAD® (polyquaternium-1; 0.001%) and Aldox® (myristamidopropyl dimethylamine; 0.0006%)	DYMED® (polyaminopropyl biguanide; 0.0001%)
Tonicity agent	Sodium chloride, sorbitol	None
Buffers	Sodium citrate, boric acid, EDTA, AMP	Sodium chloride, sodium borate, boric acid, EDTA, poloxamine
Regimen	Rub and rinse	Rub and rinse
Rewetting drops (optional)	Bausch + Lomb Sensitive Eyes Drops	Bausch + Lomb Sensitive Eyes Drops

Note: Tetronic® is a registered tradename of BASF corporation.
Abbreviations: EDTA, ethylenediamine tetra-acetic acid; AMP, 2-amino-2-methyl-1-propanol; EOBO, polyoxyethylene-polyoxybutylene; MPS, multi-purpose solution.

Pharmaceuticals, Rancho Cucamonga, CA) was wetted with a drop of saline (UNISOL® 4 preservative free saline solution). The excess was allowed to drip off and the strip touched to the superior temporal bulbar conjunctiva, 5 mm or more from the limbus.[31] After 60 seconds, circumlimbal conjunctival staining was evaluated in each of four regions (nasal, temporal, inferior, and superior) on a scale of 0–4 using a photographic reference scale. Staining was viewed and graded using the slit-lamp white-light illumination set to high intensity with the diffuser in place, positioning the light at 30 degrees to the microscope, and setting the magnification to 25×.

Sample size considerations and statistical analysis

The target sample size was computed based on the assumption of superiority of regimen 1 compared with regimen 2 as measured by responses to the primary Likert-like question assessing comfort ("When I use this solution, I can comfortably wear my lenses"). With approximately 260 completed subjects per regimen, there was 87% power to detect a difference of 0.3 points (on a scale of 1–5, given a standard deviation of 1.1) using a two-sided two-sample *t*-test and an alpha of 0.05. With an anticipated 15% early dropout rate, the target sample size was approximately 620 subjects, or 155 subjects per each of the four lens brands selected for the study (77 subjects per brand per regimen). Each site was to enroll approximately 16 subjects, and no site was to contribute more than 10 subjects to each lens brand.

Descriptive statistics for continuous variables are reported for all Likert statements, ocular comfort and symptom scales (100-point visual analog scale), average lens wear time, comfortable lens wear time, *ex vivo* lipid analysis, circumlimbal conjunctival staining sum score, and rewetting drop frequency. Differences between treatment groups for the above variables were analyzed using repeated-measures analysis of variance with the primary time point of inference being Day 30. *P* values are reported for all comparisons to serve as additional descriptors of the data. Although some of the efficacy variables were ordinal in nature, a parametric method was used instead of nonparametric method because the parametric method allows testing of the regimen by time interaction. A *P* value of <0.05 was regarded as statistically significant.

For categorical variables, Chi-square tests of association (or Fisher's Exact test if the expected count was less than five in any cell) were conducted (at alpha = 0.05 for each test) to test for differences between treatment groups. *P* values were reported for all comparisons to serve as additional descriptors of the data. Categorical variables included lens replacement incidence and causality, on-eye lens surface evaluations (wettability and deposit scales), circumlimbal conjunctival staining grade by region, and contact lens corrected distance visual acuity.

Results

Characteristics of study population

As detailed in Table 2, a total of 589 subjects were enrolled in the study and received one of the two treatment regimens: 292 subjects were randomized to receive regimen 1 and 297 subjects were randomized to receive regimen 2.

