Propylene Glycol and Hydroxypropyl Guar Nanoemulsion - Safe and Effective Lubricant Eye Drops in the Management of Dry Eye Disease

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Abstract: Dry eye disease (DED) is a chronic condition of the ocular surface characterized by a loss of the tear film homeostasis and accompanied by symptoms such as eye discomfort and visual disturbances. DED is classified as aqueous deficient dry eye (ADDE), evaporative dry eye (EDE), and mixed dry eye etiologies. The mainstay treatment in the management of DED is artificial tear drops or lubricant eye drops that replenish the aqueous and/or lipid layer of the tear film. These are available as both lipid-based and non-lipid-based formulations, with/without preservatives. Lipid-based lubricant eye drops can stabilize the tear film lipid layer, reduce tear evaporation, and improve signs of EDE. In this review, we present the formulation components, mechanism of action, and summary of preclinical and clinical evidence on a lipid-based formulation – propylene glycol-hydroxypropyl guar (PG-HPG) nanoemulsion lubricant eye drops (Systane™ Complete). These eye drops consist of the demulcent (lubricant), PG (0.6%). HPG forms a soft, thin, cross-linked in situ gel matrix with borate ions, when exposed to the tear film, which prolongs lubricant retention and provides ocular surface protection. Dimyristoyl phosphatidyl glycerol, an anionic phospholipid, helps in replenishing the lipid layer of the tear film. Moreover, the nanoemulsion formulation serves as a depot for delivery of dimyristoyl phosphatidyl glycerol to enhance ocular surface coverage. Preclinical and clinical evidence demonstrate that PG-HPG nanoemulsion lubricant eye drops are safe and effective in providing temporary relief of symptoms of DED, regardless of its subtypes. Specifically, it provides sustained reduction in dry eye symptoms, improves tear film stability/lipid layer grade, and improves ocular surface characteristics.

Keywords: artificial tears, aqueous deficient dry eye, dry eye syndrome, evaporative dry eye, lipid-based eye drops, mixed dry eye

Introduction

Dry Eye Disease

Dry eye disease (DED) is a chronic condition impacting ≥30 million people in the United States and ≥344 million people globally.1 It is a multifactorial disease of ocular surface characterized by a loss of tear film homeostasis, and accompanied by ocular symptoms such as eye discomfort and visual disturbances.2,3 The prevalence of DED with/without symptoms ranges from 5% to 50%; and based on signs alone, up to 75%.4,5 Moreover, the prevalence of DED is reportedly higher in women (9.5%) than men (6.8%); high prevalence (9.5% to 87.5%) is reported with use of digital screens (computers and smartphones).5,6

DED can be classified as aqueous deficient dry eye (ADDE), evaporative dry eye (EDE), and mixed DED.3,7 ADDE is due to tear underproduction by the lacrimal glands. EDE can occur due to causes related to either lid (meibomian gland dysfunction [MGD] or blink-related) or ocular surface (mucin deficiency and contact lens wear), resulting in abnormal lipid secretion, tear film instability, and excessive evaporation of tears.3 Although EDE is considered a leading cause of DED, ADDE can occur without obvious signs of EDE and vice versa. Therefore, as DED progresses, it increasingly adapts clinical characteristics of both ADDE and EDE, that is known as mixed DED.3,8 DED patients across the United States were approximately 3 times more likely to be subclassified as EDE (characterized by MGD) than ADDE; and
approximately 36% of patients had mixed DED. Further, iatrogenic DED could be caused by topical or systemic drugs, contact lens wear, and ophthalmic surgical/non-surgical procedures. Goblet cells, which produce mucins and contribute to the stability of the tear film and immune defenses, are extremely sensitive to toxic/inflammatory stress and are reduced in density after exposure to iatrogenic factors. Owing to the multifactorial nature of DED, medications that can target multiple underlying pathologies simultaneously are desirable.

Treatment goal for DED is to restore ocular surface and tear film homeostasis. Current treatment options in the management of DED include artificial tears or ocular lubricants, nutraceuticals, anti-inflammatory agents, tear stimulants, autologous serum, antibiotics, and other therapies (eg, physical treatments such as warm compresses, complementary medicines such as herbal products, punctal occlusion, and surgical approaches).

Artificial Tears

Artificial tears, which substitute or supplement the natural tear film, are the first line option in the management of DED. Artificial tears improve symptoms (burning, irritation, and/or discomfort), and provide temporary relief of dryness of the eye, but have not been shown to treat pathophysiology of DED. Ideal artificial tears should spread uniformly and evenly, minimize friction during blinks, have minimal visual disturbance upon instillation, be safe/convenient to use, and effectively improve the signs/symptoms of DED.

Artificial tears are formulated with polymeric lubricants, demulcents, buffering agents (compatible with ocular pH of approximately 7.5), electrolytes, osmolality adjusting excipients, and surfactants, with/without preservatives. Most of artificial tears are formulated to supplement either lipid layer or aqueous layer of the tear film. However, some eye drops are formulated as emulsions, which contain aqueous lubricants (such as hydroxypropyl guar [HPG], polyethylene glycol [PEG], and propylene glycol [PG]) and lipid ingredients (such as phospholipid and mineral oil). Lipid-based artificial tears have been shown to stabilize the tear film lipid layer, reduce tear evaporation, and improve the signs of MGD and EDE.

One of the major challenges with eye drops is low retention time. To increase the retention time, viscosity-enhancing agents such as hyaluronic acid (HA) and carboxymethyl cellulose (CMC) are incorporated in eye drops; these agents also exhibit muco-mimetic properties and reduce desiccation by forming a protective layer on the ocular surface. However, eye drops with high viscosity may cause transient visual disturbances (blurred vision) and also result in debris, leading to intolerance and non-compliance. Thus, to overcome low ocular retention, in situ gelling chemistry is used; this is achieved through HPG, a natural polysaccharide, that forms a viscoelastic gel at ocular pH through cross-linking. HPG forms the backbone in artificial tears of the Systane family (Alcon Laboratories, Inc., Fort Worth, TX, USA), which are indicated for the temporary relief of dry eye symptoms (such as burning and irritation) and ocular surface protection in patients with DED. Artificial tears of the Systane family include non-lipid-based (PEG/PG-HPG lubricant eye drop [Systane Original], PEG/PG-HPG-sorbitol lubricant eye drop [Systane Ultra] and PEG/PG-HPG/sodium hyaluronate (HA)-sorbitol lubricant eye drop [Systane Hydration]) as well as lipid-based (PG-HPG microemulsion lubricant eye drop [Systane Balance] and PG-HPG nanoemulsion lubricant eye drop [Systane Complete]) formulations.

In this review, we present the formulation components, mechanisms of action, and the summary of literature evidence of PG-HPG nanoemulsion lubricant eye drop (Systane Complete, Alcon Laboratories, Inc., Fort Worth, TX, USA) that is indicated for temporary relief of symptoms of burning and irritation in DED.

