Research Article

Renal Autologous Cell Therapy in Type 2 Diabetes with Late Stage 4 Diabetes-Related Chronic Kidney Disease: Trial Design and Early Analysis

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Abstract

Introduction: Cell-based therapies potentially delay the trajectory toward end-stage kidney disease (ESKD) in late stage 4 diabetic chronic kidney disease (DKD). We describe the trial design, baseline patient characteristics, and early results of an IRB-approved phase II multicenter clinical trial, utilizing Renal Autologous Cell Therapy (REACT) in adults with pre-ESKD due to type 2 DKD. The trial objectives were safety and tolerability of REACT by assessment of the procedure, product administration, and renal-specific adverse events in addition to evaluate the impact on renal function following injection. *Methods:* Ten adults with an eGFR of 14–20 mL/min/1.73 m^2 were enrolled in a single-arm open-label trial. Following a percutaneous kidney biopsy, an ex vivo expansion of selected renal cells that form the REACT was injected into the cortex of the biopsied kidney with CT image guidance. Each participant received two doses of the REACT product at 6-month intervals. A 6-month observation pre-trial was required to establish patients' "own" baseline and rate of DKD progression. *Results:* Five men and 5 women underwent 19 REACT injections (1 participant received only one injection). Their baseline characteristics were as follows: 3 Hispanic/Latino, 7 non-Hispanic, 7 white; mean (SD) age: 58.9 years (5.22), BMI 35.8 (8.2), eGFR (sCR) 15.5 (2.72), eGFR (sCR + Cys-C) 17.7 (3.67) mL/min/1.73 m^2, sCr 3.6 mg/mL (0.73), Cys-C 2.6 mg/mL (0.52), and log random UACR 7.9 mg/g (1.01). The pre- and post-injection eGFR slope was −6.5 mL/min/1.73 m^2 and −3.9 mL/min/1.73 m^2. No cell-related adverse events occurred, and two procedure-related hematomas required observation without transfusion or angiographic interventions. Dialysis was delayed a mean of 16 months (range 6–28 months). At 15 months, 2 patients (20%) have eGFR slope stability and have not commenced renal replacement therapy. *Conclusion:* Trials that include patients with an eGFR of <20 mL/min/1.73 m^2 are uncommon, and none to date involve autologous homologous cell-based treatments. REACT has the potential to stabilize or delay dialysis in high-risk late stage 4 DKD.

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Introduction

The most common cause of chronic kidney disease (CKD) in adults is diabetes mellitus, and for those with an estimated glomerular filtration rate (eGFR) of <20 mL/min/1.72 m^2, treatment options do not halt the progression to end-stage kidney disease (ESKD) [1, 2]. Management options are considered futile, given the accelerated loss of kidney function at this advanced CKD stage. Once nephron loss begins, changes at the cellular level have been documented [3]. Novel cell-based therapies intend to impart improvement in nephron structure, stabilize renal function, and halt the onset of ESKD [4, 5]. Delaying ESKD has positive effects upon patients' quality of life and comorbidities, reducing healthcare expenditures [6].

Findings in our preceding animal studies led to FDA-approved phase I and II clinical trials utilizing an admixture of ex vivo expanded homologous autologous selected renal cells (SRCs) obtained from a percutaneous kidney biopsy, which form the product called Renal Autologous Cell Therapy (REACT) [7–10]. Injection procedures have been well tolerated among patients with type 2 diabetes [11]. Our early trial in diabetic chronic kidney disease (DKD) patients with an eGFR >20 mL/min/1.73 m^2 has demonstrated stabilization of eGFR and UACR levels versus a standard of care comparator group [12]. We herein describe a single-arm trial where 30–65-year-old patients with late stage 4 DKD received two REACT injections in the same biopsied kidney (Clinicaltrials.gov Identifier: NCT:03270956). This is an expansion criterion from our ongoing phase II parent study (Clinicaltrials.gov Identifier: NCT02836574), utilizing the same investigational cell product, where patients have greater eGFR limits for inclusion and received two REACT injections in the same kidney. Our study's main goal determined key outcome measures in a population with very high risk for dialysis, including procedure and renal-specific adverse events and renal function changes. Our hypothesis was that patients with impending ESKD who receive REACT would have a slower decline in eGFR slope, compared to their pre-trial eGFR slope.

