The effect of lipoic acid natural supplement on cystine stone formation

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THOMAS CHI, MD

Clinical Research Protocol

The effect of lipoic acid natural supplement on cystine stone formation

Protocol Number:	16-20523
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Investigational Product:	Alpha Lipoic Acid
IND Number:	
Development Phase:	Phase 2
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Funding Organization:	Food and Drug Administration (FDA)
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Coordinating Center:	Single center

Approval:

Thomas Chi, MD
Assistant Professor of Urology, UCSF

July 26th, 2017

Date

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the FDA with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 16-20523
Protocol Title: The effect of lipoic acid natural supplement on cystine stone formation
Protocol Date: AUG 24 2016

July 26, 2017

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	adverse event
ALA	alpha lipoic acid
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CRF	case report form
CT	computed tomography
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board kidney
KUB	ureter bladder radiograph
MG	milligrams
PI	principal investigator
QoL	quality of life
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	The effect of lipoic acid natural supplement on cystine stone formation
SPONSOR	Thomas Chi, MD
FUNDING ORGANIZATION	FDA
NUMBER OF SITES	1 site
RATIONALE	Cystinuria is an inherited autosomal recessive disorder of the kidney that is the result of an inability to reabsorb cystine from the urine. Supersaturation of cystine in the urine produces crystals that precipitate and form stones in the kidney, which can be a cause of obstruction, infection, and chronic kidney disease. Cystine stones constitute a major health challenge for affected individuals with cystinuria because of the frequent recurrence of painful symptoms and the current absence of effective, patient-accepting treatment. The naturally occurring oral supplement alpha lipoic acid (ALA) has been shown in a mouse model of cystinuria to dramatically slow the initiation of cystine stone formation as well as the growth of existing stones. To date, there have been no published studies on the effect of ALA in individuals with cystinuria.
STUDY DESIGN	This study will be a single center, randomized double-blind placebo-controlled trial designed to assess how daily 1200 mg ALA supplementation for three years affects kidney stone recurrence, quantitative urinary cystine, and stone, blood and urinary metabolomic and metallomic profiles.
PRIMARY OBJECTIVE	Determine the effect of ALA on kidney stone recurrence in participants with cystinuria.
SECONDARY OBJECTIVES	Determine the effect of ALA on quantitative urinary cystine, and metallomic and metabolomics profiles in participants with cystinuria.
NUMBER OF PARTICIPANTS	50
PARTICIPANT SELECTION CRITERIA	Inclusion criteria: males and females age 18 or older; documented cystinuria on prior 24-hour urine collection and/or stone analysis; history of previous cystine kidney stones; and being able and willing to provide consent. Exclusion criteria: poorly controlled diabetes mellitus (hemoglobin A1C > 8.0% for more than 1 year); current ALA administration at the time of screening; ALA administration within the last year prior to screening; vulnerable populations including incarceration status; anticipation of

	pregnancy during the study duration; unable to give informed consent; non-English primary language; pregnancy, lactation, or child- bearing age without birth control devices; and serious illness likely to cause death within the next 5 years.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	The test product is 600 mg of ALA administered orally twice a day for three years.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	The control product is a sucrose tablet containing 10 mg of sucrose, given orally twice a day for three years.
DURATION OF PARTICIPATION AND DURATION OF STUDY	**Screening:** 1 week to determine eligibility **Treatment:** 3 years with visits every 4 months **Follow-up:** 2 years with visits every 4 months

CONCOMMITANT MEDICATIONS	**Allowed**: The participants will be allowed to continue any medications they are currently taking. **Prohibited**: No medications will be strictly prohibited. However, alpha-mercaptopropionylglycione and D-penicillamine, two medications currently used to treat cystinuria, are both thought to bind the sulfhydryl groups of cysteine preventing the molecules from binding together and resulting in the insoluble cystine molecule. Both medications are not used with great frequency and both are not very effective. As they may interfere with the mechanism of action of ALA, participants of this study who take alpha- mercaptopropionylglycione and/or D-penicillamine will be asked to stop these medications 12 weeks prior to starting the treatment portion of the study as a washout period to ensure no harmful effects result from stopping these therapies. If they chose not to stop, at the discretion of the Principal Investigator, the participant will be allowed to participate and the study will simply document the use of Thiola throughout the course of the study and may look at these participants separately in the final analysis.
EFFICACY EVALUATIONS	Efficacy evaluations will include determination of stone recurrences on clinical history, exam, and radiographic review; quantitative 24-hour urinary cystine; and urinary, blood, and stone metallomic and metabolomic profiling.
PRIMARY ENDPOINT	The primary efficacy endpoint will be assessed in two ways over the course of the 3-year treatment period: 1) symptomatic stone recurrences, defined as renal colic, stone passage, or surgical removal of a stone; 2) silent stone recurrences, classified as stone growth or new stones,

