IRB Approved at the
Protocol Level
Apr 05, 2019



**Study Title:** A prospective, randomized, and controlled clinical study to evaluate PROKERA® in the management of signs and symptoms associated with dry eye disease.

**Protocol Number:** PROKERA-CS001

**Product Name:** PROKERA® Slim

**Product Classification:** Class II Medical Device

**Product Status:** Cleared by the FDA under 510(k) #K032104

**Cleared Intended Use** In eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.

**Indication:** To reduce signs and symptoms associated with dry eye disease.

**Short Title:** PROKERA for DED

**Sponsor:** TissueTech, Inc. and Its Subsidiaries
7300 Corporate Center Drive, Suite 700, Miami, FL 33126

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| **Version:** | **2** |
| **Original Protocol:** | **[05.30.2018]** |
| **Revised:** | **April 2, 2019** |

## Confidentiality Statement

The confidential information in this document is provided to you as an Investigator, potential Investigator or consultant for review by you, your staff and applicable Institutional Review Board (IRB). It is understood that the information shall not be disclosed to others without written authorization from TissueTech, Inc., except to the extent necessary to obtain informed consent from those persons to whom the test article may be administered.

## BACKGROUND AND RATIONALE:

Dry eye disease (DED) is one of the most common ocular surface disorders in the United States and worldwide. It affects nearly 30% of the population and its symptoms, such as ocular discomfort and visual fluctuations, represent the most frequent complaints in ophthalmic practice.[1-4] Although DED starts from tear film insufficiency, it leads to inflammation and damage of ocular surface epithelial cells and stromal cells.[1,5] Despite different underlying pathogenic processes, inflammation is a common denominator in DED, which in turn induces further damage to the corneal epithelium and its underlying structures.[6] Different treatment modalities, such as steroids and cyclosporine, have been tried to suppress inflammation, however results are variable and refractory in some cases. Consequently, DED not only negatively impacts the quality of life[2] but also increases the burden on health economics.[7]

Cryopreserved amniotic membrane (AM) is designated as human cell and tissue-based product (HCT/P) by the U.S. Food and Drug Administration (FDA) when used in ocular surface reconstruction through Request for Designation in 2001. It is minimally manipulated and considered homologous when used to repair ocular surface damage.[8] The effectiveness of AM has been credited to its anti-inflammatory, anti-scarring, and anti-angiogenic effects. PROKERA® is a Class II medical device comprised of AM fastened in between a ring system and has been cleared by the FDA to cover the corneal surface without sutures via 510(k) #K032104 and is intended for use in eyes, in which the ocular surface cells have been damaged or underlying stroma is inflamed and scarred.[9] Clinical uses of both AM and PROKERA® in ophthalmology have been regarded as a standard of care in the United States and is supported by three Level I CPT Codes (65778 and 65779 for AM and 65780 for PROKERA®) issued by the American Medical Association and reimbursed by the Centers of Medicare and Medicaid Services (CMS). The clinical effectiveness of both AM and PROKERA® in managing a variety of ocular surface disorders have been supported by several hundred peer-reviewed scientific publications.[10]

Among the ocular surface disorders managed by the device, PROKERA® has been used to manage ocular signs and symptoms of DED. In a retrospective study by Cheng et al,[10] PROKERA® was placed for 5 days (Range: 2-8 days) in 15 eyes of 10 patients with moderate to severe DED. The dry eye severity ranged from Grade 1 to 4 according to the Report of the International Dry Eye Work Shop (DEWS) 2007.[1] All patients experienced symptomatic relief for a mean period of 4.2 months (Range: 0.3-6.8). Such improvement was accompanied by reduction of Ocular Surface Disease Index (OSDI) symptom scores, the use of topical medications, conjunctival hyperemia, and corneal staining as well as improvement in the quality of vision.[11] In a single site prospective, randomized, and controlled study conducted by John et al[12], PROKERA® together with standard of care was placed in 10 patients for 3.4 ± 0.7 day (Range: 3-5 days) while standard of care was instituted in another 10 patients as the control. All 20 patients presented with moderate to severe DED with DEWS Grade 2-4. Compared to the control arm of 10 patients receiving standard of care, the treatment arm of 10 patients receiving PROKERA® together with standard of care resulted in reduction of symptoms based on SPEED

