School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

PROTOCOL

The Effect of Capsaicin-Phenylephrine-Caffeine Formulation on Aborting Tilt Induced Syncope in Patients with a History of Vasovagal Syncope or Near Syncope

NCT Number: NCT04972123

Principal Investigator: Mohamed H Hamdan, MD, MBA

Version 4

Date May 4, 2023

IND Number: 140732

Phase IIa

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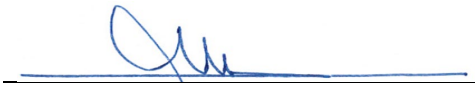
Statement of Compliance:

The signature below constitutes that the research will be conducted in accordance with the approved protocol, applicable regulations, guidelines, laws and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Printed or Typed Name	Signature	Date
Mohamed H. Hamdan, MD, MBA Principal Investigator		4MAY23

1.0 Study Synopsis

The purpose of this study is to assess the effects of sublingual administration of CPC (Capsaicin 1mg, Phenylephrine 30 mg, Caffeine 200 mg) on tilt-induced syncope.

Hypothesis: In the present study, we hypothesize that a single administration of sublingual CPC preparation during the prodromal phase aborts tilt-induced syncope or near syncope with SBP ≤ 70 mmHg in patients with a history of vasovagal syncope or near syncope.

Inclusion criteria

1. Established diagnosis of typical vasovagal syncope or near syncope
2. Age 18-50 years

Exclusion criteria

1. Systolic BP >130 mmHg
2. History of hypertension or cardiac arrhythmias
3. History of cardiovascular disease or cerebral ischemic events
4. Allergic reaction to any of the drug components
5. Contraindication to tilt testing
6. Any physical or psychological symptom, based on the clinical judgment of the investigators that would make a participant unsuitable for the study
7. Any use of a medication(s) based on the clinical judgment of the investigators that would make a participant unsuitable for the study (e.g. fludrocortisone, theophylline, prazosin, doxazosin, terazosin, MAO-inhibitors, pseudoephedrine, decongestant and PDE5 inhibitors).
8. Unwilling to discontinue Midodrine or beta-blocker therapy 48 hours before tilt table testing
9. Women who are pregnant (confirmed with pregnancy test on day of study) or lactating

Study protocol: Double-blinded, acute, proof-of-efficacy, randomized study. Eligible patients will undergo tilt table testing (20 min passive + 15 min NTG phase) with continuous BP, HR and ECG monitoring. Patients will be randomized to receive CPC or placebo preparation to be administered at the onset of prodromal symptoms (blurred vision, lightheadedness, dizziness, epigastric discomfort, nausea, sweating, …).

End-points

Primary endpoint: Comparison of the percentage of patients who have hypotensive syncope or near syncope with SBP ≤ 70 mmHg during tilt test in the active and placebo arms.

Hypotensive syncope is defined as transient loss of consciousness (unresponsive to verbal commands) associated with a SBP ≤ 90 mmHg. Near syncope is defined as sensation of “near fainting” but still responsive to verbal commands. Near syncope will be used as a primary endpoint only when it is associated with a SBP ≤ 70 mmHg.

Secondary endpoints:

- Time to syncope or near syncope after drug or placebo administration
- Percentage of patients who have asystolic pauses >3 sec in the CPC and placebo arms
- Measures of fatigue (Ordinal Scale 1-5) at 1, 4 and 8 hours after tilt test termination

Sample size: Knowing that the efficacy of current therapies for VVS range between 30% and 50%, we hypothesize a 50% reduction in syncope or near syncope rate with the CPC product. Thus, in the intent to treat population, we assume that the active treatment arm will decrease the syncope rate from an absolute value of 62% to 34.1% (31% diluted with patients not completing the protocol, see statistical methods). A total of 126 patients (63 active and 63 placebo) are needed in order to achieve a statistical power of 85.2% to detect this difference using a 2-sided overall significance level of 0.05 with a Pocock boundary (i.e. $z = \pm 2.1599$ at both interim and final analysis). Accounting for the number of subjects that might not meet eligibility criteria after virtual enrolment, inflating the total number of subjects to be enrolled to **143 patients** should result in an adequate sample size. An interim analysis is predefined at the time in which 76 total patients are randomized and evaluable.

