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Figure S1. Image of size 0-, 00-, and 000-capsules in relation to a US penny. Taken from https://i.publiclab.org/system/images/photos/000/006/729/original/caps.jpg on June 28, 2019.	Page 42

Bicarbonate Administration to Stabilize eGFR

(BASE Study)

Pilot Clinical Trials in CKD Protocol

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BASE Study
Pilot Clinical Trials in CKD

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1 INTRODUCTION

1.1 Executive Summary

Metabolic acidosis is a recognized complication of chronic kidney disease (CKD) that is usually treated with oral alkali to mitigate the effects of acidosis on bone and protein [1]. Limited data suggest that treatment of acidosis with alkali also slows CKD progression [2, 3]. However, most CKD patients have normal serum bicarbonate levels and do not receive alkali because it is not recommended by current practice guidelines under these circumstances [4, 5]. Whether alkali slows CKD progression in people with normal serum bicarbonate is uncertain, although results from several observational studies and one small interventional study support this possibility. These data provide a strong rationale to determine whether sodium bicarbonate preserves renal function in CKD patients with *normal* serum bicarbonate in a full-scale trial. Before proceeding with a Phase 3 trial, however, the optimum dose of sodium bicarbonate that would be acceptable in terms of safety and compliance needs to be determined, as was discussed at a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Conference "Reducing the Impact of Chronic Kidney Disease: Opportunities for Randomized Clinical Trials" in July 2011 [6]. The purpose of the BASE (Bicarbonate Administration to Stabilize EGFR) Pilot Clinical Trial is to help inform the decision regarding sodium bicarbonate dose for a Phase 3 trial by examining the safety, compliance, and pharmacodynamics of two rational doses of sodium bicarbonate in the CKD population that will be enrolled in that trial.

1.2 Background

CKD is a major global health problem, leads to end-stage renal disease (ESRD), promotes cardiovascular disease, and shortens life expectancy. Unfortunately there are few established therapies that slow CKD progression. Results from observational and a few small interventional trials have renewed interest in alkali as a strategy to slow CKD progression. Traditionally, the role of alkali in non-dialysis requiring CKD has been relegated to correct systemic acidosis and prevent consequent bone demineralization and protein catabolism [1]. However, results from two small interventional trials suggest that correcting systemic acidosis also slows CKD progression [2, 3].

a. In a non-randomized study, individuals with hypertensive kidney disease, estimated glomerular filtration rate (eGFR) 20–59 ml/min/1.73m^2, and *low* serum bicarbonate (<22 mEq/L) who received chronic sodium citrate 1 mEq/kg-LBW (lean body weight) daily (n=30) had higher eGFR after 24 months of treatment compared to the control group (n=29) not receiving alkali supplementation [3].

b. In a randomized study, de Brito-Ashurst et al. assigned 134 CKD patients with low serum bicarbonate levels (16–20 mEq/L) to receive either open-label chronic oral sodium bicarbonate or no sodium bicarbonate. In the intervention group, the bicarbonate dose was titrated to achieve serum bicarbonate ≥23 mEq/L. The mean dose of sodium bicarbonate required to achieve this target was 0.3 mEq/kg/day. Fewer participants treated with bicarbonate had decline in creatinine clearance by >3 ml/min/1.73m^2/yr (relative risk [RR] 0.15; p<0.0001) and fewer required dialysis (RR 0.13; p<0.001) over two years [2].

Although there are no large definitive trials on the effect of bicarbonate supplementation on CKD progression in patients with low serum bicarbonate, these results have led to significant interest in this area. Two other ongoing randomized trials, one from the United Kingdom (BiCARB Study) and one from Austria (SoBic-Study) are also examining the renal and non-renal benefits of correcting systemic acidosis in CKD patients [7, 8].

The BiCARB Trial is a multicenter, randomized, double-blinded, placebo-controlled trial. Three hundred eighty patients with stage 4 or 5 CKD, *serum bicarbonate <22 mEq/L*, and age >65 years will be enrolled. Participants will receive up to 3000mg per day of sodium bicarbonate to achieve serum bicarbonate ≥22 mEq/L. The primary outcome will be physical function measures. A secondary objective of the BiCARB Trial is to explore the effect of sodium bicarbonate on eGFR during the two-year follow-up period [8].

The SoBic-Study is a single-center, randomized, controlled, *open-label* study of 200 patients with stage 3 or 4 CKD with *serum bicarbonate <21 mEq/L*. The intervention arm will receive oral sodium bicarbonate titrated to target serum bicarbonate level of 24±1 mEq/L. The expected maximum dose in this arm is 5040 mg of sodium bicarbonate daily, although higher doses may be required to reach target levels. The control group will receive a rescue therapy of sodium bicarbonate to target serum bicarbonate level of 20±1 mEq/L. The primary objective in this study is to compare the change in eGFR between the two arms over a two-year follow-up [7], although the study is likely underpowered for this outcome.

1.2.1 Shifting the paradigm of acid-base management in CKD: Focusing on those with normal serum bicarbonate

Both BiCARB and SoBic are specifically targeting patients with *low* serum bicarbonate, probably motivated by the common belief that correcting acidosis has a number of pleiotropic benefits. In fact, correcting acidosis is recommended for CKD patients [1]. However, 85% of CKD patients have normal serum bicarbonate [5] and are not treated with alkali. Thus, a major paradigm shift in CKD treatment would occur if alkali were indeed shown to preserve renal function in people with normal serum bicarbonate concentration. Several lines of evidence support this possibility:

a. Multiple observational studies have shown that higher serum bicarbonate concentrations, *even within the normal range*, are associated with a lower risk of CKD progression, with the lowest risk observed near 28 mEq/L [9-12].

b. Mahajan et al. performed a blinded, randomized controlled trial in patients with hypertensive nephropathy, stage 2 CKD, and macroalbuminuria, comparing (i) 0.5 mEq/kg-LBW/day sodium bicarbonate (n=40), (ii) equimolar sodium chloride (n=40) and (iii) placebo (n=40). The groups had similar eGFR by cystatin C (~73 ml/min) and serum bicarbonate (~24 mEq/L) at baseline. At the end of the *5-yr* study, eGFR decline was significantly less in participants treated with sodium bicarbonate (eGFR 66.4 ml/min), compared to those who received sodium chloride (eGFR 62.7 ml/min) or placebo (60.8 ml/min) [13].

These data support the promise of alkali as a reno-protective therapy among CKD patients with normal serum bicarbonate levels. Two other ongoing studies are exploring this possibility [14,15]. One is testing pleiotropic effects of sodium bicarbonate on muscle, bone, insulin sensitivity, and reno-protection in the setting of *normal* serum bicarbonate. In this trial, 150 CKD patients with eGFR of 15-45 ml/min/1.73m^2 and serum bicarbonate 20-27 mEq/L will receive either 0.4 mEq/kg-LBW/day of sodium bicarbonate or placebo for two years. Because the trial is not powered to examine the effect on hard renal outcomes (i.e. eGFR), two intermediate injury markers, KIM-1 (kidney injury marker-1) and NGAL (neutrophil gelatinase-associated lipocalin), are used as surrogate measures [14]. The second study is investigating the effect of sodium bicarbonate (0.5 mEq/kg-LBW/day), compared to placebo, on urinary markers of renal fibrosis and complement activation in 74 diabetic veterans with stage 2-4 CKD and serum bicarbonate 20-28 mEq/L [15].

1.2.2 What is the optimum dose of sodium bicarbonate in the target population?

Although the studies in CKD patients with normal serum bicarbonate administer a dose of 0.4-0.5 mEq/kg-LBW/day, the optimum dose, with regard to reno-protective efficacy, safety, and compliance, is unknown. Based on the pathophysiological mechanisms by which alkali may reduce kidney injury, doses higher than 0.4-0.5 mEq/kg-LBW/day may increase the chances of achieving a positive efficacy result in a Phase 3 trial, so long as higher doses are safe and do not diminish compliance.

The proposed mechanism of action of the reno-protective effects of alkali is presented in Figure 1. The daily fixed acid load must be excreted in order to maintain normal systemic pH. The kidneys accomplish this by excreting H^+ in the form of ammonium (NH_4^+) and titratable acids (i.e., $H_2PO_4^-$) and reabsorbing filtered bicarbonate. Of these mechanisms, the most adaptable is the up-regulation of renal ammonia (NH_3) production and NH_4^+ excretion. In CKD, residual nephrons must compensate for the loss of functioning nephrons to excrete the fixed acid load. By necessity, NH_3 generation per functioning nephron increases [16], leading to high local tissue NH_3 concentration. The generated NH_3 leads to intrarenal activation of the alternative pathway of complement, further tubulointerstitial injury, and CKD progression [17]. In addition, endothelin-1 (ET-1)-mediated H^+ secretion in response to reduced cellular pH also leads to tubulointerstitial injury [18, 19]. Hence, alkali is expected to neutralize the daily acid load, thereby reducing renal NH_3 production and ET-1 activity and renal fibrosis. We hypothesize that these compensatory responses and consequent fibrosis could be furthered suppressed with doses of sodium bicarbonate greater than 0.4-0.5 mEq/kg-LBW/day.

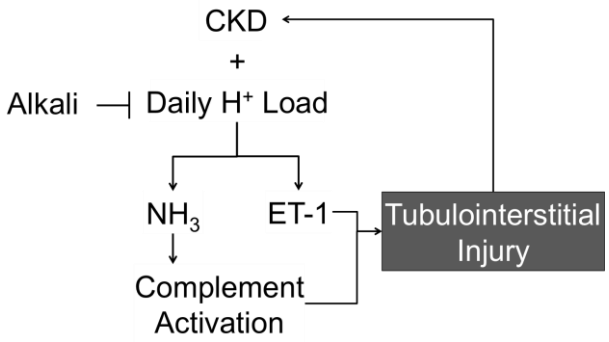


Figure 1. Proposed mechanisms of renal injury induced by the daily acid load in CKD and how alkali treatment attenuates this injury. (ET-1 = endothelin-1)

Whether higher doses are safe in CKD patients with normal serum bicarbonate levels over an extended duration is unknown. There is limited evidence that sodium bicarbonate doses >0.5 mEq/kg-LBW/day are safe, at least in the short-term. In a study by Abramowitz et al., 20 CKD patients with serum bicarbonate levels of 20-24 mEq/L received escalating doses of oral sodium bicarbonate (0.3, 0.6, and 1.0 mEq/kg-LBW/day) over 2-week intervals on each dose [20]. No significant adverse effects (including weight gain, blood pressure increase, or hypokalemia) were observed with the highest dose. It should be noted that the duration of exposure was short (2 weeks) and the sample size was small.

While a sodium bicarbonate dose of 0.5 mEq/kg-LBW/day administered over 5 years appeared to be safe in CKD patients in the Mahajan et al. study [13], the participants in that study had early (stage 2) CKD and the sample size was small (n=40). In contrast, it is likely that our potential Phase 3 trial will enroll participants with more advanced CKD (i.e., stages 3 and 4) in order to accumulate sufficient renal event rates during follow-up. Whether more advanced CKD patients can tolerate bicarbonate doses of 0.5 mEq/kg-LBW/day or higher is uncertain and will be examined as the main goal in this Pilot Clinical Trial in preparation for a Phase 3 Trial. A secondary objective is to assess the pharmacodynamics of two different doses of oral sodium bicarbonate, by measuring change in urinary NH_4^+ excretion, which will also facilitate dose selection for the Phase 3 trial

.

1.3 Goals

The long-term goal is to conduct a randomized, double-blinded, placebo-controlled Phase 3 trial that will determine if chronic oral sodium bicarbonate therapy slows CKD progression in patients with normal serum bicarbonate levels.

