Phentermine/tOpiramate to eND Obesity and Uric acid stones Trial (POuND OUT)

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Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

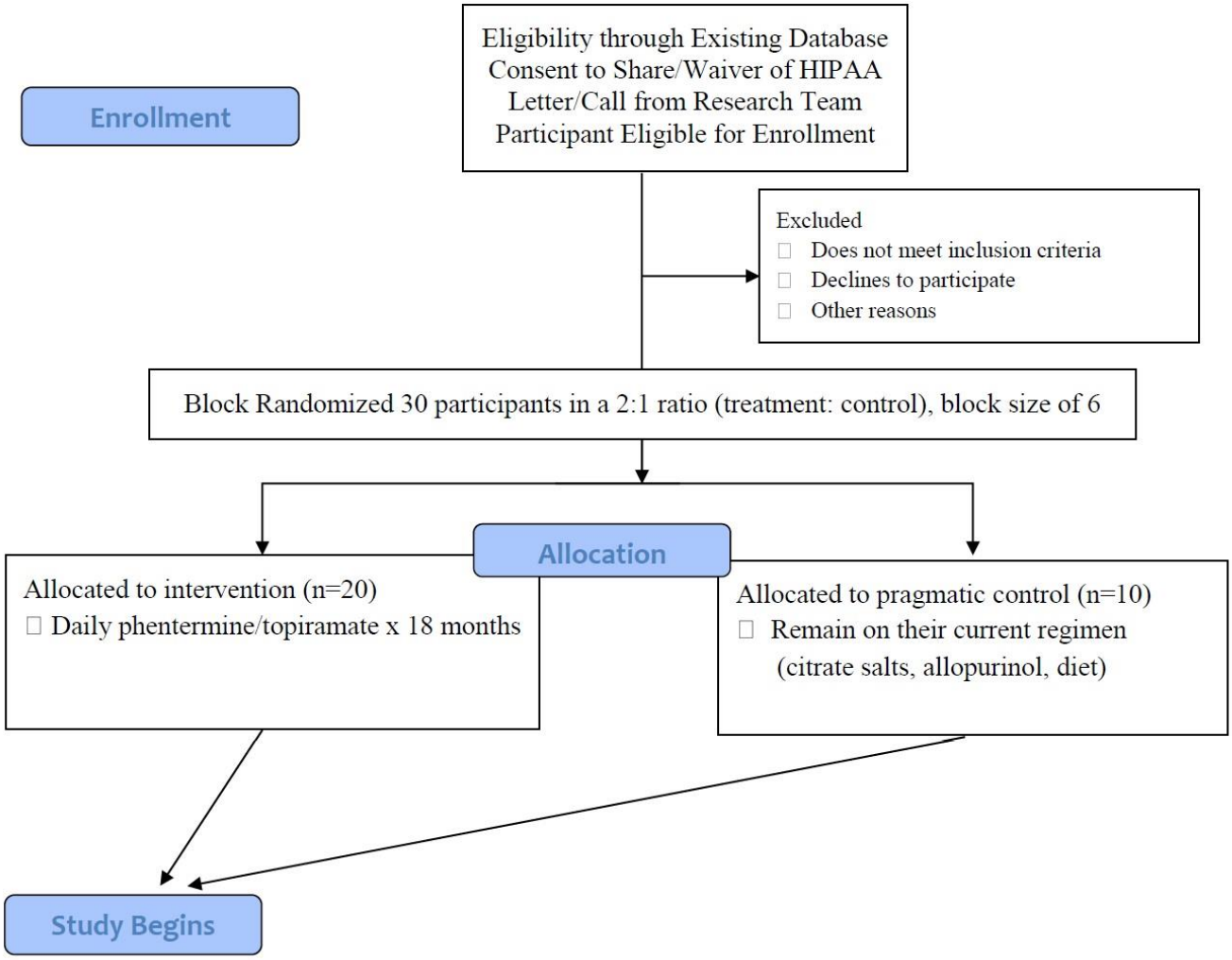
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Phentermine/tOpiramate to eND Obesity and Uric acid stones Trial (POuND OUT)
Study Description:	Mounting evidence indicates that obesity, diabetes mellitus, and kidney stones are inter-connected diseases, particularly uric acid nephrolithiasis (UAN) with or without components of calcium oxalate (CO). Obese or overweight diabetics have a six-fold increased risk to develop UAN/COUAN because they are unable to properly add buffer (ammonium) to their urine. The FDA-approved weight loss drug Qsymia® (15mg/92 mg; phentermine/topiramate-ER, Vivus Inc.) is the most effective weight loss drug (of the five currently on the market) and has a unique side effect of alkalinizing the urine, or making it less acidic. We hypothesize that treatment of obese, diabetic patients with phentermine/topiramate will reduce the incidence of UAN/COUAN by 1) direct urinary alkalinization and 2) weight loss. Weight loss will indirectly improve urinary buffering ability through improvement in insulin sensitivity and will decrease renal oxidative stress. Our group proposes an 18 month, feasibility pilot study, randomizing up to 40 obese and diabetic individuals with UAN/COUAN to either phentermine/topiramate (n=20) or a pragmatic control group (n=10) who would remain on their standard medication regimen (citrate salts, allopurinol, diet, etc).
Objectives:	Primary Objective: new stone formation, kidney stone growth Secondary Objectives: weight loss, urinary parameters
Endpoints:	Primary Endpoint: 1) kidney stone growth (mm2) as determined by non-contrast CT scan; 2) new kidney stone growth (mm2) as determined by non-contrast CT scan Secondary Endpoints: 1) change in weight over 18 months expressed by total % body weight loss (total weight loss in pounds/starting weight in pounds); 2) % change in urinary parameters (urine pH, urinary citrate, urinary calcium, urinary 8-isoprostane, urinary hydrogen peroxide) end of study compared to baseline; 3) mean change in hemoglobin A1c end of study compared to baseline.
Study Population:	We plan to enroll up to 40 adults (male and female) age 18 years – 75 years with recurrent uric acid or mixed calcium oxalate/uric acid stones (defined by at least two spontaneous kidney stone passages or procedures and at least one stone analysis >80% uric acid) who are diabetic (as demonstrated by use of anti-hyperglycemic meds or insulin) and obese (defined as BMI > 30 kg/m^2) and live in north central Florida or south Georgia (southern US).
Phase:	3
Site Description	Single site within the United States (University of Florida)
Description of Study Intervention:	Participants will take once daily oral phentermine and twice daily topiramate for weight loss and urinary alkallinization
Study Duration:	3 years
Participant Duration:	18 months

1.2 SCHEMA

Study Design Schema



1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessments	Screening	Timeline Encounters						
		Baseline						
Visit Number	1[b]	2	3[b]	4	5	6	7[b]	8
Visit Day	~ -180 to -7	1	30	90	180	365	515	545
Visit Week	~ -24 to -1	0	4	13	26	52	74	78
Informed Consent	X	X						
Entry Criteria	X	X						
Demographics	X							
Medical History[h]	X	X	X	X	X	X	X	X
Height[c],Weight,Hip and Waist Circumference		X		X	X	X		X
24-Hour Urine Collection[d]	X	X		X	X	X	X	X
Concomitant Medications	X	X						
Pregnancy Test	X	X		X	X	X		X
Vital Signs		X		X	X	X		X
Diet History/Dietician		X		X	X			X
Imaging: CT scan[e]	X							X
Imaging: BC DEXA Scan		X						X
Serum Labs		X		X	X	X		X
PHQ-9 Assessment		X		X	X	X		X
Subject Randomization[f]		X						
Study Medication Dispensed		X		X	X	X		
Med Reconcil, Compliance			X	X	X	X		X
Dose Adjust Decision[g]				X				
Adverse Event Assessment			X	X	X	X	X	X

a – All subjects will be expected to continue on treatment until end of month 17 when a medication taper x 9 days will occur. If a subject withdraws from the study after starting drug Treatment Period, an ETV should be conducted
b - Visit 1 (screening), 3 will be conducted by phone interview; Visit 7 is a home 24 hour urine
c - Height will only be taken at first visit.
d - Subjects will provide one 24-hour urine collection. The collection does not occur at the site visit. Recollection of inadequate sample will be allowed.
e - A baseline study scan is not necessary as long as one scan has been performed within last 6 months. End of study CT scan may be performed by primary physician as standard of care imaging.
f – Baseline urine pH < 5.8, ≥80% uric acid mineral, and adequate imaging are necessary to confirm eligibility prior to randomization. If subject is randomized to drug, he/she will pick up Rx at CTSI pharmacy
g – At Visit #4: At the discretion of the Benjamin Canales, MD (PI) 1) if TBWL < 5%, increase phentermine dose to 37.5 mg daily for remainder of study; 2) if urine pH < 6.5, increase topiramate to 150 mg daily and repeat 24 hour urine 6 weeks later (Visit #5). At Visit #6, if urine pH < 6.5, increase topiramate to 200 mg daily for remainder of study.
h-Medical history including medications. For visits 3-8 changes to medical history or medications will be noted.
Abbreviations: CT = computed tomography; ETV = Early Termination Visit; FUV = Follow-up Visit; TBWL = Total Body Weight Loss

2 INTRODUCTION

2.1 STUDY RATIONALE

Study Rationale

Kidney Stones and Obesity: Mounting evidence indicates that obesity, diabetes mellitus, and kidney stones are inter-connected diseases increasing in prevalence across the entire spectrum of American citizens[1-3]. Linking these three disease states is intuitive, since food quantity, dietary factors, and body size all affect urinary composition and mineral excretion. Uric acid nephrolithiasis (UAN), with or without components of calcium oxalate (CO), is the second most common kidney stone type in the US and occurs only in acidic urine (pH < 5.8)[4,5]. Obese or overweight diabetics have a six-fold increased risk to develop UAN/COUAN because they are unable to properly add buffer (ammonium) to their urine[6]. Alkali therapy, most commonly in the form of citrate salts, is the most widely used treatment for UAN/COUAN and has been reported in small series with limited follow-up to completely alkalinize urine to a normal range – thus, ridding patients of their disease[7,8]. Despite its reported simplicity, practical UAN/COUAN management with citrate salts is complicated by poor patient tolerance, early cessation, and questionable efficacy. Furthermore, diabetics with renal disease may develop hyperkalemia on the required doses of potassium citrate, and effective blood pressure medications, such as angiotensin converting enzyme inhibitors or receptor blockers, can worsen the hyperkalemia risk. Finally, these therapies do not address the two important health epidemics underlying UAN/COUAN: obesity and diabetes.

