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SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934
(Amendment No.)

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☐ Preliminary Proxy Statement

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[*The below press release was issued by ProKidney LP on June 23, 2022 and contained links to the two articles included herein.*]

ProKidney Corroborates the Mechanism of Action of REACT™ with Cell Marker Analysis in Patients with Diabetic Chronic Kidney Disease

Winston-Salem, NC, June 23, 2022 — ProKidney LP (ProKidney), a leading clinical-stage cellular therapeutics company focused on the treatment of chronic kidney disease (CKD) and the prevention of end-stage renal disease (ESRD) requiring dialysis or transplant, today published data from a patient study confirming the mechanistic action of its lead candidate REACT™ with cell marker analysis.

> **"Renal Autologous Cell Therapy to Stabilize Function in Diabetes-Related Chronic Kidney Disease: Corroboration of Mechanistic Action with Cell Marker Analysis" by Joseph Stavas et. al.**

The paper, published in *Kidney International Reports,* describes observed improvements in renal function and a wide array of clinical parameters in patients with moderate to advanced diabetic CKD treated with REACT™.

ProKidney's decade-long research, performed in multiple diseased animal models that were treated with the active biological ingredient found in REACT™, demonstrated repair of diseased kidneys and the improvement of kidney function. Extensive structural, functional, and biochemical analyses, including biopsies and dissection of the treated animal organs, highlighted that REACT™ has the potential to promote the development of new functional kidney structures, including glomeruli and tubules, as well as reduce fibrosis and inflammation. In addition, proteomics, genomic, and metabolomic analyses performed on the animal tissues support the mechanism of repair, new kidney tissue formation, and improvement in renal function promoted by the active biological ingredients in REACT™. While similar extensive tissue analyses cannot be performed on the kidneys of subjects in clinical trials, analyses of blood and urine are consistent with the findings in the animal studies.

"The translational analyses published in this paper are major foundational discoveries in understanding REACT's™ mechanism of action and what it could mean for CKD patients and their caregivers. This publication is further evidence that REACT™ may successfully stabilize and improve kidney function in patients with moderate to severe diabetic CKD," said Dr. Tim Bertram, CEO and Founder of ProKidney. "We are actively enrolling diabetic CKD patients in the Phase 3 REACT™ program, which has been aligned with regulatory authorities in the U.S. and Europe. We intend to bring this first ever autologous cell therapy for CKD through regulatory review and make it available to patients as expeditiously as possible."

REACT™ is an autologous cell therapy produced from a patient's own kidney cells that is comprised of a proprietary mixture of progenitor cells that have been selected and cultured so they can be placed back into the patient's kidney to restore the natural healing processes. REACT™ does not require immunosuppression, which is required for allogeneic (from another person) kidney or cellular transplants. ProKidney's treatment involves a minimally invasive procedure, starting with a standard kidney biopsy, followed by *in vitro* amplification of selected renal cells (SRCs), the active biological ingredient in REACT™, that are able to harness the body's intrinsic ability to repair and restore damaged kidney tissue. The injection procedure of REACT™ is done on an outpatient basis with placement in the cortex of the patient's kidney. This procedure has been shown to be well-tolerated when compared to kidney biopsy, a standard diagnostic procedure.

ProKidney's RMCL-002 multi-center, randomized Phase 2 trial enrolled 81 stage 3/4 CKD diabetic patients who received two injections in the same kidney six months apart, is ongoing and is evaluating safety, efficacy, and durability of REACT™. A paper describing the 81 subject study was published in March 2022 in the *American Journal of Nephrology*. Of the 81 subjects in RMCL-002, 22 subjects have consented to have further phenotypic and proteomic, genomic, and metabolomic analyses of the cells comprising their personalized REACT™ product. The results of these analyses were published in *The Kidney International Report* mentioned above.

All 22 subjects had moderate-to-advanced type 2 diabetic CKD. Annualized estimated glomerular filtration rate (eGFR) slopes pre- and post-REACT™ injection were compared. Fluorescent Activated Cell Sorting (FACS) analysis for renal progenitor lineages in REACT™ and vascular endothelial growth factor A (VEGF-A) analysis were performed. Annualized eGFR slope was -4.63 ml/min per 1/73 m² pre-injection and this showed a statistically meaningful improvement (P=0.015) post-injection. Around 30% of patients achieved stabilization of kidney function and seven had an eGFR slope of >0 ml/min per 1.73 m² post-injection.

Selected renal cells were found to have cell markers from ureteric bud, mesenchymal cap, and podocyte sources and there was production of VEGF, a growth factor associated with maintaining normal nephron function and repair. Improvements were observed in a wide range of clinical parameters pre- and post-injection, including serum creatinine, phosphorus, calcium, and hemoglobin.

No SAEs were associated with the biopsies and REACT™ injections. Other unrelated serious adverse events in this study were common in this population due to the comorbidities of advanced diabetic CKD and metabolic syndrome but were similar in number and characteristics to other historical CKD trials.

The conclusions in the *Kidney International Report* suggested that the selected renal cells in REACT™ may be able to stabilize and improve kidney function, potentially halting or reversing type-2 diabetic CKD progression or may initiate neo kidney like tissue development to stabilize and improve kidney function and halt type 2 D-CKD progression.

About The Phase 3 Clinical Program for REACT™

In October 2021, the FDA granted ProKidney's REACT™ Regenerative Medicine Advanced Therapy (RMAT) designation, after reviewing more than seven years of data collected from over 100 REACT™–treated patients with stages 3/4 diabetic CKD and moderate-to-severe albuminuria and guided ProKidney on a registrational clinical program and potency assay development. This program is designed to generate efficacy and safety data in two randomized, sham-controlled, blinded studies with a primary composite endpoint under a Time-to-Event design. The trials in total will include approximately 1,200 subjects globally, and a clinical evidence package based on this design may provide the necessary evidence of safety and effectiveness to support a Biologics License Application (BLA) for commercialization of REACT™

The Phase 3 program will be conducted in multiple centers in the United States, Europe, Latin America, and Asia Pacific. Study subject demographics will be consistent with previous trials involving REACT ™, including patients at high-risk-of-end-stage kidney disease: Type 2 diabetic mellitus, CKD stage 3/4, not on renal dialysis, eGFR 20-50 ml/min/1.73 m^2, and UACR ranging from 300-5000 mg/g. The robust safety profile of REACT™ after two injections in the same kidney in clinical studies thus far supports an effort to enhance efficacy potential by injecting subjects in both kidneys in the Phase 3 program. This broader injection pattern holds the potential to achieve greater efficacy as the therapy will be delivered into the patients' two kidneys – 2x the kidney mass as compared to Phase 2.

Study subjects in the treatment arm will undergo a kidney biopsy and then be injected in each kidney once with a three-month interval in between injections. Study subjects randomized to the standard of care arm of the study will receive sham biopsies and injections. Following either the second REACT™ or sham injections, subjects in the treatment or standard of care arms will be followed clinically until they reach one of the three components of the primary composite endpoint. Specifically, the primary composite endpoint for this Phase 3 clinical program is the time from the first injection to the earliest of:

- At least 40% reduction in estimated glomerular filtration rate (eGFR), which is a measure of how well the kidneys are working;
- eGFR<15mL/min/1.73m^2 sustained for 30 days and/or chronic dialysis, and/or renal transplant; or
- Death from renal or cardiovascular causes.

In addition to the primary endpoint, a set of key secondary endpoints will be included to evaluate trends in proteinuria, quality of life, other kidney associated laboratory parameters, and other metrics.

Eligible participants from the control standard of care arms of both Phase 3 trials, will be offered the opportunity to enroll into a new Phase 2 trial to allow them to be injected with REACT™ after completing the Phase 3 trial or after experiencing one of the qualifying events highlighted above. This is expected to facilitate the recruitment of study subjects by allowing them to access the potential benefits of REACT™, and at the same time expand the clinical evidence for REACT™'s efficacy and safety profile.

About ProKidney

ProKidney, a pioneer in the treatment of CKD through innovation in cellular therapy, was founded in 2015 after a decade of research. ProKidney's lead product candidate, REACT™ (Renal Autologous Cell Therapy), is a first-of-its-kind, patented, disease-modifying, autologous cellular therapy with the potential not only to slow and stabilize the progression of CKD, but in some cases drive meaningful

improvement in kidney function. REACT™ has received Regenerative Medicine Advanced Therapy (RMAT) designation, as well as FDA and EMA guidance, supporting the Phase 3 clinical program that launched on schedule in January 2022. On January 18, 2022, ProKidney announced that it would become a publicly traded company via a business combination with Social Capital Suvretta Holdings Corp. III (Nasdaq: DNAC). For more information, visit www.prokidney.com.

Additional Information and Where to Find It

In connection with the proposed transaction between SCS and ProKidney, SCS has filed a definitive proxy statement with the U.S. Securities and Exchange Commission (the "SEC"). SHAREHOLDERS OF SCS ARE ADVISED TO READ THE DEFINITIVE PROXY STATEMENT (INCLUDING ANY AMENDMENTS AND SUPPLEMENTS THERETO) AND ALL OTHER RELEVANT DOCUMENTS FILED OR THAT WILL BE FILED WITH THE SEC IN CONNECTION WITH THE PROPOSED TRANSACTION AS THEY BECOME AVAILABLE BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION. THESE DOCUMENTS ARE NOT INTENDED TO FORM THE BASIS OF ANY INVESTMENT DECISION OR ANY OTHER DECISION IN RESPECT OF THE PROPOSED TRANSACTION. The definitive proxy statement will be mailed to the shareholders of SCS as of June 2, 2022, the record date established for voting on the proposed transaction. Shareholders are also able to obtain copies of the preliminary proxy statement, the definitive proxy statement and other documents filed with the SEC that will be incorporated by reference therein, without charge at the SEC's website at http://www.sec.gov.

The documents filed by SCS with the SEC also may be obtained free of charge at SCS's website at https://socialcapitalsuvrettaholdings.com/dnac or upon written request to 2850 W. Horizon Ridge Parkway, Suite 200, Henderson, NV 89052.

Participants in the Solicitation

SCS and ProKidney and their respective directors and executive officers may be deemed to be participants in the solicitation of proxies from SCS's shareholders in connection with the proposed transaction. A list of the names of such directors and executive officers and information regarding their interests in the proposed transaction between ProKidney and SCS are contained in the definitive proxy statement. You may obtain free copies of these documents as described in the preceding paragraph.