Table 2 Subject enrollment and early withdrawal by treatment regimen and lens brand

	regimen 1	regimen 2	Total
Randomized subjects who received test article and included in safety analysis	292	297	589
VISTAKON®, Johnson and Johnson Vision Care Inc, Acuvue® Oasys™	76	78	154
CIBA Vision Air Optix™ Aqua	77	77	154
CooperVision Biofinity®	76	80	156
Bausch + Lomb PureVision®	63	62	125
Subjects excluded from intent-to-treat due to no on-regimen visits	(4)	(7)	(11)
Subjects included in intent-to-treat analysis	288	290	578
VISTAKON®, Johnson and Johnson Vision Care Inc, Acuvue® Oasys™	75	75	150
CIBA Vision Air Optix™ Aqua	77	75	152
CooperVision Biofinity®	75	79	154
Bausch + Lomb PureVision®	61	61	122
Subjects discontinued for any reason during study	(12)	(13)	(25)
Adverse event	(7)	(7)	(14)
Noncompliance	(1)	(2)	(3)
Subject's decision unrelated to an adverse event	(2)	(1)	(3)
Other	(2)	(3)	(5)
Subjects who completed study (30 days)	276	277	553

These subjects were distributed among the four lens brands as specified in the protocol, with regimen groups per lens brand ranging in size from 62 to 80 subjects (Table 2). Because of the difficulty in enrolling subjects wearing PureVision lenses, enrollment in both regimen groups for this type of lens was slightly short of the goal of 155, while the other three lens brands met their enrollment targets.

Of the 589 subjects who received the test article, 11 subjects were further excluded from the intent-to-treat dataset because they had no on-regimen follow-up visits (four subjects in the regimen 1 treatment group; seven subjects in the regimen 2 treatment group), so that a total of 578 subjects were evaluable for intent-to-treat analyses (288 in the regimen 1 treatment group; 290 in the regimen 2 treatment group).

The regimen groups were comparable with respect to age, gender, and race. Of the 578 subjects, the majority were white (80.9% for regimen 1 and 78.3% for regimen 2). Ages ranged from 18 to 69 years, with average ages of 34.5 and 34.0 years for regimen 1 and regimen 2, respectively. The majority of the subjects in the study were female (72.6% for regimen 1; 73.1% for regimen 2).

Tear film breakup time at baseline was similar between the two treatment groups, with a mean time of 8.4 ± 6.04 seconds for the regimen 1 group and 8.3 ± 5.69 seconds for the regimen 2 group. All subjects were symptomatic, as determined by reports of discomfort with their contact lenses. At screening, 76.3% of subjects in the regimen 1 group and 73.4% in the regimen 2 group agreed/strongly agreed with the statement: "During the day, I take my contacts out earlier than I like because they become uncomfortable", and 86.1% of subjects in the regimen 1 group and 91.0% in the regimen 2 group agreed/strongly agreed that "Late in the day, my contacts become uncomfortable, but I continue wearing them".

Subjective comfort and acceptability

By Day 30, subjects on regimen 1 were in higher agreement with the primary outcome statement, "When I use this solution, I can comfortably wear my lenses" compared with subjects on regimen 2 ($P = 0.047$, Figure 1) although the difference was small (0.14). Figure 1 also illustrates that for this primary Likert statement, Day 30 mean scores were higher than Day 0 scores with both treatment regimens. No notable differences were observed between treatment groups for the six other Likert statements.

The mean visual analog scale scores for symptoms of ocular scratchiness, ocular burning, and ocular stinging were all lower (more favorable) after 30 days of use in subjects using regimen 1 compared with subjects using regimen 2 (scratchiness, $P = 0.0243$; burning, $P = 0.0038$; stinging, $P = 0.0150$, Figure 2A). Of note, the scores recorded at Day 30 for ocular irritation, scratchiness, burning, and stinging were all improved when compared with the scores recorded on Day 0 (Figure 2B). Although both comfort and symptoms of dryness improved (increased in score) from baseline to Day 30 in both regimen groups, there were no notable differences between regimen 1 and regimen 2 at Day 30 for either comfort or dryness; Day 30 mean ± standard deviation comfort scores were 67 ± 22.5 in the regimen 1 group and 68 ± 23.4 in the regimen 2 group, and dryness scores were 61 ± 22.7 and 61 ± 22.7, respectively, indicating subjects reported slight lens moisture with both regimens.