PG-HPG Nanoemulsion Lubricant Eye Drops

Formulation Components

PG-HPG nanoemulsion lubricant eye drops contain the demulcent: propylene glycol (PG; 0.6%; lubricant), and inactive ingredients: dimyristoyl phosphatidyl glycerol (anionic polar phospholipid), edetate disodium, mineral oil, polyoxyl 40 stearate, sorbitan tristearate, sorbitol, boric acid, HPG, and polyquaternium-1 (Polyquad®; preservative). Preservative-free formulation option is also available for PG-HPG nanoemulsion lubricant eye drops.
PG-HPG nanoemulsion lubricant eye drops (Systane™ Complete) have similar components as that of PG-HPG microemulsion lubricant eye drops (Systane™ Balance). However, PG-HPG nanoemulsion lubricant eye drops contain 3-fold higher concentration of HPG which enhances ocular retention of the demulcent. Moreover, its nanodroplets (<100 nm) help to optimize coverage area of phospholipid delivered to the tear film which improves tear film stability, it can be used to provide temporary relief of dry eye symptoms.

**Mechanism of PG-HPG Nanoemulsion Lubricant Eye Drops**

HPG is a pH-sensitive gelling agent, and cross-links with borate ions through a condensation reaction that can occur both intramolecularly and intermolecularly. HPG exhibits low viscosity in solutions at pH 7 but increases in viscosity (from 10 cp to 10,000 cp) when exposed to the tear film (pH 7.5), due to the formation of a soft, thin, cross-linked in situ gel matrix with borate ions. Factors that control the gelation process include HPG and borate concentrations, and pH. HPG preferentially binds to the hydrophobic areas of the surface epithelium. The in situ gel matrix, due to bio-adhesive property, prolongs retention of demulcents (PG) on the damaged ocular surface. The layer of adsorbed HPG molecules forms a scaffold that holds the in situ gel; the gel layer spreads over cornea and conjunctiva (along with retained demulcents), and lubricates the eye, reduces tear film desiccation, enhances tear-film stabilization, and allows the repair of ocular surface epithelium.

The non-Newtonian characteristics (shear-thinning behavior) of HPG causes an increase in viscosity between blinks and a decrease in viscosity during blinks; which is advantageous for longer retention on the eye and comfort on the ocular surface. HPG in lubricant eye drops, owing to the characteristics described previously, lowers tear osmolarity and corneal dryness to provide long-lasting relief from DED symptoms. Overall, in situ HPG/borate gel complex prolongs the retention of demulcent (PG), enhances tear film stability and protects the ocular surface, thereby reducing the symptoms of DED.

Moreover, nanosized droplets of oil-in-water nanoemulsion serves as better depot for delivery of dimyristoyl phosphatidyl glycerol, an anionic phospholipid. Dimyristoyl phosphatidyl glycerol migrates toward the top of the tear film, and fuses with the tear lipids to supplement the gaps developed due to tear film lipid insufficiency; replenishing the tear film lipid layer. Therefore, PG-HPG nanoemulsion lubricant eye drops serve as tear replacement solution in patients with DED due to lipid deficiency, aqueous deficiency, and/or mixed dry eye.

**Multidose Preservative-Free PG-HPG Nanoemulsion with Novelia**

DED is chronic and progressive in nature, and may require repeated and long-term application of lubricant eye drops. Thus, to maintain the sterility of multidose lubricant eye drops, antimicrobial preservatives such as benzalkonium chloride and polyquaternium-1 are commonly used in the formulations. Polyquaternium-1 (Polyquad®, Alcon Inc., Fort Worth, TX, USA) is a quaternary ammonium compound with antimicrobial activity similar to benzalkonium chloride. Although both preservatives are effective, several studies demonstrated that polyquaternium-1 is less cytotoxic to ocular surface and more safe than benzalkonium chloride. Polyquaternium-1 is safe for mammalian cells owing to its large molecular size that reduces cell penetration. However, the possible effects of polyquaternium-1 on the tear film, and tolerance in patients with dry eye remain to be fully investigated.

Long-term application of artificial tears containing preservatives can cause epithelial damage and ocular surface alteration. Several studies have suggested that non-preserved drops should be used, whenever possible, to avoid eye irritation. TFOS DEWS II also recommends using non-preserved eye drops to minimize preservative-induced toxicity. Overall, preservative-free drops may be a better choice for patients who have pre-existing ocular surface conditions and/or need frequent instillation of eye drops in DED.

Preservative-free lubricant eye drops are dispensed in either unit dose or multidose systems. Unit dose vials are expensive, bulky, and difficult-to-use. Further, although the multidose preservative-free bottles improve patient compliance and limit wastage, they have challenges of filtering solution/air and avoiding bacterial entry. Therefore, multidose bottles with an intelligent design comprising unidirectional valves and a venting system (to maintain sterility of product, and to avoid contamination) are used to deliver safe, preservative-free eye drops. Novelia (Novelia®, Nemera, La Verpillière, France) is one such multidose system that avoids the need for preservatives in the formulation, and prevents contamination over the duration of treatment. One of the features of Novelia include the silicone membrane barrier system and a non-return valve.
The non-return valve in the system restricts the back flow of the contaminated liquid once dispensed from the container, thus removing the need to filter the liquid; the silicone membrane is made of solid, non-porous material that filters air and prevents entry of contaminated air.46

The previously-mentioned properties of formulation components, and mechanisms of action make PG-HPG nanoemulsion an ideal lubricating eye drop with a prolonged retention, and sustained lubrication to improve signs and symptoms in DED. This has been further supported by preclinical and clinical evidence as follows.

Preclinical and Clinical Studies of PG-HPG Nanoemulsion Lubricant Eye Drops in the Treatment of DED

A literature search was performed systematically using PubMed database, to identify pre-clinical and clinical studies reporting the efficacy/effectiveness and safety of PG-HPG nanoemulsion lubricant eye drops in alleviating the signs and symptoms of dry eye in patients with DED. Search strings used in the database were:

1. (((dry eye) OR (dry eye syndrome) OR (dry eye disease)) AND ((artificial tears) AND (lubricant)));
2. (((Propylene glycol) AND (hydroxypropyl guar)) AND ((artificial tears) OR (lubricant) OR (lubricant eye drops)));
3. (((Propylene glycol) AND (hydroxypropyl guar)) AND ((Dry eye) OR (Dry eye disease) OR (Dry eye syndrome)));
4. (((Dry eye) OR (dry eye syndrome) OR (dry eye disease)) AND ((artificial tears) OR (lubricant) OR (lubricant eye drops) OR (eye drops)) AND (Systane Complete) OR ((HP guar) OR (hydroxypropyl guar))).

