

The Effectiveness of Systane PRO in providing relief from multiple symptoms of dry eye disease, and its impact on daily functioning and overall comfort in patients with mild to moderate dry eye disease.

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Study Summary

Title	The Effectiveness of Systane PRO in providing relief from multiple symptoms of dry eye disease, and its impact on daily functioning and overall comfort in patients with mild to moderate dry eye disease.
Protocol Number	GSNVI-SYSTANEPRO1
Methodology	Prospective, unmasked, single-center, single-arm interventional study.
Study Duration	12 Months
Study Center	Single-center
Objectives	To show that consistent use of Systane PRO will significantly improve the signs and symptoms of Dry Eye Disease in patients with mild-moderate DED.
Number of Subjects	30
Main Inclusion & Exclusion Criteria	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. Patients aged 18 and older with mild-moderate DED (as determined by an OSDI score between 13-22). <p>Exclusion:</p> <ol style="list-style-type: none"> 1. Patients unwilling to discontinue all concomitant ophthalmic medications and dry eye therapies for the duration of the study.
Study Product, Dose, Route, Regimen	IP: Systane PRO (Topical Ophthalmic) Regimen: 1gtt OU, QID
Duration of Subjects Participation	Three visits spread out over 30 days: Day 0 (Baseline), Day 7 (± 3 days), and Day 30 (± 7 days).
Reference Product	N/A

1. Introduction

1.1 Background:

Dry eye disease (DED) is a common, multifactorial disorder of the tear film and ocular surface, characterized by symptoms such as discomfort, visual disturbance, and tear film instability, often accompanied by inflammation and damage to the ocular surface. In the United States, approximately 16.4 million adults are estimated to be diagnosed with DED, approximately 6.8% of the population, with increased risk particularly affecting older adults (Farrand K et al, 2017). Additionally, DED can cause considerable impairment in quality of life, visual function, and daily activities (Uchino M, et al 2013). Key risk factors include aging, female gender, meibomian gland dysfunction, autoimmune conditions, and environmental exposures (Deo N, et al 2024). The primary therapeutic goals are symptom relief, ocular surface restoration, and stabilization of the tear film.

Artificial tears are the mainstay of treatment for mild to moderate DED. They act by supplementing the deficient tear film, improving ocular surface hydration, and providing symptomatic relief (Semp, DA et al 2023). While traditional formulations offer temporary benefit, many patients with mild to moderate DED experience persistent symptoms and ongoing ocular surface damage, highlighting an unmet need for more effective lubricants with durable protective effects (Karpecki PM, et al 2023). Systane PRO is a preservative-free, advanced lubricant formulation leveraging a unique combination of polymers to enhance tear film stability, extend surface protection, and promote epithelial healing.

1.2 Literature Review:

Numerous randomized clinical trials and observational studies have confirmed the effectiveness of artificial tears in improving both subjective and objective measures of DED. In 2017, Craig et al. concluded that artificial tears broadly improve DED symptoms, ocular staining, and tear film breakup time, regardless of their specific formulation, though molecular composition, including polymer type and preservatives, may influence the result between products. Previous studies on advanced lubricants have demonstrated that preservative-free artificial tears containing carboxymethylcellulose and hyaluronic acid significantly improve OSDI scores and ocular surface staining. Additionally, these preservative-free artificial tears were superior to their preservative-containing counterpart in reducing ocular discomfort and pain (Aragona et al., 2020).

Systane's hydroxypropyl guar/PEG/propylene glycol formulation has demonstrated efficacy in improving TBUT, corneal staining, and visual function (Labetoulle et al., 2017; Torkildsen, 2009). Additionally, in severe DED populations, Systane has been shown to significantly improve both subjective symptoms and signs of DED, as evaluated by OSDI and corneal fluorescein staining (Mocanu et al., 2011).

Regarding methods, validated questionnaires such as OSDI and SPEED are widely used to assess patient-reported outcomes, while objective measures like TBUT, corneal fluorescein staining, and BCVA are standard endpoints in both regulatory and clinical trial contexts (Schiffman et al., 2000; Ngo et al., 2013).

