



**ORIGINAL ARTICLE**

# Exploratory-Data and Statistical Analyses of AB070597, an Amino Acid/Peptide Complex, on Blood-Serum Creatinine Concentration and Estimated Glomerular Filtration Rate: A Non-Randomized Pilot Trial of Five Humans with Declining Renal Function

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**Keywords:**

- AB070597 may be a useful clinical tool for the management of CKD and naturally declining RF in humans.
- No serious adverse effects were reported.

**Abstract:**

**Background:**

Chronic kidney disease (CKD) develops from persistent, irremediable loss of renal function (RF). Animal studies show that dietary supplement, AB070597, an amino acid/peptide complex, can stabilize, and in some instances, reverse CKD. Previous human CKD studies demonstrate that dietary treatment with specific keto acids and amino acids can lower blood-serum creatinine concentration (SCr) and increase glomerular filtration rate (GFR). This pilot trial was performed to determine whether a future randomized controlled human clinical trial of AB070597's effect on CKD was justified.

**Methods:**

The trial was structured as a consecutive case series to evaluate whether oral treatment with AB070597 could slow CKD progression, as gaged by SCr, and estimated glomerular filtration rate (eGFR). Eligibility requirements: Non-diabetic white males under current medical care in the United States, diagnosed with CKD, or with histories of increasing SCr and declining eGFR, resulting from CKD or natural consequence of aging. Exclusion criteria: Concurrent or suspected comorbidities unrelated to CKD. Participants ingested 6-g bi-daily doses of AB070597 for periods up to 24 months. SCr was measured and eGFR calculated at approximate tri-monthly intervals.

**Results:**

Results were presented as individual-participant and group SCr and eGFR vectors, and initial-data-analysis diagrams.

Treatment reversed SCr slopes from positive to negative, and eGFR slopes from negative to positive. When individual participant's median monthly eGFR rate-of-change (positive) was compared with the median monthly eGFR rate-of-change (negative) in a sample of 2870 humans with CKD, differences were significant in favor of the AB070597 treatment group in 4 of 5 participants: (P = 0.0625, 95% CI: 0.368-8.368), (P = 0.0313, 95% CI: 0.368-1.038), (P = 0.0039, 95% CI: 0.368-0.698), (P = 0.0010, 95% CI: 0.118-2.868), (P <0.0001, 95% CI: 0.368-10.370).

**Conclusion:**

Oral AB070597 treatment produced an apparently favorable change in CKD trajectory in 4 humans and in 1 with naturally age-related declining RF. The magnitude and direction of change hint that treatment may have had a beneficial effect on CKD progression and age-related RF. In and of themselves, this pilot trial's results seem to favor CKD treatment with AB070597, but because there was no randomization, no control group, and a small sample size, it is not possible to extend results beyond its bounds. They do, however, support the rationale for a future randomized controlled trial.

## 1 | INTRODUCTION

This trial explored the influence of bi-daily oral doses of AB070597 on SCr and eGFR in a small group of individuals with histories of rising SCr and negatively correlated eGFR.

CKD develops from persistent, irremediable loss of RF. Complicating dynamics, such as hypertension, anemia, renal-osteodystrophy, pericarditis, cardiovascular disease are common sequelae; followed by end-stage renal failure, and death. Currently, 37 million American adults have CKD, and 1 in 3 is at risk due to diabetes mellitus, hypertension, heart disease, obesity, or genetics (1). United States Centers for Disease Control and Prevention data reveal that CKD prevalence is 38% in individuals over 65 years old, 13% in those 45-64 years of age, 7% in those 18-44 years old, and is 15% in women versus 12% in men. 16% of non-Hispanic blacks, 13% of non-Hispanic whites, and 14% of Hispanics have CKD [2]. Diabetes mellitus and hypertension are the main causative factors (2, 3)

Progressively declining GFR is the hallmark of CKD. GFR declines predictably in most humans with advancing age (4). Acute physical trauma to renal tissue, infection, and drug or chemical-induced nephrotoxicity can cause GFR to fall precipitously, but values usually return to normal, or near-normal, with proper medical intervention. On the other hand, GFR does not normalize in patients who develop CKD. GFR continues to decay, and irrespective of the primary cause, evolves to progressive tubulointerstitial fibrosis with deteriorating RF and reduced nephron count; thus, its measurement becomes a useful means for judging RF and CKD status. Direct GFR measurement is the benchmark for assessing renal performance; but direct measurement requires multiple urine and blood-sample collections; along with continuous intravenous infusion of inulin, and hence does not easily lend itself to clinical implementation. In order to surmount this limitation, an alternate indirect method was developed to estimate GFR by utilizing steady-state SCr, a metabolite of creatine phosphate, which is found mainly in muscle; along with other factors such as age, race, and gender. Indirectly measured GFR is referred to as estimated glomerular filtration rate (eGFR). SCr and

calculated eGFR were the parameters measured in this investigation.