No Offer or Solicitation

This communication shall not constitute a solicitation of a proxy, consent or authorization with respect to any securities or in respect of the proposed transaction. This communication shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sale of securities in any states or jurisdictions in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of such state or jurisdiction. No offering of securities shall be made except by means of a prospectus meeting the requirements of Section 10 of the Securities Act of 1933, as amended, or an exemption therefrom.

Forward-Looking Statements

This communication may contain certain forward-looking statements within the meaning of the federal securities laws, including with respect to the proposed transaction between ProKidney and SCS and the timing of enrollment of ProKidney's clinical trials, availability of clinical data, obtainment of regulatory approvals and manufacturing cost reductions. These forward-looking statements generally are identified by the words "believe," "project," "expect," "anticipate," "estimate," "intend," "strategy," "future," "opportunity," "plan," "may," "should," "will," "would," "will be," "will continue," "will likely result," and similar expressions. Forward-looking statements are predictions, projections and other statements about future events that are based on current expectations and assumptions and, as a result, are subject to risks and uncertainties. Many factors could cause actual future events to differ materially from the forward-looking statements in this communication, including but not limited to: (i) the risk that the proposed transaction may not be

completed in a timely manner or at all, which may adversely affect the price of SCS's securities, (ii) the risk that the proposed transaction may not be completed by SCS's business combination deadline and the potential failure to obtain an extension of the business combination deadline if sought by SCS, (iii) the failure to satisfy the conditions to the consummation of the proposed transaction, including the adoption of the definitive agreement related to the business combination between SCS and ProKidney (the "Business Combination Agreement") by the shareholders of SCS and the satisfaction of the minimum cash condition, (iv) the lack of a third-party valuation in determining whether or not to pursue the proposed transaction, (v) the inability to complete the private placement entered into in connection with the transaction, (vi) the occurrence of any event, change or other circumstance that could give rise to the termination of the Business Combination Agreement, (vii) the effect of the announcement or pendency of the transaction on ProKidney's business relationships, operating results, and business generally, (viii) risks that the proposed transaction disrupts current plans and operations of ProKidney and potential difficulties in ProKidney employee retention as a result of the transaction, (ix) the outcome of any legal proceedings that may be instituted against ProKidney or against SCS related to the Business Combination Agreement or the proposed transaction, (x) the ability to maintain the listing of SCS's securities on a national securities exchange, (xi) the price of SCS's securities may be volatile due to a variety of factors, including changes in the competitive and highly regulated industries in which SCS plans to operate or ProKidney operates, variations in operating performance across competitors, changes in laws and regulations affecting SCS's or ProKidney's business, and changes in the combined capital structure, (xii) the ability to implement business plans, forecasts, and other expectations, including manufacturing cost reductions, after the completion of the proposed transaction, and identify and realize additional opportunities, (xiii) the risk of downturns and a changing regulatory landscape in the highly competitive biotechnology industry, and (xiv) uncertainties inherent in cell therapy research and development, including the actual time it takes to initiate and complete clinical studies and the timing and content of decisions made by regulatory authorities. The foregoing list of factors is not exhaustive. You should carefully consider the foregoing factors and the other risks and uncertainties described in the "Risk Factors" section of SCS's definitive proxy statement on Schedule 14A (File No. 001-40560), including any amendments and supplemented thereto, filed with the SEC on June 10, 2022, SCS's annual report on Form 10-K for the year ended December 31, 2021 filed with the SEC on March 28, 2022, including those under "Risk Factors" therein and other documents filed by SCS from time to time with the SEC. These filings identify and address other important risks and uncertainties that could cause actual events and results to differ materially from those contained in the forward-looking statements. Forward-looking statements speak only as of the date they are made. Readers are cautioned not to put undue reliance on forward-looking statements, and ProKidney and SCS assume no obligation and do not intend to update or revise these forward-looking statements, whether as a result of new information, future events, or otherwise. Neither ProKidney nor SCS gives any assurance that either ProKidney or SCS, or the combined company, will achieve its expectations.

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CLINICAL RESEARCH

Renal Autologous Cell Therapy to Stabilize Function in Diabetes-Related Chronic Kidney Disease: Corroboration of Mechanistic Action With Cell Marker Analysis

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Introduction: Chronic kidney disease (CKD) is a worldwide disease without cure. Selected renal cells (SRCs) can augment kidney function in animal models. This study correlates the phenotypical characteristics of autologous homologous SRCs (formulated product called Renal Autologous Cell Therapy [REACT]) injected into patients' kidneys with advanced type 2 diabetes-related CKD (D-CKD) to clinical and laboratory findings.

Methods: A total of 22 adults with type 2 D-CKD underwent a kidney biopsy followed by 2 subcortical injections of SRCs, 7 ± 3 months apart. There were 2 patients who had only 1 injection. We compared annualized estimated glomerular filtration rate (eGFR) slopes pre- and post-REACT injection using the 2009 CKD-EPI formula for serum creatinine (sCr) and the 2012 CKD-EPI Creatinine-Cystatin C equation and report clinical/laboratory changes. Fluorescent Activated Cell Sorting (FACS) Analysis for renal progenitor lineages in REACT and donor vascular endothelial growth factor A (VEGF-A) analysis were performed. Longitudinal parameter changes were analyzed with longitudinal linear mixed effects model.

Results: At baseline, the mean diabetes duration was 18.4 ± 8.80 years, glycated hemoglobin (Hgb) was 7.0 ± 1.05, and eGFR was 40.3 ± 9.35 ml/min per 1.73 m^2 using the 2012 CKD-EPI cystatin C and sCr formulas. The annualized eGFR slope (2012 CKD-EPI) was –4.63 ml/min per 1.73 m^2 per year pre-injection and improved to – 1.69 ml/min per 1.73 m^2 per year post-injection (P = 0.015). There were 7 patients who had an eGFR slope of >0 ml/min per 1.73 m^2 postinjection. SRCs were found to have cell markers of ureteric bud, mesenchyme cap, and podocyte sources and positive VEGF. There were 2 patients who had remote fatal adverse events determined as unrelated with the biopsies/injections or the REACT product.

Conclusion: Our cell marker analysis suggests that SRCs may enable REACT to stabilize and improve kidney function, possibly halting type 2 D-CKD progression.

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KEYWORDS: cell-based therapy; chronic kidney disease; estimated glomerular filtration rate; selected renal cells; type 2 diabetes mellitus

Approximately 37 million US adults have CKD, a major public health concern, as it is a progressive condition that culminates in end-stage kidney disease (ESKD).[1,2] The economic/societal costs of CKD are substantial.[2,3] In 2018, ESKD represented 7.2% US Medicare spending.[4] CKD is underreported with inconsistency in kidney disease testing.[5] Large registry-based studies indicate that D-CKD is the most common cause of ESKD.[6]

The pathomorphologic sequence of nephron loss with glomerular decapitation and progressive tubular fibrosis has been described in diabetic nephropathy.[7] Once nephron loss begins, no new organoids can be formed.[7] There is no cure for CKD and treatments are

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small molecules targeting biochemical pathways in the kidney to affect related comorbidities; however, the underlying glomerular and tubulointerstitial dysfunction remains unaltered. Cell-based therapies are a promising treatment, and in preclinical CKD models, they reduce inflammation and fibrosis, resulting in kidney function stabilization.[8,9]

In animal models, we revealed that isolated and expanded SRCs injected into diseased kidneys augment kidney function and improve survival.[10,11] On the basis of this evidence, we are conducting Federal Drug Administration-approved human clinical trials.[12-14] Elucidating the mechanism of how SRC injections restore kidney function in humans is key to understanding the potential of this therapy for stabilizing CKD.

SRCs are the bioactive product in REACT derived from the patients' own kidney cells. The REACT product is an admixture principally of epithelial cells from the proximal tubules and glomeruli and smaller numbers of other cell subpopulations, such as interstitial cells, collectively called SRCs.[15] Animal models suggest that kidney restoration with SRC-based therapies may mirror fetal kidney development.[11] REACT may afford the diseased kidney components of the developmental pathway to initiate a cascade of events that halt disease progression and/or restore kidney function.[16,17] We present early findings in a subpopulation of 22 patients with moderate to advanced type 2 D-CKD who received REACT as a part of our larger ongoing clinical trial (NCT02836574). We describe change in kidney function and characterize the progenitor cell lines of the REACT product with FACS analysis of membrane-bound nuclear transcription factors, representing cap mesenchyme, ureteric bud, and glomerular lineages (Supplementary Appendix 1), correlating levels of these factors with observed kidney outcomes. We also evaluated secretion of VEGF-A in conditioned media sourced from human SRCs. This is a proof-of-concept clinical trial suggesting that SRC therapy may enable kidney function stabilization through neo kidney-like tissue.[16]

METHODS

Study Population

We enrolled 30- to 80-year-old patients with type 2 D-CKD from multiple institutions across the USA, who had an eGFR of 20 to 50 ml/min per 1.73 m^2 and had consented to the parent study.[18] The diagnosis of type 2 D-CKD was made by clinical diagnosis and did not require histopathologic evidence. Their comorbidities were managed with standard of care, and sodium-glucose transport protein 2 receptor blockade treatment was not a contraindication. Except for diabetes-related conditions, patients with incapacitating comorbidities were excluded. Our cohort only included selected REACT-treated patients from the parent study who consented to this publication and whose SRCs were characterized by FACS.

Biopsy and REACT Injection Procedures

All patients underwent an image-guided standard percutaneous kidney biopsy to isolate and expand kidney cells, creating autologous homologous SRCs. The SRCs were formulated in thermolabile hydrogel to manufacture a fresh REACT product. The first computed tomography (CT)-guided percutaneous injection of patient's autologous SRCs occurred approximately 3 months after the biopsy, and the second percutaneous injection occurred 7 ± 3 months after the first injection (based on clinical observations and trial protocols).[18,19] There were 2 patients who received only 1 injection. The REACT dosing was patient specific, based on kidney volume calculated by magnetic resonance imaging. The cumulative REACT dose ranged from 8 to 16 ml (8.0–16 × 10^8 SRCs) for 20 patients receiving 2 injections and 4.5 to 5.5 ml (4.5–5.5 × 10^8 SRCs) for 2 patients who received only 1 injection. All procedures were under conscious sedation protocols using i.v. midazolam and fentanyl and same-day-admission outpatient visits.

