A PHASE II, OPEN-LABEL SAFETY AND TOLERABILITY STUDY OF A RENAL AUTOLOGOUS CELL THERAPY (REACT) IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE (REGEN-003)

Protocol Number: REGEN-003

Protocol Version: 1.7

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STATISTICAL ANALYSIS PLAN

Version 1.1

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A PHASE II, OPEN-LABEL SAFETY AND TOLERABILITY STUDY OF AN AUTOLOGOUS NEO-KIDNEY AUGMENT (NKA) IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE (REGEN-003)

STATISTICAL ANALYSIS PLAN

Version 1.1

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full analysis set
FDA	Food and Drug Administration
g	Gram(s)
Hb	Hemoglobin
HbA1c	Glycosylated Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR-QoL	Health-Related Quality of Life
IAS	Injection analysis set
IB	Investigator's Brochure
ICH	International Conference On Harmonization
I /E	Inclusion /Exclusion
iPTH	Intact Parathyroid Hormone
KDQOL	Kidney Disease Quality-of-Life Survey
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NKA	Neo-Kidney Augment
PE	Physical Examination
PT	Preferred Term
PT-INR	Prothrombin Time-International Normalization Ratio
SAE	Serious Adverse Event
sCr	Serum Creatinine
UACR	Urine albumin to creatinine ratio

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # REGEN-003 v1.7, dated 12 January 2021, titled "A Phase II, Open-Label Safety And Tolerability Study of a Renal Autologous Cell Therapy (REACT) in Patients With Type 2 Diabetes And Chronic Kidney Disease (REGEN-003)". See the study protocol for details.

This document details the statistical methods planned to perform the final analysis of the study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Study objectives are to assess safety and explore efficacy during the 24 months following last REACT injection.

2.1.1 Primary Objective

To assess the safety of REACT injected in one recipient kidney.

2.1.2 Secondary Objective

To assess the safety and tolerability of REACT administration by assessing renal-specific adverse events (AEs) over a 24 month period following the last injection.

2.1.3 Exploratory Objective

To assess the impact of REACT on renal function over a 24-month period following the last injection and on the Quality of Life.

2.2 Endpoints

2.2.1 Primary Endpoint

Procedure and/or product related AEs through 24 months post last injection.

2.2.2 Secondary Endpoints

Renal-specific laboratory assessments through 24 months post last injection. Renal-specific laboratory assessments include: eGFR as estimated by three Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [2009 CKD-EPI serum creatinine equation[1], 2012 CKD-EPI cystatin C equation[2], and 2012 CKD-EPI serum creatinine-cystatin C equation[3]], random urine albumin to creatinine ratio (UACR), 24 hour urine albumin, 24 hour urine protein, cystatin C, serum creatinine, blood urea nitrogen, bicarbonate, potassium, phosphorus, calcium, intact parathyroid hormone (iPTH), hemoglobin, and hematocrit.

2.2.3 Exploratory Endpoints

Exploratory endpoints include:

1) Clinical diagnostic and laboratory assessments of renal structure and function (including eGFR, serum creatinine, and proteinuria) to assess changes in the rate of progression of renal disease.

a. Clinical diagnostic assessments of renal structure and function consist of results from renal ultrasounds (cortical thickness, length, and volume by treated/untreated kidney) and renal scintigraphy (differential renal function by treated/untreated kidney).
b. Laboratory assessments considered exploratory endpoints include: eGFR as estimated by three Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [2009 CKD-EPI serum creatinine equation, 2012 CKD-EPI cystatin C equation, and 2012 CKD-EPI serum creatinine-cystatin C equation], serum creatinine, 24 hour urine albumin, and 24 hour urine protein.

2) Patient-reported outcomes from Kidney Disease Quality of Life (KDQOL) and EQ-5D-5L surveys obtained at baseline (i.e., before REACT injection) through 24 months after the last REACT injection.

3) Time to dialysis

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a multi-center, prospective, open-label, single-group study. Up to 10 subjects who complete screening procedures and satisfy all inclusion and exclusion criteria specified in the protocol will be enrolled into the study immediately prior to the biopsy. All subjects will be treated with two REACT injections 6 months (+4 weeks) apart after biopsy. Subjects will be followed over a 24 month period post the last injection. See Appendices A-B for the Schedule of Events.

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

This is a single-arm, open-label study. No randomization scheme or treatment arm assignment applies to this study.

If a subject withdraws from the study before having the renal biopsy, the subject will be considered a screen failure. If a subject withdraws from the study following the renal biopsy but before the first REACT injection, the subject will not be a screen failure, but will not be considered enrolled and may be replaced. If a subject withdraws from the study after REACT injection but before the end of the follow-up period, the subject cannot be replaced.

3.2.2 Blinding

Not applicable since this is an open-label study.

3.2.3 Dosing Schedule

The dose of REACT will be $3x10^6$ cells/g estimated kidney weight and the dosing volume will be 3.0 mL for each 100 g of kidney weight. It is anticipated that all subjects will receive two planned REACT injections to allow dose-finding and evaluate the duration of effects. The series of 2 REACT injections will be administered 6 months apart with a study visit window of 4 weeks.

3.2.4 Treatment Compliance

Eligible subjects will receive their autologous REACT preparations via a series of up to two injections. The investigational product will be administered into the biopsied kidney using a percutaneous approach. REACT product preparation and dosing procedures are specified in this protocol as well as the Study Reference Manual.

It is anticipated that all subjects will receive two REACT injections. In some cases, a subject or the Investigator may elect to delay or withhold the second REACT injection. For example, if there appears to be any untoward safety risk, or if the subject's health status would, in the judgment of the Investigator, be jeopardized, then the second REACT injection should not be administered.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations (n), mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum. Categorical variables will be summarized by presenting frequency count and percentage for each category. All tabulations will be based on pooled data across centers. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, 25% and 75% quartiles will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

CTI Clinical Trial and Consulting Services will perform all efficacy and safety statistical analyses using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

Subject data will be listed, sorted by subject number.

4.1 Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis.

All SAS programs used to create analysis data sets, tables, and listings will be double programmed. The SAS outputs will be compared, and the programs will be updated until the outputs match.