The goal of this Pilot Clinical Trial is to determine the dose of sodium bicarbonate to be employed in the Phase 3 trial. To achieve this goal, we will conduct a 28-week three-arm, parallel, randomized, double-blinded, placebo-controlled trial in 192 patients with moderate-to-severe CKD and normal serum bicarbonate levels. In addition to placebo, there will be two active treatment groups, a lower-dose sodium bicarbonate group and a higher-dose sodium bicarbonate group. The dose of sodium bicarbonate that will be tested in the lower-dose group is 0.5 mEq/kg-LBW/day. The dose of sodium bicarbonate that will be tested in the higher-dose group is 0.8 mEq/kg-LBW/day.

1.3.1 Specific Aims

Specific Aim 1. The primary aim of this Pilot Clinical Trial is to determine the feasibility, in terms of *safety and tolerability*, of prescribing one of two doses of oral sodium bicarbonate (0.5 or 0.8 mEq/kg-LBW/day) in a Phase 3 trial that will test whether this intervention slows CKD progression in patients with moderate-to-severe CKD and normal serum bicarbonate concentration. The primary analysis will examine, as co-primary endpoints, the percentage of participants in each dose group that are *prescribed* at the end of the 28-week intervention period:

a. the full randomized dose of sodium bicarbonate according to the protocol, *and*
b. at least 25% of the randomized sodium bicarbonate dose according to the protocol.

Specific Aim 2. A secondary objective of the Pilot Clinical Trial is to determine the effect of the 0.5 and 0.8 mEq/kg-LBW/day sodium bicarbonate doses on urinary NH_4^+ excretion, compared to placebo, as a pharmacodynamic assessment.

Hypothesis: Urinary NH_4^+ excretion will decrease with both sodium bicarbonate doses, however, the magnitude of the reduction will be greater with the higher dose.

1.3.2 Co-Primary Endpoints for Specific Aim 1

The two co-primary endpoints provide an assessment of the feasibility, in terms of *safety and tolerability*, to implement either dose in a Phase 3 trial. These endpoints are influenced by a number of factors, including medication intolerance (e.g., due to gastrointestinal symptoms or fluid retention), side effects (e.g., difficult-to-manage hypertension, hypokalemia, or metabolic alkalosis), and participant drop-out or loss to follow-up. Although compliance will be evaluated by pill counts, *compliance will not be considered in the co-primary endpoints* assessments because (i) poor compliance will not trigger a reduction in the prescribed dose unless there is intolerability or an adverse safety event, and (ii) obtaining pill counts from participants has many limitations. Nonetheless, the compliance data will be analyzed secondarily.

We anticipate that most participants in each active treatment arm will complete the study *prescribed* the full dose as randomized according to the protocol because they did not have a protocol mandated dose reduction due to side effects or intolerance. On the other hand, some participants may require a reduction in the prescribed dose due to side effects or intolerance (as discussed in Section 8). Participants who do not complete the study will be considered treatment failures.

Therefore, the appropriateness of employing one of these sodium bicarbonate doses in a Phase 3 trial will be evaluated by two co-primary safety and tolerability endpoints in this Pilot Study:

1. The percent of participants within each active treatment arm who are prescribed the full randomized sodium bicarbonate dose according to the protocol at the end of the 28-week intervention period, *and*
2. The percent of participants within each active treatment arm who are prescribed at least 25% of the randomized sodium bicarbonate dose according to the protocol at the end of the 28-week intervention period.

The participant's prescribed dose at the end of the intervention period will be compared to the participant's randomized dose to determine if an intended dose reduction occured as described in Section 8.

1.3.3 Benchmarks for co-primary endpoints

We would consider that the benchmark is achieved if:

1. at least 67% of participants in each active treatment arm are prescribed the full randomized sodium bicarbonate dose according to the protocol at the end of the 28-week intervention period, *and*
2. at least 80% of participants in each active treatment arm are prescribed at least 25% of the randomized sodium bicarbonate dose according to the protocol at the end of the 28-week intervention period.

For example, if 70% of participants in an active treatment arm are prescribed the full randomized dose at the end of the 28-week intervention period, an additional 10% in that arm would need to complete the intervention period on at least 25% of the randomized dose to achieve 80% and satisfy the second criterion.

Our rationales for these benchmark cutoffs consider: (i) a potential loss to follow-up and drop-out rate of 5-15% in the active treatment arm, (ii) that, in order for a dose to be prescribed in a longer-duration Phase 3 trial, the vast majority of participants who are not lost to follow-up or do not drop-out should not require a dose reduction for safety or intolerance during this shorter 28-week Pilot Study, and (iii) participants who take lower than the randomized doses may still benefit from the therapy, so long as the percentage of such participants is low in this 28-week Pilot Study.

Therefore, if the total percent of (i) participants taking <25% of the randomized dose at the end of the intervention period, (ii) loss to follow-up, and (iii) drop-out is >20% in an active treatment arm, the feasibility of employing that dose in a longer-duration Phase 3 trial would be questionable. Also, if <67% of participants are prescribed the full randomized dose for that treatment arm at the end of the intervention period, this would also suggest that such a dose would not be feasible in a long-term Phase 3 clinical trial.

1.3.4 Overall assessment of feasibility

In addition to the co-primary *safety and tolerability* endpoints in Specific Aim 1, the appropriateness of the dose interventions for a Phase 3 trial will also consider the response of urinary NH_4^+ excretion to the two dose levels of sodium bicarbonate in Specific Aim 2 and participant compliance as assessed by pill counts. As mentioned, compliance will not be considered in the co-primary endpoints analyses. Hence, the determination of whether one of these doses is suitable for evaluation in a Phase 3 trial will be based first on whether pre-

specified benchmarks for the co-primary safety and tolerability endpoints are achieved, but will also consider the full spectrum of results of the Pilot Clinical Trial as well as the results of other sodium bicarbonate interventional trials.

1.4 Interventions

Capsules containing one gram of sodium bicarbonate powder will be prepared for this Pilot Clinical Trial. One gram of sodium bicarbonate delivers 12 mEq of bicarbonate and 275 mg of elemental sodium. The number of pills prescribed will be determined by the participant's LBW and treatment assignment (see Table 2 below). Matching placebo capsules will contain cornstarch.

1.5 Study Design

The study is a three-arm, parallel, randomized, double-blinded, placebo-controlled trial. Although this is a three-parallel-arm study, the placebo group will be divided into lower-dose and higher-dose placebo groups to maintain the blind. Except for pill count summaries, analyses that include comparisons with placebo will consider the two placebo groups jointly. The three study arms are:

1. Higher-dose (0.8 mEq/kg-LBW/day) oral sodium bicarbonate (n=88)
2. Lower-dose (0.5 mEq/kg-LBW/day) oral sodium bicarbonate (n=52)
3. Placebo (n=52).

1.5.1 Rationale to include more participants in the higher-dose sodium bicarbonate arm

The rationale to include more participants in the higher-dose arm is the following. There are two other ongoing studies comparing 0.4-0.5 mEq/kg-LBW/day sodium bicarbonate with placebo in similar, albeit somewhat different patient populations. These other trials will also contribute substantial amounts of data on safety and tolerability of the 0.5 mEq/kg-LBW/day dose, *although they will not provide direct comparisons with a higher dose*. Assigning more participants to the 0.8 mEq/kg-LBW/day dose in this Pilot Clinical Trial will provide more experience with this dose, which is essential for selecting the dose for the Phase 3 trial.

1.5.2 Rationale for the placebo arm

Although direct comparisons of the active treatment groups with the placebo group will not be required to determine if the pre-specified benchmarks for the co-primary safety and tolerability endpoints are met, there are several reasons to include a placebo group in this Pilot Clinical Trial. First, a placebo group is required for Specific Aim 2, which will evaluate the reduction in urinary NH_4^+ excretion by sodium bicarbonate compared to placebo. Second, if a placebo group were not included the investigators and participants would know that they are receiving sodium bicarbonate, which could influence medical management during the Pilot Clinical Trial as well as participant's perception of side effects. Third, the inclusion of a placebo group will provide estimates of the proportions of participants who are classified as failures by the co-primary endpoints due to factors unrelated to the actual exposure of the participant to sodium bicarbonate; these estimates will clarify the interpretation of the failure rates observed for the co-primary endpoints in the two active treatment groups. Fourth, evaluation of pill counts in the placebo group will address the extent to which pill burden contributes to limitations in compliance, independent of side effects. Finally, several potential side effects of sodium bicarbonate, such as increase in blood pressure and fluid retention, commonly occur in CKD patients. Inclusion of a placebo group will better allow us to assess the safety of sodium

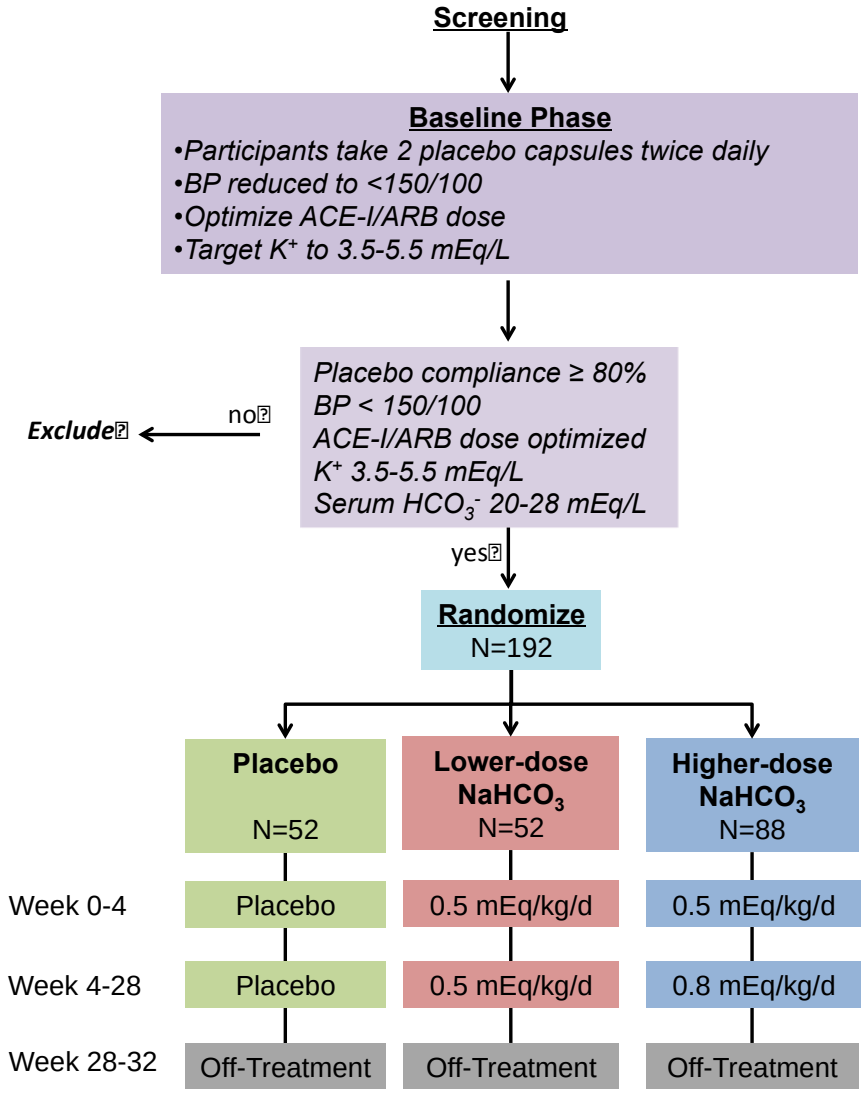
bicarbonate in this population.