score and signs such as superficial punctate keratitis (SPK) measured by fluorescein staining, leading to an overall reduction of the mean DEWS severity score from 2.9 ± 0.3 at baseline to 1.1 ± 0.3 at 1 month and 1.0 ± 0.0 at 3 months, respectively (both $p \leq 0$ 001).These palliative benefits are correlated with an increase of corneal nerve density measured by *in vivo* confocal microscopy from 12,241 ± 5,083 µm/mm$^2$ at baseline to 16,364 ±3,734 µm/mm$^2$ at 1 month, and 18,827 ±5,453 µm/mm$^2$ at 3 months(both p=0.015). The increase of corneal nerve density is also correlated with an increase of corneal sensitivity measured by a monofilament in the Bonnet-Crochet esthesiometer. A lasting benefit for more than 3 months after one placement of PROKERA® was also demonstrated in a retrospective study by McDonald et al[13] in 97 eyes of 84 of patients with moderate to severe DED (DEWS 2-4), of which the majority presented with symptoms of ocular discomfort, blurry vision, ocular pain, redness, and light sensitivity. Most of the cases manifested the ocular sign of SPK due to exposure keratitis, filamentary keratitis, epithelial defect, and neurotrophic keratitis. A single placement of PROKERA® for 5.4 ± 2.8 days leads to notable improvement of DED symptoms and reduction of ocular signs in 74 subjects (88%) as evidenced by notable reduction of the mean DEWS severity score from 3.25to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months. Collectively, these data suggest that a single placement of PROKERA® is effective in reducing signs and symptoms of DED for a period lasting at least three months, presumably through a number of mechanisms known for AM including anti-inflammation as well as the resultant benefit to promote the return of corneal nerve density and corneal sensitivity, which has been reported to decline as DED increases its severity.[12]

The present study is designed to further substantiate the effectiveness of PROKERA® in reducing signs and symptoms of DED.

## STUDY OBJECTIVES

The primary objective is to evaluate the safety and effectiveness of PROKERA® in reducing signs and symptoms of dry eye disease (DED).

## STUDY DESIGN:

We propose to conduct a prospective randomized, and controlled study to compare the effectiveness of PROKERA® plus standard of care (SOC) in the PROKERA® Arm to SOC alone in the Control Arm. Subjects presenting with moderate DED defined as corneal fluorescein staining score of $\geq 3$ points out of 9,[14] will be recruited and screened at the two to three participating clinical site(s) in the United States.

Following a run-in period of 2 weeks during which enrolled subjects will use standard dry eye therapies consistent with what is described in the 2007 Report of the International Dry Eye WorkShop (DEWS)[1,15] [e.g. preservative-free artificial tears, Restasis® (0.05% Cyclosporine A, Allergan, Inc. Irvine, CA), Xiidra® (5% lifitegrast ophthalmic solution, Shire, Lexington, MA), punctal occlusion, etc.], enrolled subjects who still present with signs and symptoms of moderate

