COVER PAGE

Artificial Tears, Tear Lipids and Tear Film Dynamics

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STUDY PROTOCOL

Effects Of Artificial Tears on Tear Lipid Films and Tear Film Dynamics *In Vivo*

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I. INTRODUCTION & RATIONALE

Dry eye disease (DED) is pervasive with some reports estimating over 16 million adults diagnosed with DED in the United States.[1] Currently, artificial tears remain an integral part of managing dry eyes and are mainly used for symptomatic relief. Recent studies have shown there may be therapeutic benefits with regular use of lipid based artificial tears to improve the structure of the tear film.[2,3,4] Lipid based artificial tears have been shown to increase lipid layer thickness and improve tear film breakup time in addition to providing subjective improvements of dry eye symptoms.[2,3,4] The ability to increase lipid layer thickness and improve tear film stability could possibly reduce evaporative dry eye disease. In this study we propose to recruit a large group of subjects spanning a range of ages and ethnicities and administer three lipid based artificial tears against a non-lipid based artificial tear to compare their effects on the subject's tear lipid film and tear film dynamics.

II. SPECIFIC AIMS

We plan to accomplish our goals by pursuing the following specific aims and testing the associated hypotheses:

Aim 1 (Primary): Determine if the change in lipid layer thickness at 3 months compared to post-run-in baseline is different between Systane Complete PF and Refresh Relieva PF

Hypothesis: The change in tear lipid layer thickness will be significantly greater with Systane Complete PF compared to Refresh Relieva PF.

Aim 2 (Exploratory): Compare the 3-month changes in tear lipid layer uniformity and tear film thinning dynamics between the Systane Complete PF and Refresh Relieva PF

Hypothesis: The 3-month change in lipid layer uniformity will be significantly better with Systane Complete PF compared to Refresh Relieva.

Hypothesis: The 3-month change in tear film dynamics will be significantly better with Systane Complete PF compared to Refresh Relieva.

Aim 3 (Exploratory): Compare the 3-month changes in tear lipid layer thickness between the Systane Complete PF and the other two lipid products (Refresh Optive Mega-3 PF, CVS Health Lubricant Eye Drop (PG 0.6%))

Hypothesis: The 3-month change in tear lipid layer thickness will be significantly greater with Systane Complete PF compared to the other lipid-containing products.

Aim 4 (Exploratory): Compare the 3-month changes in tear lipid layer uniformity and tear film thinning dynamics between the Systane Complete PF and the other two lipid products (Refresh Optive Mega-3 PF, CVS Health Lubricant Eye Drop (PG 0.6%))

Hypothesis: The 3-month change in lipid layer uniformity will be significantly greater with Systane Complete PF compared to the other lipid-containing products.

Hypothesis: The 3-month change in lipid layer uniformity and tear film dynamics will be significantly greater with Systane Complete PF compared to the other lipid-containing products.

Aim 5 (Exploratory): Compare the 3-month changes in symptoms between the Systane Complete PF and the other two products (Refresh Relieva PF, Refresh Optive Mega-3 PF, CVS Health Lubricant Eye Drop (PG 0.6%))

Hypothesis: The 3-month change in symptoms will be significantly greater with Systane Complete PF compared to the other products.

III. STUDY DESIGN

Subjects

A total of 84 subjects will complete the study with 21 subjects in each study arm. This four-visit study will be conducted at the University of California Berkeley, School of Optometry, Clinical Research Center (Berkeley, CA, USA). Subjects will be recruited via email and fliers. Subjects will be screened prior to the study visit with an IRB approved phone screening survey.

Inclusion Criteria

- Adult (≥18 years) subjects who have a best corrected visual acuity of 20/30 or better
- Have symptoms of dry eye (OSDI ≥ 13)

Exclusion Criteria

- Currently using any topical eye medication (not including OTC drops)
- Have known systemic health conditions that might alter tear film physiology, have a history of viral eye disease, have a history of diabetes, have a history of ocular surgery, have a history of severe ocular trauma, have an active ocular infection or inflammation, are currently using isotretinoin-derivatives, or if pregnant or breast feeding
- Contact lens wearers
- Subjects with a condition or in a situation, which in the examiner's opinion, may put the subject at significant risk, may confound the study results, or may significantly interfere with their participation in the study will be excluded.