Setting and timeline: The study will be conducted at the University of Wisconsin, Madison WI. It is estimated that the duration of enrolment will be 1-2 years.

2.0 Background

Syncope is defined as transient loss of consciousness associated with inability to maintain postural tone with rapid and spontaneous recovery (Shen et al 2017). The presumed cause is cerebral hypoperfusion. The prevalence depends on the population being evaluated and has been reported to be as high as 41% with recurrent syncope occurring in 13.5% (Lamb et al 1960). In the emergency department, syncope accounts for 0.8% to 2.4% of all visits (Olde Nordkamp et al 2009; Day et al 1982; Morichetti and Astorino 1998). Hospital costs associated with the inpatient evaluation of syncope exceed $2.4 billion per year in the United States (Sun 2013).

Vasovagal syncope (VVS) is the most common type of syncope. It is defined as syncope occurring after prolonged standing or with exposure to emotional stress, pain, or medical settings, and is associated with features such as diaphoresis, warmth, nausea, and pallor. Patients with VVS often experience fatigue following the event (Sheldon et al 2015). Vasovagal syncope is very common affecting up to 42% of woman and 32% of men by the age of 60 (Ganzeboom et al 2006; Serletis et al 2006). The outcome in patients with VVS is benign however, the 1-year recurrence rate is 25-35% leading to significant impairment in quality of life including injuries and loss of employment (Sumner et al 2010).

The mechanism of VVS is reflex-mediated triggered by various afferent input to the brain. The efferent response includes vagal activation leading to cardio-inhibition (CI) and brady-arrhythmias, and sympathetic withdrawal leading to a decrease in systemic vascular resistance and vasodilatation (VD) (Morillo et al 1997; Mosqueda-Garcia 2000). The result is cerebral hypoperfusion. The hemodynamic pattern, i.e. cardioinhibitory, vasodepressive, or both, is independent of the trigger evoking reflex syncope. In patients where the trigger is prolonged standing, a reduction in preload alone is thought to be sufficient to reduce cerebral hypoperfusion without the need for sympathoinhibition (Fu and Levine 2014; Jardine et al 2002; Cook and Convertino 2002). Adenosine is an ATP derivative that impacts strongly the cardiovascular system through the activation of its membrane receptors A1R, A2AR, A2BR, or A3R, based upon their pharmacological properties. Activation of A1R leads to sinus bradycardia or AV block, while activation of A2AR leads to vasodilation (Shryock and Belardinelli 1997). Endogenous adenosine is implicated in most forms of reflex syncope. VVS patients have high adenosine plasma levels, high A2AR expression and special A2AR gene polymorphism (Saadjian et al 2002 and 2009, Deharo et al 2012). Theophylline, a non-specific antagonist of adenosine receptors, is a useful daily treatment of some forms of reflex syncope (Brignole et al 2016).

While several drugs are indicated in the treatment of VVS, to our knowledge, there is no current treatment of an impending syncopal attack. We have recently tested the effects of a new drug containing Capsaicin, Phenylephrine and Caffeine on blood pressure (BP). The rationale for using these 3 drug components is listed below:

Capsaicin is an active alkaloid subtracted from chili peppers. It is an irritant for mammals including humans, and produces a sensation of burning in any tissue with which it comes into contact. These effects are secondary to the activation of transient receptor potential (TRVP1), which are vanilloid receptors present in great amount in C Fibers (Seabrook GR et al 2002). In our product, we chose Capsaicin for two reasons. First, Capsaicin causes local irritation which should elicit sympathetic activation. Second, Capsaicin causes local vasodilatation which

should facilitate the absorption of the two other compounds, namely Phenylephrine and Caffeine.

We chose a dose of 1 mg of Capsaicin (corresponding to 60 µL of capsaicin 0.5%) to be included in our CPC product. This dose is close to the 0.75 mg dose used orally in the stratification of patients with functional dyspepsia (Fuhrer M, et al 2011).