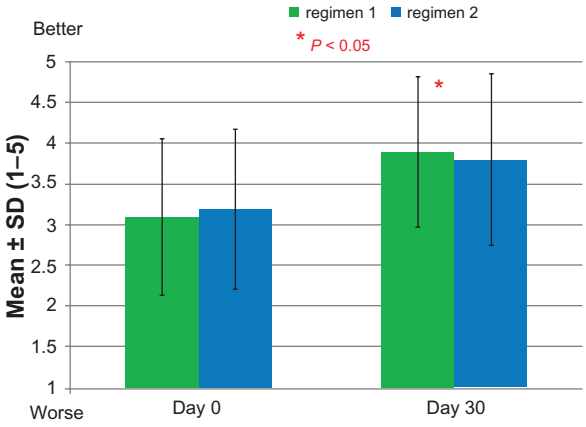

Figure 1 Mean ± standard deviation score for primary outcome at Day 30 "When I use this solution, I can comfortably wear my lenses", rated on a scale of 1 (strongly disagree) to 5 (strongly agree).
Abbreviation: SD, standard deviation.

Average wearing time and rewetting drop usage

At each visit, subjects recorded their average daily wearing time over the previous 3 days. Mean ± standard deviation wearing times as reported on either Day 14 or Day 30 ranged from 12.6 ± 3.25 hours to 12.9 ± 3.59 hours per day for the regimen 1 and regimen 2 groups, respectively, with no statistically significant differences between the two groups. Lens wear time is influenced by comfort of the lenses, as well as lifestyle factors, such as work and sleep schedules. In symptomatic subjects, a more relevant and sensitive measure may be the number of hours that lenses can be worn comfortably. When subjects were asked how long they had comfortably worn their lenses, there was an advantage for regimen 1 compared with regimen 2 at Day 30 (mean 10.2 ± 3.86 hours versus 9.8 ± 4.17 hours, $P = 0.041$, Figure 3). Of note, when compared with baseline comfortable

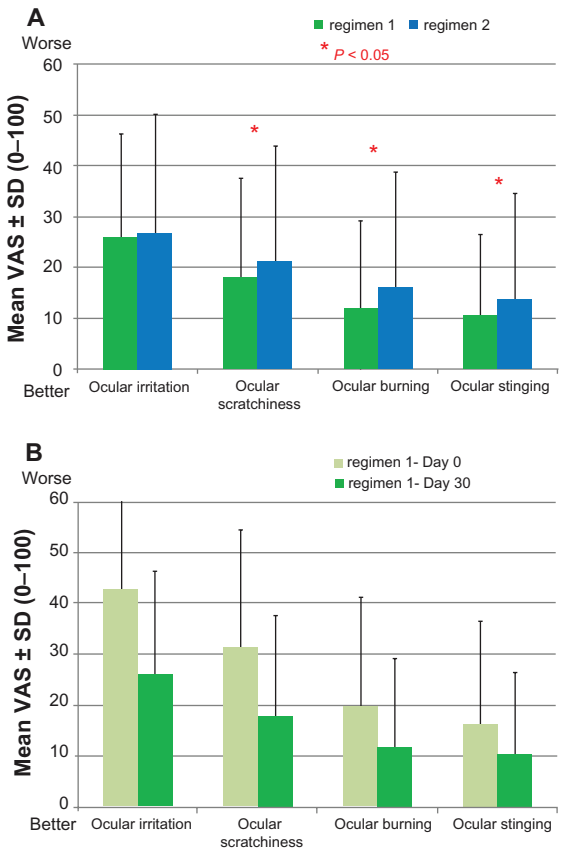

Figure 2 Mean ± standard deviation scores of ocular symptoms from visual analog scale ranging from 0 (none) to 100 (worst imaginable) and comparing (**A**) regimen 1 on Day 30 with regimen 2 on Day 30, and (**B**) regimen 1 on Day 0 with regimen 1 on Day 30.
Abbreviations: SD, standard deviation; VAS, visual analog scale.

wear time, Day 30 comfortable wear time was increased by an average of 1.8 ± 3.87 extra hours of comfortable lens wear time compared with baseline for subjects using regimen 1 ($P < 0.0001$). In the regimen 2 group, the average increase from baseline to Day 30 was 1.2 ± 4.0 hours ($P < 0.0001$).

