Safety and Feasibility of Cultivated Autologous Limbal Epithelial Cell Transplantation in the Treatment of Limbal Stem Cell Deficiency (CALEC)

Statistical Analysis Plan

Version 1.0

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VERSION HISTORY

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1.0 Study Objectives

The objectives of the "Safety and Feasibility of Cultivated Autologous Limbal Epithelial Cell (CALEC) Transplantation in the Treatment of Limbal Stem Cell Deficiency" study are as follows.

Excerpt from Protocol Section 2:

The main aim of the study is to preliminary estimates of the safety and feasibility of cultivated autologous limbal epithelial cell (CALEC) transplantation in the treatment of unilateral LSCD. Secondarily, efficacy of CALEC will be investigated and both safety and efficacy of CALEC will be compared to CLAU. These secondary objectives are intended to be exploratory rather than conclusive.

PRIMARY OBJECTIVES

1. **Safety (within CALEC group):** To establish the safety of CALEC transplantation by determining the incidence of primary ocular adverse events through 18 months of follow-up.

2. **Feasibility (within CALEC group):** To establish feasibility of manufacturing CALEC for corneal surface reconstruction.

SECONDARY OBJECTIVES

1. **Safety (CALEC versus CLAU):** To investigate whether CALEC is similar to standard treatment with CLAU by comparing incidence of primary ocular adverse events through 18 months of follow-up

2. **Efficacy (within CALEC group):** To investigate whether CALEC transplantation is efficacious in treatment of LSCD participants by comparing pre-operative to post-operative clinical parameters at months 3, 12, and 18.

3. **Efficacy (CALEC versus CLAU):** To investigate whether CALEC is similar to standard treatment with CLAU by comparing between-group changes from pre-operative to post-operative clinical parameters at months 3, 12, and 18.

STUDY CONCLUSIONS

The results of this Phase I/II study will provide guidance on whether to continue to a larger Phase III study and will also provide preliminary data to help determine sample size for future trials. Generally, if the study is not halted for feasibility issues, and there are no major safety or efficacy trends that favor CLAU, a larger study of CALEC could be considered. However, caveats of the study data and other potential factors outside of the trial will need to be considered and weighed in the ultimate decision of whether to proceed.

Treatment assignment will have two sequential phase – Phase A followed by Phase B. Phase A is non-randomized; all patients will receive CALEC treatment (investigational arm). Phase B is randomized; patients will be randomly assigned to CALEC or CLAU in a 2-to-1 ratio. The goal of Phase A is to establish initial safety and feasibility of a few CALEC cases prior to initiating the randomized Phase B. The sample size determination accounts for these 2 phases.

2.0 Study Outcomes

Excerpt from Protocol Section 7:

PRIMARY OUTCOME MEASURES
SAFETY MEASURES

Safety will be assessed in both the CALEC and CLAU groups. The occurrence of the following adverse events at any time during the 18 months of follow-up in the recipient eye will serve as the **primary safety events of interest**:

1. Ocular infection (defined as endophthalmitis or microbial keratitis [bacterial, fungal, parasitic])
2. Corneal perforation
3. Graft detachment ≥50%

In addition to the primary safety events, all adverse events (systemic and ocular in donor and recipient eyes) will be captured. The severity of each adverse event and the relationship of the event to the cell therapy procedure will be assessed by an independent Medical Monitor(s) (MM). The independent Medical Monitor's (see Section 9.3) coding of the adverse event and designation of severity and relatedness to treatment will serve as final to use for adverse event reporting and safety outcome analysis.

FEASIBILITY MEASURES

Manufacturing feasibility will be evaluated in the CALEC group, for each biopsy attempt. At least one CALEC construct will be attempted to be manufactured from each biopsy, as detailed in the MOP. Each attempted construct will undergo Quality Control (QC) testing to determine product conformity to CMCF release criteria per MOP, which includes assessments of cell growth, cell viability, and culture contamination. If all of these QC release criteria are met for at least one CALEC construct, the biopsy attempt is considered a feasibility success.

