Formulation of CoQ10

Co Q10 (400mg max strength, 200 capsules) High absorption vegan Coenzyme Q10 powder- Ubiquinone supplement pills, Extra antioxidant Co Q10 enzyme vitamin Capsules

Other ingredient Vegetable cellulose (capsule), Dextrin, Rice flour

Commercial labels of drug products:

- **CoQ10 - CoQ10 (400mg Max Strength, 200 Capsules) - High Absorption Vegan Coenzyme Q10 Powder - Ubiquinone Supplement Pills, Extra Antioxidant CO Q-10 Enzyme Vitamin Capsules**

formulation glutathione

L- Glutathione- Reduced Glutathione 500 mg per serving supplement -200 capsules- L-Glutathione Antioxidant capsules

L- Glutathione (Reduced form) 500 mg

Other ingredient Vegetable cellulose (capsule), Dextrin, Rice flour

Commercial labels of drug products:

- **CoQ10 - CoQ10 (400mg Max Strength, 200 Capsules) - High Absorption Vegan Coenzyme Q10 Powder - Ubiquinone Supplement Pills, Extra Antioxidant CO Q-10 Enzyme Vitamin Capsules**

16.3 CELLULOSE

Stock code 0567

Starting material Cellulose pulp obtained from wood. A number of tree varieties are utilized in the production of high purity cellulose pulp used for manufacturing microcrystalline cellulose for the pharmaceutical and nutraceutical industries. The timber resources used to make wood pulp are referred to as pulpwood. Wood pulp comes from softwood trees such as spruce, pine, fir, larch and hemlock, and hardwoods such as eucalyptus, aspen and birch. Some pulping processes use the entire tree, while others use parts of the tree that cannot be used to make lumber. The trees are harvested in accordance with best practices, chipped, aged, and processed to make high-purity alpha-cellulose pulp. The manufacture selects the appropriate pulp for the production of microcrystalline cellulose. The pulp goes through several processing steps to make the finished product. As such, the finished product, microcrystalline cellulose, is a highly refined and purified cellulose product, meeting pharmaceutical standards.

BSE -TSE Based on the ingredients, the product is in compliance with the note for the guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

GMO not genetically modified.

Allergen Please note that there may be several steps before the raw material is produced and access to data on manufacturing raw materials is not easily obtained for the starting materials and intermediates used in the production process. The following items are not used in the manufacturing process of the product, and although manufacturer does not specifically assay for the presence of the items below, it is unlikely that any traces of these items are present in the starting materials or in the final product. The product is unlikely to contain the following - Cereals containing gluten and products thereof Corn and products thereof. Celery and products thereof Soybeans and products thereof Yeast Fish and crustacean shellfish and products thereof Eggs and products thereof Dairy Products (Milk, Lactose, Caseinates, Whey) Peanuts and products thereof Tree nuts (oils) or derivatives Mustard and products thereof Sesame Oil Preservative Sulfites >10ppm Artificial Colours and Flavours Beef, Chicken, Pork derivatives Additives Latex This statement is provided for informational purposes only, as instructed to Medisca by the manufacturer, and is not meant to be a guarantee of absence of the above stated allergens.

TITLE PAGE
(version13) 2/12/2024

Protocol Title

Prevent Cardiac Surgery Associated AKI trial
Prevent CSA-AKI trial

Efficacy of Mitochondrial directed therapy in prevention of cardiac surgery associated AKI

TABLE OF CONTENTS

Efficacy of Mitochondrial directed therapy in prevention of cardiac surgery associated AKI
Prevent Cardiac Surgery Associated AKI trial (Prevent CSA-AKI trial)

1 Brief summary of the study

Prevent CSA-AKI trial is a double blinded randomized controlled trial, 242 patients undergoing elective cardiopulmonary bypass surgery (CPB)will either receive a placebo or daily 1200 mg of Co enzyme Q10 (CoQ10) and 1000 mg of Glutathione (GSH), the first dose will be given the day before surgery and continues while admitted up to 1 week. Blood and urine samples will be collected. Adverse events related to the study drugs will be collected.