No differences were observed between regimen 1 and regimen 2 at any of the visits for rewetting drop frequency. Average rewetting drop use reported at baseline and at each of the study visits ranged from 0.5 times per day to 0.7 times per day for both groups.

Circumlimbal conjunctival lissamine green staining

To test for potential cytotoxicity of the ingredients in the formulation, two types of staining investigations were conducted in the study. Fluorescein staining is used to indicate that breaks have occurred in the epithelial layer of the cornea, while lissamine green stains damaged conjunctival epithelial cells.[32]

For each subject, circumlimbal conjunctival staining was assessed across four regions around the cornea (nasal, temporal, inferior, superior) and the four scores were summed for analysis. In both regimen groups, circumlimbal conjunctival staining was highest in the nasal area, and lowest in the superior area, with temporal and inferior displaying intermediate levels of staining (not shown). A difference between the two regimen groups was observed in the staining sum score at Day 30, with subjects using regimen 1 (all lenses combined) having lower mean summed staining scores (more favorable) compared with subjects using regimen 2 ($P = 0.021$) (Figure 4). Circumlimbal conjunctival staining was dependent on lens type, with the highest amount of staining noted with Biofinity. With all four lenses, the difference between regimen 1 and regimen 2 favored regimen 1, but was not statistically significant except for Biofinity ($P = 0.018$, Figure 4).

Slit-lamp findings and corneal staining

For corneal fluorescein staining scored on a scale of 0–4, a lower level of staining was reported with regimen 1 compared

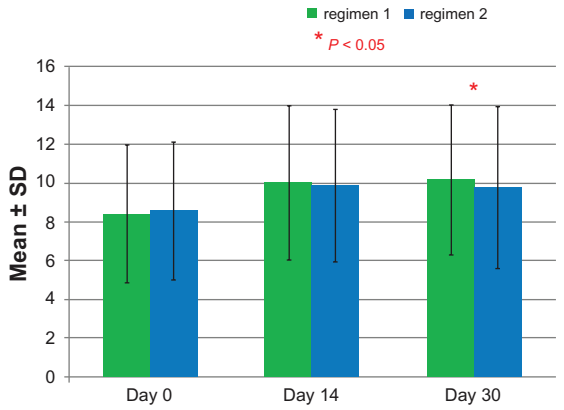

Figure 3 Mean ± standard deviation daily hours of comfortable lens wear for all lenses.
Abbreviation: SD, standard deviation.

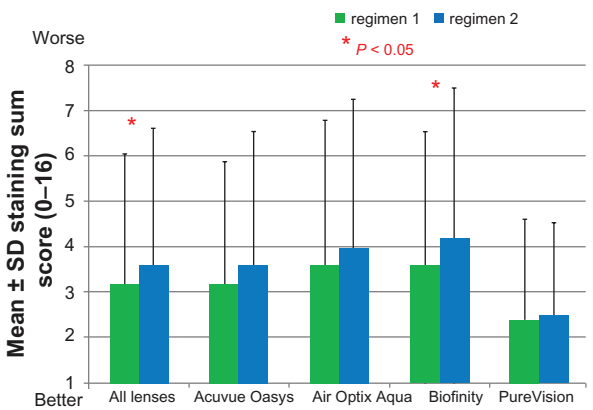

Figure 4 Mean sum scores from circumlimbal conjunctival lissamine green staining for all lenses and by lens brand.
Abbreviation: SD, standard deviation.

with regimen 2 (Table 3). When observing both eyes at all post-baseline study visits, there were 88 observations of staining graded 2 or higher out of 1151 total observations in the regimen 1 group (7.6%) compared with 152 observations graded 2 or higher out of 1144 total observations in the regimen 2 group (13.3%).