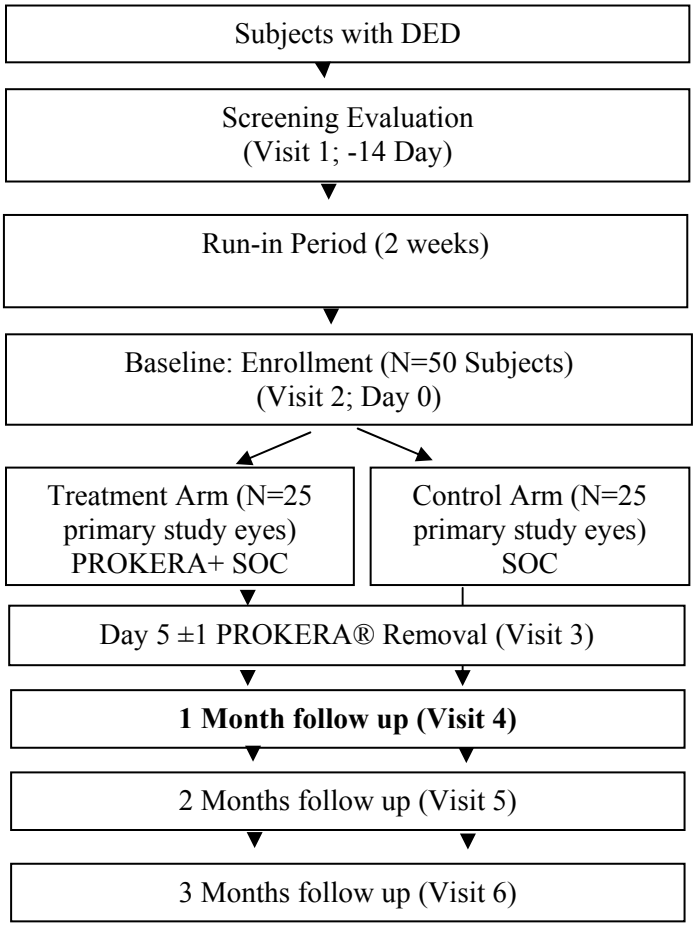
DED at the screening visit, will continue in the study. Those subjects whose signs and symptoms abate during the run-in period will be discontinued from the study. Subjects who continue in the study will be assigned an appropriate study identification code, and randomized to receive either PROKERA plus SOC or SOC alone.

Subjects assigned to PROKERA plus SOC will have PROKERA inserted into one eye (study eye) and will then restart the SOC treatment for both eyes after randomization. After the PROKERA application for 5 ±1 days together with SOC, all subjects in the PROKERA® Arm will return to the clinic to have the PROKERA removed and will continue with the SOC treatment for both eyes. Subjects assigned to the Control Arm will start the SOC treatment for both eyes after randomization and will not return to the clinic at 5-day visit. Clinical symptoms will be evaluated by OSDI scale[16] and the Eye Dryness Score (EDS).[17,18] Signs of corneal epithelial damage will be evaluated by corneal fluorescein staining at the baseline, one month, two months and three months. To assess the potential for a contralateral effect, the above evaluation will also be conducted, for the subject's fellow eye (i.e. non-study eye). In order to eliminate bias, all evaluators will be masked as to the treatment assignment.

## STUDY SUBJECTS AND RANDOMIZATION:

Subjects will first be randomized in a 1:1 ratio to either PROKERA® Arm (i.e., PROKERA plus SOC) or Control Arm (i.e., SOC only) by a computer-generated randomization code. For the PROKERA® Arm, one eye of each subject will be randomly assigned as the primary study eye.

## STUDY FLOWCHART:




## STUDY PRODUCT AND MODE OF ADMINISTRATION:

PROKERA® is manufactured by TissueTech, Inc. (Miami, FL), and is distributed by BioTissue, Inc., which is a solely owned subsidiary of TissueTech, Inc. PROKERA® is a corneal-epithelial insert, consisting of an ophthalmic conformer that incorporates cryopreserved amniotic membrane. PROKERA® is a Class II medical device that was cleared by the FDA under 510(k) #K032104 with the intended use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.

Following the evaluations performed at the baseline visit, PROKERA®(Slim) will be inserted in the subject's primary study eye between the ocular surface and the eyelid as follows:

1. Apply topical anesthesia
2. Hold the upper eyelid

3. Ask the subject to look down
4. Insert the PROKERA® into the superior fornix
5. Pull lower eyelid down and slide PROKERA® under the lower eyelid
6. Check centration under the slit lamp
7. Apply a tape-tarsorrhaphy over the lid crease (standardized/specified in the full study protocol).