1.1 Hypothesis

We hypothesize that Co Q10 and GSH will confer protection and enhancement of kidney recovery in renal ischemia-reperfusion injury (RIRI) to patients undergoing CBP surgery.

1.2 Primary Objective

Determine the safety, tolerability and efficacy of Co Q10 and GSH in lowering the incidence, severity and progression of acute kidney injury (AKI) in patients undergoing CBP surgery. In a prospective randomized trial, patients undergoing elective cardiac surgery will be studied.

We will also asses the changes in the levels of plasma Co Q10 and Glutathione, plasma and urinary mitochondrial DNA (mtDNA) before and after CPB surgery.

In an exploratory aim, we will evaluate for Renal replacement therapy free days, Mechanical ventilator-free days, Shock-free days and death in the ICU at 28 days or during hospitalization. Additionally, kidney function, dependence on renal-replacement therapy, length of hospitalization, and readmission are evaluated at 90 days. (Definitions page5)

1.3 Describe how the research results/finding will be used and will contribute to generalizable knowledge (publishing, establishing national standards).

Despite the accumulating evidence on the relevance of mitochondrial dysfunction in AKI initiation and progression and the crucial role mitochondrial therapies such as Co Q10 & GSH play in renal protection and recovery, human data in this field are very limited. This study will the first to examine the safety and efficacy of Co Q10 and GSH

2 How will the data be analyzed?

2.1 Sample Size

Incidence of AKI after cardiac surgery requiring cardiopulmonary bypass is up to 30% (2). This trial aims to show the superiority of the intervention outlined in this proposal in reducing AKI post cardiopulmonary bypass. In absence of previous data, it is hypothesized that the intervention will reduce the incidence of AKI (primary endpoint in this study) to 15%. Group sample sizes of 121 in Group 1 (treatment) and 121 in Group 2 (reference) achieve 80.2% power to detect a difference of 15% between the group proportions. The Group 2 proportion is 30%. The Group 1 proportion is assumed to be 30% under the null hypothesis of no difference and 15% under the alternative hypothesis. The primary endpoint will be analyzed using a two-sided Chi-square test, assuming a 5% level of significance (α). Sample size calculation was performed using PASS V.15 Power Analysis and Sample Size Software (NCSS, Kaysville, Utah, USA).

2.2 Analysis Plan

The primary efficacy analysis (hypothesis: outcome in intervention group will be superior to the reference group) will be performed on the study population on an intent-to-treat basis, i.e., all randomized patients with outcome data will be analyzed according to their allocation groups. Selected demographic and clinical characteristics of the study population will be presented using descriptive statistics. Values will be displayed as frequency (percentage), mean (standard deviation) and median (inter-quartile range) as appropriate. The treatment groups will be compared using the Chi-square test or Fisher's exact test (when 20% or more expected cell counts less than 5), for categorical variables and the Student's t-test or its non-parametric equivalent, Mann-Whitney U-test (when the data in non-normally distributed), for continuous variables. 95% Confidence Interval estimates will be generated for all parameters. Potential confounders will be examined using logistic regression models. Exploratory analysis for secondary endpoints will be performed using descriptive and inferential statistics, with correction for multiple testing as and if necessary. A two-sided p-value less than 0.05 will be considered statistically significant. All analyses will be done in SAS version 9.4 (SAS Institute Inc., Cary NC).

3. Describe how long the entire study is expected to last including the data analysis

The total anticipated study duration is approximately 3 years, with anticipated enrolment

and study conduct duration of 24 months. The remaining 12 months will be needed for data analysis.

4 Selection of trial population

4.1 Inclusion criteria

Adult 18-70 years of age, undergoing elective CPB surgery with baseline GFR equal or more than 45 ml/min

4.2 For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse and donating eggs) or use contraceptive measures as defined below

- Women must remain abstinent or use contraceptive methods with a failure rate of less than 1% per year during the treatment period. Women must refrain from breastfeeding and donating eggs during this same period of time.
- Examples of contraceptive methods with a failure rate of less than 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

4.3 Exclusion criteria

GFR <45 ml/min

Solitary kidney

Status post-kidney transplant

Pregnancy

History of allergy to Co Q10

History of allergy to Glutathione

History of allergy to cellulose

4.3 How and from whom information regarding inclusion criteria will be obtained

Study coordinators and physicians will identify patients admitted to the George Washington University Hospital (GWUH) for elective CBP surgery by accessing their medical records. Cardiothoracic surgery team will inform the research coordinate bout any patients being scheduled for CPB, coordinators will obtain an informed consent prior to surgery.