1.5.3 Description of the study phases

The study consists of three consecutive phases after enrollment (Figure 2):

1. *Baseline Phase*. During baseline, participants will take 2 placebo capsules twice daily for two weeks. In addition, blood pressure (BP) will be reduced to <150/100 mm Hg, locally measured serum potassium targeted to 3.5-5.5 mEq/L, and angiotensin converting enzyme-inhibitor (ACE-I) or angiotensin receptor blocker (ARB) dose will be optimized (i.e., tolerable dose up to the maximum recommended dose). Participants will be randomized if compliance with the placebo is at least 80%, BP is <150/100 mm Hg, serum potassium is 3.5-5.5 mEq/L, the average of the two most recent serum bicarbonate concentrations measured during baseline is 20-28 mEq/L, and the ACE-I or ARB is optimized in the opinion of the site investigator.
2. *On-Treatment Phase*. Participants take the assigned intervention for 28 weeks.
3. *Off-Treatment Phase*. Participants take no research pills for 4 weeks and then return for a close-out visit.

Figure 2. Design of the BASE Pilot Clinical Trial


Screening
Baseline Phase
•Participants take 2 placebo capsules twice daily
•BP reduced to <150/100
•Optimize ACE-I/ARB dose
•Target K+ to 3.5-5.5 mEq/L
Placebo compliance ≥ 80%
BP < 150/100
ACE-I/ARB dose optimized
K+ 3.5-5.5 mEq/L
Serum HCO3- 20-28 mEq/L
no
Exclude
yes
Randomize
N=192
Placebo
N=52
Lower-dose NaHCO3
N=52
Higher-dose NaHCO3
N=88
Week 0-4
Placebo
0.5 mEq/kg/d
0.5 mEq/kg/d
Week 4-28
Placebo
0.5 mEq/kg/d
0.8 mEq/kg/d
Week 28-32
Off-Treatment
Off-Treatment
Off-Treatment

1.6 Sample size

One hundred ninety-two (192) participants will be randomized. Fifty-two (52) will be assigned to the placebo group (26 each to the lower-dose and higher-dose placebo groups), eighty-eight (88) to the higher-dose sodium bicarbonate group, and fifty-two (52) to the lower-dose sodium bicarbonate group. It is recognized that some participants will be excluded prior to randomization, so a higher number of participants will be enrolled in baseline as needed based on the observed exclusion rate as the trial unfolds.

1.7 Study Timeline

Participants will be enrolled over an 18-month period. We anticipate the last participant will be randomized before the end of the 21st month and the last visit will occur before the end of the 29th month.

1.8 Study Visits

Table 1. Summary of visit schedule

PERIOD	Screening	Baseline			Random-ization†	On Treatment								Off Treatment
VISIT NAME	S0	B0	B1	B2,3,etc‡		W0†	W4	W8	W12	W16¶	W20	W24¶	W28	W32
TIME (approximate number of weeks from randomization)	-12	-8 to -2				0	4	8	12	16	20	24	28	32
Medical history review	x													
Medication review	x	x	x	x			x	x	x		x		x	x
Height^, Weight, Blood pressure, Pulse, Edema	x	x	x	x			x	x	x		x		x	x
Informed consent	x													
Pregnancy test (local)	x													
Serum (local): Chemistry panel (Bicarbonate, Potassium, Creatinine, Sodium, Chloride, Urea Nitrogen, Glucose, Calcium)	x	x	x	x*			x	x	x		x		x	x
Serum (local): Phosphorus and Albumin		x							x				x	
Spot Urine (local): Albumin /Creatinine	x	x							x				x	
Dispense study medication		x				x	x	x	x		x			
Venous blood gas+		x							x				x	
Randomization					x									
24-hour urine (central)			x						x				x	
Gastrointestinal symptoms questionnaire		x	x				x	x	x		x		x	x
Pill counts			x				x	x	x		x		x	
Adverse events assessment							x	x	x	x	x	x	x	x
Collection of blood/urine for biorepository			x						x				x	

^ *measured only at screening visit*

* *if required to assess serum K^+ and HCO_3^- prior to randomization*

‡ *additional baseline visits may be held to achieve target blood pressure, potassium, and optimize ACE-I/ARB dose*

† *The purpose of W0 is to dispense randomized drug. Randomization will sometimes be done at a baseline visit. If this occurs, a separate W0 visit is not required.*

¶ *conducted by telephone*

+ *venous blood gas substudy participants*

2 PATIENT SELECTION

2.1 Introduction

The participant characteristics in the Pilot Clinical Trial are selected to match the entry criteria that we anticipate will be used in the Phase 3 trial, with a few exceptions. Participants will have normal to slightly low serum bicarbonate (20-28 mEq/L) and moderate to severe CKD.

2.2 Inclusion and Exclusion Criteria

A. Inclusion

1. Serum bicarbonate 20–28 mEq/L at screening (the average of the two most recent values in Baseline must be 20-28 mEq/L prior to randomization)
2. Moderate to severe CKD at the time of screening, defined as one of the following:
   a. eGFR 20.0–44.9 ml/min/1.73m^2 or
   b. eGFR 45.0–59.9 ml/min/1.73m^2 plus random urinary albumin:creatinine (ACR) ≥50 mg/gm
3. Blood pressure <160/100 mm Hg at screening (must be <150/100 mm Hg prior to randomization)
4. Lean body weight 37.5–96.0 kg
5. Age allowing legal consent without parental involvement (18-21 years, depending on individual state regulations)
6. Able to provide consent
7. Able to travel to study visits
8. Able to read English
9. In the opinion of the site investigator, willing and able to follow the study treatment regimen and comply with the site investigator's recommendations
10. In the opinion of the site investigator, medically stable
11. Have at least one ankle available to measure for edema

B. Exclusion

1. Use of chronic daily oral alkali (such as sodium bicarbonate, sodium citrate, potassium citrate, etc) with one exception: calcium carbonate ≤1500 mg/day is allowed, as some will take this for the indication of bone health
2. In the judgment of the PI, the participant's blood pressure medication regimen cannot be escalated (by adding a drug or increasing a dose) if the participant's blood pressure were uncontrolled
3. Serum potassium <3.3 or ≥5.5 mEq/L at screening (must be 3.5-5.5 mEq/L prior to randomization)
4. Self-reported vegetarian
5. New York Heart Association Class 3 or 4 heart failure symptoms, known left ventricular ejection fraction ≤30%, or hospital admission for heart failure within the past 3 months
6. Frequent urinary tract infections (≥2 in the past year)
7. Presence of indwelling urinary catheter or urinary conduit (such as neobladder or urostomy)
8. Factors judged to limit adherence to interventions (e.g., alcoholism, history of missing clinic visits, chronic gastrointestinal disorder that makes compliance with the intervention unreliable)
9. Organ transplant recipients (excluding cornea)
10. Active glomerular disease requiring or potentially requiring immunosuppressive treatment
11. Chronic immunosuppressive therapy for any indication. This does not include oral steroids ≤10 mg per day, inhaled steroids, or topical steroids
12. Anticipated initiation of dialysis or kidney transplantation within 12 months as assessed by

the site investigator
13. Current participation in another interventional research study
14. Malignancy requiring therapy within 2 years (skin cancer other than melanoma and localized prostate cancer are exempted)
15. Pregnancy or planning to become pregnant or currently breast-feeding. Women of childbearing potential (pre-menopausal and not surgically sterilized) will have urine pregnancy test before enrollment.
16. Life expectancy <12 months as determined by the site investigator
17. Institutionalized individuals, including prisoners and nursing home residents
18. Plans to leave the immediate area within the next 12 months
19. Routinely leaves town for multiple weeks each year such that protocol visits would be missed
20. Chronic use of supplemental oxygen
21. Use of both ACEI and ARB

For laboratory criteria, local results will be used. These lab tests can be performed at the time of screening, or results measured within 2 calendar months of the screening visit can be used to determine eligibility. When multiple measures are available, the most recent results will be used to determine eligiblity.

Exclusion criteria 6 (frequent urinary tract infections ≥2 in the past year) and 7 (presence of indwelling urinary catheter or urinary conduit, such as neobladder or urostomy) are included because these may affect urinary NH_4^+ concentration. These urinary exclusion criteria are not expected to be included in the Phase 3 trial because urinary NH_4^+ is not expected to be measured in that trial.

2.3 Identification of participants for screening

Patients will be screened from clinics at recruiting institutions. It is expected that at most institutions, BASE Trial personnel will review the local medical record to identify patients who meet key entry criteria such age, eGFR, and other laboratory criteria. A waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization and waiver of informed consent will be obtained from local Institutional Review Boards (IRBs) for any pre-reviews of medical records.

2.4 Informed Consent procedures

It is expected that most patients will be approached at the time of their routine clinic visits. This will occur as follows. After obtaining verbal permission from the clinical provider, study coordinators will approach potential participants at the time of the routine clinic visit and inform them of the nature and purpose of the trial in a private room. Patients expressing interest in participation will be told about the entry criteria and given ample time to ask questions about the study, risks, benefits, and study-related procedures. Patients will be informed that research participation is voluntary and the refusal to participate will in no way affect their medical care. Those who meet the entry criteria and are interested in participating will sign the informed consent document and will be provided with a copy of the signed informed consent document.

2.4.1 Consent and Withdrawal of Consent for the NIDDK Biosample Repository

Participants may consent or withdraw consent for the Repository at any time during the BASE Pilot Study. If a participant consents to the NIDDK Biosample Repository, his or her samples

will be stored at the NIDDK Biosample Repository indefinitely. A participant may withdraw consent for the Repository during the study by notifying the principal investigator at the site. This physician will notify the DCC staff of this request in writing. The DCC will then notify the NIDDK repository. After obtaining approval from NIDDK, the Repository will destroy and discard the samples with its biological and laboratory waste. The DCC will follow through to make sure the samples have been destroyed. After the BASE Pilot Study ends, the BASE study IDs will be removed and participants may no longer withdraw consent for the Biosample Repository, as there will no longer be a way to link any individual with any stored specimen.

2.5 Privacy and security

Local clinical sites will store participant information in a secure manner, and HIPAA privacy rules will be followed. For purposes of this study, participants will be identified only by an assigned identification number and a randomly generated alphanumeric code. The study database will be password protected, and clinical site personnel will be restricted from seeing data for participants from centers other than their own. The study database will reside on a password-protected computer at the Data Coordinating Center (DCC). No individual identifiers (participant name, social security number, or device serial number) will be stored. Data will be entered with strong encryption and a Thawte, Inc., system will be used for secure transmission of data from clinical sites to the DCC. The DCC ensures accuracy and reliability of computer systems used for this study with detailed edit checks and tests of data interface screens, reports, and procedures before implementation. Computer-generated, time-stamped audit trails are kept. The database is incrementally backed up daily, with full back ups performed weekly. Backups are stored at a secure location separate from the site of the database server.

In those instances where a participant document (such as a hospital discharge summary or death certificate) is sent to the DCC, the site study coordinator will de-identify this prior to electronically transmitting it to the DCC.

Clinical site and DCC staff members will be required to change their passwords every 75 days, and staff who are no longer active in the study will be blocked from database access.

3 SCREENING & BASELINE PHASES

3.1 Screening

Screening will consist of completion of the screening form and collection and documentation of laboratory data. Participants who have signed the consent document, but do not have the necessary laboratory data specified in the entry criteria within two calendar months will have the missing screening tests performed as part of the study protocol. If laboratory entry criteria are not met, participants can be considered for rescreening later at the discretion of the investigator.

3.2 Description of Baseline Phase

The purpose of the Baseline Phase is to assess the participant for potential non-compliance, titrate antihypertensive medications to achieve goal blood pressure (<150/100 mm Hg), adjust serum potassium to the target range (3.5-5.5 mEq/L), and adjust ACE-I/ARB to the maximum tolerable dose prior to randomization. Although participants can be randomized if blood pressure is <150/100 mm Hg, blood pressure will be treated to target <140/90 mm Hg during the study.

It is anticipated that the Baseline Phase will consist of 2 to 4 visits, but more visits may be held if necessary. The visits during Baseline will be approximately two weeks apart.

Patients who agree to participate in the study and meet all entry criteria will be scheduled for the first baseline visit (B0). B0 will occur within 4 weeks of the screening visit. Participants who do not attend B0 within four weeks of screening may be rescreened after one week has passed.