	diagnosed on the basis of renal ultrasound, plain KUB x-ray, or if clinically indicated, computed tomography.
SAFETY EVALUATIONS	After participants are enrolled at 3-4 weeks during the treatment period, a study coordinator will contact each participant to check compliance, tolerability, and side effects with ALA supplementation. Any concern for a potential adverse event will be reviewed by the study investigators. Patient clinical care will continue as per the current standard for the duration of this study. Tolerability and side effects will be reviewed at each scheduled clinic visit which normally occur every four months. All reported adverse events will be reviewed by the study investigators. Depending on the severity of the adverse event, the study investigator may determine the need for un-blinding, and the participant may be advised to stop ALA intake if it is determined that ALA is the cause.
PLANNED INTERIM ANALYSES	When 50% of target participants have been enrolled and on the study protocol for 6 months, an interim analysis will be performed by an un-blinded statistician to evaluate for ALA clinical effects.
STATISTICS **Primary Analysis Plan**	The analysis will be performed on the intention-to-treat principle in the treatment and placebo groups. The primary efficacy endpoint will be assessed by comparing the rates of symptomatic and silent stone recurrences using the t-test with a two-sided p-values and calculated 95% confidence intervals. In addition, the analysis of secondary endpoints will compare quantitative urinary cystine, and metallomic and metabolomics profiles using repeated measures of analysis of variance.
Rationale for Number of Participants	The target enrollment for this study is 50 participants, based on a conservative approach to determine the sample size needed to evaluate the effect of ALA supplementation. Two recent studies evaluating the medical management of cystinuric individuals have reported that among individuals who are compliant in taking medications, the average number of stone events per person is approximately 1 per year (Reference #'s 5, 9). The current study design will be powered at 90% to detect a clinically meaningful reduction of stone events at 50% (0.5 stone events per year) with two-tailed alpha = 0.05. Based on a two-sided t-test, the following scenarios were considered for the standard deviation (SD) for the sample and sample size (n): SD 0.5, n=11; SD 0.75, n=24; SD 1, n=42. To account for a small dropout rate over the study duration, the enrollment goal of 50 participants was proposed.

1 BACKGROUND

Cystinuria is an inherited autosomal recessive disorder of the kidney that is the result of a defect in the dibasic amino acid transporter in the apical membrane of the renal proximal tubule and small intestine. The disease causes hyperexcretion of cystine, lysine, arginine, and ornithine into the urine. Of these amino acids, only cystine is poorly soluble in urine. Supersaturation of cystine in the urine produces crystals that precipitate and form calculi, which can be a cause of obstruction, infection, and chronic kidney disease.[1] Cystine stone disease has an estimated prevalence of up to 1 in 1,000 in some parts of Europe and 1 in 17,000 in the United States,[2] and comprises up to 2% of all kidney stone disease overall and up to 10% of stone disease in children.[3] As it is a rare disease, pharmaceutical treatments for cystinuria are considered "orphan drugs" based on the U.S. Orphan Drug Act of 1983, which was passed to encourage pharmaceutical companies to develop treatments for diseases with a small market.[4] However, cystine stones constitute a major health challenge for affected individuals because of the frequent recurrence of painful symptoms and the current absence of effective, patient-accepting treatment.[5, 6]

Two primary factors known to affect the solubility of cystine include are cystine concentration and pH.[7] Therefore, the current mainstays of therapy include aggressive hydration to 2.5 to 3 liters of fluid intake daily, lowering of dietary sodium intake, urinary alkalinization to pH >7.0, and thiol derivative medications to bind urinary cystine to reduce urinary cystine concentrations to less than 250 mg/l, the level above which cystine becomes insoluble in urine.[8] Thiol derivatives in current use including D-penicillamine and alpha-mercaptopropionylglycione increase the solubility of cystine by forming more soluble mixed amino acid-disulfide products. However, these medications are difficult to tolerate due to their side effect profiles and, therefore, compliance is poor.[9] Furthermore, the medications require regular monitoring of complete blood count, liver enzymes, and urinary protein excretion. In our own kidney stone clinic population, even when compliance is high, cystinuric patients taking D-penicillamine and alpha-mercaptopropionylglycione often continue to form recurrent cystine stones. It is not surprising that because cystinuria is a lifelong disease and current medical management is difficult to achieve and not very effective, these individuals have frequent stone recurrences and a higher risk of kidney loss compared to the average calcium oxalate stone former.[10] Therefore, additional well-tolerated and effective medical therapies to treat cystinuria are desperately needed.

2 STUDY RATIONALE

One potential therapeutic is the thiol-containing compound alpha-lipoic acid (thioctic acid, 5-(1,2-dithiolan-3- yl) pentanoic acid, ALA). ALA is an over-the-counter supplement and antioxidant found in nutrition supplement stores. ALA is a naturally occurring compound involved with mitochondrial energy metabolism as an enzymatic cofactor. ALA is both synthesized in the body as well as absorbed in the diet. Once ALA is transported into the cell, it is reduced to dihydrolipoic acid (DHLA). Both ALA and DHLA have direct antioxidant activity, and they can regenerate endogenous

antioxidants including ascorbic acid and vitamin E.[11] ALA can also increase intracellular coenzyme Q10[12] and glutathione levels.[13] ALA and DHLA also have additional biochemical effects as metal chelators, reactive oxygen species scavengers, and modulators of signaling transduction of several pathways.[11]

While the potential therapeutic effects of ALA have been studied in a number of diseases including, including Alzheimer's disease, obesity, cardiovascular disease, hypertension, and several cancers,[11] the efficacy of ALA has been best studied in type 2 diabetic peripheral neuropathy.[14,15] Safety of long-term administration of once- daily 600mg ALA over 4 years was established in the NATHAN 1 trial.[15] Doses up to 1200 mg daily have also been used and appear well tolerated.[16-19] Given this history safe use in clinical medicine and, most importantly, based upon our positive findings of ALA effectiveness in a mouse model of cystinuria (described below), we propose a pilot study on the use of this supplement in cystinuric participants.

