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Human Clinical Article

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Abstract

Chronic kidney disease (CKD) poses a significant global health burden by reducing quality of life and increasing mortality. Current therapies remain inadequate in halting its progression, necessitating novel treatments to improve outcomes. Adipose-derived stem cells (ADSCs) have emerged as a promising therapeutic option. Phase I/II clinical trials evaluated the efficacy, safety, and tolerability of ELIXCYTE in slowing CKD progression. This multicenter, randomized, open-label study monitored estimated glomerular filtration rate (eGFR) changes over a 48-week period following a single intravenous infusion of ADSCs. Participants were allocated to one of three dosage groups, with primary outcomes assessing eGFR changes and secondary outcomes focusing on safety and tolerability. Results confirmed a favorable safety profile, with no dose-limiting toxicities observed in the low- and moderate-dose groups. Group-based trajectory modeling (GBTM) indicated that, overall, 88.24% of patients exhibited a trend of improvement or stabilization. In the low-dose group, 72.23% of patients demonstrated a stable trend, which was more consistent than in other dosage groups. Furthermore, patients with CKD stage 3B showed a numerically higher proportion of improving trajectories compared to those with stage 4 disease. The low-dose ADSC group exhibited a trend toward more favorable renal function trajectories and fewer adverse events than higher doses, suggesting that lower dosing may provide a balanced profile of safety and potential efficacy. However, despite the preliminary results indicating that ELIXCYTE may effectively slow CKD progression, further large-scale clinical trials are necessary to corroborate these findings and verify the efficacy of ADSC treatment.

Key words: Adipose-derived mesenchymal stem cells; chronic kidney diseases; glomerular filtration rate; clinical trial.

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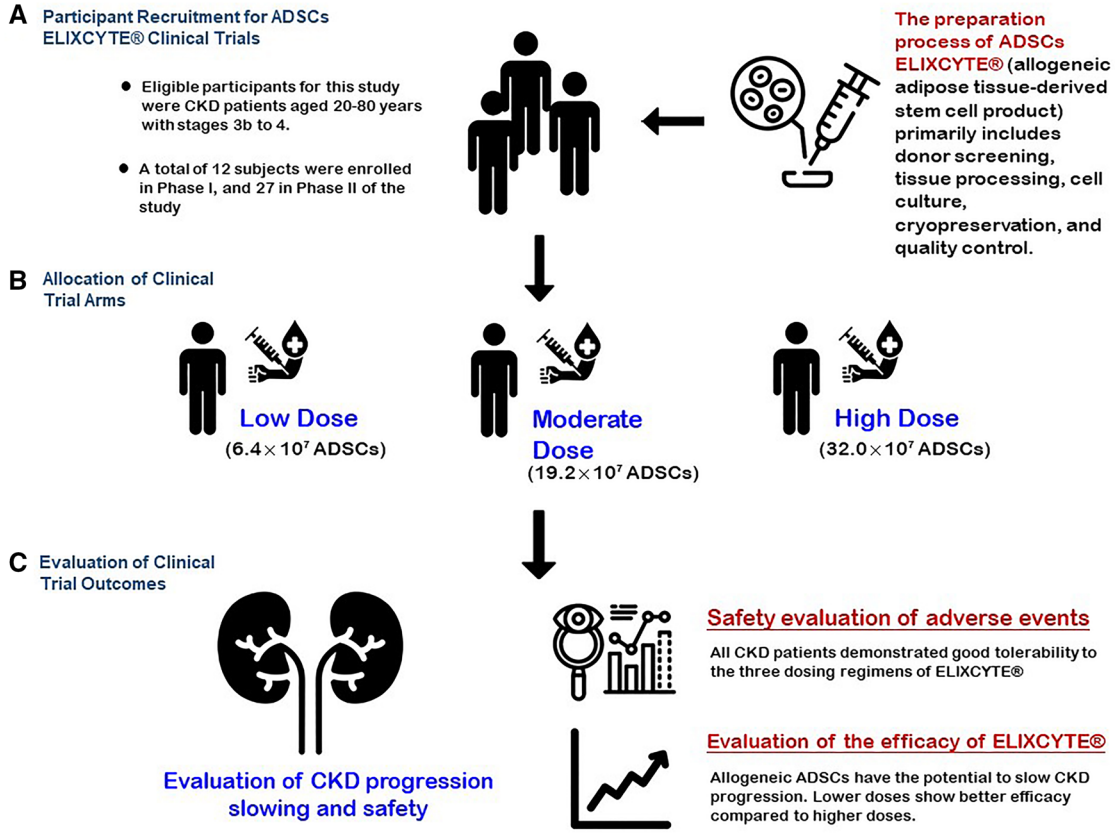
Graphical abstract



The graphic abstract summarizes the ELIXCYTE clinical trials, highlighting recruitment of CKD patients, allocation to low, moderate, and high-dose arms of allogeneic adipose-derived stem cells (ADSCs), and outcome evaluation. The trials confirmed good safety, slowed CKD progression, and showed better efficacy at lower doses, emphasizing the therapeutic potential of ELIXCYTE for CKD treatment.