Clinical and Laboratory Data

Clinical and laboratory data were collected at the time of the first REACT injection and every 3 months for 1 year after the first injection. Biochemical measures included electrolytes Hgb, sCr, urea nitrogen, phosphorus, calcium, potassium, bicarbonate, glycated Hgb, log-transformed intact parathyroid hormone, and log-transformed urinary albumin/sCr ratio (UACR). eGFR was estimated using the 2009 CKD-EPI formula for IDMS traceable serum sCr alone and the 2012 CKD-EPI formula for sCr and cystatin C (nephelometry with certified reference materials).[20,21] We analyzed the cohort before and after they received the first REACT injection, establishing their eGFR slope pre- and post-intervention. Patients were classified based on their annualized eGFR slopes (in ml/min per 1.73 m^2 per year) as low responders (<0), moderate responders ($0 and ≤2), and high responders (>2), but for analysis purposes, we combined the moderate and high responder groups and compared them with low responders.

Serious Adverse Events

Serious adverse events (SAEs) were determined by event seriousness and intensity per reporting from the

Medical Dictionary for Regulatory Activities version 23.0 into Preferred Terms and System Organ Classes.

Ethics and Trial Registration

The trial was approved by the research ethics board of the participating centers and registered at http://clinicaltrials.gov/ct2/show/NCT02836574. The first patient consented to the study on March 9, 2017. The trial protocol was approved by each site's Institutional Review Board or Ethics Committee on human research and the patients provided written informed consent to perform cellular analyses of their SRCs.

Phenotypic Marker Analysis of SRCs

FACS analysis determined whether the SRCs contained markers associated with cap mesenchyme, ureteric bud, and glomeruli. The analysis of these proteins, which are mostly transcription factors to describe SRC phenotype (Supplementary Appendix 1), was per-formed as described by Burnette and Bruce in 2013.[22]

VEGF-A Enzyme-Linked Immunosorbent Assay

Three different human SRC cultures (TCHK-030, 031, 032) produced identically to the REACT product from cadaveric donor tissue with conditioned media, and negative control media were analyzed. Individual and average VEGF concentrations were measured at 1-month intervals in triplicate using the Human VEGF Quantikine enzyme-linked immunosorbent assay (R&D Systems), according to the manufacturer's protocol.

Statistics

We used simple descriptive statistics for screening demographic and laboratory measures. Normally distributed parameters (determined by Shapiro-Wilk normality test) were expressed as mean ± SD. Not normally distributed parameters were log-transformed. Longitudinal data were compared using a longitudinal linear mixed effect models with a correlated random intercept and slope (for time).[23] Patient identifier was a random effect, time was a fixed effect, and eGFR was the dependent variable. This analysis was summarized as the annualized slope: the average change in eGFR over 1 year time. To perform this analysis, the pre-injection annualized slope used all measurements from screening until and including day of injection, as this measurement was taken before the injection. The postinjection annualized slope used all measurements from the day after injection to the end of each patient's follow-up. All retest measurements and unscheduled visits were included in the analysis for both the pre-and post-injection analyses. We did not perform a power calculation, as the sample size was small. Some patients had a 24-hour UACR rather than a random sample, and here the random UACR was imputed.

RESULTS

Patients

A total of 28 patients were eligible for this interim analysis. Six did not consent to have their data published. In the final sample of 22 patients, 2 received only 1 injection of REACT; after their first injection, 1 patient commenced on clopidogrel and the second one had uncontrolled hypertension. In the remaining 20 patients with 2 REACT injections, blood pressure did not change (data not shown). Because only 3 patients were on phosphate binders, 2 on erythropoietin supplementation, and 4 on potassium binders, we did not analyze the impact of REACT on phosphorus, Hgb, or potassium levels. Of the 22 patients, 10 were treated with an angiotensin-converting enzyme inhibitor, 13 patients received an angiotensin II receptor blocker, and 3 patients were treated with sodium-glucose transport protein 2 inhibitors.

Laboratory values at screening are depicted in Table 1, with a mean CKD-EPI 2009 eGFR of 37.3 ± 8.91 ml/min per 1.73 m^2 and a mean glycated Hgb of 7.0 ± 1.05%. Consistent with the expected decline, the eGFR dropped to 33.0 ± 8.91 ml/min per 1.73 m^2 at the time of the first REACT injection. Using linear mixed effect model, the annualized eGFR slope improved significantly between pre-injection (-3.98 ml/min per 1.73 m^2 per year) and post-injection of REACT (-1.27 ml/min per 1.73 m^2 per year) in the full cohort ($P = 0.032$).

Using the 2012 CKD-EPI equation based on both sCR and cystatin C, the annualized eGFR slope improved from -4.63 ml/min per 1.73 m^2 per year preinjection

Table 1. Patient characteristics at the time of screening

Characteristic at the time of screening *n* = 22, 17 males	Value [mean ± (SD)]
Age	66.0 (9.04) yr
BMI	33.9 (5.87) kg/m2
Duration of diabetes	18.4 (8.80) yr
Race	82% White, 4.5% African American, 4.5% Native American, 9% others
eGFR based on 2009 CKD-EPI using sCr only	37.3 (8.91) ml/min per 1.73 m2
eGFR based on 2012 CKD-EPI (combined sCr and cystatin C)	40.3 (9.35) ml/min per 1.73 m2
Log(urinary albumin/creatinine ratio, mg/g)	5.7 (2.00)
Hemoglobin	12.4 (1.57) g/dl
Serum calcium	9.3 (0.55) mg/dl
Serum phosphate	3.7 (0.66) mg/dl
Log(intact parathyroid hormone, pg/ml)	4.1 (0.58)
Potassium	4.7 (0.51) mmol/l
Bicarbonate	20.4 (2.70) mmol/l
Hemoglobin A1c	7.0 (1.05)%

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; sCR, serum creatinine.

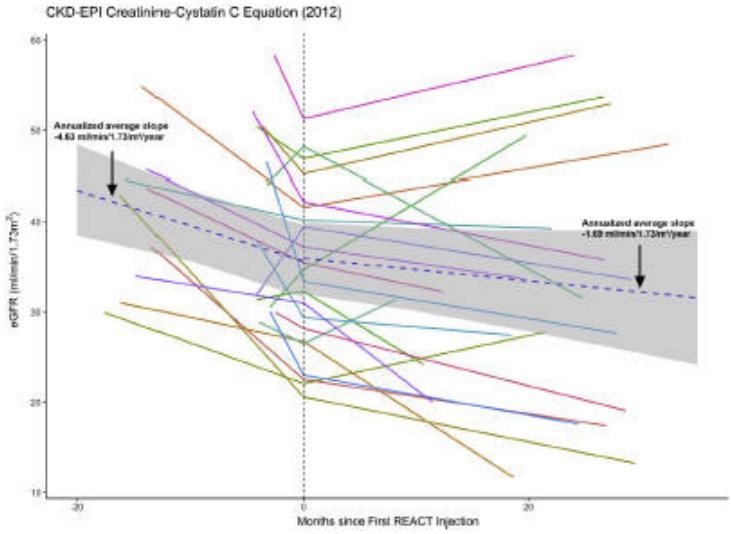

Figure 1. Response of eGFR (creatinine and cystatin C, 2012 CKD-EPI) to SRC injection. Although the overall group had a stabilization of the eGFR decline, 7 patients had a sustained increase of their eGFR. Day 0 represents the date of the first injection. Using linear mixed effects model, the annualized eGFR slope significantly improved from –4.63 ml/min per 1.73 m^2 per year to –1.69 ml/min per 1.73 m^2 per year (P = 0.015). CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; REACT, Renal Autologous Cell Therapy; SRC, selected renal cell.

and improved to -1.69 ml/min per 1.73 m^2 per year (P = 0.015) postinjection (see Figure 1). Median follow-up was 24.3 (interquartile range 18.8, 27.7) months. Linear mixed effect model analyses (see Table 2) revealed that REACT slowed the increase of log parathyroid hormone (P = 0.04) and UACR (P = 0.001).

There were 7 patients (32%) who had a positive postinjection eGFR slope (3 were "moderate responders" and 4 were "high responders"). Annualized slope of the moderate/high responders was 5.88 ml/min per 1.73 m^2 per year, compared .73 m^2/yr. On average, the moderate/high responders received their second injection 7.8 months after their first (compared with 6.2 months in the low responders' group). Their baseline (last pre-injection measurement) average eGFR was 38.9 ± 6.69 ml/min per 1.73 m^2, compared with the remaining "low responders": 30.2 ± 7.80 ml/min per 1.73 m^2. These 7 patients with a positive eGFR slope had an average log UACR of 4.6 ± 2.005 mg/mg, compared with other 15 patients with 6.4 ± 1.56 mg/mg at baseline. High/moderate responders received a mean REACT cumulative dose of 10.4 ± 2.84 ml, whereas the low responders received a cumulative dose of 11.2 ± 2.74 ml. Other laboratory values were not significantly different (data not shown). A longitudinal linear mixed effects model also revealed that change in

Table 2. Linear mixed effects model analysis of various clinical parameters comparing preinjection and postinjection annualized slope

Study parameter	Preinjection annualized slope	Postinjection annualized slope	*P* value
eGFR (CKD-EPI creatinine 2009 equation)	-3.98 ml/min per 1.73 per m2 per yr	-1.27 ml/min per 1.73 per m2 per yr	0.032
eGFR (CKD-EPI creatinine-cystatin C 2012 equation)	-4.63 ml/min per 1.73 per m2 per yr	-1.69 ml/min per 1.73 per m2 per yr	0.015
Serum creatinine	0.14 mg/dl per yr	0.18 mg/dl per yr	0.54
Cystatin C	0.1 mg/l per yr	0.13 mg/l per yr	0.59
BUN	4.74 mg/dl per yr	0.72 mg/dl per yr	0.07
Phosphorus	0.12 mg/dl per yr	0.15 mg/dl per yr	0.82
Calcium	0.02 mg/dl per yr	-0.12 mg/dl per yr	0.10
Serum potassium	0.02 mEq/l per yr	0.00 mEq/l per yr	0.83
Serum Bicarbonate	-0.47 mEq/l per yr	0.33 mEq/l per yr	0.13
Log (PTH)	0.8	0.19	0.04
Hemoglobin	-0.09 g/dl per yr	-0.07 g/dl per yr	0.93
Log (UACR)	-0.42	0.23	0.001

BUN, bound urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; sCR, serum creatinine;UACR, urinary albumin/sCr ratio.