Novel Indication: Weight Loss + Urinary Alkalinzation: Phentermine plus topiramate-ER (Qsymia ®), the most successful FDA-approved drug for weight loss[9], has the unique drug side effect of urinary alkalinzation due to excessive bicarbonate excretion. Since no new drugs have been introduced for kidney stone prevention in over 30 years, the potential impact of this proposal will be to establish phentermine/topiramate as a *novel* alternative stone disease therapy for obese and diabetic UAN/COUAN prevention.

CAI Raise Urine pH: The intended use of phentermine/topiramate in this proposal is unique given that no study to date has examined the impact of topiramate in combination with phentermine (and attendant weight loss) on urinary alkalinization. However, the urinary alkalinizing properties of CAI like topiraminate have long been recognized. In 1975, Freed first described how acetazolamide, an older CAI, stabilized both cystine and UAN in 12 patients recalcitrant to citrate therapy[10] while Sterrett (2008[11]) described the urinary changes in a similar group of 5 patients (Table 1). Two separate prospective collections of 24-hour urines have been performed before and after starting the CAI topiramate in non-stone formers with chronic headaches[12,13]. Although small in number, both studies suggest that CAI can substantially increase urine pH while decreasing relative supersaturation of uric acid. The study we propose, has not been undertaken prospectively in obese, diabetic uric acid stone formers.

2.2 BACKGROUND

I. Study Background and Significance

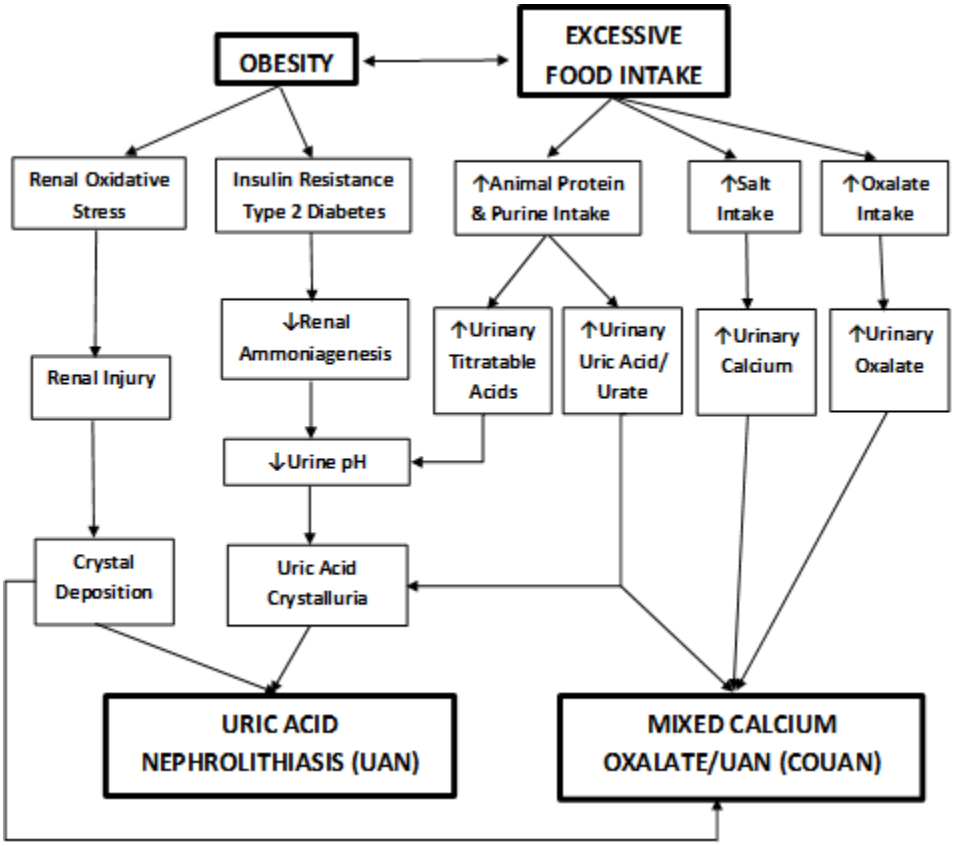
The Kidney Stone Epidemic is Fueled by Obesity and DM: Kidney stones are a painful and costly disease. Hospitalizations, interventions, and work days lost due to kidney stones impose a major economic burden, estimated in 2006 to be greater than $10 billion[14]. A 2010 survey estimated that US adults have a 1/12 (8.4%) lifetime chance of having a kidney stone, up from 1/20 (5.3%) 15 years ago[1]. Epidemiologically linked to this rise in stone prevalence is the rampant increase of obesity, metabolic syndrome, and type 2 diabetes mellitus (DM) in the US. After adjusting for age, dietary factors, fluid intake, and thiazide use across three large cohorts (n>240,000), obesity increased kidney stone risk by 44% in obese men of any age, 89% in older women, and 92% in young women[15,16]. Furthermore, cross-sectional data in a cohort of over 12,000 diabetic men and women from NHANES (2007-2010) found that those with poor glycemic control (hemoglobin A1C >6.5% versus <5.7%) were 2 times more likely to have a history of kidney stones, despite multivariate adjustment[17].

Food Quality and Positive Energy Balance Affect Stone Risk: The urinary components that raise stone risk (elevated urinary calcium, oxalate, uric acid, sodium; reduced urinary citrate) have repeatedly been shown to be more common in patients with obesity and/or DM versus non-obese/DM patients[18-20]. Although body size and renal mechanisms may be partially responsible for these findings, diet high in salt/animal protein and low in fruits/vegetables also plays a role[16].

Obesity and DM Cause Acidic Urine: A number of elegant metabolic studies have demonstrated that DM and obese patients with insulin resistance have decreased renal ammonium production, resulting in overly acidic urine pH[21,22]. This condition predisposes DM and obese patients to pure UAN (10% of US stones)[4,5] as well as mixed COUAN (5-8% of US stones[5,23]), even in the presence of normal urinary uric acid excretion[24,25]. Daudon analyzed ~2500 stones and found that the proportion of UA stones was 35.7% in patients with type 2 diabetes and 11.3% in patients without type 2 diabetes ($P < 0.0001$)[26,27]. Reciprocally, the proportion of patients with type 2 diabetes was significantly higher among UA than among calcium stone formers (27.8% vs 6.9%; $P < 0.0001$). Furthermore, stepwise regression analysis identified DM and obesity as independent predictors of UAN, with proportion of UAN ranging from 6% in non-obese, 17% in obesity only, and 36% in patients who were both obese and diabetics[26,27].

Obesity and DM Cause Renal Oxidative Stress: Finally, the ability of adipose tissue to secrete pro-inflammatory molecules and generate a chronic, low grade inflammatory state has long been studied in cardiovascular disease states such as atherosclerosis[28]. Moreover, inflammatory mediators, such as tumor necrosis factor, vascular NAD(P)H oxidase, and monocyte chemoattractant protein-1, are believed to be at least partly responsible for systemic oxidative stress and excessive production of reactive oxygen species (ROS) seen in obese kidney stone formers[29,30]. These mediators are thought to promote crystal adherence to renal tubular epithelial cells, one of the first phases in stone formation[31].

FIGURE 1: Conceptual Model of UAN and COUAN



II. UAN and COUAN Formation/Prevention

UAN: Uric acid is poorly soluble at pH<5.35 and forms crystals, even in low UA concentration[32]. Conversely, 95% of uric acid exists in the more soluble sodium urate form at urine pH>6.5 (Figure 2). Based on this, urinary alkalinization using alkali salts (potassium citrate, sodium bicarbonate) is more important than reduction of uricosuria for UAN prevention. Thus, a common strategy for most UA patients is to alkalinize first-line and reserve urinary uric acid lowering drugs such as allopurinol for resistant cases, such as in patients with bowel disease, DM, or gout. In fact, alkali therapy is so clinically effective that no randomized controlled trial (RCT) has been performed for UAN[33,34].

COUAN: High urine uric acid (hyperuricosuria) can promote CO stones by reducing the solubility of CO (termed "salting out" or "gouty diathesis"), acting as a crystal seed to initiate CO stones[35,36]. This type of heterogeneous nucleation explains why the urate-lowering drug allopurinol reduced CO recurrence by 50% in a RCT of hyperuricosuric patients[37].

Modern Medical Prevention/Citrate Shortfalls: Despite its reported simplicity, practical UAN/COUAN medical management is complicated by poor patient tolerance, early cessation, and questionable efficacy. In a review of all citrate RCT for stones, 20% of patients developed upper GI disturbance and/or rash leading to a four-fold increase in drop-out compared to placebo[38]. In a retrospective study of 144 stone formers prescribed citrate salts, over half discontinued the medication within 2 years of the prescription[39]. This citrate noncompliance is also supported by recent claims data[40]. Finally, in a large

series of stone formers prescribed citrate salts who were compliant in taking their potassium citrate, less than half were able to raise their urine pH or citrate levels to a normal range, even on the prescribed dose[41]. This proposed intervention will offer an alternative to this poorly-tolerated, ineffective therapy while targeting both obesity and DM that drives UAN/COUAN.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Patients will be asked to take a combination of two drugs, phenteramine and topiramate. First, a brief overview of both drugs and risks is appropriate.