Significance Statement

Chronic kidney disease (CKD) remains a major global health concern with limited treatment options, and adipose-derived stem cells (ADSCs) are emerging as a novel therapy to slow its progression. This study highlights the significance of adipose-derived stem cells (ADSCs) as an emerging therapy for chronic kidney disease (CKD), offering improved kidney function with fewer adverse effects, particularly at low doses. These findings contribute to advancing regenerative medicine by introducing a potentially more effective treatment option that may enhance quality of life and slow disease progression for CKD patients worldwide.

Introduction

Chronic kidney disease (CKD) affects approximately 10% of the global population, with 30% progressing to stages 3B to 5, characterized by severe renal dysfunction[1], increased complications, reduced quality of life, and elevated mortality[2–5]. Pathological hallmarks include glomerulosclerosis, tubulointerstitial fibrosis, and vascular damage, which are aggravated by chronic inflammation and fibrosis[6], ultimately driving kidney failure[7]. Developing targeted therapies to mitigate these pathological processes is a priority in CKD research.

Mesenchymal stem cell (MSC) therapy, an emerging approach, demonstrates potential in decelerating CKD progression through immunomodulation, anti-inflammatory effects, and tissue regeneration. MSCs secrete growth factors and cytokines that reduce inflammation, inhibit fibrosis, and repair renal tissue[6,8], while modulating immune responses to prevent autoimmune damage[9,10]. Preclinical and early clinical studies have shown improvements in renal function and injury reduction, establishing MSCs as a promising therapeutic candidate[11–13].

Among MSCs, adipose-derived stem cells (ADSCs) are particularly advantageous due to their high availability, ease of collection, and robust self-renewal and differentiation capabilities[14]. ADSCs release factors that promote angiogenesis, suppress inflammation, and inhibit fibrosis, thereby improving renal function and decelerating CKD progression[15].

Although clinical data on ADSCs in CKD are still limited, phase I trials of the allogeneic adipose-derived product ELIXCYTE have demonstrated favorable safety results (Zheng CM et al., 2022)[16]. This study aims to assess the efficacy of

ELIXCYTE in phase I and II trials, with a focus on slowing moderate to severe CKD progression, offering valuable insights for future therapeutic strategies.

Materials and methods

This Phase II multicenter, randomized, open-label study on ELIXCYTE was conducted across Taipei Medical University Shuang Ho Hospital, LinKou Chang Gung Memorial Hospital, and Taichung Veterans General Hospital. Data from a prior Phase I trial was integrated for a comprehensive evaluation. The trials spanned April 2018 to June 2023, enrolling 12 CKD patients in Phase I and 27 in Phase II, totaling 39 participants.

Study population and criteria

Participants were CKD patients aged 20–80 years at stages 3 b to 4 (eGFR 15–44 ml/min/1.73 m^2). Exclusion criteria included hypersensitivity to study components, hematologic or hepatic insufficiency, uncontrolled diabetes (HbA1c > 8.0%), HIV, hepatitis, autoimmune diseases, and ongoing dialysis. Certain nephrotoxic drugs were also grounds for exclusion. Patients maintained routine medications as determined by investigators. The number of participants included and excluded, along with the criteria for inclusion and exclusion and the randomization process, is detailed in Supplementary Information S1 and consort flow diagram.

Treatment protocol

A total of 39 participants were enrolled (Phase I: 12; Phase II: 27) and randomized using permuted block randomization to ensure balanced allocation across dosage groups. In Phase I, the low-, moderate-, and high-dose groups (6.4×10^7, 19.2×10^7, and 32.0×10^7 ADSCs, respectively) included 3, 3, and 6 participants, while in Phase II, each group initially enrolled 9 participants. All participants received a single intravenous injection and were monitored for 48 weeks. Five participants did not complete all scheduled visits due to personal or health-related reasons and were excluded according to the Per-Protocol (PP) principle, resulting in a PP population of 34 (Phase I: 3, 3, 6; Phase II: 8, 7, 7 for low-, moderate-, and high-dose groups, respectively), which formed the basis for efficacy and safety analyses.