4.2 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full Analysis Set (FAS): The FAS will consist of all subjects who are enrolled in the study. Subjects are considered enrolled once biopsy is taken.

Injection Analysis Set (IAS): The IAS will include all subjects who receive at least one REACT injection.

4.3 Study Day

Study day 1 will be the day of the first REACT injection. That is, the treatment start date is the date of the first REACT injection. For assessments/events on or after the treatment start date, the

study day is calculated as the date of assessment/event minus the date of treatment start + 1. For assessments before treatment start date, the study day of the assessment is defined as the date of assessment minus the date of treatment start.

4.4 Assessment Windows

No analysis windows are planned for the study regarding data collected outside the protocol specified windows. All data will be included in the analysis based on the visit as it is recorded in the database.

4.5 Handling of Dropouts or Missing Data

Missing data will remain missing. No imputation of missing data will be performed.

4.6 Multiple Comparisons

No multiple comparisons are planned for the study.

4.7 Baseline Definition

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first REACT injection.

4.8 Partial Concomitant Medication (CM) and Adverse Event (AE) Date Handling

For the purpose of inclusion in prior and/or concomitant medication and AE tables, incomplete medication and AE start and stop dates will be imputed as follows:

Partial start dates (where UK, UNK and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY:
  - If the month and year are different from the month and year of the treatment start date, assume 01-MMM-YYYY.
  - If the month and year are the same as the treatment start date month and year, then impute start date as the earliest of treatment start date and end date of CM/AE.

- DD-UNK-YYYY/UK-UNK-YYYY:
  - If the year is different from the year of the treatment start date, assume 01-JAN-YYYY of the collected year.
  - If the year is the same as the treatment start date year, then impute start date as the earliest of treatment start date and end date of CM/AE.

Partial stop dates (where UK, UNK and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month.

- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

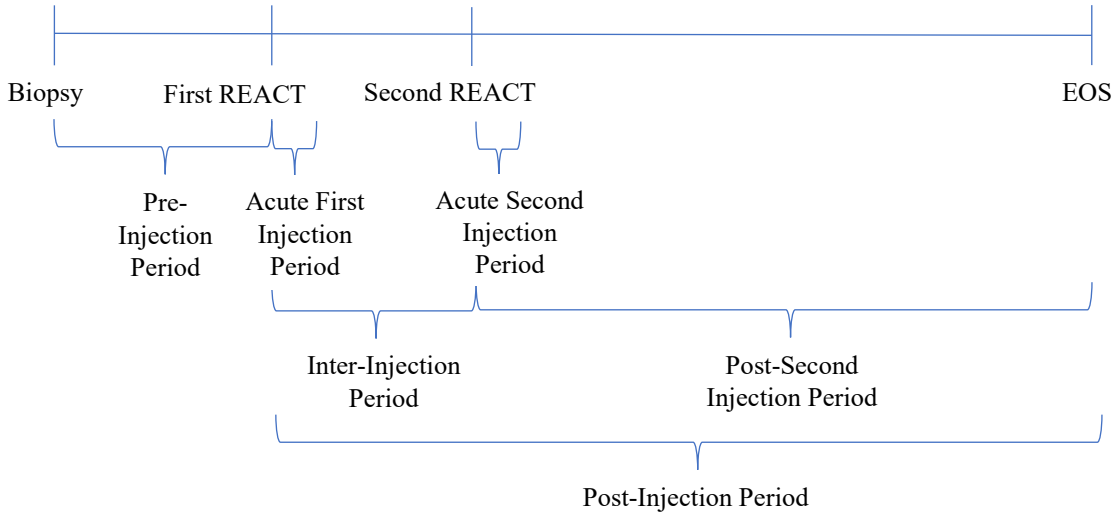
4.9 Analysis Periods

The following analysis periods will be defined as:

- Pre-Injection Period: from the start day of biopsy to the first REACT injection.
- Acute First Injection Period: from the first REACT injection to 1 month following the first REACT injection. The acute first injection period is a subset of the inter-injection period defined below.
- Inter-Injection Period: from the first REACT injection to either the second REACT injection or (if no such second injection was delivered) trial withdrawal or completion.
- Acute Second Injection Period: from the second REACT injection to 1 month following the second REACT injection. The acute second injection period is a subset of the post-second-injection period defined below.
- Post-Second Injection Period: from the second REACT injection to trial withdrawal or completion. This period will not apply to participants for whom only one REACT injection was delivered.
- Post-Injection Period: from the first REACT injection to trial withdrawal or completion. This period includes both the inter-injection and post-second injection periods.

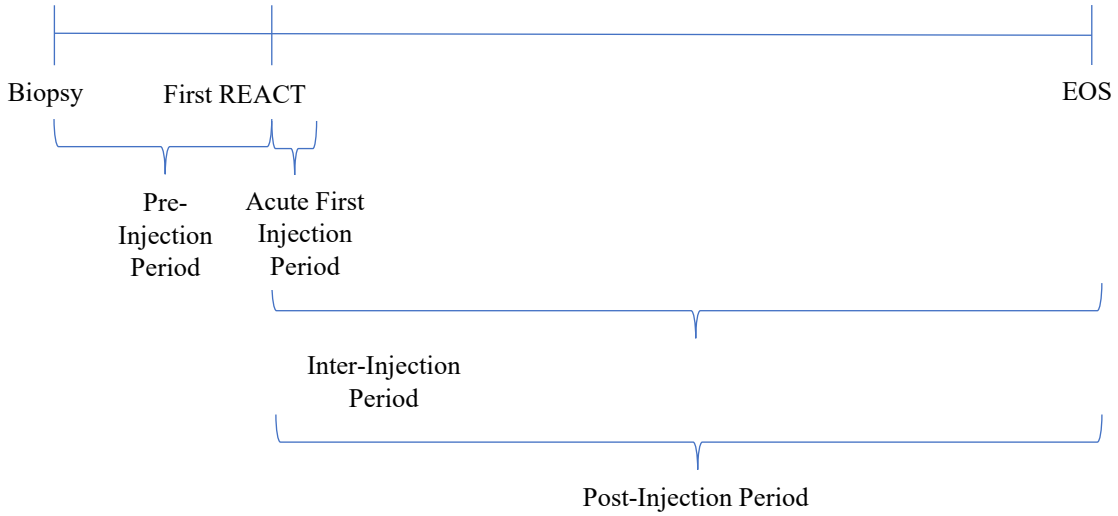
If necessary, imputed dates will be used to determine the analysis period for adverse events.

