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TITLE: Vision Restoration with a Collagen Crosslinked Boston Keratoprosthesis Unit

PRINCIPAL INVESTIGATOR: Joseph B. Ciolino, MD

CONTRACTING ORGANIZATION: Massachusetts Eye and Ear Infirmary
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Joseph Ciolino

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Infirmary
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Boston, MA 02114

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14. ABSTRACT

The Boston Keratoprosthesis is the most widely used keratoprosthesis worldwide and is implanted in the eyes of patients who are not candidates for a traditional corneal transplant. Unfortunately, the most common cause of keratoprosthesis failure is due to keratolysis (corneal melts), which can result in devastating sight-threatening complications and /or loss of the eye. Within the keratoprosthesis unit, corneal melts typically develop in the corneal graft that serves as a carrier for the optic. We have developed a method to reduce the incidence or potentially eliminate corneal melts by strengthening the keratoprosthesis carrier tissue by collagen-crosslinking the cornea graft ex vivo using vitamin B2 (riboflavin) and ultraviolet light. The overall objective of this study is to prevent sight-threatening keratoprosthesis corneal melts and identify an improved treatment for patients who are not candidates for traditional corneal transplants.

15. SUBJECT TERMS

Boston Keratoprosthesis, corneal melts, collagen-crosslinking

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Introduction:

The goal of this proposal is to evaluate the safety and efficacy of a new method for preparing and transplanting an artificial cornea (keratoprosthesis) unit by using a novel procedure, known as corneal cross-linking, to reduce the incidence of corneal melts and improve the outcomes of keratoprosthesis surgery. The Boston Keratoprosthesis is the most widely used keratoprosthesis worldwide and is implanted when patients are not candidates for a traditional corneal transplant. Unfortunately, the most common cause of keratoprosthesis failure is due to corneal melts, which can lead to permanent vision loss. We have developed a method to reduce the incidence or potentially eliminate corneal melts by strengthening the keratoprosthesis carrier cornea using tissue that has been cross-linked using vitamin B2 (riboflavin) and ultraviolet light prior to prosthesis assembly. This study's population will include patients who are both candidates for a Boston KPro and had either a history of corneal melting (keratolysis) or have high risk for corneal melting.

Key Words:

Keratoprosthesis

Corneal Cross-Linking

Corneal Melting (Keratolysis)

Accomplishments:

What were the major goals of the project?

This project has four major goals that are listed below.

1. IRB, HRPO and FDA Approval of the study protocol
2. Study Start-Up with DSMB, contractors and sub-sites
3. Enrollment and Completion of Study Assessments
4. Data Analysis and Publications

What was accomplished under these goals?

The following tasks (numbered to correspond with Gantt chart in the SOW) have been completed or are in progress.

Major Goal 1: The initial application was submitted to the Mass Eye and Ear Infirmary (MEEI) IRB and it was determined that the study was eligible for IRB review with WIRB. The study was submitted to WIRB on 10/15/15 and the WIRB Approval has since been obtained**.** Received report from DoD review of protocol. Preparing response to review comments. Submitted IND to FDA. Received email confirmation that we are clear to proceed.

Major Goal 2: We have held weekly meetings here internally at MEEI regarding study-start-up activities. The principal investigator, Dr. Ciolino, met with the participating investigators and their site staff at the American Academy of

Ophthalmology meeting in November 2015 to discuss the study including the rationale, study design, study endpoints, study collaborations, objectives, preparation of investigational tissue, eligibility criteria, data collection, and the overall study progress to date.

The team at MEEI has continued working with StudyTrax to further eCRF development. StudyTrax is the web-based program that will be used at all sites to collect information on subjects, including clinical assessments, subject medications, adverse events, as well as OCT images and corneal photographs. A meeting has been scheduled with StudyTrax to discuss set-up and the next steps for implementation of the data capture system.

Regulatory documents were drafted by the staff at MEEI during quarter 2. Additionally, My Files, the data sharing website that will be used throughout this study, was developed. My Files will be used for upload of all of regulatory documentation from sites.

A meeting with site sub-investigators at ARVO took place in May 2016 where timelines and goals were discussed.

Currently, a modified version of the informed consent form as been approved and we are currently working with the sub-sites to update their informed consent documents for IRB submission. Additionally, MEEI staff are coordinating with Avedro, the supplier of the Riboflavin solution and UV light source, for delivery of equipment and treatment solution to Tissue Bank International, the tissue bank for this study. Finally, MEEI study staff continue to work with sub-sites to have them list Tissue Bank International as a vendor for tissue.

Major Goal 3: The trial is still in start-up phase and no subjects have been enrolled to date. Although we anticipated enrollment to commence in Quarter 4, Avedro Inc has reported greater delays in providing the UV source; The KXL system, as well as Riboflavin solution necessary to complete the corneal cross-linking. We have been working closely with Avedro and expect these components to be provided within the next quarter.