Blood-serum amino acid concentrations in humans with CKD are abnormal, when compared to concentrations in those with normal RF. Abnormal values include increased L-citrulline and decreased L-arginine, which correlate with elevated SCr (5, 6). Renal L-arginine synthesis is also markedly reduced (7). Plasma L-glutamine and L-histidine are notably lower (8, 9). Plasma asparagine levels decline progressively in patients with inflammation, malnutrition, or both (10); and finally, intracellular L-carnosine is reduced in uremic patients (11). Previous studies show that oral treatment with certain keto acids and amino acids arrest time-related SCr elevations in some CKD patients (12, 13). Dietary L-arginine supplementation increases GFR (14). L-carnosine augments bone morphogenetic protein-7 (BMP-7) gene expression in human periodontal ligament cells (15). Zeisberg et al., demonstrated that BMP-7 counteracts transforming growth factor-B1-induced epithelial-to-mesenchymal transition, thereby reversing chronic kidney injury (16). In a study by Archer (2019), human primary proximal renal tubule epithelial cells (hPRTEC) incubated with L-carnosine, at 1.763 ug/ml, increased BMP-7 messenger RNA (mRNA) expression 2.13-fold (17). L-carnosine is not detectable in blood-serum by current assay methods in fasted humans (18, 19).

Various amino acid concentrations are also abnormal in cats with CKD (20). In a previous study, cats with CKD experienced a significant median SCr reduction over 104 weeks ( $P=0.0084$ ), as well as a significant reduction in mean International Renal Interest Society (IRIS) disease stage ( $P=0.0184$ ), when treated orally with AB070597 (21). Moreover, hPRTECs incubated with AB070597 at 3.125 ug/ml,

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## EXPLORATORY ANALYSES OF AMINO ACID/ PEPTIDE COMPLEX AB070597 IN HUMANS WITH DECLINING RENAL FUNCTION

showed a 3.29-fold increase in BMP-7 mRNA expression (17).

Based on the foregoing information, we hypothesized that oral treatment with AB070597 might have potential to stabilize or lower SCr, and recover RF in humans with CKD, or in those with naturally declining RF. AB070597 was formulated as a compound of amino acids and a peptide, chosen to address the deficits discussed above, and to increase exogenous BMP-7 expression. The amino acids and peptide in AB070597 are commercially available and are generally regarded as safe when taken individually by humans as dietary supplements. Previous studies demonstrated the safety of these combined ingredients in cats (21) and in dogs (22). A study by Archer, J. (2019) found no AB070597 cytotoxicity in cell viability assays using hPRTEC (17).

## 2 | MATERIALS AND METHODS

### 2.1 | Design

This trial was structured as a consecutive case series to determine if oral dosing with AB070597 could slow CKD progression, as gaged by SCr and calculated eGFR.

### 2.2 | Participants

Participants were recruited from Southern California medical practices from November 2016 to November 2017. Data collection occurred from November 2016 to November 2018. Ages ranged from 63 to 80 years. Participants were identified as [AB0705970n (xx)], where n = 0-4, and where xx = age in years at trial entry: AB07059700 (74), AB07059701 (63), AB07059702 (80), AB07059703 (66), and AB07059704 (66). Eligibility requirements: 1) Non-diabetic white males under current medical care in the United States, diagnosed with CKD or with a history of increasing SCr resulting from CKD or natural consequence of aging. Exclusion criteria: Concurrent or suspected comorbidities unrelated to CKD. Two participants, AB07059700 and AB07059701, were prescribed low-protein diets by their supervising nephrologists. Participants were

instructed to dissolve the contents of 6 capsules of AB070597 in a one-half cup of water or fruit/vegetable juice and consume as a beverage, once in the morning and once in the evening, for a total of 12 g/day. Physician-prescribed medications were allowed, and non-prescription supplements or herbal remedies were prohibited. Pre-trial retrospective SCr and eGFR data, and time-in-trial varied among participants.