Phenylephrine is an alpha-adrenergic agonist that produces vasoconstriction. The increase in vascular resistance results in a dose-dependent increase in BP and reflex decrease in HR. When given systemically via the intravenous route, the effects are immediate and can last 15-20 minutes. The half-life of the distribution (alpha) phase is around 5 minutes with the terminal elimination (beta) lasting 2-3 hours. The drug is excreted in the urine mostly as inactive metabolites (Hengstmann and Goronzy 1982; Kanfer I et al 1993). When given as an IV bolus for the treatment of hypotension, the dose is 100-500 mcg every 10-15 minutes (Rhodes A et al 2017). In the ACLS guidelines, the dose for the treatment of severe hypotension (systolic BP < 70 mm Hg) and low total peripheral resistance is 0.1 to 10 mcg/kg/minute (van Diepen S et al 2017). The initial dose is 0.5 to 2 mcg/kg/minute with up titration to effect (Peberdy MA et al 2010). Cardiovascular adverse reactions can include exacerbation of angina, hypertension, reflex bradycardia and worsening heart failure. Other side effects include anxiety, excitability, headache, chest discomfort and restlessness.

The dose of Phenylephrine (30 mg) in our CPC product was determined based on the results of the Phase I study (see below).

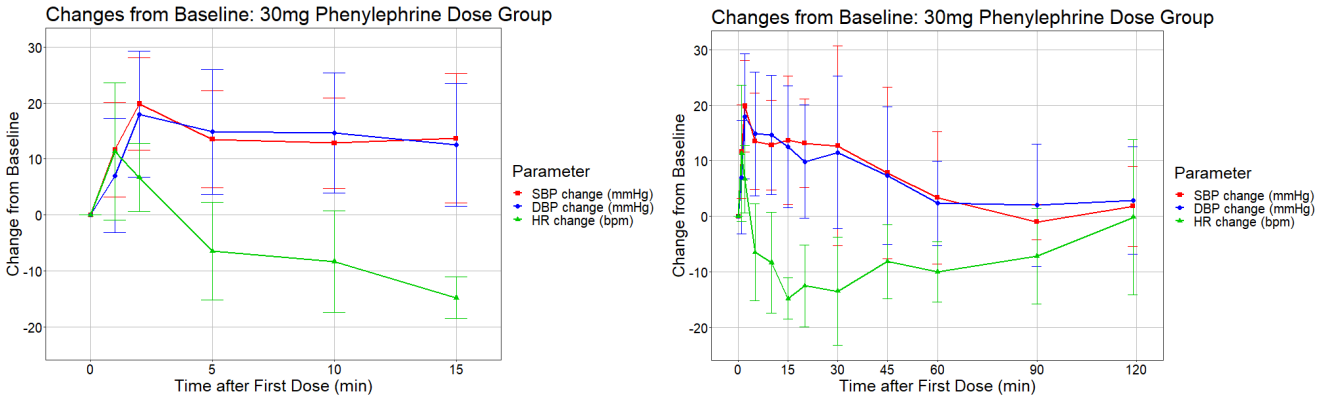
Caffeine is a methylxanthine derivative which is contained in many foods and drinks including tea, coffee, cola and chocolate. It is the most widely consumed psychoactive drug. Caffeine has been shown to cause an increase in BP and vascular resistance at rest and during exercise (Daniels J et al 1998; Robertson D et al 1978; Sung et al 1990). Following the administration of a single dose of caffeine (250mg orally), the peak increase in BP was noted at 30 minutes with a gradual return to baseline at 180 minutes (Mosqueda-Garcia R et al 1990). In another study including healthy, normotensive non-smoking adults, the ingestion of 3.3 mg/Kg of caffeine resulted in 4.1 and 3.8 mmHg increases in systolic and diastolic BP in men, and 4.5 and 3.3 mmHg increases in women, respectively. Of interest, the mechanism was an increase in vascular resistance in men and an increase in cardiac output in woman (Hartley TR et al 2004). Acute ingestion but not chronic use of caffeine has also been shown to decrease baroreflex sensitivity. These effects are in part due to the blockade of adenosine A_1 and A_2 adenosine receptors (Fredholm BB 1985). Inhibition of A_1 adenosine receptors leads to an increase in heart rate (HR), while inhibition of A_{2A} adenosine receptors leads to vasoconstriction. In addition, caffeine has been shown to increase muscle sympathetic nerve activity in both habitual and nonhabitual coffee drinkers.