Major Goal 4: As patients have yet to be enrolled in the study, data analysis has not yet occurred.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period we will finalize the study-start up process.

Regulatory Management: We continue to work with sub-sites to send the updated informed consent for to their local IRBs for approval. The approved site documents and approval letters, once obtained, will be submitted to the FDA and HRPO.

All regulatory documents continue to be finalized and distributed to the sites electronically. We will work with the sites to collect all required regulatory documentation and submit to the FDA. The eCRF system via Study Trax is near completion and once finalized, will be shared with all sites.

Data Safety Monitoring Committee: A Data Safety Monitoring Committee has been assembled. This group is comprised of researchers and physicians who are not associated with the trial. A date of the introductory meeting has not been determined.

All sub-sites have been invited to attend the scheduled investigators meeting at AAO in Chicago on October 14, 2016 where Dr. Ciolino will review the protocol details as well as provide a forum for discussion.

Impact:

What was the impact on the development of the principal disciplines(s) of the project?

As a result of our proposed study and the technique that it describes, some keratoprosthesis surgeons around the world have begun cross linking tissue used as a carrier for the keratoprosthsesis. During presentations, the investigators have cited our previous work that was included in our preliminary data for this grant application. At this time, it is not known whether this approach is effective which is what we intend to evaluate with this study. Through personal correspondence with cornea surgeons from around the world, MEEI has been told that they are eager to see the results from our study to help guide their clinical practice.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

Changes/Problems:

Changes in approach and reasons for change:

Nothing to report

Actual or anticipated problems or delays and action or plans to resolve them:

Although we anticipated enrollment to begin during Quarter 4, Avedro Inc has reported greater delays in providing the UV source, The KXL system, as well as Riboflavin solution necessary to complete the corneal cross-linking. We have been working closely with Avedro and expect these components to be provided within the next quarter.

The original statistician hired during year 1 has left the organization. The statistician funding that was budgeted for year 1 of the study will be carried forward to year 2 and used for the same purpose.

Changes that had a significant impact on expenditures:

Nothing to Report

Significant Changes in use of care of human subjects, vertebrate animals, biohazards, and/or select agents:

Nothing to Report

Significant changes in use of care of human subjects:

Nothing to Report

Significant changes in use of care of vertebrate animals:

Nothing to Report

Significant Changes in use of care of biohazards:

Nothing to Report

Products:

Publications, conference papers, and presentations:

Nothing to Report

Website(s) or other Internet site(s):

Nothing to Report

Technologies or Techniques:

Nothing to Report

Other Products:

Nothing to Report

Participants & Other Collaborating Organizations:

What individuals have worked on the project?

Name: *Joseph Ciolino, MD*

Project Role: *Principal Investigator*

Researcher Identifier (e.g. ORCID ID): *N/A*

Nearest person month worked: *12*

Contribution to Project: Dr. Joseph Ciolino is the Principal Investigator of this study and assumes all the roles associated with a principal investigator.

Name: *Marie Le*

Project Role: *Clinical Study Supervisor*

Researcher Identifier (e.g. ORCID ID): *N/A*

Nearest person month worked: *1*

Contribution to Project: Ms. Le Was responsible for overseeing all aspects of the project including enrollment, site coordination, data collection activities, regulatory compliance, IRB/FDA submissions, and working with key collaborators (TBI and Avedro)

Name: *Arden Tesmer*

Project Role: *Project Manager*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Ms. Tesmer was responsible for overseeing all aspects of the project including enrollment, site coordination, data collection activities, regulatory compliance, IRB/FDA submissions, and working with key collaborators (TBI and Avedro).

Name: *AnnMarie Fatal*

Project Role: *Project Manager*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Ms. Fatal was responsible for overseeing all aspects of the project including enrollment, site coordination, data collection activities, regulatory compliance, IRB/FDA submissions, and working with key collaborators (TBI and Avedro).

Name: *Ellen Fitzgerald*

Project Role: *Clinical Study Supervisor*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Ms. Fitzgerald is responsible for overseeing all aspects of the project including enrollment, site coordination, data collection activities, regulatory compliance, IRB/FDA submissions, and working with key collaborators (TBI and Avedro). Ms. Fitzgerald assumed these functions upon AnnMarie leaving MEEI.

What other organizations were involved as partners?