Table 3. Serious adverse events by system organ class and preferred terminology based on the medical dictionary for regulatory activities. N = 15 of 22 patients

System organ class N = 15	Preferred terminology
Cardiac disorders (*n* = 16)	
Acute myocardial infarction	6
Atrioventricular block complete	1
Cardiac arrest	2
Cardiac failure acute	2
Coronary artery disease	3
Left ventricular failure	1
Myocardial infarction	1
Gastrointestinal disorders (*n* = 2)	
Diarrhea	1
Diverticulum	1
Hepatobiliary disorders (*n* = 1)	
Cholecystitis acute	1
Infections and infestations (*n* = 12)	
Cellulitis	2
Cholecystitis infective	1
Clostridium difficile infection	1
Coronavirus infection	1
Device related infection	1
Infected bite	1
Peritonitis	1
Pneumonia	2
Sepsis	1
Staphylococcal infection	1
Injury (*n* = 2)	
Fall	1
Patella fracture	1
Metabolism and nutrition disorders (*n* = 5)	
Dehydration	1
Hypercalcemia	1
Hyperkalemia	3
Musculoskeletal disorders (*n* = 1)	
Meniscal degeneration	1
Neoplasms benign/malignant (*n* =1)	
Squamous cell carcinoma of lung	1
Nervous system disorders (2)	
Cerebrovascular accident	1
Syncope	1
Psychiatric disorders (1)	
Hallucination, visual	1
Renal and urinary disorders (9)	
Acute kidney injury	8
End-stage renal disease	1
Respiratory, thoracic, and mediastinal disorders (6)	
Acute respiratory failure	1
Chronic obstructive pulmonary disease	1
Pneumothorax	1
Respiratory distress	1
Respiratory failure	2
Vascular disorders (3)	
Aortic stenosis	1
Deep vein thrombosis	1
Hematoma	1
Total	61

eGFR over time changes depended on the expression of RET on the REACT product. This interaction trended toward significance ($P = 0.09$).

Serious Adverse Events

SAEs were common in this population due to the comorbidities of advanced diabetic kidney disease (DKD) and metabolic syndrome but were similar to other historical CKD trials. No SAEs were associated with the biopsies and REACT injections. A total of 61 SAEs occurred in 15 of 22 patients, with the 5 most common categories being cardiac, infectious, renal, respiratory, and metabolic (see Table 3). Among those with 2 REACT injections, 2 had fatal SAEs and 1 progressed to ESKD. One patient experienced squamous cell carcinoma of the lung, causing left lung collapse/postobstructive pneumonia and hypercalcemia, resulting in death 12 months post second REACT injection. An autopsy was declined by the family. A second patient had a myocardial infarction, and the third patient (screening eGFR of 33 ml/min per 1.73 m^2 and heavy proteinuria) had rapid decline in eGFR to 20 ml/min per 1.73 m^2 at 6 months and was placed on hemodialysis 11 months post-second REACT injection.

Cell Protein Marker Analysis in the REACT Bioactive Product (SRCs)

Results are summarized in Table 4. Correlation of various markers on FACS analysis revealed evidence for co-expression (Figure 2). Patients with a positive post-injection slope had a greater expression of RET with an average expression of 47.6% in the high/moderate group versus 20.6% in the low group ($P = 0.027$). All other cell markers were not different among patients with a positive versus a negative slope after the first injection. There was also a significant positive correlation between Six2 and RET ($P = 0.0497$). Correlation between various cell markers is depicted in Figure 2.

VEGF-A Analysis

VEGF-A was absent in negative control media using unconditioned serum-free renal cell growth media, but VEGF-A was detectable in SRC-conditioned, serum-free renal cell growth media (range 4.32–7.39 ng/ml) for up to 4 months.

DISCUSSION

Cell-based therapies may have the potential to modulate disease stability and offer new therapeutic options for CKD. In this cohort with moderate/severe type 2 D-CKD, percutaneously injected REACT into their kidney cortex resulted in a statistically significant improvement in eGFR decline, suggesting stabilization of renal function. eGFR, the most widely used parameter of kidney function,[24] improved in the moderate/high responders with a positive regression line slope. Clinical/ laboratory findings suggest that the SRCs in REACT may stabilize renal function. We are unaware of any

Table 4. Compiled data for fluorescent activated cell sorting analysis

Study parameter	Six 2	OSR1	LHx1	RET	FGF8	RACK-1	Nephrin	Podocin
Number of values	19	22	22	22	18	11	10	5
Minimum	0.1200	43.77	0.8700	1.260	0.01000	80.50	68.55	95.12
25% Percentile	0.6200	65.05	10.92	2.865	0.2225	91.00	78.99	95.42
Median	1.900	75.72	32.29	16.53	1.015	93.70	89.43	97.46
75% Percentile	9.500	93.38	91.93	56.12	4.403	99.00	95.47	97.71
Maximum	30.70	99.10	99.10	78.38	58.50	99.40	98.53	97.74
Range	30.58	55.33	98.23	77.12	58.49	18.90	29.98	2.620
Mean	5.929	76.88	44.59	29.18	6.980	93.63	86.79	96.74
SD	8.207	17.17	38.01	28.83	15.50	5.647	9.861	1.232
SEM	1.883	3.661	8.104	6.148	3.652	1.703	3.118	0.5508

studies that have revealed significantly sustained improvement of eGFR in type 2 D-CKD patients beyond our own phase I data.[25] Importantly, in these patients, 2 injections were used, a change from our phase I trial.

All patients tolerated all procedures. This contrasts with the SAEs noted in our phase I safety trial, where REACT injections were performed by surgical laparoscopy and general anesthesia.[25] There were 2 patients who had SAEs unrelated to the procedures, preventing a second REACT injection. The SAE profile in this high-risk population is comparable with that reported in similar CKD trials. [19,26]

We broadly witnessed 3 types of renal function responses, namely high responders (n = 4) with a substantial improvement of eGFR and a posttreatment slope >+2, moderate responders (n = 3) with a slope between zero and +2, and low responders (n = 15) with a slope < 0 ml/min per 1.73 m^2 . Overall, the eGFR slope became less negative in all patients, suggesting kidney function stabilization, while patients with a negative slope still had some improvement. Of note, those with a positive slope had a higher eGFR at entry. However, the number of participants is low, and more patients need to be analyzed to justify any conclusions about whether a higher entry eGFR should be favored.

Blood urea nitrogen, potassium, Hgb, and bio-markers of kidney osteodystrophy did not change. By contrast, we observed slight worsening of log parathyroid hormone and log UACR, although the magnitude of these changes may not be clinically relevant and could not be adjusted because of the small number of participants. Glycated Hgb level was not a factor in eGFR recovery. Blood pressure was unchanged except in 1 patient who received only 1 REACT injection.

REACT is composed principally of selected kidney epithelial cells from the nephron, including proximal tubules, glomeruli, and smaller numbers of other cells.[15] We have previously revealed that SRC implantation in rodents can induce neo kidney-like tissue histologic changes at the site of implantation.[10,11,16] In this study, we did not trace the cells. However, using MR imaging in 2 rodent models, implanted SRCs were detectable 7 days and up to 6 months postinjection into the kidney tissue.[10, 11] Our novel data include compositional analysis of REACT, revealing the presence of cellular markers associated with the earliest stages of nephron development. Unfortunately, institutional review board concerns prevented us from performing follow-up kidney biopsies to assess histology. However, the improvements in eGFR observed, the analysis of the REACT product, and evidence from animal models suggest a similar mechanism may be occurring.

We provide data on the SRC protein expression, including SIX2, Osr1, RET, LHx1, FGF8, Rack1, Nephrin (NPHS1), and Podocin (NPHS2) using FACS analysis, and moderate/high responders were found to have more RET. Osr1 was consistently expressed in the SRCs and is the earliest marker of the intermediate mesoderm that form the gonads and kidneys.[27] This

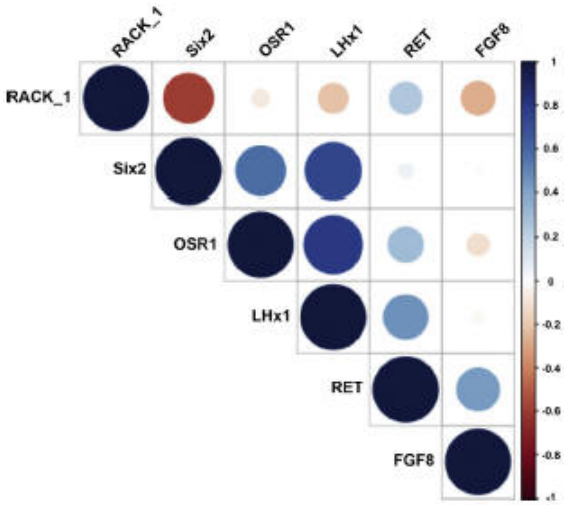

Figure 2. Correlations between the positivity of cell markers of the SRCs. A dark blue represents a correlation coefficient of +1, and a dark red a correlation coefficient of –1. The correlations between LHx1 and Six2 and OSR1 indicated strongest and RACK_1 weakest positivity. SRC, selected renal cell.

expression is not essential for the formation of intermediate mesoderm but is essential for the differentiation toward renal and gonadal structures.[27] Progenitor cells are descendants of stem cells that then further differentiate to create specialized cell types. Therefore, we hypothesize that the REACT product does contain renal progenitor cells.