5 Recruitment process

5.1 Description

Out patients will be screened for eligibility at Cardiac surgery clinic, patients who directly admitted to GWUH with no prior outpatient visit will be screened for eligibility by cardiac surgery team on the day of admission. Medical records and laboratory studies at cardiac surgery clinic and GWUH will be reviewed to assess eligibility for enrollment. Once the preliminary eligibility is confirmed, a research team member will approach the patients and invite them to learn about the study and obtain consent if interested.

5.2 What steps taken to avoid coercion or undue influence in the recruitment of research participants

Participants will be given time to review the consent and ask questions, teach-back method to validate patient's understanding, consent discussion will private.

6. Risks and benefits

Co Q12 supplement is safe and widely available as an over-the-counter, dose of 1200 mg chose based on safety shown in many clinical trial data, mild digestive side effects like abdominal discomfort, nausea, vomiting, diarrhea, rash and appetite loss, higher doses of Warfarin might be needed if taken together.
CoQ10 supplementation has been reported to improve glycemic control in diabetics, to mitigate this, patient's Blood sugar will be checked daily for non-diabetic patients and three times a day for diabetic patients, the blood glucose checks are part the standard of care.
GSH supplement is safe and already available over the counter, this was baes on many studies. Long term use of GSH may lower zinc level.

6.1 Unknown risks

Though it's less likely but possible that there are side effects of the study medications that are not know this time especially with possible changes in the acute sitting of sickness

6.2 Steps taken to minimize risks

Patients will have hemoglobin, platelets and INR checked in the week prior to surgery as part of pre-operative CBC, CMP and Coagulation profile

Inpatient daily lab includes CBC, CMP and INR

Drugs will be stopped immediately and permanently If allergic reaction developed.

6.3 Describe anticipated benefits of this research for the individual subject:

Renal protection and faster recovery from acute kidney injury

6.4 Anticipated benefits of this research for society

This study will be the first one to examine the renal protection of Co Q10 and GSH in high risk population that undergo CBP surgery. Also the study will add to the body of data and expand he knowledge about plasma and urinary mt DNA in AKI, additionally will examine the Co Q10 and GSH level changes and relationship with development and progression of AKI.

Information collected will be coded with patient's unique Patient ID number. This will be used internally at GWUH. Specimens collected will be de-identified, coded then sent to NIH labs for processing. The link to patient's information will be kept in a locked file cabinet with the research coordinator. All identifiable information will be kept in the research records, de-identified data will be kept indefinitely for publication the code will be destroyed after final publication of the data. Future protocols will be reviewed by ORB before the specimens and the data are used again. All study materials will be stored in locked file cabinets. Only authorized study personnel will have access. Study regulatory binders and patient charts will be maintained for at least 6 years.

7 Data safety monitoring

7.1 Data safety monitoring plan

Careful monitoring of the recruitment, enrollment, retention, informed consent process, adverse events, and study procedures will help to protect the safety of study subjects, the quality of data, and the integrity of the study. As part of the safety plan for this study, after each patient enrollment, the PI and the study coordinators will review the EHR to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Subject records include consent forms, case report forms, flow of data forms, laboratory specimen

records, inclusion/exclusion forms, cumulative toxicities and/or adverse event logs, and medical charts. An annual Data and Safety Report of this assessment will be forwarded to the local IRB.

7.2 Plan for adverse event reporting

PI and the study coordinators will be monitoring for and documenting adverse events, whether anticipated or unanticipated. The PI will be evaluating each adverse event and determining attribution as well as the impact of the adverse event on the risk/benefit ratio.