Figure 1. Analysis Period Diagram for Subjects that Received Two Injections



Abbreviations: EOS = End of Study

Figure 2. Analysis Period Diagram for Subjects that Received One Injection



Abbreviations: EOS = End of Study

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject disposition including number of subjects screened, frequency count and proportion of screen failures will be summarized for all screened subjects. Additionally, a summary of enrolled/biopsied, received one or two REACT injections, stage of withdrawal and reason, completed study will be summarized for all screened subjects by presenting frequency counts and the proportion of subjects. A by subject listing of all screened subjects will also be provided.

5.2 Protocol Deviations

Distribution for the types of protocol deviations and the number and percent of subjects that deviate from the protocol will be tabulated using the FAS. A listing of all protocol deviations will be provided.

5.3 Demographic and Screening Characteristics

For the FAS, demographics including age, gender, race, and ethnicity will be summarized using descriptive statistics. Additionally, the following measurements taken at screening will be summarized using descriptive statistics for the FAS: height, weight, BMI, treated kidney cortical thickness, untreated kidney cortical thickness, treated kidney volume, and untreated kidney volume.

Cortical thickness is measured by MRI and ultrasound. For this summary, the screening result for

cortical thickness taken from the MRI assessment will be used, if available. If the MRI assessment is unavailable, the cortical thickness as measured by ultrasound will be used, if available. Volume is measured by MRI and CT scan. For this summary, the screening result for volume taken from the MRI assessment will be used, if available. If the MRI assessment is unavailable, the volume as measured by the CT scan will be used, if available.

If the FAS and IAS are different, then demographics and screening characteristics will be summarized for the IAS as well.

5.4 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT using the FAS. A by-subject listing will also be created.

5.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the most recent World Health Organization (WHO) drug dictionary available at the time of analysis. The number and percent of subjects in the FAS using prior and concomitant medications will be tabulated by default Anatomical, Therapeutic, and Chemical (ATC) class level 4 and by generic name. In the case where ATC Level 4 value is not available (i.e. no term per WHO dictionary), the next non-missing lowest ATC level will be used for this summary. For example, if the ATC level 3 value is blank, then the ATC level 2 value will be used. If the ATC level 2 value is blank, the ATC level 1 value will be used. A listing of all prior and concomitant medications recorded in the database will be provided.

Additionally, there are several classes of medications that are of special interest. Separate tables for prior and concomitant medications of special interest will present the number and percentage of subjects in the FAS using medications in the following categories of special interest along with the generic name of the medication. The listing of prior and concomitant medications will identify whether each medication listed meets criteria for inclusion into one of the categories of special interest, and which category the medication falls into. The categories of special interest include: sodium-glucose cotransporter-2 (SGLT2) inhibitors [e.g., dapagliflozin, canagliflozin, empagliflozin], mineralocorticoid receptor antagonists [e.g., finerenone], angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, hyperkalemia therapy [e.g., lokelma, kayexalate], sodium bicarbonate, anemia therapy [e.g., epogen], phosphate binders [e.g., PhosLo, renagel], secondary hyperparathyroidism therapy [e.g., calcitrol], and medications to treat edema [e.g., Lasix, bumex].

A prior medication is defined as one which administration ended within 30 days before Biopsy. A concomitant medication is defined as any medication taken after Biopsy.

6. EFFICACY ANALYSIS

6.1 Primary Efficacy Endpoint and Analysis

The primary endpoint of this study is safety related and therefore there is no primary efficacy endpoint.

6.2 Secondary Efficacy Endpoints and Analyses

The secondary efficacy endpoints are renal-specific laboratory assessments including: eGFR as estimated by three CKD-EPI equations [2009 CKD-EPI serum creatinine equation, 2012 CKD-EPI cystatin C equation, and 2012 CKD-EPI serum creatinine-cystatin C equation], random urine albumin to creatinine ratio (UACR), 24 hour urine albumin, 24 hour urine protein, cystatin C, serum creatinine, blood urea nitrogen, bicarbonate, potassium, phosphorus, calcium, intact parathyroid hormone (iPTH), hemoglobin, and hematocrit.

Measurements taken after dialysis has started will be removed from all efficacy analyses.
Listings of lab assessments will include a notation for assessments taken after the start of dialysis so that it is clear which records are included in the efficacy analyses.

Renal-specific lab values will be summarized by presenting descriptive statistics of raw data and change from baseline values at each time point using the IAS.

6.3 Exploratory Efficacy Endpoints and Analyses

The exploratory endpoints are:

- Clinical diagnostic and laboratory assessments of renal structure and function (including eGFR, serum creatinine, and proteinuria) to assess changes in the rate of progression of renal disease.
    - Clinical diagnostic assessments of renal structure and function consist of results from renal ultrasounds (cortical thickness, length, and volume by treated/untreated kidney) and renal scintigraphy (differential renal function by treated/untreated kidney).
    - Laboratory assessments considered exploratory endpoints include: eGFR as estimated by the 2009 CKD-EPI serum creatinine equation, serum creatinine, 24 hour urine albumin, and 24 hour urine protein.
- Patient-reported outcomes from the Kidney Disease Quality of Life (KDQOL) and EQ-5D-5L surveys obtained at baseline (i.e., before REACT injection) through 24 months after the last REACT injection.
- Time to dialysis

6.3.1 Quality of Life (QoL)

An exploratory analysis will be conducted to examine potential changes in health-related Quality of Life (HR-QoL). Subjects will complete the KDQOL-SF™ survey (i.e., Kidney Disease and Quality of Life Short Form) and EQ-5D-5L survey at baseline and through 24 months after the last REACT injection.

The KDQOL-SF is a 36-item, validated, HR-QoL instrument relevant to patients with kidney disease. [4] This disease-specific, HR-QoL instrument consists of the following subscales:

- The “SF-12 measure of physical (PCS) and mental (MCS) functioning” contains items about general health, activity limits, ability to accomplish desired tasks, depression and anxiety, energy level, and social activities.
- The “Burden of Kidney Disease subscale” contains items about how kidney disease

interferes with daily life, takes up time, causes frustration, or makes the respondent feel like a burden.