ELIXCYTE production

The ADSC product was manufactured under TFDA and IRB-approved GMP conditions using adipose tissue from a single screened donor. The stromal vascular fraction was isolated and expanded to passage ≤7. The final product expressed $CD73^+$, $CD90^+$, $CD105^+$, and lacked CD14, CD34, CD45, and HLA-DR, meeting ISCT criteria. ELIXCYTE showed tri-lineage differentiation, ≥90% viability, and passed sterility, mycoplasma, and endotoxin tests before cryopreservation (8×10^6 cells/mL). Detailed information on ELIXCYTE production is provided in Supplementary Information S2.

Outcomes

The primary outcome was the longitudinal change in eGFR, analyzed continuously over time as a percentage difference from baseline. To enhance the evaluation of renal function dynamics, percentage changes in eGFR are utilized, calculated by determining the proportional difference between the eGFR value at each visit and the baseline eGFR value, expressed as:

$$\text{Change Percentage in eGFR} = \frac{\text{eGFR}_{\text{visit}} - \text{eGFR}_{\text{baseline}}}{\text{eGFR}_{\text{baseline}}} \times 100$$

Secondary outcomes included changes in albumin, creatinine, UACR, total protein, and HbA1c. These measures were assessed at multiple follow-up points post-treatment.

Statistical analysis

Group-based trajectory modeling (GBTM) was employed to classify participants into trajectory groups[17,18] (improved, stable, or declining kidney function) based on longitudinal changes in eGFR and other biomarkers. The purpose of GBTM was to identify distinct patterns of kidney function dynamics over time, providing a nuanced assessment of ELIXCYTE's therapeutic efficacy. By analyzing the percentage change from baseline at each follow-up visit, GBTM enabled researchers to determine the proportion of patients demonstrating clinical improvement or stabilization. A higher prevalence of improved or stable trajectories indicated a favorable response to treatment. To further validate these findings, generalized linear mixed models (GLMM) and unpaired t-tests were applied to assess the statistical significance of eGFR changes across trajectory groups. Adjustments for baseline variability and participant heterogeneity were incorporated to enhance the accuracy of efficacy estimates. All analyses were performed using SAS 9.4 software.