At present we can only hypothesize on the possible mechanism(s) of action of ALA. First, ALA may modulate intracellular cysteine levels through its effects on the cystine/glutamate exchanger and thereby increase glutathione production.[20, 21] Second, ALA may counteract oxidative stress by induction of nuclear factor erythroid related factor 2 (Nrf2), which is involved in cellular cystine uptake.[22] Third, ALA may directly reduce insoluble cystine to form a mixed-disulfide compound to increase urinary solubility of cystine. Fourth, ALA may reduce zinc levels in the kidney,[23] which has been identified as a cofactor in stone formation.[24, 25] No matter which mechanism(s) ultimately emerge(s) as the appropriate explanation, we believe that oral administration of lipoic acid will decrease the amount of quantitative urinary cystine and, most critically, slow the rate of stone formation and growth, thereby reducing the frequency of stone events in cystine stone formers.

In our lab, a mouse model of cystinuria lacking the Slc3a1 gene was employed to study the formation and growth of urinary cystine stones. Slc3a1-/- male mice develop cystine stones at about 2-3 months of age and accumulate stone volume at an approximate rate of 1 mm^3/day, measured by micro-computed tomography. In initial work, 1-month old Slc3a1-/- mice were treated with ALA administered through supplementation in the diet (0.5% by weight). By day 45, 1 of 8 mice on the ALA-supplemented diet had developed stones, in contrast to 7 of 7 control mice fed a regular chow diet. In addition, 3-month old untreated stone-forming mice that were then fed ALA grew cystine stones at a dramatically slower rate (stone volume accumulation 10% of controls, n=9) over 120 days. In summary, these initial results show that ALA markedly slows the initiation of cystine stone formation as well as the growth of existing stones. Moreover, based upon body weight, feeding behavior and activity level ALA appears to be very well tolerated in the mouse.

To date, there have been no published studies on the effect of ALA in human stone formers.

2.1 Risk / Benefit Assessment

ALA is an over-the-counter supplement and naturally occurring antioxidant. Safety and tolerability of ALA has been demonstrated in several large randomized, placebo-controlled

trials for the treatment of diabetic polyneuropathy. In the SYDNEY 2 trial, diabetic participants received once-daily oral ALA at 600mg, 1,200 mg, or 1,800 ALA over 5 weeks. Rates of adverse events compared to placebo were higher with higher dosing but primarily isolated to minor gastrointestinal side effects.[16] Other large, placebo-controlled randomized trials reported no severe adverse events at 1,200 mg daily dosing.[17, 19, 26] In the longest prospective trial (NATHAN 1) currently published, 600mg ALA daily was administered in 230 diabetic participants in the treatment arm over 4 years.[15] Rates of noncompliance (<10%) and discontinuation due to treatment tolerability (<1%) were similar in both groups. No statistically significant differences were seen in serious adverse events between the two groups. Furthermore, dose-adjustment is not necessary in individuals with chronic renal insufficiency, which is relevant in a population of chronic kidney stone formers, as it does not affect the pharmacokinetics of ALA.[27] Therefore, we do not anticipate a significant number of adverse side effects from administration based on prior studies at the same dose

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the effect of ALA on kidney stone recurrence in participants with cystinuria. Stone recurrence in this study will be assessed in two ways:

1) symptomatic stone recurrences, defined as renal colic, stone passage, or surgical removal of a stone.

2) silent stone recurrences classified as stone growth or new stones, diagnosed on the basis of renal ultrasound, plain KUB x-ray, or, if clinically indicated, computed tomography.

3.2 Secondary Objectives

The secondary objectives of this study are to determine the effect of ALA on quantitative urinary cystine, cystine solubility, and metallomic and metabolomics profiles in participants with cystinuria. Quantitative urinary cystine is determined by 24-hour urine collection. The metallomic and metabolomics profiles of urine and stone samples will be compared in our lab as a new set of markers to understand how ALA has an effect on the stone-forming process and how its efficacy can be followed during treatment.