Materials and Methods

Trial Design
Single-arm treatment group of ten participants. See Figure 1 for trial design.

Study Location
Five sites across the USA enrolled patients.

Objectives
The primary objective is to assess the safety of REACT injected into one recipient kidney with the endpoints of procedure and/or product-related adverse events through 24 months post-injection. The secondary objective is to determine the safety/tolerability of REACT, 24-month post-injection. Exploratory endpoints are the impact of REACT on renal function and disease progression rate.

Patient/Procedures
We included adults who had type 2 diabetes and late stage 4 DKD with an eGFR of 14–20 mL/min/1.73 m^2. Inclusion/exclusion criteria were assessed at the screening visit, prior to renal biopsy and before each REACT injection (online suppl. Material 1; see www.karger.com/doi/10.1159/000527582 for all online suppl. material). Eligible patients provided IRB-approved informed consent.

At screening, patients underwent updated physical exams, review of inclusion/exclusion criteria and renal scintigraphy with split kidney function to measure each kidney's contribution to total function. Ultrasounds confirmed the presence of two kidneys with anatomic features and adequacy for percutaneous biopsy. We determined kidney size and volume with MRI to calculate the REACT product dose.

Renal Biopsy
Within 60 days of the first screening, patients underwent an image-guided percutaneous biopsy of either kidney as out-patients with local standard of care and observation. To provide sufficient material for the manufacture of REACT, we collected 2–4 biopsy cores. Biopsy-related bleeding was assessed by pre-discharge renal ultrasound and hemoglobin levels. An additional biopsy for histologic analysis was at the discretion of the sites' principal investigators. Biopsy cores were shipped overnight in specialized transport medium to the manufacturing site in North Carolina, USA.

REACT Manufacturing/Logistics
One to 2 weeks after receiving the kidney biopsy cores, ProKidney notifies each site if the tissue was of sufficient size and quality. If the cores are appropriate, SRC culture would start following good manufacturing process protocols, but if the biopsy samples were not adequate, the patient would be discontinued from the study. SRCs that form the REACT product are formulated in a thermolabile gelatin-based hydrogel concentration of 100×10^6 cells/mL. ProKidney overnight ships the manufactured REACT as a fresh product to the trial sites for next-day injection.