### 2.3 | AB070597

AB070597 amino acids and peptide weights were extrapolated from human and animal studies that showed positive correlation with improved RF in CKD subjects. Amino acids and peptide were supplied, compounded as capsules, bottled, and labeled by Albert Max, Inc., a United States Food and Drug Administration registered manufacturing facility (Chino, California, USA). Each 1-g capsule included 83 mg L-arginine, 167 mg glycine, 167 mg L-glutamine, 83 mg L-histidine, 167 mg L-aspartic acid, 167 mg L-glutamic acid, and 167 mg L-carnosine.

### 2.4 | Body Weight

A digital automatic-calibration body-weight scale (EatSmart Products, #: ESBS-05, Oak Brook, Illinois, USA) was issued to each participant, along with a daily diary to document dosing compliance, record weekly body-weight measurements, and any unusual symptoms.

### 2.5 | Blood-Sample Collection and Laboratory Measurements

SCr was measured and eGFR calculated approximately every 3 months, up to 24 months or participant trial departure. Blood samples (5 mL) were collected at local Quest Diagnostics, Inc. clinics (Corporate Headquarters, 500 Plaza Dr., Secaucus, NJ 07094). Measurements from the first clinic visit (pre-dosing) served as baselines for SCr and eGFR for each participant. eGFR was assessed by SCr, utilizing the Chronic Kidney Disease Epidemiology Collaboration formula (23). Participants' diaries

were collected at trial end or departure.

## 2.6 | Safety

Safety was assessed using adverse event (AE) reporting. An AE was defined as an unexpected medical event occurring during treatment, or untoward medical occurrence, which did not necessarily have a causal relationship with treatment. Expected AEs included early-on transient gastrointestinal distress. AEs were collected from the time a participant took his first dose until the final clinic visit. AEs were identified through observation, participant comment or question. AEs were followed until they resolved, were clinically stable, or until 30 days after a participant departed the trial.

## 3 | STATISTICAL ANALYSIS

Pre-treatment and treatment vectors were plotted to visualize any SCr or eGFR slope change. Vectors were also plotted to picture changes from treatment-start baselines to study end (exploratory data analysis [EDA]).

A non-parametric one-sample Wilcoxon signed-rank test (initial data analysis [EDA]) was used to compare participant eGFR median-rate-of-change per unit time to eGFR median-rate-of-change per unit time of 2870 CKD patients in a study by Tsai et al. (24), at 0.05 significance, using GraphPad Prism (San Diego, California, USA). Post-trial statistical power was calculated from Tsai et al. (24) eGFR rate-of-change mean; trial treatment eGFR rate-of-change mean, and pooled standard deviation at 0.05 significance (DSS Research, <https://www.dssresearch.com>). The probability of an individual participant attaining a particular study-end vector state or trend was calculated by comparing their study-end vector state to all possible vector states or trends

## 4 | RESULTS

### 4.1 | Statistical Analyses: Exploratory Data Analysis, Initial Data Analysis

At treatment baseline (vector head-tail intersections) Figures 1 and 2, SCr vector slopes changed from positive to negative, and eGFR vector slopes changed from negative to positive for all participants. Figure 3 shows that SCr decreased from treatment baseline versus time for all participants. Figure 4 illustrates the opposite trend for eGFR, with rates increasing from treatment baseline for each participant.

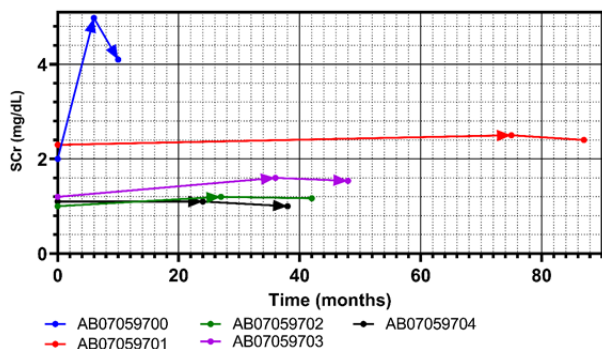
The one-sample Wilcoxon signed-rank test quantified significant eGFR decline rate reversals in 4 of 5 participants Figure 5 Table 1.