4 STUDY DESIGN

4.1 Study Overview

This study will be a single center, randomized double-blind placebo-controlled trial designed to assess the effect of daily 1200 mg ALA supplementation for three years on kidney stone recurrence in participants with cystinuria. Participants will be computer sequence-randomized to receive either oral daily dosing of 1200 mg ALA or placebo. Participants will be allowed to continue potassium citrate treatment, the currently mainstay of cysturia treatment, so as to avoid inducing worsened clinical events. If participants are taking D-penicillamine and alpha-mercaptopropionylglycione at the time of study enrollment, they will be asked to stop these medications 12 weeks prior to starting the treatment portion of the study as a washout period to ensure no harmful effects result

from stopping these therapies. If they chose not to stop, at the discretion of the Principal Investigator, the participant will be allowed to participate and the study will simply document the use of Thiola throughout the course of the study. A minority of cystinuric stone formers take D-penicillamine and alpha- mercaptopropionylglycione and our clinical experience reflects that these medications do not demonstrate a high efficacy for stone prevention. We therefore do not think that stopping these drugs will worsen clinical stone outcomes, but to ensure this is the case, participants who are on these medications and choose to stop, will be observed for a 12-week washout period after stopping D-penicillamine and alpha-mercaptopropionylglycione and prior to starting ALA. We anticipate participant enrollment to last 6-8 months. The secondary objectives of this study are to determine the effect of ALA on quantitative urinary cystine, cystine solubility, and metallomic and metabolomics profiles in participants with cystinuria to help determine the mechanism(s) of action of ALA in cystinuric individuals. Both study participants and study team members will be blinded to the treatment.

Clinical data including medical history, plain KUB x-ray and renal ultrasound, routine blood work, and 24-hour urine collections for all participants will be collected as part of normal clinical care at routine clinical visit intervals, which currently occur every 4 months. Routine clinical care for participants will not be altered in any way outside of administration of the supplement or placebo. Routine clinical care generally consists of office visits every 4 months at which time, as medically necessary as determined by the study investigator, an imaging study is performed (plain KUB x-ray, ultrasound, or CT scan if clinically indicated), a 24-hour urine collection is done to check quantitative urinary cystine levels, and blood is drawn to evaluate electrolyte levels as well as renal function. During routine visits for blood and urine tests, any discarded blood and urine specimens will be collected for research testing. No additional blood draw or urine collection will be performed for this study. From discarded routine specimens provided during these clinic visits, metallomic and metabolomics profiling will be performed for all participants using discarded samples material. This is comprised of mass spectrometry and elemental analysis of samples performed in our research lab. Quality of life measurement, as recorded by the Wisconsin Stone-quality of life questionnaire (Wisconsin Stone-QoL), will also be evaluated.

Recurrent stone events, defined by symptomatic or silent stone recurrence, is the primary endpoint in this study. It will be documented in this study cohort, and compared between treatment and placebo groups to determine treatment effect. If stones are removed for surgery or spontaneously passed by participants, any discarded stone specimens not needed for clinical care will also be subjected to metabolomic and metallomic analysis.

At the end of the three years of study drug treatment, all participants will undergo a low dose non-contrast CT scan to look for a silent change in stone size. As this is a pilot study, recruitment will be limited to target enrollment of 50 participants (25 for each treatment arm). Treatment will continue for a total of 3 years and after treatment completion, participants will be followed for an additional 2 years to evaluate for change in clinical status or adverse events resultant from ALA administration.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be assessed in two ways over the course of the 3-year treatment period:

1) Symptomatic stone recurrences, defined as renal colic, stone passage, or surgical removal of a stone

2) Silent stone recurrences, classified as stone growth or new stones, diagnosed on the basis of renal ultrasound, abdominal flat-plate examinations, or if clinically indicated, computed tomography.

These clinical endpoints are already collected as a part of the participants' routine clinical care and exist as part of their medical record. Data will simply be abstracted from clinical encounters.

5.2 Safety Evaluations

After participants are enrolled at 3-4 weeks during the treatment period, a study coordinator will contact each participant to check compliance, tolerability, and side effects with ALA supplementation. Any concern for a potential adverse event will be reviewed by the study investigators. In addition, tolerability and side effects will be reviewed at each scheduled, four-month clinic visit. All adverse events will be reviewed by the study investigators. Depending on the severity of the adverse event, the study investigator may determine the need for un-blinding, and the participant may be advised to stop ALA intake if it is determined that ALA is the cause.

In addition, during the informed consent process, all potential side effects and drug interactions will be discussed. Enrolled participants will be provided the email address of the study coordinator and a 24-hour contact phone number of a physician if any adverse events occur during the study period.

When 50% of participants have been in the study for 6 months, an interim analysis will be performed. If it is found that clinical outcomes for ALA-treated participants are significantly improved compared to the placebo arm, study investigators may elect to complete the trial early and provide all participants with ALA.

6 PARTICIPANT SELECTION

6.1 Study Population

Participants with a diagnosis of cystinuria who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

Inclusion criteria will include: males and females age 18 or older; documented cystinuria on prior 24-hour urine collection and/or stone analysis; history of previous cystine kidney stones; and being able and willing to provide consent.

6.3 Exclusion Criteria

Exclusion criteria will include: poorly controlled diabetes mellitus (hemoglobin A1C > 8.0% for more than 1 year); current ALA administration at the time of screening; ALA administration within the last year prior to screening; vulnerable populations including incarceration status; anticipation of pregnancy during the study duration; unable to give informed consent; non-English primary language; pregnancy, lactation, or child- bearing age without birth control devices; and serious illness likely to cause death within the next 5 years.

