Supplementation with HydroEye® as a Treatment for Contact Lens Discomfort

Study Protocol & Statistical Analysis Plan

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I. BACKGROUND

An estimated 40.9 million people in the United States aged 18 or older wear contact lenses.[1] While newer and healthier contact lens materials are constantly being developed, discomfort remains the top reason for contact lens discontinuation, and dropout rates are estimated to be as high as 15.9% in the United States.[2] The Report of the International Workshop on Contact Lens Discomfort stated in 2013 that dryness is a primary reason for contact lens intolerance.[3] Indeed, when a contact lens is placed on the eye, the tear film structure becomes altered resulting in a pre-lens thinned lipid layer and a post-lens thinned aqueous layer.[4] As a result of this disruption from the contact lens, the tear film tends to have an increased rate of evaporation leading to poor wetting on the surface of the contact lens and inadequate lubrication on the surface of the eye. Because of these ocular surface dynamics, contact lens wear has been cited as one of several initiating factors that can induce dry eye disease.[5]

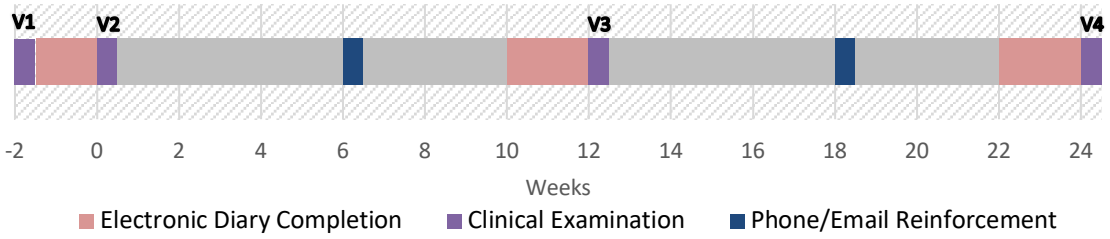
According to the 2007 Report of the Dry Eye Workshop,[5] dry eye disease is a multifactorial disease of the tears and ocular surface. Inflammation is a core component of its pathophysiology, and the presence of inflammatory biomarkers in the tear film has been reported extensively in the literature.[6-8] To combat this inflammation, many therapeutic options intervene in the inflammatory cascade. One such anti-inflammatory option is the use of omega fatty acids. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated omega-3 fatty acids that have been linked to reduction of many inflammatory cytokines, including prostaglandin E_2.[9-11] Gamma-linolenic acid (GLA), an omega-6 fatty acid, has also demonstrated anti-inflammatory activity and improvement in the signs and symptoms of dry eye disease, alone or when combined with EPA and DHA in fish oil.[12] A comprehensive review of the use of omegas in dry eye has recently been published.[13]

HydroEye® is a dietary supplement that contains the fatty acid, GLA from black currant seed oil, as well as the fatty acids EPA and DHA from fish oil. It also includes vitamins A, E, C, B6, and magnesium and other nutrients, many of which are involved in fatty acid metabolism. In 2013, Sheppard et al. tested HydroEye® in dry eye patients who were not contact lens wearers and found symptom improvement, lower levels of inflammatory biomarkers and a smoother corneal surface compared with placebo..[14] To date, HydroEye® has not been assessed in patients with contact lens discomfort; therefore, the purpose of this clinical trial is to determine the efficacy of a revised HydroEye® formulation (see Appendix) as a treatment for contact lens discomfort.