- The "Symptoms and Problems subscale" contains items about how bothered a respondent feels by sore muscles, chest pain, cramps, itchy or dry skin, shortness of breath, faintness/dizziness, lack of appetite, feeling washed out or drained, numbness in the hands or feet, nausea, or problems with dialysis access.
- The "Effects of Kidney Disease on Daily Life subscale" contains items about how bothered the respondent feels by fluid limits, diet restrictions, ability to work around the house or travel, feeling dependent on doctors and other medical staff, stress or worries, sex life, and personal appearance.

The subscales for burden of kidney disease, symptoms and problems, and effects of kidney disease, as well as the composite scores for PCS and MCS will be calculated as described in the reference [4].

The EQ-5D-5L is a five-item, validated, HR-QoL instrument [5]. EQ-5D-5L health states can be summarized by a single summary number (index value) which reflects how good or bad a health state is according to the preferences of the general population of a country/region.

The actual and change from baseline in KDQOL scores and EQ-5D-5L index values at each time point post REACT injection will be summarized descriptively using the IAS.

Measurements taken after dialysis has started will be removed from all efficacy analyses. Listings of QOL assessments will be provided for the FAS and will include a notation for assessments taken after the start of dialysis so that it is clear which records are included in the efficacy analyses.

6.3.2 Renal Ultrasound

The actual and change from baseline values for the renal ultrasound measurements of cortical thickness, length, and volume for the treated and untreated kidney will be summarized descriptively at each time point post REACT injection using the IAS.

Measurements taken after dialysis has started will be removed from all efficacy analyses. All renal ultrasound measurements will be presented in a data listing for the FAS. The listing will include a notation for assessments taken after the start of dialysis so that it is clear which records are included in the efficacy analyses.

6.3.3 Renal Scintigraphy

The actual and change from baseline values for the differential renal function results for the treated and untreated kidney renal scintigraphy results will be summarized descriptively at each time point post REACT injection using the IAS.

Measurements taken after dialysis has started will be removed from all efficacy analyses. A listing of all renal scintigraphy assessments will be provided for the FAS and will include a notation for assessments taken after the start of dialysis so that it is clear which records are included in the efficacy analyses.

6.3.4 Rate of Progression of Renal Disease

Using the IAS, the rate of progression of renal disease will be assessed graphically for eGFR as estimated by the 2009 CKD-EPI serum creatinine equation, serum creatinine, and 24 hour urine albumin, and 24 hour urine protein. For each subject a plot of the lab result versus time (in study days) will be displayed, showing vertical lines at biopsy date, 1st and 2nd injection, and the initiation of dialysis, if it is administered. Additionally, for eGFR, the rate of progression of renal disease will be assessed by estimating the annualized eGFR slope over time for each subject. Each subject will serve as his or her own control. The subject's previous medical history, which must include a minimum of 6 months of observation of renal function, will serve as the control for rate of progression of renal insufficiency. The historical eGFR measurements as well as all on study measurements taken prior to the first REACT injection will constitute the pre-injection period for this analysis.

The annualized rate of eGFR decline for the pre-injection, post-second injection, and post-injection periods will be estimated separately by linear mixed effects models. That is, separate models will be fit for each of the specific time periods: pre-injection, post-second injection, and post-injection periods. Each subject with a minimum of 3 observations during the period of interest will be modeled. The model will include unscheduled visits, and only the last measurement if there was a re-test on the same day.

For the pre-injection period, the linear mixed effects model will include eGFR as the dependent variable, and time (in years, derived as study day/365) as the independent variable. To account for between-subject variability in eGFR trajectories, random slopes and intercepts will be included. An unstructured covariance matrix will be used for the model. If the model cannot be fit with the unstructured covariance matrix, the following structure will be tried in the order listed below (decreasing number of parameters) until the one of them fit the model:

1. First-order autoregressive mobbing average (ARMA(1,1))
2. First-order autoregressive (AR(1))
3. Compound symmetry (CS)
4. Variance Components (VC)

For the post-secondary period, and separately for the post-injection period as a whole, linear mixed effects models will be fit including eGFR as the dependent variable, time (in years, derived as study day/365) as the independent variable, and baseline eGFR as a covariate. To account for between-subject variability in eGFR trajectories, random slopes and intercepts will be included. An unstructured covariance matrix will be used for the model. . If the model cannot be fit with the unstructured covariance matrix, the same procedure as for the pre-injection period will be followed.

A table will be presented to display the following for each time period of interest: number of subjects included in the model, the estimated slope for the time variable, and the associated standard error. If no model can be fit, the table will simply display a message "Model did not converge."

6.3.5 Time to Dialysis

Using the IAS, the number and percentage of subjects who started dialysis will be reported along with the Kaplan-Meier estimates for the quartiles of the distribution for time to dialysis.

Additionally, a Kaplan-Meier plot and a listing of the derived time to dialysis values will be presented.

Time to dialysis is defined as the time in months from the first REACT injection to the start of dialysis. Subjects who did not start dialysis during the study will be censored as of their last visit date.

7. SAFETY ANALYSIS

Safety assessments will include adverse events, clinical laboratory assessments, vital signs, imaging, pregnancy test, and ECG. Safety evaluation will be performed according to the schedule of events presented in the Appendix A-B. No hypothesis testing will be performed.

7.1 Biopsy and REACT Injections

The number of subjects biopsied, total number of injections received, and the total volume of REACT injected will be summarized and presented for the FAS. All biopsy and injection data will be listed for the FAS.

7.2 Adverse Events

An adverse event (AE) is the development of an undesirable medical condition (including abnormal laboratory findings) or the deterioration of a pre-existing medical condition following or during exposure to a study treatment, whether or not considered to have a causal relationship with study procedures or the investigational product. The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the subject that occur from the day of the biopsy procedure through 24 months after the final injection of REACT are monitored and recorded in the subject's medical record as well as the CRF.

7.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE that started after the first injection of REACT or started prior to the first injection but increased in severity or frequency after the first injection of REACT. For missing onset or end dates, the rules stated in Section 4.8 will be followed. The imputed dates will be used to determine if the AE is treatment emergent.