I. Phentermine: Phentermine hydrochloride is a sympathomimetic agent approved by the US Food and Drug Administration (FDA) in 1959 as an appetite suppressant for short-term weight loss in doses up to 37.5 mg/daily[42]. Phentermine is the most widely used anti-obesity drug in the US and is the agent-of-choice among physicians specializing in obesity treatment[43]. Like other amphetamines in this class, side effects include hypertension, CNS stimulation, and tachyphylaxis or diminished response to drug over time. Because of this relationship with amphetamines, it was determined by the FDA to have the potential for abuse and designated as a Schedule IV controlled substance. These expectations were based on the chemical structural similarities between phentermine and amphetamine and on evidence in rats that phentermine stimulated spontaneous activity. However, after almost 60 years of use, there is no evidence in the peer-reviewed medical literature to support the hypothesis that phentermine has significant human addiction potential[42-44]. Although a part of the Fen-Phen and Dex-Phen scandal of 1997, Phentermine was shown **not** be the causative agent of valvular heart disease and was never withdrawn by the FDA[45]. Study participants will be reassured in this regard.

II. Topiramate: Topiramate was approved by the FDA in 1996 for the treatment of epilepsy and in 2004 for migraine prophylaxis[46]. Its "calming" central nervous system effects, and perhaps even its satiety and weight loss effects, occur through blockade of voltage-gated sodium and calcium channels, potentiation of γ-aminobutyric acid activity, and inhibition of glutamate receptor function and carbonic anhydrase II and IV[46]. In migraine studies at doses 100-200 mg, adverse effects occurred in 65-82% of subjects and were generally mild to include paresthesias, fatigue, weight loss, cognitive complaints, dry mouth, taste perversion, and nausea[47]. Less common adverse effects of TPM include kidney stones (primarily calcium phosphate due to alkaline urine), acute angle closure glaucoma, palinopsia, Stevens–Johnson syndrome, tremor, and myoclonus[48]. One long-term safety study of topiramate in epileptic patients (mean use 5.3 years, dose ranging from 200 to 600 mg) showed a non-surgical stone incidence rate of 1.5%[47]. Other studies report symptomatic stone rates of 2.1-10.7% and asymptomatic stone in up to 20% of TPM users[49]. Based on the pathophysiology of UAN and the reported difficulty in alkalinizing urine in this population, we do not expect the development of calcium phosphate stones on topiramate. However, as this medication has not previously been studied for UAN, patients at one year may be noted to have an increase in UAN/COUAN stone size or new stone development if the drug does not effectively change urine parameters. In these cases, we will counsel with the patient and consider adding alkali therapy with the expectation of stone stabilization and perhaps even dissolution.

III. Combination therapy: Phentermine/topiramate-ER (Qsymia ®15mg phentermine hydrochloride/92 mg topiramate extended-release; Vivus Inc.) was approved by the FDA in 2012 for use along with reduced dietary caloric intake for the management of obese subjects or overweight subjects with at least one weight related comorbidity[50]. The Table discusses the major findings from the three Phase III RCTs and one extension study, including changes in total body weight, blood pressure and fasting glucose.

Table: Overview of outcomes, safety, and tolerability of Qsymia ®15/92 mg in Phase III RCTs

Study Name	Study Population	Study Duration	P=# placebo Q=# Qsymia	Total Weight Loss (%)	Δ BP Systolic (%)	Δ fasting glucose, mg/dl	SAE (%)	Δ in HCO3, mEq/L
EQUATE[50] 2012	BMI ≥ 35 No DM	28 weeks	P=103	-1.7	-1.8	NR	2.7	NR
			Q=103	**-9.2**	**-5.2**	NR	3.1	NR
EQUIP[51] 2012	BMI ≥ 35	56 weeks	P=498	-1.6	+0.9	+1.9	2.5	-0.3
			Q=498	**-10.9**	**-2.9**	**-0.6**	2.5	**-1.7**
CONQUER[52] 2011	BMI 27-45 + comorbid	56 weeks	P=979	-1.2	-2.4	+0.13	4.0	+0.5
			Q=981	**-9.8**	**-5.6**	**-0.07**	5.0	**-1.0**
SEQUEL[53] 2012	BMI 27-45 + comorbid	2 years	P=227	-1.8	-3.2	+3.7	6.2	+2.2
			Q=295	**-10.5**	-4.3	**-1.2**	8.1	**+0.2**

Overall, Qsymia > was generally well tolerated and the reported drug side effects were as anticipated based on the individual component medications. The most common and important side effects observed (noted in 5% of study participants, observed at least 1.5 x more than in the placebo treatment arms) were paraesthesia, weight loss, dizziness, dysguesia, insomnia, constipation and dry mouth[42]. Serious adverse events (Table) were not significantly different between placebo and treatment groups, and rates of discontinuation were 3.1 – 9.0% for placebo and 4.4-19.3% for Qsymia[54]. As expected given the inhibition of carbonic anhydrase by topiramate, a decrease in the concentration of serum bicarbonate was observed in two of the three studies. However, the decrements were small and bicarbonate levels tended to return toward baseline over time without need for clinical intervention. Finally, antiepileptic drugs, including topiramate, carry a label precaution that they may increase the risk of suicidal thoughts or behavior[54]. Across all trials including those open to patients with controlled depression at baseline, incidence of suicidality or suicidal behaviors were not increased versus placebo. However, each of the potential risks will be reviewed in detail with the patients, and they will be questioned at each study visit as to suicidal thoughts or behaviors. Should these develop, the patient will immediately be referred to psychiatry, and the medication discontinued.

IV. Other potential risks: #1- Because CAI cause urinary alkalinization through persistent bicarbonuria, its long-term use can cause mild metabolic acidosis (Table). The renal response to acidosis is to retain urinary macromolecules that can be used systemically as buffers – namely urinary citrate. Since citrate is a natural inhibitor of calcium oxalate crystal growth, hypocitraturia is a risk factor for kidney stones

disease. Qsymia® (15/92 mg) decreased serum bicarbonate levels by 1.0 – 1.7 mEq/L in one year cohort trials (EQUIP[51], n=498; CONQUER[52], n=981) but increased serum bicarbonate by 0.2 mEq/L in the two-year cohort trial (SEQUEL[53], n=295). Urinary citrate levels have not previously been reported for Qsymia®. Finally, although calcium phosphate (alkaline) kidney stones have been reported with topiramate use[49], kidney stones were not reported as an adverse event in any Qsymia® trial to date. As an alternative to this, all patients recruited to the study will have baseline and follow-up interviews with dieticians who will disclose this pitfall. All patients will be asked to increase their dietary citrate intake can increase urinary citrate up to 250 mg/day (normal is >350 mg/day). We expect the bicarbonaturia effect of CAI and the increase in dietary citrate to counter any potential citrate side effect of the drug. Should hypocitraturia persist despite dietary intervention, patients will be asked to supplement with 400 ml of low calorie Crystal Light or lemonade 2-3x daily, which has been shown to normalize urinary citrate levels[55,56].

V. Other potential risks: #2- Bone density and weight are tightly regulated and interconnected processes. Intentional weight loss up to 10% is associated with a 1-2% total bone loss, termed “skeletal unloading,” which is a normal physiologic response to decreased body weight[57]. This unloading coupled with the potential for metabolic acidosis, could cause calcium bone mobilization and, potentially, hypercalciuria. As an alternative, all recruited patients will be counseled to increase urinary volume to >2 liters/day which should offset any transient rise in urinary calcium, and this will be followed by serial 24-hour urine collections.

2.3.2 KNOWN POTENTIAL BENEFITS

I. Weight loss benefits : Obesity and DM adversely affect mortality, morbidity, and quality of life[58]. Since we are targeting obese patients with DM, there is potential for benefit to the subject related to weight loss Qsymia with respect to reducing obesity-related complications, such as improved cardiovascular and glycemic control (see Table in section 2.3.1).

II. UAN/COUAN : In addition to weight loss, Qsymia treatment is expected to alter urinary pH and solute concentrations to favor decreased urinary supersaturations of not only UAN but also mixed COUAN and reduced related kidney stone disease - a hypothesis based on preliminary and historical data. However, in order to prove the benefit of this combination drug, the experimental portion of this study must be performed. The risks listed in section II are generally similar to those of placebo and are extremely reasonable in relation to the anticipated benefits of weight loss, improvement in DM and stone dissolution in UAN/COUAN.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Over 1,300 patients like the ones we will be recruiting (patients who are obese and have diabetes) have been studied on Qsymia® for one to two year periods. Using this randomized trial data, the FDA approved the sale of Qsymia® in the US in 2012[50]. We plan to study the same population that was studied by investigators in the CONQUER trial (2011[52]) and SEQUEL trial (2012[53]). However, the specific endpoints such as acid stones or urinary alkalinization were not examined in those studies. Overall, the benefits to the patients of having 18 months on the best weight loss drug on the market should far outweigh any potential risk of this drug therapy.