Goals of Baseline Phase:

1. Assess for potential non-compliance. At B0, participants will be given 100 placebo capsules and asked to take two pills twice daily until the next visit (B1). The B1 visit will be scheduled to occur in two weeks (range of 7-25 days to better accomodate the participant's schedule). Participants will bring back the pill bottle and pill counts will be performed. If compliance as assessed by the pill count is <80%, the participant will be removed from the study. Participants with ≥80% pill count compliance can proceed to randomization provided other Baseline targets are achieved.

2. Obtain 24 hour urine collection. Participants will be provided with urine collection supplies and instructions on how to collect the first 24-hour sample at B0. Participants will bring in the 24-hour urine collection to the B1 visit. If the 24-hour urine collection is deemed inadequate, it will be repeated prior to randomization provided other Baseline targets are achieved. Adequacy will be determined by asking the participant if they emptied their bladder prior to beginning the collection, did not miss collecting any urine, and if the time of the urine collection was close to 24 hours, as defined in the Manual of Operations.

3. Reduce blood pressure to <150/100 mm Hg. Blood pressure will be measured three times, one minute apart, and the mean of the second and third measure will be considered the BASE protocol visit blood pressure. The target BP during BASE is <140/90 mm Hg; however, participants can be randomized if blood pressure is <150/100 mm Hg. If blood pressure is above target, life-style changes (i.e., dietary salt restriction) and/or antihypertensive therapy will be initiated or escalated at the discretion of the site investigator. Maximizing ACE-I/ARB dose will be given priority.

4. Target serum potassium 3.5-5.5 mEq/L. If serum potassium is below goal, dietary recommendations and/or potassium supplements will be given at the discretion of the investigator. If serum potassium is above target and the sample is not hemolyzed, then potassium will be lowered at the discretion of the investigator. (If serum potassium is above target and the sample is hemolyzed, it will be repeated.) The strategy may include dietary potassium restriction, diuretics, reducing ACE-I/ARB dose, and blood glucose control. If diuretics or ACE-I/ARB doses change during baseline, the serum potassium will be repeated so it reflects serum potassium on the most recent diuretic and ACE-I/ARB dose.

5. Initiate, titrate ACE-I/ARB. If a participant is not on ACE-I/ARB, she/he will be questioned about prior use and side effects. If there is a history of allergic reactions or documented intolerance, ACE-I/ARB will not be started. If there has been no prior exposure, an ACE-I/ARB will be started at the discretion of the investigator, taking into consideration blood pressure and potassium concentration. ACE-I/ARB dose will be increased to the maximum dose for proteinuric participants (i.e., the equivalent of 40 mg/d of lisinopril) provided that blood pressure and serum potassium are acceptable. If a participant is not uptitrated to the equivalent of 40 mg/day of lisinopril, the reason will be documented. The rationales of maximizing the ACE-I/ARB dose in the Baseline Phase are two-fold: (i) the reno-protective effects of bicarbonate in the Phase 3 trial should be examined on the background of currently acceptable therapy; and (ii) avoidance of ACE-I/ARB dosage manipulation after randomization in the trial, which may affect serum potassium and bicarbonate concentrations and eGFR.

Achievement of the compliance goal is defined as a pill count compliance ≥80%. Achievement of the blood pressure requirement is defined as the last protocol measured blood pressure <150/100 mm Hg. Achievement of the serum potassium goal is defined as the last protocol measured serum potassium with the range of 3.5-5.5 mEq/L. Achievement of the serum bicarbonate goal (20-28 mEq/L) is defined as the average of the two most recent serum bicarbonate measures obtained during baseline. Achievement of appropriate ACE-I/ARB dose will be determined by the site investigator and will take into account the participant's blood pressure, serum potassium, and proteinuria status.

Participants can spend a maximum of 12 weeks in the Baseline Phase. The minimum number of Baseline visits will be two, which allows us to identify potential non-compliers using the placebo capsules. More visits can be held if necessary to achieve target BP and potassium, and to titrate the ACE-I/ARB dose so long as the time spent in Baseline is not > 12 weeks. Those who do not achieve all goals by the end of the Baseline Phase will be removed from the trial but can be rescreened after one week has passed from the date of baseline drop-out, at the discretion of the investigator. Participants who satisfy all Baseline Phase criteria and are still willing will proceed to randomization.

3.3 Baseline collection of concurrent medications at study entry

Participants will be asked to bring in their medications including over-the-counter preparations to the first baseline (B0) visit. Study staff will record these.

3.4 Comorbidities assessment

Study staff will record medical history, including history of tobacco and alcohol use.

3.5 Maximum time allowed in Baseline

The maximum time allowed between screening and B0 is 4 weeks. The maximum time from B0 to randomization is 12 weeks.

Since consented participants will have blood pressure and potassium concentrations near the level required to proceed beyond Baseline, we anticipate that most will be randomized within 8 weeks of screening. Hence, the target time from screening to randomization is 8 weeks.

3.6 Reasons for Baseline Phase drop-out

Study staff will document reasons for pre-randomization drop-out during Baseline.

3.7 Assessment of readiness for randomization

Study staff will run the "Ready-to-Randomize Report" checklist for each participant to check that the participant meets all criteria.

4 RANDOMIZATION AND RECRUITMENT MONITORING

4.1 Randomization in an intent-to-treat clinical trial

The study site investigator or a designated site investigator will review the screening and Baseline data and the Ready to Randomize report and confirm that the participant is eligible and should be randomized. Randomization marks the participant's official and irrevocable entry into the Follow-up period. Once a participant has been randomized, efforts will be made to conduct all evaluation and data collection irrespective of whether the participant starts the study treatment regimen, how long the participant continues on the study treatment regimen, and how well the participant complies with the study treatment regimen.

Routine data collection will end when a participant begins dialysis, receives a pre-emptive kidney transplant, dies, or is deemed completely lost to follow-up.

If a participant withdraws consent for some types of data collection, other data will continue to be collected. All efforts will be made to continue data collection through the end of study follow-up even if a participant's medication never begins, the participant is not compliant, or the participant must stop randomized medications for a safety-related reason or any other reason. The primary analysis will be performed as intent-to-treat, that is, by randomized treatment group.

4.2 Logistics of randomization

The DCC will prepare randomization schedules prior to the start of recruitment. Randomization will be stratified by participating site. Randomly permuted blocks of different sizes, ordered in a random sequence, will be used to help meet the protocol-defined ratios of numbers of participants assigned to each treatment regimen. This method guarantees that at no time during randomization will the number of participants in any arm be grossly off target and ensures that the sites will be unable to predict assignments of future participants based on knowledge of assignments of past participants. All randomization schedules will remain confidential and known only by select members of the DCC staff.

Baseline data that have been categorized as essential must be in the database and support eligibility in order for a subject to be randomized. The study coordinator can run the Ready to Randomize Report at any time during baseline to check the participant's status with respect to meeting eligibility requirements.

When the site investigator signs off that a participant should be randomized and the participant's Ready to Randomize Report shows eligibility criteria have been met, the Study Coordinator will use his or her current database password to access an on-line interactive randomization program. The program will verify eligibility and Baseline criteria to confirm that the participant is eligible and ready to be randomized and a randomized treatment assignment will be recorded for that participant, based upon his or her stratum. The study is blinded, so treatment assignment will not be displayed. The computer will display the participant's initial bottle numbers for the appropriate number of bottles given his or her LBW and treatment assignment. Confirmation of randomization will be displayed on the screen and emailed to the participating Clinical Center. The treatment assignment will be used to assign the participant with his or her first four weeks coded packages of study drug.

4.3 How recruitment will be monitored

The DCC will email study-wide weekly recruitment reports showing study-wide weekly and cumulative enrollment in baseline and randomization. The reports will include each site's current

baseline goal, achievement of baseline goal, randomization goal, and achievement of randomization goal. Clinical site investigators will meet regularly with their study teams to discuss progress on weekly goals, identify barriers and problems, and revise recruitment plans as necessary. The investigators from multiple sites will meet by conference call at regular scheduled intervals to review each site's recruitment progress, share problems and successes, and revise recruitment plans as necessary.

5. TREATMENT ARMS

5.1 Initiation of intervention

Participants who have met eligibility criteria, provided informed consent, and successfully completed the Baseline Phase will be randomized.

Participants will be randomized to one of four groups:
1. Lower-dose (0.5 mEq/kg-LBW/day) oral sodium bicarbonate
2. Higher-dose (0.8 mEq/kg-LBW/day) oral sodium bicarbonate
3. Lower-dose oral placebo
4. Higher-dose oral placebo

5.1.1 Lower-dose sodium bicarbonate

52 participants will be randomized to the lower-dose sodium bicarbonate group. They will take 0.5 mEq/kg-LBW daily during the On-Treatment Phase of the Pilot Clinical Trial. The number of capsules will be rounded to the nearest whole capsule.

5.1.2 Higher-dose sodium bicarbonate

88 participants will be randomized to the higher-dose sodium bicarbonate group. They will take 0.5 mEq/kg-LBW daily for the first four weeks post randomization, W0 to W4. The clinical center will evaluate the following at W4:

- Systolic blood pressure ≥170 mm Hg
- Diastolic blood pressure ≥110 mm Hg
- Increase in weight by ≥5 kg from baseline
- Severe edema defined as $\geq$10% increase in total ankle circumference from baseline
- Severe GI symptoms as reported on the GI symptoms questionnaire

If none of these has occured, the clinical center team will increase the dose to 0.8 mEq/kg-LBW daily at W4. The number of capsules will be rounded to the nearest whole capsule.
This dose will be continued for the remainder of the On-Treatment Phase. If adverse events are observed at the W4 visit, including results from lab work measured at the W4 visit, this adverse event will be managed as described in section 8 below.

5.1.3 Lower-dose placebo

26 participants will be randomized to the lower-dose placebo group. They will take the same number of capsules as if they were assigned to receive 0.5 mEq/kg-LBW/day of sodium bicarbonate during the On-Treatment Phase. The number of capsules will be rounded to the nearest whole capsule.

5.1.4 Higher-dose placebo

26 participants will be randomized to the higher-dose placebo group. During the first four weeks, these participants will take the same number of capsules as if they were to take 0.5mEq/kg-LBW/day of sodium bicarbonate. If there are no significant side effects, as discussed in Section 5.1.2, they will increase the number of capsules to the amount that they would have taken had they been assigned to receive 0.8 mEq/kg-LBW/day of sodium bicarbonate. The number of capsules will be rounded to the nearest whole capsule.

5.1.5 Dosing schedule

Participants will take half the total daily dose in the morning and the other half in the evening. If the number of capsules is an odd number, the greater number of capsules will be taken in the morning.

5.1.6 Calculation of lean body weight

Gender-specific formulas to calculate LBW are presented below [21, 22]. Body mass index (BMI) is calculated as the weight (in kg) divided by the height (in meters^2).

$$LBW\,(kg)_{Male} = \frac{9270 \times Wt}{6680 + (216 \times BMI)}$$

$$LBW\,(kg)_{Female} = \frac{9270 \times Wt}{8780 + (244 \times BMI)}$$

5.1.7 Rationale for LBW entry criteria

Only participants with LBW 37.5-96 kg will be enrolled in the Pilot Clinical Trial. The rationale to exclude people with LBW >96 kg is to limit the maximum number of pills to 6 per day for those in higher-dose assignments. The reason to exclude people with LBW <37.5 kg is because there will be no separation in the number of pills between the higher-dose and the lower-dose groups for some weights <37.5 kg. For example, a participant with LBW of 36 kg would take 2 pills per day (after rounding) whether assigned to the 0.5 or 0.8 mEq/kg-LBW/day dose levels. It is unlikely that these LBW restrictions will limit recruitment appreciably, as 94% of participants in the Chronic Renal Insufficiency Cohort (CRIC) Study have LBW within these ranges.