Results

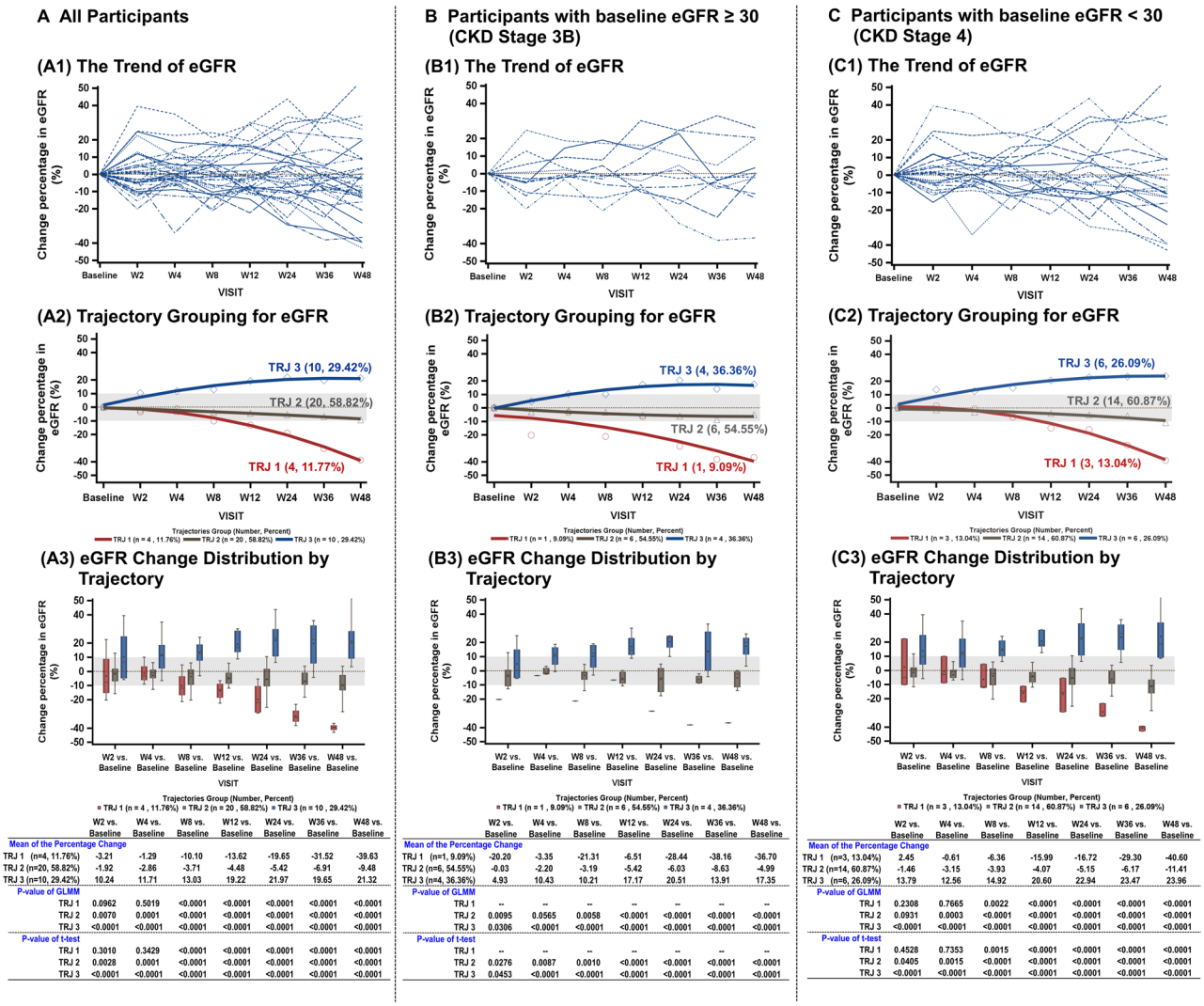
Baseline characteristics of subjects

The baseline characteristics of study participants are summarized in Supplementary Information S3 and Table S2. Participants were divided by ELIXCYTE dosage, and the groups exhibited balanced baseline characteristics with no statistically significant differences. The average age was 50.8 years, with 38.2% female participants. Common comorbidities included hypertension, gout, hyperlipidemia, and glomerulonephritis (all >50%). Over 80% of participants used proteinuria-reducing drugs, ARBs, and uric acid-lowering agents.

Change percentage in eGFR for different trajectory groups and CKD stages

The eGFR percentage change analysis classified participants into three trajectory groups using GBTM. The ±10% change in eGFR from baseline was used to define the stability range, with trajectories within this interval considered stable, above +10% as improved, and below −10% as declined[19,20]. From Figure 1 part A, it can be observed that participants' eGFR change trends vary. TRJ 1 (11.76%) exhibited a 40% decline in eGFR, TRJ 2 (58.82%) maintained stable kidney function, and TRJ 3 (29.42%) showed up to a 20% improvement. Statistical analysis confirmed significant differences in eGFR between trajectory groups, especially at Week 24.

Participants with baseline eGFR ≥ 30 (CKD stage 3B) and < 30 (CKD stage 4) displayed distinct eGFR trajectories. From Figure 1 part B and C, it can be observed that these changes vary depending on the CKD stage. In stage 3B, 54.55% maintained stability (TRJ 2) and 36.36% improved



	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=4, 11.76%)	-3.21	-1.29	-10.10	-13.62	-19.65	-31.52	-39.63
TRJ 2 (n=20, 58.82%)	-1.92	-2.86	-3.71	-4.48	-5.42	-6.91	-9.48
TRJ 3 (n=10, 29.42%)	10.24	11.71	13.03	19.22	21.97	19.65	21.32
P-value of GLMM							
TRJ 1	0.0962	0.5019	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.0070	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P-value of t-test							
TRJ 1	0.3010	0.3429	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.0028	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=1, 9.09%)	-20.20	-3.35	-21.31	-6.51	-28.44	-38.16	-36.70
TRJ 2 (n=6, 54.55%)	-0.03	-2.20	-3.19	-5.42	-6.03	-8.63	-4.99
TRJ 3 (n=4, 36.36%)	4.93	10.43	10.21	17.17	20.51	13.91	17.35
P-value of GLMM							
TRJ 1	--	--	--	--	--	--	--
TRJ 2	0.0095	0.0565	0.0058	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	0.0306	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P-value of t-test							
TRJ 1	--	--	--	--	--	--	--
TRJ 2	0.0276	0.0087	0.0010	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	0.0453	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=3, 13.04%)	2.45	-0.61	-6.36	-15.99	-16.72	-29.30	-40.60
TRJ 2 (n=14, 60.87%)	-1.46	-3.15	-3.93	-4.07	-5.15	-6.17	-11.41
TRJ 3 (n=6, 26.09%)	13.79	12.56	14.92	20.60	22.94	23.47	23.96
P-value of GLMM							
TRJ 1	0.2308	0.7665	0.0022	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.0931	0.0003	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P-value of t-test							
TRJ 1	0.4528	0.7353	0.0015	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.0405	0.0015	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Figure 1. Change percentage in eGFR for all participants and participants with baseline eGFR ≥ 30 and < 30. Panel A shows data for all participants, Panel B for participants with baseline eGFR ≥ 30, and Panel C for participants with baseline eGFR < 30. (A1), (B1), and (C1) Trend of eGFR: Blue lines represent the change percentage trend in eGFR for individual participants. (A2), (B2), and (C2) Trajectory Grouping for eGFR: Participants are grouped based on eGFR change percentage trends using GBTM, with the number and proportion of participants in each trajectory group indicated. (A3), (B3), and (C3) Distribution of eGFR Change percentage by Trajectory Group: Box plots display the distribution of eGFR change percentage for each trajectory group. GLMM and t-tests are used to assess the statistical significance of eGFR change percentages at each visit. The gray-shaded area represents the stability range, defined by ±10% change in eGFR from baseline. Trajectories with mean values within this range are classified as stable, those above +10% as improved, and those below −10% as declined.