3 OBJECTIVES AND ENDPOINTS

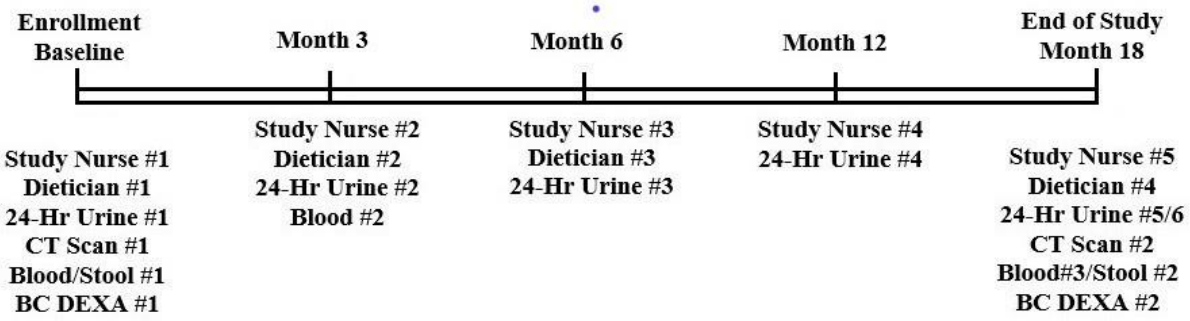
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1) New uric acid/mixed uric acid kidney stone formation 2) Existing uric acid/mixed uric acid kidney stone growth	1) Kidney stone growth (mm2) as determined by non-contrast CT scan. 2) New kidney stone growth (mm2) as determined by non-contrast CT scan	Ultimately, stone recurrence or growth prevention is the target for this patient population because it leads to morbidity and high cost of care. Uric acid stones are poorly seen on plain radiography, and the specificity and sensitivity of renal ultrasonography in the setting of obesity is low. Non-contrast CT scan is the gold standard for the assessment of uric acid stones.
Secondary		
1) Weight loss 2) Urinary parameters 3) Body Composition DEXA, Hgb A1c	1) Change in weight over 18 months expressed by total % body weight loss (total weight loss in pounds/starting weight in pounds). 2) % change in urinary parameters (urine pH, urinary citrate, urinary calcium, urinary 8-isoprostane, urinary hydrogen peroxide) end of study compared to baseline. 3) Mean change in insulin resistance end of study compared to baseline as calculated by the homeostasis model assessment method (HOMA-IR) using fasting glucose and insulin levels	Total body weight loss is the standard way of reporting the effect of weight loss drugs in the literature. We have chosen a number of secondary endpoints that may reflect improvement in reactive oxygen species in the urine. Finally, HOMA-IR is the gold standard to assess improvements in fasting glucose compared to insulin over time.
Tertiary/Exploratory		

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study is a prospective, randomized clinical trial utilizing a pragmatic control group. The experimental arm will consist of 20 individuals randomized to treatment regimen phentermine/topiramate x 18 months who have stopped all oral alkalinization agents (potassium citrate, sodium bicarbonate). To compare outcomes, a control group consisting of 10 individuals will be randomized to remain on their current medication regimen (citrate salts, allopurinol, diet, etc).

Study Visit and Laboratory Timeline



	Pre-Study	Enrollment Baseline	1M Visit	3M Visit	6M Visit	12M Visit	17M Visit	18M Visit
Visit Number	#1	#2	#3	#4	#6	#7	#8	#9
Phone Call	XX		XX				XX	
On-site Visit		XX		XX	XX	XX		XX

This protocol involves 8 study encounters:

Encounter #1: This is a pre-study phone call to discuss enrollment. Participants will be contacted by phone via three previously identified sources (see Section 5.5). Study coordinator will review entry criteria, and if subject appears to meets entry criteria. The study coordinator or PI will review the "screening" consent over the phone. The participant will have the option to complete the initial screening consent in paper form sent to them or online through RedCap. If the consent is mailed two copies will be sent. One for the participant to sign and return in the self-addressed envelope and one for them to keep. The consent checklist that has been uploaded to IRB will be used to document both procedures. Note: participants on the diabetic medications Canagliflozin (Invokana, Ivokamet), or Dapagliflozin (FARXIGA, Qtern, Qternmet Xigduo) or Empagliflozin (Jardiance, Glyxambi, Synjardy) must be taking them for at least 12 weeks prior to entering the participation part of the study.

The second "participation" consent will be completed with a face to face meeting with the study coordinator in the CRC. In both cases the consent will be reviewed, questions answered and checked for understanding. Coordinator will review consent and complete consent checklist. **Stage 1 Informed Consent (screening).** This consent will allow study coordinator to capture all external medical records (if

necessary), and to ask patient to hold all alkalinizing urine pH medications (potassium citrate, sodium bicarbonate). Participant will then be asked to complete a 24 hour urine after HOLDING all oral alkalinizing agents (potassium citrate, sodium bicarbonate) for ~4 weeks. Encounter #2 will also be scheduled.

Encounter #2: This baseline, on-site, face to face visit will involve: confirmation of entry criteria, medical history, height/weight, waist and hip circumference, completion of the PHQ-9 mental health questionnaire, 24-hour urine, vital signs, dietary history/dietician visit#1, blood collection for serum labs, signing of Stage 2 Informed Consent (study participation), subject randomization, and body composition DEXA scan. Should it be necessary, an enrollment study non-contrast CT scan will also be performed (if none over previous 6 months). If subject is randomized to medication, he/she will be dispensed on this day by CRC pharmacy. If subject is female and of child-bearing age, she will be asked to take a pregnancy test as part of your screening for enrollment.

Encounter #3: This 1-month follow-up phone call will be to review medication compliance/ reconciliation as well as assess adverse events.

Encounter #4: This 3-month, on-site, face to face visit will involve: weight, hip and waist circumference, vital signs, dietary history/ dietician visit#2, 24-hour urine, and serum labs. For those randomized to drug, medication compliance/reconciliation, adverse events, and PHQ-9 will be assessed. If total body weight loss is>5% and urine pH>6.5 (24 hr urine month 3), medications for months 4, 5, 6 will be dispensed by CRC pharmacy.

At the discretion of Dr. Canales, MD (PI), If total body weight is <5%, phentermine dose will be increased to 37.5 mg and subject will remain on this through study duration. If urine pH<6.5 (24 hr. urine month 3), topiramate dose will be increased to 150 mg daily. Medications will be adjusted appropriately for months 4, 5, 6 and dispensed by CRC pharmacy.

Encounter #5: This 6-month, face to face, on-site visit will involve: weight, hip and waist circumference, vital signs, dietary history/ dietician visit#3, 24-hour urine, PHQ-9, and serum labs. For those randomized to drug, medication compliance/ reconciliation, adverse events will be assessed.

Encounter #6: This 12-month, face to face, on-site visit will involve: weight, hip and waist circumference, vital signs, 24-hour urine, PHQ-9, and serum labs. For those randomized to drug, medication compliance/reconciliation, adverse events will be assessed.

Encounter #7: This 17-month phone call is to remind subjects to collect their fifth 24-hr urine. For those randomized to drug, adverse events will be assessed and study coordinator will also remind participants to begin a 9-day topiramate drug taper as soon as collection is completed and to collect a final 24 hour urine sample 3 weeks after drug washout.

Encounter #8: This 18-month, face to face, end-of study, on-site visit will involve: weight, hip and waist circumference, physical examination/vital signs, dietary history/dietician visit # 4, 24-hour urine, blood collection for serum labs, PHQ-9 assessment, and body composition DEXA scan. For those randomized to drug, final drug reconciliation and adverse events will be recorded. Should it be necessary, an end-of-study non-contrast CT scan will also be performed (if none performed for standard of care).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Because we do not know the long-term effect of phentermine/topiramate on uric acid stone disease, a prospective feasibility trial is the most appropriate study design. However, a control group is needed to compare outcomes. Therefore, our pragmatic control group will consist of a small number of uric acid stone formers who will remain on their current medication regimen (citrate salts, allopurinol, diet, etc).

4.3 JUSTIFICATION FOR DOSE

Phentermine 15 mg and topiramate at a dose of 92 mg (Qsymia™) was approved by the FDA in 2012 for use along with reduced dietary caloric intake for the management of obese subjects or overweight subjects with at least one weight related comorbidity[52]. We will be performing a dose titration study of the generic equivalent to assess both weight loss and 24Hr urine pH in our population. This titration is necessary, since we do not know the extent to which these medications will alter urine pH or if urine pH will change over the duration of the study time.

For phentermine generic, the tablet is 37.5 mg and is scored. We will start our dosing at 1/2 generic pill or 18.75 mg daily. At the discretion of Benjamin Canales, MD (PI) At month 3 mark, we will measure total body weight loss. If it is >5%, the participant would remain on 18.75 mg dose throughout the remainder of study. If total body weight loss <5%, we will discuss increasing the dose to a full tablet (37.5 mg) with the participant. He/she would then remain on this dose throughout the remainder of the study.

We will use generic capsules of topiramate at daily dosages: 25 mg, 50 mg, 100 mg, or 150 mg. Based on package insert and manufacturer recommendations, participants will be asked to take one Topiramate 25 mg capsule QHS x 1 week, then two 25 mg capsules (50 mg) QHS x 1 week, then 25 mg topiramate QAM and 50 mg topiramate QHS x 1 week (75 mg), then move to 50 mg topiramate QAM and 50 mg topiramate QHS until Study month 3 (100 mg). At this point, participant will collect a 24-hour urine. If 24-Hr urine pH >6.5, he/she will continue at this dose until Study month 6. However, if 24-Hr urine pH<6.5, he/she will be asked to increase topiramate dose to 50 mg topiramate QAM and 100 mg topiramate QHS x 6 weeks (150 mg). A repeat 24-Hr urine will be collected and participant will remain at that dose for study duration (150 mg is the maximum dose in the trial.)

At the end of month 17, participants will discontinue phentermine and being a 9-day topiramate taper (per package insert recommendations). This is due to the possibility of precipitating a seizure if topiramate is discontinued abruptly. Thus, on days 1-3, participants will take 25 mg topiramate QAM and 50 mg topiramate QHS. During days 4-6, participants will take 25 mg topiramate QAM and 25 mg QHS topiramate. Finally, on days 7-9, participants will take 25 mg topiramate QHS only, and cease topiramate on day 10.