7.3 DSMB committee includes

Chair: Dr. Sabyasachi Sen (Professor of medicine Chief Division of Endocrinology GW VA)
Member: Dr. Afsoon Roberts (Associate professor of medicine, ID consultant)
Member: Sarah Conway (Assistant professor of medicine Hospital Medicine MD)
Member: Timothy S. Harlan (Associate professor of medicine Primary Care MD

No federal Certificate of Confidentiality (CoC)

All information associated with the participant's study ID, but not associated with their names, addresses, social security number, or other protected health information (PHI). The link between he PHI and study identifiers will be kept in a locked file cabinet that can only be accessed by authorized individuals.

8. Definitions:

8.1 AKI is defined as 2012 KDIGO guideline
•Increase in SCr by equal or more than 0.3 mg per dl (equal or more than 26.5 µmol per l) within 48 hours; or
•Increase in SCr to equal or more than 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
•Urine volume less than 0.5 ml per kg per h for 6 hours

8.2 Ventilator free days (VFDs) defined as the number of days between successful weaning from mechanical ventilation and day 28 after study enrollment.

8.3 Ventilator-free day is defined as the receipt of less than 2 hours of invasive or noninvasive ventilation within a 24-hour period.

8.4 Shock-free days defined as less than 2 hours of receipt of any vasoactive therapy provided by continuous infusion within a 24-hour period.

8.5 RRT dependence defined by the receipt of any form of RRT within + or - 14 days of the 90-day time point following randomization.

8.6 RRT free days defined as the number of days between s successful weaning from RRT and day 28 after study enrollment.

8.7 Adverse events Definition (AE)

An AE is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to the participant's participation in the research.

8.7.1 Serious Adverse Events

A Serious Adverse Event **(SAE)** is defined as any AE that results in any of the following outcomes:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- results in congenital anomalies or birth defects
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.

9. Labs, measurements of plasma levels of Co Q10 & total glutathione, plasma and Urinary mtDNA

9. 1Labs

labs checked in the week prior to surgery includes CBC, CMP and INR

Daily CBC, CMP & INR while on medication

Daily Blood sugar for non-diabetics

Blood sugar Q8H for diabetics

9.2 Samples collection

1st samples collection of 5 mL of blood and 40 ml of urine will be collected the day prior to surgery before taking the supplements, 2nd samples collection will be on the Day of surgery (Day 0), 3rd and last collection will happen 1 days after surgery (Day 1) (preferable 2nd & 3rd collections should happen about 24 & 48 hours from the first doses of Co Q10 & Glutathione).

Urine and blood will undergo 2-step centrifugation (1000 x g for 10 min, followed by 16,000 x g for 10 min), supernatants to be collected and kept frozen at −80^{O}C until analysis.

9.3 Measurements of levels of serum Glutathione and Co Q10

Plasma Co Q10 and total glutathione (GSSG + GSH), as well as plasma and urinary mitochondrial DNA (mtDNA) will be measured at baseline the week before surgery and prior to taking the first dose of the supplements, second level is checked the day of surgery and the third level will be checked the day after surgery.

9.4 Quantification of plasma and Urinary mtDNA

DNA are extracted with the QIAamp DNA Mini and Blood Mini kit (Qiagen, Germantown, MD) from plasma or urine, after 2-step centrifugation. A Taqman assay for real-time qPCR is then performed. For absolute quantification using qPCR, a mitochondrial DNA standard was prepared by PCR of liver mitochondrial DNA with these primers, purified using a QIAquick PCR Purification Kit (Qiagen, Germantown, MD), and serially dilute

9.5How are the samples getting to NIH

Samples will be placed on dry ice and transported by NIH personnel.

9.6Who is receiving the samples at NIH

NIH personnel, Naoki Hayase, MD PhD and Peter Yuen, PhD will receive samples. All personnel receiving samples have been trained and are approved to receive human samples.

9.7How are the samples being stored at NIH

Samples will be stored at -80 degrees C, and when ready to process, samples will be thawed and DNA will be isolated, then any leftover purified DNA will also be stored at -80 degrees C.