REACT Injections
On the day of injection, REACT is warmed and percutaneously injected with CT image guidance into the renal cortex of the same kidney that underwent the renal biopsy. The REACT dose is 3×10^6 cells/g estimated kidney weight, determined by renal volume analysis, with a dose range of 3–8 mL. All injections are performed as outpatient procedures under conscious sedation [10, 11]. Post-injection renal ultrasounds, hemoglobin, hematocrit, and chemistry levels are obtained during the recovery period and at 24 h, to detect adverse events. Each patient receives two injections of REACT 3–6 months apart, in the same kidney where the biopsy was obtained. Therefore, only one kidney was accessed in this study. Because of IRB regulations, we were unable to perform post-procedure biopsies to demonstrate histological changes.
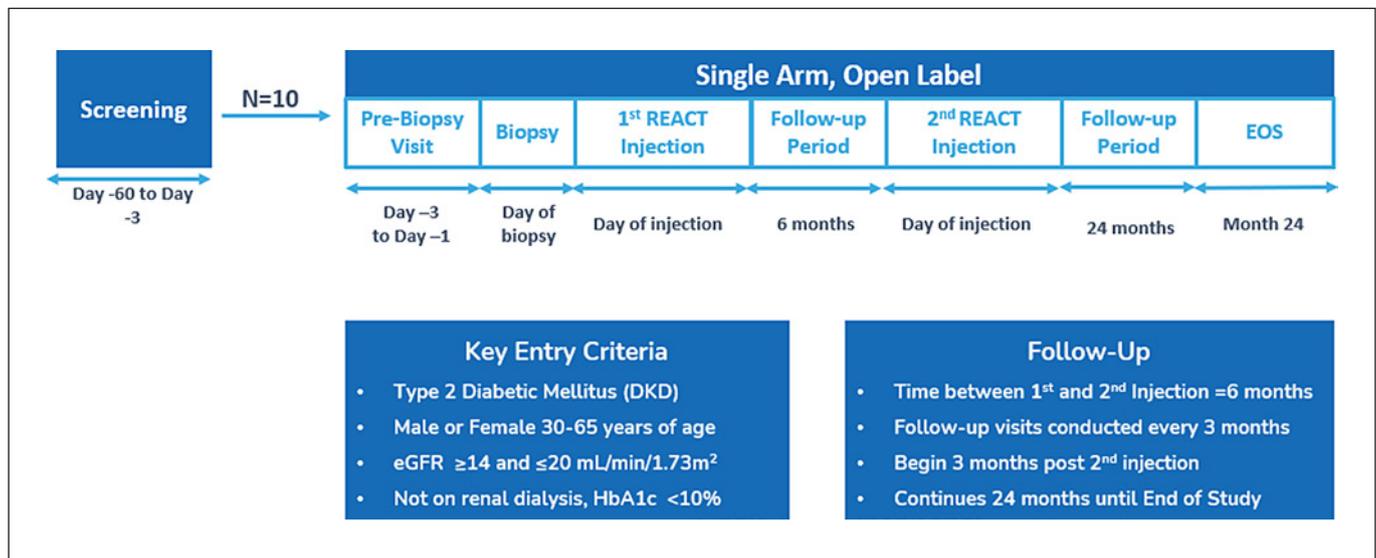
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Fig. 1. Trial design schematic.

Follow-Up Evaluations

Patients underwent evaluations on days 1, 7, 14, 28 (±3 days) and months 2, 3, 4, and 5 (±7 days) after the first REACT injection, and on days 1, 7, 14, 28 (±3 days) and months 2 and 3 (±7 days) after the second REACT injection. Following the second REACT injection, assessments of safety and efficacy through 24 months took place. Noncontrast MRIs during screening and at the end of study assessed morphologic changes. Renal scintigraphy evaluated split function prior to the 1st and 2nd REACT injections, at 6 and 12 months post-second injection and at the end of the study.

Disease Progression

We classified patients into those with stable renal function and those who required renal replacement therapy (RRT). Before the REACT injections, we calculated risk of dialysis with the Kidney Failure Risk Equation (8 Variable), based on Tangri et al. [13, 14].

Adverse Events

Biopsy-, procedure-, and cell-related adverse events were monitored and recorded based on seriousness and intensity, per the Medical Dictionary for Regulatory Activities Version 23.0, into Preferred Terms and System Organ Classes. In addition, all other remote adverse events were recorded.

Ethics and Trial Registration

The trial was approved by the research ethics board of the participating centers and registered at https://clinicaltrials.gov/ct2/show/NCT03270956.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) oversees patient safety and consists of three members who have expertise in protocol-specified activities. The DSMB functions independently, and its members have no other engagement with ProKidney. The DSMB meets at regular intervals and advises ProKidney on patient safety,

study data, and gives feedback to the sponsor, investigators, regulators, and Institutional Review Boards/Ethics Committees.

Statistical Analysis Methods

All analyses were descriptive in nature to characterize the patients' demographic, clinical, and laboratory information. Our sample size was not powered for statistical significance. Categorical variables were summarized by frequency count and percentages. Normally distributed continuous variables were summarized by presenting the mean and standard deviation (SD); otherwise, the median was reported for not normally distributed continuous variables. Annualized eGFR slope was calculated using longitudinal linear mixed effect models with a correlated random intercept and slope [15]. The progression score was calculated using the 2011 Kidney Failure Risk Equation with age, sex, eGFR, UACR, calcium, phosphorus, albumin, and bicarbonate as predictors [13]. UACR is reported as random UACR, but if random UACR is missing and 24-h UACR is collected, then it was imputed. Baseline was defined as the last measurement before their first REACT injection.