In the event that a construct met all QC release criteria, but surgery was not performed for a reason unrelated to the development of construct for transplant, the case would still be considered a feasibility success for the biopsy attempt.

Up to two biopsy attempts of a single participant may be performed according to Section 5. Feasibility analysis will explore both the number of biopsies per participant and the number of construct attempts per biopsy, and whether those construct attempts met QC release criteria. Each of the individual QC testing and acceptance criteria will be documented to further describe constructs that did not meet the criteria for release.

SECONDARY OUTCOME MEASURES

Efficacy Measures: Efficacy will be assessed in both CALEC and CLAU groups. The primary efficacy outcome will be a binary "Complete Success" of the graft, as defined below. Secondarily, "Partial Success" will also be considered according to a 3 category outcome defined below.

1. "Complete Success" will be defined as *improvement* in corneal surface integrity
2. "Partial Success" will be defined as
    a. No improvement in corneal surface integrity and
    b. Improvement in either
        i. Extent of corneal vascularization or
        ii. Participant symptomatology
3. Otherwise, not a success

Improvement in each area is defined as follows, where changes are measured relative to the Baseline visit:

- Corneal surface integrity
    - Decrease in epithelial defect surface area (based on clinical assessment by an independent investigator, not the treating surgeon, as described in the MOP) by ≥75% or
    - Decrease in corneal surface staining (based on clinical assessment by an independent investigator, not the treating surgeon, using NEI grading scale) by ≥50%
- Extent of corneal vascularization
    - Decrease in neovascular area (based on digital slit lamp photographs, using mathematical software to calculate as described in the MOP) by ≥25%
- Participant symptomatology

- Decrease in Ocular Surface Disease Index (OSDI) score by ≥25% or
- Decrease in Symptom Assessment in Dry Eye (SANDE) score by ≥25%

The primary efficacy time points will be at 3 months (to assess early success), as well as 12 and 18 months (to assess late success). Efficacy outcomes at all interim post-3 month time points will also be evaluated secondarily.

OTHER OUTCOME MEASURES

In addition to the primary and secondary outcome measures defined above, distribution of data and summary statistics will be evaluated on the following in both groups at each time point where relevant data are collected: IOP, impression cytology, corneal opacification, visual acuity. All reported adverse events will also be tabulated in both groups.

3.0 Study Hypotheses

Safety: We expect the probability of seeing at least one primary safety event in the recipient eye (infection, perforation, or detachment) in the CALEC group will be close to 5% (based on current literature, see separate document ***Summary of Previous Literature***).

Feasibility: We expect 5-10% or fewer CALEC constructs will fail to meet the feasibility criteria prior to transplantation as defined in the protocol (based on preliminary experiments at the Connell and O'Reilly Families Cell Manipulation Core Facility, which will manufacture the CALEC construct for this study).

Efficacy: We hypothesize that the proportions with early and late graft success as defined above in the CALEC group will be similar to that of the CLAU group. Based on current literature (see separate document ***Summary of Previous Literature***) we expect the percentage to be between 70-80% in each group

4.0 Sample Size Considerations

The primary objectives of this study are to establish feasibility and to show safety of the CALEC transplantation by estimated the incidence of ocular adverse events (infection, corneal perforation, and/or graft detachment) through 18 months of follow-up. The secondary efficacy objectives are intended to be exploratory rather than conclusive. The efficacy results will provide preliminary data on potential effect size and variability, to help select sample size for future trials. No formal hypothesis testing comparing CALEC to CLAU is planned/ Sample size will not be based on a power calculation for a formal statistical comparison of CALEC to CLAU.

