**March 25, 2020**

**CHAIKIN EYECELL CLINICAL PROTOCOL**

**Title:**

**Trans-Palpebral Microcurrent Treatment of Age-related Macular Degeneration using a Frequency Specific Approach**

**Background:**

Age-related macular degeneration (AMD) is a leading cause of central visual loss in the Western world with limited treatment options. It presents in two forms, with the more common form referred to as “dry”, which may progress to the “wet” form, which is associated with more rapid loss of vision. The wet form is characterized by neovascularization, which has been treated with the use of anti-VEGF injections. Otherwise, clinical recommendations include taking vitamins and following the AREDS-II study guidelines.

The use of microcurrent bioelectric stimulation is one approach for slowing both the wet and dry forms of AMD that has been reported for over 150 years, with encouraging demonstration of both safety and efficacy using a variety of signals and amperage (1, 2). Devices used have included low amperage instruments with limited variance of frequency, as well as low amperage frequency specific applications (FDA). A previous study using dual frequency stimulation showed preservation of vision with no adverse effects (1).

This study will compare the use of two forms of bioelectric signaling, using specific frequencies to either target tissues of patients with the dry form of AMD, which are known to be associated with the disease, such as inflammation, sub-retinal fluid accumulation, scarring, and others or to target specific proteins present in the retinal tissue such as Klotho and Insulin-lie Growth Factor (IGF). The latter have been shown to be beneficial in cellular repair and regeneration, as well as stem cell homing signals such as SDF. The upregulation of the target signals has been confirmed in both animal studies as well as direct stimulation of isolated retinal cells in a dish. There will be no signals used that could improve vascular supply to the eye to avoid development of neovascularization.
The study will utilize two types of bioelectric stimulators including the dual-channel type that was used without problem in a recent study conducted by the overall study PI, Dr Laurie Chaikin, and a Mettler model 740 stimulator which has been used in over 100 patients for other indications in studies conducted by the sponsor and over 800 patients by the manufacturer without report of adverse event or malfunction.

**GOAL**:
The goal of this study is to attempt to halt the natural progression of dry Macular Degeneration, and preserve vision over the course of the study.

**Study Design/Description**:

This will be a prospective, randomized, double blind, placebo-controlled, 3 arm study comparing use of two forms of bioelectric stimulation vs placebo in the treatment of patients with established diagnosis of dry Macular Degeneration and stable vision. The Principal Investigator will not be present during the treatment double blind will be maintained by simulating initiation of the bioelectric stimulation (BES) with the technician turning the stimulator away from each patient to prevent awareness of the stimulator being turned on or the stimulator used. The stimulation will be delivered via goggles worn over the eyes.

Visual acuity will be measured every two weeks to identify any patients with decline in visual acuity, and if documented by the examinations used for this study, will have a detailed examination by the patient’s Ophthalmologist to evaluate for bleeding or other causes of vision reduction. If the wet form develops the patient will be removed from the study.

**Cross-Over Option**

If the study proves superior preservation of visual acuity in either of the treatment groups at the end of the 3 month treatment period, they will be offered the option to receive another 3 months of treatment with the best therapy shown.

**Target Number of Participants**: 40

**Target Number of Enrolling Sites**: Up to 4

**Length of Treatment:** 3 months

**Number of Treatment Arms**: 4

Control patients who will receive sham treatment with any BES

Bioelectric Stimulation Using Inspirstar stimulator

Bioelectric Stimulation Using the Mettler stimulator

Use of equal period of both the Inspirstar and Mettler Stimulators

**Frequency of Treatments**: 2 X’s/week

**Duration of Each Treatment:** 40-60 minutes

**Delivery Methods**: Eye Goggles- which will be supplied by the sponsor

**Stimulators to be used**: Mettler model 740; InspirStar Model IS02BA

**Treatment Location**: All treatments will take place only in the office of one of the study sites participating in this study.

**Equipment Supplied by the Sponsor:**

Mettler 740 stimulator

InspirStar stimulator

Goggles

Supply of gel to interface goggles and skin for enhanced signal conduction

**Primary End Points:**

1. Change in visual acuity by multiple tests over time comparing active therapy to control.

**Secondary End Point:**

1. Any adverse effects of pain, irritation, or other symptoms possibly related to the therapy.
2. Any improvement or decline in vision in any treatment group
3. Any changes documented by OCT (Optical Coherence Tomography)

The study, including the protocol and consent form, will have been approved without stipulations by a local or certified National Institutional Review Board as meeting safe and good clinical practice before any subject will be enrolled.