Table 3 also displays other slit-lamp findings graded as 2 or higher, including corneal edema, corneal neovascularization, corneal infiltrates, injection, tarsal abnormalities, or other complications. Overall, there were few clinically relevant observations. No differences were observed between regimens for slit-lamp findings after Day 0, except for corneal staining as described above.

On-eye lens surface evaluation

Wettability, film deposits, and discrete deposits were each rated by the investigator on a scale of 0–4 according to protocol-defined criteria. No differences were noted between the two regimen groups in any of the three evaluations at any of the study visits (Table 4). Of note on Day 30, 202 subjects in the regimen 1 group (73.5%) and 196 subjects in the regimen 2 group (71.3%) had a smooth uniform reflecting surface (wettability score of 0).

Ex vivo lipid analysis

No notable differences were observed between regimen 1 and regimen 2 at Day 30 for quantitative *ex vivo* lipid analysis conducted on lenses that had been worn for 30 days (Table 5). The lens type that most accumulated total lipids was the Acuvue Oasys lens (Table 5).

Unscheduled lens replacement incidence and causality

A total of 31 subjects required unscheduled lens replacement during the study. More subjects in the regimen 2 group required lens replacement, although the difference between the two groups was not statistically significant (6.2% versus 4.5%). Most of the lens replacements were due to lost lenses in the regimen 1 group and to damaged lenses in the regimen 2 group.

Contact lens corrected Snellen visual acuity

Visual acuity was generally maintained consistent with baseline throughout the study in both groups (77.1% of subjects using regimen 1 and 78.8% using regimen 2 had

Table 3 Significant slit-lamp findings and corneal fluorescein staining findings (Grade 2 or greater) by visit

	Grade	Day 0		Day 14		Day 30		Early Exit and Unscheduled		All visits > Day 0	
		Eyes	%	Eyes	%	Eyes	%	Eyes	%	Eyes	%
regimen 1											
Edema	2	2	0.3	0	0.0	0	0.0	2	6.7	2	0.2
Neovascularization	2	17	2.9	11	2.0	11	2.0	4	13.4	26	2.3
Injection	2	49	8.4	34	6.0	26	4.7	7	23.3	67	5.8
	3	0	0.0	0	0.0	2	0.4	1	3.3	3	0.3
Tarsal abnormalities	2	89	15.2	71	12.5	70	12.7	1	3.3	142	12.3
Infiltrates	3	0	0.0	0	0.0	0	0.0	1	3.3	1	0.1
Other complications	2	0	0.0	0	0.0	0	0.0	2	6.7	2	0.2
	3	0	0.0	0	0.0	0	0.0	1	3.3	1	0.1
Corneal staining	2	53	9.1	38	6.7	39	7.1	3	10.0	80	7.0
	3	1	0.2	4	0.7	0	0.0	3	10.0	7	0.6
	4	0	0.0	0	0.0	0	0.0	1	3.3	1	0.1
Total number of observations[a]		584	100	570	100	551	100	30	100	1151	100
regimen 2											
Edema	2	1	0.2	0	0.0	3	0.5	0	0.0	3	0.3
Neovascularization	2	12	2.0	10	1.7	10	1.8	2	14.3	22	1.9
Injection	2	44	7.4	26	4.5	30	5.4	0	0.0	56	4.9
	3	0	0.0	0	0.0	1	0.2	0	0.0	1	0.1
Tarsal abnormalities	2	81	13.6	79	13.7	75	13.5	0	0.0	154	13.5
Infiltrates	2	0	0.0	0	0.0	2	0.4	0	0.0	2	0.2
Other complications	2	2	0.3	0	0.0	1	0.2	0	0.0	1	0.1
Corneal staining	2	53	8.9	82	14.2	61	11.0	1	7.1	144	12.6
	3	0	0.0	3	0.5	4	0.7	1	7.1	8	0.7
Total number of observations[a]		594	100	576	100	554	100	14	100	1144	100

Note: [a]Total number of observations = number of subject visits × two eyes.