7 CONCURRENT MEDICATIONS

All participants should be maintained on the same medications throughout the entire study period with no introduction of new chronic therapies, as medically feasible.

7.1 Allowed Medications and Treatments

No medications will be strictly prohibited. However, alpha-mercaptopropionylglycione and D-penicillamine, two medications currently used to treat cystinuria, are both thought to bind the sulfhydryl groups of cysteine preventing the molecules from binding together resulting in the insoluble cystine molecule. Both medications are not used with great frequency and both are not very effective. As they may interfere with the mechanism of action of ALA, participants of this study who take alpha- mercaptopropionylglycione and/or D-penicillamine will be asked to stop these medications 12 weeks prior to starting the treatment portion of the study as a washout period to ensure no harmful effects result from stopping these therapies. If they choose not to, at the discretion of the Principal Investigator, the participant will be allowed to participate and the study will simply document the use of Thiola throughout the course of the study and may look at these participants separately in the final analysis. .

8 STUDY TREATMENTS

8.1 Method of Assigning Participants to Treatment Groups

Participants will be computer sequence-randomized to receive either oral daily dosing of 1200 mg ALA or placebo.

8.2 Blinding

Both participants and study team members will be blinded to treatment arm. The following study procedures will be in place to ensure double-blind administration of study treatments:

- Randomization will occur at time of first screening visit and results will be

provided to the UCSF Pharmacy compounding services

- Randomization will be controlled by the UCSF Pharmacy compounding service who will provide treatment packages to the study coordinator who will provide them to the study participant. Treatment packages will contain insert materials but no markings that will allow participants to know which study arm they have been randomized to.
- Access to randomized code will be strictly controlled; study investigators and clinical coordinators will not have access to the randomized code unless a need for un-blinding arises.
- Packaging and labeling of test and control treatments will be identical.

The study blind will be broken on completion of the clinical study and after the study database has been locked. In the event of an adverse event, the study investigator may decide to un-blind himself to determine if ALA is the cause. In addition, when 50% of target participants have been enrolled and on the study protocol for 6 months, an interim analysis will be performed by an un-blinded statistician to evaluate for ALA clinical effects. At that point, if it is found that clinical outcomes for ALA-treated participants are significantly improved compared to the placebo arm, study investigators may elect to complete the trial early and provide all participants with ALA.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

The test product will be comprised of 1200mg alpha-lipoic acid formulated for oral administration with no identifiable markings. ALA is currently commercially available from a variety of manufacturers and suppliers. For our mouse experiments, we used alpha lipoic acid sold by GNC. In our lab, purity testing with mass spectrometry revealed that this ALA contained no significant additional materials outside of ALA. Since this is a commercially available product with tablet markings on it, we will obtain our alpha lipoic acid from the Wellspring Pharmacy. (https://wellspringrx.com/). Wellspring Pharmacy maintains strict adherence to all regulations set by the California Board of Pharmacy. The requested formulation of ALA for this study will be two tablets containing 600 mg ALA. Wellspring Pharmacy will maintain control of the test product and provide it to the study team in packaging identical to placebo packaging.

8.3.2 Formulation of Control Product

The control product will be designed to appear identical as the test product to serve as the placebo. It will contain 10 mg sucrose and be obtained from Wellspring Pharmacy (https://wellspringrx.com). Wellspring Pharmacy maintains strict adherence to all regulations set by the California Board of Pharmacy.

8.3.3 Packaging and Labeling

Because both participants and study team members will be blinded to treatment arm, the test product and control products will appear identical.

Packaging: Study supplement or placebo is supplied in cartons containing 240 tablets (a four- month supply). The tablets will be packaged in sets of 60 enclosed within a plastic bottle. Four bottles will be contained in each carton.

Labeling: Each carton of study supplement or placebo will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the sponsors, and directions for patient use and storage. Each tablet will be labeled with the study protocol number.

8.4 Supply of Study Drug at the Site

The Test Product and Control Product will be stored in a locked cabinet in a locked office at the Compounding and Research Support Pharmacy at UCSF. There will only be one study site. After participants are randomized, treatment packages will be provided to the study coordinator who will provide them to study participants. Pill counts will be performed during each clinical visit and extra study drugs will be discarded. During clinical visits, if more study treatment packages are needed, they will be requested from the Compounding and Research Support Pharmacy at UCSF and provided to participants.

8.4.1 Dosage/Dosage Regimen

600 mg of the ALA supplement or placebo will be taken orally twice daily for three years. The pharmacology of ALA is such that bioavailability should be highest three hours after administration. Participants will be encouraged to take the study tablet at night prior to bed to facilitate consistent bioavailability between participants.

8.4.2 Dispensing

The ALA supplement or placebo will be given to the participant with sufficient quantity for administration at home, with a 4-month supply (240 tablets) to be given at each interval visit. At subsequent visits, remaining pills will be counted and counts recorded to reflect compliance for participants.

8.4.3 Administration Instructions

The ALA supplement or placebo is to be taken orally twice daily.