Figure 1 describes the flow chart of literature screening process, with key inclusion and exclusion criteria. Articles were screened for studies published from January 2017 to February 2022 and in English language. After removing

\[\text{Figure 1 Flow chart of literature screening strategy, with key inclusion and exclusion criteria. Search strings: 1. (((dry eye) OR (dry eye syndrome) OR (dry eye disease)) AND ((artificial tears) AND (lubricant)))); 2. (((Propylene glycol) AND (hydroxypropyl guar)) AND ((artificial tears) OR (lubricant) OR (lubricant eye drops)))); 3. (((Propylene glycol) AND (hydroxypropyl guar)) AND ((Dry eye) OR (Dry eye disease) OR (Dry eye syndrome)))); and 4. (((Dry eye) OR (dry eye syndrome) OR (dry eye disease)) AND ((artificial tears) OR (lubricant) OR (lubricant eye drops) OR (eye drops)) AND (Systane Complete) OR ((HP guar) OR (hydroxypropyl guar))).} \]

Abbreviations: DED, dry eye disease; HPG, hydroxypropyl guar; PG, propylene glycol; QoL, quality of life.
duplicates, 236 articles were identified; of these, 9 relevant articles with preclinical or clinical studies were included after screening (Figure 1). Moreover, 1 abstract was identified using the same inclusion criteria from Google Scholar, and was considered for inclusion in this review. A total of 10 studies (preclinical and clinical) were evaluated and reviewed with common consensus of all authors. Tables 1–3 represent the methods, population, treatment, outcomes and results of preclinical and clinical studies.

Preclinical and clinical studies have demonstrated that PG-HPG nanoemulsion lubricant eye drops are associated with improvements in the signs and symptoms of dry eye, and are well tolerated in patients with DED, irrespective of its subtypes.

**Preclinical Evidence**

**Long-lasting Lubrication and Ocular Surface Protection with PG-HPG Nanoemulsion Eye Drops**

Preclinical evaluation using different corneal epithelial models demonstrated the effectiveness of PG-HPG nanoemulsion artificial tear formulation compared to vehicle/control and microemulsion for treatment of DED (Table 1). In human corneal epithelial cells, PG-HPG nanoemulsion showed higher hydration protection and retention against desiccation compared to vehicle (approximately 32- to 40- fold higher; p<0.05) and microemulsion (approximately 3- to 5.5-fold higher; p<0.05). PG-HPG nanoemulsion showed higher cell recovery at 48 hours after benzalkonium chloride-exposure of human corneal epithelial cells (p<0.05 for PG-HPG nanoemulsion vs positive control). Moreover, in simulated blinking experiment, surface friction in bovine pericardial samples was significantly lower with PG-HPG nanoemulsion versus microemulsion and versus vehicle, during posttreatment (1 minute after removal of treatment; both p<0.05). Additionally, elastic filament strength was significantly higher with PG-HPG nanoemulsion versus microemulsion and

| Table 1 Preclinical Studies of PG-HPG Nanoemulsion Lubricant Eye Drops in the Treatment of DED |
|--------------------------------------------------|-----------------------------------------------|--------------------------|
| Treatment                                         | Outcome Parameters                             | Results                  |
| Rangarajan and Ketelson, 2019;48                | **Corneal epithelial cell models**            |                          |
| PG-HPG nanoemulsion vs microemulsion vs vehicle (nanoemulsion without HPG)/no treatment | **Hydration protection against desiccation** | Cell viability (n=33 vs 63 vs 38): 39.5±14.6% vs 7.1±10% vs −0.1±1.9%; p<0.05 for nanoemulsion vs vehicle |
|                                                  | **Hydration retention after desiccation**     | Cell viability (n=73 vs 99 vs 63): 32.6±13.6% vs 11.0±8.5% vs −1.2±0.6%; p<0.05 for nanoemulsion vs vehicle |
|                                                  | **Cell recovery (to normal barrier function) after benzalkonium chloride exposure** | Fluorescein permeability (n=18 for all): 2.66±0.2 RFU vs 2.76±0.2 RFU vs 3.11±0.4 RFU; p<0.05 for nanoemulsion vs positive control |
|                                                  | **Corneal epithelium fluorescein permeability** | CF uptake (n=5 for all): 9.6±2.3 ng CF/g vs 13.12±2.8 ng CF/g vs 22.6±5.1 ng CF/g; p<0.05 for nanoemulsion vs positive control and for microemulsion vs positive control |
|                                                  | **Surface lubricity**                          | Friction co-efficient (n=3 for all): At treatment (2 min after application): 0.09±0.01 vs 0.08±0.01 vs 0.38±0.05; p<0.05 for nanoemulsion vs vehicle and for microemulsion vs vehicle Post-treatment (1 min after rinsing): 0.18±0.04 vs 0.27±0.03 vs 0.42±0.04; all p<0.05 |
| Rangarajan et al, 2019;48                       | **Biological surface models**                  |                          |
| PG-HPG nanoemulsion vs Refresh Optive-Advanced vs Soothe-XP | **Cell viability**                            | 81% vs 45% vs 31%, p<0.05 |
|                                                  | **Cell protection from desiccation stress**   | 28% vs 5% vs 4%, p<0.05 |

**Abbreviations:** CF, carboxy-fluorescein; DED, dry eye disease; HPG, hydroxypropyl guar; microemulsion, Systane™ Balance; PG, propylene glycol; PG-HPG nanoemulsion, Systane™ Complete; positive control, benzalkonium chloride treated cells; RFU, relative fluorescence units.
### Table 2 Clinical Studies of PG-HPG Nanoemulsion Lubricant Eye Drops in the Management of DED