9.8 NIH involvement

This is a collaborative work between the research team at GW and research team at NIH. NIH team will be helping by measuring the plasma levels of Glutathione and CoQ10, and plasma & urinary mitochondrial DNA levels at NIH lab with no cost. NIH will not be funding the study. The funding is local from the Cardiac ICU at GWUH.

10 Randomization

Patients requiring bypass surgery will be randomized to two groups

- Group A: CoQ10 1200 mg orally with Glutathione 1000 mg orally or
- Group B: Placebo CoQ10 orally and Placebo Glutathione orally

11 Blindness

The MFA research pharmacy will generate a randomization sequence which will assign patients to either treatment group. The randomization sequence list will be kept securely in the pharmacy, as the study team members will all be blinded to the patient's treatment. Unblinding will be done at the end of the trial. If a patient can't receive the supplements orally then their feeding tube will be used, only in this case the ICU nurse responsible for administering the medicine will be able to know if a patient receiving a placebo as the capsule will be empty upon opening, the ICU nurse will not inform the research team to maintain blindness.

12 Study Drug Compounding

- Active
    - White-colored CoQ10 400 mg capsules will be dispensed (if CoQ10 400 mg capsules are unavailable, the CoQ10 200 mg capsules will be procured).
    - White colored L-Glutathione 500 mg capsules will be dispensed.
- Placebo
    - A placebo to exactly match the CoQ10 will be made with white gelatin empty capsules containing cellulose. These capsules will be compounded at the MFA research pharmacy.
    - A placebo to exactly match the L-Glutathione will be made with white gelatin empty capsules containing cellulose. These capsules will be compounded at the MFA research pharmacy

13 Clinical Treatment Logistics

- The following process will apply to all patients
    1. Day -1 (1st dose of the drug)
        - Outpatient patients will be seen in Clinic at the MFA location on K street and first dose will be handed to take the day before their surgery.
        - Inpatient patients will be admitted at GWUH the day before surgery
    2. Day 0 Day of Surgery (2nd dose of the drug)
        - Outpatient patients will present to GWUH for surgery. Inpatients will already be at GWUH ready for surgery.
        - CoQ10/Glutathione or Placebo doses are administered during Day 0 after surgery
    3. Day 1 thru Day 5
        - CoQ10/Glutathione or Placebo doses are administered every day.

14 Drug Dispensing Process

Drug will be dispensed for outpatients only if the patient is getting admitted to the hospital on the day of surgery.

- **Outpatients**
    1. Outpatients will be seen in the Clinic at the MFA location on K street 5 days before surgery
    2. The prescriber will submit an EPIC RX to the MFA research pharmacy
    3. MFA Research pharmacy will dispense only a one-time dose for the patient to administer drug at home prior to surgery (Day -1).
    4. Study coordinator will retrieve the drug from the research pharmacy and hand-deliver to patient
    5. Day 0 – 5 MFA research pharmacy dispenses the rest of the oral doses to inpatient pharmacy to dispense on daily basis for inpatient administration by the nursing staff. Chain of Custody logs will document the transfer of drug from pharmacy to the study coordinator or nursing unit.

- **Inpatients**
    1. Inpatients will be seen in the GWU hospital the day before surgery (Day -1)
    2. The prescriber will submit an EPIC RX to the MFA research pharmacy
    3. MFA Research pharmacy will dispense the oral doses to inpatient pharmacy to dispense on a daily basis for inpatient administration by the nursing staff. Chain of Custody logs will document the transfer of drug from pharmacy to the study coordinator or nursing unit.
    4. Patient will only receive daily doses while in hospital up to 7 doses total, no more doses after discharge.

15 Background and Scientific Rationale

AKI is a serious and common complication post Cardiac surgery requiring cardiopulmonary bypass (CPB), the incidence is up to 30% (2)
Independent predictor for 30-day mortality, with a 41 % & % 62% in AKI stage III without and with the needs for RRT respectively (4)
It's also associated with an a 3-fold increase in the long-term risk of ESR (3)
Despite the high burden of CPB-induced AKI, our understanding of the pathophysiology still primitive, that makes us limited in designing directed therapies for prophylaxis, early detection and interventions that can lower its incidence, severity and progression.