Table 4 On-eye lens surface evaluation after 30 days of solution use (Wettability, Film deposits, Discrete deposits)

	regimen 1 (n = 275)	regimen 2 (n = 275)	Least Squares Mean Difference[a]	*P* value
Wettability				
Mean (standard deviation)	0.3 (0.48)	0.3 (0.52)	–0.03 (0.03)	0.390
Film deposits				
Score of 0 or 1 (n, %)	252 (91.6%)	251 (91.3%)		0.380
Score of 2 (n, %)	16 (5.8%)	20 (7.3%)		
Score of 3 (n, %)	5 (1.8%)	2 (0.7%)		
Score of 4 (n, %)	2 (0.7%)	2 (0.7%)		
Discrete deposits				
Score of 0 or 1 (n, %)	256 (93.1%)	247 (89.8%)		0.206
Score of 2 (n, %)	16 (5.8%)	20 (7.3%)		
Score of 3 (n, %)	3 (1.1%)	6 (2.2%)		
Score of 4 (n, %)	0 (0.0%)	2 (0.7%)		

Note: [a]Standard error for mean difference.

no change in Snellen visual acuity from baseline to Day 30). A number of patients experienced a decrease in visual acuity from baseline to Day 14 or Day 30 as measured by an increase of 1 or 2 lines in the Snellen distance chart, but there were no statistically significant differences between the two regimens. The total number of eyes with final corrected visual acuity showing greater than or equal to a 2 Snellen line increase was 6 for both regimen 1 and regimen 2 on Day 14, and 6 for regimen 1 and 5 for regimen 2 on Day 30. These changes were usually attributed to normal fluctuation and/or increased lens deposits, and were not characterized by the investigators as adverse events related to the test article or the comparator.

Adverse events

The overall rate of ocular adverse events was low, with only 36 subjects (18 in each group; 6.1%) reporting ocular adverse events (Table 6). One subject in each of the two regimen groups experienced a serious adverse event that was deemed unrelated to the test article (schizoaffective disorder bipolar type in the regimen 1 treatment group; spontaneous abortion in the regimen 2 treatment group).

Adverse events considered related to the regimen were non-serious, mild, or moderate in intensity, generally resolved without treatment, and did not cause the subjects to withdraw from the study, except for 14 subjects. In the regimen 1 group, seven subjects (2.4%) discontinued study participation due to ocular adverse events (whether or not deemed related to the test article), comprising two subjects with ocular discomfort, two with keratitis, and one each for ocular hyperemia, ulcerative keratitis, and reduced vision acuity (one subject had two reasons, ie, ocular discomfort and ocular hyperemia). In the regimen 2 group, seven subjects (2.4%) withdrew from the study due to adverse events, comprising two subjects for

Table 5 Mean (SD) lipid deposits on worn lenses after 30 days of solution use (in μg/lens)

	regimen 1 (n = 235)	regimen 2 (n = 227)	Least Squares Mean Difference[a]	*P* value
Cholesterol esters	50.2 (60.30)	61.5 (92.23)	–9.85 (6.73)	0.144
Phospholipids/triglycerides	2.6 (3.93)	2.9 (4.01)	–0.26 (0.28)	0.359
Fatty acids/diglycerides/monoglycerides	0.5 (0.75)	0.5 (0.92)	0.02 (0.08)	0.780
Cholesterol	5.2 (4.73)	4.8 (4.56)	0.38 (0.29)	0.192
Total lipids				
All lenses	58.5 (63.41)	69.8 (95.43)	–9.68 (6.91)	0.162
VISTAKON®, Acuvue® Oasys™[†]	n = 59	n = 59		
	112 (77.6)	129 (141.1)	–15.0 (13.7)	0.275
CIBA Vision Air Optix™ Aqua	n = 61	n = 57		
	17 (24.2)	27 (53.3)	–9.5 (13.6)	0.485
CooperVision Biofinity®	n = 59	n = 54		
	49 (42.1)	51 (63.4)	–0.3 (14.0)	0.981
Bausch + Lomb PureVision®	n = 56	n = 57		
	57 (56.7)	69 (60.2)	–13.9 (13.9)	0.320