Results

We enrolled 5 men and 5 women who underwent 19 REACT injections (1 participant received only one injection), and all core biopsy samples produced an adequate amount of SRCs. Their baseline characteristics are depicted in Table 1. Mean and SDs were for age 58.9 (5.22) years; BMI 35.8 (8.2); age at diagnosis 58.9 (5.22) years; and time with T2DM 13.7 years (range 5–27). See Table 1 for further cohort characteristics including baseline laboratory results and concomitant medications.

Table 1. Patient baseline characteristics and medications (N = 10)

Patient information	Mean (SD)/n (%)	Concomitant medications	n (%)
Age	58.9 (5.22)	ACEi	2 (20)
Gender (male)	5 (50%)	ARBs	6 (60)
Gender (female)	5 (50%)	Beta blockers	6 (60)
Hispanic or Latino	3 (30%)	Alpha 2 agonist	0 (0)
Non-Hispanic or Latino	7 (70%)	Diuretics	10 (100)
Asian	1 (10%)	Platelet aggregate inhibitors	6 (60)
White	7 (70%)	Potassium lowering agents	3 (30)
Other race	2 (20%)	Polystyrene sulfonate	0 (0)
Body mass index	35.8 (8.2)	Potassium-binding agents	1 (10)
		Glucose lowering therapies	9 (90)
Laboratory		Insulin	7 (70)
eGFR CKD-EPI (sCr)	15.5 (2.72)	Metformin	0 (0)
eGFR CKD-EPI (sCr + Cys-C)	17.7 (3.67)	Sulfonylurea	2 (20)
Serum creatinine, mg/dL	3.6 (0.73)	DPP-4 inhibitors	1 (10)
Cystatin C, mg/L	2.6 (0.52)	GLP-1 agonists	2 (20)
Phosphorus, mg/dL	4.8 (0.89)	SGLT2 inhibitors	0 (0)
Hemoglobin, g/dL	10.5 (1.12)	TZDs	1 (10)
Hematocrit, %	32.1 (4.08)	Meglitinides	0 (0)
UACR random log, mg/g	7.9 (1.01)	Phosphate binders	4 (40)
UACR random IQR, mg/g	3,198 (1,733–5,524)	Antianemic preparations	8 (80)
Urea nitrogen, mg/dL	60.8 (16.4)	Iron preparations	5 (50)
Serum potassium, mEq/L	5.2 (0.49)	Erythropoietins	7 (70)
Serum sodium, mEq/L	140.4 (2.8)	Other blood products	0 (0)
Serum bicarbonate, mEq/L	19.2 (2.49)	Vitamin B12 and folic acid	2 (20)
HbA1c, %	7.7 (1.59)	Bicarbonate supplement	5 (50)
Intact PTH, pg/mL	5.2 (0.83)	1–25 OH vitamin D	1 (10)
Calcium, mg/dL	9.0 (0.62)	Other antihypertensives	5 (50)
Albumin, mg/dL	4.0 (0.42)		

Table 2. Individual pre- and post-REACT injection slopes corresponding to linear mixed effect model string plots (Fig. 2)

Patient[#]	Pre-injection slope	Post-injection slope
1	−5.9 mL/min/1.73 m²	−4.8 mL/min/1.73 m²
2	−4.3 mL/min/1.73 m²	−3.7 mL/min/1.73 m²
3	−7.5 mL/min/1.73 m²	−6.0 mL/min/1.73 m²
4	−22.2 mL/min/1.73 m²	−3.3 mL/min/1.73 m²
5	−4.4 mL/min/1.73 m²	−0.2 mL/min/1.73 m²
6	−8.8 mL/min/1.73 m²	−2.3 mL/min/1.73 m²
7	+14.5 mL/min/1.73 m²	0.3 mL/min/1.73 m²
8	−3.5 mL/min/1.73 m²	−7.1 mL/min/1.73 m²
9	−3.8 mL/min/1.73 m²	−5.9 mL/min/1.73 m²
10	4.2 mL/min/1.73 m²	−1.6 mL/min/1.73 m²