The sample size for Phase A will be 3 participants completing a CALEC transplant. The sample size for Phase B will be 21 participants randomized 2:1 using a block stratification (see protocol excerpt at the end of this section for details on randomization method), resulting in 13-15 CALEC participants and 6-8 CLAU participants. This process would ultimately yield a total of 24 participants (16-18 CALEC participants and 6-8 CLAU participants) across Phase A and B. About 5% of participants may withdraw from the study before reaching 18 months of follow-up (approximately 1 in each group). Thus, the total number of CALEC participants (Phase A and B) with complete follow up could be as few as 15. This minimum target of 15 CALEC participants is what was used to confirm that the sample size would be acceptable for the study, which is also supported by the analyses below which (1) describes the precision on safety rate estimates with 15 CALEC participants and (2) describes the ability to detect occurrence of the primary safety events of interest within a range around 15 CALEC participants.

(1) With a sample size of 15 in the CALEC group, the table below shows the 95% confidence interval for the percentage of participants with at least one primary safety event for varying potential observed results (the same table could apply to either a combined outcome or each type of event separately). For example, if 1 of 15 CALEC group participants experiences a graft detachment event in the study, the 95% confidence interval around the estimated percentage of patients that we expect would

experience a graft detachment event after CALEC would be from 0 to 32%. The potential level of precision on these estimates was considered reasonable for the objective to select preliminary estimates of incidence of these ocular adverse events.

	Number of CALEC participants out of 15 total with at least one event					
	0	1 (7%)	2 (13%)	3 (20%)	4 (27%)	5 (33%)
95% Confidence Interval (exact binomial)	(0, 22%)	(0, 32%)	(2%, 40%)	(4%, 48%)	(8%, 55%)	(12%, 62%)

(2) We also projected the probability of observing at least one primary safety event given varying hypothetical primary safety event rates and varying CALEC group sample sizes (the same table could apply to either a combined outcome or each type of event separately). With a sample size of 15, the chance is >50% that an adverse event that occurs 5% of the time will occur at least once during the trial. If the event rate is closer to 20%, there will be a 96% chance that a primary safety event will be observed at least once during the trial.

	Adverse event rate			
Sample size	30%	20%	10%	5%
10	0.99	0.89	0.65	0.40
15	0.99	0.96	0.79	0.54
20	0.99	0.99	0.88	0.64

The following protocol excerpt describes how the treatment assignment will occur under each phase to reach the desired sample size. The excerpt also describes what will count towards the final sample size of 3 Phase A participants and 21 Phase B participants.

Treatment Assignment, Randomization Procedures, and Final Sample Size

Excerpt from Protocol Section 5.5:

There will be two sequential phases of treatment assignment – Phase A followed by Phase B. Phase A is non-randomized; all participants in this part of the study will be assigned to receive CALEC treatment (investigational arm). Phase B is randomized – participants will be randomly assigned to CALEC or CLAU in a 2-to-1 ratio.

Phase A – Non-Randomized Treatment Assignment

During Phase A, three eligible participants completing the screening and baseline visits will not be randomized to a treatment arm; rather they will be placed in a staggered fashion (described below) into the investigational arm to receive CALEC. This will be the assignment procedure until three participants in Phase A complete a CALEC transplant (or until halting guidelines apply, see Section 9.4). During Phase A, the following will apply:

- If a participant enrolls during Phase A but withdraws from the study prior to transplant, the participant will not count towards the recruitment goal of three participants required for Phase A
- If a biopsy is done for a participant in Phase A, and the biopsy is unable to generate a viable cell sheet for transplant, a second biopsy may be attempted according to the procedure in Section 5.6.
- Once a given Phase A biopsy attempt has either (1) failed or (2) succeeded and participant has completed the 2-week visit, the study team can then proceed to either of the following:
  - Schedule a second biopsy attempt for any prior Phase A participant whose first biopsy failed (according to Section 5.6)
  - Consent and enroll a new participant in Phase A

- **Phase A enrollment ends after three participants in Phase A have completed a CALEC transplant and the 2-week visit after transplantation. After this occurs, Phase B will begin.** Some additional Phase A participants whose first biopsy failed may complete a second biopsy after Phase B begins, and would count towards the Phase A cohort.