1.3 Unmet Medical Need:

Although artificial tears are widely used, current literature suggests many patients continue to suffer from mild to moderate symptoms, necessitating newer formulations. Systane PRO, with its preservative-free triple action formula, is hypothesized to offer good duration of action and symptom relief, yet there is limited clinical data to prove this in patients with mild to moderate DED. This study aims to evaluate clinical efficacy of Systane PRO in this population with objective clinical and subject patient endpoints.

2. Study Objectives

The primary objective of this study is to show that consistent use of Systane PRO over a 30 period will significantly improve the signs and symptoms of Dry Eye Disease and decrease patients' ocular surface disease index score for patients diagnosed with mild-moderate (DED).

3. Study Design

3.1 Methodology

30 eligible participants with mild-moderate dry eye disease (DED) will be enrolled based on predefined Inclusion/Exclusion criteria. All assessments are performed on Day 0, capturing the initial status of several subject-reported symptoms and clinical features of DED. Participants will then commence daily administration of Systane PRO, QID, will be reassessed after 30 days of continuous use. All initial assessments will be repeated on Day 30 to generate paired data for all subject-reported and clinical data. This paired design will minimize cross-subject variability and improve the statistical power of the study.

Subject-reported symptoms of DED will be assessed by: the Ocular Surface Disease Index (OSDI) questionnaire, the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, Visual Analog Scale (VAS) Questionnaires for Ocular Stinging and Grittiness, and the Work Productivity and Activity Impairment (WPAI) questionnaire for DED. These instruments provide comprehensive insight into patient experience, capturing frequency, severity, and the daily impact of symptoms.

Clinical measurements include: LogMAR-converted Best-Corrected Distance Visual Acuity (BCDVA), Corneal Fluorescein Staining (NEI Scale), and Tear Breakup Time

(TBUT). Collectively, these clinical measurements will serve as secondary endpoints for this study and will be used to corroborate any changes observed in the primary endpoint, change in OSDI score.

Additionally, a Manifest Refraction will be performed once at baseline to assess BCDVA, the same refraction will be used to assess BCDVA at Day 30. A Wratten-12 filter will be utilized for Corneal Fluorescein Staining Grading and Tear Breakup Time assessments to facilitate accurate visualization of the tear film.

At study completion, changes from baseline in both subjective and objective measures are systematically analyzed according to the Statistical Analysis Plan.

3.2 Study Endpoints:

The primary endpoint is a decrease in OSDI score from baseline to day 30. Secondary endpoints are an increase in Tear Breakup Time (TBUT), a decrease in Corneal Fluorescein Staining (NEI Scale), and a decrease in SPEED questionnaire scores (capturing ocular dryness, grittiness, scratchiness, irritation, burning, watering, soreness, and eye fatigue) from baseline to day 30. Exploratory endpoints include (1) a decrease in Work Productivity and Activity Impairment (WPAI) questionnaire, tailored for dry eye, score, (2) decrease in Visual Analog Scale score for ocular stinging, and (3) decrease in Visual Analog Scale score for ocular grittiness from baseline to day 30.

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Adults 18 years and older with an OSDI score rating 13-32 (mild to moderate)
2. Previous history of DED, clinician diagnosed, or patient reported, within the previous 3 months before the Screening visit.
3. Be willing and able to attend all study visits as required by protocol.

4.2 Exclusion Criteria

1. Significant underlying ocular or systemic disease that, in the opinion of the investigator, may interfere with study procedures or assessments.
2. Dry eye treatments in the past 6 months, such as Lipiflow, iLux, or IPL.
3. Use of artificial tears or any concomitant ophthalmic medications indicated for Dry eye disease within 30 days of screening or during study (with exception of drops in study design).
4. Use of any concomitant ophthalmic medications.

5. History of ocular surgery within 6 months before visit 1, including punctal cauterization, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision).
6. History of corneal transplantation in either eye.
7. Use of contact lenses in either eye within 7 days prior to visit 1 or planned use during the study.
8. Punctal or intracanalicular plug present in either eyelid at visit 1.
9. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days before visit 1, or if a change in dosage is anticipated during the study.