5.1.8 Rationale for the selected doses of sodium bicarbonate tested in this Pilot Clinical Trial

The rationale to use the 0.5 mEq/kg-LBW/day dose of sodium bicarbonate is because of a previous positive experience in terms of efficacy and safety with this dose [13]. The rationale to use 0.8 mEq/kg-LBW/day as the higher dose of sodium bicarbonate is two-fold. First is for safety, as this limits the extra sodium load to ≤1.65 grams. Second, is to reduce pill burden, as this dose in this formulation limits the number of pills to six per day. We are concerned that compliance will be poor if participants are required to take ≥7 pills per day.

Table 2 presents the number of pills per day, daily bicarbonate dose delivered (mEq), actual dose received for the level of LBW (mEq/kg-LBW) per day, and the additional daily sodium load according to LBW.

Table 2. Number of pills, daily dose of bicarbonate, actual dose delivered per kg-LBW per day, and milligrams of sodium for representative LBW. Shaded region shows the LBW ranges expected to be most frequently encountered in the Pilot Clinical Trial.

	# capsules/day		$HCO3^-$ delivered (mEq/day)		Actual Dose (mEq/kg-LBW/day)		Na^+ delivered (mg/day)	
DOSE	**0.5**	**0.8**	**0.5**	**0.8**	**0.5**	**0.8**	**0.5**	**0.8**
LBW (kg)								
37.5	2	3	24	36	0.64	0.96	550	825
38	2	3	24	36	0.63	0.95	550	825
40	2	3	24	36	0.60	0.90	550	825
42	2	3	24	36	0.57	0.86	550	825
44	2	3	24	36	0.55	0.82	550	825
46	2	3	24	36	0.52	0.78	550	825
48	2	3	24	36	0.50	0.75	550	825
50	2	3	24	36	0.48	0.72	550	825
52	2	4	24	48	0.46	0.92	550	1100
54	2	4	24	48	0.44	0.89	550	1100
56	2	4	24	48	0.43	0.86	550	1100
58	2	4	24	48	0.41	0.83	550	1100
60	3	4	36	48	0.60	0.80	825	1100
62	3	4	36	48	0.58	0.77	825	1100
64	3	4	36	48	0.56	0.75	825	1100
66	3	4	36	48	0.55	0.73	825	1100
68	3	5	36	60	0.53	0.88	825	1375
70	3	5	36	60	0.51	0.86	825	1375
72	3	5	36	60	0.50	0.83	825	1375
74	3	5	36	60	0.49	0.81	825	1375
76	3	5	36	60	0.47	0.79	825	1375
78	3	5	36	60	0.46	0.77	825	1375
80	3	5	36	60	0.45	0.75	825	1375
82	3	6	36	72	0.44	0.88	825	1650
84	4	6	48	72	0.57	0.86	1100	1650
86	4	6	48	72	0.56	0.84	1100	1650
88	4	6	48	72	0.55	0.82	1100	1650
90	4	6	48	72	0.53	0.80	1100	1650
92	4	6	48	72	0.52	0.78	1100	1650
94	4	6	48	72	0.51	0.77	1100	1650
96	4	6	48	72	0.50	0.75	1100	1650

5.2 Source of sodium bicarbonate and placebo

Eminent Services Corporation will prepare the sodium bicarbonate and placebo capsules according to good manufacturing practice (GMP) standards. Each capsule of active treatment will contain one gram of sodium bicarbonate. Matching placebo capsule will contain cornstarch. Fisher Clinical Services will bottle the capsules, label the bottles with code numbers to maintain the study's double blind, and ship the bottles to the participating clinical centers approximately quarterly.

5.3 Initial distribution and resupply to participants

Each participant's initial supply (provided just after randomization) and subsequent resupplies will be initiated by the site study coordinator. The study coordinator will determine which bottles to give to a participant by running the online Bottle Number Assignment report. It is anticipated that the coordinator will hand the appropriate bottles directly to the participant or accompany the participant to the local clinical center pharmacy, where the local pharmacist will hand the bottles to the participant.

5.4 Maintaining blinding

Clinical Center personnel will know whether a participant has been randomized to the higher or lower dose but will be blinded as to whether a participant has been randomized to active sodium bicarbonate or placebo.

The encapsulator will prepare the sodium bicarbonate and the cornstarch placebo capsules in such a way that the placebo resembles the active drug (sodium bicarbonate) in appearance, taste, and smell. It is recognized that participants receiving active sodium bicarbonate may experience bloating because bicarbonate produces carbon dioxide when exposed to hydrochloric acid in the stomach.

It is also recognized that knowledge of urinary NH_4^+ results could unblind clinical center staff members, since NH_4^+ is expected to decrease with sodium bicarbonate and remain unchanged with placebo. Thus, the Central Laboratory at Litholink will measure urinary NH_4^+ and transmit results to the DCC but these results will not be forwarded to the local clinical centers.

While it is possible, we do not expect that serum bicarbonate levels will increase with active treatment based on results from previous studies [13, 20]. Serum bicarbonate levels may decrease in participants receiving placebo as a result of natural CKD progression. Since serum bicarbonate is measured locally, investigators cannot easily be kept blinded to serum bicarbonate results. Blinding data will be captured on the visit form at the end of treatment (Week 28) to allow for evaluation of the double blind.

5.5 Unblinding

Emergency unblinding is not expected to be necessary as knowledge of the treatment group would not affect clinical care. The *potential* side effects of sodium bicarbonate, such as edema, hypertension, and hypokalemia are common in CKD and those taking diuretics and can be managed without unblinding the treatment assignment of the participant. In the rare circumstance that the investigator feels that unblinding would be helpful or influence participant management, the investigator will formally request unblinding. Unblinding will be reviewed and confirmed by the Event Review Committee.

6. FOLLOW-UP

6.1 Follow-up visit schedule

The follow-up visit schedule is presented in Table 1. In-person follow-up visits will occur at 4 weeks (W4), 8 weeks (W8), 12 weeks (W12), 20 weeks (W20), 28 weeks (W28) and 32 weeks (W32) after randomization (W0). Additional PRN follow-up visits will be held at the discretion of the site investigator. A W16 and W24 follow-up telephone call (phone visit) will be made between the W12 and W20 and the W20 and W28 visits to reinforce compliance and assess for potential adverse events, including a review of recent home blood pressure measurements (if available), that would require a special follow-up visit. Additional telephone calls will occur at the discretion of the site investigator and/or study personnel.

6.2 Data elements collected during in-person visits

Table 3. Data collected during follow-up.

Data Elements	Visits Assessed
• Review non-study medications • Targeted physical exam • Serum chemistry panel: Na^+, K^+, Cl^-, HCO_3^-, BUN, Cr, Ca^{2+} • Adverse event assessment • Gastrointestinal symptoms questionnaire	All follow-up visits
• Pill count	All visits except W32
• Serum phosphorus and albumin • Random urinary albumin/creatinine • Venous blood gas (substudy)	B0, W12, W28
• 24-hour urine collection • Collection of blood for biorepository	B1, W12, W28

6.3 Monitoring compliance with treatment

Compliance will be reinforced monthly, either at the face-to-face visit or via telephone in between study visits. Compliance at visits will be determined using pill counts. We are aware of other methods of assessing pharmacoadherence and recognize the potential shortcoming of the pill-count technique, but decided that this is an optimal approach, taking into account several factors including costs. The pharmacodynamics that we are proposing to assess in Specific Aim 2 reflects pharmacoadherence, but is also affected by other factors, such as gastrointestinal absorption of bicarbonate.

Only those who demonstrate appropriate compliance during Baseline will be randomized. After randomization, those who show poor compliance by pill counts (<80%) or by phone discussion will be queried about barriers to compliance. Participants will be counseled about the importance of taking the assigned treatment and asked to think of ways they can improve compliance. If the reason for non-compliance is abdominal discomfort, a proton-pump inhibitor may be recommended or prescribed to inhibit gastric acid production and consequent carbon dioxide gas-forming effects of bicarbonate. Other strategies to improve compliance, such as filling pillboxes, will be discussed with the participant; study coordinators will assist participants

in obtaining and filling pillboxes if this seems advisable. Additional follow-up phone calls will be performed as needed to reinforce compliance.

6.4 Participants who start dialysis, undergo kidney transplantation, or become pregnant

Participants who start chronic dialysis during the study will be censored, given the complex nature of acid-base physiology in these patients. Participants who receive a pre-emptive kidney transplant during the study will also be censored because many other confounding factors, such as transplant rejection, delayed graft function, and calcineurin inhibitor nephrotoxicity, will have major impact on kidney function and acid-base status. Participants who become pregnant will also be censored.

7 MEASUREMENT TECHNIQUES

7.1 Serum chemistry panel

Local clinical laboratories at each clinical site will measure serum chemistry panel (Na^+, K^+, Cl^-, HCO_3^-, BUN, creatinine, glucose, Ca^{2+}, albumin, phosphorus). The local laboratory, instead of the Core Laboratory, will perform these measurements primarily because falsely low serum bicarbonate results commonly occur when the assay of serum samples is delayed [23]. Also, serum bicarbonate and potassium results must readily be available to the local investigators as these are important safety measurements.

Serum creatinine will be used to estimate GFR. eGFR will be calculated using the CKD-Epidemiology (CKD-EPI) equation [24].

7.2 24-hour urine collection & measurements

Participants will be provided with instructions and supplies to perform the 24-hour urine collection (see Manual of Operating Procedures for details). 24-hour urine measurements will be performed by a Central Laboratory (Litholink) and include the following:

Measurement	Rationale
NH_4^+	Pharmacodynamics marker
Na^+, K^+, Cl^-	Compare urinary anion gap with NH_4^+ measurement
Phosphate	Used with urine pH to estimate titratable acid excretion
Creatinine	To calculate creatinine clearance
Urea	Used with urine K^+ to calculate net endogenous acid production (NEAP), and estimate protein intake [26]
pH	Used with urine phosphate to estimate titratable acid excretion. Also to explore effect of the intervention on urine pH.

7.3 Local laboratory tests using random urine samples

Urine albumin and creatinine will be performed locally at each clinical center's laboratory using standard assays in that laboratory.

7.4 Physical examination measurements

Height will be measured at baseline. Weight will be measured at each visit using standard clinic equipment. After 5 minutes of quiet rest, blood pressure will be measured three times, one minute apart. The average of the second and third measurements will be used for data analysis and clinical decision-making. Pulse will be recorded from the third blood pressure measurement (or measured once after completing the blood pressure measurements). Edema will be assessed by measuring ankle circumference 7 cm proximal to the medial malleolus bilaterally [27], and severe edema will be defined as a $\geq$10% increase in total ankle circumference from baseline.

7.5 Pill Counts

Study personnel or local research pharmacy personnel will perform pill counts.

7.6 Gastrointestinal symptoms questionnaire

Participants will be asked to complete a gastrointestional symptoms questionnaire at each follow-up visit to assess the tolerability of the intervention. Briefly, participants will be asked to rate symptoms of nausea, bloating, and diarrhea on a scale of 1-5.

7.7 Collection of biological samples (serum, plasma, urine) for the NIDDK biosample repository

Serum, plasma, and random urine samples will be collected at B1, W12, and W28. These will be sent in batches to the NIDDK Repository. The details of the collection procedure are in the Manual of Operations.

7.8 Pregnancy test

Serum or urine pregnancy tests, if required, will be perform at the local clinical site using the laboratory's standard technique.

7.9 Venous blood gas substudy

Venous blood gas measurements will be obtained in a subset of study participants at B0, W12, and W28 to evaluate the effect of the two dose levels on acid-base status indicators. The details of the collection and measurement processes are in the MOP. Briefly, venous blood will be collected 2 minutes after release of the tourniquet. Blood gas measurements will be obtained using the Abbott iSTAT handheld device with CG8+ cartridge, which measures pH, pO_2, pCO_2, total CO_2, HCO_3^- (calculated), base excess, oxygen saturation, ionized calcium, sodium, potassium, glucose, hematocrit, and hemoglobin.