4.4 END OF STUDY DEFINITION

The final point of data capture will be 18 months after enrollment. Study participants will begin a 9 day topiramate drug taper after month 17 and will be asked to provide one final 24 hour urine sample 3 weeks after drug washout in order to capture the effect of weight loss (in the absence of drug) on 24 hour urine parameters.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

We will enroll up to 40 adults (to reach goal of 30) age 18 years – 75 years who:
1) have recurrent pure uric acid nephrolithiasis (UAN) or mixed calcium oxalate (CO)/UAN. Recurrent stone disease is defined as at least two spontaneous kidney stone passages, two previous kidney stone procedures, or one previous stone passage and one previous procedure. Pure UAN is defined as at least one previous stone analysis demonstrating 100% uric acid mineral content. Mixed COUAN will be defined as at least one previous stone analysis with any mix of uric acid ≥80% and ≤20% calcium oxalate. If participant has more than one stone analysis, the most recent will be considered the current stone type.
2) have obesity, defined as BMI > 30 kg/m2.
3) have type 2 diabetes mellitus or pre-diabetes, defined as previously diagnosed by laboratory testing (hemoglobin A1c, fasting plasma glucose, or oral glucose tolerance test) or as demonstrated by use of anti-hyperglycemic medications or insulin.
4) have at least one 24-hour urine study off medications demonstrating urine pH < 5.8 or a study 24-hr urine demonstrating urine pH < 5.8

5.2 EXCLUSION CRITERIA

Based on label warnings, we will exclude patients with:
1) contraindications to topiramate, including: recurrent major depression, current substantial depressive symptoms, uncontrolled depression by PHQ 9 score >= 10, history of suicidal ideation or behavior with intent to act (versus exclude those with depression); current pregnancy or attempting to conceive; pre-existing chronic kidney disease with eGFR < 60 at time of enrollment; active cancer or active treatment for cancer (chemotherapy, radiation); and non-ambulatory.
2) contraindications to phentermine, including: unstable cardiovascular disease defined as decompensated heart failure, unstable angina, atrial fibrillation, uncontrolled blood pressure (>160 systolic), hyperthyroidism; monoamine oxidase inhibitor use; current history of drug or alcohol abuse.

5.3 LIFESTYLE CONSIDERATIONS

The largest lifestyle consideration in this trial is the expectation of weight loss and diet. With the help of the co-investigators, a registered dietitian at our CRC will meet with all participants (treatment and controls) at several pre-determined visits (regularly (see Figure: Baseline and Months 3, 6, and 18) to develop specific dietary and behavioral targets for each individual participant's weight loss program. This comprehensive program will include tailored calorie reduction, increased physical activity, and behavioral changes. Participants will be encouraged to adopt components of "Dietary Approaches to Stop Hypertension" (DASH) diet[59], which can lower blood pressure and calcium stone risk. Other than verbal feedback, no other form of dietary compliance will be assessed during the trial, and lack of compliance with dietary recommendations will not be a reason to withdraw a study subject.

Study Visit and Laboratory Timeline

5.4 SCREEN FAILURES

We plan to use the NIH Tool "Site Screening and Enrollment Log" to record the consent and screening of all subjects and the outcome of each screening. The log will provide a comprehensive list of all subjects who were consented and screened for eligibility, including screen failures. The log will not contain any identifying information.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit participants for this study from three sources.

#1: Any uric acid stone former at the University of Florida who has previously signed "Consent2Share" identified using diagnosis codes through the integrated data repository (IDR).

#2: Uric acid stone formers identified by their kidney stone provider.

#3: Members of the community who contact our research group based on flyers, or e-mails. for the study

Recruitment will begin by accessing **source #1**. Uric acid stone formers at the University of Florida who have previously signed "Consent2Share" will be identified by chart review using diagnosis codes through the integrated data repository (IDR). IDR will provide MRNs for Consent2Share patients who meet inclusion criteria. If the patient appears to meet eligibility criteria [diabetes/prediabetes; obesity BMI >

30 kg/m^2; and either recurrent pure uric acid stones (100%) or mixed uric acid/calcium oxalate stones (≥80%/≤20%)] by chart review, he/she will be placed in random order and will be called by study coordinator to gauge their interest in participating in this study. During that call, study coordinator will review study entry criteria and take every measure to provide an easy exit for patients who are contacted such that, if they are not interested, the conversation ends quickly. If he/she is interested in potentially enrolling in the study, he/she will be directed to the University of Florida REDCap site or mailed a paper consent. Coordinator will review the consent and complete the consent checklist for the **Stage 1 informed consent** for screening. This consent will allow study coordinator to capture all external medical records (if necessary), and to ask patient to hold all alkalinizing urine pH medications (potassium citrate, sodium bicarbonate). They will then receive a letter from our research team containing details of 1) study overview, 2) expectation for their upcoming visit, 3) blank POuND OUT Informed Consent Form, and 4) an invitation for face to face study along with a date and time of their visit. In addition, they will also be mailed a home 24-hour urine kit and will be provided direction on when to collect it, roughly 30 days after stopping alkalinizing urine pH medications.

Concurrently, individuals who present in nephrology or urology clinic (**source #2)** may be identified as meeting study criteria by their clinical provider and will gauge his/her interest in learning more about this particular research study. The clinician will give the patient an IRB approved recruitment flier. If patient is interested in hearing more about the research project, the clinic staff will invite a research staff member to meet and discuss the study with the patient/family during that clinic visit (should the patient desire) or provide the consent to contact form. Any research staff discussing, recruiting, or enrolling/consenting research participants will be listed on the IRB protocol and approved by the IRB.

Study coordinator will then have a face to face visit with the individual to evaluate his/her potential participation. General study inclusion criteria will be reviewed during that visit. Should study coordinator identify that the patient does not meet criteria or should the patient not seem interested in study participation, the conversation ends quickly. If he/she is interested in potentially enrolling in the study, he/she will be directed to the University of Florida REDCap site or consented over the phone after they receive paper consent. The coordinator will review the consent and complete the consent checklist for the **Stage 1 informed consent** for screening. This consent will allow study coordinator to capture all external medical records (if necessary), and to ask patient to hold all alkalinizing urine pH medications (potassium citrate, sodium bicarbonate). They will then receive a letter from our research team containing details of 1) study overview, 2) expectation for their upcoming visit, 3) blank POuND OUT Informed Consent Form, and 4) an invitation for face to face study along with a date and time of their visit. In addition, they will also be mailed a home 24-hour urine kit and will be provided direction on when to collect it, roughly 30 days after stopping alkalinizing urine pH medications.

Finally, members of the community who respond to flyers, etc (**source #3**) will contact study coordinator who will review study criteria and evaluate his/her potential for enrollment. During that call, every measure will be taken to provide an easy exit for patients if they are not appropriate study candidates. Should he/she be potential candidates for study enrollment, he/she will be directed to the University of Florida REDCap site or sent a paper consent. The coordinator will review the consent and

complete the consent checklist for the Stage **1 informed consent** for screening. This consent will allow study coordinator to capture all external medical records (if necessary), and to ask patient to hold all alkalinizing urine pH medications (potassium citrate, sodium bicarbonate). They will then receive a letter from our research team containing details of 1) study overview, 2) expectation for their upcoming visit, 3) blank POuND OUT Informed Consent Form, and 4) an invitation for face to face study along with a date and time of their visit. In addition, they will also be mailed a home 24-hour urine kit and will be provided direction on when to collect it, roughly 30 days after stopping alkalinizing urine pH medications. This process will continue until the target sample of 30 is achieved. We expect we may need 26 individuals (25-30% drop-out) in drug group and 13 in controls to reach target sample of 30.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

All participants in the experimental group (n=20) will receive oral generic tablet phentermine (18.75 or 37.5 mg dose) and topiramate (daily 100 mg or 150 mg dose) after completing initial visit requirements, enrollment, and randomization. Control participants (n=10) will complete initial visit requirements and study enrollment and will be maintained on their current therapy.

With the help of the co-investigators, a registered dietitian at our CRC will meet regularly with all participants (treatment and controls) at the baseline visit and others to develop specific dietary and behavioral targets for each individual participant's weight loss program. This comprehensive program will include tailored calorie reduction, increased physical activity, and behavioral changes. Participants will be encouraged to adopt components of "Dietary Approaches to Stop Hypertension" (DASH) diet, which can lower blood pressure and calcium stone risk[60].

6.1.2 DOSING AND ADMINISTRATION

All participants in the experimental group (n=20) will begin by breaking in half the scored generic tablet form of phentermine hydrochloride (37.5 mg; Teva Pharma, Inc). Participants will be asked to take 1/2 pill PO QD 2 hours after breakfast (or 12 hours prior to expected bedtime) until end of Study month 3. At that time, total body weight loss will then be calculated. At the discretion of Benjamin Canales, MD (PI) If it is >5%, participant will continue at this dose for the remainder of study duration. If total body weight loss is <5%, participants will be asked to increase dose to one 37.5 mg pill daily through study end. In addition, If participant is unable to tolerate phentermine dosage of 18.75 it will be reduced to 8mg (Lomaira).

Concomitantly, participants will be asked to take one Topiramate 25 mg capsule QHS x 1 week, then two 25 mg capsules (50 mg) QHS x 1 week, then 25 mg topiramate QAM and 50 mg topiramate QHS x 1 week, then move to 50 mg topiramate QAM and 50 mg topiramate QHS until Study month 3. At this

point, participant will collect a 24-hour urine. At the discretion of Benjamin Canales, MD (PI), If 24-Hr urine pH >6.5, he/she will continue at this dose until Study month 6. However, if 24-Hr urine pH<6.5, he/she will be asked to increase topiramate dose to 50 mg topiramate QAM and 100 mg topiramate QHS x 6 weeks. A repeat 24-Hr urine will be collected and participant will remain at that dose for study duration (150 mg is the maximum dose in the trial.)