Phase B – Randomized Treatment Assignment

During Phase B, eligible participants completing the screening and baseline visits will be randomized in a 2:1 allocation to either the study intervention (CALEC) or standard care (CLAU)

- The randomization schedules will be generated using a permuted block method, with randomly selected block sizes of 3 or 6. Within each block the ratio of CALEC to CLAU will be 2:1. The blocked randomization provides balance between treatment groups over time and the random block size decreases the predictability of assignment to CALEC or CLAU and thereby the possibility of selection bias. The CC will have additional prespecified criteria in place to reject potential schedules in which future allocations could be easily predicted; the clinical site will be masked to these criteria.

During Phase B, the following will apply:

- If a participant enrolls during Phase B but withdraws from the study prior to randomization, the participant will not count towards the recruitment goal.
- Once randomized, participants will be counted towards the study cohort, regardless of whether biopsy, transplant, or follow-up is completed.
- If a biopsy is done for a participant in Phase B who is assigned to the CALEC group, and the biopsy is unable to generate a viable cell sheet for transplant, a second biopsy can be attempted according to the procedure in Section 5.6.
- **Study enrollment ends when the 21st transplant of the Phase B randomized participants has occurred. This means the randomization schedule will include more than 21 allocations to account for some participants who were randomized but did not complete a transplant.**

Total Study Cohort

The total study cohort will include:

- **All participants in Phase A who completed a CALEC transplant (at least 3; may include additional who complete a second biopsy after)**
- **All participants who were randomized in Phase B (at least 21 who completed their transplant).**

The Statistical Analysis Plan documents how participants in the study cohort will be analyzed.
In both Phases, investigators, participants, and those involved in the study assessments will all be aware of (unmasked to) the study intervention received and appropriate protocol procedures.

In addition, the following protocol excerpt describes criteria under which the target sample size may not be reached because of potential concerns with feasibility or safety.

Study Halting Guidlines

Excerpt from Protocol Section 9.3:

The DSMC may recommend at any time whether the study should continue per protocol, be further investigated, be discontinued, or be modified and then proceed. The FDA may also suspend additional enrollment and study interventions/administration of study product for the entire study, if applicable.

There will be no formal halting guidelines for safety, as the DSMC will receive full safety reports on Phase A participants as noted in Section 9.2 above, and will also expeditiously receive some events as noted in Section

9.2 above throughout the duration of the study.

Formal interim analyses to demonstrate early efficacy of CALEC over CLAU are not planned, given the nature of the study (phase I/II) and small sample size.

Halting guidelines for feasibility are as follows:

- A temporary suspension of enrollment will occur if four of the first eight CALEC biopsies, across Phases A and B, result in failure.
  - This could include two biopsies originating from one participant, (i.e., each biopsy would count separately)
  - Multiple construct attempts based on the same biopsy would be considered inclusive of a single biopsy

5.0 Statistical Analysis Plan

Safety Analysis

Coding of all adverse events for analysis will be based on the MedDRA coding determined by the Medical Monitor. The following safety analyses will be performed.

1. **Primary Safety Analysis (within-CALEC group evaluation of primary safety outcomes):**
   a. The primary safety events of interest (ocular infection, corneal perforation, and graft detachment >=50%) in the recipient eye will be summarized as the numbers and percentages (and 95% exact confidence intervals) of participants having each event and the number and percentage (and 95% exact confidence intervals) of participants having any of the three events, up to 18 months.
      i. These events will be evaluated in CALEC Group Phase A and Phase B participants combined. Only participants who completed transplant and only events occurring after transplant will be included.