It is unclear whether the difference in the expression of RET is responsible for the stronger effect on eGFR. The FACS analysis suggests that membrane-bound and nuclear transcription factors representing ureteric bud, cap mesenchyme, and glomerular lineages were present in each patient's REACT product. The ureteric bud is an epithelial tube that arises from the nephric duct and branches repetitively to give rise to the kidney collecting duct system, while also generating inductive signals with the cap mesenchyme that directs mesenchymal-to-epithelial transformation and promotion of nephrogenesis by the surrounding metanephric mesenchyme cells.[28]

SIX2 defines and regulates a multipotent self-renewing nephron progenitor population throughout mammalian kidney development, as SIX2-expressing cells give rise to all cell types of the main body of the nephron, during all stages of nephrogenesis.[29] During normal development, SIX2 expression and SIX2+ nephron progenitor cells in the cap mesenchyme both rapidly disappear after birth.[30] However, in a rat model, preserved SIX2 expression was found after partial nephrectomy in a 1-day-old neonatal rats, resulting in neonephrogenesis.[31] The presence of SIX2 in 19 of 22 patients and a companion CM marker, OSR1, revealed lineage to the cap mesenchyme progenitor line in the SRCs.

Moreover, the LIM-class homebox transcription factor LHx1 is expressed early in the intermediate mesoderm and is one of the first genes to be expressed in the nephric mesenchyme. LHx1 is required for the specification of the renal progenitor cell field.[32] Using an explant culture system to induce kidney tissue, Cirio *et al*.[32] revealed that expression of genes from both proximal and distal kidney structures is affected by the absence of LHx1.

A key signal that promotes ureteric bud morphogenesis is GDNF, a protein secreted by metanephric mesenchyme cells that signals to ureteric bud cells by the rearrangement in transformation RET receptor tyrosine kinase, messaging the mesenchymal-to-epithelial cell transformation. In the ureteric bud and collecting ducts, RET receptor tyrosine kinase, a GDNF, and its co-receptor, GDNF family receptor α 1, initiate a signaling cascade that triggers the growth of RET-positive cells from the nephric duct toward GDNF cells of the metanephric mesenchyme.[33]

Detection of RET-positive cells in our SRC population suggests the presence of a cell population capable of responding to extracellular signaling and giving rise to neo kidney-like tissue. There was significantly higher RET-positive cell expression in the patients with a positive eGFR slope after the first injection. With embryologic nephrogenesis, RET signaling, by Etv4 and Etv5, promotes competitive cell rearrangements in the nephric duct, in which the cells with the highest level of RET signaling preferentially migrate to form the first ureteric bud tip. [33,34] RET signaling in ureteric bud cells is key for controlling cell movement, cell clustering, and ureteric bud formation during nephrogenesis. [34] Whether RET expression is indeed the most important factor requires further evaluation.

Functional evaluation of SRCs provides evidence that activation of certain key developmental pathways may represent a potential mechanism of regenerative bioactivity. Molecular genetics of these developmental pathways and critical proteins that mediate nephro-genesis and their potential relevance to regeneration have been described. [17] Nephrogenesis is a dynamic cellular migration/differentiation, induced by crosstalk signaling in resident cells. It is an integral part of nephron development.

Nephrin and podocin are markers at the slit diaphragm and podocyte pedicels, respectively, and imply glomerulus lineage at the Glomerular Basement Membrane (GBM). Nephrin and the GBM form the filtration barrier , critical to repel albumin and other macromolecules from entering the Bowman's capsule, preventing epithelial inflammatory change. Glomerulogenesis is divided into the following stages: vesicle, comma- and S-shaped, glomerular capillary loop stage, and mature glomerulus,[35] and we have revealed these stages on histology in our animal models of SRCs.[16] Animal model images closely resemble human nephrogenesis.[36] Furthermore, the expression of cap mesenchyme, [37-39] ureteric,[34] and glomerular cell markers [40,41] resembles *in utero* embryologic studies. Animal data may not completely be applicable to humans, given species evolutionary differences, but they provide a practical model. Although we have no histopathologic evidence from the patients, cell markers presented in REACT have been described as essential for nephrogenesis. The populations of SRCs contained cells responsible for nephrogenesis, and the markers analyzed represent the critical pathway for the development of the renal cortex, medullary interstitium, angioblasts, and mesangium (Table 4). These data align with our hypothesis that any improved renal function resultant from REACT injections may be due to neo kidney-like tissue development, mirroring embryonic kidney development.

In cadaveric donor-derived SRCs processed identically to REACT, we also revealed limited evidence for the expression of VEGF-A in vitro. VEGF is a proan-giogenic glycoprotein in the platelet-derived growth factor family, essential for the survival, proliferation, and differentiation of endothelial cells.[42,43] VEGF has a role in angiogenesis/vasculogenesis during embryogenesis, maintaining renal homeostasis during cell migration and is expressed throughout the life of podocytes and tubular cells.[44-46] VEGF-A was expressed by donor SRCs, providing indirect evidence for angiogenesis promoting cell division, migration, endothelial cell survival, and vascular sprouting.[47,48] Our data begin to reveal a putative mechanism of action for REACT, providing the cells involved in a developmental pathway that stimulates cell migration into the diseased tissue, contributing toward neo kidney-like tissue and kidney function stabilization.

This report may serve as a proof-of-concept in humans. Additional data and analysis are required to identify which patients may benefit most from REACT therapy and to provide further evidence on the mechanism of action. Larger phase III human trials of REACT are underway (http://www.prokidney.com/clinical-trials/, accessed January 30, 2022).

Limitations

Our sample is underpowered to evaluate the impact of all covariates and bias assessment. Most patients were Caucasian and there were missing data. Our cohort is part of a larger parent study, and for this report, only 22 patients had functional SRC studies and consented for publication. Some participants had small residual cell volumes after their REACT injections, preventing full FACS analysis. There may be inherent technical limitations of the FACS analysis such as cell asynchrony. Furthermore, we only characterized the SRCs with FACS analysis after the expansion, and it is possible that this expansion process altered the results. Moreover, we did not measure CD24 and CD133 or the stem-cell specific transcription factors Oct-4 and Bml-1 and cannot confirm the presence of pluripotent stem cells responsible for formation of glomeruli as revealed by Sagrinati *et al*.[49]

The patients with a positive slope tended to have a higher entry eGFR, and although their UACR progressed slower, the number of patients is small. We were unable to study the impact of pretreatment eGFR slope over 3 months in several patients based on the study protocol. In some patients, we had a much shorter preinjection slope (see Figure 1) which may explain why some patients had a positive slope before injection, given intrapatient variability of sCr. Nonetheless, the sustained increase in eGFR in 7 of 22 patients is remarkable. We also do not have exogenous benchmark GFR measurements, such as iohexol. However, in our studies with 70% nephrectomized canines, SRCs increased iohexol clearance.[15]

Although usable SRCs could produce REACT from all biopsies, there is a possibility that the yield of usable cells from the biopsy might have been lower from patients with lower eGFR, as much of their kidney tissue could have more fibrosis, affecting FACS positivity. [7,50] Additional studies are needed to confirm our findings and are underway.[13,14,19] Moreover, we must analyze more SRCs for the various expressions of cell line markers to determine minimum requirements for the injectable product. Further analyses with genome-wide transcriptional and epigenetic profiling of SRCs may lend support to complex developmental pathways as mechanisms of action for regenerative CKD therapies. Finally, data from animal studies cannot necessarily be extrapolated into humans and only *in vitro* data are presented to support the hypothesis that the GFR stabilization may be due to neo nephrogenesis.

Summary

Mechanisms of action and potency of cell therapy products are complex and recognized by regulatory agencies.[51] Autologous homologous CKD cell therapies are equally complex due to multiple cell types and the many potential functional effects at the various levels in the nephron, spanning from the glomerulus to the distal convoluted tubule and collecting duct.

We have revealed that the SRCs in the REACT product evolved from preclinical trials[12] and successfully stabilized kidney function in adults with type 2 D-CKD (abstract 3611676 “Renal autologous cell therapy (REACT) for type 2 D-CKD: preliminary results with renal cortex implantation” for the American Society of Nephrology Renal Week 2021). On the basis of preclinical animal studies and this preliminary evidence, it is hypothesized that SRCs in the REACT product may function in part by promoting the assembly of progenitor cells lines, through secretion of pro-angiogenic factors, such as VEGF-A, repairing effete nephrons and possibly producing neo kidney-like tissue.

In conclusion, our trial findings suggest that the SRCs of the REACT product may initiate neo kidney-like tissue development to stabilize and improve kidney function and halttype 2 D-CKD progression. There may be benefits for a higher entry eGFR, multiple doses of REACT, and/or personalized dosing intervals to accommodate disease progression; however, the best treatment regimen remains to be elucidated.

DISCLOSURE

JS, DJ, JWL, JB, RP, EB, and TB are employees of ProKidney and received wages. GF and MF received consulting fees from ProKidney. GF, JL, JB, and MF received fees for advisory roles at ProKidney.

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Data Availability Statement

Current trial efficacy data are not publicly available due to active status of the trial.

AUTHOR CONTRIBUTIONS

JS and TB conceived the original study idea and provided funding, intellectual insight, and supervision and editing. JS developed Tables 1 to 3. GF drafted/edited the manuscript, performed analyses, and developed the figures and tables. DJ, JL, RP, and JB developed the remaining figures. They also wrote the relevant basic science sections and conducted the *in vitro* experiments. MF, GF, JS and TB provided major intellectual insight into the clinical trial and the manuscript writing and editing of each version. EB and RP performed the statistical analysis. EB produced the final Figures 1 and 2. All authors contributed to and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Appendix 1. Composition of cap mesenchyme, ureteric bud, and glomerular cell lines using cell biomarkers.
STROBE Checklist. Strobe Checklist for prospective cohort study.