II. STUDY DESIGN

A. Overview and analysis plan

The proposed research study is a randomized, double-masked, controlled clinical trial to test the efficacy of HydroEye® nutraceutical in subjects with contact lens discomfort. Forty-two subjects will be recruited and randomized in a 1:1 ratio of HydroEye® to placebo. The trial will span 26 weeks, consisting of four clinical visits, two phone encounters to reinforce study drug compliance (investigator will ask about supplement usage and will ask subject contact lens survey question), and three two-week intervals of subject-entered, electronic data collection in the form of a daily diary (Figure 1). Visit 1 (V1) is the Screening Visit to ensure that patients meet all inclusion and exclusion criteria. For two weeks following V1, subjects will complete daily diary entries using Qualtrics Research Suite to assess their daily symptoms and comfortable contact lens wear time. V2 is the Baseline Visit and will occur two weeks after V1. If a subject meets all inclusion and exclusion criteria through V2, then randomization will occur, and study product will be dispensed. Six weeks after V2, staff will call and email the subject to reinforce the importance of study product compliance. V3 will occur at 3 months from V2. All clinical testing will be identical except that previous study product will be collected and new product will be dispensed. Again, phone and email reinforcement will occur 6 weeks after V3, and V4 will occur 3 months after V3. At the conclusion of the clinical trial, significant knowledge will be gained regarding the clinical utility of HydroEye® in patients with contact lens discomfort.



Testing to be performed at each clinical visit:

	Visit 1 Screening Visit	**Visit 2 Baseline Visit**	**Visit 3 3 months**	**Visit 4 6 months**
Informed consent	X			
Ocular and medical history, including contact lens wear history	X	X	X	X
CLDEQ-8 Questionnaire	X	X	X	X
SPEED Questionnaire	X	X	X	X
NPSI Questionnaire	X	X	X	X
Visual acuity	X	X	X	X
Slit lamp examination	X	X	X	X
Capillary tear collection	X	X	X	X
Tear break-up time		X	X	X
Corneal staining		X	X	X
Conjunctival and lid wiper staining		X	X	X

Schirmer's I Test	X	X	X	X
Meibography with Oculus Keratograph	X			
Study drug or placebo dispense	X	X	X	
Study drug collection		X	X	X
Expected Duration	45 mins	60 mins	60 mins	60 mins

B. Sample Size and Analysis

LTB_4 values will serve as a primary biological outcome for judging if HydroEye® is able to improve ocular surface health. Work from Masoudi et al. suggests that LTB_4 is significantly different between symptomatic (0.32 ± 0.06 ng/mL) and asymptomatic (0.17 ± 0.04 ng/mL) contact lens wearers. A 0.06 ng/mL difference (equivalent to one standard deviation) in in LTB4 concentration will be considered a meaningful improvement in LTB_4 concentration. Thus, 16 subjects per group will be needed to determine if there is no difference in LTB_4 concentration between groups at the final outcome visit (power = 80%; alpha = 0.05). After adjusting for 10% dropout, a total sample size of 36 subjects will be needed to determine if there is a statistical difference between subject groups.

CLDEQ-4 scores (Rasch validated version; max score of 18) will serve as the primary outcome for judging if HydroEye® is able significantly improve contact lens comfort.[27] Data from Pucker et al. suggests that the average contact lens wearer has a mean CLDEQ-4 score of 7.6 ± 3.8.[27] A 4-point difference in CLDEQ-4 scores will be considered a meaningful improvement in CL comfort. Therefore, 19 subjects per group will be needed to determine if there is no difference in contact lens comfort between the two groups at the final outcome visit (power = 90%; alpha = 0.05). After adjusting for 10% dropout and subject withdrawals, a total sample size of 42 subjects will be needed to determine if there is a statistical difference in contact lens comfort scores between subject groups. Since the sample size based upon CLDEQ-4 is larger, 42 subjects will be recruited.

An additional 10 subjects are being requested to account screen fails, and 8 more subjects are being requested for assay protocol development. Therefore, this study is requesting a maximum of 60 subjects. If additional subjects are not needed to account for screen fails, recruitment will be stopped accordingly.

Baseline data of the active and placebo groups will be analyzed at study completion. Primary and all secondary outcomes will be compared to baseline and between groups. SPSS will be used for all analysis.