2. **Primary Safety Analysis (CALEC versus CLAU comparison of primary safety outcomes):**
   a. The primary safety events of interest (ocular infection, corneal perforation, and graft detachment >=50%) in the recipient eye will be summarized as the numbers and percentages (and 95% exact confidence intervals) of participants having each event and the number and percentage (and 95% exact confidence intervals) or participants having any of the three events, up to 18 months.
      i. These events will be evaluated within each treatment group, in Phase B participants only. All participants who were randomized will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included. All events occurring after randomization will be included. Events prior to randomization will not be included.
   b. The two treatment groups will also be compared by computing the differences in percentages (and 95% exact confidence intervals) having each event and the difference in percentages (and 95% exact confidence intervals) having any of the three events.

3. **Secondary Safety Analysis (explore/evaluate all adverse events):** All reported adverse events up to 18 months (including systemic, recipient, and donor eye events) will be evaluated as follows.

a. Within each MedDRA system organ class, tabulate the number and percentage of participants having at least 1 event within the given system organ class. Evaluate both of the following ways:
    i. ***Within-CALEC group:*** Evaluate in CALEC Group Phase A and Phase B participants combined. Only participants who completed transplant will be included. Only events occurring after transplant will be included.
    ii. ***CALEC versus CLAU comparison:*** Evaluate within each treatment group, in Phase B participants only. All randomized participants will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included. All events occurring after randomization will be included. Events prior to randomization will not be included.

b. Within each adverse event term (MedDRA lower level term), tabulate the number of events and number of participants with at least 1 event, separately for systemic, recipient eye, and donor eye events. Evaluate the data in both of the following ways:
    i. ***Within-CALEC group:*** Evaluate in CALEC Group Phase A and Phase B participants combined. Only include participants who completed transplant and only include events occurring after transplant.
    ii. ***CALEC versus CLAU comparison:*** Evaluate within each treatment group, in Phase B participants only. All participants who were randomized will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included. All events occurring after randomization will be included. Events prior to randomization will not be included.

4. **Additional Safety Analyses for DSMC Monitoring Purposes Only**:
    a. The mean number of events per patient will be calculated as the total number of events reported in the treatment group, divided by the total number of patients in the treatment group. Evaluate the data in both of the following ways:
        i. ***Within-CALEC group:*** Evaluate in CALEC Group Phase A and Phase B participants combined. Include only participants who completed transplant and include only events occurring after transplant.
        ii. ***CALEC versus CLAU comparison***: Evaluate within each treatment group in Phase B participants only. All participants who were randomized will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included. All events occurring after randomization will be included. Events prior to randomization will not be included.

    b. Adverse Events designated by the DSMC as requiring expedited reporting (defined in the DSMC Charter) will be tabulated. The Charter describes in detail whether the events of interest are related to the donor or recipient eye and the time frame for classifying an event as an expedited event. CALEC Group Phase A, CALEC Group Phase B, and CLAU Group will be tabulated separately.

Feasibility Analysis

Feasibility will be assessed in the CALEC group only, using patients from both Phase A and Phase B. Each biopsy attempt will be classified as a "**feasibility success**" if it produced at least one construct that met all of the Quality Control (QC) release criteria in the CALEC Manual of Procedures. Secondarily, the number of biopsy attempts for each patient, as well as the QC results of all construct attempts for each biopsy, will be explored.

The following feasibility analyses will be performed.

1. **Primary Feasibility Analysis:** On a biopsy level (denominator is the total number of biopsies performed)
    - Number and percentage of biopsy attempts resulting in a feasibility success

2. **Secondary Feasibility Analysis**: On a patient level (denominator is all patients for whom at least 1 biopsy was performed)
    - Categorize the number and percentage of patients for whom the biopsy (1) produced a feasibility success on the first biopsy attempt, (2) failed first attempt but produced a success on a second biopsy attempt, (3) failed 2 attempts, or (4) failed first attempt and a second was not attempted

3. **Secondary Feasibility Analysis**: On a construct level
    - Categorize the number and percentage of constructs that met all QC release criteria
        - The QC criteria that failed and the data for each individual QC release criteria will also be explored

Efficacy Analysis

The following efficacy analyses will be performed.