| Study Treatment | Outcome Parameters | Results |
|-----------------|--------------------|---------|
| **Silverstein et al, 2020**<sup>16</sup> A phase IV, multicenter, open-label, single arm interventional study in adult patients with DED (N=134) of aqueous-deficient (n=41), evaporative (n=44), and mixed (n=49) subtypes | Change in VAS score at 0 h; 4 h; and 8 h (median, 95% CI) Overall cohort: -1 (-3.0, -1.0); -2 (-3.0, -2.0); and -2 (-2.0, -1.0), respectively ADDE: -2 (-3.0, -1.0); -2 (-3.0, -1.0); and -2 (-3.0, -1.0), respectively EDE: -2 (-3.0, -1.0); -2 (-3.0, -1.0); and -2 (-3.0, -1.0), respectively Mixed DED: -2 (-3.0, -1.0); -2 (-3.0, -1.0); and -2 (-3.0, -1.0), respectively | **PG-HPG nanoemulsion (Systane<sup>TM</sup> Complete)** Dry eye symptoms: VAS score, 0 (no symptoms) to 10 (worst imaginable symptoms) | **Soothing sensation: VAS score, 0 (eyes feeling good) to 10 (no soothing feeling at all)** VAS score at 0 h; 4 h; and 8h (median [range]) Overall cohort: 3 (0–10); 3 (0–10); and 3.5 (0–10), respectively ADDE: 3 (0–9); 2 (0–8); and 3 (0–8), respectively EDE: 3 (0–10); 3 (0–10); and 4 (0–9), respectively Mixed DED: 3 (0–10); 3 (0–10); and 3 (0–10), respectively **Tolerability assessment: VAS score, 0–5 (no symptoms to mild symptoms); 6–10 (moderate to severe symptoms)** Patient (%) with tolerability assessment score range 0–5 for burning, stinging, blur, and foreign body sensation Overall: 97.0%, 96.3%, 92.5%, and 94.8%, respectively ADDE: 97.6%, 97.6%, 90.2%, and 100%, respectively EDE: 95.5%, 95.5%, 93.2%, and 93.2%, respectively Mixed DED: 98.0%, 95.9%, 93.9%, and 91.8%, respectively |
| **Yeu et al, 2020**<sup>18</sup> A phase IV, multicenter, open-label, single arm interventional study in adult patients with DED (N=134) of aqueous-deficient (n=41), evaporative (n=44), and mixed (n=49) subtypes | Change in TFBUT from baseline to Day 14 (mean±SD): Overall cohort: 1.5±2.8 seconds ADDE: 1.1±2.41 seconds EDE: 2.4±3.17 seconds Mixed: 1.2±2.63 seconds Change in TFBUT from baseline to Day 28 (mean±SD): Overall cohort: 1.4±2.8 seconds ADDE: 0.6±1.47 seconds EDE: 2.5±3.94 seconds Mixed: 1.1±2.08 seconds Tear film stability: TFBUT TFBUT at baseline (mean±SD): 2.6±1.01 seconds | **PG-HPG nanoemulsion (Systane<sup>TM</sup> Complete)** Tear film stability: TFBUT | **Ocular discomfort: VAS score (0–100)** VAS score at baseline (mean±SD): 45.9±24.33 Change in VAS score from baseline to Day 14 (mean±SD): Overall cohort: -17.3±24.80 ADDE: -22.0±21.73 EDE: -17.6±24.17 Mixed: -13±27.49 | **Ocular surface characteristics: corneal staining** Patient (%) with corneal staining absent/minimal and mild/moderate/mark at Day 28 Overall cohort: 104 (77.6%); and 26 (19.4%), respectively ADDE: 33 (80.5%); and 8 (19.5%), respectively EDE: 35 (79.5%); and 8 (18.2%), respectively Mixed: 36 (73.5%); and 10 (20.4%), respectively |
### Safety: AEs/SAEs

Treatment-emergent AEs: 19 in 9 (6.7%) patients  
Patients (%) with ocular AEs: 6 (4.5%); one AE of blurred vision that was mild, transient, and not related to product  
Patients (%) with non-ocular AEs: 8 (6%)  
No severe ocular or non-ocular AEs reported  
Treatment discontinuation due to AEs: n=2; eye pruritis: 1 (0.7%); and viral conjunctivitis: 1 (0.7%)

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### Weisenberger et al, 2020

Part 1, crossover study comparing nanoemulsion vs non-emollient eye drops followed by part 2, a 1-month observational study of nanoemulsion eye drops in patients with dry eye symptoms (N=20)

#### Part 1, PG-HPG nanoemulsion (Systane Complete) vs non-emollient (Systane Ultra) eye drops: Part 2, 1-month follow-up of patients treated with PG-HPG nanoemulsion (Systane Complete)

| Lipid layer thickness | LLT at baseline (mean±SD): 45.15±12.42 nm | Change in LLT (nm) from baseline to 15 min after instillation (mean±SD), p-value vs baseline |
|-----------------------|---------------------------------------------|----------------------------------------------------------------------------------|
| Overall               | 4.89±15.57, p<0.05 vs −1.03±7.92, p<0.05    |                                                                                   |
| Superior              | 3.69±14.34, p<0.05 vs −0.69±6.38, p>0.05     |                                                                                   |
| Middle                | 4.86±18.20, p>0.05 vs −0.99±8.48, p>0.05     |                                                                                   |
| Inferior              | 6.08±16.39, p<0.05 vs −1.97±9.98, p>0.05     |                                                                                   |
| Patients with baseline LLT <50 nm (n=15) |                                                                                   |                                                                                   |
| Overall               | 8.51±13.95, p<0.05 vs −1.34±5.35, p>0.05     |                                                                                   |
| Superior              | 6.13±13.41, p<0.05 vs −1.05±3.95, p>0.05     |                                                                                   |
| Middle                | 9.33±16.84, p>0.05 vs −1.19±5.01, p>0.05     |                                                                                   |
| Inferior              | 9.15±14.60, p<0.05 vs −1.79±7.32, p>0.05     |                                                                                   |
| Patients with baseline LLT ≥50 nm (n=5) |                                                                                   |                                                                                   |
| Overall               | −5.97±16.53, p<0.05 vs −0.99±13.75, p>0.05   |                                                                                   |
| Superior              | −3.62±16.08, p<0.05 vs 0.39±11.53, p<0.05    |                                                                                   |
| Middle                | −8.55±16.77, p<0.05 vs −3.88±15.70, p>0.05   |                                                                                   |
| Inferior              | −3.14±19.71, p>0.05 vs −2.51±16.48, p>0.05   |                                                                                   |

#### Ocular symptoms for dryness

| Change in VAS score from baseline to time points (mean±SD), p value vs baseline |
|-----------------------|---------------------------------------------|----------------------------------------------------------------------------------|
| All patients (N=20)   |                                                                                   |                                                                                   |
| 15 min                | −14.1±19.1, p<0.05 vs −15.3±17.3, p>0.05                                           |                                                                                   |
| 1 h                   | −14.9±18.9, p<0.05 vs −14.3±21.0, p>0.05                                            |                                                                                   |
| 2 h                   | −12.2±16.3, p<0.05 vs −16.0±21.9, p>0.05                                            |                                                                                   |
| 6 h                   | −8.6±16.7, p<0.05 vs −9.8±19.9, p<0.05                                               |                                                                                   |
| 1 month of QID use of nanoemulsion: −10.2±21.2, p<0.045                             |                                                                                   |
| Patients with baseline LLT <50 nm (n=15) |                                                                                   |                                                                                   |
| 15 min                | −9.8±17.4, p<0.05 vs −17.2±17.1, p<0.05                                             |                                                                                   |
| 1 h                   | −12.1±16.8, p<0.05 vs −11.0±20.5, p>0.05                                            |                                                                                   |
| 2 h                   | −13.0±17.3, p<0.05 vs −15.5±21.6, p>0.05                                            |                                                                                   |
| 4 h                   | −9.5±13.8, p<0.05 vs −17.7±22.7, p>0.05                                            |                                                                                   |
| 6 h                   | −5.3±13.6, p<0.05 vs −10.8±19.9, p>0.05                                            |                                                                                   |
| 1 month of QID use of nanoemulsion: −7.1±14.6, p>0.05                               |                                                                                   |
| Patients with baseline LLT ≥50 nm (n=5):                                              |                                                                                   |
| 15 min                | −21.0±24.6, p<0.05 vs −9.4±18.6, p>0.05                                             |                                                                                   |
| 1 h                   | −20.2±26.2, p<0.05 vs −11.6±22.9, p<0.05                                            |                                                                                   |
| 2 h                   | −20.4±24.6, p<0.05 vs −10.6±21.1, p<0.05                                            |                                                                                   |
| 4 h                   | −20.4±21.9, p<0.05 vs −10.6±20.9, p<0.05                                            |                                                                                   |
| 6 h                   | −18.2±22.8, p<0.05 vs −6.8±21.7, p<0.05                                            |                                                                                   |
| 1 month of QID use of nanoemulsion: −19.2±35.3, p>0.05                               |                                                                                   |
### Table 2 (Continued).