Trial Design

This will be a prospective, double-masked, randomized, controlled, parallel-group study designed to compare the impact of Systane Complete PF artificial tears on tear lipid layer thickness compared with a control, Refresh Relieva PF. Secondarily, the study will compare the differences in changes in tear lipid layer thickness, lipid layer uniformity, tear film thinning dynamics, and symptoms between Systane Complete PF and other study products (Refresh Optive Mega-3 PF and CVS Health Lubricant Eye Drop (PG 0.6%)). The study will include 4 clinic visits, including one week of single-masked run-in with Systane Ultra PF followed by 3 months of study treatment dosing. Participants will be asked to instill drops QID, regardless of assigned drops, throughout the study period.

Visit Schedule will be as follows:

Outcomes

Primary: Mean change from post-run-in baseline at 3 months in tear lipid layer thickness (Systane Complete PF vs Refresh Relieva PF)

Secondary:

- Mean change from post-run-in baseline at 3 months in tear lipid layer uniformity (Systane Complete PF vs Refresh Relieva PF)
- Mean change from post-run-in baseline at 3 months in tear film thinning rate (Systane Complete PF vs Refresh Relieva PF)

Exploratory:

- Mean change from post-run-in baseline at 1 and 3 months in tear lipid layer thickness (Systane Complete PF vs all lipid drops)
- Mean change from post-run-in baseline at 1 and 3 months in tear lipid layer uniformity (Systane Complete PF vs all lipid drops)
- Mean change from post-run-in baseline at 1 and 3 months in tear film thinning rate (Systane Complete PF vs all lipid drops)
- Mean change from post-run-in baseline at 1 and 3 months in symptoms (Systane Complete PF vs all lipid drops)

Sample Size

The primary outcome of this study will be the difference in mean 3-month change in tear lipid layer thickness between Systane Complete PF and Refresh Relieva PF. Fogt and colleagues were able to establish statistical significance in the differences in short-term (15 min) change from baseline in tear lipid layer thickness when comparing a lipid-emulsion to non-emulsion in two separate studies with 20 subjects (10 subjects/arm).[3, 4] In this study we are implementing a complete 3-month treatment regimen, and additionally will increase the target sample size to N=84 (4 study arms, 21 subjects/arm), and therefore can be reasonably assured of having sufficient statistical power to detect any treatment-control differences that may present.

Surveys and Clinical Tests

Clinical measurements will be obtained from both eyes of each subject and testing will be performed in the below order. Testing order was designed to sequentially administer the least invasive to most invasive test. This methodology will ensure that a previous procedure will have a minimal effect on subsequent assessments

Study Visit

A. <u>Baseline/Screening Visit</u>

(Visit 1A)
1. Subject History, Eligibility, Informed Consent: Subjects will be asked to repeat the IRB approved screening survey at the study visit to verify that they are still eligible for the study. Non-eligible subjects will be dismissed or rescheduled depending upon the reason for ineligibility. Eligible subjects will be enrolled, consented, and requested to sign a privacy document.

2. Baseline Questionnaires: Subjects demographics, lifestyle, ocular and medical history will be collected. They will be asked to complete the PSQ, Likert, DEFC, SPEED II, OSDI, VAS, SANDE, and DEQ-5 questionnaires to determine baseline comfort.

(Visit 1B)

1. Baseline Visual Acuity: The subject's habitual visual acuity will be measured.

2. Tear Lipid Layer Thickness and Blinks: The Lipiview interferometer will be used to determine the subject's tear lipid layer thickness and blinks.

3. Tear Meniscus Height, Ocular Redness, and Keratometry: The Oculus Keratograph 5M will be used to determine the tear meniscus height, redness, and curvature of the eyes.

4. Non-Invasive Tear Breakup Time (NITBUT): The Oculus Keratograph 5M and Medmont Topographer will be used to determine NITBUT with the machine's standard software by taking one to three successive measurements.

5. Slit-Lamp Biomicroscopy: The investigator will use a slit-lamp biomicroscope to document normal and/or remarkable findings of the anterior eye structures: eyelashes (blepharitis), eyelids, conjunctiva, and cornea.