In addition to the overall treatment-emergence period defined above, the analysis periods defined in section 4.9 will be used for analysis of the AEs:

7.2.2 Adverse Event Intensity

Intensity will be assessed by the Investigator using the "Common Terminology Criteria for Adverse Events" (CTCAE) version 4.03, from the US National Cancer Institute[6] (refer to http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

If an AE is not included in the CTCAE, then the Investigator will determine the intensity of the AE according to the following criteria:

- **Mild (Grade 1)**: The AE is noticeable to the subject but does not interfere with routine

activity.

- **Moderate (Grade 2)**: The AE interferes with routine activity but responds to symptomatic therapy or rest.
- **Severe (Grade 3)**: The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. Severe events are usually incapacitating.
- **Life-Threatening (Grade 4)**: The subject is at immediate risk of death.
- **Death (Grade 5)**

If the intensity is missing, then the adverse event is assumed to be grade 5.

7.2.3 Adverse Event Relationship to Investigational Product or Procedure

An Investigator listed on Form FDA 1572 may make the determination of relationship to the biopsy, REACT injection procedure or REACT investigational product for each AE. Definitions of relatedness categories are:

- **Not Related:** Exposure to the study treatment did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the study treatment.
- **Unlikely Related:** The study treatment and the AE were not closely related in time, and/or the AE could be explained more consistently by causes other than exposure to the study treatment product.
- **Possibly Related**: The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the study treatment product.
- **Related**: The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the study product than by other causes, or the study treatment was the most likely cause of the AE.

For the purpose of safety analyses, all AEs judged by the Investigator to be "possibly related" or "related" will be considered treatment-related adverse events. If relationship to biopsy, REACT injection, or REACT product is missing, then the adverse event is assumed to be related for analysis purposes.

7.2.4 Serious Adverse Events

A serious adverse event (SAE) is an adverse event that occurs during any phase of the study (i.e., baseline, treatment, washout, or follow-up) at any dose of the investigational product, comparator, or placebo, and fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity

- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur from the day of the biopsy procedure, during treatment, or within 24 months following the final REACT injection, whether or not they are related to study procedures or the investigational product, must be recorded in the subject's medical record as well as the CRF provided by the Sponsor or its designee.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) will be classified by SOC and PT using MedDRA.

For AEs, the following will be summarized and presented for the IAS. Note that summaries of treatment-emergent AEs only apply to the IAS as all subjects in the IAS have been treated. Summaries of AEs during the pre-injection period apply to both the IAS (treated) and FAS (biopsied). Firstly, the overall summary of AEs and summaries for the pre-injection period will be presented for the IAS. If there are more subjects in the FAS (biopsied) than the IAS (treated), then the overall summary of AEs and the pre-injection period tables will be presented for the FAS as well.

An overall summary of –AEs will be presented, which includes:

a. the number and percentage of subjects experiencing an AE in pre-injection period
b. the number and percentage of subjects experiencing a TEAE during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods
c. the number and percentage of subjects experiencing an AE by greatest intensity in pre-injection period
d. the number and percentage of subjects experiencing a TEAE by greatest intensity during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods
e. the number and percentage of subjects experiencing an AE related to biopsy during the pre-injection period
f. the number and percentage of subjects experiencing a TEAE related to biopsy during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods
g. the number and percentage of subjects experiencing a TEAE related to REACT investigational product during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods
h. the number and percentage of subjects experiencing a TEAE related to REACT injection procedure during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods
i. the number and percentage of subjects experiencing an SAE during the pre-injection period

j. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE) during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods

k. the number and percentage of subjects experiencing a TEAE leading to study discontinuation during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods

l. the number and percentage of subjects experiencing a TEAE leading to death during the acute first injection, inter-injection, acute second injection, post-second injection, and post-injection periods

In the overall summary of AEs table, besides tabulating the number and percentage of subjects, the total number of AE episodes will also be provided. If a subject has repeated episodes of a particular AE, all episodes will be counted in the summary table.

Additionally, each of the categories of events presented in the overall summary of AEs table will be summarized by SOC and PT in individual tables. In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the analysis set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to biopsy, REACT product, or REACT injection procedure will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total number of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the same SOC could appear greater than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in those SOCs.

All AEs will be presented in tables in descending order from the SOC with the highest incidence to the SOC with the lowest incidence. Within each SOC, AEs will be sorted in descending order from the PT with the highest incidence to the PT with the lowest incidence.

The occurrences of all AEs will be listed for each subject. Individual listings of each of the categories of AEs described above will also be presented (e.g., TEAEs leading to study discontinuation). Listings will contain all collected information using the FAS. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates. The listing will display the dates as they are collected. That is, if imputed dates were used to determine if the AE is treatment emergent, the imputed dates will not be displayed in the listing.

7.3 Clinical Laboratory Assessments

Measurement of clinical laboratory parameters will be conducted at the time points presented in the Appendix B. For purposes of analyses, laboratory results based upon standardized units will be used.

Results from all clinical laboratory parameters including pregnancy test will be presented in data

listings for the FAS.

For the IAS, a summary of the laboratory parameters at baseline, each scheduled post-baseline visit and change from baseline will be provided by test category (e.g., chemistry, hematology, etc.). Continuous clinical laboratory values will be summarized by presenting descriptive statistics. UACR will be considered as a categorical variable with three categories: <30 mg/g, 30 – 299 mg/g, and ≥ 300mg/g. Qualitative results at each time point measured will be summarized by presenting the number and percentage of subjects.

Laboratory assessment results from unscheduled visits will be excluded from table summaries but will be included in data listings. When there are repeat measurements for a given visit (i.e. retests), only the last measurement will be listed and used in the table summaries.

Results that are reported as above or below the limit of quantitation (e.g. <4, >10) will be not be imputed and will be treated as missing values for summarization purposes. The originally reported result (e.g. <4, >10) will be displayed in the listings.

Laboratory abnormalities will be defined using the NCI CTCAE grading scheme. Abnormal laboratory values will be flagged as above or below the normal range.

For the IAS, the incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade between baseline and post-baseline up to six months following REACT injection, will be summarized. If baseline and pre-injection data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered as treatment-emergent. These values will be summarized descriptively for the IAS.