| Study Treatment | Outcome Parameters | Results |
|-----------------|--------------------|---------|
| **Lipid-based artificial tear: PG-HPG nanoemulsion lubricant eye drop (Systane™ Complete) vs non-lipid-based artificial tear; PEG/PG-HPG lubricant eye drop (Systane™ Ultra)** | Dry eye symptomatology | SANDE score (out of 100) (mean±SD): Baseline: 44±24 vs 45±23, p=0.99 Post instillation: 19±16 vs 24±17, p=0.17 Post exposure to adverse environment: 22±16 vs 33±16, p=0.006 |
| Tear film quality: NITBUT, tear film layer grade | NITBUT (mean±SD): Baseline: 8.3±3.8 vs 8.2±4.1, p=0.99 Post instillation: 11.1±4.5 vs 10.2±5.4, p=0.51 Post exposure to adverse environment: 10.4±5.6 vs 8.3±4.7, p=0.02 Tear film grade (median [IQR]): Baseline: 2 (1–3) vs 2 (1–3), p=0.98 Post instillation: 3 (2–4) vs 2 (1–3), p=0.003 Post exposure to adverse environment: 3 (2–3) vs 2 (0–2), p<0.001 |
| Safety: AEs | No AEs reported during the study period |
| **Craig et al, 2021**; Prospective, multicenter, randomized, double-masked, parallel group, six-month efficacy trial at clinical academic sites in Australia, Canada, New Zealand and the UK in participants fulfilling the TFOS DEWS II diagnostic criteria for DED (N=99) | Lipid-aqueous eye drop (Systane™ Complete), and aqueous-based eye drop (Systane™ Ultra) | Ocular symptoms: OSDI, DEQ-5, and SANDE scores Consistent reductions in OSDI, DEQ-5, and SANDE scores from Day 30 onwards in both treatment groups (all p≤0.01, multiplicity-adjusted post-hoc analysis) |
| Tear film stability: NITBUT | Consistent improvement from Day 120 onwards in both treatment groups (all p<0.05, multiplicity-adjusted post-hoc analysis) |
| Tear film lipid layer quality | Improvements in tear film lipid layer quality from Day 90 onwards only with the lipid-based tear drops (all p<0.05, multiplicity-adjusted post-hoc analysis), with measurements being greater compared to non-lipid containing eye drop (all p<0.05) Subgroup analysis showed that significant change in tear film lipid layer grade during the study period was limited to participants with a baseline grade ≤3 (median change of +1 versus 0 grades, p=0.01). |
| Ocular surface characteristics: lid wiper epitheliopathy grade, and sodium fluorescein and lissamine green staining scores | Superior lid wiper epitheliopathy grade significantly decreased in both treatment groups from Day 60 onwards (all p<0.01, multiplicity-adjusted post-hoc analysis) Sodium fluorescein and lissamine green staining scores improved from Day 120 onwards in both groups (all p<0.05, multiplicity-adjusted post-hoc analysis) |
| Safety: AEs | Non-significant AE related to drops: 1 (itching and irritation following application); non-significant AE unrelated to drops: 2 (conjunctivitis); all AEs resolved within 3–7 days after onset |

**Abbreviations:** ADDE, aqueous deficient dry eye; AEs, adverse events; CI, confidence interval; DED, dry eye disease; DEQ-5, dry eye questionnaire-5; EDE, evaporative dry eye; HPG, hydroxypropyl guar; LLT, lipid layer thickness; NITBUT, non-invasive tear break-up time; OSDI, ocular surface disease index; PG, propylene glycol; QID, quarter in a day; SAEs, serious adverse events; SANDE, Symptom Assessment Questionnaire in Dry Eye; SD, standard deviation; TFBUT, tear film break-up time; TFOS DEWS II, Tear Film and Ocular Surface Society Dry Eye WorkShop II; UK, United Kingdom; VAS, visual analog scale.
Table 3 Clinical Studies of PG-HPG Nanoemulsion Lubricant Eye Drops in Improvement of Contact Lens Discomfort

| Study Treatment | Outcome Parameters | Results |
|-----------------|-------------------|---------|
| **Pucker et al, 2020**;53 | Contact lens comfort and dry eye: CLDEQ-4, CLDEQ-8, and SPEED scores | **CLDEQ-8 score (mean±SD):**<br>Baseline: 20.41±4.0 vs 18.92±4.9, p=0.25<br>2-week: 12.86±6.40 vs 17.92±5.30, p=0.006<br>Difference from baseline at week 2: 7.55±4.96, p<0.0001 vs 1.00±4.11, p=0.26 |
| PG-HPG nanoemulsion (Systane™ Complete) vs no treatment | **CLDEQ-4 score (mean±SD):**<br>Baseline: 10.91±3.28 vs 10.38±2.41, p=0.42<br>2-week: 7.14±3.50 vs 10.13±2.83, p=0.005<br>Difference from baseline at week 2: 3.77±2.65, p<0.0001 vs 0.25±2.42, p=0.56 |
|  | **SPEED score (mean±SD):**<br>Baseline: 10.27±3.60 vs 9.67±3.93, p=0.90<br>2-week: 7.55±4.31 vs 9.29±4.14, p=0.17<br>Difference from baseline at week 2: 2.72±2.86, p<0.0001 vs 0.38±3.66, p=1.00 |
|  | **Self-perceived eye comfort** | Self-perceived eye comfort at 2 weeks:<br>Same: 31.82% vs 83.33%; better: 59.09% vs 0.0%; worse: 9.09% vs 16.7%; p<0.0001 |
|  | **Safety: AEs** | No AEs were reported during the study |
| **Pucker et al, 2021**;54 | Contact lens comfort and dry eye symptoms: CLDEQ-8 and SPEED scores | **CLDEQ-8 score (mean±SD):**<br>Baseline: 20.6±5.3 vs 20.5±5.5 vs 21.8±5.0, p=0.67<br>2-week: 14.7±5.3 vs 14.8±4.7 vs 21.2±6.0, group comparison p<0.0001 (artificial tears vs rewetting drops, p=0.94)<br>Difference from baseline: 6.0±6.3, p<0.0001 vs 5.8±4.3, p<0.0001 vs 0.5±3.8, p=0.49 |
| PG-HPG nanoemulsion (Systane™ Complete) vs rewetting drops (Sensitive Eyes) vs no treatment | **SPEED score (mean±SD):**<br>Baseline: 9.4±3.9 vs 10.3±4.6 vs 10.7±5.0, p=0.61<br>2-week: 7.3±3.1 vs 8.4±4.6 vs 10.2±4.9, group comparison p=0.065 (artificial tears vs rewetting drops, p=0.37)<br>Difference from baseline: 2.1±4.1, p=0.016 vs 1.8±4.3, p=0.50 vs 0.5±3.6, p=0.50 |
|  | **Self-perceived eye comfort** | Self-perceived eye comfort at 2-weeks:<br>Same: 44% vs 21% vs 75%; better: 52% vs 79% vs 4%; worse: 4% vs 0% vs 21%; group comparison p<0.0001 (artificial tears vs rewetting drops, p=0.15) |
|  | **End-of-day contact lens comfort just prior to removal (VAS 0–100 scale)** | VAS scores (mean±SD):<br>1-week: 58.56±21.44 vs 63.00±27.14 vs 44.25±28.95, group comparison p=0.038 (artificial tears vs rewetting drops, p=0.55)<br>2-week: 62.96±26.80 vs 71.38±21.85 vs 40.29±31.07, group comparison p=0.0004 (artificial tears vs rewetting drops, p=0.28) |
|  | **Safety: AEs** | No AEs were self-reported or detected during the study |