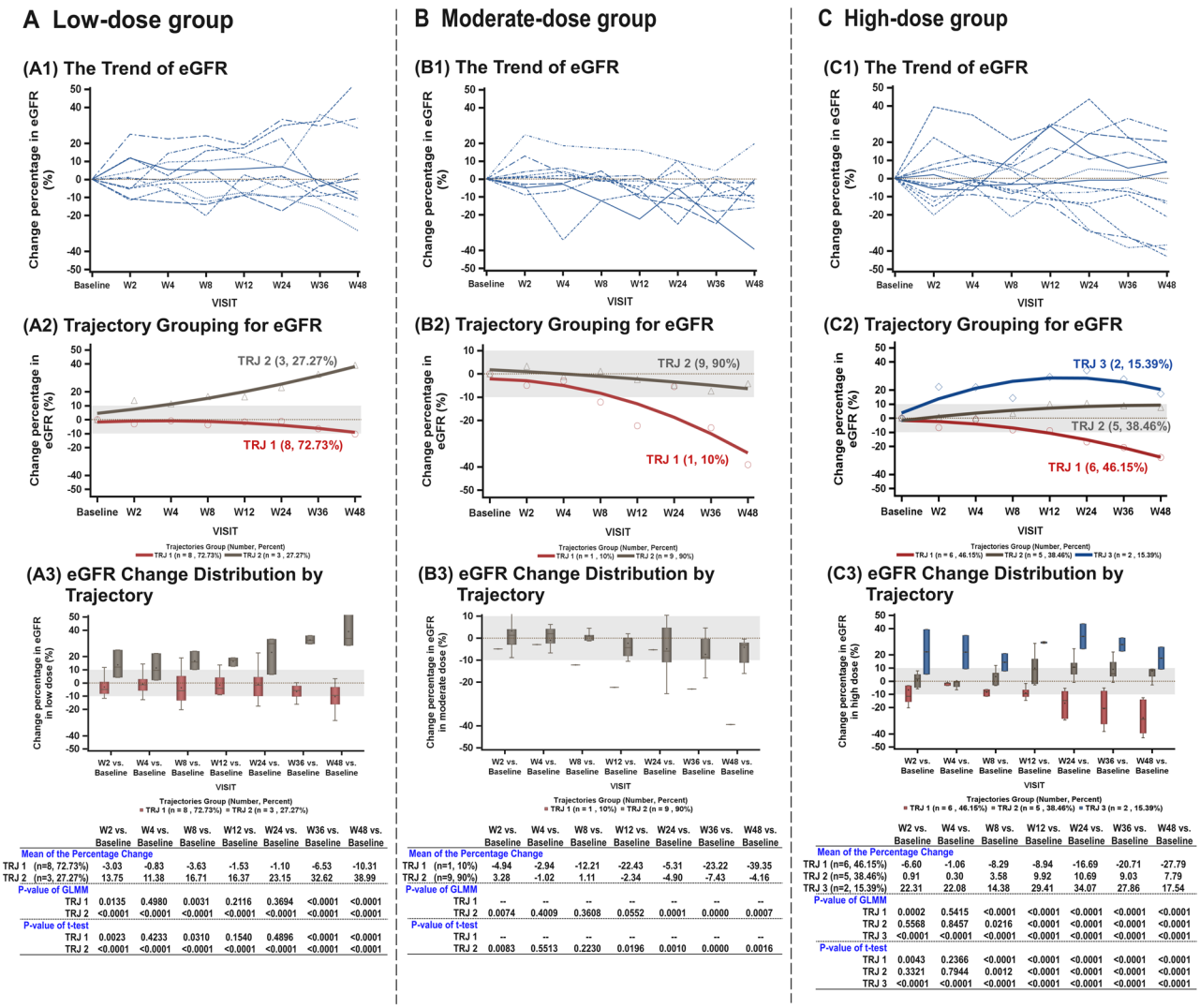
(TRJ 3), while in stage 4, 60.87% were stable, and only 26.09% improved. Stage 4 participants experienced a greater decline (TRJ 1: 13.04%) compared to stage 3B (9.09%), suggesting a potential trend toward favorable renal outcomes with stage 3B.