## STUDY POPULATION/ DURATION:

A minimum of 50 subjects with moderate DED will be enrolled and randomized in this study. Following the baseline visit at which the subject will be randomized to either PROKERA® Arm or the Control Arm, one of the two eyes will be designated as the primary study eye. Each subject will be evaluated for a period of three months.

## PARTICIPANTS' ELIGIBILITY:

### Inclusion Criteria

- Subjects with moderate dry eye defined as corneal fluorescein staining score of ≥ 3
- Age ≥ 18 years
- Distance best corrected visual acuity better than 20/60 Snellen equivalent in each eye
- Willing to sign a written informed consent to participate
- Able to follow study instructions, with the intention of completing all required visits

### Exclusion Criteria

- Presence of persistent corneal epithelial defect or ulcer in either eye
- Presence of active ocular infection in either eye
- Presence of ocular inflammation that is not related to keratoconjunctivitis sicca, e.g., allergy, severe blepharitis
- Presence of other corneal disorder(s) that give rise to reduced corneal sensitivity, such as recurrent herpes keratitis
- Presence of corneal diseases other than dry eye that can disturb the pre-corneal tear film such as epithelial basement membrane dystrophy (EBMD)
- Contact lens wear
- History of recent ocular surgery/trauma, which could affect corneal sensitivity, e.g., corneal transplantation, LASIK
- Presence of cicatricial ocular surface diseases
- A medical or ocular condition, or a personal situation, which in the principal investigator's opinion, is not appropriate for participation in the trial

- Any scheduled or planned ocular or systemic surgery or procedure during the study
- Pregnancy and women who are expecting to be pregnant.
- Current enrolment in another interventional drug or device study or participation in such a study within 30 days of anticipated entry into this study

## ENDPOINTS/ OUTCOME MEASURES:

### 1) EFFECTIVENESS ASSESSMENTS:

**Primary Effectiveness Endpoint:**

The primary effectiveness endpoint will be defined as the difference in mean change of the total corneal fluorescein staining score of the primary study eye from baseline to 1 month.

**Secondary Effectiveness Endpoints**

The secondary effectiveness endpoint will be defined as:

- The difference in mean change of the EDS score from baseline to 1 month.
- The difference in mean change of the OSDI score from baseline to 1 month.

**Exploratory Outcomes:**

- The mean changes of the corneal fluorescein staining score of the primary study eye from baseline at 2 months and 3 months.
- The mean change of the EDS score from baseline at 1 week, 2 months and 3 months.
- The mean change of the OSDI score from baseline at 1 week 2 months and 3 months.
- The same analyses at each time point for the study eye will also be conducted for the subject's fellow eye (i.e. non-study eye)

The Dry eye sign of each eye will be evaluated by the degree of corneal fluorescein staining score. The corneal fluorescein staining score is the sum of three scores by subdividing the entire cornea into upper 1/3, middle 1/3, and lower 1/3, of which each will be graded from 0 (no staining) to 3 (diffuse staining). Thus, corneal fluorescein staining score ranges from 0 to 9, with higher scores representing more severity.

Dry eye symptoms will be evaluated using the EDS visual analog scale (VAS) to provide a direct assessment of the subject's perception of their current eye dryness symptoms. The VAS has frequently been used for the collection of patient-reported outcomes and has been

commonly used to assess dry eye symptoms in clinical studies. As such, the 2007 report of the International Dry Eye Workshop (DEWS) listed the VAS as a well-defined symptom assessment methodology suitable for use in dry eye clinical trials. Specifically, patient-reported outcomes assessed using the EDS (via VAS) have been used in other dry eye studies and were recently used as the primary symptom endpoint for FDA approval of lifitegrast (Xiidra) for the treatment of the signs and symptoms of dry eye disease.