The caffeine dose in our product is 200mg, the equivalent of the amount of caffeine present in a 6-ounce cup of brewed drip coffee. It should be tolerated well with no significant side effects.

In Phase 1 study, a total of 17 subjects received CPC sublingually with various doses of Phenylephrine. In the 6 participants who received CPC with the highest dose of PE (Capsaicin 1 mg, Phenylephrine 30 mg, Caffeine 200 mg), a peak increase in SBP was noted at 2 minutes with an average of 21 mmHg (range 15-33 mmHg). The increase in BP persisted for at least 15 minutes with a gradual decline over 2 hours (p value < 0.05 when compared to baseline at 1, 2, 5 and 15 minutes for both SBP and DBP). The increase in BP was associated with an initial

increase in HR followed by a decrease to below baseline over the 2-hour period (Figures 1A and 1B).

Figures 1A and 1B



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3.0 Study Hypothesis and End-points

In the present study, we hypothesize that a single administration of sublingual CPC preparation during the prodromal phase aborts tilt-induced syncope or near syncope with SBP ≤ 70 mmHg in patients with a history of vasovagal syncope or near syncope.

Primary endpoint:

Comparison of the percentage of patients who have hypotensive syncope or near syncope with SBP ≤ 70 mmHg during tilt test in the CPC and placebo arms.

Hypotensive syncope is defined as transient loss of consciousness associated with SBP ≤ 90 mmHg. Near syncope is defined as sensation of “near fainting” while still being responsive to verbal commands. Near syncope will be used as a primary endpoint only when it is associated with a SBP ≤ 70 mmHg.

Secondary endpoints:

- Time to syncope or near-syncope after CPC or placebo administration
- Percentage of patients who have asystolic pauses >3 sec in the CPC and placebo arms
- Measures of well-being at 1,4 and 8 hours after tilt test termination (Ordinal scale 1-5 for fatigue)

4.0 Study Design

Patients with an established diagnosis of typical VVS or near syncope will be contacted by phone for enrollment and the start of the informed consent discussion. All participants will be asked to sign the approved consent and HIPAA authorization document before any study related procedures are completed.

After verbal agreement to participate via phone, patients on Midodrine (COR 2A) and beta-blockers (COR 2B) will be asked to discontinue the medication 48 hours before tilt testing.

4.1 Inclusion Criteria

1. Established diagnosis of typical vasovagal syncope or near syncope
2. Age 18-50 years

4.2 Exclusion Criteria

1. Systolic BP >130 mmHg
2. History of hypertension or cardiac arrhythmias
3. History of cardiovascular disease or cerebral ischemic events
4. Allergic reaction to any of the drug components
5. Contraindication to tilt testing
6. Any physical or psychological symptom, based on the clinical judgment of the investigators that would make a participant unsuitable for the study
7. Any use of a medication(s) based on the clinical judgment of the investigators that would make a participant unsuitable for the study (e.g. fludrocortisone, theophylline, prazosin, doxazosin, terazosin, MAO-inhibitors, pseudoephedrine, decongestant and PDE5 inhibitors).
8. Unwilling to discontinue Midodrine or beta-blocker therapy 48 hours before tilt table testing.
9. Women who are pregnant (confirmed with pregnancy test on day of study) or lactating.

4.3 Concomitant Therapy

As stated above, patients taking Midodrine and beta-blockers must discontinue such drugs at least 48 hours before the test. Patients can continue taking concurrent medications that do not conflict with eligibility requirements for the study. Concurrent medications taken 48 hours before tilt table testing and caffeine intake on the day of the study will be recorded.

4.4 Randomization and Blinding

Eligible patients are assigned, according to a central computer-generated randomization list, to one of the 2 study arms: CPC or Placebo. The transcript of the CPC identification code is blind to the investigators and to patients.

4.5 Dosing and Administration

Prior to administration, the research RN will warn the subject that some people may experience a minor burning sensation. The CPC or placebo will be administered as fast as possible from an oral syringe sublingually. The participant must allow the gel to reside under the tongue for 1 minute before the gel is swallowed. After swallowing CPC, sips of water will be allowed.