Change percentage in eGFR for participants receiving low-, moderate-, and high-dose of ELIXCYTE

The eGFR percentage change trajectories across the three ELIXCYTE dose groups revealed distinct patterns, as illustrated in Figure 2. Most participants in the low-dose group maintained stable or improved renal function, whereas a greater proportion of decline was observed in the high-dose group. A negative dose-related trend was evident, with no eGFR decline in the low-dose group, 10% decline in the moderate-dose group, and 46.15% decline in the high-dose group, showing that the proportion of renal function decline increased with higher ADSC doses.

Change percentage in other biomarkers (secondary outcomes)

Changes in other biomarkers (albumin, creatinine, UACR, protein, and HbA1c) were also analyzed using GBTM, excluding extreme values for accuracy (see Supplementary Information S4 and Figure S2). For albumin, 85.29% showed stable (61.76%) or improving (23.53%) trajectories. Creatinine analysis indicated 96.88% maintained stability (56.25%) or improved (40.63%). HbA1c improved for 88.23% of



	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=8, 72.73%)	-3.03	-0.83	-3.63	-1.53	-1.10	-6.53	-10.31
TRJ 2 (n=3, 27.27%)	13.75	11.38	16.71	16.37	23.15	32.62	38.99
P-value of GLMM							
TRJ 1	0.0135	0.4980	0.0031	0.2116	0.3694	<0.0001	<0.0001
TRJ 2	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P-value of t-test							
TRJ 1	0.0023	0.4233	0.0310	0.1540	0.4896	<0.0001	<0.0001
TRJ 2	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=1, 10%)	-4.94	-2.94	-12.21	-22.43	-5.31	-23.22	-39.35
TRJ 2 (n=9, 90%)	3.28	-1.02	1.11	-2.34	-4.90	-7.43	-4.16
P-value of GLMM							
TRJ 1	--	--	--	--	--	--	--
TRJ 2	0.0074	0.4009	0.3608	0.0552	0.0001	0.0000	0.0007
P-value of t-test							
TRJ 1	--	--	--	--	--	--	--
TRJ 2	0.0083	0.5513	0.2230	0.0196	0.0010	0.0000	0.0016

	W2 vs. Baseline	W4 vs. Baseline	W8 vs. Baseline	W12 vs. Baseline	W24 vs. Baseline	W36 vs. Baseline	W48 vs. Baseline
Mean of the Percentage Change							
TRJ 1 (n=6, 46.15%)	-6.60	-1.06	-8.29	-8.94	-16.69	-20.71	-27.79
TRJ 2 (n=5, 38.46%)	0.91	0.30	3.58	9.92	10.69	9.03	7.79
TRJ 3 (n=2, 15.39%)	22.31	22.08	14.38	29.41	34.07	27.86	17.54
P-value of GLMM							
TRJ 1	0.0002	0.5415	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.5568	0.8457	0.0216	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P-value of t-test							
TRJ 1	0.0043	0.2366	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 2	0.3321	0.7944	0.0012	<0.0001	<0.0001	<0.0001	<0.0001
TRJ 3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Figure 2. Change percentage in eGFR for participants receiving low, moderate, and high doses of ELIXCYTE. Panel A shows data for participants receiving a low dose, Panel B for those receiving a moderate dose, and Panel C for those receiving a high dose. (A1), (B1), and (C1) Trend of eGFR: Blue lines represent the change percentage trend in eGFR for individual participants. (A2), (B2), and (C2) Trajectory Grouping for eGFR: Participants are grouped based on eGFR change percentage trends using GBTM, with the number and proportion of participants in each trajectory group indicated. (A3), (B3), and (C3) Distribution of eGFR Change percentage by Trajectory Group: Box plots display the distribution of eGFR change percentage for each trajectory group. GLMM and t-tests are used to assess the statistical significance of eGFR change percentages at each visit. The gray-shaded area represents the stability range, defined by ±10% change in eGFR from baseline. Trajectories with mean values within this range are classified as stable, those above +10% as improved, and those below −10% as declined.

participants, with stable (58.82%) or decreasing (29.42%) trends. Both protein and UACR showed stability for 84.38% of patients, with minor increases (15.62%). These findings demonstrate that ELIXCYTE treatment contributes to the stabilization or improvement of key biomarkers in most patients.