8 ADVERSE EVENTS (AEs)

8.1 Expected study-related AEs

Sodium bicarbonate may cause bloating, belching and abdominal discomfort when it neutralizes gastric acid, resulting in the formation of carbon dioxide. Sodium bicarbonate may also cause

edema to develop or worsen, increase fluid weight, and increase blood pressure, although previous studies using sodium bicarbonate have not reported significant changes in edema, weight, or blood pressure (as discussed in Section 1.2.2 above). Other studies suggest that the fluid retention that occurs with excess sodium is greater when it is accompanied by the chloride anion (i.e., table salt) rather than the bicarbonate anion [28-30]. If retained rather than excreted in the urine, sodium bicarbonate may cause metabolic alkalosis and hypokalemia. These are anticipated AE that participants will be informed about and will be monitored during the course of this Pilot Clinical Trial.

The following are considered "expected AE," although they may not occur.

- Serum bicarbonate >32 mEq/L
- Systolic blood pressure ≥170 mm Hg
- Diastolic blood pressure ≥110 mm Hg
- Serum potassium <3.0 mEq/L
- Increase in weight by ≥5 kg from baseline
- Severe edema
- Severe GI symptoms as documented on the GI symptoms questionnaire
- Serum bicarbonate ≤16 mEq/L (serum bicarbonate may fall as a result of natural CKD progression, particularly in the placebo group)

8.2 How AEs will be reported

AE that are based on laboratory measurements will be detected when results are sent to the DCC. AE based on physical examination or symptoms will be transmitted to the DCC by filling out a web-based study form.

8.3 Serious Adverse Event (SAEs), hospitalization, and death reporting

The following SAEs will be reported in detail to the DCC, Data Safety Monitoring Board (DSMB) and the Event Review Committee.

1. Death
2. Life-threatening event
3. Hospitalization
4. Persistent or significant disability/incapacity
5. Emergency room visit for:
   a) Edema, heart failure, or pulmonary edema
   b) Hypertension
   c) Low serum potassium level
   d) High serum potassium level
   e) High serum bicarbonate level
   f) Low serum bicarbonate level.

8.4 Strategy for the management of adverse events, including reducing or terminating the assigned intervention

8.4.1 Reducing and/or stopping the randomized intervention for safety reasons

In general, the anticipated side effects of sodium bicarbonate can be medically managed by adjusting antihypertensive and/or diuretic agents, providing potassium replacement, and by dietary changes. At every visit during the trial, blood pressure will be recorded and reviewed by the site investigator and adjustments to the antihypertensive and/or diuretic regimen will be

made to target blood pressure <140/90 mm Hg, although participants will be randomized if blood pressure is < 150/100 mm Hg. Similarly, serum potassium will be measured and reviewed with adjustments to target potassium to 3.5-5.5 mEq/L. Excess fluid will be treated with diuretics at the discretion of the investigator. These adjustments are designed to keep participants on the assigned intervention and randomized dose level, prevent the development of serious side effects, and minimize dose reduction and discontinuation of treatment as much as possible.

If medical management is ineffective, doses of the assigned intervention will be reduced by 1/2 followed by discontinuation of therapy if the side effect persists. The strategy for dose reduction and discontinuation of the assigned intervention, if necessary, for anticipated problems are:

1. **Serum bicarbonate >32 mEq/L**
   - When the first serum bicarbonate >32 mEq/L is measured, the intervention dose will be reduced by 50% and diuretics will be adjusted as appropriate. The participant will return for a visit at least one week later (preferably within two weeks).
   - If serum bicarbonate is >32 mEq/L at the next visit despite these changes, the intervention will be stopped. Participants will continue to have serum bicarbonate measured (preferably every week) until it is ≤30 mEq/L.
   - Plasma ionized calcium will be checked if serum bicarbonate is >32 mEq/L at any visit. Management of low ionized calcium will be at the discretion of the site investigator.

2. **SBP ≥170 or DBP ≥110 mm Hg**
   - Potential reasons for elevated blood pressure will be explored with the participant, such as poor compliance or running out of anti-hypertensive medications. Recent home blood pressure readings, if available, will also be considered in the management plan. If potential explanations are identified, then appropriate action will be taken. The participant will follow-up one week later (preferably within two weeks).
   - If no identifiable cause of the elevated blood pressure is identified, the anti-hypertensive and/or diuretic therapy will be escalated. The participant will return for a visit at least one week later (preferably within two weeks).
   - If blood pressure at these levels is observed at the second visit, the anti-hypertensive and/or diuretic therapy will be escalated and the intervention dose will be reduced by 50%. The participant will return for a visit at least one week later (preferably within two weeks).
   - If blood pressure at these levels is observed at the third visit, the intervention will be stopped and the anti-hypertensive and/or diuretic therapy will be escalated. Participants will continue to have PRN visits (preferably every week) until blood pressure is <160/90 mm Hg.

3. **Serum potassium <3.0 mEq/L**
   - When the first serum potassium <3.0 mEq/L is observed, the intervention dose will be reduced by 50%, diuretics will be adjusted as appropriate, and potassium replacement will be prescribed. The participant will return for a visit at least one week later (preferably within two weeks).
   - If serum potassium <3.0 mEq/L is observed at the next visit, the intervention will be discontinued, diuretics adjusted as appropriate, and potassium replacement will be prescribed. Participants will continue to have potassium checked (preferably every week) until >3.5 mEq/L.

4. **Clinically severe fluid retention and weight gain**
   - If in the opinion of the investigator clinically severe fluid retention is observed and another cause of excess fluid retention cannot be readily identified, then the dose of the intervention will be reduced by 1/2 and diuretics will be adjusted. If fluid retention remains severe, the assigned intervention will be discontinued.

The BASE Trial Event Review Committee (ERC) will review the data for any participant who is told to stop blinded medications for safety reasons. The ERC will confirm whether or not the participant met the protocol definition to stop blinded medications for safety reasons.

8.4.2 Reducing and/or stopping the randomized intervention for other reasons

1. Abdominal discomfort
   - If abdominal upset such as bloating or excess burping is felt to be due to the intervention and affecting or potentially affecting compliance, a proton pump inhibitor may be prescribed to reduce gastric acid production. If these symptoms persist, the dose of the intervention will be reduced by 1/2, followed by discontinuation of therapy if symptoms persist.

2. The assigned intervention will be discontinued for these reasons as well, however these events will be considered censoring events.
   - Initiation of chronic dialysis
   - Kidney transplant
   - Pregnancy

8.5 Restarting the intervention and/or increasing reduced doses back to the full randomized dose

The decision to increase the dose back to the randomized dose or to restart therapy will be at the discretion of the site investigator and will consider whether the reason(s) for reducing or stopping treatment have resolved as well as the participant's willingness to restart or escalate the assigned treatment.

8.6 Rescue therapy with oral sodium bicarbonate

1. Serum bicarbonate ≤ 16 mEq/L
   - Although unlikely during this short Pilot Clinical Trial, serum bicarbonate may fall due to natural progression of CKD, particularly in the placebo group. Rescue therapy with open-label sodium bicarbonate will be initiated if serum bicarbonate is ≤16 mEq/L on two consecutive measurements at least one week apart. In this circumstance, open-label sodium bicarbonate will be given to target serum bicarbonate of 20-22 meq/L. Participants will not discontinue study medications if open-label sodium bicarbonate is prescribed.

2. Serum bicarbonate 17-19 mEq/L with refractory hyperkalemia
   - Rescue therapy will also be instituted if serum bicarbonate is 17-19 mEq/L and serum potassium is ≥5.5 mEq/L and the hyperkalemia is unresponsive to other interventions (such as reducing ACE-I/ARB dose and dietary potassium restriction) or is present because of concomitant hyperglycemia. In these circumstances, open-label sodium bicarbonate will be given to target serum bicarbonate of 20-22 meq/L. Participants will not discontinue study medications if open-label sodium bicarbonate is prescribed.

8.7 DSMB

NIDDK has established an independent DSMB for this clinical trial. The DSMB includes experienced nephrologists, biostatisticians, and other experts. The DSMB is advisory to the NIDDK. Initially, the DSMB will serve as a protocol review committee and review the design of the trial prior to implementation. Upon initiation of the clinical trial, the DSMB will meet at least once annually, or more often as necessary, to review the progress of the trial including recruitment, data quality, participant safety, and final analyses of outcomes. A summary of the open discussions of the DSMB is sent to the Principal Investigators by the NIDDK Project Scientist. The recommendation of the DSMB to continue the trial (or not) will be made available to each clinical center so this can be submitted to each IRB for annual renewal.

9 ANALYSIS PLAN and POWER CALCULATIONS

9.1 Baseline characteristics

Participant characteristics will be summarized using standard descriptive statistics for all enrolled participants and, separately, by randomized group, for randomized participants. These summaries will be provided for the full cohort, and for subgroups defined by age, gender, and baseline eGFR. If substantial deviations of the distribution of urinary NH_4^+ or other continuous variables used as outcome variables are identified, consideration will be given to transforming these variables to better approximate normality prior to subsequent analyses.

9.2 Analysis plan for Specific Aim 1

9.2.1 Analysis of Co-Primary Endpoints

The primary analysis of *safety and tolerability* will tabulate the proportions of the participants assigned to each of the three dose interventions (placebo, 0.5 mEq/kg-LBW/day, and 0.8 mEq/kg-LBW/day) who:

1. Are prescribed the full randomized sodium bicarbonate dose according to the protocol at the end of the On-Treatment Phase of the Pilot Clinical Trial, and

2. Are prescribed at least 25% of the randomized dose according to the protocol at the end of the On-Treatment Phase of the Pilot Clinical Trial.

The dose prescribed for each participant at the last On-Treatment visit (week 28) will be used to determine whether the participant completes the study on the full randomized prescription or at least 25% of the randomized prescription. This will take into consideration any protocol mandated reductions that should have occurred at the last On-Treatment visit had the Pilot Clinical Trial continued. We will not consider whether the prescription could have been restarted or if the dose could have been increased at the last On-Treatment visit, because it would be uncertain whether restarting or increasing the dose would have been safe or tolerated.

Because participants who fail to complete the intervention period will be designated as failures for both of the co-primary endpoints, these endpoints will be defined for all randomized participants. The primary analysis (safety and tolerability) will be regarded as supporting a dose intervention for evaluation in a Phase 3 trial if:

1. At least 66.7% of participants in each intervention arm are prescribed the full randomized sodium bicarbonate dose according to the protocol at the last On-Treatment visit (W28), and

2. At least 80% of participants in each intervention arm are prescribed at least 25% of the randomized dose according to the protocol at the last On-Treatment visit (W28)

In further analyses, exact 90% binomial confidence intervals will be constructed for the proportions of subjects reaching each of the co-primary endpoints in each of the three dose groups, and for differences between the proportions reaching each of the co-primary endpoints in the active dose groups vs. the placebo group.

9.2.2 Secondary Analyses of Feasibility of the Dose Interventions

Main Secondary Analyses. Exact 90% binomial confidence intervals will also be constructed for the proportions of individuals in each treatment group who:

a. Reduce and/or discontinue treatment for safety reasons
b. Reduce and/or discontinue treatment because of medication intolerance or pill burden
c. Have ≥ 80% pill count compliance.

These three endpoints will respectively address the safety, medication intolerance/pill burden, and compliance for each dose group during the 28-week intervention period. In contrast to the co-primary endpoints, each of these endpoints will be treated as missing if they cannot be ascertained due to loss-to-follow-up or missing data. Exact 90% binomial confidence intervals will also be constructed for the differences between the proportions of subjects reaching these endpoints in the active dose groups and the proportion who reach these endpoints in the placebo group.