CPB induced AKI is multifactorial, however, renal ischemia-reperfusion injury (RIRI) is considered a major factor, poor renal perfusion driven by hemodynamic and volume changes, increased systemic inflammation, endothelial and epithelial cell injury
and perioperative use of nephrotoxic agents all contribute to IR induced AKI post cardiac surgery (6,7,8).

Renal mitochondrial dysfunction has been implicated in the pathogenesis of IRI, reperfusion following ischemia causes opening of mitochondrial permeability transition pore (MPTP), leading to depolarization of mitochondrial membrane, increased production of reactive oxygen species (ROS) and release of apoptotic proteins (1,9,19) mitochondrial disruption contributes to impairment of ATP dependent cellular repair mechanisms, cell death, and persistent suppression of mitochondrial biogenesis, a process of which cells form new mitochondria(12) furthermore, cell injury releases mitochondrial endogenous damage-associated molecular patterns (DAMPs), Mitochondrial DAMPs (MTD) activates toll-like receptor-9 (TLR9
) which results in innate immune cascade activation and further renal injury (13,14)

Loss of Mitochondrial function and integrity has been linked to initiation, progression and recovery phases of ischemia/ reperfusion acute kidney injury (1,5). In mice subjected to Sham surgery, UmtDNA increased after 10 min of ischemia, positively correlated with ischemia time and negatively correlated with renal cortical mtDNA and mitochondrial gene expression (1)

Levels of UmtDNA in AKI was evaluated in 2 studies with different population and different results. In the study by Whitaker et al. [1], UmtDNA level correlated with renal function

recovery but not with AKI severity following cardiac surgery. In the study by Ho et al. (15) same finding of correlation between UmtDNA with renal recovery was observed but wasn't statistically significant, additionally UmtDNA level reflected the severity of AKI and duration of renal replacement therapy in patients admitted with AKI

15.1 Co enzyme Q10

Co Q10 or ubiquinone is an essential mitochondrial co-factor that has a critical role as a component of the electron transport chain and free radical scavenger. Co Q10 levels were found to be low in critically ill patients (16,17), lower levels found in post cardiac arrest with correlation poor neurological outcome and higher mortality (18) American heart association included CoQ10 as a promising neuroprotective agent (20)

In the Controlled Rosuvastatin Multinational Study in HF (CORONA) trial, significantly lower left ventricular ejection fractions (LVEFs) seen in in the lowest tertile of CoQ10 (23) Biopsies taken from patients with cardiomyopathy showing increasing severity of heart disease correlate with levels of lower levels of serum and myocardial deficiency of CoQ10, supplementation with CoQ10 resulted in significant increases in both myocardial and serum levels as well as reduction of disease severity (22) In the randomized double-blind, multicenter trial, Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure, (Q-SYMBIO) , it demonstrated that CoQ10 supplement reduced the primary 2-year end point of cardiovascular death, hospital stays for HF, or mechanical support or cardiac transplant. Large randomized trial also demonstrated that CoQ10 reduced the risk of congestive heart failure hospitalization and its complications like pulmonary edema and cardiac asthma (24,26)

Q10 supplement is safe and widely available as an over-the-counter, CoQ10 is available as ubiquinol (reduced form) or ubiquinone (oxidized form), Additionally, the ubiqinol containing formulation resulted in a higher plasma CoQ10 levels compared with ubiquinone formulations after a single dose of supplement (25,26)

Dose of 1200 mg chose based on safety shown in many clinical trial data for CoQ10 (27) The half-life of CoQ10 is 21.7 h (28**).** Mitochondria consume about 90% of the cellular O_2 for ATP synthesis through oxidative phosphorylation., optimizing mitochondrial function and reducing oxygen free radicals may enhance cellular function and mitigate cellular injury thereby leading to improved outcome**.** Despite the accumulating evidence on the relevance of mitochondrial dysfunction in AKI initiation and progression and the crucial role mitochondrial therapies such as Co Q10 & Glutathione would play in renal protection and recovery, human data in this field are very limited. There are three experimental studies reported the role of CoQ10 in RIRI (29,30,31) no human trial published until now (32) Using renal scintigraphy & immunohistochemically evaluation, Akbulut et al demonstrated CoQ10 decreased tissue oxidative stress levels, scores of histopathology and apoptosis; and decreased quantitative scintigraphic parameters with increased split renal function in ischemic kidney (29)