6. Fluorescein Tear Breakup Time (FTBUT): The investigator will instill 1 µl of 1% w/v of sodium fluorescein by pipette and take 3 successive measurements for each eye.

7. Slit Lamp Recordings with EasyTear View: Capture videos with diffuse white light and cobalt blue light to analyze tear film lipids (thickness and uniformity) and tear film thinning dynamics.

8. Schirmer's Test: Investigator will use a modified technique[3] for aqueous tear production rate measurement.

9. Meibomian Gland Expression: The investigator will use the Korb Meibomian gland expressor to apply pressure along both the upper and lower eyelids and score gland secretion quality on central/nasal/temporal regions of each lid (i.e., ~5 glands in each region) with scores ranging from 0-3 (0=no secretion, 1=inspissated, 2=cloudy, 3=clear), such that each lid will have a maximum score of 45.

10. Lissamine Green Evaluation: The investigator will evaluate the quality of the front surface of the eyes by instilling a small amount of lissamine green ophthalmic dye.

11. Meibography: The Oculus Keratograph 5M will be used to image the tear glands (e.g., Meibomian glands) of the upper and lower eyelids.

12. Dispense Run-In Drops and Instructions: Investigators will dispense one week's worth of Systane Ultra PF (label removed) to all qualified, enrolled subjects and instruct them to instill drops 4 times daily for one week. Patients are then scheduled for their next visit at least 90 minutes after their planned last dose.

B. Visit 2: Post-Run-In Period, Randomization, Treatment

1. Subject History: Subjects will be asked to confirm any changes to medical or ocular history.

2. Questionnaires: Subjects will be asked to complete an abbreviated questionnaire package to determine comfort.

3. Visual Acuity: The subject's habitual visual acuity will be measured.

4. Tear Lipid Layer Thickness and Blinks: The Lipiview interferometer will be used to re-assess the subject's tear lipid layer thickness and blinks.

5. Tear Meniscus Height, Ocular Redness, and Keratometry: The Oculus Keratograph 5M will be used to determine the tear meniscus height, redness, and curvature of the eyes.

6. Non-Invasive Tear Breakup Time (NITBUT): The Oculus Keratograph 5M will be used to determine NITBUT with the machine's standard software by taking three successive measurements.

7. Slit-Lamp Biomicroscopy: The investigator will use a slit-lamp biomicroscope to document normal and/or remarkable findings of the anterior eye structures: eyelashes (blepharitis), eyelids, conjunctiva, and cornea.

8. Fluorescein Tear Breakup Time (FTBUT): The investigator will instill 1 µl of 1% w/v of sodium fluorescein by pipette and take 3 successive measurements for each eye.

9. Slit Lamp Recordings with EasyTear View: Capture videos with diffuse white light and cobalt blue light to analyze tear film lipids (thickness and uniformity) and tear film thinning dynamics.

10. Confocal Microscope: The confocal microscope will be used to examine anatomy and physiology of the front surface of the eyes.

11. Randomize, Dispense Study Drops, and Instructions: Subjects will be randomized to one of four study drops (Refresh Relieva PF, Systane Complete PF, Refresh Optive Mega-3 PF, or CVS Health Lubricant Eye Drop (PG 0.6%)). Investigators will dispense a 1-month supply of the assigned study drops and provide instructions to instill drops 4 times daily for 3 months. Patients are then scheduled for their 1-month follow-up visit, ensuring visit is scheduled at least 90 minutes after their planned last dose.

C. Visit 3: One Month Follow-Up

1. Repeat measurements (Part B) 1-9 and 11 from baseline visit.

2. Dispense study drops. The investigator will dispense drops for the next two months and schedule the follow-up phone call at 2 months and the final visit at 3 months.

D. Phone Call: Two Month Follow-Up

1. Subject History: Subjects will be asked to confirm any changes to medical or ocular history.

2. Follow-up to ensure no changes in habitual regimen, protocol is being followed, supply of drops is adequate to reach the end of the study.