DKD Progression

For the study cohort, average eGFR slope changed from −6.5 mL/min/1.73 m² per year pre-injection to −3.9 mL/min/1.73 m² per year post-injections of REACT (see Fig. 2). The individual pre- and post-REACT injection slopes indicated 6/10 improved their eGFR or slowed progression (stabilization) and 4/10 had eGFR progression, as shown in Table 2. At 10.1 months post-REACT injection, 3 patients had not begun dialysis and 2 at 15 months post-second injection (21-month total follow-up); however, 1 patient died after the second injection from diabetes-related myocardial infarction without dialysis but was considered lost to follow-up due to an administrative error. A second patient died after the second injection due to COVID-19 infection 1 day following their first episode of hemodialysis during the hospitalization. This patient was included in the dialysis count despite the singular dialysis session. Seven patients required RRT at a median time of 16.2 months (range 6–28 months) with eGFRs of 6–16 mL/min/1.73 m², at the time of initial dialysis. One patient with a screening eGFR of 19 mL/min/1.73m² had rapid clinical deterioration and heavy proteinuria and commenced dialysis 6 months after the first REACT injection. To date, all remaining participants have received two injections. A straight-line extrapolation of the pre-injection eGFR slope (−6.5 mL/min/1.73
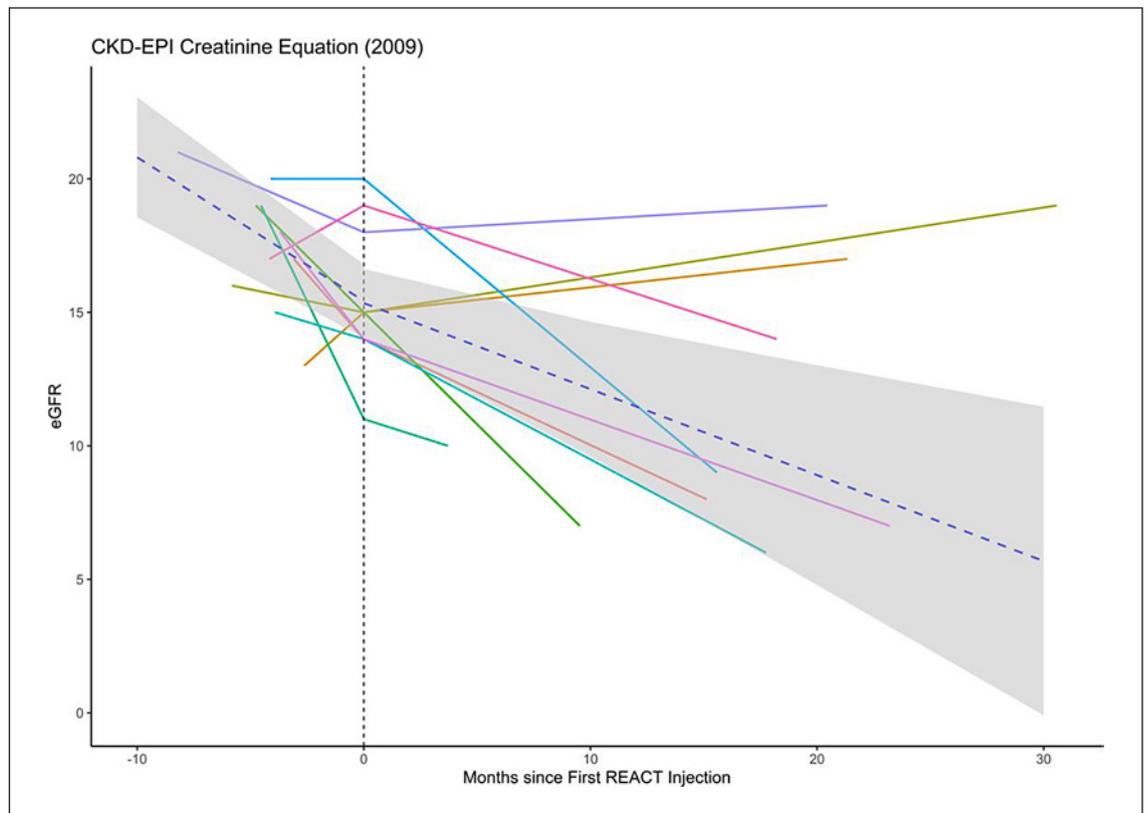
Fig. 2. Linear mixed effects model: eGFR pre- and post-REACT injection with cohort (blue dashed line) and individual slopes (colored lines). Slope deceleration occurs at first injection, time = 0.