Additionally, for the IAS, shift tables (shift from baseline to the worst post-baseline value) will be presented split by the inter-injection, post-second injection period, and the post-injection period as described in section 4.9. Shift tables will describe the shift in CTCAE grades when available, or the shift from low/normal/high when CTCAE grades are not available.

7.4 Vital Signs

Vital signs are taken throughout the procedure during biopsy and first/second REACT injections. As peri-procedure vital signs will be impacted by the procedure (e.g., sedation), the baseline value for all vital signs will be defined as the last non-missing value taken on a date *prior* to the date of first REACT injection. Diastolic and systolic blood pressure measurements are taken in triplicate at the pre-biopsy visit (Day -3 to Day -1), and the pre-injection visit (Day -14 to -10). The average of the blood pressure measurements will be used analysis purposes. For example, in most cases, the baseline blood pressure will come from the pre-injection visit (Day -14 to -10). In those cases, the baseline will be set to the average of the measurements taken for that visit.

Descriptive summaries of the vital signs (both raw and change from baseline values) including systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, weight and BMI will be prepared by visit using the IAS. A listing of all the vital sign measures will also be provided for the FAS.

Vital sign results from unscheduled visits will be excluded from table summaries but will be included in data listings. Additionally, measures taken during procedures will not be summarized, only listed.

If there is a difference between the IAS and FAS, then summaries conducted using the IAS will

be repeated using the FAS.

7.5 ECG

Electrocardiogram interval measurements, including heart rate (bpm), PR interval (msec), QRS (msec), uncorrected QT interval (msec), and QTcF interval (msec) will be summarized by presenting descriptive statistics of raw data and change from baseline values at each visit measured, using the IAS. Sites enter whichever version of corrected QT interval is provided on the ECG report. For analysis purposes, as it is unclear which method of correction is used for the values entered on the CRF, the QTcF value will be calculated from the CRF data and included in the summary.

The Fridericia's correction to the QT Interval (rounded by 1) will be computed and included in the summaries by the formulae:

$$QTcF(m\sec) = QT(m\sec) \times \left(\frac{VentricularRate(bpm)}{60} \right)^{1/3}$$

In addition, counts and percentages for ECG overall interpretation (normal, abnormal, clinically significant, and not clinically significant) will be presented for each scheduled assessment.

A listing of all collected ECG measures will also be provided for the FAS. The listing will also include the calculated QTcF value.

ECG results from unscheduled visits will be excluded from table summaries but will be included in data listings.

7.6 Physical Examination

The number and percentage of subjects with physical examination abnormalities at each visit will be summarized and presented for each body system for the IAS. A listing of all physical examination data will also be provided for the FAS.

A comprehensive examination at screening will look at the following body systems:

HEENT, Cardiovascular, Respiratory, Gastrointestinal, Genitourinary, Skin, Musculoskeletal, Neurological, Hematologic, Allergic, Psychiatric, and any other deserving the examination.

Subsequent examinations will focus on abnormalities, as per SAP Appendix A.

7.7 Safety Ultrasound

The number and percentage of subjects with abnormalities present on the safety ultrasound will be summarized at each visit for the FAS. A listing of all safety ultrasound data will be provided in a listing for the FAS.

7.8 Other Safety Measures

The results from computerized tomography (CT), magnetic resonance imaging (MRI), and

funduscopic retinal examination assessments will be provided in data listings for the FAS.

8. INTERIM ANALYSIS

8.1 Data Safety Monitoring Board (DSMB)

A DSMB will be chartered to oversee subject safety, especially as it relates to unexpected investigational product-related events. The DMSB will minimally consist of 3 members who have expertise directly related to protocol specified activities. It will function independently, and its members will have no other engagement with ProKidney. The DSMB will meet by teleconference at regular intervals, depending on the speed of subject enrollment and the amount of new data generated. The DSMB will advise ProKidney on aspects concerning the safety of subjects participating in the clinical trial. Apart from reviewing study data, the DSMB will consider feedback from the Sponsor and Investigators. The DSMB will share its recommendations with the study centers, Institutional Review Boards /Ethics Committees, and regulatory authorities, as appropriate. Other specific activities and responsibilities of the DSMB will be detailed in the DSMB charter.

DSMB analyses are outside the scope of this SAP.

8.2 Interim Analysis

No interim analysis is specified in the Protocol.

9. SAMPLE SIZE

Up to 10 subjects who complete screening procedures and satisfy all inclusion and exclusion criteria will be enrolled. Statistical analyses will be primarily descriptive in nature and no statistical hypothesis testing is planned for the study.

10. DIFFERENCES BETWEEN SAP AND PROTOCOL

In this SAP, we have specified that the secondary endpoint analysis for eGFR will use three CKD-EPI equations [2009 CKD-EPI serum creatinine equation, 2012 CKD-EPI cystatin C equation, and 2012 CKD-EPI serum creatinine-cystatin C equation] For the exploratory analysis of eGFR only the 2009 CKD-EPI serum creatinine equation will be used. This is done to ensure consistency with all other REACT studies. A protocol clarification letter dated 25May2021 was issued to clarify that the CKD-EPI 2009 Creatinine equation will be used for analyses rather than the CKD-EPI 2012 Creatinine-Cystatin C based equation.

The efficacy analyses as specified in section 6 of this SAP are consistent with the objectives and endpoints section of the protocol. This differs slightly from the primary versus secondary endpoint identification in the statistical section of the protocol.

The exploratory endpoint of time to dialysis was added to this SAP. This endpoint is of clinical interest, but was not previously specified in the protocol.