Adverse events in ELIXCYTE phase I/II trial

Adverse events (AEs) were analyzed in the phase I/II trial (Tables 1 and Supplementary Information S5 and Table S3). Most AEs (74.2%) were Grade 1 in intensity, with higher-grade events more common in the high-dose group. Serious adverse events (SAEs) were rare (4.5%), with no dose-limiting toxicity (DLT) reported in the low or moderate-dose groups and only 1.1% in the high-dose group. The majority of AEs (89.9%) were unrelated to treatment, suggesting ELIXCYTE is well-tolerated.

Discussion

This study investigated the longitudinal eGFR trajectories of CKD patients following ELIXCYTE therapy. Most participants maintained stable renal function, particularly in the low-dose group, where 72.73% demonstrated stability and 27.27% improved. Consistent findings were observed across other renal biomarkers, including albumin, creatinine, and cystatin C, which remained stable or improved in most participants. This finding may reflect the paracrine effects of ADSCs that suppress inflammation and protect residual nephrons, thereby maintaining renal stability.

The overall safety profile was favorable, with adverse events (AEs) predominantly mild and no dose-limiting toxicity (DLT) in the low- and moderate-dose cohorts, indicating good tolerability. Although a few serious adverse events (SAEs) such as rapidly progressive glomerulonephritis and end-stage renal

Table 1. Summary of event-based adverse events in ELIXCYTE phase I/II trial.

	ELIXCYTE Low-Dose	ELIXCYTE Moderate-Dose	ELIXCYTE High-Dose	Total
Number of AEs	20	26	43	89
Event by intensity				
Grade 1	12 (60.0%)	18 (69.2%)	36 (83.7%)	66 (74.2%)
Grade 2	8 (40.0%)	7 (26.9%)	4 (9.3%)	19 (21.3%)
Grade 3	0 (0.0%)	1 (3.8%)	2 (4.7%)	3 (3.4%)
Grade 4	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Event by relationship to study treatment				
Definitely related	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Probably related	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Possibly related	0 (0.0%)	1 (3.8%)	2 (4.7%)	3 (3.4%)
Unlikely	0 (0.0%)	2 (7.7%)	3 (7.0%)	5 (5.6%)
Not related	19 (95.0%)	23 (88.5%)	38 (88.3%)	80 (89.9%)
Event by seriousness				
Serious	0 (0.0%)	1 (3.8%)	3 (7.0%)	4 (4.5%)
Non- serious	20 (100%)	24 (96.2%)	36 (93.0%)	80 (95.5%)
Event by dose- limiting toxicity				
Yes	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)
No	20 (100%)	25 (100%)	38 (97.7%)	83 (98.9%)

disease occurred, none were attributed to treatment. The slightly higher AE frequency in the high-dose group may reflect transient immune or metabolic stress following infusion, consistent with safety observations in previous MSC-based trials[21,22].

Participants with higher baseline eGFR (stage 3B) showed a slightly greater proportion of stable or improving trajectories compared with those with stage 4 disease, though the overall patterns appeared broadly similar between stages. This observation aligns with prior reports suggesting that patients with relatively preserved renal function may exhibit more favorable responsiveness to stem cell therapy[16,22], while advanced fibrosis and microvascular rarefaction in stage 4 could constrain regenerative effects[23,24]. Future clinical trials could explore urinary $CD133^+/SSEA4^+$ extracellular vesicles as biomarkers of regenerative potential.

A negative dose–response trend was observed, as participants in the low-dose group showed lower rates of renal function decline compared with those receiving moderate or high doses. Establishing the dose–response relationship is essential for defining the therapeutic window of ADSC therapy. Previous studies reported that MSC efficacy peaks within a narrow range of $100–150 \times 10^6$ cells, whereas higher doses may attenuate therapeutic effects through excessive paracrine signaling, local inflammatory activation, or metabolic stress within renal microenvironments[25–28]. Similar findings were reported by Packham et al., where 300×10^6 cells produced less renal improvement than 150×10^6 cells[22]. Our findings suggest that lower-dose ELIXCYTE achieves more stable renal trajectories and may inform optimal dosing strategies for future phase III CKD trials.