m²) from the time of first injection approximates a time to dialysis of 10.1 months without REACT treatment, with the assumption of a dialysis initiation at an eGFR of 10 mL/min/1.73 m² (see Fig. 3).

Adverse Events

Of all 10 single renal biopsies and 19 percutaneous injections of the REACT product, there were two instances of renal hematomas (one post-biopsy and one post-injection) that did not require blood transfusions or interventions. One patient developed a post-biopsy arteriovenous fistula that spontaneously resolved in less than 7 days. The most common system organ class side effects were in the renal and urinary disorder category ($n = 7$) and infectious class, with two COVID-19 infections and one non-COVID-19 pneumonia. There were no reported cell product SAEs (see Table 3).

Discussion

Patients nearing stage 5 DKD face the challenges of few available therapies that slow the rapid trajectory to ESKD and RRT initiation. Most management algorithms focus on DKD comorbidities, such as ardent hypertension control. At this stage of DKD, patients and families recognize the time to dialysis is impending. In this single-arm trial of 30–65-year-old patients with late stage 4 DKD who received two injections of the REACT product, we demonstrated a decrease in eGFR slope from −6.5 mL/min/1.73 m² per year at baseline to −3.9 mL/min/1.73 m² per year. Their CKD progression scores stabilized or improved in 6/10 cases. At the time of this preliminary analysis, 2 patients were dialysis-free and alive, 1 patient died of CO-VID-19 infection and underwent one episode of hemodialysis the day before death, and a second patient died of a myocardial infarction 10.1 months after their second injection. Seven required RRT at a mean time of 16 months (range 6–28 months) post-REACT injection. This was compared to an approximate 10-month prediction of di-
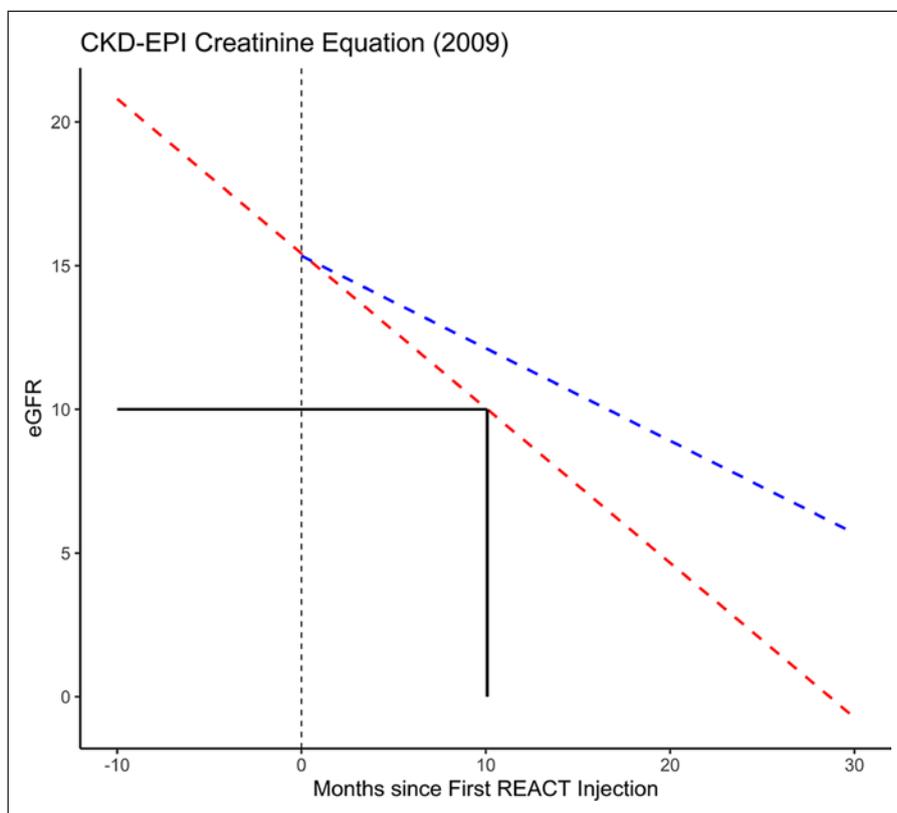
Fig. 3. Red line: Extrapolated pre-injection eGFR slope (−6.5 mL/min/1.73 m²) from the time of first REACT injection extended to 30 months. Blue line: Calculated eGFR slope post-first REACT injection (−3.9 mL/min/1.73 m²) extended to 30 months. Black lines: estimated time to dialysis is approximately 10.1 months based upon an assumed start of dialysis with an eGFR of 10 mL/min 1.73 m² eGFR without REACT treatment.