8.4.4 Storage

The ALA supplement will be stored under dry conditions and at room temperature in a locked cabinet in a locked office within the Compounding and Research Support Pharmacy at UCSF.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each participant will be maintained on an ongoing basis by a member of the study team. The number of study drug dispensed and returned by the participant will be recorded on the Investigational Drug Accountability Record. A member of the study team will verify these documents throughout the course of the study. After participants are enrolled at 3-4 weeks, a study coordinator will contact each participant to check compliance, tolerability, and side effects with ALA supplementation.

8.6 Measures of Treatment Compliance

Participants will be asked to keep a diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their participant diary to each study visit along with all used and unused study drug containers.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the participant or participant's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at baseline/screening initial visit and at all Study Visits (as is the current standard for clinical care), and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at the initial visit.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent family and social history, and information regarding underlying diseases will be recorded at the initial visit. The determination of symptomatic stone recurrences, defined as renal colic, stone passage, or surgical removal of a stone will be performed.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub investigator who is a physician at the initial visit. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical

exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed every 4 months as part of their routine normally scheduled visits.

9.1.6 Other Clinical Procedures

Imaging studies will be performed at scheduled clinic visits as medically needed and at the discretion of the investigator. The imaging studies may include plain KUB x-ray and renal ultrasound, or CT scan if medically necessary (see below). This information will allow determination of silent stone recurrences classified as stone growth or new stones compared to prior radiologic exams. All participants will undergo low dose non-contrast CT scans at the end of the three years of study drug treatment (Visit10). This non-contrast CT scan at the end of the three-year study period will be considered a research imaging study (not a part of routine clinical care) and paid for by study funding.

In addition, quality of life surveys with Wisconsin Stone-QoL will be administered during regularly scheduled clinic visits.

If participants collect stones that pass during the course of the study, these will also be collected and analyzed for composition.

All of these clinical procedures are part of the current standard of care for patients with cystinuria undergoing management at UCSF with the exception of the CT scan performed at the completion of the study. With the exception of this radiographic study, the current study will not alter standard clinical care for participants.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Blood Chemistry Profile

Blood tests will include CBC, chemistries, BUN, and creatinine that will be collected at regularly scheduled clinic visits as medically needed and at the discretion of the investigator. During routine visits for blood tests, any discarded blood will be collected for research testing. No additional blood will be taken outside of their normal routine medical care.

9.2.2 Pregnancy Test

No participant who is pregnant or is planning to be pregnant will be allowed into the study

per the exclusion criteria.

9.2.3 Urinalysis

Routine urinalysis (glucose, protein, blood, nitrite, pH) and 24-hour urine collections for quantitative urinary cystine (Litholink, Chicago, IL) will be performed at regularly scheduled clinic visits as medically needed and at the discretion of the investigator. Urinary metabolomic and metallomic profiles will be performed on urine collected at regularly scheduled clinic visits. No additional urinalysis studies will be collected outside of their normal routine medical care.

10 EVALUATIONS BY VISIT

After enrollment into the study, during the initial visit (Visit 1), participants will undergo a complete medical history and physical exam by either the investigator or a sub investigator who is a physician. Blood and urine will be collected if medically necessary as determined by the study investigator to perform blood chemistry profiling, urinalysis, and quantitative urinary cystine, as part of routine management for cystine stone patients. Leftover blood and urine specimens will be collected for further analysis in this study. Additionally, quality of life survey with the Wisconsin Stone-QoL will be performed for research purposes.

As per normal clinical care, at subsequent visits, study participants will be seen every 4 months to obtain serum labs (CBC, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator and 24-hour urine studies (quantitative urinary cystine level). Routine medical management will be continued in all participants, which includes hydration, lowering of dietary sodium intake, and urinary alkalinization.
Plain KUB x-ray with renal ultrasound will be performed on a routine basis if medically necessary as determined by the study investigator.CT scans will also be performed only if medically necessary. These imaging studies will document stone size, location, and any interval changes in stone burden between study visits. No additional visits will be scheduled outside their normal clinical care. These are part of routine evaluation for patients with cystinuria that has been undertaken at UCSF for over 20 years.

At the 36-month visit, in addition to the routine surveillance information collected as noted above, a low-dose non-contrast CT scan of the abdomen will be performed to obtain the data of silent stone recurrence which is one of the primary endpoints in this study.

After the 36-month treatment period, study participants will stop administration of ALA or placebo. They will be seen an additional 24 months at a 4-month interval to obtain routine studies, including serum labs, imaging (plain KUB x-ray and renal ultrasound), and 24-hour urine if medically necessary as determined by the study investigator.

10.1 Visit 1 (Initial Visit)

1. Review the study with the participant (participant's legal representative) and obtain written informed consent and HIPAA authorization.
2. Assign the participant a unique study ID number.

3. Record demographics data.
4. Record medical history, including a history of stone disease and family history of stone disease, date of first diagnosis, and prior surgical interventions.
5. Record concomitant medications.
6. Perform a complete physical examination and record vital signs if possible
7. Administer the Wisconsin Stone-QoL survey.
8. Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator
9. Perform routine 24hr urine testing.
10. Collect passed stone specimens, if presented.
11. Collect discarded blood and urine specimens for research purposes if presented.