(Continued)
versus vehicle (polymer filament break-up time [PFBUT] at 10^{-1} s shear rate: 0.031±0.008 s vs 0.016±0.005 s vs 0.017 ±0.001 s, both p<0.05). Overall, PG-HPG nanoemulsion (vs vehicle and/or microemulsion) showed greater hydration protection and retention, higher cell recovery, better cell barrier function, higher surface lubricity, and increased elastic filament strength in corneal epithelial models. In another preclinical study, Rangarajan et al assessed the performance of phospholipid containing PG-HPG nanoemulsion in comparison to two other lipid-containing artificial tears (Refresh Optive-Advanced; and Soothe-XP) using biological surface models. PG-HPG nanoemulsion (vs Refresh Optive-Advanced, and vs Soothe-XP) showed significantly (p≤0.05) greater cell viability and cell protection against desiccation, and improved lubrication. These results suggest that the phospholipid containing PG-HPG nanoemulsion provides long-lasting lubrication and surface protection in the eye, compared to other lipid-containing eye drops (Table 1).

Clinical Evidence
PG-HPG Nanoemulsion Lubricant Eye Drops in the Treatment of All DED Subtypes
Recently, Craig et al demonstrated the treatment of DED according to disease subtype and severity. In a multicenter, double-masked, parallel group, randomized controlled trial, 99 participants (mean age, 44±16 years; 64% female) with DED were enrolled. Participants instilled either lipid-based PG-HPG nanoemulsion drops (Systane Complete) or non-lipid-based aqueous drops (Systane Ultra) ≥4 times daily for 6 months; dry eye symptomology, and tear film and ocular surface characteristics were assessed. Both treatments demonstrated sustained reduction in DED symptoms (Ocular Surface Disease Index [OSDI], Dry Eye Questionnaire-4 [DEQ-4], and Symptom Assessment Questionnaire in Dry Eye [SANDE] scores) from Day 30 onwards (all p≤0.01) and decreased superior lid wiper epitheliopathy grades from Day 60 onwards (all p≤0.01) (Table 2). Further, non-invasive tear film breakup time (NITBUT), and sodium fluorescein and lissamine green staining scores consistently improved from Day 120 onwards in both groups (all p<0.05). Tear film lipid layer grades increased only with PG-HPG nanoemulsion eye drops (from Day 90 onwards); with significantly greater improvement in patients with low lipid layer thickness at baseline (lipid layer grade ≤3; p=0.01). Hence, both lipid-based and non-lipid-based artificial tears provided symptom relief within a month. Improvements in the tear film stability and ocular surface characteristics were slower than the symptomatic improvements. Further, both formulations showed long-term efficacy and a good tolerability profile across DED subtypes; however, improvement in tear film lipid layer grade was observed only with PG-HPG nanoemulsion drops; particularly in subgroup of patients with evaporative DED due to tear lipid insufficiency (with baseline lipid layer grade

### Table 3 (Continued).

| Study Treatment | Outcome Parameters | Results |
|-----------------|--------------------|---------|
| PG-HPG nanoemulsion (Systane Complete) and HPG/HA eye drop (Systane Hydration) vs saline | Dry eye symptoms | Percentage of patients reporting dryness symptom improvement at 5 min after lens application: Dryness: 50% and 42% vs 0% Improvement in symptoms (estimate±standard error), p-value vs saline (negative statistics: less symptoms at a time point earlier than saline): Dryness: −1.69±0.58, p=0.005 and −1.13±0.56, p=0.049 fluctuation of vision: −1.50±0.57, p=0.011 and −0.15±0.56, p=0.78 Grittiness, burning, and stinging: −1.99±0.58, p=0.001 and −0.84±0.56, p=0.14 Foreign body sensation: −1.61±0.57, p=0.006 and −0.44±0.55, p=0.43 |

Abbreviations: AEs, adverse events; CLDEQ-4, contact lens dry eye questionnaire-4; CLDEQ-8, contact lens dry eye questionnaire-8; HA, hyaluronic acid; HPG, hydroxypropyl guar; PG, propylene glycol; SD, standard deviation; SPEED, standard patient evaluation of eye dryness questionnaire; VAS, visual analog scale.
In line with this study, data from previous clinical trials also demonstrated similar findings with PG-HPG nanoemulsion (Systane™ Complete) for the treatment of dry eye symptoms in all DED types. In a Phase IV, open-label, single-arm, multicenter trial, patients with DED (N=134; 56.6±14.8 years; 75.4% female) instilled one drop of PG-HPG nanoemulsion in each eye, twice daily for 28 days. The instillation of PG-HPG nanoemulsion eye drops increased tear film break-up time (TFBUT) by 1.5±2.8 seconds at 14 days; and the improvement remained consistent through 28 days (Table 2). It also improved (decreased) ocular discomfort at 14 days (mean±SD change in visual analog scale [VAS] score, −17.3±24.80). Moreover, subgroup analysis of patients with ADDE, EDE, and mixed DED indicated that PG-HPG nanoemulsion was effective and well tolerated in all three types of DED. PG-HPG nanoemulsion improved tear film stability, and signs and symptoms of DED.