3. Questionnaires: Subjects will be asked to complete an abbreviated questionnaire package to determine comfort.

E. Visit 4: Three Month Follow-Up

1. Repeat measurements (Part B) 1-10 from baseline visit.

2. Exit Visual Acuity: The subject's habitual visual acuity will be measured.

3. Study Completion: Subjects will be compensated for their time and exited from the study.

F. Schedule of Study Procedures and Assessments

Procedure/Assessment	Visit 1	Visit 2	Visit 3	Phone Call	Visit 4
Inclusion/Exclusion	✓				
Informed Consent	✓				
Demographics	✓				
Medical and Ocular History	✓	✓	✓	✓	✓
PSQ, Likert, DEFC, SPEED II, OSDI, VAS, SANDE, & DEQ-5	✓	✓	✓	✓	✓
Randomization		✓			
Visual Acuity	✓	✓	✓		✓
Tear Lipid Layer Thickness and Blinks	✓	✓	✓		✓

Tear Meniscus Height, Ocular Redness and Keratometry	✓	✓	✓		✓
Non-Invasive Tear Breakup Time	✓	✓	✓		✓
Slit-Lamp Exam	✓	✓	✓		✓
Fluorescein Tear Breakup Time	✓	✓	✓		✓
Easy TearView Recordings	✓	✓	✓		✓
Schirmer's Test	✓		✓		✓
Meibomian Gland Expression	✓				✓
Lissamine Green Evaluation	✓				
Meibography	✓				
Confocal Microscope		✓			✓
Adverse Events		✓	✓	✓	✓
Exit					✓

Data Analysis

Primary Model (Aim 1):

- The primary outcome of tear lipid layer thickness (LipiView) change from post-run-in baseline to 3 months will be analyzed using a repeated measures mixed effects model. This modeling approach will produce an unbiased estimate of the treatment effects (Systane Complete PF vs. Refresh Relieva PF), while accounting for the internal correlations engendered by the repeated measures study design (repeat visits, two eyes per subject).

Additional Analyses (Aims 2-5, Exploratory):

- The same modeling approach will be employed to analyze the changes from post-run-in baseline to 3 months in tear lipid layer uniformity and in tear thinning time between the Treatment (Systane Complete PF) and Control (Refresh Relieva PF) solutions.
- The same modeling approach will be employed to analyze changes from post-run-in baseline to 3 months in lipid layer thickness and uniformity, tear thinning time, and symptom scores among 3 solutions (Systane Complete PF, Refresh Optive Mega-3 PF, CVS Health Lubricant Eye Drop (PG 0.6%)).
- Additional exploratory modeling for all outcomes will be performed to determine the impact of baseline subject characteristics including demographics, visual acuity, tear film stability (NITBUT and FTBUT), tear production (Schirmers), and any ocular surface findings.
- Exploratory models will be assessed by F-test p-values, residual and other diagnostic plots, fit statistics such as the log-likelihood and the AIC, and clinical relevance of effect sizes. Both additive and interaction models will be examined.
- All study variables will also be subjected to a thorough descriptive analysis, in order to better understand the modeling results and the relationships among the model variables. This analysis will include descriptive statistics (minimum, maximum, median, mean, SD), histograms of the distributions of continuous variables (including lipid layer thickness and coefficient of variation, tear thinning rate, non-invasive and fluorescein tear breakup times, modified Schirmer strip wetted lengths and tear production rate, and symptom questionnaire scores), and tabulations of ordinal and categorical variables (including clinical grades of the anterior eye structures cornea, conjunctiva, eyelids and lashes).
- Additional exploratory analyses will examine the basic univariate relationships between the model outcome variables and potential explanatory variables via box-and-whisker plots, scatterplots, and simple linear regressions / t-tests / univariate ANOVA models (as appropriate for the data types).

IV. Study Timeline

	2022	2022	2022	2023	2023	2023	2023	2023	2023	2023	2023
	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July	Aug
Activity											
Contracting											
IRB Preparation											
Data Collection											
Data Analysis											
Final Study Report											

VI. Publication Plans

An abstract describing the comparison of tear film lipid layer between Systane Complete and Refresh Relieva will be submitted for presentation at American Academy of Optometry 2023. A manuscript describing the initial drop experience and drop comfort data will be submitted to *Optometry and Vision Science or Contact Lens and Anterior Eye or Eye and Contact Lens, or Scientific Reports.*

References

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