C. Objectives

CO-PRIMARY OBJECTIVE

To assess changes in comfortable contact lens wear time and subjective symptom severity (CLDEQ-4) in response to HydroEye® supplementation in those who experience contact lens discomfort

SECONDARY OBJECTIVE

To assess changes in LTB_4 levels in response to HydroEye® supplementation in those who experience contact lens discomfort

D. Endpoints

CO-PRIMARY ENDPOINTS

Mean change in the difference between overall wear time and comfortable wear time at 6 months

Mean change in CLDEQ-4 scores at 6 months

SECONDARY ENDPOINTS

Mean change in LTB_4 levels at 6 months

Mean change in SPEED scores at 6 months

Mean change in NPSI scores at 6 months

Mean change in TBUT at 6 months

Mean change in Schirmer I at 6 months

Mean change in corneal staining at 6 months

Mean change in conjunctival staining at 6 months

Mean change in lid wiper epitheliopathy at 6 months

Mean change in tear cytokine levels (RayBiotech Human Inflammation Array Q3) at 6 months

E. Inclusion Criteria

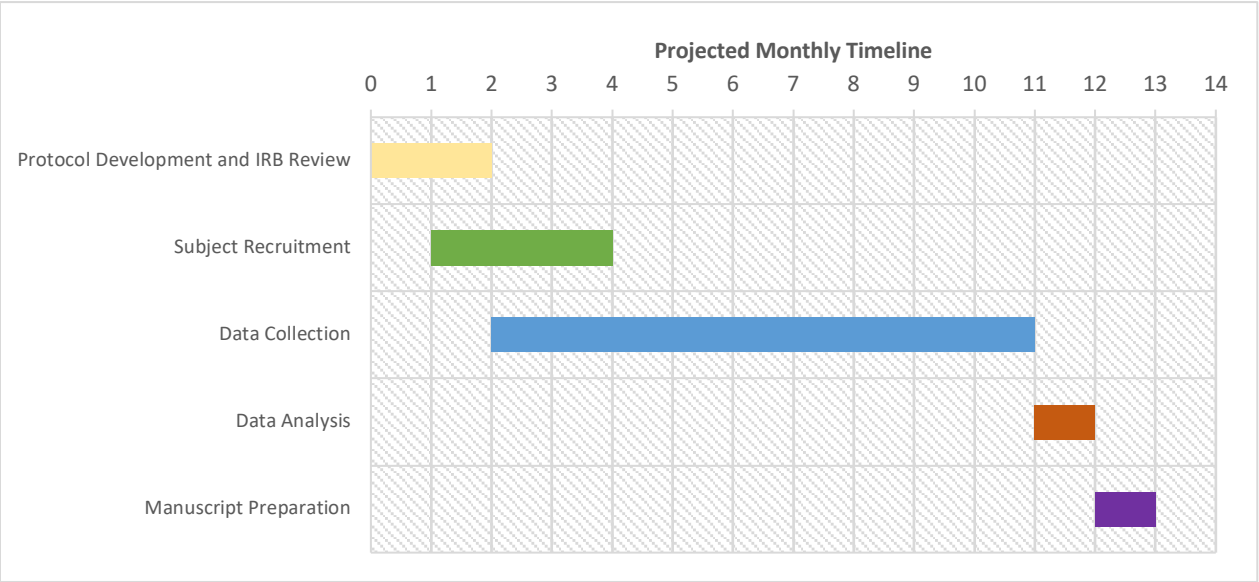
1. Age ≥18 years
2. Provide informed consent and authorization to disclose protected health information
3. Willing to follow study protocol
4. Habitual, contact lens-corrected visual acuity of at least 20/30 in each eye
5. Wear soft contact lenses as daily wear for at least 6 hours per day and at least 5 days per week for the past 30 days
6. Have at least a 2-hour difference between overall wear time and comfortable wear time of contact lenses
7. Have symptoms consistent with Contact Lens Dry Eye based on CLDEQ-8 (score ≥ 12)
8. Increased severity of dry eye symptoms with contact lens wear by at least 25% as determined by patient self-report

9. Clinical assessment that contact lens material, fit, prescription, and care system are not reasons for contact lens discomfort
10. Demonstrate at least 80% compliance in completion of daily electronic diary (submitted through Qualtrics Research Suite) between V1 and V2
11. Willing to discontinue use of any current dry eye treatment (including use of commercial hygiene masks, and except for artificial tears) for 4 weeks before randomization and during the course of the 6-month study.