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Novel Renal Autologous Cell Therapy for Type 2 Diabetes Mellitus Chronic Diabetic Kidney Disease: Clinical Trial Design

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Keywords
Renal autologous cell therapy · Neo-kidney augment • Chronic kidney disease • Diabetic nephropathy • Diabetes-associated chronic kidney disease • Renal outcomes

Abstract
Background: Cell therapies explore unmet clinical needs of patients with chronic kidney disease with the potential to alter the pathway toward end-stage kidney disease. We describe the design and baseline patient characteristics of a phase II multicenter clinical trial utilizing the novel renal autologous cell therapy (REACT), by direct kidney parenchymal injection via the percutaneous approach in adults with type 2 diabetic kidney disease (T2DKD), to delay or potentially avoid renal replacement therapy. ***Design:*** The study conducted a prospective, multicenter, randomized control, open-label, phase II clinical trial between an active treatment group (ATG) receiving REACT from the beginning of the trial and a contemporaneous deferred treatment group (DTG) receiving standard of care for 12 months before crossing over to receive REACT. ***Objectives:*** The objective of this study was to establish the safety and efficacy of 2 REACT injections with computed tomography guidance, into the renal cortex of patients with T2DKD administered 6 months apart, and to compare the longitudinal change in renal function between the ATG and the DTG. ***Setting:*** This was a multicenter study conducted in major US hospitals. ***Patients:*** We enrolled eighty-three adult patients with T2DKD, who have estimated glomerular filtration rates (eGFRs) between 20 and 50 mL/min/1.73 m^2. ***Methods:*** All patients undergo an image-guided percutaneous kidney biopsy to obtain epithelial phenotype selective renal cells isolated from the kidney tissue that is then expanded ex vivo over 4–6 weeks, resulting in the REACT biologic product. Patients are randomized 1:1 into the ATG or the DTG. Primary efficacy endpoints for both study groups include eGFR measurements at baseline and at 3-month intervals, through 24 months after the last REACT injection. Safety analyses include biopsy-related complications, REACT injection, and cellular-related adverse events. The study utilizes Good Clinical and Manufacturing Practices and a Data and Safety Monitoring Board. The sample size confers a statistical power of 80% to detect an eGFR change in the ATG compared to the DTG at 24 months with an $\alpha = 0.05$. ***Limitations:*** Blinding cannot occur due to the intent to treat procedure, biopsy in both groups, and open trial design. ***Conclusion:*** This multicenter phase II randomized clinical trial is designed to determine the efficacy and safety of REACT in improving or stabilizing renal function among patients with T2DKD stages 3a–4.

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Introduction

Cell therapies attempt to address unserved clinical expectations and needs of patients and medical professionals for various chronic medical conditions, including chronic kidney disease (CKD) [1, 2]. CKD affects about 18% of the world population (850 million individuals), with up to 50% secondary to type 2 diabetes which encumbers large cost expenditures, given its risk for progression to end-stage kidney disease [3–5]. Current type 2 diabetic kidney disease (T2DKD) treatments such as renal angiotensin system inhibitors and SGLT2 inhibitors utilize small molecules to modulate biochemical mechanisms of action, albeit in a damaged structural environment [6–8]. In comparison, cell therapies have the potential to induce structural nephro-restoration to stabilize or improve renal function with infrequent dosing and few or no immunologic concerns [9–11].

Most cell-based therapies under investigation for CKD utilize intravascular-delivered mesenchymal cell lines with variable dosing, potency, stability, and end-organ effect. REACT endeavors to address these shortfalls by using a personalized treatment approach with autologous, homologous cells intended to restore nephron structure, improve kidney function, and decrease CKD-related co-morbidities. REACT consists of selective renal cells (SRCs) isolated and expanded using Good Manufacturing Process (GMP) from kidney biopsy tissue obtained from CKD patients.

Our preclinical experience with renal autologous cells demonstrated improved renal function and nephron repair, based on surrogate markers and histologic findings in diabetic models [12]. A first-in-human phase I trial in moderate to advanced T2DKD patients confirmed cell safety and stabilization of various renal function surrogate markers during laparoscopic-guided direct renal cortex REACT delivery [13]. We herein report the design of a novel phase II open-label cell therapy trial of REACT, whereby expanded autologous renal cells are percutaneously reinjected into patients with T2DKD stages 3a–4, in a specific locoregional site of the kidney identified with computed tomography (CT) imaging. Our clinical trial design is shown in Figure 1 and is registered at the following website: https://clinicaltrials.gov/ct2/show/NCT02836574.

Our clinical trial objectives are to establish the efficacy and safety of 2 image-guided percutaneous injections of REACT into the renal cortex of patients with T2DKD, administered 6 months apart, and to compare the change in renal function between an active treatment group (ATG) and a contemporaneous deferred treatment group (DTG).

Materials and Methods

Trial Design

This is a prospective, multicenter, randomized control, open-label, phase II clinical trial. Patients were randomized in a 1:1 ratio into 2 groups (ATG n = 42 or DTG n = 41) after manufacturing confirmed the adequacy/quality of the donor kidney biopsy material and the date of REACT injection. Randomization was performed with the Interactive Web Randomization System. Since this is an open-label study, the study participants, investigators, site staff, and sponsor are not blinded to the treatment assignment. Following a kidney biopsy, patient randomization takes place into the ATG or DTG cohorts. The ATG receives REACT treatment from the beginning of the trial, whereas the DTG will receive SOC for 12 months before crossing over to receive the REACT treatment.

Participants

We included 83 patients, ages 30–80 years, who have T2DKD and an established declining estimated glomerular filtration rate (eGFR) between 20 and 50 mL/min/1.73 m2 (CKD stages 3a–4). Patients are from 17 institutions in the USA. To define the rate of CKD progression, baseline renal function was determined by 2 or more eGFR measurements, at least 3 months apart and 18 months pre-intervention. Patient demographics including clinical/laboratory characteristics and concomitant medications are shown in Table 1. The patient's blood pressure must be <150/90 mm Hg on stable doses of antihypertensives (defined as dose adjustment to no less than one-half of the current dosage or to no more than 2 times the current dosage), 6 weeks prior to the REACT injection, but dose interruptions for up to 7 days due to medical necessity are allowed. If their antihypertensives included an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, treatment must have been initiated at least 8 weeks prior to their renal biopsy. Participants refrain from consuming nonsteroidal anti-inflammatory drugs (including aspirin), fish oil, platelet inhibitors, and anticoagulants 7 days before and after the renal biopsy and REACT injections. Inclusion and exclusion criteria are described in Table 2.

Biopsy and REACT Injection Procedures

All patients underwent an outpatient percutaneous renal biopsy and then were randomized to either the ATG or the DTG of the trial. ATG patients receive a REACT dose as soon as REACT is manufactured and delivered to the research site, whereas the DTG patients received the intervention after 12 months of SOC treatment. Patients received 2 injections of REACT given 6 months apart. In addition, each patient's rate of renal function change (based on the previous 18 months) serves as a comparator to establish the rate of DKD progression. Furthermore, the DTG patients serve only as contemporaneous comparators to the ATG patients for the 12 months during SOC treatment and against themselves once they cross over to receive REACT. The final statistical analysis will reflect the comparator time line and account for expected progression of CKD in the DTG.

A selective population of renal cells are obtained from the patient's renal cortex via percutaneous kidney biopsy, using a standard-of-clinical-care image-guided method (ultrasound or CT). Two 16-gauge or 4 18-gauge core samples >1.5 cm in length are obtained and placed immediately in the transport medium and

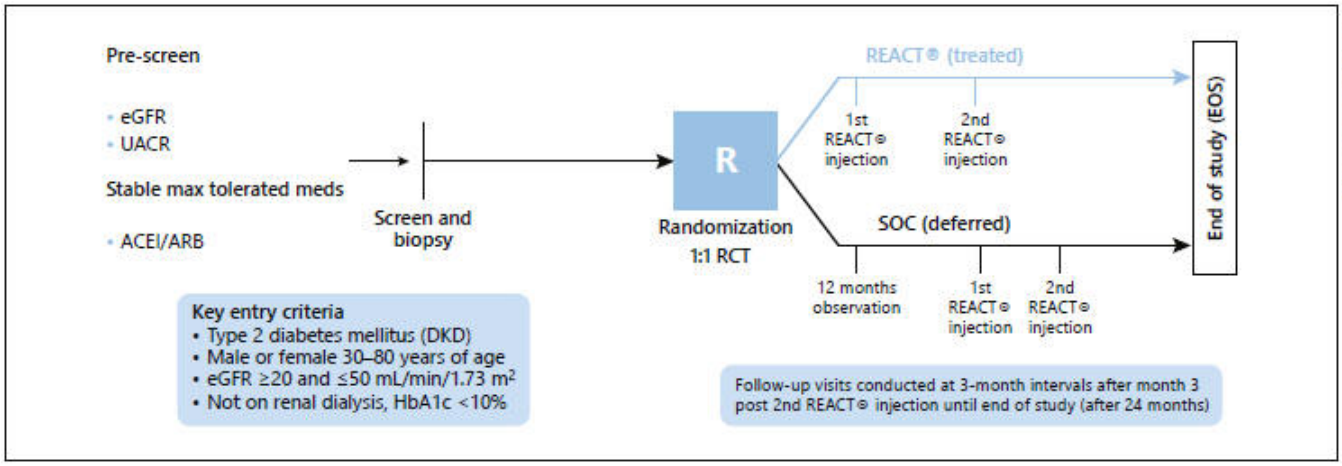

Fig. 1. Trial design outline. R occurs after kidney biopsy into ATG or DTG. The deferred group receives REACT following 12 months of SOC. R, randomization; SOC, standard of care; REACT, Renal Autologous Cell Therapy; ATG, active treatment group; DTG, deferred treatment group; DKD, diabetes kidney disease.

Table 1. Baseline characteristics, laboratory values, and concomitant medications for patients enrolled in the study

Patient information (*N* = 83)	Mean (SD, %)	Concomitant medications	*N* (%)
Age	65.2 (9.43)	ACEi's	34 (41.0)
Male	56 (67.5)	ARB's	37 (44.6)
Female	27 (32.5)	Beta blockers	42 (50.6)
Ethnicity (Hispanic or Latino)	11 (13.3)	Alpha 2 agonists	9 (10.8)
Ethnicity (non-Hispanic or Latino)	72 (86.7)	Diuretics	51 (61.4)
American Indian	1 (1.2)	Loop diuretics	28 (33.7)
Asian	1 (1.2)	Platelet aggregate inhibitors	50 (60.2)
Black or African American	7 (8.4)	Potassium lower agents	3 (3.6)
White	68 (81.9)	Polystyrene sulfonate	1 (1.2)
Other	6 (7.2)	Calcium polystyrene sulfonate	1 (1.2)
		Potassium-binding agents	1 (1.2)
Laboratory	Mean (SD, %)	Glucose lowering therapies	78 (94.0)
eGFR CKD-EPI (serum creatinine)	32.8 (8.6)	Insulin	48 (57.8)
eGFR CKD-EPI (cystatin-C)	37.8 (8.8)	Metformin	28 (33.7)
Serum creatinine, mg/dL	2.0 (0.8)	Sulfonylurea	22 (26.5)
Cystatin C, mg/L	1.8 (0.5)	DPP-4 inhibitors	13 (15.7)
Phosphorus, mg/dL	3.9 (0.5)	GLP-1 agonists	21 (25.3)
Hemoglobin, g/dL	12.6 (1.7)	SGLT2 inhibitors	7 (8.4)
Hematocrit, %	37.5 (4.8)	TZDs	7 (8.4)
UACR random, mg/g	3,948.4 (2,841.0)	Meglitinides	1 (1.2)
UACR 24 h, mg/g	1,401.9 (2,748.1)	Phosphate binders	5 (6.0)
Urea nitrogen, mg/dL	39.0 (16.0)	Antianemic preparations	28 (33.7)
Serum potassium, mEq/L	4.7 (0.5)	Iron preparations	15 (18.1)
Serum sodium, mEq/L	139.9 (2.6)	Erythropoietins	3 (3.6)
Serum bicarbonate, mEq/L	20.4 (3.2)	Other blood products	3 (3.6)
HbA1c	7.2 (1.0)	Vitamin B12 and folic acid	12 (14.5)

eFGR, estimated glomerular filtration rate; CKD, chronic kidney disease; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting-enzyme inhibitor.