**TABLE 1:** Wilcoxon Signed-Rank Test of eGFR Decline Rate Reversal (Overall Post-Trial Statistical Power = 99.2%)

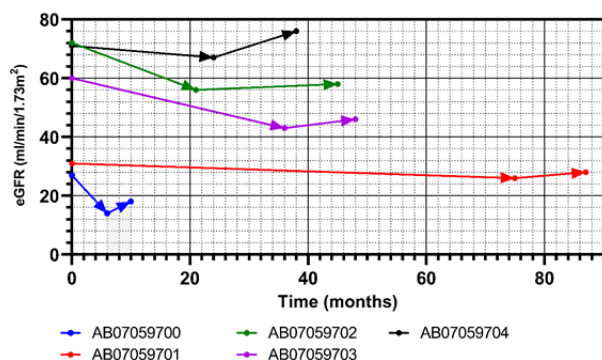
Participant ID	95% Confidence Intervals	P-value
AB07059700	0.368-8.368	0.0625
AB07059701	0.368-1.038	0.0313*
AB07059702	0.368-0.698	0.0039*
AB07059703	0.118-2.868	0.0010*
AB07059704	0.368-10.370	< 0.0001*

\* = significant at  $P \leq 0.05$

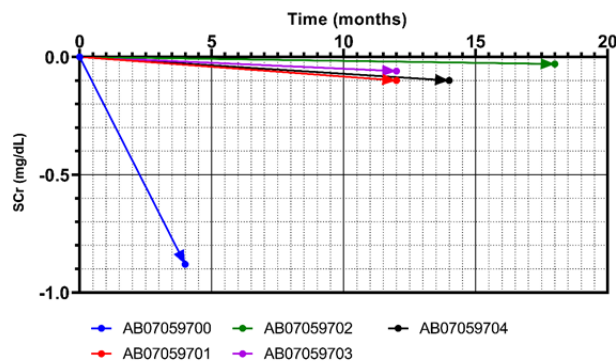
The compound probability of arriving at the group's study-end vector-state gave insight as to whether the observed treatment effect was true (i.e., plausible by P value). There were 5 possible SCr and eGFR study-end vector-states and trends: 1) no change from pre-treatment slope (i.e., no treatment effect), 2) increasing slope, 3) decreasing slope, 4), steady-state (vector slope = 0, progression halted), and 5) pre-treatment and treatment slope reversals (i.e., CKD reversal). The probability of a single participant's study-end vector-state or trend was 1/5. The compound probability of all 5 participants attaining SCr and eGFR slope reversals was  $(1/5)^5 = 0.00032$  (i.e.,  $P < 0.001$ ).



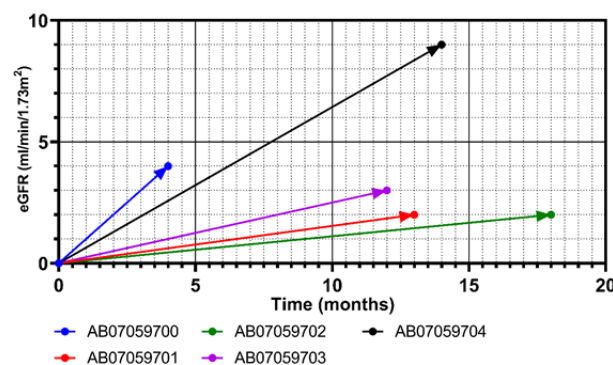
**FIGURE 1:** eGFR<sup>a</sup> Pre-Treatment and Treatment Vectors a = blood-serum creatinine concentration. Pre-treatment SCr vector slopes were sign-positive from trial baseline (x-axis= 0) to treatment baseline (vector head-tail intersections) for allparticipants, then vector slopes reversed to sign-negative.



**FIGURE 2:** eGFR<sup>a</sup> Pre-Treatment and Treatment Vectors a = estimated glomerular filtration rate. Pre-treatment SCr vector slopes were sign-positive from trial baseline(x-axis = 0) to treatment baseline (vector head-tail intersections) for allparticipants, then vector slopes reversed to sign-negative. Pre-treatment eGFR vector slopes were sign-negative from trial baseline(x-axis = 0) to treatment baseline (vector head-tail intersections) for allparticipants, then vector slopes reversed to sign-positive.