Additional Analyses of Pill Counts. Pill counts will be expressed as a percent of the number of pills prescribed for a particular participant under the protocol and summarized by treatment group at each follow-up visit using box plots and histograms. 90% confidence bounds will be constructed for the average pill count as a percent of prescribed pills as well as for the proportion of participants whose counts meet a target of ≥80% compliance for each treatment group and each follow-up visit during the 28-week intervention period.

*Additional analyses of binary safety endpoints***.** Frequencies and proportions of subjects developing each AE (as described in Section 8.1) and SAE (as described in Section 8.4) during the 28 week intervention period will be tabulated for each of the three treatment groups. For each AE or SAE category, these tabulations will be provided for the frequencies and proportions of subjects who are required to a) reduce the dose of the study drug, b) who are required to either temporarily or permanently discontinue the study drug, and c) who are required to permanently discontinue the study drug. Because the proportions of subjects developing side effects in this Pilot Clinical Trial are expected to be relatively low, the tabulations of side effect frequencies will be primarily descriptive. However, exact 90% confidence limits will be constructed for each proportion tabulated, and additional exact 90% confidence limits will be constructed for the differences in the proportions in the two active treatment groups and the placebo group.

Additional safety analyses will be performed to compare the proportion of participants who:

- Increase the number of antihypertensive medications, including diuretics, by ≥ 2
- Have an increase in leg circumference by ≥ 5 cm in either leg
- Start a proton-pump inhibitor or H_2 blocker.

Assessment of continuous safety-related endpoints. Box plots will be constructed to display the distributions of systolic and diastolic blood pressure, serum potassium, serum bicarbonate, and

participant weight by treatment group at baseline and each follow-up visit during the 28 week intervention period. Mixed-effect analyses will also be used to compare the mean systolic and diastolic blood pressure, serum potassium, serum bicarbonate, and participant weight between the 0.8, 0.5 mEq/kg-LBW/day and placebo groups at each of the follow-up visits while assuming equal mean levels for each randomized group at baseline to increase the statistical power of the treatment comparisons. The covariance structure of the mixed models will be determined based on likelihood ratio tests comparing the fit of nested covariance models and by comparisons of the Bayes Information Criterion for non-nested models.

9.2.3 Statistical Power for Aim 1 Analyses

Primary Analysis of Achievement of Benchmarks. Chance variation may lead to two types of errors in our application of the 66.7% and 80% benchmarks for the percent of participants in each group who complete the intervention period prescribed either the full dose or at least 25% of the full dose. First, chance variation may lead to a higher percent of subjects successfully completing an intervention in the study sample than the true percent in the study population, in which case we may falsely conclude that an intervention is suitable for evaluation in a Phase 3 trial when it is not, representing a Type 1 error. Second, chance variation may lead to a lower percent of subjects attaining the benchmarks in the study sample than in the study population, in which case we may falsely conclude that an intervention is not suitable for evaluation in a Phase 3 trial when in fact it is suitable.

Using exact binomial calculations, the Type 1 error for falsely concluding suitability based on the 66.7% benchmark will be ≤0.035 for the higher dose group (with N = 88) and ≤0.085 for the lower dose group (with N = 52) if the true percent prescribed the full randomized dose is ≤57%. The statistical power for attaining the 66.7% benchmark will be at least 0.87 in the higher dose group and 0.82 in the lower dose group if the true percent prescribed the randomized dose is at least 72%. For the 80% benchmark, the Type 1 error will be ≤0.018 for the higher dose group and ≤0.057 for the lower dose group if the true percent prescribed at least 25% of the randomized dose is ≤70%. The statistical power for attaining the 80% benchmark will be at least 0.84 in the higher dose group and 0.80 in the lower dose group if the true percent prescribed at least 25% of the randomized dose is ≥84%.

Precision of 90% Confidence Limits. The expected margin of error (expressed as ½ the width of a 90% exact confidence interval) for estimates of a proportion of participants meeting a binary endpoint in the high dose group will be 0.075 if the true proportion is 0.20 and 0.093 if the true proportion is 0.50 when the proportion can be evaluated in all 88 subjects. If the endpoint is missing in 15% of subjects, the corresponding margins of error are 0.083 if the true proportion is 0.20 and 0.101 if the true proportion is 0.50.

The margin of error for estimates of a proportion of participants meeting a binary endpoint in the placebo or lower dose groups will be 0.100 if the true proportion is 0.20 and 0.122 if the true proportion if 0.50 when the proportion can be evaluated in all 52 subjects. If the endpoint is missing in 15% of subjects, the corresponding margins of error are 0.109 if the true proportion is 0.20 and 0.132 if the true proportion is 0.50.

9.3 Analysis plan for Specific Aim 2

Specific Aim 2: To determine the effect of the 0.5 and 0.8 mEq/kg-LBW/day sodium bicarbonate doses on renal NH_4^+ excretion, compared to placebo, as a pharmacodynamics assessment.

Renal NH_3 production is central to the pathogenic mechanism of acid-induced kidney injury, and urinary NH_4^+ is a reflection of renal NH_3 production [17]. To this end, urinary NH_4^+ will be used as the main pharmacodynamics outcome parameter of oral bicarbonate therapy in this Pilot Clinical Trial.

The effect of the treatment intervention on urinary NH_4^+ excretion will be investigated from two perspectives. The first perspective will characterize the distributions of NH_4^+ standardized by body weight in the respective treatment groups, as weight-standardized NH_4^+ is expected to best reflect the biological effect of the bicarbonate intervention on long-term clinical outcomes. These analyses will focus on the W28 measurements, which are more likely to reflect the participant's long-term kidney exposure to NH_4^+ in the Phase 3 trial.

The second perspective will investigate the pharmacodynamics response of NH_4^+ excretion to the administered dose of bicarbonate. The pharmacodynamics analyses will evaluate the differences in the mean NH_4^+ measurements at the W12 and W28 follow-up assessments compared to the baseline assessment, without standardizing for weight as the pharmacodynamics dose-response is not expected to be modified by the participant's weight.

9.3.1 Distributions of weight-standardized urinary NH_4^+ excretion

Comparison of mean weight standardized NH_4^+ excretion levels by treatment group. A linear mixed effects model with an unstructured covariance matrix and separate fixed effect indicator variables for each treatment group at each follow-up time will be used to compare mean weight-standardized NH_4^+ excretion levels between the randomized treatment groups at weeks 12 and 28, with primary emphasis being given to the week 28 comparisons as noted above. The mixed model will assume a common mean NH_4^+ excretion level for each treatment group at baseline to increase the statistical power of between group comparisons.

Overlap of the distributions of urinary NH_4^+ excretion between the treatment groups at week 28. The full distributions of weight-standardized NH_4^+ will be summarized using box plots and histograms for each of the three randomized groups at week 28. The amount of overlap in the weight-standardized NH_4^+ will be described by computing Mahalanobis distances between the mean values for each pair of treatments (e.g., 0.5 mEq/kg-LBW/day vs. placebo, 0.8 mEq/kg-LBW/day vs. placebo, and 0.8 vs. 0.5 mEq/kg-LBW/day), and by reporting the proportion of pairs of participants in the respective treatment groups for whom the weight-standardized NH_4^+ measurements are lower for the participants in the higher of the two dose groups being compared. The same approach will be used to summarize the changes in weight-standardized NH_4^+ excretion from baseline to W28.

9.3.2 Pharmacodynamics analyses of NH_4^+ excretion

The main pharmacodynamics analyses will relate the changes in urinary NH_4^+ (without weight standardization) from the baseline NH_4^+ measurement to the W12 and W28 NH_4^+ measurements to the actual prescribed bicarbonate dose based on the number of pills assigned to the participant.

Two sets of analyses will be performed. The first set will relate the mean changes in unstandardized NH_4^+ from baseline to weeks 12 and 28 to the average dose (defined by multiplying 12 mEq/pill by the average number of pills administered) in each of the three dose groups (placebo, 0.5, and 0.8 mEq/kg-LBW per day) preceding each of the two follow-up assessments. As in the weight standardized analyses in Section 9.3.1, the adjusted mean changes in NH_4^+ will be obtained for each of the 3 dose groups at each assessment by using a

linear mixed model with unstructured covariance matrix and indicator variables for the three dose groups at each of the two follow-up measurements, with a common mean NH_4^+ level assumed for each randomized group at baseline. The adjusted mean changes in NH_4^+ will be plotted against the average bicarbonate dose (defined as 12 mEq/pill x the number of pills prescribed) to summarize the dose-response relationships at both the week 12 and week 28 visits.

The second set of analyses will relate the mean change in NH_4^+ to the actual prescribed dose of bicarbonate given by multiplying 12 mEq/pill by the actual number of bicarbonate pills prescribed to the participant. Thus in this analysis there will be a total of 7 dose groups, corresponding to 0, 1, 2, 3, 4, 5, and 6 bicarbonate pills, where the number of pills is prescribed based on the participant's randomized dose group and the participant's LBW. We will use a linear mixed model with indicator variables for number of pills at each of the week 12 and week 28 visits to relate the change in NH_4^+ to the number of bicarbonate pills prescribed (as a categorical variable). In contrast to the mixed models used for direct comparisons of randomized groups, in this case different mean NH_4^+ levels will be assumed in the different dose groups at baseline since the dose groups are defined in part by the participant's weight rather than randomized assignment. We will test if the dose-response relationship of the mean change in NH_4^+ vs. dose deviates from linearity at each of the week 12 and week 28 visits by modifying the mixed effects model to compare the slope of the relationships between 2.1 and 6 pills to the slope between 0 and 2.1 pills using a 2-slope linear spline in the estimated mean NH_4^+ values with a knot at 25.2 mEq, corresponding to 2.1 pills. Subsequently, a smooth nonparametric estimate of the dose-response curve will be estimated by fitting a cubic spline to relate the adjusted mean change in NH_4^+ to the number of pills administered. In subsequent analyses, the mixed models will be modified to relate the change in NH_4^+ to the average of the two follow-up assessments to the average of the two dose levels preceding the two assessments.

In further secondary analyses, both approaches for evaluating the dose response relationship will be repeated after adjusting the dose levels downwards to account for any pills not consumed as indicated by pill counts.

9.3.3 Power calculations for comparisons of change in NH_4^+ between dose groups

Oster et al. report a pooled standard deviation of the percent change in NH_4^+ excretion over a 5 day period of 21.8% in 20 subjects [31]. Because Oster et al. used averages of two 24-hour urine assessments at both the baseline and follow-up time points, and because the time interval of 5 days in that study is shorter than the 12 week or 28 week intervals planned for the BASE study, we consider possible standard deviations for percent change of 24% or 30%. Allowing for 10% missing follow-up measurements, the Pilot Clinical Trial will provide 80% power with 2-sided α=0.05 to detect a mean difference of 12.5% for the high dose vs. placebo and high dose vs. low dose comparisons, and of 14.0% for the low dose vs. placebo comparison if the standard deviation for the percent change is 24%. If a mean baseline NH_4^+ excretion of 30 mEq/24 hr is assumed [32], these differences represent 3.75 and 4.20 mEq/24 hr, respectively. If the standard deviation of the per cent change is 30%, the minimum detectable effects are increased to 15.6% and 17.2%, respectively, corresponding to differences of 4.68 and 5.16 mEq/24 hr, respectively.