11. REFERENCES

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12. APPENDICES

12.1 Appendix A: Time and Events Table

Clinical Assessment:	Screening Visit	Renal Biopsy		Optional*	Preparation and Shipment of REACT Product	First REACT Injection			Follow-up First REACT Injection				Optional[b]	Interval Between REACT Injections = 6 Months (+) 4 Weeks**	Last REACT[c] Injection			Follow-up Last REACT Injection				Follow-Up Long-Term	
	Day - 60 to -3[a]	Day -3 to -1	Day 0 Biopsy	Day 1 Follow-up		Day –14 to – 10	Day 0 REACT	Day 1 Follow-up	Day 7 (±) 3 days	Day 14 (±) 3 days	Day 28 (±) 3 day	Months 2, 3, 4, and 5 (±) 7 days	Month 6 (±) 7 days		Day** –14 to – 10	Day 0 REACT	Day 1 Follow-up	Day 7 (±) 3 days	Day 14 (±) 3 days	Day 28 (±) 3 days	Month 2 Month 3 (±) 7 days	Months 6, 9, 12,15,18, 21 (±) 7 days	EOS[d] Month 24 (±) 7 days
Obtain Informed Consent[e]	X																						
Verify I/E Criteria	X	X	X			X	X								X	X							
Obtain Demographic Data	X																						
Obtain Medical History	X	X																					
Record ConMeds	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Perform Comprehensive PE[f]	X																						
Perform Interim PE[f]		X				X					X				X					X		X	X
Measure Vital Signs[g]	X	X	X	X		X	X[h]	X	X	X	X	X	X		X	X[h]	X	X	X	X	X	X	X
Conduct Laboratory Tests[i]	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X	X	X
Perform 12-lead ECG	X	X				X					X				X					X		X	X
Perform Ultrasound	X[j]		X[k]	X[k]		X[j]	X[k]	X[k]							X[j]	X[k]	X[k]						X[j]
Perform MRI Study	→→→	X[l]																					X
Perform Renal Scintigraphy						X[m]									X[m]							X[m]	X[m]
Admit to Hospital			X[p]				X[p]									X[p]							
Perform Kidney Biopsy			X																				
Monitor /Record AEs			X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Inject Autologous REACT							X[n]									X[n]							
CT Scan[o]							X									X							
Discharge			→→→X[p]				→→→X[p]									→→→X[p]							
Funduscopic Exam of Retinae	X																					X[q]	X
Administer KDQOL Survey	X						X				X	X	X			X				X	X	X	X
Administer EQ-5D-5L Survey	X						X				X	X	X			X				X	X	X	X

Abbreviations: AE (adverse event); ConMeds (concomitant medications); DSMB (Data Safety and Monitoring Board); ECG (electrocardiogram); EOS (End-of-Study Visit); I /E (inclusion /exclusion); KDQOL (Kidney Disease Quality of Life Survey); MRI (magnetic resonance imaging); REACT (Renal Autologous Cell Therapy); PE (physical examination).

Notes:

* Day 1follow-up visit should only be conducted if there is a safety event identified during or after the kidney biopsy.

**Every attempt should be made to ensure the second REACT injection is administered 6 months (+4 weeks) after the first injection. In the event that the subject cannot schedule his/her second REACT injection 6 months after receiving the first injection or cannot keep his/her scheduled 6-month visit, ProKidney and the Medical Monitor must be notified immediately. The expectation is that the subject and the clinical center will accommodate the Sponsor's preference that the series of 2 REACT injections should be administered no more than 6 months apart.

a. If the screening assessment falls outside of the 60-day window before renal biopsy, re-screening will be performed as described in Screening (Section 6.1).
b. Because the second REACT injection will occur 6 months (+4 weeks) after the first injection, the 6-month visit may not be scheduled.
c. In the event that a second REACT injection will not be administered, the subject will undergo all follow-up assessments after the last REACT injection at the 24-month EOS Visit.
d. The EOS Visit will take place 24 months after the last REACT injection, or when the subject is terminated from the study by the Investigator (Section 8.6) or when the subject voluntarily discontinues from the study (Section 5.4).
e. The Informed Consent Form must be signed and dated prior to conducting any study-specific procedures, including those at the Screening Visit. Signing the Informed Consent Form starts the 60-day timeline for screening.
f. The PE and interim PE are described in Section 7.2.2.
g. Vital signs include heart rate, resting blood pressure, respiration rate, and body temperature. (Section 7.2.1). At the Pre-Biopsy Visit (Day -3 to Day -1) and the Pre-Injection Visit (Day -14 to Day -10) three BP measurements will be taken and the average will be used to satisfy entry criteria.
h. Vital signs (included are heart rate, blood pressure, and respiration rate) will be measured throughout the procedure. Temperature is not required to be recorded throughout the procedure.
i. Refer to Table 2 for a schedule of laboratory assessments.
j. Ultrasound will be performed at the Screening Visit to verify subject eligibility and to obtain baseline echogenicity reading. Subsequent Ultrasounds will monitor echogenicity.
k. Ultrasound will be performed following the in-patient renal biopsy on Day 0 and Day 1, and following the in-patient REACT injection(s) on Day 0 and Day 1 with the aim of monitoring possible, subclinical AEs.
l. A MRI study without contrast will be performed at the Screening Visit through Day -1 before renal biopsy to determine kidney size and volume.
m. Renal scintigraphy will be performed before the first REACT injection, before the last REACT injection, at the 6-Month Visit after the last REACT injection, at the 12-Month Visit after the last REACT injection, and at the month 24/EOS Visit.
n. The REACT preparation will be handled and injected according to procedures described in the Study Reference Manual.
o. CT Scan must be used in conjunction with ultrasound for the REACT injection procedure.
p. Subjects may be admitted to hospital per site standard practice. Subjects who do not experience complications may be discharged the same day consistent with site standard practice.
q. Subjects will undergo a funduscopic exam with retinal photography of both retinae to monitor diabetic retinopathy at screening, month 12, and month 24/EOS visit.