**FIGURE 3:** SCr<sup>a</sup>: Change from Treatment-Baseline Vectors a = blood-serum creatinine concentration. SCr declined from treatment baseline (x-axis = 0) for all participants.



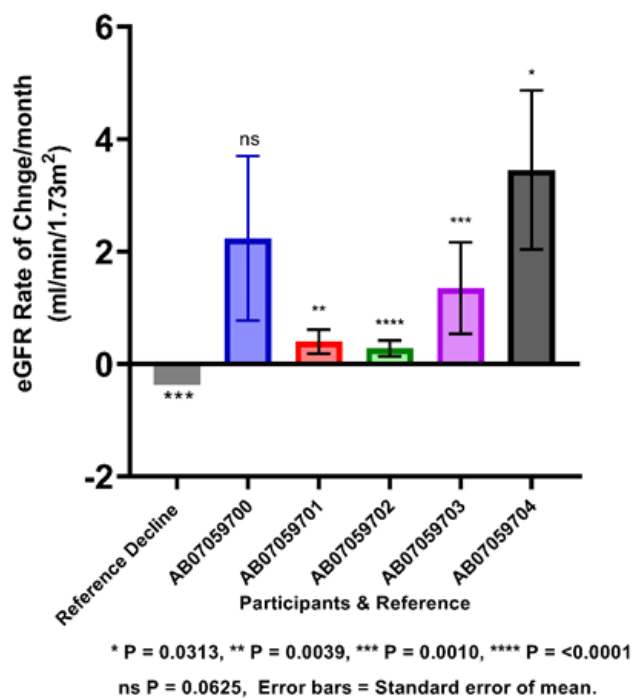
**FIGURE 4:** eGFR<sup>a</sup> Change from Treatment-Baseline Vectors a = estimated glomerular filtration rate. eGFR increased from treatment baseline for all participants.

#### 4.2 | Safety

Overall, AB070597 was well tolerated by participants. AB07059703 and AB07059704 experienced mild diarrhea for 1 and 2 days, respectively. No other AEs were reported.

#### 4.3 | Body Weight

Participant body weights did not change notably during the treatment period (data not shown).



**FIGURE 5:** Figure 5 Median eGFR<sup>a</sup> Treatment Rate of Change per Month a = estimated glomerular filtration rate.

Grey bar represents median monthly eGFR decline in 2870 humans with CKD in a study by Tsai et al. (24) [24]. Blue, red, green, purple, and black bars represent median monthly eGFR increases for this trial's participants.

## 5 | DISCUSSION

Examination of disease progression in individuals can reveal information and offer insights that the frequentist approach to data analysis (e.g., models and hypothesis tests of groups) sometimes obscures. Tukey (1977) developed methods for visually observing data to grasp overall structure (25). This trial used EDA, as set forth by Tukey, in the form of SCr and eGFR vectors, in conjunction with the IDA non-parametric one-sample Wilcoxon signed-rank test, to analyze the effect of oral AB070597 supplementation on SCr and eGFR in 5 humans with declining RF.

EDA is a statistical approach to gain visual insight to the shape and structure of data-sets beyond that which formal modeling or hypothesis testing can reveal. EDA was chosen for its ability to visually

display pre-treatment and treatment-interval SCr and eGFR vector-slopes and trends. IDA was selected because it made conventional hypothesis test calculations possible (i.e., P values), thus, offering a way to correlate visual observations with a null-hypothesis. Figure 1 and Figure 2 graphically display each participant's SCr and eGFR vector-state during 2 important intervals: 1) pre-treatment baseline (x-axis = time 0) to treatment baseline (head-tail intersection), and 2) treatment baseline to final laboratory measurement (head-tail intersection to head). Visual comparisons of SCr and eGFR vector slopes revealed uniform treatment responses by all participants, with SCr moving from positive (declining RF), to negative (improving RF). eGFR vectors moved from negative to positive, as would be expected, since eGFR correlates negatively with SCr. Each participant's SCr and eGFR vectors represented the mean of all vectors that followed CKD progression between laboratory measurements, and as such, did not give precise information about how SCr and eGFR moved along the pathway from pre-treatment baseline to final laboratory measurement. With all data available, it would have been possible to display all incremental vectors, but in the spirit of EDA, we chose to display mean vectors to gain the overall view. SCr and eGFR change-from-treatment baselines vectors Figures 3 and 4 presented the uniform response of participants to treatment, with SCr decreasing and eGFR increasing, versus time.