Note: [a]Standard error for mean difference, [†]Acuvue Oasys lenses are 2-weeks old

Table 6 Number of subjects who experienced ocular adverse events during the study

Adverse event	Ocular events regardless of relationship to test article or comparator		Ocular events deemed related to test article or comparator		Ocular events leading to subject withdrawal from study	
	regimen 1 n = 292	regimen 2 n = 297	regimen 1 n = 292	regimen 2 n = 297	regimen 1 n = 292	regimen 2 n = 297
Eye irritation	3 (1.0%)	5 (1.7%)	1 (0.3%)	2 (0.7%)	1 (0.3%) R	1 (0.3%) R
Ocular discomfort	3 (1.0%)	1 (0.3%)	3 (1.0%)	1 (0.3%)	2 (0.7%) R	1 (0.3%) R
Dry eye	1 (0.3%)	2 (0.7%)	–	2 (0.7%)	–	–
Punctate keratitis	1 (0.3%)	2 (0.7%)	1 (0.3%)	2 (0.7%)	1 (0.3%) R	1 (0.3%) R
Keratitis	2 (0.7%)	–	2 (0.7%)	–	2 (0.7%) R	–
Ocular hyperemia	2 (0.7%)	–	1 (0.3%)	–	1 (0.3%) R	–
Conjunctivitis	–	2 (0.7%)	–	2 (0.7%)	–	2 (0.7%) R
Ulcerative keratitis	1(0.3%)	–	–	–	1 (0.3%) Unr	–
Conjunctival hyperemia	1 (0.3%)	–	–	–	–	–
Vision blurred	1 (0.3%)	–	–	–	–	–
Vision acuity reduced	1 (0.3%)	–	–	–	1 (0.3%) Unr	–
Lacrimation increased	1 (0.3%)	–	–	–	–	–
Asthenopia	–	1 (0.3%)	–	–	–	1 (0.3%) Unr
Conjunctivitis, allergic	–	1 (0.3%)	–	–	–	–
Eye pain	–	1 (0.3%)	–	1 (0.3%)	–	1 (0.3%) R
Conjunctival hemorrhage	–	1 (0.3%)	–	–	–	–
Corneal staining	3 (1.0%)	4 (1.3%)	2 (0.7%)	4 (1.3%)	–	1 (0.3%) R
Total	17 subj[a–c] (5.8%)	18 subj[d,e] (6.1%)	8 subj[a,b] (2.7%)	13 subj[d] (4.4%)	8 subj[a] (2.7%)	8 subj (2.7%)

Notes: [a]Subject 1387 had two test article-related events that led to withdrawal, ie, ocular discomfort and ocular hyperemia; [b]Subject 4308 had two test article-related events, ie, keratitis (led to withdrawal) and corneal staining; [c]Subject 2661 had two events not related to test article (not leading to withdrawal), ie, dry eye and corneal staining; [d]Subject 3701 had two test article-related events (not leading to withdrawal), ie, dry eye and corneal staining; [e]Subject 3625 had two events not related to test article, ie, eye irritation and asthenopia (led to withdrawal).
Abbreviations: Subj, subjects; R, related; Unr, unrelated.

conjunctivitis and one each for ocular discomfort, punctate keratitis, asthenopia, eye pain, and corneal staining.

Discussion

This randomized, well controlled, double-masked study involving a large number of symptomatic subjects and a representative sample of silicone hydrogel lens brands was the second large-scale clinical study conducted to evaluate the safety and efficacy of the newly developed product, OPTI-FREE® PureMoist multi-purpose disinfecting solution. This new product utilizes the same disinfection platform as other OPTI-FREE® products currently on the market, and has been proven to be safe and effective. The main difference between previous OPTI-FREE® formulations and the new formulation is the addition of EOBO, a linear multifunctional diblock copolymer. EOBO acts as an active surface agent and, in combination with TETRONIC® 1304, provides improved lens wetting properties for silicone hydrogel and traditional soft lenses. The product is a rub and rinse formulation.