9.4 Analysis of the relationship between bicarbonate dose and serum bicarbonate level

In a prior study, the 0.5 mEq/kg-LBW/day dose of sodium bicarbonate did not raise serum bicarbonate concentration [13]. While we expect that this will also be the case with this dose in the Pilot Clinical Trial, it is possible that serum bicarbonate may increase above baseline values

in the 0.8 mEq/kg-LBW/day sodium bicarbonate dose group. It would, therefore, be important to monitor the serum bicarbonate levels in relationship to the oral dose, i.e., assessing the pharmacokinetics of oral bicarbonate. Mixed-effect analyses will be used to compare the mean serum bicarbonate levels between the 0.8, 0.5 mEq/kg-LBW/day and placebo groups at the week 4, 8, 12, 20, 28 and 32 visits while controlling for the baseline serum bicarbonate values. Additional analyses using quantile regression will be used to compare the upper tails of the serum bicarbonate distributions between the treatment groups. Since the ability of the kidney to eliminate bicarbonate may be affected by eGFR, we will examine the pharmacokinetics of the two oral bicarbonate doses according to eGFR levels (20-44 and 45-59 ml/min/1.73m^2). The interaction between eGFR and oral bicarbonate dose on pharmacokinetics will also be examined. We do not anticipate that the degree of albuminuria would appreciably affect the renal excretion of bicarbonate, however, we may consider this interaction in additional exploratory analyses.

9.5 Exploratory Analyses of Treatment Effects on albuminuria and eGFR

Fixed acid presumably exerts its detrimental effects on the kidney tubules, instead of the glomerulus. Urinary albumin excretion is, therefore, not expected to be substantially increased in acid-induced kidney damage, as in most types of interstitial-tubular diseases. Nonetheless, glomerulo-tubular balance occurs, and the glomerulus often undergoes fibrosis over time even when the injury is initiated in the tubules. We will compare the effect of lower-dose and higher-dose sodium bicarbonate on urinary ACR and eGFR. Importantly, these analyses will be interpreted as exploratory only, and will not be incorporated in the evaluation of the appropriateness of conducting a Phase 3 trial of oral bicarbonate intervention. The rationales for designating the analysis of eGFR also as exploratory are as follows. Previous small randomized trials over 2-5 years in somewhat different CKD populations have already shown that oral bicarbonate therapy attenuates eGFR decline, as discussed above. Because of its short duration and limited sample size, this Pilot Clinical Trial will have very limited statistical power to detect significant differences in eGFR changes between the arms.

It is likely that urinary ACR will be positively skewed. If this skewed distribution is confirmed, ACR will be log-transformed. Mixed-effects models will be applied to relate the changes from baseline to W12 and W28 in log-transformed urinary ACR to indicator variables for the randomized treatments. The mixed models will assume the same baseline mean in the study population for each treatment group (placebo, lower-dose, and higher-dose), so that the analysis will have the structure of an ANCOVA to increase power. The primary treatment comparisons will contrast the low-dose and high-dose bicarbonate groups to placebo; the head-to-head comparisons between the two bicarbonate groups will be a secondary analysis. A similar mixed-effect model will be used to compare the mean change in eGFR between the treatment groups, but in this case only the mean change in eGFR from baseline to 28 weeks, after controlling for baseline eGFR, will be evaluated.

9.6 Other exploratory pharmacodynamics analyses

Other exploratory analyses will be performed to provide further information on the pharmacodynamics of bicarbonate therapy. These exploratory analyses are:

- Effect of oral bicarbonate therapy on renal acid excretion, calculated as NH_4^+ plus titratable acid (TA, calculated using urine pH and phosphate excretion)
- Correlation between NH_4^+ and urinary anion gap (UAG) and response of UAG to the dose interventions

- Effect modification of dose on NH_4^+ by baseline level of net endogenous acid production (NEAP)
- Effect of oral bicarbonate therapy on NEAP

9.7 Comparisons of the response of blood pressure, serum bicarbonate, serum potassium, and weight after discontinuing treatment

The mixed effects models described in Section 9.2.2 for evaluating mean changes in systolic and diastolic blood pressure, serum bicarbonate, serum potassium, and weight will be extended to include the final study visit after discontinuation of treatment. Linear contrasts will be constructed to estimate the mean changes in each of these outcomes between the Off-Treatment and the last On-Treatment visit, and to compare the Off-Treatment mean values to the baseline mean values within each treatment group. The indicated mean changes will also be compared between the two active treatment groups and the placebo group.

9.8 How will this study be considered successful?

The purpose of this Pilot Clinical Trial is to determine whether it is feasible to proceed with a Phase 3 trial that will test the effect of sodium bicarbonate on slowing CKD progression in people with advanced CKD and normal serum bicarbonate, and if so, what dose to deliver. The primary analysis will be interpreted as suggesting that an intervention is suitable for evaluation in a Phase 3 trial if at least 80% complete the study prescribed at least 25% of the randomized dose and no less than 2/3 of participants in their respective arm are prescribed the full randomized dose at the end of the On-Treatment phase of the study. The full assessment of the suitability of the lower and higher dose interventions will also consider the global results of this Pilot Clinical Trial, such as compliance, and other ongoing sodium bicarbonate trials.

If both dose groups are successful, then comparisons of the reduction in urinary NH_4^+ excretion from baseline between the two dose levels will help determine which dose to employ in the Phase 3 trial. If NH_4^+ excretion were significantly lower in the higher-dose group, this dose will be recommended for the Phase 3 trial. If there is no substantial difference in urinary NH_4^+ excretion between the dose levels, the lower dose will be recommended in order to reduce excess pill burden and potential adverse events.

10 PLANS FOR THE STUDY DESIGN OF THE PHASE 3 TRIAL

The Phase 3 trial will be a well-powered, double-blinded, randomized, controlled trial with two parallel arms, testing the long-term safety and efficacy of oral sodium bicarbonate on kidney function against placebo. The primary outcome will likely be the composite of a 50% decrease in eGFR and progression to ESRD. The dose determined to be the most promising in terms of safety, compliance, and pharmacodynamics in this Pilot Clinical Trial will be used in the Phase 3 trial.

11 REFERENCES

1. National Kidney Foundation, K/DOQI. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis, 2000. 35(6 Suppl 2): p. S1-140.
2. de Brito-Ashurst I, Varagunam M, Raftery MJ, and Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol, 2009. 20(9): p. 2075-84.

3. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH, and Wesson DE. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int, 2010. 77(7): p. 617-23.
4. Eustace JA, Astor B, Muntner PM, Ikizler TA, and Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int, 2004. 65(3): p. 1031-40.
5. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP, M'Rad M B, Jacquot C, Houillier P, Stengel B, and Fouqueray B. Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol, 2009. 20(1): p. 164-71.
6. http://www3.niddk.nih.gov/fund/other/ckdclintrials2011/CkdInterventionSummaryOfTalksFinal.pdf
7. Gaggl M, Cejka D, Plischke M, Heinze G, Fraunschiel M, Schmidt A, Horl WH, and Sunder-Plassmann G. Effect of oral sodium bicarbonate supplementation on progression of chronic kidney disease in patients with chronic metabolic acidosis: study protocol for a randomized controlled trial (SoBic-Study). Trials, 2013. 14(1): p. 196.
8. Witham MD. Bicarbonate for chronic kidney disease and acidosis. http://www.controlled-trials.com ISRCTN09486651.
9. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, Hostetter T, Jaar B, Lora CM, Nessel L, Ojo A, Scialla J, Steigerwalt S, Teal V, Wolf M, and Rahman M. Association of Serum Bicarbonate With Risk of Renal and Cardiovascular Outcomes in CKD: A Report From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis, 2013. 62(4): p. 670-8.
10. Kanda E, Ai M, Yoshida M, Kuriyama R, and Shiigai T. High serum bicarbonate level within the normal range prevents the progression of chronic kidney disease in elderly chronic kidney disease patients. BMC Nephrol, 2013. 14: p. 4.
11. Raphael K, Wei G, Baird B, Greene T, and Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int, 2011. 79(3): p. 356-362.
12. Kovesdy CP, Anderson JE, and Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant, 2009. 24(4): p. 1232-7.
13. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, and Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int, 2010. 78(3): p. 303-9.
14. Hostetter T. Alkali therapy in chronic kidney disease. http://www.clinicaltrials.gov NCT 01452412.
15. Raphael K. Investigations of the optimum serum bicarbonate level in renal disease. http://www.clinicaltrials.gov NCT01574157.
16. Kim HY, Baylis C, Verlander JW, Han KH, Reungjui S, Handlogten ME, and Weiner ID. Effect of reduced renal mass on renal ammonia transporter family, Rh C glycoprotein and Rh B glycoprotein, expression. Am J Physiol Renal Physiol, 2007. 293(4): p. F1238-47.
17. Nath KA, Hostetter MK, and Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. J Clin Invest, 1985. 76(2): p. 667-75.
18. Wesson DE, Nathan T, Rose T, Simoni J, and Tran RM. Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production. Kidney Int, 2007. 71(3): p. 210-7.
19. Wesson DE and Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. Kidney Int, 2010. 78(11): p. 1128-35.

20. Abramowitz MK, Melamed ML, Bauer C, Raff AC, and Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. Clin J Am Soc Nephrol, 2013. 8(5): p. 714-20.
21. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, and Green B. Quantification of lean bodyweight. Clin Pharmacokinet, 2005. 44(10): p. 1051-65.
22. Mitchell SJ, Kirkpatrick CM, Le Couteur DG, Naganathan V, Sambrook PN, Seibel MJ, Blyth FM, Waite LM, Handelsman DJ, Cumming RG, and Hilmer SN. Estimation of lean body weight in older community-dwelling men. Br J Clin Pharmacol, 2010. 69(2): p. 118-27.
23. Kirschbaum B. Spurious metabolic acidosis in hemodialysis patients. Am J Kidney Dis, 2000. 35(6): p. 1068-71.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, and Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med, 2009. 150(9): p. 604-12.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, and Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med, 1999. 130(6): p. 461-70.
26. Frasetto LA, Todd KM, Morris RC, and Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr, 1998. 68(3): p. 576-83.
27. Brodovicz KG, McNaughton K, Uemura N, Meininger G, Girman CJ, and Yale SH. Reliability and feasibility of methods to quantitatively assess peripheral edema. Clin Med Res, 2009. 7(1-2): p. 21-31.
28. Luft FC, Zemel MB, Sowers JA, Fineberg NS, and Weinberger MH. Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. J Hypertens, 1990. 8(7): p. 663-70.
29. Luft FC, Steinberg H, Ganten U, Meyer D, Gless KH, Lang RE, Fineberg NS, Rascher W, Unger T, and Ganten D. Effect of sodium chloride and sodium bicarbonate on blood pressure in stroke-prone spontaneously hypertensive rats. Clin Sci (Lond), 1988. 74(6): p. 577-85.
30. Kotchen TA and Kotchen JM. Dietary sodium and blood pressure: interactions with other nutrients. Am J Clin Nutr, 1997. 65(2 Suppl): p. 708S-711S.
31. Oster JR, Stemmer CL, Perez GO, and Vaamonde CA. Comparison of the effects of sodium bicarbonate versus sodium citrate on renal acid excretion. Miner Electrolyte Metab, 1988. 14(2-3): p. 97-102.
32. Uribarri J, Douyon H, and Oh MS. A re-evaluation of the urinary parameters of acid production and excretion in patients with chronic renal acidosis. Kidney Int, 1995. 47(2): p. 624-7.

12 Table of Abbreviations

ACE-I	Angiotensin converting enzyme inhibitor
ACR	Albumin to creatinine ratio (urinary)
AE	Adverse event
ARB	Angiotensin receptor blocker
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease - Epidemiology
Cr	Creatinine
CRIC	Chronic Renal Insufficiency Cohort
DCC	Data Coordinating Center

DSMB	Data Safety Monitoring Board
EDTA	Ethylenediaminetatraacetic acid
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
ET-1	endothelin-1
GMP	Good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
KIM-1	Kidney injury marker-1
LBW	Lean body weight
MDRD	Modification of Diet in Renal Disease
mEq	milliequivalent
NGAL	neutrophil gelatinase-associated lipocalin
NH_3	ammonia
$NH4^+$	ammonium
NIDDK	National Institute of Diabetes Digestive and Kidney Diseases
RR	Relative risk
SAE	Serious adverse event

Figure S1. Image of size 0-, 00-, and 000-capsules in relation to a US penny. Taken from https://i.publiclab.org/system/images/photos/000/006/729/original/caps.jpg on June 28, 2019.