Mean vectors, as opposed to vectors constructed as linear regression lines, were used for analysis in order to give the most accurate assessment of treatment effect. Regression line vectors would have moved vector heads and tails from their laboratory measured values, thereby changing pre-treatment and treatment baselines, as well as the final measurement points. All participants shared similar SCr and eGFR vector slope signs at the final clinic visit; with the combined probability of such an occurrence at  $P < 0.001$ . Parallel analyses by EDA and IDA gave a visually compelling picture of treatment effect on CKD progression and its effect on age-related RF, as well as a graphical display with associated P-values.

These observations contrast sharply with common SCr and eGFR trajectories in patients with CKD or

naturally declining RF, wherein SCr and eGFR increase and decrease, respectively. Biological mechanisms that relate to AB070597's composition exist that might explain these contrasts. For instance, SCr positively correlates with blood-serum concentrations of endogenous nitric oxide synthase inhibitors, asymmetrical dimethylarginine (ADMA) and symmetrical dimethylarginine (SDMA), in humans with CKD (26). ADMA inhibits nitric oxide synthase directly, while SDMA limits nitric oxide synthesis by acting as a competitive inhibitor of L-arginine transport (27). L-arginine in AB070597 may have contributed to increased nitric oxide production since it is its unique biological substrate. Zoccali et al. described the pathogenic role of blocked nitric oxide synthesis in humans and its negative impact on RF (28). L-arginine supplementation consistently improves GFR in diverse models of renal disease in humans (29). Glycine infusion increases effective renal plasma flow and GFR in rats and reduces proximal and distal tubule Na<sup>+</sup> reabsorption (30). The deleterious effects of reactive oxygen species (ROS) production in renal cells is generally accepted. L-aspartic and L-glutamic acids are efficient ROS scavengers (31). Glutamine suppresses proteolysis and stimulates protein synthesis in skeletal muscle (32). L-histidine is an essential amino acid in normal and chronically uremic humans (33). Lastly, L-carnosine-increased BMP-7 gene expression might have improved RF by inducing non-functional nephrons to differentiate and regain their normal phenotype, thus increasing the functional nephron number.

## 6 | CONCLUSIONS

AB070597 treatment produced an apparently favorable change in CKD trajectory, as gauged by SCr and eGFR in 4 humans with CKD and in 1 with naturally declining RF. The magnitude and direction of change hints that treatment may have had a beneficial effect on the progression of CKD and age-related RF. In and of themselves, this pilot trial's results seem positive, but because there was no randomization,

no control group, and a small sample size, it is not possible to extend results beyond its bounds. They do, however, support further investigation of AB070597, and forms the rationale for a randomized controlled trial with greater treatment and control groups.

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**8 FUNDING :** Major funding was provided by the John T. Fulton Trust with additional minor funding from Applied Research Laboratory.

## 9 COMPLIANCE WITH ETHICAL STANDARDS

**10 CONFLICT OF INTEREST :** I, the author, declare I have no competing or conflicting interests. I was, however, granted United States patents US 966,910 B2, US 10,668,037 B2 and European Patent EP 2928461 for my work on AB070597. I have assigned all rights to Bio Health Solutions, (Reno, Nevada, USA). I have not received and will not receive payment or compensation of any kind for those assignments. I have no financial interest in Bio Health Solutions, and it did not fund or support my research, either directly or indirectly.

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**11 ETHICAL APPROVAL :** In accordance with the Declaration of Helsinki and Department of Health and Human Services regulations (USA), the 'AB070597 Case Report' trial was reviewed by Pearl Independent Review Board and granted exemption (Pearl IRB 16-BOS-101) from requiring ethics approval and oversight under 45 CFR 46.102(d) and 45 CFR 46.101(b)(4). All participants signed informed consent.

## 12 DATA AVAILABILITY AND TRIAL REGISTRATION

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request. The International Standard Randomized Controlled Trial Number assigned to this study is ISRCTN44802329.

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## EXPLORATORY ANALYSES OF AMINO ACID/ PEPTIDE COMPLEX AB070597 IN HUMANS WITH DECLINING RENAL FUNCTION

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