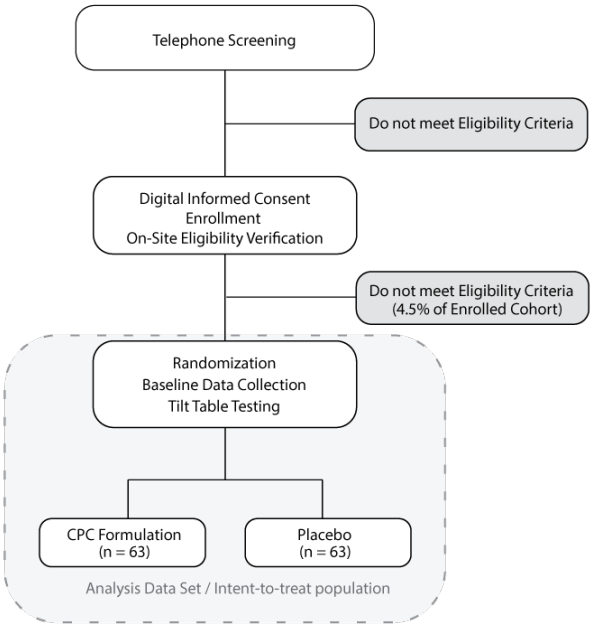
4.6 Tilt Test Procedure

Patients will undergo tilt tablet testing using the Italian protocol, which is slightly different than the current UW-Health protocol (Bartoletti et al, 2000). The Italian protocol includes 20 minutes of passive tilt at 70 degrees (Passive Phase) followed by nitrogylcerin (NTG) administration and tilt testing for another 15 minutes (NTG Phase). The current protocol at UW-Madison is similar except for the NTG Phase which is 10 minutes instead of 15 minutes. Continuous non-invasive monitoring and recording of arterial blood pressure (BP), heart rate (HR) and ECG tracings will be obtained.

If patients experience no prodromes (blurred vision, lightheadedness, dizziness, epigastric discomfort, nausea, sweating, …), the tilt test will be performed until completion of both phases or until syncope occurs. No CPC or placebo will be administered.

If patients experience prodromes (blurred vision, lightheadedness, dizziness, epigastric discomfort, nausea, sweating, …) CPC or placebo will be administered from a syringe sublingually as fast as possible. Patients will be asked to allow the gel to reside under the tongue for 1 minute before it can be swallowed, followed by sips of water as needed. Tilt testing will then continue for an additional 5 minutes as described below or until syncope occurs, whichever comes first:

Figure 2



- If the CPC or Placebo are administered in the passive phase and the required additional 5 minutes extend beyond the usual 20 minutes, upright tilt is continued until the completion of the additional 5 minutes without the subsequent administration of NTG.
- If CPC or Placebo are administered in the NTG phase and the required additional 5 minutes extend beyond the usual 15 minutes, upright tilt is continued until the completion of the additional 5 minutes even if the total duration of tilt now exceeds the 35-minute duration.

Measurements (baseline and during tilt test):

- Baseline supine BP and HR
- Time of CPC administration during upright tilt
- Symptoms, BP, HR at onset of prodromes, 1 minute, 2 minutes and 5 minutes after CPC or Placebo administration. Measurements will be interrupted if the patient is back in the supine position.
- Time to syncope or near syncope after CPC or placebo drug administration
- BP, HR and ECG tracing during syncope or near syncope when applicable
- BP, HR immediately after resumption of supine position and at 5, 15 and 30 min
- Symptoms during the duration of tilt testing including post-CPC or placebo administration

After the tilt test, patients will be asked to complete a self-administered fatigue evaluation. Participants will remain in clinic until the 1-hour evaluation is completed and will be given the 4-hour and 8-hour form to be completed at home and mailed back to the study team. Patients will be instructed not to take any medications until completion of the 8-hour evaluation. After the 8-

hour waiting period, they will be asked to resume Midodrine and beta-blockers if previously prescribed.

5.0 Drug Information

CPC and placebo gel will be provided by Hybrid Pharma (1015 W. Newport Center Dr, Suite 106A, Deerfield Beach, FL 33442), an external pharmaceutical company (RBD) that is GMP certified.