Table 2. REACT for type 2 diabetes mellitus chronic DKD: clinical trial inclusion and exclusion criteria

Inclusion criteria
The participant is male or female, 30–80 years of age on the date of informed consent
The participant has an established diagnosis of T2DM
The participant has an established diagnosis of diabetic nephropathy as the underlying cause of renal disease
The participant has an established diagnosis of CKD not requiring renal dialysis, defined as having an eGFR between 20 and 50 mL/ min/1.73 m^2 inclusive at the screening visit and prior to REACT injection
The participant has blood pressure less than 150/90 at the screening visit, prior to renal biopsy, and prior to REACT injection(s). At the time of the biopsy and injections, the subject's BP should not be significantly below the previously recorded stable pressure
The participant has stable blood pressure and is maintained on a stable anti-hypertensive medication regimen if treatment for hypertension is necessary. If treatment includes an ACEi or an angiotensin receptor blocker, that treatment must have been initiated at least 8 weeks prior to renal biopsy. Treatment must be stable during the 6-week period immediately prior to REACT injection. Stable treatment is defined as dose adjustment to no less than one half of the current dosage or to no more than 2 times the current dosage. Dose interruptions up to 7 days due to medical necessity are allowed
A minimum of 2 measurements of eGFR or serum creatinine should be obtained at least 3 months apart prior to the screening visit or within the previous 18 months to define the rate of progression of CKD. The subject should have adequate historical clinical data to provide a reasonable estimate of the rate of progression of CKD. The medical monitor may be consulted to ensure that there are sufficient data
The participant is willing and able to refrain from NSAID consumption (including aspirin) as well as clopidogrel, prasugrel, or other platelet inhibitors during the period beginning 7 days before through 7 days after both the renal biopsy and REACT injection(s)
The participant is willing and able to refrain from consumption of fish oil and platelet aggregation inhibitors, such as dipyridamole (i.e., Persantine®), during the period beginning 7 days before through 7 days after both the renal biopsy and REACT injection(s)
The participant is willing and able to cooperate with all aspects of the protocol
The participant is willing and able to provide signed informed consent
Exclusion criteria
The participant has a history of type 1 diabetes mellitus
The participant has a history of renal transplantation
The participant has a serum HbA1c level greater than 10% at the screening visit
The participant has uncontrolled diabetes (defined as metabolically unstable by the investigator)
The participant has abnormal coagulation status as measured by APTT, PT-INR, and/or platelet count at the screening visit
The participant has a bleeding disorder(s) or is taking anticoagulants, such as warfarin or direct thrombin inhibitors that, in the judgment of the investigator, would interfere with the performance of study procedures
The participant has small kidneys (average size less than 9 cm) or has only one kidney, as assessed by ultrasound and/or MRI prior to renal biopsy, unless earlier radiology reports (generated within 1 year of the screening visit) are made available to confirm kidney size and number
The participant has known allergy(ies) or contraindication(s) or has experienced severe systemic reaction(s) to kanamycin or structurally similar aminoglycoside antibiotic(s)
The participant has a history of anaphylactic or severe systemic reaction(s) or contraindication(s) to human blood products or materials of animal origin (e.g., bovine and porcine)
The participant is not a good candidate to undergo percutaneous REACT injection, in the judgment of the surgeon or physician who will perform the procedure. This includes individuals who are morbidly obese (defined as BMI greater than 45 kg/m^2), have excessive fat surrounding the kidney, or who are otherwise at excessive risk for serious complications
The participant has a history of severe systemic reaction(s) or any contraindication to local anesthetics or sedatives
The participant has a clinically significant infection requiring parenteral antibiotics within 6 weeks of REACT injection

Table 2 (continued)

The participant has acute kidney injury or has experienced a rapid decline in renal function during the last 3 months prior to REACT injection
The participant has any of the following conditions prior to REACT injection: renal tumors, polycystic kidney disease, anatomic abnormalities that would interfere with the REACT injection procedure, or evidence of a urinary tract infection
Note: Anatomic abnormalities are not exclusionary if the kidney remains accessible and meets the criteria to receive the REACT injection
The participant has incapacitating cardiac and/or pulmonary disorders
The participant has a history of cancer within the past 3 years (excluding non-melanoma skin cancer and carcinoma in situ of the cervix)
The participant has clinically significant hepatic disease (ALT or AST greater than 3-times the upper limit of normal) as assessed at the screening visit
The participant is positive for active infection with HBV, or HCV, and/or HIV as assessed at the screening visit
The participant has a history of active TB requiring treatment within the past 3 years
The participant is immunocompromized or is receiving immunosuppressive agents, including individuals treated for chronic glomerulonephritis within 3 months of REACT injection
Note: Inhaled corticosteroids and chronic low-dose corticosteroids (≤7.5 mg per day) are permitted as are brief pulsed corticosteroids for intermittent symptoms (e.g., asthma)
The participant has a life expectancy less than 2 years
The female participant is pregnant, lactating (breast feeding), or planning a pregnancy during the study. Or the female participant is of child-bearing potential and is not using a highly effective method(s) of birth control, including sexual abstinence. Or the female participant is unwilling to continue using a highly effective method of birth control throughout the duration of the study
Note: A highly effective method of birth control is defined as one that results in a low failure rate (i.e., less than one percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or a vasectomized partner
The participant has a history of active alcohol and/or drug abuse that, in the judgment of the investigator, would impair the subject's ability to comply with the protocol
The participant's health status would, in the judgment of the investigator, be jeopardized by participating in the study
The participant has used an investigational product within 3 months prior to REACT injection without receiving written consent from the medical monitor

REACT, Renal Autologous Cell Therapy; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; PT-INR,prothrombin time-international normalized ratio; DKD, diabetic kidney disease; CKD, chronic kidney disease; eFGR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; TB, tuberculosis; IUDs, intrauterine devices.

sent to the GMP facility for processing. An additional biopsy for local site histopathologic evaluation is allowed at the discretion of the investigator after obtaining the required cores for REACT manufacturing, depending on benefit versus risk of bleeding complications.

Selective Epithelial Renal Cell Isolation and Expansion: The cells are isolated by enzymatic digestion and expanded ex vivo, using standard cell culture techniques over approximately 4 weeks. SRCs are selected by density gradient centrifugation and formulated to produce REACT. REACT is shipped overnight as a thermolabile gelatin-based hydrogel fresh product to the clinical site, to be administered within 72 h from manufacturing release. REACT is warmed to room temperature for 30 min before the image-guided percutaneous injection into the patients' renal cortex of the same donor kidney, typically targeting a lower pole region. A 20-gauge outer guide needle (COOK Inc, Bloomington, IN, USA) is inserted into the subcapsular kidney, followed by co-axial insertion of an inner noncutting pencil tip 25-gauge needle (IMD, Huntsville, UT, USA) into the renal cortex within 5 mm of the renal capsule as shown in Figure 2. The injection target is a few millimeters deep to the subcapsular region to maximize cell deposition within the cortex microenvironment of the REACT source. The procedure is performed in an outpatient setting and with moderate sedation. Proceduralists undergo training, certification, and onsite proctoring.

The dose of REACT is 3×10^6 cells/g estimated kidney weight by volumetric imaging analysis from a noncontrast MRI scan of the kidneys, obtained during patient screening. An individualized dose volume is predetermined and divided into multiple REACT deposits into the kidney. We conduct real-time assessment of nee-

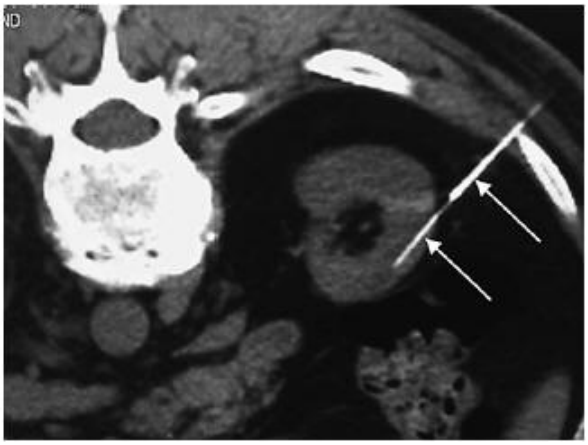

Fig. 2. Percutaneous CT-guided REACT injection. Patient in prone position in CT scanner. Insertion of outer guide and inner injection needles into the renal cortex in subcapsular location (arrows). CT allows real-time evaluation of needle location, REACT deposit, and bleeding complications. REACT, renal autologous cell therapy; CT, computed tomography.

dle location and REACT deposition, and determine any perinephric bleeding during intermittent CT scanning. Post-REACT recovery care is per local site, and it includes laboratory tests and delayed renal ultrasound to assess any procedure-related complication (i.e., renal hematoma). A 24-h follow-up clinical assessment, laboratory tests, and renal ultrasound are performed to determine renal function or delayed subclinical perinephric hematoma formation. A second REACT injection occurs approximately 6 months later into the same kidney.

Serial serum creatinine measurements are collected prerandomization and at 3-month intervals through 24 months after the last REACT injection, to calculate the eGFR by the CKD-EPI equation with serum creatinine. The rate of CKD progression for both the ATG and DTG will be compared. Additionally, each patient's disease progression rate pre-injection (eGFR slope derived from adequate historical clinical data) will be compared against the longitudinal rate of renal function decline, through the 24 months after the final REACT injection.