The Dry eye symptoms will also be evaluated using the validated, 12-item Ocular Surface Disease Index (OSDI) (Allergan, Inc., Irvine, CA), which assesses symptoms of ocular discomfort, effects on visual function, and the impact of environmental triggers. The 12 items are graded on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score is then calculated on the basis of the following formula: OSDI= [(sum of scores for all questions answered) × 100]/ [(total number of questions answered) × 4]. Thus, the OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability.

**2) SAFETY ASSESSMENTS:**

Adverse events (AEs) during this study are expected to have the same probability of occurrence and of the same magnitude as would be found with subjects with DED and not participating in the study. These could include worsening of the signs and symptoms of dry eye. Some adverse events might be related to PROKERA® placement (adverse device effects -ADEs) which include PROKERA® intolerance, eye irritation, lid swelling and mucus discharge. However, these device related risks are no different in type or frequency when the device is used for dry eye as compared to use of the device for other ocular surface disorders which are already on-label under the FDA 510(k) clearance.

Safety will be assessed by documenting ADEs, in which the severity, cause and the resolution will be evaluated and reported. The Investigators will determine the severity, assign attribution, and report the event according to the Protocol guidelines. Serious ADEs such as vision threatening conditions may indicate patient withdrawal or termination of the study.

## STATISTICAL METHODS:

The primary effectiveness analysis will be conducted on the primary effectiveness measure, the corneal fluorescein staining score change from baseline of the primary study eye, using a mixed-effects model of repeated measures (MMRM) for all randomized eyes within the intent-to-treat (ITT) population, with 1 month being defined as the primary effectiveness endpoint. The MMRM model will utilize Statistical Analysis System's (SAS) PROC MIXED program to perform this analysis and define treatment (PROKERA plus SOC vs. SOC) at 1 month and

treatment-by-month as fixed effects and subject as random effect as well as the baseline corneal fluorescein staining score of the primary study eye as the covariate. The effect of month includes 3 assessments at 1 month, 2 months, and 3 months. The comparison between PROKERA plus SOC and SOC at each month will be conducted, using a model-based t-test procedure, at the significance level of 0.05 (2-sided). The comparison between PROKERA plus SOC and SOC at 1 month will be defined as the primary effectiveness endpoint, whereas the comparisons at 2 months and 3 months will be exploratory analyses.

The OSDI total score change of the primary study eye from baseline over 3 months of the treatment assessment will be analyzed using the same MMRM model described above for the primary effectiveness measure. The comparison between PROKERA plus SOC and SOC at 1 month will be defined as the secondary effectiveness endpoint whereas the comparisons at 1 week, 2 months and 3 months will be exploratory analyses.

To assess the potential for a contralateral eye effect, the above analyses will also be conducted, the subject's fellow eye (i.e. non-study eye) as another exploratory outcome.

## SAMPLE SIZE CALCULATION

The sample size is estimated according to the outcomes reported by John et al.[11]The mean corneal fluorescein staining score does not change in the control group (2.8 at baseline and 2.9 at 3 months) while PROKERA® group reduces the corneal staining from the mean grading score of 2.8 at baseline to 0.8 (SD=0.4) at 1 month and 0.6 (SD=0.5) at 3 months in patients with moderate to severe DED. This result yields a reduction of more than 70% or an effect size of more than 2.0 over 3 months from baseline.

Assuming a large effect size of at least 0.85 for the PROKERA® Arm (i.e., PROKERA® plus SOC) against the Control Arm (i.e., SOC only) at 1 month from baseline for the corneal fluorescein staining score, 23 subjects per group or 46 subjects in total are needed to be randomized to yield an 90% power at a 2-tailed significance level of 0.05, using two-sample t-test, to detect such a difference between the two treatments. The effect size of 1.00 is equivalent to a reduction of approximately 35% in corneal fluorescein staining score from baseline for the PROKERA® Arm compared to the Control Arm. To further account for an around 10% dropout, the study plans to enroll and randomize 50 subjects in total.

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