12.2 Appendix B: Laboratory Time and Events Table

Laboratory Evaluation:	Screening Visit	Renal Biopsy		Optional*	Preparation and Shipment of REACT Product	First REACT Injection			Follow-up First REACT Injection			Optional[b]	Interval Between REACT Injections = 6 Months (+) 4 Weeks**	Last REAC T[c] Injection			Follow-up Last REACT Injection			Follow-up Long-Term	
	Day -60 to -3[a]	Day -3 to -1	Day 0 Biopsy	Day 1 Follow-up		Day -14 to -10	Day 0 REACT Injection	Day 1 Follow-up	Day 14 (±) 3 days	Day 28 (±) 3 days	Months 2, 3, 4, and 5 (±) 7 days	Month 6 (±) 7 days		Day** -14 to -10	Day 0 REACT Injection	Day 1 Follow-up	Day 14 (±) 3 days	Day 28 (±) 3 days	Month 2 Month 3 (±) 7 days	Months 6, 9, 12, 15, 18, 21 (±) 7 days	EOS[d] Month 24 (±) 7 days
Clinical Chemistry																					
Standard panel	X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Renal analytes	X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Lipid panel	X					X								X							X
Pregnancy test[e]	X	X				X								X							X
FSH test[f]	X																				
Serology																					
HIV, HBV, HCV	X																				
Hematology																					
Standard cell counts/indices	X	X		X		X		X	X	X	X	X		X		X	X	X	X	X	X
Hemoglobin, Hematocrit[g]			X[h]				X[h]								X[h]						
Coagulation Status																					
Platelet count	X	X				X								X							
APTT	X	X				X								X							
PT-INR	X	X				X								X							
Urine Collection																					
Standard panel (Micro and Macro)	X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Urine Chemistry		X		X		X	X	X		X				X	X	X	X	X			
24-hour	X										X	X							X	X	X
Test stick (Spot Urine)		X[i]	X[i]	X[i]		X[i]	X[i]	X[i]				X		X[i]	X[i]	X[i]					
Additional Tests																					
HbA_{1c}	X																			X	X
Drugs of abuse	X					X								X							
iPTH	X	X				X				X	X	X		X				X	X	X	X
ß2-microglobulin[j]	X	X				X				X		X		X				X		X	X
NGAL	X	X				X				X	X	X		X				X		X	X
Research (reserve) samples[k]	X	X				X				X	X	X		X				X	X	X	X

Abbreviations: APTT (Activated Partial Thromboplastin Time); FSH (Follicle Stimulating Hormone; HbA_{1c} (glycosylated hemoglobin); HIV (Human Immunodeficiency Virus); HBV (Hepatitis B Virus); HCV (Hepatitis C Virus); NGAL (Neutrophil Gelatinase-Associated Lipocalin); REACT (Renal Autologous Cell Therapy); i PTH (Parathyroid Hormone, intact); PT-INR (Prothrombin Time-International Normalized Ratio)

Notes:

* Day 1 follow-up visit should only be conducted if there is a safety event identified during or after the kidney biopsy.

** Every attempt should be made to ensure the second REACT injection is administered 6 months (+ 4 weeks) after the first injection. In the event that the subject cannot schedule his/her second REACT injection 6 months after receiving the first injection, or cannot keep his/her scheduled 6-month visit, ProKidney and the Medical Monitor must be notified immediately. The expectation is that the subject and the clinical center will accommodate the Sponsor's preference that the series of 2 REACT injections should be administered no more than 6 months apart.

a. If the screening assessment falls outside of the 60-day window before renal biopsy, re-screening will be performed as described in Screening (Section 6.1).
b. Because the second REACT injection will occur 6 months (+4 weeks) after the first injection, the 6-month visit may not be scheduled.
c. In the event that a second REACT injection will not be administered, the subject will undergo all follow-up assessments after the last REACT injection at the 24-month EOS Visit.
d. The EOS Visit will take place 24 months after the last REACT injection, or when the subject is terminated from the study by the Investigator (Section 8.6), or when the subject voluntarily discontinues from the study (Section 5.4).
e. The clinic will perform a urine dip-strip pregnancy test. If positive, then a confirmatory test will be performed by the central laboratory.
f. Post-menopausal women with a confirmatory FSH test do not have to undergo pregnancy testing throughout the study.
g. Within 48 hours before Days 0 for renal biopsy and REACT injection(s), hemoglobin levels will be verified as > 9 g/dL per site standard practices.
h. On Days 0 for renal biopsy and REACT treatment (s), hemoglobin and hematocrit will be measured before and after procedure per site standard practice at the local lab. These samples will be processed by the site's local laboratory to accelerate notification of results and subsequent decisions affecting clinical care. Additionally, blood samples for hemoglobin and hematocrit after procedure will be sent to the central laboratory where results can be entered into the study database.
i. Prior to, day of, and day after biopsy and REACT injection(s), microscopic urinalysis will be performed using a dip (test) stick
j. β2-microglobulin will be assessed in both serum and urine samples.
k. Research samples (serum/plasma and urine) will be collected, frozen, and stored for the evaluation of novel biomarkers.

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Jose Luis Nabut jnabut@ctifacts.com Principal Biostatistician CTI Facts Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Uploaded Signature Image Signature ID: C115D9B7-FB2B-471A-9073-D73B1482C899 Using IP Address: 204.11.86.69 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 11/4/2022 3:28:20 PM Viewed: 11/4/2022 3:28:39 PM Signed: 11/4/2022 3:29:02 PM
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Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Emily Butler Emily.butler@prokidney.com Security Level: Email, Account Authentication (Required)	Emily Butler Signature Adoption: Pre-selected Style Signature ID: AF7DD78C-1234-4331-A978-ED8788C7BC87 Using IP Address: 68.80.85.80 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/10/2022 9:13:15 AM Viewed: 11/10/2022 9:14:35 AM Signed: 11/10/2022 9:15:58 AM
Electronic Record and Signature Disclosure: Accepted: 8/30/2021 12:05:50 PM ID: 1f1c6964-3939-468a-b5f3-f691d5112aa1		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	11/4/2022 3:28:20 PM
Certified Delivered	Security Checked	11/10/2022 9:14:35 AM
Signing Complete	Security Checked	11/10/2022 9:15:58 AM
Completed	Security Checked	11/10/2022 9:15:58 AM

Payment Events	Status	Timestamps

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If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to

receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact CTI Clinical Trial and Consulting Services:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
Please send an email to esign@ctifacts.com

To advise CTI Clinical Trial and Consulting Services of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at esign@ctifacts.com and in the body of such request you must state: your previous email address, your new email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from CTI Clinical Trial and Consulting Services

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to esign@ctifacts.com and in the body of such request you must state your email address, full name, mailing address, and telephone number.

To withdraw your consent with CTI Clinical Trial and Consulting Services

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to esign@ctifacts.com and in the body of such request you must state your email, full name, mailing address, and telephone number.

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify CTI Clinical Trial and Consulting Services as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by CTI Clinical Trial and Consulting Services during the course of your relationship with CTI Clinical Trial and Consulting Services.