Table 3. Severe adverse events: system organ class and preferred term

System Organ Class	Number
Renal and urinary disorders	**7**
PT: acute kidney injury	2
PT: CKD	1
PT: end-stage renal disease	2
PT: renal hematoma	2
Infections and infestations	**5**
PT: cellulitis	1
PT: COVID-19	2
PT: COVID-19 pneumonia	1
PT: pneumonia	1
Blood and lymphatic system	**2**
PT: anemia	2
Respiratory and thoracic	**2**
PT: acute respiratory failure	2
Vascular disorders	**2**
Renal arteriovenous fistula	**1**
Hypertensive emergency	**1**
General conditions	**1**
PT: fatigue	1
Metabolism and nutrition	**1**
PT: diabetic complication	1
Nervous system disorders	**1**
PT: cerebrovascular accident	1

alysis-free living in the nontreated group based on a straight-line extrapolation of the pre-injection eGFR slope from the time of the first REACT injection. In a Chronic Renal Insufficiency Cohort (CRIC) study, the median time spent in each CKD stage, from 3a to 5, was evaluated. Stage 5, which corresponds to our baseline eGFR of 15.5 mL/min/1.7 m², had a median time of 0.8 years and matches the 10-month untreated prediction estimate in this trial cohort, suggesting the REACT treated group faired better than receiving no treatment regardless of their high comorbidities [16].

Despite being a high-risk population, all injection procedures were well tolerated and adverse events commensurate with our previous percutaneous injections of REACT [11]. Our hypothesis was that the bioactive SRCs in the REACT product would stabilize disease progression in advanced type 2 DKD, based on their presumed mechanism of action. In pre-clinical trials of animal DKD models, 3 cell markers composing the SRC admixture were identified arising from the cap mesenchyme, ureteric bud, and podocyte. The injected SRCs integrated within areas of diabetic kidney inflammation and reduced CKD progression by imputed paracrine effects

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Table 4. 5-year risk ESKD

Patient	5-year risk ESKD[a], %	Time to dialysis or death, months, post-REACT injections
1	100	6.0
2	99.9	16.2
3	99.8	27.9
4	99.5	20.3
5	99.2	6.1
6	98	19.4 (death)[b]
7	91.9	13.2
8	91	10.1 (death)[c]
9	75	Stable CKD 4
10	65	Stable CKD 4

[a]Kidney failure risk equation prediction compared to posttreatment time to dialysis or death [14]. [b]COVID-19-related death with one episode of hemodialysis 1 day prior to death. [c]Myocardial infarction-related death and not on dialysis at time of death. ESKD, end-stage kidney disease.

from cytokine secretion and disease modulation attenuating glomerular sclerosis and tubulointerstitial fibrosis [8, 17]. The biodistribution of the cells was global and allowed widespread SRC bioactivity in the kidney following a locoregional injection into the cortex [18].