**Inclusion Criteria:**

1. Age 50-80 years of age
2. Established diagnosis of wet or dry Macular Degeneration by a certified ophthalmologist
3. Must speak, read, and understand English
4. Able and willing to give informed consent and follow study instructions.
5. Able to tolerate up to 60 minutes of BES
6. Able and willing to make the required study visits.
7. Stable vision for the past 6 months

**Exclusion Criteria**:

1. Undergoing therapy for malignancy of any type aside from skin.
2. Individuals with diminished decision-making capacity
3. Renal replacement therapy
4. History of non-compliance with regular medical visits

5. Significant media opacities that may interfere with visual acuity assessments.

1. Presence of pigment epithelial tears or rips
2. Diabetic retinopathy
3. Presence of retinal neovascularization
4. Any treatment with an investigation agent in the last 30 days
5. Any history of seizure disorder

**Informed Consent:**

All patients must sign the Consent Form prior to being enrolled in the study.

**Randomization:**

An individual or company not involved in the study will conduct the randomization to one of the four treatment arms for each enrolled subject.

**Identity Protection:**
No personal information will be shared with the sponsor. Each patient will receive an enrollment number at the time of randomization and will be the only identifying information used throughout the study and data analysis.

**Screening Evaluation of BES**:

All subjects who have signed an informed consent and are enrolled in the study will undergo an increasing period of bioelectric stimulation beginning at 5, and advancing to 15, 30, 45 minute period delivered in the same method as will be experienced in the study to assess any adverse symptoms and comfort. If no adverse symptoms, they will be accepted to enter treatment.

Patients will also have an assessment of sensitivity and tolerance to an escalating amperage of the stimulation signal from each device. For the Inspirstar, beginning at 25 uAmps, and increasing by 25 uAmps to a maximum of 125 uAmps. The current that the patient selects for individual tolerance will then be the current used for each treatment for that patient. For the Mettler unit the beginning stimulation signal would be \_\_\_\_\_\_mAmps\_, increased by \_\_\_\_\_mAmps to a maximum of \_\_\_\_\_\_\_\_\_mAmps.

Phosphene perception, which has in the literature, been noted to be an indication that the BES was received in the eye. (will be used to define the duration of therapy which will be used for the individual patient throughout the study.) Delete

**Protocol:**

Each patient will have a baseline visual acuity examination and provide a set of goggles to be worn during each treatment period. A gel provided by the sponsor will be applied to the electrode on the front of the google and to the comb electrode wells which touch the scalp on the back, then the goggles are secured in place. The goggles will then be connected to the stimulator to which the patient was randomized, and the microamp current turned up to the level selected by the patient during the pre-study screening examination. Each treatment period will last from 40-60 minutes. The patient may terminate a treatment session at any time.

Visual acuity will be tested every two weeks throughout the study.

**Treatment Schedule:**

The treatments will take place 2 times/week for a period of up to 60 minutes, for 12 consecutive weeks.

**Follow Up Evaluations**:

Each patient enrolled in the study will have a vision check every two weeks by the same method at each investigator site. In addition, they will be asked about any potential adverse events.

A visual acuity examination will also be conducted at the end of the study and again at 6 and 12 weeks post therapy by the Investigator or their designated staff.

 **Stopping Rules**:

The Study will be paused if a total of 3 of the study subjects experience a treatment-related side effect of at least moderate severity. It will be restarted when additional investigation yields a clear cause and effective action plan has been implemented.

**Data Analysis**:

Data will be collected for each patient and visual acuity results read by a Board Certified Ophthalmologist not involved in the study, who will attest to the accuracy of the visual acuity results.

If the study demonstrates no change or a slowing of progression of the natural history of a decline in visual acuity over time, patients will be allowed to continue the study for another 3 months with repeated measurement of acuity at

the next 6 and 12 weeks of treatment.

Patients randomized to control group will be offered treatment with the BES arm showing the best benefit.

If a subject drops out for any reason during the study, a replacement patient can be enrolled.

REFERENCES

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3. Anastassiou G, Schneegans AL, Selbach M, Kremmer S. [Transpalpebral electrotherapy for dry age-related macular degeneration (AMD): an exploratory trial.](https://www.ncbi.nlm.nih.gov/pubmed/23760223) Restor Neurol Neurosci. 2013;31(5):571-8.
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