The short-term effects of PG-HPG nanoemulsion were assessed by Silverstein et al. The study reported that a single drop of PG-HPG nanoemulsion provided immediate and sustained symptom relief up to 8 hours, and was well tolerated in all DED subtypes (Table 2). In the overall cohort, improvement in dry eye symptom scores (VAS) was observed as early as 0 hours and lasted until 8 hours after eye drop instillation on Day 1 (median change in symptom score from baseline [95% CI], −1.0 [−3.0, −1.0] at 0 hours, −2.0 [−3.0, −2.0] at 4 hours, and −2.0 [−2.0, −1.0] at 8 hours). A majority of patients (>80%) had a soothing sensation as early as 0 hours which persisted throughout 8 hours (median soothing sensation score on VAS, 3 at 0 hours, 3 at 4 hours, and 3.5 at 8 hours; range, 0–10). Subgroup analyses demonstrated improvements in dry eye symptom scores and soothing sensation scores, over 8 hours, in all dry eye subtypes (ADDE, EDE, and mixed DED) that were comparable to the overall cohort (Table 2). A majority of patients (>92%) had no or minimal symptoms of burning sensation, stinging sensation, blur and foreign body sensation on a tolerability assessment (Table 2). Overall, PG-HPG nanoemulsion lubricant eye drops were effective in the improvement of ocular symptoms and tear film stability, and well tolerated in DED patients, regardless of its types; provided prominent improvement of lipid layer grade in patients with EDE due to tear lipid insufficiency.

**PG-HPG Nanoemulsion Lubricant Eye Drops in Prophylactic Treatment of DED Under Environmental Conditions**

In a prospective, double-masked, contralateral, randomized cross-over trial (N=28; mean age, 29±9 years; 57% female), lipid-based (PG-HPG nanoemulsion; Systane™ Complete) and non-lipid-based (Systane™ Ultra) artificial tear drops were evaluated for their prophylactic benefits in a simulated adverse environment. Both eye drops improved the SANDE scores and NITBUT after instillation. After adverse environment exposure, the improvement in SANDE scores (p=0.006) and NITBUT (p=0.02) were significantly greater with lipid-based compared to non-lipid-based artificial tear drops (Table 2). Moreover, improvement in tear film lipid layer grades after adverse environment exposure was greater in patients treated with lipid-based artificial tear drops than those with non-lipid-based artificial tear drops (p<0.001). In this study, lipid containing PG-HPG nanoemulsion lubricant eye drops had superior prophylactic efficacy against adverse environment exposure in patients with DED.

**PG-HPG Nanoemulsion Lubricant Eye Drops in Treatment of DED with Low Lipid Layer Thickness**

A study by Weisenberger et al evaluated the effects of two eye drops (PG-HPG nanoemulsion and non-emollient) on lipid layer thickness (LLT) and dry eye symptoms. Part 1 was a double-masked, cross-over, randomized study in which diurnal effects of single-drop instillation were evaluated. This was followed by Part 2, an observational study, which assessed the effects of 1-month use of nanoemulsion eye drops in all subjects. Overall, 20 subjects (mean age, 45.6±7.9 years, 15 female) completed the study. Of this, 15 subjects with low baseline LLT (<50 nm) had a significant increase in LLT at 15 min after instillation of PG-HPG nanoemulsion eye drops (overall, 8.51±13.95, p=0.03 vs baseline; inferior third, 9.15±14.60, p=0.03 vs baseline); LLT values did not increase significantly with the non-emollient eye drops. In all subjects, both eye drops showed improvement (reduction) in ocular dryness up to 6 h after instillation (change in VAS scores [±SD] from baseline: PG-HPG nanoemulsion eye drops, 8.6±16.7 mm, p=0.03; non-emollient eye drops, 9.8±19.9, p=0.02). However, 1-month observational study revealed no significant improvement in LLT with 1-month use of PG-HPG nanoemulsion QID (4 times in a day). Further, significant improvement in dryness was observed even after 1-month QID use of PG-HPG nanoemulsion (change in VAS scores [±SD] from baseline to 1 month: 10.2±21.2;
PG-HPG Nanoemulsion Lubricant Eye Drops in Improvement of Contact Lens Discomfort

In a prospective, investigator-masked, 2-week, randomized clinical trial, 46 adult subjects (symptomatic Contact Lens Dry Eye Questionnaire-8 scores [CLDEQ-8 scores] ≥12) were recruited to evaluate PG-HPG nanoemulsion eye drops in treating contact lens discomfort. Subjects were randomized to either no treatment (n=24; mean age, 28.8±11.2 years; 20.8% female) or to PG-HPG nanoemulsion eye drops (before and after contact lens use; n=22; mean age, 32.7±13.1 years; 9.1% female). Clinical signs and symptoms at baseline and 2 weeks were assessed (Table 3). Subjects using PG-HPG nano-emulsion eye drops had significantly better symptom scores (CLDEQ-4, CLDEQ-8 and standard patient evaluation of eye dryness questionnaire [SPEED] scores) at 2 weeks compared to baseline (p<0.0001); whereas, symptoms did not differ significantly in the group without treatment (p>0.05). Moreover, CLDEQ-8 and CLDEQ-4 scores at 2 weeks were significantly better in subjects with PG-HPG nanoemulsion than those without treatment (12.86 ±6.40 vs 17.92±5.30, p=0.006; and 7.14±3.50 vs 10.13±2.83, p=0.005, respectively); SPEED scores at 2 weeks were similar between both groups (p=0.17). Clinical signs (such as NITBUT, corneal staining, and Schirmer’s test) were not significantly different at 2 weeks versus baseline in either group (all p>0.05). Similarly, at 2 weeks, clinical signs were not significantly different between the two groups (all p>0.05). Further, more subjects reported “better” perceived eye comfort at 2 weeks with PG-HPG nanoemulsion eye drops than those without treatment (59.09% vs 0.0%, p<0.001). These data suggest that PG-HPG nanoemulsion application before and after contact lens wear could be used to improve contact lens discomfort in symptomatic subjects who wear contact lenses.

Another prospective, 2-week, double-masked, randomized, clinical trial compared PG-HPG nanoemulsion (Systane™ Complete) vs rewetting drops (Sensitive Eyes®) vs no treatment in 73 participants (mean age, 30.3±11.5 years; 18% male) with contact lens discomfort and CLDEQ-8 scores ≥12. The study reported significant improvement in CLDEQ-8 scores at 2 weeks compared to baseline in both PG-HPG nanoemulsion and rewetting drops groups (6.0 ±6.3, p=0.0001 and 5.8±4.3, p<0.0001, respectively), but not in the control group (p=0.49). CLDEQ-8 scores at 2 weeks were similar between PG-HPG nanoemulsion and rewetting drops groups (p=0.94). End-of-day contact lens comfort just before removal of contact lens was also significantly better with both PG-HPG nanoemulsion and rewetting drops versus control group after 2 weeks (62.96±26.80 and 71.38±21.85 vs 40.29±31.07, group p=0.0004); comfort experienced by subjects was similar between PG-HPG nanoemulsion and rewetting drops (p=0.28). Moreover, no safety concerns were reported with PG-HPG nanoemulsion eye drops when instilled in the eyes before, during, and after daily disposable contact lens wear.