List of Sub-Sites

Site #	Site Name	Site Location	Site PI	Contribution
1	Massachusetts Eye and Ear Infirmary Harvard Medical School	243 Charles Street Boston MA 02114	Joseph Ciolino, MD	Facilities and Collaboration
2	San Antonio Uniformed Services Health and Educational Consortium	2200 Bergquist Drive Lackland AFB, TX 78236	Major Richard Townley, MD	Facilities and Collaboration
3	The Wilmer Eye Institute Johns Hopkins Hospital	600 N. Wolfe Street Baltimore, MD 21287	Esen Akpek, MD	Facilities and Collaboration
4	W.K Kellogg Eye Center University of Michigan	1000 Wall Street Ann Arbor, MI 48105	Shahzad Mian, MD	Facilities and Collaboration
5	The Jules Stein Eye Institute University of California, Los Angeles	100 Stein Plaza Los Angeles, CA 90095	Anthony Aldave, MD	Facilities and Collaboration
6	Illinois Eye and Ear Infirmary University of Illinois College of Medicine	809 S. Marshfield Avenue Chicago, IL 60612	Jose De La Cruz, MD	Facilities and Collaboration
7	Cincinnati Eye Institute University of Cincinnati	580 South Loop Road, Suite 200 Edgewood, KY 41017	Edward Holland, MD	Facilities and Collaboration
8	Health System Eye Centre University of California Davis	4869 Y Street, Suite 2400 Sacramento, CA 95817	Mark Mannis, MD	Facilities and Collaboration
9	Tauber Eye Center	4400 Broadway, Suite 202 Kanas City, MO 64111	Joseph Tauber, MD	Facilities and Collaboration
10	University Hospital Eye Institute	11100 Euclid Ave, Cleveland, OH 44106	Pankaj Gupta, MD	Facilities and Collaboration
11	David and Llene Flaum Eye Institute University of Rochester Medical Centre	210 Crittenden Blvd, Rochester, NY 14642	James Aquavella, MD	Facilities and Collaboration
12	Shiley Eye Institute University of California, San Diego	9415 Campus Point Dr, La Jolla, CA 92093	Natalia Afshari, MD	Facilities and Collaboration
13	Bascom Palmer Eye Institute University of Miami Leonard M. Miller School of Medicine	900 NW 17th St, Miami, FL 33136	Victor Perez, MD	Facilities and Collaboration

List of Partnering Institutions:

Number	Partner Name	Location	Contribution
1	Avedro Incorporated	201 Jones Rd, Suite 5 Waltham, MA 02451	In-Kind
2	Tissue Bank International	815 Park Ave Baltimore, MD 21201	In-Kind

Special Reporting Requirements:

Collaborative Awards:

Nothing to Report

Quad Charts:

Vision restoration with a collagen crosslinked keratoprosthesis unit
MR141163
W81XWH-15-2-0044

PI: Joseph B. Ciolino **Org:** Massachusetts Eye and Ear **Award Amount:** $2,773,704

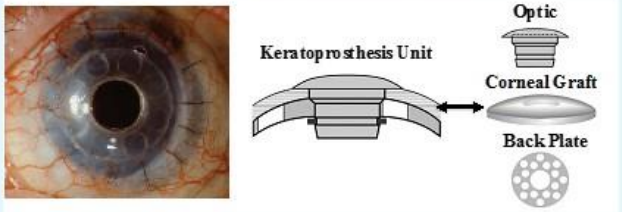
Study/ Product Aims

• To determine the **safety** (Aim 1) and **efficacy** (Aim 2) of using a collagen cross-linked cornea as a carrier for the Boston Keratoprosthesis in patients who are at high risk for corneal melts and are not candidates for a standard corneal transplant.

Approach

- This is a phase I/II prospective, randomized, multicenter, double-masked, vehicle-controlled study.
- Treat ½ of eyes with corneal cross-linked cornea and ½ with untreated corneal graft as a keratoprosthesis carrier. Recruit 84 subjects who are high risk for Keratoprosthesis corneal melts across 10 sites.
- Primary endpoint is time to keratoprosthesis loss through 12 months.
- Secondary endpoints include keratoprosthesis retention at 12 months, OCT corneal thickness metrics, etc.

Corneal Cross-linked Keratoprosthesis Unit



FDA approved IND for protocol.

Timeline and Cost

Activities CY	15	16	17	18
FDA IND amendment, Site IRB Approvals, & HRPO				
Subject Enrollment				
Subjects Complete Study				
Data Analysis and Reporting				
Estimated Budget ($)	**$570**	**$729**	**$867**	**$608**

Updated: (09/28/2016)

Goals/Milestones

CY15 Goal – To amend the PI's FDA IND to include all sites for a multicenter trial and a change in the supplier of the riboflavin/ UV light. To secure institutional review board approval at all participating sites.
☑ FDA IND approval for multicenter trial
☐ Secure IRB approval at all sites and begin recruitment
☑ Submit to HRPO for review

CY16-17 Goals – To complete recruitment and enrollment of 84 subjects.
☐ Secured enrollment of 84 subjects by second quarter of 2017.

CY18 Goal – To analyze data and report findings.
☐ Complete data analysis
☐ Submit findings to FDA and report results in manuscript submission

Budget Expenditure to Date
Projected Expenditure: $569,981.56
Actual Expenditure: $246,481.55

Appendices: