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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

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Odeta Dyrmishi, Senior Clinical Research Project Manager

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PERFORMING ORGANIZATION NAME

Massachusetts Eye and Ear Infirmary
243 Charles Street
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 (KPro) 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 Sponsor Site completed its yearly IRB continuing review and is currently approved through March 2022. The Sponsor's IRB last continuing review documentation was submitted to HRPO and the related Continuing Review Acceptance Memorandum was received from HRPO on April, 2021. The Sponsor continues to send FDA yearly reports. The most recent FDA annual report was sent June, 2021, and the next report will be completed in June 2022.

Major Goal 2: The Sponsor Site identified personnel to be included on the Data Safety Monitoring Committee, which included the study Medical Monitor, the Study Biostatistician and an Ophthalmologist not associated with the study. The Committee held the last meeting in October 2021.

The Sponsor Site continues to work with Avedro Incorporated for supply of the study solution and UB light device. The Sponsor also continues to work with CorneaGen (formerly KeraLink International) which is the tissue bank providing corneal tissue according to the randomization schematic. The Sponsor continues to use the StudyTrax secure electronic data capture program for

collecting all subject related data. The Sponsor now also uses StudyTrax as a secure way for sites to send study related optical imaging.

There are a total of 16 sites participating in this study. 1 site is the Sponsor Site, Massachusetts Eye and Ear, and 15 Sub-Sites listed below. During this past reporting period enrollment was completed. Of the 16 Sites listed below, 14 sites completed all study activities including data collection.

Complete list of Sub-Sites and Principal Investigators:

Site #	Site Name	Principal Investigator
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino
~~2~~	~~San Antonio Uniformed Services~~	~~Dr. James Townley~~
~~2~~	~~Columbia New York Presbyterian Harkness Eye Institute~~	~~Dr. Danielle Trief~~
3	The Willmer Eye Institute	Dr. Esen Akpek
4	W.K. Kellogg Eye Center	Dr. Shahzad Mian
5	The Jules Stein Eye Institute	Dr. Anthony Aldave
6	Illinois Eye and Ear Infirmary	Dr. Jose De La Cruz
7	Cincinnati Eye Institute	Dr. Edward Holland
8	UC Davis Health System Eye Center	Dr. Mark Mannis
9	Tauber Eye Center	Dr. Joseph Tauber
10	University Hospital Eye Institute	Dr. ~~Pankaj Gupta~~ Ahmed Omar
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella
12	Shiley Eye Institute	Dr. Natalia Afshari
13	Bascom Palmer Eye Institute	Dr. Guillermo Amescua
14	Duke Eye Center	Dr. Victor Perez
15	Wills Eye	Dr. Brandon Ayres
~~16~~	~~New York Eye and Ear Infirmary of Mt Sinai~~	~~Dr. John Seedor~~

Of the Sub-Sites, the following have secured IRB approval:

Site #	Site Name	Principal Investigator
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino
3	The Wilmer Eye Institute	Dr. Esen Akpek
4	W.K. Kellogg Eye Center	Dr. Shahzad Mian
5	The Jules Stein Eye Institute	Dr. Anthony Aldave
6	Illinois Eye and Ear Infirmary	Dr. Jose De La Cruz
7	Cincinnati Eye Institute	Dr. Edward Holland
8	UC Davis Health System Eye Center	Dr. Mark Mannis
9	Tauber Eye Center	Dr. Joseph Tauber
~~10~~	~~University Hospital Eye Institute~~	~~Dr. Pankaj Gupta~~
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella
12	Shiley Eye Institute	Dr. Natalia Afshari
13	Bascom Palmer Eye Institute	Dr. Guillermo Amescua
14	Duke Eye Center	Dr. Victor Perez
15	Wills Eye	Dr. Brandon Ayres

Of the above IRB approved Sub-Sites the following have secured HRPO approval:

Site #	Site Name	Principal Investigator
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino
3	The Wilmer Eye Institute	Dr. Esen Akpek
4	W.K. Kellogg Eye Center	Dr. Shahzad Mian

5	The Jules Stein Eye Institute	Dr. Anthony Aldave
6	Illinois Eye and Ear Infirmary	Dr. Jose De La Cruz
7	Cincinnati Eye Institute	Dr. Edward Holland
8	UC Davis Health System Eye Center	Dr. Mark Mannis
9	Tauber Eye Center	Dr. Joseph Tauber
~~10~~	~~University Hospital Eye Institute~~	~~Dr. Pankaj Gupta~~
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella
12	Shiley Eye Institute	Dr. Natalia Afshari
13	Bascom Palmer Eye Institute	Dr. Guillermo Amescua
14	Duke Eye Center	Dr. Victor Perez
15	Wills Eye	Dr. Brandon Ayres

A final investigator's meeting was held on November 12, 2021. A final investigator's meeting will be held before the end of study to review study outcomes.

Major Goal 3: All study related activities have been completed. Study is currently working on analyzing study data.

Site #	**Site Name**	**Principal Investigator**	**# Subjects who Received KPro surgery**
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino	5
3	The Wilmer Eye Institute	Dr. Esen Akpek	9
4	W.K. Kellogg Eye Center	Dr. Shahzad Mian	13
5	The Jules Stein Eye Institute	Dr. Anthony Aldave	14
6	Illinois Eye and Ear Infirmary	Dr. Jose De La Cruz	3
7	Cincinnati Eye Institute	Dr. Edward Holland	1
8	UC Davis Health System Eye Center	Dr. Mark Mannis	1
9	Tauber Eye Center	Dr. Joseph Tauber	6
~~10~~	~~University Hospital Eye Institute~~	~~Dr. Pankaj Gupta~~	~~0~~
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella	2
12	Shiley Eye Institute	Dr. Natalia Afshari	5
13	Bascom Palmer Eye Institute	Dr. Guillermo Amescua	1
14	Duke Eye Center	Dr. Victor Perez	7
15	Wills Eye	Dr. Brandon Ayres	2
		Total	69

Major Goal 4: Analysis of photos and images by designated staff has been completed. Analysis of all other data has also been completed.