A very recent prospective, single-center, nondispensing, randomized, double-masked, three arm study evaluated filling solutions for the application of miniscleral contact lenses in participants (N=24; average age, 29.3±5.4 years; 13 female; 11 male). The study compared PG-HPG nanoemulsion (Systane™ Complete), HPG/HA eye drops (Systane™ Hydration), and no treatment (saline). Results demonstrated that PG-HPG nanoemulsion eye drop instillation in combination with non-preserved saline for application of miniscleral contact lenses during 6 hours of wear effectively improved subjective dryness (estimates±standard error [SE], −1.69±0.58, p=0.005); grittiness/burning/stinging (−1.99 ±0.58, p=0.001), and foreign body sensation (−1.61±0.57, p=0.006); and fluctuating vision (−1.50±0.57, p=0.011) compared to saline. Dryness symptoms improved faster with PG-HPG nanoemulsion and HPG/HA eye drops than saline, as indicated by higher percentage of patients reporting improvement in dryness at 5 min after lens application (50% vs 42% vs 0%). In this study, PG-HPG nanoemulsion eye drops (along with saline) were effective in improving various symptoms faster than saline, whereas HPG/HA eye drops only improved symptoms of dryness. Overall, PG-HPG nanoemulsion also improved ocular surface symptoms as indicated by a decrease in OSDI score from baseline to 1-month post-eye drop QID use (5.3 units, p=0.03). In this study, PG-HPG nanoemulsion was associated with short-term changes in LLT, with no effects sustained over 1 month of QID use. However, a study by Craig et al showed consistent improvement in tear film lipid layer grades from 90 days onwards with daily use of PG-HPG nanoemulsion. Moreover, a study by Muntz et al also demonstrated improvement in tear film lipid layer grades with the use of PG-HPG nanoemulsion eye drops, with the effect being sustained even after exposure to adverse environment. Overall, both single dose and sustained use of PG-HPG nanoemulsion eye drops demonstrated improvement in dry eye symptoms (Table 2).
HPG nanoemulsion lubricant eye drops improved subjective outcomes of symptoms and comfort, and was well tolerated in patients with daily contact lens wear.\textsuperscript{53–55}

Cumulatively, preclinical evidence showed that PG-HPG nanoemulsion lubricant eye drops provide better hydration retention and protection, greater cell viability, long-lasting lubrication, and ocular surface protection compared to other lipid-containing formulations (eg, Refresh Optive-Advanced, Soothe-XP) or microemulsion lubricant eye drops.\textsuperscript{24,48} Clinical evidence demonstrated that PG-HPG nanoemulsion lubricant eye drops were effective in the improvement of ocular symptoms and tear film stability, and well tolerated in subjects with DED, regardless of its subtypes (EDE, ADDE, and mixed DED).\textsuperscript{38,49,50} Additionally, PG-HPG nanoemulsion lubricant eye drops improved LLT, in subjects with low baseline LLT (<50 nm), compared to non-emollient lubricant eye drops.\textsuperscript{49,52} PG-HPG nanoemulsion lubricant eye drops also improved subjective outcomes of symptoms and comfort similar to rewetting drops (Sensitive Eyes\textsuperscript{®}), but better than other lubricant eye drops (Systane\textsuperscript{TM} Hydration)/saline, and was well tolerated in patients with daily contact lens wear.\textsuperscript{53–55}

Other lipid-based lubricant eye drops (including emulsions) have been reported to mimic the composition of the tear film, and provide ocular surface benefits to improve DED, particularly in subjects with EDE associated with MGD.\textsuperscript{12,56} Further, a systematic review reported that lipid-containing lubricants (liposomal lid sprays and lipid-containing eye drops) are effective in improving signs of dry eye.\textsuperscript{18} Preclinical evidence of liposome-based artificial tear formulations showed the potential to serve as a tear substitute by replenishing the tear film lipids, restoring the tear film, protecting corneal epithelium, and demonstrating good tolerance.\textsuperscript{12,57,58} A pilot clinical study in patients with mild-to-moderate DED reported that a new formulation of eye drops (combination of viscosity-enhancing HA, trehalose, and cationic liposomes containing stearyl amine and phospholipids) improved objective signs and subjective symptoms.\textsuperscript{59} However, there is a need for large-scale controlled clinical studies to obtain more robust evidence on the efficacy.\textsuperscript{59}

The limitations of this review need to be acknowledged. The scope of the literature search was limited in obtaining and presenting evidence of PG-HPG nanoemulsion lubricant eye drops since 2017. Further, there is a paucity of evidence showing head-to-head comparison of PG-HPG nanoemulsion lubricant eye drops with other lipid-based and/or liposome-based lubricant eye drops to infer comparative efficacy.

**Summary**

DED is a multifactorial condition with ADDE, EDE, and mixed etiologies. Artificial tears are the backbone in the management of DED. Lipid-based lubricant eye drops with viscoelastic characteristics are beneficial in providing temporary relief of dry eye symptoms. PG-HPG and borate components in PG-HPG nanoemulsion lubricant eye drops form a thin viscoelastic layer that prolongs retention of demulcent; thus, provides long-term surface hydration and moisture retention, and ocular surface protection by improving cell barrier functions and cell recovery, and temporary relief of symptoms in DED. Moreover, it provides tear film stability between and during blinks owing to viscoelastic properties of HPG. Further, PG-HPG nanoemulsion formulation helps to optimize ocular surface coverage of lipids that is beneficial in replenishing the tear film lipid layer. Additionally, PG-HPG nanoemulsion lubricant eye drops in the form of multidose preservative-free system (with Novelia\textsuperscript{®} bottles) is effective, convenient, and well tolerated in DED patients who have intolerance to preservatives with long-term eye drop use.

Clinically, PG-HPG nanoemulsion lubricant eye drops have been shown to improve dry eye symptoms, enhance tear film stability, and lipid layer thickness; hence, they help to restore eye surface health and provide symptom relief in patients with DED, regardless of subtypes. Moreover, PG-HPG nanoemulsion relieves ocular dryness and discomfort associated with daily contact lens wear, and in prophylactic treatment of dry eye against adverse environmental conditions. Conversely, other lipid-based and/or liposome-based lubricant eye drops, shown to mimic tear film composition, provide ocular surface benefits and improve signs of dry eye; however, large-scale controlled clinical studies are required to obtain more robust evidence on the efficacy.

With over a demi-decade of usage, PG-HPG nanoemulsion lubricant eye drops are effective, convenient to use, and well tolerated in DED, regardless of its subtypes.
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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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