4.3 Subject Recruitment and Screening

Subjects will be recruited from the investigator's patient base. All subjects will be screened for suitability and interest in proceeding with all study exams and use of product. Following IRB approval, it is estimated that recruitment will take 3 months to complete. Any subject unwilling to proceed with the study will be terminated and replaced with a new subject.

4.4 Early Withdrawal of Subjects

Early withdrawal of subjects will be performed for any safety concerns, failure of subject to adhere to protocol requirements, subject withdrawal of consent, or disease progression necessitating intervention outside of the parameters of the study.

5 Study Product (IP)

5.1 Description

The study product, SYSTANE PRO PF, is the first and only multi-dose preservative-free triple action formula with hyaluronate. The addition of nano-sized lipids and HP-Guar to the formula help Propylene Glycol (the active ingredient) provide hydration and protection of the ocular surface. The unique formulation can also stabilize the lipid layer of the tear film to reduce tear evaporation.

5.2 Treatment/Dosing Regimen

Subjects will use Systane PRO QID for the duration of the study, except for Day 0 on which subjects will take up to four doses per eye. The first dose will be administered in-clinic by study staff, after which subjects will use Systane PRO QID, with doses spread throughout the day.

5.2 Randomization

IP will be dispensed to all eligible subjects, no randomization.

5.3 Compliance Monitoring

Subjects will be provided with an IP log (Diary) to track their daily compliance with the IP. Subject IP diaries will be checked at visits 2 and 3. Significantly non-compliant subjects will be exited from the study.

5.4 Accountability

All IP will be logged and stored in a secure, temperature controlled, location. An accountability log will be maintained to track all IP received and dispensed to subjects.

6 Study Procedures

Subjects' Dry Eye Disease will be examined and monitored with a number of separate approaches. Questionnaires will capture subjective disease state: OSDI, WPAI, SPEED, and VAS (Ocular Stinging and Grittiness) Questionnaires. Clinical assessments such as Tear Breakup Time, Corneal Fluorescein Staining grading, and slit lamp examination will be used to monitor the clinical signs of Dry Eye Disease. Best-corrected distance visual acuity (with manifest refraction at screening) will be assessed for safety.

6.1 Schedule of Assessments

Assessment	Screening Visit 1 (Day 0)	Visit 2 (Day 7)	Visit 3 (Day 28)
Informed Consent	X		
Medical & Ocular History	X		X
Questionnaires : OSDI, WPAI, SPEED, VAS (Ocular Stinging & Grittiness)	X		X
Tear Breakup Time	X		X
Corneal Fluorescein Staining	X		X
Slit Lamp Examination	X	X	X
Manifest Refraction	X		
ETDRS Distance VA (Best Corrected)	X	X	X
AE Assessment		X	X
IP Accountability	X	X	X

7 Statistical Analyses

7.1 Sample Size Justification

Based on a minimally clinically important difference in OSDI score of 4.5, and an estimated standard deviation in OSDI score of 10 points, we aim to enroll at minimum, 30 participants. All subjects will receive identical dosing instructions and be seen by the same providers for the duration of their participation in this study.

7.2 Statistical Methods

Statistical analysis will follow a hierarchical approach using the following order of testing, only proceeding to the next test if the prior test achieves statistical significance at a level of $\alpha=0.05$.

1. Primary Endpoint: change in OSDI score Baseline vs. Follow-up
2. Secondary Endpoint: change in SPEED score Baseline vs. Follow-up
3. Secondary Endpoint: change in Tear Break-up Time Baseline vs. Follow-up
4. Secondary Endpoint: change in Corneal Fluorescein Staining Score Baseline vs. Follow-up
5. Exploratory: change in WPAI score Baseline vs. Follow-up
6. Exploratory: change in Grittiness and Stinging VAS scores Baseline vs. Follow-up

7.3 Endpoint Analysis

7.3.1 Primary Endpoint

Change in OSDI Score will be analyzed with a Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change and the proportion of subjects with a ≥ 4.5 -point decrease in score will be reported.

7.3.2 Secondary Endpoint

Change in SPEED questionnaire score will be analyzed with the Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change and the proportion of subjects with a ≥ 4 -point decrease in score will be reported.