Liu et al experimented delivering The mitochondria-targeted Triphenylphosphine CoQ10 nanoparticles (T-NP_{CoQ10}) which resulted in alleviation of mtDNA damage, suppressed inflammatory and apoptotic responses, and improved renal function in both cell and animal models (30,31). In human Co Q10 with Trimetazidine significantly lowered the incidence of Contrast induced nephropathy in a single center randomized, double-blind, controlled trial done by Chen et al (32)

15.2 Glutathione (GSH)

In addition to Oxidative stress as a key in cardiac surgery associated AKI; Ferroptosis, iron-dependent lipid peroxidation resulting in cell death play an important role, this process starts with intracellular glutathione (GSH) depletion (43).
Glutathione S-transferases (GST) are a diverse group of phase II detoxification enzymes that works as a scavenger through conjugation of glutathione to a wide variety of electrophiles and reactive oxygen species (40,41). Alpha-GST isoform(a-GST) has specificity for the proximal tubule, and pi- GST isoform(pi-GST) that's confined to distal tubule (39,40,41).

Several studies demonstrated that post cardiac surgery Urinary pi- GST levels predicted development of AKI and overall prognosis (33,34,42)

Zager et al demonstrated in ischemia/reperfusion mouse models that total GST activity is reduced by ~35% during (0-4 h) AKI "initiation" and (18 or 72 h) "maintenance" phases (41).
Matsubara et al studied Acute kidney injury model established by systemic glutathione depletion in mice (45)

In patients undergoing cardiac surgery, Low levels of cardiac and systemic glutathione found to correlate to the functional status and structural cardiac abnormalities of patients with cardiac diseases (44)
Tojanović et al demonstrated that that high levels of serum GST Pi in the first 6 h after birth are associated with an increased AKI and mortality in prematurely born neonates (38)
Experiment showed exogenous glutathione supplement alleviated Gentamicin induced AKI in rats intoxicated with GM, partially by inhibiting oxidative stress, and intrinsic apoptosis (35)

Glutathione supplements are safe and already available over the counter, studies have shown effectiveness of daily Glutathione administration at elevating stores of Glutathione and impacting the immune function and levels of oxidative stress (36,37,)

16 Study Products

Co Q12 and GSH supplements are safe and widely available as an over-the-counter, their antioxidant, anti-peroxidative, anti-apoptotic and anti- inflammatory properties that have a great potential in in renal protection and recovery in renal ischemic reperfusion injury.

16.1 Formulation of CoQ10

Co Q10 (400mg max strength, 200 capsules) High absorption vegan Coenzyme Q10 powder-Ubiquinone supplement pills, Extra antioxidant Co Q10 enzyme vitamin Capsules
Other ingredient Vegetable cellulose (capsule), Dextrin, Rice flour

Commercial labels of drug products:

- **CoQ10 - CoQ10 (400mg Max Strength, 200 Capsules) - High Absorption Vegan Coenzyme Q10 Powder - Ubiquinone Supplement Pills, Extra Antioxidant CO Q-10 Enzyme Vitamin Capsules**

16.2 formulation glutathione

L- Glutathione- Reduced Glutathione 500 mg per serving supplement -200 capsules- L-Glutathione Antioxidant capsules
L- Glutathione (Reduced form) 500 mg
Other ingredient Vegetable cellulose (capsule), Dextrin, Rice flour

- **L-Glutathione - Reduced Glutathione 500mg Per Serving Supplement - 200 Capsules - L-Glutathione Antioxidant capsules**