Although participants with pre-existing chronic kidney disease (eGFR < 60 or creatinine clearance less than 50 mL/min) will not be enrolled in this study, it is possible that a participant may develop kidney disease over the course of the study. Should this occur, the doses of both medications will be lowered and dispensed as 18.75 mg phentermine and 50 mg topiramate for the remainder of the study (total 18 months) or until renal impairment improves. As recommended by manufacturer, all participants at the end of study month 17 will discontinue topiramate gradually by taking a 75 mg dose x 3 days, a 50 mg dose x 3 days, and a 25 mg dose x 3 days, then complete drug cessation. This is due to the possibility of precipitating a seizure.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The two drug study agents will be shipped to the principal investigator directly from the manufacturer and will be acquired by the participants through the UF Health/Shands Clinical Research Center pharmacy.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Both these generic medications are commercially available for human use in the form, route, and dose planned in this trial. The formulations used for this trial will appear as the following:
Phentermine hydrochloride tablets (37.5 mg, Teva Pharma) is equivalent to the 30 mg phentermine base. This scored white capsule shaped tablet is imprinted with letter "b" on one side, " E 7" on the other. Phentermine is packaged in bottles of #100.
Topiramate 25 mg is a coated, off-white, round tablet with “OMN” and "25" on opposing sides.
Topiramate 50 mg is a coated, yellow, round tablet with “OMN” and "50" on opposing sides.

Participants will be dispensed tablets and capsules in a unit of use bottle #60.

6.2.3 PRODUCT STORAGE AND STABILITY

Bottles should be stored at room temperature. Container should be closed tightly and protected from moisture.
Stability studies have been carried out on production-scale batches of phentermine/topiramate. The parameters tested during stabilities studies were: assay, appearance, related substances and moisture. Long term studies for up to 5 years at 25°C /60% RH and accelerated studies for up to 6 months at 40 C/75% RH showed that no significant degradation could be observed and all the results

remained within the specification. Stress stability studies under heat, acid, basic, light and oxidative conditions were performed. Minimal degradation was observed under light and oxidative conditions.

6.2.4 PREPARATION

Phentermine and topiramate will be delivered in two separate medication forms. All the excipients used in both phentermine and topiramate tablets are compendial excipients and made with pharmaceutical grade raw materials.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

In an effort to reduce selection bias, we will block randomize up to 40 participants in a 2:1 ratio (treatment: control respectively) with a block size of 6, resulting in approximately 20 in treatment (phentermine/topiramate) group and 10 controls. While we lack sufficient information for a formal power analysis, this data will prove instrumental to obtain a power analysis for further larger scale study.

We are primarily interested in estimates of outcome variability and covariability that will aid in the proper planning of a larger, sufficiently powered and planned efficacy trial. Our total sample size, allowing for a 20% attrition rate by 18 months, would give us reliable estimates of recurrence rates as well as the variability in change in stone size (Aim 1) and other continuous measures (Aim 2). We also want to establish preliminary evidence of efficacy; thus a power analysis was performed on the change from baseline in kidney stone size as the primary outcome. Based our center's data, approximately 30% of UA stone formers had CT-documented stone recurrence at 18 months. We found that every 0.2 increase in urine pH was associated with a 15% decrease in stone size compared to those whose urine pH did not change. Based on our best estimates, we expect to see a 0.6 increase in urine pH on phentermine/topiramate (45% decrease in stone recurrence size) and a 0.2 urine pH increase in our control group (15% decrease in stone recurrence size). Using this 30% difference in stone recurrence size and with an assumed 20% attrition rate, we would have >90% power (two-sided α=0.05) to detect a 4 mm difference in stone growth relative to controls. This size difference would be considered clinically significant.

6.4 STUDY INTERVENTION COMPLIANCE

At each study visit, participants randomized to study drugs will be asked about study drug compliance. Additionally, pharmacy records will be reviewed and documented by the study nurse coordinator to ensure appropriate drug quantity is being dispensed.

Study control participants in the pragmatic arm will be asked during dietary counseling and routine physician visits regarding his/her compliance with standard dietary and/or medication regimen (citrate salts, allopurinol, diet, etc.). No attempts will be made to confirm this by pharmacy records, as this is not a controlled factor in the study.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants are free to withdraw from participation in the study at any time upon request. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator will make all reasonable efforts to ascertain the reason(s), while fully respecting the participant's rights.

An investigator may terminate participation in the study if:
1) Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
2) The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator will make all reasonable efforts to ascertain the reason(s), while fully respecting the participant's rights.

7.3 LOST TO FOLLOW-UP

We will consider any participant "lost to follow-up" should, without properly informing the investigator associated with the clinical trial, they not be contactable. This includes participants who have opted to withdraw from the clinical trial, moved away from the particular study site during the clinical trial, or become ill and unable to communicate or are deceased. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator will make all reasonable efforts to ascertain the reason(s), while fully respecting the participant's rights.

Data gained from these participants through the date of their loss to follow-up will not be excluded from final analysis. However, total study power will be affected.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Assessments for urine pH efficacy will be made as per study assessment flow chart and evaluated in real time by the PI per our dose titration protocol. Ultimate and final assessment of efficacy, however, will not be made until study completion when final CT imaging is performed to ascertain stone formation or growth, our primary outcome. Furthermore, final efficacy to affect 24-hour urine stone parameters will be made when the final 24-hour urine is collected at 18 months. Beyond stone formation/growth and 24-hour urine parameters, assessment of efficacy on weight loss will be noted with each study visit (participant is weighed) but final assessment will not be made until 18-month follow-up is complete. Specific study procedures will be defined in our Manual of Procedure (MOP).

8.2 SAFETY AND OTHER ASSESSMENTS

Mental Health: Antiepileptic drugs, including topiramate, carry a label precaution that they may increase the risk of suicidal thoughts or behavior. Across all randomized controlled trials of this drug including those open to patients with controlled depression at baseline, incidence of suicidality or suicidal behaviors were not increased versus placebo. However, each of the potential risks will be reviewed in detail with the patients, and they will be questioned at each study visit as to suicidal thoughts or behaviors. Increases in participant PHQ-9 score to > 10 along with 50% increase from the pretreatment score will be identified by study nurse coordinator as a sign of clinically significant worsening of depression. The patient's primary care physician will be contacted, and we will discuss psychiatric intervention along with discontinuation of study drug.
Specifically, for PHQ-9 Section 1, question on line i: “Over the last two weeks, how often have you been bothered by…Thoughts that you would be better off dead or of hurting yourself in some way”
Should participant have any positive response (several days, more than half the days, nearly every day) to this question, study coordinator will refer the individual to the Crisis Hot Line and offer to call and connect the individual with the Crisis Hot Line on his/her behalf. Study PI will also be contacted and will document the referral.

Hypocitraturia and/or calcium phosphate stones: Because CAI cause urinary alkalinization through persistent bicarbonuria, its long-term use can raise urine pH and cause mild metabolic acidosis. The renal response to acidosis is to retain the urinary macromolecule citrate. Because citrate is urinary macromolecule that naturally inhibits crystal aggregation and stone growth, low urinary citrate levels (hypocitraturia) and/or the development of alkaline-based stones (calcium phosphate) are possible. In long term trials, Qsymia® (15/92 mg) decreased serum bicarbonate levels by 1.0 – 1.7 mEq/L in one year cohort trials (EQUIP[51], n=498; CONQUER[52], n=981) but increased serum bicarbonate by 0.2 mEq/L in the two-year cohort trial (SEQUEL[53], n=295). Urinary citrate levels have not previously been reported for Qsymia®. Although calcium phosphate (alkaline) kidney stones have been reported with topiramate use[49], kidney stones were not reported as an adverse event in any Qsymia® trial to date. Far more common in the medical literature is prescription of topiramate for prevention of headache or seizure –

both of which are FDA-approved indications. When this literature is reviewed, some associations with topiramate-induced acid-base side effects such as metabolic acidosis, hypokalemia, and stone disease, have all been noted. The best systematic review article was published in 2014 by Dell'Orto et al[49]. Their group reviewed 47 reports published between 1996 and 2013 (5 case–control studies, 6 longitudinal studies) that addressed these potential topiramate side effects. At doses of topiramate in 200-600 mg range (far higher than the range of our proposal), they noted a significant tendency towards the development of mild-to-moderate hyperchloremic metabolic acidosis (serum bicarbonate ≤21.0 mmol) in ~30% of cases and mild hypokalaemia (serum potassium ≤3.5 mmol) in ~10% of cases. They also report that patients on topiramate who developed kidney stones tended to have significantly lower urinary citrate levels (hypocitraturia, recognized promoter of renal stone formation) when on the drug. None of the patients included in these reports had uric acid stones – instead, they all developed calcium-based alkaline-stones as a result of excessive bicarbonuria effect of topiramate[61-65].

Two of the better studies in this area were done prospectively, collecting 24-hour urines before and after starting the topiramate in neurology patients with chronic headaches[12,13]. Welch et al performed a short-term (3 month) longitudinal study in 7 neurology patients who were about to start topiramate (6F, 1 M; mean age 44+/-15 yrs, 2 previously had kidney stones; all had normal renal function, Table)[12]. At mean dose of 107 +/- 45 mg/day (range 50 - 200 mg), they found a urine pH increase 6.18 to 6.76 (only one individual had pH <6 prior to starting therapy). All individuals ended up with urine pH ≥6.5 with a decrease in urinary citrate from mean 819 to 378 mg/day[12]. Jhagroo et al found a similar (0.4) increase in urine pH 60 days after starting topiramate in 7 non-kidney stone formers with chronic headache[13]. Urinary citrate was also noted to decrease from mean 526 to 218 mg/day.