Although clinical evaluation of a multifunctional solution is not able to identify the effects of one particular component, the study found a significant difference in favor of the new multi-purpose disinfecting solution with EOBO (regimen 1) over the chosen comparator (regimen 2). When subjects were asked about the statement "I can comfortably wear my lenses" on Day 30, subjects using regimen 1 were in stronger agreement compared with subjects using regimen 2 ($P = 0.047$). Although the difference was small and its clinical significance cannot be ascertained in this study, other study parameters were also in favor of improved comfort with regimen 1. An increase in comfortable wear time of nearly 2 hours was noted for subjects using regimen 1, and longer mean comfortable wear time was reported at Day 30 for regimen 1 versus regimen 2 ($P = 0.041$). Further supporting the increase in comfort were improvements in comfort and symptoms of dryness, scratchiness, burning, stinging, and irritation by Day 30 compared with baseline. While some improvement was seen on both regimens, statistically significant differences in favor of regimen 1 were noted for the symptoms of scratchiness, burning, and stinging. Taken together these findings suggest that the new formulation with the EOBO wetting agent provides comfort benefits for symptomatic contact lens wearers. A primary reason for contact lens patients dropping out of contact lenses is dryness and discomfort.[2–8] Although this 30-day study did not address dropout rate, it is possible that an improvement in

perceived comfort may help reduce the dropout rate in this population of subjects who often experiences discomfort with contact lens wear.

Another notable difference in ocular signs between the two regimens was circumlimbal conjunctival staining using lissamine green. The degree of circumlimbal conjunctival staining among these symptomatic wearers was statistically lower with regimen 1 compared with regimen 2 on Day 30. Recent studies have shown that silicone hydrogel lenses are associated with conjunctival staining.[33,34] Although lissamine green has been mostly applied to evaluate complaints of dryness, it has also been suggested as a tool to detect conjunctival changes associated with contact lens wear.[35] More recently, contact lens-induced circumlimbal conjunctival staining has been reported in patients wearing silicone hydrogel lenses.[36,37] Due to the high modulus of some silicone hydrogel lenses, the fit may be less forgiving than with a traditional hydrogel lens and may worsen the impact of the lens edge design. The clinical relevance of the differences in circumlimbal conjunctival staining found in the present study remains to be investigated, because the relationship between circumlimbal conjunctival staining and comfort or other clinical outcomes has not been elucidated.[37]

Among multiple factors, comfort is influenced by cleanliness of the lens and the presence of lens deposits. In the present study, on-eye lens surface evaluation scores (lens deposits and wettability) were not different between regimen 1 and regimen 2. The subjective nature of these on-eye assessments may explain some of the difficulty in detecting small differences between solutions using these scales. Likewise, *ex vivo* lipid deposits as quantified by high-performance liquid chromatography did not detect any significant differences between regimen 1 and regimen 2. Lipid measurements showed relatively large interpatient variability in this study, similar to other studies,[38] and future studies should focus on reducing interpatient variability, possibly through identification of a more targeted study population or application of a crossover study design.

No safety issues were identified in this population of symptomatic silicone hydrogel contact lens wearers using either regimen for up to 30 days based upon a review of adverse events and an assessment of ocular safety parameters. There were no clinically relevant differences in other slit-lamp findings between the two regimens during the study, and no serious adverse events attributable to the regimens were reported. Both regimens had a low adverse event rate and only a few patients (2.4%) discontinued study participation for ocular event-related reasons.

Conclusion

The results of this study confirm that the new multi-purpose disinfecting solution provides comfort benefits and symptom reduction in a population of symptomatic silicone hydrogel lens wearers.

Disclosure

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