The influence of underlying diseases and concomitant medications on renal outcomes was further evaluated. No significant differences in comorbidities or medication use were observed among the three eGFR trajectory groups, suggesting that variations in renal trajectories following ELIXCYTE treatment were not significantly affected by comorbid conditions or concomitant medications (see Supplementary Information S6).

Based on the findings illustrated in Figure 1, both the stable and improved groups exhibited an accelerated rate of renal function decline after 24 weeks, although mean values largely remained within the ±10% stability range. This pattern is consistent with previous reports showing that stem cells display limited persistence and gradually diminishing paracrine activity following a single administration[29,30]. These results provide preliminary evidence supporting the need for future studies to verify the potential benefits of repeated dosing and to identify appropriate treatment intervals for sustained efficacy.

Short-term stabilization of eGFR observed with ADSC therapy may help mitigate rapid renal deterioration, which is known to predict dialysis initiation and mortality, particularly in advanced CKD[20,31]. These findings warrant further confirmation in larger real-world studies.

Conclusion

Allogeneic ADSCs show promise in mitigating CKD progression, particularly in moderate to severe cases, with an acceptable safety profile. The low-dose regimen was associated with fewer adverse events and a trend toward renal function stabilization. Overall, these findings provide preliminary clinical evidence supporting the potential of ADSC therapy to decelerate short-term renal deterioration, which warrants further confirmation through large-scale, well-controlled clinical trials.

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Author contributions

Yi-Chun Lin (Conceptualization [Equal], Data curation [Lead], Formal analysis [Lead], Methodology [Lead], Validation [Equal], Writing—original draft [Lead], Writing—review & editing [Equal]), Yi-Pei Hung (Conceptualization [Supporting], Funding acquisition [Lead], Formal analysis [Supporting], Investigation [Equal], Project administration [Equal], Writing—review & editing [Equal]), Ya-Chung Tian (Formal analysis [Supporting], Investigation [Equal] , Writing—original draft [Supporting] , Writing—review & editing [Equal]), Ming-Ju Wu (Formal analysis [Supporting], Investigation [Equal], Writing—review & editing [Equal]), Han-Chun Lin (Data curation [Equal], Formal analysis [Supporting], Validation [Equal], Writing—review & editing [Equal]), Szu-Ying Chen (Data curation [Equal], Formal analysis [Supporting], Validation [Equal], Writing—review & editing [Equal], Mai-Szu Wu (Conceptualization [Equal], Formal analysis [Supporting], Investigation [Equal], Project administration [Lead], Supervision [Lead], Writing—review & editing [Equal], and Hung-Yi Chiou (Conceptualization [Equal], Formal analysis [Lead], Methodology [Lead], Project administration [Lead], Validation [Equal], Supervision [Lead] , Writing—original draft [Lead], Writing—review & editing [Equal])

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Conflicts of interest

YPH was employed by the UnicoCell BioMed Co., Ltd The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that this study received funding from UnicoCell BioMed Co., Ltd The funder had the following involvement with the study: design and analysis.

Data availability

The data relevant to this study's findings can be obtained from the corresponding authors upon request, subject to data access regulations. However, due to patient privacy and ethical restrictions, the data from the Taipei Medical University Clinical Research Database and the ELIXCYTE clinical trial are not publicly available.

Ethics approval and consent to participate

The study received approval from the institutional review boards at all participating centers. The title of the approved project is A Phase I/II Study to Evaluate the Safety and Efficacy of Allogeneic Infusion of Adipose Derived Stem Cells in Moderate to Severe Chronic Kidney Disease. Ethical approval was granted by the Taipei Medical University Shuang Ho Hospital, with the TMU-Joint Institutional Review Board issuing Approval Number N201710032 on November 24, 2017. LinKou Chang Gung Memorial Hospital approved the study through the Chang Gung Memorial Institutional Review Board, with Approval Number 201900020A0 issued on April 24, 2019. Additionally, the Institutional Review Board I&II of Taichung Veterans General Hospital reviewed and approved the study under Approval Number SF20136B on July 24, 2020. Written informed consent was obtained from all participants. The trial was conducted in accordance with the principles outlined in the Declaration of Helsinki.

The ELIXCYTE phase I/II clinical trial was registered on ClinicalTrials.gov (NCT02933827) on October 13, 2016 (https://clinicaltrials.gov/study/NCT02933827), under the title A Phase I/II Study to Evaluate the Safety and Efficacy of Allogeneic Infusion of Adipose-Derived Stem Cells in Moderate to Severe Chronic Kidney Disease.

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