10.2 Visit 2-9 (every 4th month)

1. Record any Adverse Experiences and/or Review participant diary for adverse experiences and dosing compliance.
2. Concomitant medications review.
3. Perform pill count.
4. Perform abbreviated physical examination and record vital signs if possible
5. Administer the Wisconsin Stone-QoL survey.
6. Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator.
7. Perform routine 24hr urine testing.
8. Perform routine KUB x-ray and renal ultrasound if medically necessary as determined by the study investigator.
9. Perform CT scan if medically necessary as determined by the study investigator.
10. Collect passed stone specimens, if presented.
11. Collect discarded blood and urine specimens for research purposes if presented.

10.3 Visit 10 (month 36)

1. Record any Adverse Experiences and/or Review participant diary for adverse experiences and dosing compliance.
2. Concomitant medications review.
3. Perform pill count.
4. Perform abbreviated physical examination and record vital signs if possible
5. Administer the Wisconsin Stone-QoL survey

6. Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator
7. Perform routine 24hr urine testing.
8. Perform low-dose CT scan for research purposes.
9. Collect passed stone specimens, if presented.
10. Collect discarded blood and urine specimens for research purposes if presented

10.4 Visit 11-16 (every 4th month to 5 years mark)

1. Record any Adverse Experiences and/or Review participant diary for adverse experiences.
2. Concomitant medications review.
3. Perform abbreviated physical examination and record vital signs if possible
4. Administer the Wisconsin Stone-QoL survey.
5. Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator
6. Perform routine 24hr urine testing.
7. Perform routine KUB x-ray and renal ultrasound if medically necessary as determined by the study investigator
8. Perform CT scan if medically necessary as determined by the study investigator.
9. Collect passed stone specimens, if presented.
10. Collect discarded blood and urine specimens for research purposes if presented.

10.5 Early Withdrawal Visit

1. Record any Adverse Experiences and/or Review participant diary for adverse experiences and exclusionary medication use.
2. Concomitant medications review.
3. Perform pill count.
4. Perform abbreviated physical examination and record vital signs if possible
5. Administer the Wisconsin Stone-QoL survey.
6. Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine) if medically necessary as determined by the study investigator
7. Perform routine 24hr urine testing.
8. Perform routine KUB x-ray and renal ultrasound if medically necessary as determined by the study investigator
9. Perform CT scan if medically necessary as determined by the study investigator.
10. Collect passed stone specimens, if presented.
11. Collect discarded blood and urine specimens for research purposes if presented.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the participant, for the occurrence of AEs during each participant visit and record the information in the site's source documents. Adverse events will be recorded in the participant CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Thomas Chi, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone : (415) 699-0617
Pager : (415) 443-1475

12 DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

12.1 Early Discontinuation of Study Drug

A participant may be discontinued from study treatment at any time if the participant, the investigator, or the Sponsor/Investigator feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Participant withdrawal of consent (or assent)
- Participant is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a participant is withdrawn from treatment due to an adverse event, the participant will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All participants who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents (Refer to Section 10) for early termination procedures.

12.3 Withdrawal of Participants from the Study

A participant may be withdrawn from the study at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents. As noted above, participants who discontinue study treatment early (i.e., they withdraw prior to Visit 4) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Participants who withdraw after Visit 1 but prior to Visit 4 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Participants

Participants who withdraw from the study treatment will not be replaced.

Participants who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the participant, investigator, or FDA fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to orally intake prescribed dosage on a daily basis
- Intake of ALA supplement exceeds the prescribed daily dosage

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The FDA will determine if a protocol violation will result in withdrawal of a participant.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

The study investigator will work with the study team to ensure that participants' privacy and information is protected. They both have access to experienced clinical trials offices and expertise in conducting clinical research similar to the one proposed in this application, ensuring that safe and ethical practices will be followed. Physical risk will be minimized by the study design since routine clinical care will not be altered with inclusion in this study. All health-system source/legacy data files will be stored at the UCSF local health system and will be accessed only by the programmers/analysts working on this study. Since confidential information will be collected from the medical charts, we will not directly link personal identifiers with the data collected nor will we

use personal identifiers in any reports, materials, or presentations that emanate from this work. All electronic files containing personal identifiers will be stored only on the UCSF site file servers located behind a firewall. Information transferred to the server for backup purposes will be done via secure ftp. Files may be transferred to other computers temporarily via the Internet to facilitate central upload. In these circumstances, the files will be protected by encryption. The UCSF site file servers are only accessible by network support specialists working in secure locations. The on-site file server will be electronically accessible only to study investigators through user password protection. Access to study data is protected and participant to the same security protections as other confidential health system data. Computer passwords are changed on a regular basis. Individual identifiers such as names and medical record numbers will be removed from study data files in the data processing steps and will not be accessible to collaborators accessing the database for further study as described in this study application.