In total, the CAI-effect of topiramate is expected to cause bicarbonuria, raise urine pH, and may temporarily lower serum bicarbonate levels. In obese diabetics, topiramate combined with phentermine has been shown to cause between +0.2-1.7 changes in serum bicarbonate levels, out to 2 years. Urinary citrate levels were not monitored in these major prospective trials but are expected to decline. For this reason, we have proposed serial monitoring of urinary citrate over the entire course of the study. Dieticians will consistently discuss methods for participants to increase dietary forms of citrate, including fruits, vegetables, and fruit juices (lemonade, orange juice, etc) in order to obviate this potential side effect[55,56]. In our population, we feel that changes in urine pH will affect uric acid mineral supersaturations much more significantly than any mild decrease in urinary citrate level.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

We define adverse event as untoward medical occurrence associated with the use of an intervention, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or

substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

We will assess severity of events by the following method of grading:
1) Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2) Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3) Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The examining clinician will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:
1) Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
2) Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3) Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or"definitely related," as appropriate.
4) Unlikely to be related – A clinical event, including an abnormal laboratory test result, whosetemporal relationship to drug administration makes a causal relationship improbable (e.g., theevent did not occur

within a reasonable time after administration of the trial medication) and inwhich other drugs or chemicals or underlying disease provides plausible explanations (e.g., theparticipant's clinical condition, other concomitant treatments).
5) Not Related – The AE is completely independent of study drug administration, and/or evidenceexists that the event is definitely related to another etiology. There must be an alternative,definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Dr. Benjamin Canales will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.
The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The Principal Investigator, Dr. Benjamin K. Canales, will be responsible for subject safety and well-being as well as adverse event monitoring and reporting procedures during the conduct of the study. Due to potential side effects, our study team has created a DSMB composed of three members of medical disciplines necessary to interpret the data from the clinical trial and to fully evaluate participant safety. We have created a **3-member DSMB panel** that will meet quarterly once all patients have been enrolled along with one "pre-study" meeting. Our panel will be composed of experts in endocrinology, obesity clinical trials, and nephrology/stone disease, to include:

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Diana Barb, MD
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Initial DSMB meeting will occur just prior to study initiation. At this meeting, the DSMB will discuss the protocol and analytic plan, model informed consent form, data collection instruments, other important trial documents, and present any suggestions for modifications to the sponsor and/or steering committee. At this meeting, we will discuss regulatory considerations and complete plans for monitoring the safety and effectiveness data, including: meeting schedule; format for submission of interim reports; timing of the DSMB report delivery; definition of DSMB "quorum"; and handling of meeting minutes/other aspects.

Based on expected rate of accrual over a 6 month period and low expected event occurrence rate, we will most likely schedule quarterly meetings once all participants have been randomized. Should a concern about emerging safety problem arise, the frequency will be increased or an "emergency" meeting called. Each quarterly meeting, most likely by Zoom as a closed meeting, is expected to last no more than one hour to discuss study concern. Documents describing the organization, responsibilities, and operation of this monitoring entity will be provided to the IRB and the CRC Research Subject Advocate. The results of these reviews will be distributed to the CRC Research Subject Advocate through the IRB. Components of the study to be monitored for safety purposes will be 1) study accrual rate, 2)

compliance with eligibility criteria, 3) participant adherence with assigned intervention or control, 4) study adherence with the approved protocol/investigative plan, 5) adverse events and other problems or trends that may indicate a safety concern for participants, and 6) an interim analysis to determine if the study will be able to answer the study hypotheses or meet study aims.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report forms (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:
1) All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the NIDDK, UF IRB, and sponsor within 24 hours of site awareness.
2) Other SAEs regardless of relationship, will be submitted to the DCC/study sponsor within 72 hours of site awareness.
All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the NIDDK or UF IRB and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the Principal Investigator will follow the reporting requirements for serious and unexpected adverse events outlined in the UF IRB Adverse Event Policy. All unanticipated, serious, fatal and/or life-threatening adverse events will be reported to the UF IRB, CRC Program Director and Research Subject Advocate, and the sponsor within 24 hours of occurrence or recognition. Aggregate reports of adverse events will be prepared and reported on a quarterly basis to the DSMB and forwarded to the IRB and CRC at annual review.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

We will report serious adverse events to participants if requested by UF IRB, DSMB, or study sponsor or if the PI feels participants may be impacted by the adverse event in a similar manner.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Topiramate can cause fetal harm, specifically increased risk of oral cleft defects during first trimester of pregnancy. Therefore, all females of reproductive age will be required to have a negative pregnancy test before starting topiramate and will be required to use effective contraception (barrier) during

topiramate therapy. Additionally, the study participant will be counseled of the potential risk to the fetus should she become pregnant. We will exclude any woman who is currently pregnant, attempting to conceive, or becomes pregnant at any time during the study. Should a study participant become pregnant while taking topiramate, we will discontinue treatment immediately, and the patient will be once again apprised of the potential hazard to the fetus.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

We will consider unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:
1) Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2) Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The PI will record all unanticipated problems with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. These problems will be followed for outcome information until resolution or stabilization

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

We will report unanticipated problems to participants if requested by UF IRB or study sponsor or if the PI feels participants may be impacted by the problem in a similar manner.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

The objective for Aim 1 is two-fold: to investigate the 18 month phentermine/topiramate effects on 1) uric acid/mixed uric acid kidney stone growth compared to baseline and 2) uric acid/mixed uric acid kidney stone size change from baseline with respect to controls. We will use CT scan parameters to evaluate for stone growth, which will increase study precision. We will conduct both parametric and nonparametric test. To compare kidney stone growth between baseline and 18 month within phentermine/topiramate group, we would use paired samples t-test and Wilcoxon signed rank sum test. To compare the kidney stone size at 18 month change from baseline between drug and control group, we will fit an ANCOVA model with the baseline kidney stone size included as an independent variable (ANCOVA is more efficient than ANOVA). Alternatively, we will also conduct non-parametric test by using permutation test.

- Secondary Efficacy Endpoint(s):

Outcomes for Aim 2 are change in key 24-hour urine parameters (urine pH, urinary citrate, urinary calcium), serum diabetic labs (as calculated by hemoglobin A1c), fat/lean muscle/bone by body composition DEXA, weight (total % body weight loss), and urinary markers of oxidative stress (urinary 8-isoprostane, urinary hydrogen peroxide) over the 18 months of follow-up time. We will use a mixed effects model to take into account the correlation among observations within each subject. In this pilot study with small sample size, within group comparison would adopt ANCOVA model and evaluate the treatment effects at each fixed time point for those repeatedly measured outcomes and include the baseline of the dependent variable and other factors such as BMI and age in the model. To compare secondary efficacy end points between groups, pairwise comparisons will be made using contrast statements within the framework of ANOVA with treatment group as a factor.

9.2 SAMPLE SIZE DETERMINATION

Sample size considerations are driven by published guidance regarding pilot study planning. We are primarily interested in estimates of outcome variability and covariability that will aid in the proper planning of a larger, sufficiently powered and planned efficacy trial. Our total sample size, allowing for a 20% attrition rate by 18 months, would give us reliable estimates of recurrence rates as well as the variability in change in stone size (Aim 1) and other continuous measures (Aim 2). We also want to establish preliminary evidence of efficacy; thus a power analysis was performed on the change from baseline in kidney stone size as the primary outcome. Based our center's data, approximately 30% of UA stone formers had CT-documented stone recurrence at 18 months. We found that every 0.2 increase in urine pH was associated with a 15% decrease in stone size compared to those whose urine pH did not change. Based on our best estimates, we expect to see a 0.6 increase in urine pH on

phentermine/topiramate (45% decrease in stone recurrence size) and a 0.2 urine pH increase in our control group (15% decrease in stone recurrence size). Using this 30% difference in stone recurrence size and with an assumed 20% attrition rate, we would have >90% power (two-sided α=0.05) to detect a 4 mm difference in stone growth relative to controls. This size difference would be considered clinically significant.

9.3 POPULATIONS FOR ANALYSES

We will be recruiting thirty adults age 18 years – 75 years who have recurrent uric acid or mixed uric acid kidney stones, have diabetes mellitus, are obese, and have a 24 hour urine demonstrating "acidic" urine pH < 5.8 within the last year. We will be recruiting in the southeast United States from a single academic center (University of Florida) and the surrounding areas. Taking advantage of north Florida's large patient population including two large medical centers that are unrelated to University of Florida, we plan IRB approval of advertisements, flyers, information sheets, notices, internet postings and social media to recruit subjects should we not be able to recruit enough through our existing UF Health/Shands Nephrology and Urology Stone database.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This is a limited feasibility study using a small control group to compare outcomes. Therefore, the statistical approach is relatively straightforward.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

We will conduct both parametric and nonparametric tests. To compare kidney stone growth between baseline and 18 month within treatment group, we would use paired samples t-test and Wilcoxon signed rank sum test. To compare the kidney stone size at 18 month change from baseline between treatment and control group, we will fit an ANCOVA model with the baseline kidney stone size included as an independent variable (ANCOVA is more efficient than ANOVA). Alternatively, we will also conduct non-parametric test by using permutation test.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will use a mixed effects model to take into account the correlation among observations within each subject. In this pilot study with small sample size, within group comparison would adopt ANCOVA model and evaluate the treatment effects at each fixed time point for those repeatedly measured outcomes and include the baseline of the dependent variable and other factors such as BMI and age in the model. To compare secondary efficacy end points between groups, pairwise comparisons will be made using contrast statements within the framework of ANOVA with treatment group as a factor.