F. Exclusion Criteria

1. Meibomian gland dropout ≥75% in either eyelid
2. Any changes to the contact lens material, fit, prescription, or care system in the 30 days preceding enrollment or anticipates needing to make changes during the course of the study
3. Any systemic disease known to be associated with dry eye
4. Any significant ocular surface abnormality that could be associated with ocular surface discomfort, such as ectropion, entropion, trichiasis, infection, severe allergic conjunctivitis, severe eyelid inflammation, etc.
5. Any overnight wear of contact lenses
6. Any previous corneal surgery, including all types of corneorefractive surgery
7. Have temporary and/or permanent punctal plugs inserted
8. Use of supplemental fish oil, or seed oils from borage, evening primrose, sea buckthorn, flaxseed, or black currant within the last 60 days
9. Routine, usual dietary intake of more than 8 oz. of cold-water fatty fish (tuna, salmon, mackerel, sea bass, sardines or herring) per week).
10. Use of anticoagulant therapy or regular, daily use of aspirin, NSAIDs, or steroid medications within the past 30 days, or a history of easy bruising
11. Allergy or intolerance to fish or any ingredients contained in the active or placebo formulas [See appendix or ingredient list]
12. Participation in a clinical trial in the past 30 days
13. Current pregnancy or breast feeding as indicated by self-report

III. TIMELINE AND REPORTING



IV. BUDGET

The following budget outlines the estimated costs associated with the proposed clinical trial.

Item	Unit Cost	Total
Clinical Assessment		
Consumables (fluorescein, lissamine green, alcohol pads, charts, Schirmer strips, etc.)	--------	$550.00
Salaries		
Clinician (3.75 h/subject * 55 subjects = 112.5 clinician hours)	$150.00/hour	$30,937.5
Study coordinator (0.5 hours/visit * 120 visits = 60 coordinator hours)	$50.00/hour	$3,000.00
Subject Compensation		
Subject Visit ($20 for V1; $40 for each V2-V4)	$140.00/subject	$4,200.00
Laboratory Assessment		
RayBiotech Human Dry Eye Disease Array Q1 (32-50 sample kit, Qty 3)	$4,694.00	$14,082
Enzolife Sciences LTB4 ELISA Kit (50 sample kit, Qty 3)	$559	$3,501
Other		
Protocol development and IRB review	$2,500.00	$2,500.00
Report and publication in peer-reviewed journal	$4,000.00	$4,000.00
UAB Study Management Fee	---------	$5650
TOTAL DIRECT COSTS		$68,709.78
TOTAL INDIRECT COSTS (30%)		$20,612.93
	TOTAL	$89,322.71

*Both HydroEye® and placebo will be supplied by sponsor.

V. REFERENCES

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VI. APPENDIX

Combined Ingredient List – Active and Placebo Formulas

CONFIDENTIAL STUDY MATERIALS – FOR INVESTIGATOR REFERENCE ONLY

Ingredients in the study formulations may variously include:

- Sunflower seed oil
- Black currant seed oil
- Bovine gelatin
- Calcium carbonate
- Glycerine
- Vitamin C (ascorbic acid)
- N-acetyl-cysteine (NAC) (antioxidant)
- Beeswax
- Fish oil (USP-Verified)
- Sunflower Lecithin
- Magnesium sulfate
- Lemon oil
- Vitamin E (d-alpha tocopherol)
- Vitamin B6 (pyridoxine-5-phosphate)
- Caramel color (MEI-4 free, gluten free; from organic cane juice)
- Titanium dioxide
- Trans-pterostilbene (plant extract from *pterocarpus marsupium*) (antioxidant)
- Vitamin A (retinyl palmitate)
- Vitamin B12 (methylcobalamin)
- Vitamin D3 (cholecalciferol)