During our phase I trial, seven males with type 2 DKD received a single injection of SRCs by a hand-assisted laparoscopic technique with general anesthesia and at 24 months post-injection iohexol renal clearance and albumin:creatinine ratio remained unchanged, suggesting disease stabilization [9]. In that trial with a more invasive approach, nine serious adverse events occurred related to the laparoscopic and general anesthesia procedures, but there were no conclusive serious adverse events related to the SRCs. Subsequent trials were converted to an outpatient imaged-guided percutaneous injection of REACT under conscious sedation, decreasing the rate of serious adverse events. Performing both injections into the same kidney was endorsed by the FDA to protect the contralateral kidney from bleeding and causing adverse events. The two post-procedure hematomas in this cohort received conservative management, and no cell product adverse events were reported.

Our novel trial of severe type 2 DKD demonstrated stabilization of kidney function in several patients who would otherwise progress to ESKD at a faster rate, based on their annual eGFR slope. In addition, with analysis based on the 8 Variable Kidney Failure Risk Equation, 8 patients had a predictive score ≥91% for reaching ESKD

within 5 years [13, 14]; see Table 4. Two patients not on dialysis with stabilized CKD stage 4 and lower predictive scores (65% and 75%) had lower albuminuria (UACRs 407 and 719 mg/g) compared to the RRT group (UACRs range 1,487–10,889 mg/g). Our findings confirm interim results in a phase II trial with DKD at greater eGFR levels (20–50 mL/min/1.73 m^2), which showed an annualized improvement of 4.2 mL/min/1.73 m^2 at 12 months post-two injections versus a comparator group decline of −3.3 mL/min/1.73 m^2 [12]. Halting DKD progression translates into improvement of quality of life and decreased medical costs. In a US national study of Medicare claims data in patients with CKD due to type 2 diabetes, the post-acute 4-month period cost was USD $11,879 (USD $937 Std. Error) in CKD stage 4 versus USD $49,573 (USD $2,476 std. error) for those undergoing dialysis [19]. These figures do not consider other nonmedical expenses related to dialysis.

While our results are encouraging given an eGFR improvement of +2.6 mL/min/1.73 m^2 from the baseline slope, the sample size does not allow us to generalize our findings to late-stage DKD or to exam the findings by Ku et al. [20] regarding the time to initiate RRT. End-of-study analysis of clinical outcomes will be correlated with morphologic MRI changes in the kidney and nuclear medicine split renal function to assess patient response variability. Furthermore, our sample did not include a diverse representation of races. Future work is focusing on global phase III trials, congenital CKD conditions, eGFR inclusion of 50–14 mL/min/1.73 m^2, and bilateral kidney injections using re-dosing triggers [21, 22].

Conclusions

Autologous cell therapy may impart DKD nephron structural restoration and improved renal function, wherein a delayed dialysis may be possible in a high-risk DKD population. This would translate into a reduction of healthcare costs and improvement in quality of life.

Acknowledgments

Statement of Ethics

This study protocol was reviewed and approved by WCG IRB, approval number: 1189651. Written informed consent from participants was obtained, and the trial is listed on ClinicalTrials.gov Identifier: NCT03270956.

Conflict of Interest Statement

Joseph Stavas and Emily Butler are employed by ProKidney. Arnold Silva and Steven Coca are paid consultants for ProKidney. Anna Burgner is a paid consultant for Bayer on diabetic kidney disease. Randal Detwiler and Bijin Thajudeenb have nothing to disclose.

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Author Contributions

Joseph Stavas and Emily Butler made substantial contributions to the conception and design of the manuscript and revisions and accountable for accuracy and result interpretation. Emily Butler performed the statistical analysis and designed Figures 2 and 3 and Tables 1 and 3. Bijin Thajudeen, Steven Coca, Arnold Silva, Randal Detwiler, and Anna Burgner reviewed and edited the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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