9.4.4 SAFETY ANALYSES

As the study is single site and involves an FDA-approved drug administered to non-high risk individuals, a local Data and Safety Monitoring plan will created through UF CTSI. A local Safety Officer (Dr Diana Barb) will serve in a safety advisory capacity to monitor participant safety, evaluate the progress of the study, review procedures for maintaining the confidentiality, quality, management, and analysis of the data and data collection. Due to the small number of participants, no additional safety analysis of data is required unless specified by UF IRB or the requesting agency.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The study groups will be compared at baseline for important demographic and clinical characteristics (including outcome variable) to assess similarities. Continuous variables will be summarized for each group by the mean and standard deviation. For an asymmetrical data, the median and a centile range (such as the 25th and 75th centiles) will be given. Simple paired t-test will be used to compare means of two related observations (i.e., before-after per subject) while independent sample t-test will be used to compare means of two independent groups. Correlation statistics will be used to measure linear association between two continuous variables while simple linear regression will be used to observe the linear relationship between our predictors and outcome variable.

9.4.6 PLANNED INTERIM ANALYSES

As this is a feasibility study, there are no planned interim analyses.

9.4.7 SUB-GROUP ANALYSES

Due to the small number of recruits, there will be no sub-group analyses performed.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be collected and compared by use of paired t-test or mixed effects model to take into account the correlation among observations within each subject.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Our study requires enrollment of individuals with acidic urine (pH <5.8) while NOT on medication. Thus, in order to determine the urine pH of all our participants' urine, we felt that two separate informed consents were appropriate – one consent for screening and another consent for randomization/study participation.

#1) Our Screening Informed Consent will be performed during the initial phone call visit. Study coordinator will "walk" the participant through the online "REDCap" website consenting process or the paper consent sent to their home. The consent process will be documented on the consent checklist. The consent allows our investigative team to freely ask participants about their medical and kidney stone history, to perform the mental health status questionnaire (PHQ-9), and to determine if participant has contra-indications to drugs phentermine and topiramate. If patient appears to be a candidate for enrollment in randomization/study participation AND in order to provide potential participants ample time to review the informed consent and discuss with family or other support persons, we will mail a copy of the Participation Informed Consent and an information packet to the potential participant prior to their study date. The next face to face visit will also be scheduled. Meanwhile, participant will be asked to hold any urinary alkalinizing medications (potassium citrate, sodium bicarbonate) for a 30 day washout period. After this washout, each participant will collect a 24-hour urine to assess urine pH at baseline, off all medications.

#2) Our Participation Informed Consent will be done at the first face to face study visit after participant complete baseline 24-hour urine. Within the Clinical Research Center located on first floor of CTSI building, study personnel will review informed **Participation Informed Consent** form in great deal to the potential participant in a private setting but in the presence of any family or relatives they desire to have in the room. They will be given as much time as needed to ask questions and have those questions answered.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The study participant will receive a copy of their signed consent form to keep for their records. We will also provide them with a paper outlining information about the dosing and potential side effects of the study drug (if they are randomized to drug). Even though this information will be in the consent form, we want to be sure the participants have this information again clearly stated.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

We plan to use the NIH Tool "Site Screening and Enrollment Log" to record the consent and screening of all subjects and the outcome of each screening. The log will provide a comprehensive list of all subjects who were consented and screened for eligibility, including screen failures. The log will not contain any identifying information.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Upon study completion, the participant will be given an outgoing letter of appreciation for their participation.

10.1.3 CONFIDENTIALITY AND PRIVACY

All informed consents will be taken at the UF CTSI Clinical Research Center in a private room. Family and relatives will be allowed to be present during the process if so desired by the potential participant. The participant will be allowed to ask question and have their questions answered. Once informed consent is complete, the paper copy of the informed consent will be stored in a secure location in a locked office in a locked cabinet accessible only by the PI and the study coordinator.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

We currently have no plans to collect or store specimens for future research use.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

PI: Benjamin K. Canales MD	Study Trial Nurse: John Marks
Co-I: Muna T. Canales, MD	Diana Barb, MD (DSMB Member)
Co-I: Michelle Cardel, PhD, RD	David S. Goldfarb, MD (DSMB Member)
Co-I: W. Troy Donahoo, MD	Megan A. McVay, PhD (DSMB Member)
Co-I: Xiang Yang, PhD	Dietician: Jean Michelson

10.1.6 SAFETY OVERSIGHT

As there is more than minimal risk to the participants, a DSMB will be appointed by the study PI to oversee a clinical research project and patient safety. At each monitoring interval, DSMB will notify NIDDK Program Official that they reviewed the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence, and study participant safety issues. This review will focus on AEs and reasons for losses to follow up, raising any concerns or issues with the NIDDK and the PI, and recommending to the NIDDK and PI the continuation, modification or conclusion of the trial, while protecting the confidentiality of the trial data and the results of monitoring.

10.1.7 CLINICAL MONITORING

This proposal involves up to 40 recurrent uric acid stone formers randomized to either weight loss drugs plus diet counseling OR to a pragmatic group receiving dietary counseling alone. They will be asked to collect 6 different 24-hour urine specimens over the 18 months of the study duration (Baseline, 3-month, 6 month, 12 month, 17 month, 18 month), and these will be reviewed "real time" by the PI and study nurse coordinator. We expect the bicarbonaturia effect of topiramate and the increase in dietary citrate to counter any potential citrate side effect of the drug. Should hypocitraturia persist despite dietary intervention, patients will be asked to supplement with 400 ml of low-calorie Crystal Light or lemonade 2-3x daily, which has been shown to normalize urinary citrate levels. In addition to

monitoring of metabolic urinary values, a 3-month basic metabolic serum chemistry panel will be performed to rule out metabolic acidosis or electrolyte abnormalities.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Dr. Benjamin K. Canales will be responsible for QA/QC of the study. QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

Our team will use University of Florida CTSI electronic data capture software called REDCap (Research Electronic Data Capture). This secure, Web-based application will be used to support data capture for all elements of this research proposal. The PI and his team are familiar with REDCap's streamlined process and have a number of previously developed databases within this system. In addition to ease of use, REDCap features include automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, on-line consenting modules, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.
For initial record keeping, patient name and medical record number will serve as the identifier until all data has been collected, cleaned, and verified (36 months). At that point, participants will be assigned a unique subject ID code and all PHI will be eliminated from the database. Only the PI, study co-investigators, and study nurse coordinator will have access to subject identities.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Ms. Guanhong Miao is a data management analyst and graduate student in the Department of Health Outcomes and Biomedical Informatics at the University of Florida. Ms. Miao has a BS in Statistics and is completing her doctorate in Epidemiology. Under the direction of Drs. XiangYang Lou and Canales along with input from the entire study team, Ms. Miao will develop the online data collection forms through REDCap. The data entry forms will be designed with as few open-ended text fields, and as many user-friendly drop-down answer boxes or check boxes as possible with little opportunity for responses to be provided with implausible values. The entry forms will be developed with built-in range checks and automatically-calculated fields to reduce the possibilities of data entry errors. The database will be pilot-tested after development, with feedback from the study team on ease of use. During participant enrollment, Ms. Miao will regularly check for data inconsistencies, omissions, and errors, confirming with the study team when outliers and unusual values are observed. Ms. Miao will randomly select 5% of data on a quarterly basis to be checked for data entry quality. Discrepancies will trigger review of data

collection and entry procedures as appropriate. Upon completion of the study, Ms. Miao will create analysis data sets from the REDCap database to be used for statistical analysis for each aim of the study. She will also generate analysis reports and work with Dr. Lou on the final data analysis. She will also communicate results to the study team and will contribute to the manuscripts that arise from the study. Dr. Lou and Ms. Miao will attend all study meetings to ensure constant communication about data issues that may arise throughout the study.

Laboratory data (serum chemistries, urine) and imaging will be reviewed real time. Any alert lab values or abnormal imaging findings will be reviewed by study PI and managed appropriately. For values felt to require emergent attention, the participant will be immediately notified and asked to go to the emergency room. For values felt to be more elective in nature, results will be mailed to both participant and his/her primary care physician.

10.1.9.2 STUDY RECORDS RETENTION

Per NIH policy, research records will be retained for a minimal of 3 years after the research is completed and the study closed with the IRB, approximately 6 total years.

10.1.10 PROTOCOL DEVIATIONS

Protocol deviations will first be classified as due to subject, the sponsor, or the investigational team. Minor divergence of a study from the approved protocol will be classified as a deviation while one that which affects the quality of data or impacts subjects' safety will be classified as a protocol violation. Examples of protocol deviations/violations may include, but are not limited to, the following:

- Randomization of an ineligible participant
- Failure to obtain Informed Consent
- Enrollment of a participant into another study
- Failure to keep IRB approval up to date
- Wrong treatment administered to participant

Site study coordinator will maintain a log of all protocol deviations using the NIH template "Protocol Deviation Log" form. All deviations, when discovered, will immediately be reported to site PI Dr. Benjamin K. Canales, where it will be classified as deviation or violation. Protocol violations that impact participant safety will be reported to the IRB within 24 hours of occurrence, if possible, or as soon as they are discovered. All other deviations will be reported routinely to IRB and the independent data safety monitoring body. We will follow all local UF IRB requirements for reporting protocol deviations to the Board.

10.1.11 PUBLICATION AND DATA SHARING POLICY

As NIH resources will be used for the development of these research findings, we plant to make them readily available for research purposes to qualified individuals within the scientific community.
We are committed to resource sharing the data generated by this project using several mechanisms:

1) Clinical trials information will be entered into the clinicaltrials.gov database. Relevant design information will also be provided as a file on our local research server as this information will be needed to interpret and analyze any data.
2) Any raw data deemed to be useful to the research community will also be provided on appropriate websites, according to UF and institutional guidelines and consistent with the archiving goals of this program.

10.1.12 CONFLICT OF INTEREST POLICY

Based on NIH requirements, we will disclose all potential conflicts for all study investigators in order to be free from investigator bias. We will define "investigator" as the PD/PI or any other person, regardless of title or position, who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding which may include, for example, collaborators or consultants. We will respect UF Institutional policies that require up-to-date, written disclosure of all financial conflicts of interest to comply with federal regulations. These policies are available via a publicly accessible Web site.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report

GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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