16.3 CELLULOSE

Stock code 0567

Starting material Cellulose pulp obtained from wood. A number of tree varieties are utilized in the production of high purity cellulose pulp used for manufacturing microcrystalline cellulose for the pharmaceutical and nutraceutical industries. The timber resources used to make wood pulp are referred to as pulpwood. Wood pulp comes from softwood trees such as spruce, pine, fir, larch and hemlock, and hardwoods such as eucalyptus, aspen and birch. Some pulping processes use the entire tree, while others use parts of the tree that cannot be used to make lumber. The trees are harvested in accordance with best practices, chipped, aged, and processed to make high-purity alpha-cellulose pulp. The manufacture selects the appropriate pulp for the production of microcrystalline cellulose. The pulp goes through several processing steps to make the finished product. As such, the finished product, microcrystalline cellulose, is a highly refined and purified cellulose product, meeting pharmaceutical standards.

BSE -TSE Based on the ingredients, the product is in compliance with the note for the guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

GMO not genetically modified.

Allergen Please note that there may be several steps before the raw material is produced and access to data on manufacturing raw materials is not easily obtained for the starting materials and intermediates used in the production process. The following items are not used in the manufacturing process of the product, and although manufacturer does not specifically assay for the presence of the items below, it is unlikely that any traces of these items are present in the starting materials or in the final product. The product is unlikely to contain the following - Cereals containing gluten and products thereof Corn and products thereof. Celery and products thereof Soybeans and products thereof Yeast Fish and crustacean shellfish and products thereof Eggs and products thereof Dairy Products (Milk, Lactose, Caseinates, Whey) Peanuts and products thereof Tree nuts (oils) or derivatives Mustard and products thereof Sesame Oil Preservative Sulfites >10ppm Artificial Colours and Flavours Beef, Chicken, Pork derivatives Additives Latex This statement is provided for informational purposes only, as instructed to Medisca by the manufacturer, and is not meant to be a guarantee of absence of the above stated allergens.

17 Clinical pharmacology & drug interactions

Many studies have shown that doses of CoQ10 1200 & Glutathione 1000 mg are safe (47, 57,58,59,63,64)
Because of its structural similarity to vitamin K, CoQ10 has been suggested that CoQ10 may have procoagulant activity, this indicates that patients on anticoagulant therapy may need to have their INR monitored and anticoagulant dosage adjusted accordingly (59)

CoQ10 has an excellent safety records, the safety of high doses ingested over long periods of time has been documented in human subjects (47, 57,58,59). Pharmacokinetics of CoQ10 has been studied in human and animal models (52,53,54,55,56).
The side effects reported in human studies are generally limited to mild gastrointestinal symptoms such as nausea and stomach upset seen in a small number of subjects (59). No adverse effects were observed with daily doses ranging from 600 to 1200 mg in two trials on Huntington's [60] and Parkinson's [61] disease, 2,400 mg/d of CoQ10 was used for 12 months in patients with progressive supra nuclear palsy (48)

RCT examined the effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin. Changes in plasma CoQ10 levels showed no relation to the changes in serum AST, ALT and CK levels. (49)
Coenzyme Q10 was studied in a prospective, randomized, double-blinded, placebo-controlled trial, 38 patients younger than 18 years with idiopathic dilated cardiomyopathy to receive either coenzyme Q10, patient were on medications including digoxin, loop diuretic, inhibitors of angiotensin converting enzyme, spironolactone, and carvedilol, no drug interactions noted.

Sharing same population Q-SYMBIO, a 2-year RCT included 420 patients with moderate to severe heart failure, CoQ_{10} 100 mg 3 times daily or placebo, about 50 % of patients were on anticoagulation, study concluded that CoQ10 is safe and lower adverse events than placebo, 13% versus 19% respectively, no drug interaction or bleeding reported (50)
No scientific report indicates any significant Plavix CoQ10 drug interaction.

To minimize the risk Hemoglobin and Coagulation will be checked in the week prior to surgery as well as daily while receiving the medications.
CoQ10 supplementation has been reported to improve glycemic control in diabetics (66,67), to mitigate this, patient's Blood sugar will be checked daily for non-diabetic patients and three times a day for diabetic patients.

18 Principal Investigator's info

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