The participating collaborators will maintain a data link from the study data but not to the personal identifiers (to permit reanalysis of the data files). In addition, all investigators and support staff involved with collection or entry of clinical data are HIPAA certified and have completed and are current with regard to IRB training. Investigators and project staff will sign confidentiality pledges annually HIPAA training annually. Datasets shared with external collaborators will be stripped of any identifying information according to HIPAA policy.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

Data sets from all participants enrolled in the study will be analyzed.

The primary efficacy endpoint will be assessed by medical history and physical exam, in addition to radiographic imaging performed at each study visit.

The secondary efficacy endpoints will be assessed by 24-hour urine collections (Litholink, Chicago, IL), and the analysis of the metallomic and metabolomics profiles of urine and stone samples that are collected.

15.2 Analysis of Primary Endpoint

The primary efficacy endpoint will be assessed in two ways over the course of the 3-year treatment period: 1) symptomatic stone recurrences, defined as renal colic, stone passage, or surgical removal of a stone; and 2) silent stone recurrences classified as stone growth or new stones, diagnosed on the basis of renal ultrasound, plain KUB x-ray, or if clinically indicated, CT scan. The analysis will be performed on the intention-to-treat principle in the treatment and placebo groups.

15.3 Sample Size and Randomization

The target enrollment for this study is 50 participants, based on a conservative approach to determine the sample size needed to evaluate the effect of ALA supplementation. Two recent studies evaluating the medical management of cystinuric individuals have reported that among individuals who are compliant in taking medications, the average number of stone events per person is approximately 1 per year (Reference #'s 5, 9). The current study design will be powered at 90% to detect a clinically meaningful reduction of stone events at 50% (0.5 stone events per year) with two-tailed alpha = 0.05. Based on a two-sided t- test, the following scenarios were considered for the standard deviation (SD) for the sample and sample size (n): SD 0.5, n=11; SD 0.75, n=24; SD 1, n=42. To account for a small dropout rate over the study duration, the enrollment of 50 participants was proposed. At UCSF, clinical volume approximates 60 nephrolithiasis patients per week, including those with cystinuria. At a recent cystinuria outreach event led by Drs. Stoller and Chi at UCSF (http://stollerlab.ucsf.edu/?q=news/june-18-2015-cystine-patient-symposium), over 50 individuals with cystinuria attended among over 100 participants overall. We anticipate that 6-8 months will be required to accrue these participants.

Participants will be computer sequence-randomized to receive either ALA or placebo.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study drug.

Entry will be performed electronically by the study coordinator directly into UCSF REDCap, a HIPAA-compliant data management system incorporated into the UCSF electronic medical record system, or uploaded in an automated fashion from our electronic medical record into REDCap. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a participant number.

If a correction is required for any data entry, the time and date stamps track the person entering or updating data and creates an electronic audit trail.

The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a REDCap database. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the REDCap system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

All electronic files containing personal identifiers will be stored only on the UCSF site file servers located behind a firewall. Information transferred to the server for backup purposes will be done via secure ftp. Files may be transferred to other computers temporarily via the Internet to facilitate central upload. In these circumstances, the files will be protected by encryption. The UCSF site file servers are only accessible by network support specialists in locked rooms. The on-site file server will be electronically accessible only to study investigators through user password protection. No non-electronic files (such as paper surveys, consent forms, pathology data, etc.) will be kept for this study. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (participant files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring will be conducted by the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator / Sponsor (or designee), will allow appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Participant Confidentiality

Clinical data for these participants will be collected in our REDCap database, which is a secure, online HIPAA-compliant research data collection portal.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked file cabinet and code sheets linking a participant's name to a participant identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor/Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to participants. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning participant recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the FDA prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the participants of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and s participants (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the participant will also be obtained. If a participant is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the participant. A copy of the signed consent form (and assent) will be given to the participant or legal representative of the participant and the original will be maintained with the participant's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor/Investigator. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).

3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the participants.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	VISIT 1 (Initial Visit)	VISITS 2-9 (Month 4-32)	VISIT 10 (Month 36)	VISITS 11-16 (Month 40-56)
Informed Consent	X			
Medical History	X	X	X	X
Complete Physical Exam	X			
Abbreviated Physical Exam		X	X	X
Vital Signs	X	X	X	X
Wisconsin Stone-QoL survey	X	X	X	X
Record any Adverse Experiences		X	X	X
Concomitant medications review	X	X	X	X
Pill Count		X	X	X
Collect routine blood for clinical laboratory tests (CBCs, chemistries, BUN, creatinine).	If medically indicated	If medically indicated	If medically indicated	If medically indicated
Perform routine 24hr urine testing	X	X	X	X
Perform routine plain KUB x-ray and renal ultrasound	If medically indicated	If medically indicated	If medically indicated	If medically indicated
Perform low-dose CT abdomen	If medically indicated	If medically indicated	X	If medically indicated
Collect discarded blood and urine for research purposes, if presented	X	X	X	X
Collect passed stone specimens, if presented	X	X	X	X

APPENDIX 2. PACKAGE INSERT OF ALPHA LIPOIC ACID

Please see the attached document.

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