1. **Primary Efficacy Analysis (within-CALEC evaluation of primary efficacy outcome):**
    a. The primary efficacy outcome measure is the binary outcome "Complete Success" of the graft versus not (as defined in the Protocol). This measure will be evaluated at each of the following three time points: 3, 12 and 18 months. The number and percentage of participants meeting the "Complete Success" criteria will be tabulated at each of these time points.
        i. Evaluate in CALEC Group Phase A and Phase B participants combined. Only participants who completed transplant will be included.
        ii. For all participants with missing data on the primary efficacy outcome at any of the time points, multiple imputation will be performed for the "Complete Success" status using logistic regression.

2. **Primary Efficacy Analysis (CALEC versus CLAU comparison of primary efficacy outcome):**
    a. The primary efficacy outcome measure is the binary outcome"Complete Success" of the graft versus not (as defined in the Protocol). This measure will be evaluated at each of the following three time points: 3, 12 and 18 months. The number and percentage of participants meeting the "Complete Success" criteria will be tabulated at each of these time points.
        i. Evaluate within each treatment group, in Phase B participants only. All participants who were randomized will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included.
        ii. Participants who were randomized but did not receive a transplant will be included in the analysis as a failure.
        iii. For all participants with missing data on the primary efficacy outcome at any of the time points, multiple imputation will be performed for the "Complete Success" status using logistic regression.

    b. The two treatment groups will also be compared by computing the differences in percentages meeting "Complete Success" and 95% confidence intervals around those differences, at each time point.

    c. As a secondary analysis, a longitudinal model of the percentage of patients with "Complete Success" at each protocol-specified examination time (including visits in-between 3, 12 and 18

month) will be applied using a mixed effects logistic regression, including time by treatment group interactions.

3. **Secondary Efficacy Analysis (within-CALEC group evaluation of secondary efficacy outcome):**
   a. The secondary efficacy outcome measure is the 3 level categorical outcome ("Complete Success", "Partial Success", "Not a Success", as defined in the Protocol). This measure will be evaluated at each of the following three time points: 3, 12 and 18 months. The number and percent of participants in each outcome category will be tabulated at each of these time points.
      i. Evaluate in CALEC Group Phase A and Phase B participants combined. Only participants who completed transplant will be included.
      ii. Missing data will not be imputed for this secondary analysis.

4. **Secondary Efficacy Analysis (CALEC versus CLAU comparison of secondary efficacy outcome):**
   a. The secondary efficacy outcome measure is the 3 level categorical outcome ("Complete Success", "Partial Success", "Not a Success", as defined in the Protocol). This measure will be evaluated at each of the following three time points: 3, 12 and 18 months. The number and percent of participants in each outcome category will be tabulated at each of these time points.
      i. Evaluate within each treatment group, in Phase B participants only. All participants who were randomized will be included regardless of whether transplant was completed. Phase B participants who discontinued prior to randomization will not be included.
      ii. Participants who are randomized but do not receive a transplant will be included in the analysis as failures.
      iii. Missing data will not be imputed for this secondary analysis.
      iv. Comparisons between CALEC and CLAU will be made between the two Phase B (randomized) groups only by computing the differences in percentages and 95% confidence intervals around those differences, at each time point.

5. **Secondary Efficacy Analyses (explore the individual efficacy outcome measures that contributed to the primary and secondary composite outcome measures):**
   Efficacy will be explored by evaluating each outcome listed below at each protocol-specific time point where the data are collected.