Randomization

We utilized a 1:1 randomization into 2 groups (ATG n = 42 or DTG n = 41) after manufacturing confirms the adequacy/quality of the donor kidney biopsy material and the date of REACT injection. The site investigator randomly assigned participants to either the ATG or the DTG using the Interactive Web Randomization System. Since this is an open-label study, the study participants, investigators, site staff, and sponsor are unblinded to the treatment assignment.

Power

Eighty-three patients who satisfied all the inclusion criteria were randomized 1:1 into either treatment group. The sample size was calculated based upon the phase I trial using an 80% power with an a = 0.05, assuming a 33% dropout rate to detect a difference of 50% in the eGFR between groups, as the primary efficacy endpoint. The trial size also allows sufficient safety information from the procedures and REACT product to be collected.

Statistical Analysis

Utilizing eGFR slope, standard error, and sample size for each study arm, a two-sample Walsh t test will compare renal function and disease progression by CKD-EPI eGFR (2009), serum Cr, cystatin C, BUN, and urinary albumin at prerandomization, and through 24 months post-REACT injection. Patients will serve as their own control. The significance level of a = 0.05 will be set. We will evaluate the mean and standard deviation of the eGFR slope over time and at each endpoint, using a t test to determine the difference between the ATG and the DTG. Values for missing data will not be imputed. c^2 analysis will compare the number of patients who experience AEs in both study groups.

The complete analysis set will include all patients enrolled in the study. The injection analysis set will include all patients who receive at least 1 REACT injection. Subgroup analyses will be performed to compare the safety and efficacy data from patients who received only a single REACT injection (e.g., due to exclusion criteria occurrences, dropout, death, or other reasons) versus patients who receive 2 REACT injections. Patient disposition (including screen failure, enrolled, successful biopsy, group assignment, number of REACT injections, withdrawn pre-injection or post-injection reasons, lost to follow-up, or completed study) will be summarized for the full analysis set by frequency and the proportion of patients.

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term, and we will present this information summarized. Treatment-emergent AEs by seriousness, intensity, the site investigator's assessment of relationship to the kidney biopsy, REACT injection procedure or REACT product, patient discontinuation due to AEs, or deaths will be included. The number of events (occurrence) and the number of participants (incidence) who experienced AEs will be reported. The number and percent of patients who develop clinically significant laboratory abnormalities longitudinally or exhibit changes on their physical examinations will be summarized.

Clinical Outcomes

The primary objective is to assess the safety and efficacy of up to 2 percutaneous REACT injections delivered 6 months (+4 weeks) apart, into the donor kidney. The primary safety endpoint is to assess procedure- and REACT product-related adverse events through 24 months after the last REACT injection, and the primary efficacy endpoint is the measurement of eGFRs from prerandomization through 24 months after the last REACT dose. Renal-specific AEs will be monitored. Other laboratory parameters, including urinary albumin, serum BUN, and urine microalbumin/ creatinine and protein/creatine ratios, were obtained prerandomization and through 24 months after the last REACT injection. Noncontrast MRI and renal scintigraphy imaging are performed during the trial to assess morphologic change and analysis of split renal function between treated and nontreated kidneys.

Patient-Reported Outcomes

Quality of life and patient satisfaction surveys are used as subjective patient assessments. Patient-reported outcomes from the kidney disease quality of life (KDQOL) and EQ-5D-5L surveys

were obtained at baseline (defined as after randomization and before REACT injection) and through 24 months after the last REACT injection. A two-sample *t* test will compare mean KDQOL and EQ-5D-5L scores between groups using a significance level of a = 0.05. Each patient's baseline KDQOL and EQ-5D- 5L scores will be compared against the individual patient's scores obtained through 24 months after the last REACT injection.

Data Safety and Monitoring

An independent Data and Safety Monitoring Board (DSMB) has been chartered to oversee patient safety, especially related to unexpected investigational product-related events. The DSMB consists of 3 members with expertise directly related to protocol-specified activities. It functions independently, and its members have no other engagement with the study sponsor. The DSMB meets at regular intervals depending on the rate of patient enrollment and new data generated, and advises the sponsor on aspects concerning the safety of patients participating in the clinical trial, specifically before the patients in the DTG receive their initial REACT injection. The DSMB reviews all safety and efficacy data obtained from interim analysis and may advise on dosing plans, protocol-specified evaluations, and follow-up procedures. The DSMB shares its recommendations with the study centers, institutional review boards/ethics committees, and regulatory authorities, as appropriate. Details of specific activities and responsibilities of the DSMB are in the DSMB charter.

Discussion

T2DKD imparts a large global burden on healthcare systems and economic costs to society. Diabetes may affect 25–28% of the US population by 2050, with >40% developing CKD, resulting in high-cost comorbidities including end-stage kidney disease and renal replacement therapy [5, 14, 15]. Since the advent of renin-angiotensin system inhibitors, multiple classes of small molecule drugs have entered the clinical development pipeline to reduce DKD comorbidities, while targeting biochemical pathways that modulate metabolic, anti-inflammatory, or hemodynamic responses [6, 16, 17]. Nephroprotective effects of recent DKD therapies have demonstrated modest early reductions in declining eGFRs, although none impart improvement in the structural repair of the nephron. In addition, small molecule drugs are usually ineffective in advanced stages of DKD. Our phase II multicenter clinical trial of the novel intervention REACT will assess the safety and efficacy of autologous, homologous cell therapy in T2DKD and attempt to demonstrate nephro-restorative improvement in renal function.

Our preclinical studies with experimental models of CKD including DKD-induced and nephrectomy CKD models, showed increased survival, augmented renal function, and improved comorbidities after the cortex injection of SRCs, the active biological ingredient in REACT [18, 19]. Preclinical cell markers identified an admixture of 3 cell sources (cap mesenchyme, ureteric bud, and podocyte), while lower levels of serum creatinine, blood urea nitrogen, and serum protein improved filtration correlating to a subpopulation of glomerular epithelial cells in SRCs. In addition, decreased glomerular sclerosis and mesangial proliferation in SRC-treated diabetic ZSF1 rodents were identified during necropsy at multiple interim analyses and may be predictive of positive cellular effects on multiple renal tissues in human DKD [12]. Ongoing evaluation of glomerular epithelial dysfunction in DKD may further define podocyte phenotypes that support the potential use of cellular therapies targeting renal function and proteinuria in CKD [20, 21].

Cell integration into areas of renal inflammation and fibrosis was shown by in vivo confirmation of attenuated NF-kB and PAI-1 responses to monocytic and macrophage infiltration and upregulation of tubular expansion via trophic cues [22]. Local paracrine effects by exosome secretion of cytokines modulating repair of diabetes related damage from microvesicles may also have participated in the mechanism that resulted in observed anti-fibrosis and anti-inflammatory effects, and improved renal function [12].

Cell bioactivity and biodistribution of the SRCs were confirmed by injecting the labeled active biological product into the lower or upper renal pole regions of large and small animals [12, 23]. Superparamagnetic iron oxide contrast MRI and high-content image-based immune-fluorescent analysis identified cellular dispersion throughout the kidney after locoregional injections, suggesting global implantation of cells into multiple nephrons. Gate signaling cytokines were identified in the cell mixture that elicit a chemotaxis response and mediate migration. In addition, the SRCs were identified in repaired glomeruli and tubules at necropsy utilizing immunohistology/histochemical methods and morphometric analysis [12, 23].

The SRCs of REACT biodistribution, improvement in renal function, reduced DKD comorbidities, and nonimmunogenic properties of selected renal autologous cells supported a phase I trial design. The phase I trial demonstrated feasibility and safety using hand-assisted laparoscopic access to the kidney under general anesthesia. Seven male patients underwent laparoscopic-guided cell injections with direct visualization using a large gauge needle [13]. Screening serum creatine was stable and unchanged to 18 months and increased at 24 months postinjection in 5 of 7 patients. In addition, renal clearance (calculated by Iohexol) and ACR were unchanged at 12 and

24 months, respectively, whereas cystatin C eGFR was lower at 12 and 24 months than screening levels.

Nine serious postprocedure adverse events were determined to be related to the surgical procedures with general anesthesia in the Phase I study. No conclusive adverse events were associated with the cell-based product [13].

In the present phase II clinical trial, we converted the laparoscopic injection to a CT-guided percutaneous approach, given the advances in minimally invasive procedures with smaller-platform medical devices, imaging methods, and conscious sedation in an outpatient setting. These changes will mitigate adverse procedural events, and image guidance will ensure REACT enters the renal cortex. This approach currently is also used in a phase I open label trial of CKD due to congenital anomalies of the urinary tract [24].

Conclusions

REACT holds the promise to achieve improved renal function by nephron-repair and restoration of the diseased kidney with its unique cell composition and delivery method. The anti-fibrotic, anti-inflammatory, and non-immunologic features of REACT may ameliorate the progression of DKD and reduce the need for renal replacement therapy. An improved structural function could complement and enrich the bioactivity of other small molecules affecting T2DKD renal function and comorbidities.

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Statement of Ethics

The trial protocol was approved by each site's institutional review board or ethics committee on human research, and the participants provided written informed consent. The trial identifier number is NCT:02836574 and found at https://clinicaltrials.gov/ ct2/show/NCT02836574.

Conflict of Interest Statement

J. Stavas, A. Johns, D. Jain, and T. Bertram are employed by ProKidney. S.G. Coca has received fees for advisory boards or steering committee roles for Renalytix, CHF Solutions, Bayer, Boehringer Ingelheim, Takeda, Vifor, Quark, ProKidney, and Akebia in the past 3 years. He owns equity in Renalytix, and receives salary and research support from Renalytix, ProKidney, XORTX, and the Renal Research Institute. A. Silva and M. Díaz-González de Ferris received fees for advisory board roles for ProKidney.

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Author Contributions

J.S. and M.F. made substantial contributions to the design of the work, drafting, revising, and final approval of the version to be published and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A.S., D.G., S.C., A.J., D.J., and T.B. contributed to revisions and final approval of the version to be published. G.B. contributed to trial design and final approval.

Data Availability Statement

Current trial safety and efficacy data are not publicly available due to active status of the trial.

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