Abstract:

Objective: To assess whether cross-linking the carrier donor cornea of the Boston Keratoprosthesis (BKPro) improves the retention of the device in participants who are at high risk of sterile keratolysis.

Design: Prospective, randomized, multicenter, double-masked clinical trial.

Participants: Sixty-eight adult participants with a previous history of sterile keratolysis and/or known systemic autoimmune disease who were deemed ineligible for conventional donor corneal transplantation and scheduled for BKPro implantation were enrolled. Thirteen sites within the United States contributed participants between 2017 - 2020.

Methods: Masked participants were randomized to receive either a cross-linked (CXL) or non-cross-linked (non-CXL) donor corneal carrier managed by a central non-masked eye bank. The surgical technique and post-operative care were standardized. Kaplan-Meier event-free survival according to study group was determined by the product-limit method and compared by the log-rank test to examine if survival curves were different between the CXL and non-CXL groups.

Main outcome measures: The primary outcome of the study was time from surgery to BKPro removal. Secondary endpoint was twelve-month retention rate. Safety measures included incidence of delayed epithelial healing, retroprosthetic membrane formation and vitritis.

Results: A total of 68 participants were enrolled and randomized 1:1 to each group. The average age at the time of surgery was 62 [24-89] years and 42 (62%) participants were male. The overall BKPro retention rate was 70% during a mean follow-up time of 93 (6 - 201) weeks. A total of 20 BKPros were removed, ten in the CXL group and ten in the non-CXL group, with 18 requiring removal due to sterile keratolysis. At twelve months, there was no significant difference in the retention rate in the CXL group (94%) versus the non-CXL group (82%, P = 0.150). Additionally, there was no difference in the time to removal between the groups during the study (P = 0.910). Analysis of all safety endpoints showed no difference between the two groups with regards to both rate of occurrence and or time to-event.

Conclusion: In this prospective study, cross-linking of the carrier donor cornea prior to BKPro implantation did not reduce the incidence of sterile keratolysis or increase device retention among participants at high risk for this complication.

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

Nothing to Report

How were the results disseminated to communities of interest?

The number of enrolled study subjects across the study has been distributed to all sites each time new subjects are scheduled for KPro surgery. The study outcomes have been shared with the all study sites. Currently the study is seeking to publish the data analysis outcomes. We are currently waiting to hear back regarding the publication of the manuscript.

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

N/A. Awards has been closed and this is the last reporting period.

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:

An additional one year No Cost Extension from DoD has been requested and is pending review from the DoD.

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:

Preliminary results were presented at the Cornea and Eye Banking Forum on Friday November 12th in New Orleans, LA. Currently waiting to hear back from a number of publications regarding the publication of the study manuscript.

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: *3 in this reporting period*

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

Name: *Ellen Fitzgerald*
Project Role: *Clinical Study Supervisor*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *2 in this reporting period*

Contribution to Project: Ms. Fitzgerald is responsible for overseeing study staff employed by the Center for Clinical Research Operations, as well as working on

Name: *Odeta Dyrmishi, MPA*
Project Role: *Project Manager*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *10 in this reporting period*

Contribution to Project: Ms. Dyrmishi 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 (CorneaGen/KeraLink, and Avedro).

Name: *Elizabeth Grimm, JD*
Project Role: *Project Manager (Back-Up)*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *2 in this reporting period*

Contribution to Project: Ms. Grimm is responsible for providing back-up support while the primary Project Manager is not available. This includes site coordination, data collection activities, regulatory compliance, and IRB/FDA submissions.

Name: *Aditya Raj*
Project Role: *Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *5 in this reporting period*

Contribution to Project: Ms. Raj is responsible for supporting of sub-sites with their data sharing. He reviews ongoing data collection she communicates directly with sites regarding document and data collection.

Name: *Michael Cheung*
Project Role: *Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *7 in this reporting period*

Contribution to Project: Mr. Cheung is responsible for supporting of sub-sites with their data sharing. He reviews ongoing data collection she communicates directly with sites regarding document and data collection.

Name: *Tony Succar*
Project Role: *Study Monitor*
Researcher Identifier (e.g. ORCID ID): *N/A*
Nearest person month worked: *7 in this reporting period*

Contribution to Project: Mr. Succar is responsible for monitoring conduct of the study at sub-sites, including periodic monitoring calls and review of source documentation.

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	Columbia/New York Presbyterian Harkness Eye Institute	635 West 165th Street, Box 25 New York, NY 10032	Danielle Trief, 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~~ Ahmed Omar, 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	Guillermo Amescua, MD	Facilities and Collaboration
14	Duke University Eye Center	Department of Ophthalmology Hudson Building DUHS Box 3802 2351 Erwin Road Durham, NC 27710	Victor Perez, MD	Facilities and Collaboration
15	Wills Eye	100 Presidential Boulevard Suite 200 Bala Cynwyd PA 19007	Brandon Ayres, MD	Facilities and Collaboration
16	New York Eye and Ear Infirmary, Mt Sinai	310 E 14th Street Suite 219 New York, NY 10003	John Seedor, 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	CorneaGen (previously known as KeraLink International)	815 Park Ave Baltimore, MD 21201	In-Kind

Special Reporting Requirements:

Collaborative Awards:

Nothing to Report

Quad Charts:

Please see attached Quad Chart for this reporting period.