   1) Percentage change from baseline in frank epithelial defect surface area (clinical assessment*) - continuous variable
   2) Proportion of participants with decrease in frank epithelial defect surface area (clinical assessment*) ≥75%
   3) Percentage change from baseline in surface staining (clinical assessment, NEI grading scale) - continuous variable
   4) Proportion of participants with decrease in surface staining (clinical assessment ,NEI grading scale) by ≥50%
   5) Percentage change from baseline in neovascular area (photographic images) - continuous variable
   6) Proportion of participants with decrease in neovascular area (photographic images) by ≥25%
   7) Percentage change from baseline in OSDI score - continuous variable
   8) Proportion of participants with decrease in OSDI score by ≥25%
   9) Percentage change from baseline in SANDE score - continuous variable
   10) Proportion of participants with decrease in SANDE score by ≥25%

   * Epithelial defect surface area based on photographic images will also be evaluated.

   Continuous efficacy variables will be summarized by sample size, mean, median, standard deviation, minimum and maximum. Discrete efficacy variables will be summarized by frequencies and percentages.

   These summary statistics will be presented within each of the following:

- ***Within-CALEC group:*** Evaluate in CALEC Group Phase A and Phase B participants combined. Only participants who completed transplant will be included.
- ***CALEC versus CLAU comparison***: Evaluate within each treatment group, in Phase B participants only. All randomized participants will be included regardless of whether the transplant was completed. Phase B participants who discontinued prior to randomization will not be included.
  - Exact 95% confidence intervals for the difference between treatment groups in means for continuous variables and in proportions will be provided.

Missing data will not be imputed for this secondary analysis.

Additional Tabulations and Analyses

Baseline demographic and clinical characteristics will be tabulated according to treatment group. Continuous variables will be summarized by sample size, mean, median, standard deviation, minimum and maximum. Discrete variables will be summarized by frequencies and percentages

A flow chart will be constructed that accounts for all participants. Visit completion rates will be tabulated according to group. The percentage of participants with completed visits in window, out of window, and missed will also be tabulated. The number of dropouts and deaths and the completion rate excluding deaths will also be tabulated separately by treatment group.

Additional data related to both safety and efficacy will be explored by evaluating each of the following at each follow-up visit where data were collected as part of the protocol specified visit:

- Visual acuity
- IOP
- Corneal opacification
- Impression cytology results

Longitudinal models of these continuous measurements will be performed using mixed effects linear regression methods, including time by treatment group interactions.

Continuous variables will be summarized by sample size, mean, median, standard deviation, minimum and maximum. Discrete variables will be summarized by frequencies and percentages.

Appendix

CALEC Scenarios Summary – a quick reference guide of how participants in different scenarios are counted towards recruitment, what the follow up schedule is, and which analyses they are included in

	Phase A Participants			Phase B Participants			
	No biopsy	Biopsy but no transplant	Transplant	Not Randomized	Randomized		
					No biopsy	Biopsy but no transplant	Transplant
Count towards Recruitment Goal (A: 3 / B: 21)	No	No	Yes	No	No	No	Yes
Count towards Total Study Cohort*	No	No	Yes	No	Yes	Yes	Yes
Continue Follow-Up Visit Schedule	No	No –but monitor donor eye 30 days	Yes – Full schedule	No	Yes – 3/12/18M only, timed from rand+30days	Yes – 3/12/18M only, timed from rand+30days	Yes– Full schedule
Include in Feasibility Analysis – Within-CALEC objectives	No	Yes	Yes	No	No	Yes	Yes
Include in Safety Analysis – Within-CALEC objectives	No	No	Yes	No	No	No	Yes
Include in Efficacy Analysis – Within-CALEC objectives	No	No	Yes	No	No	No	Yes
Include in Safety Analysis – CALEC v CLAU objectives	No	No	No	No	Yes	Yes	Yes
Include in Efficacy Analysis – CALEC v CLAU objectives	No	No	No	No	Yes	Yes	Yes

*NOTE: Refers to those being followed through 18 months.
–Additional Phase A biopsy-only participants would be in the feasibility analyses.
–And ALL consented participants would be tracked and in a study flow chart summary as enrolled in the study.

GENERAL NOTE: For safety mointoring purposes, all adverse events that occur after baseline will be collected and reported, regardless of scenarios