Change in Tear Breakup Time will be analyzed with the Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change and the proportion of subjects with a ≥ 1 second increase in tear film stability will be reported.

Change in Corneal Fluorescein Staining will be analyzed with the Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change and the proportion of subjects with a ≥ 1 point decrease in corneal staining will be reported.

7.3.3 Exploratory Endpoint

Change in VAS scores for both ocular stinging and grittiness will be analyzed with the Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change and the proportion of subjects with a ≥ 20 mm decrease in score will be reported. Change in WPAI score for Dry Eye Disease will be analyzed with the Wilcoxon signed-rank test comparing Baseline vs. Follow-up. Median change, individual

domain improvements, as well as the proportion of subjects with a ≥ 4 -point decrease in score will be reported.

8 Safety and Adverse Events

8.1 Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject who was administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal IP, whether related to the IP.

If any concerning or abnormal results are identified during the eye exam conducted as part of this research study, the participant will be promptly notified. A qualified member of the research team, typically the study doctor, will contact the participant directly, either in person, by phone, or in writing, depending on the urgency and nature of the findings.

Participants will be informed in clear, understandable terms about the nature of the findings, their potential implications, and recommended next steps. While the study team does not provide medical treatment, participants will be advised to seek further evaluation or care from their primary eye care provider or another appropriate healthcare professional. If needed, the study team can offer referrals or assistance in locating appropriate follow-up care.

8.2 Recording and Reporting Adverse Events

The study team is responsible for notifying the appropriate authorities of Reportable Events (serious adverse events, pregnancy reports) within 24 hours of learning of the event. It is our mission to protect the health and safety of patients using any of the products in our study.

8.3 Stopping Rules

In the event that there are multiple severe adverse events or any serious adverse events occur throughout the conduct of the study, investigators will assess whether stoppage of the clinical trial is warranted. Any adverse events that may impair a patient's vision will be considered for immediate termination of the study and reported. Minor adverse events, and adverse events that cannot be reasonably attributed to the IP or study procedures will be noted and subjects will be allowed to continue in the study contingent on participants' continued consent and investigator's discretion. Should there be unforeseen challenges or amendments to the study protocol, the trial may be stopped or modified to accommodate these changes.

8.4 Medical Monitoring

The investigators of this clinical trial will serve as the medical monitors for this study, overseeing all adverse events.

9 Risks and Benefits

9.1 Risks of Study Product and Procedures

The primary risk associated with study participation is the potential for allergic reaction to the study product, or to topical ophthalmic fluorescein used in the study procedures (3.1, 5.1, 6). Additional potential side effects of the study product include:

- Temporary blurred vision
- Mild eye irritation
- Light sensitivity
- Itchiness and redness
- Eyelid swelling or watering

Additional risks of topical ophthalmic fluorescein include:

- Temporary ocular surface and skin discoloration
- Eye irritation
- Temporary blurred vision

9.2 Risks to Subject Privacy

There is a risk of loss of confidentiality of subject information. The site will take adequate measures to minimize this risk by safeguarding all documents associated with subject and the study and by using a unique, anonymized, subject identifying number for each subject.

9.3 Potential Benefits of Participation

Subjects enrolled in this study may experience an improvement in the clinical signs and symptoms of their dry eye disease.

10 Data Handling and Record Keeping

All personal and medical information collected from participants will be kept confidential and stored securely. Information will only be accessible to the study team members directly involved in the trial. Access to the study data will be restricted to authorized personnel only. The study team will have a designated file storage system where all data will be securely stored. Participants' identities will be kept anonymous and assigned a unique identification code. This code will be used to track their progress throughout the trial. Any data shared with external organizations or individuals will be de-identified to ensure that patient confidentiality is maintained.

10.1 Source Documentation

The following documents are defined as source documents for this study:

Informed Consent Documentation.

Case Report Forms

Medical Records

Adverse Event Reports

10.2 Records Retention

All study records will be retained for a minimum of 7 years after the completion of the study or termination of the study, in accordance with applicable regulatory requirements. The PI and the sponsor are responsible for ensuring that all study records are retained in accordance with this protocol. All study records will be stored securely in a locked cabinet or a password-protected electronic system to prevent unauthorized access or loss. Study records will be made available to regulatory authorities upon request, and the Sponsor and PI will retain access to the study records for the duration of the retention period. At the end of the retention period, study records will be destroyed in a manner that maintains participant confidentiality and privacy.

11 Study Monitoring, Auditing, and Inspection

The study monitoring team will be composed of the PI and designated study staff. The team will be responsible for monitoring the study progress, identifying, and resolving issues, and reporting to the Institutional Review Board (IRB) and other regulatory authorities. The study monitoring team will review the study data on an ongoing basis to ensure accuracy, completeness, and timeliness. This will include reviewing case report forms (CRFs) and adverse event reports. The study monitoring team will monitor and review all adverse events reported during the study to ensure that they are being appropriately documented, reported, and managed. The study monitoring team will review all protocol deviations and violations to ensure that they are appropriately reported and managed. The study monitoring team will monitor compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulations. This will include reviewing the Investigator Site File (ISF) and ensuring that all required study documentation is maintained and up to date. The study monitoring team will conduct quality control activities to ensure that the study is being conducted to the highest standards. This will include reviewing the study monitoring plan, SOPs, and other study-related documents. Regular reports will be provided to the PI, IRB, and other regulatory authorities as required.

12 References

1. Aragona P, Rolando M, Rania L, et al. Safety and efficacy of preservative-free artificial tears containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized controlled trial. *BMC Ophthalmol.* 2020;20(1):63.
2. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II: Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628.
3. Deo N, Nagrale P. Dry Eye Disease: An Overview of Its Risk Factors, Diagnosis, and Prevalence by Age, Sex, and Race. *Cureus.* 2024 Feb 11;16(2):e54028. doi: 10.7759/cureus.54028. PMID: 38481927; PMCID: PMC10934010.
4. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of Diagnosed Dry Eye Disease in the United States Among Adults Aged 18 Years and Older. *Am J Ophthalmol.* 2017 Oct;182:90-98. doi: 10.1016/j.ajo.2017.06.033. Epub 2017 Jul 10. PMID: 28705660.
5. Karpecki PM, Nichols KK, Sheppard JD. Addressing excessive evaporation: an unmet need in dry eye disease. *Am J Manag Care.* 2023 Oct;29(13 Suppl):S239-S247. doi: 10.37765/ajmc.2023.89448. PMID: 37844320.
6. Labetoulle M, Rolando M, Baudouin C, et al. Hydroxypropyl Guar/Polyethylene Glycol/Propylene Glycol-Based Tear Supplementation in Patients With Dry Eye Disease: A Randomized, Controlled Study. *Adv Ther.* 2017;34(9):2152-2164.
7. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, Asbell PA, Pflugfelder SC. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol.* 2010 Jan;128(1):94-101. doi: 10.1001/archophthalmol.2009.356. PMID: 20065224.
8. Mocanu C, Mălăescu M, et al. Effect of Systane in the Treatment of Severe Dry Eye. *Oftalmologia.* 2011;55(3):46-51.
9. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the Standard Patient Evaluation of Eye Dryness questionnaire. *Cornea.* 2013;32(9):1204-1210.
10. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and Validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118(5):615-621.
11. Semp DA, Beeson D, Sheppard AL, Dutta D, Wolffsohn JS. Artificial Tears: A Systematic Review. *Clin Optom (Auckl).* 2023 Jan 10;15:9-27. doi: 10.2147/OPTO.S350185. PMID: 36647552; PMCID: PMC9840372.
12. Torkildsen G. The Effects of Recurring Instillation of an Artificial Tear Solution with Hydroxypropyl Guar Compared with a Controlled Saline Placebo: A Multicenter, Double-Masked, Randomized Controlled Study. *Clin Ther.* 2009;31(7):1577-1587.
13. Uchino M, Schaumberg DA. Dry Eye Disease: Impact on Quality of Life and Vision. *Curr Ophthalmol Rep.* 2013 Jun;1(2):51-57. doi: 10.1007/s40135-013-0009-1. PMID: 23710423; PMCID: PMC3660735.