5.1 Packaging and Labeling

For CPC Product per 1mL:

Active Components

Capsaicin 1 mg/mL
Caffeine 200 mg/mL
Phenylephrine 30 mg/mL

Inactive Components

Povidone (polyvinylpyrrolidone, PVP)
Polyethylene glycol 3350 (PEG 3350)
Peppermint Oil
FD&C Blue #1 Lake
Polyethylene glycol 400 (PEG 400)
Propyl gallate

For Placebo per 1 mL:

Inactive Components

Povidone (polyvinylpyrrolidone, PVP)
Polyethylene glycol 3350 (PEG 3350)
Peppermint Oil
FD&C Blue #1 Lake
Polyethylene glycol 400 (PEG 400)
Propyl gallate

Dose Delivery for CPC or Placebo

CPC or placebo dose of 1 mL will be loaded in a 3 mL syringe, sealed with a tip cap.

5.2 Preparation

All clinical drug research protocols within UW Hospital and Clinics, must be coordinated through the UW Pharmaceutical Research Center (PRC). For this study, PRC will randomize participants to treatment group, and maintain the randomization code list. PRC will prepare CPC or Placebo dose, for administration by study team during tilt test.

PRC Product Dispensing Label:
Name_____ Date_____
Participant ID# _____MR#_____ RPH: _____
CPC Compound: Capsaicin 1mg, Phenylephrine 30 mg, Caffeine 200mg or Placebo
Directions: Give 1 ml sublingually, hold under tongue for 1 minute, then swallow
FOR INVESTIGATIONAL USE ONLY HSC# XXXX-XXXX
Dr Hamdan, MD PH: 608-262-0143
UW Health – University Hospital; 600 Highland Avenue, Madison WI 53792

5.3 Storage *and Stability*

The product will be stored at refrigeration temperatures (4 C) and in the dark for long term storage. After loading into a 3 mL oral syringe, the dose can be stored for at least a week at controlled room temperature, shielded from direct sunlight.

5.4 Investigational Product Accountability

A perpetual inventory of study drug will be kept by the UW PRC. Unused or partially-dispensed dosages will be returned to the PRC for return to stock or disposal, as appropriate.

6.0 Assessment of Safety

6.1 Potential Risks and Mitigation Strategies

6.1.1 Known Risks related to CPC product and Mitigation Strategies

Cardiovascular Risks: A common side effect is palpitations due to the increase in sympathetic activity and associated tachycardia. A common side effect of increased blood pressure (BP) is headache. We believe this risk to be minimal because of the transient duration of BP increase and the exclusion of patients with a history of hypertension and cardiac arrhythmias. Results from the Phase I study revealed an average increase in SBP of 21 mmHg at 2 minutes with a range of 15-33 mmHg. In the 6 participants that received the proposed dose, no serious side effects were reported.

GI Risks: The oral pain from the administration of the capsaicin-containing product is expected, and may provide part of the therapeutic effect in future treatment of patients with VVS. Gastric discomfort and nausea is expected while participants are fasting, due to capsaicin. Participants will be able to drink water one minute after the application of dose. In the 6 participants that completed the Phase 1 study, the highest Pain Score was at 2 minutes with a mean of 5 and a range of 3-8 (scale 1-10). All participants swallowed the medication after keeping it sublingual for 1 minute and no participant refused the second dose at 2 hours.

6.1.2 Risks related to Tilt Table Test

Tilt Table Testing is generally safe and complications are rare. However, the known risks of the test are: low blood pressure, pauses between heart beats, nausea or vomiting after fainting, weakness that can last several hours. These symptoms generally improve when the table is placed in the flat position. Of note, these symptoms are similar to what patients experience when they have an event outside the hospital. The difference is that these events will be monitored and a provider will be available if needed. NTG administration can result in a headache. Participants may be required to sign the standard UW Health clinical consent for a Tilt Table Test as well.

There is risk of loss of confidentiality as participation in this study will be noted in the UW-Health EMR. Data obtained during the study, will be keep in password protected files and/or locked offices.

6.2 Adverse Event Collection:

Adverse Events will be collected during the tilt test including drug or placebo administration and up to 8 hours post drug or placebo administration based on participants' self-report.

The presence of a syncopal event during the tilt test, with the associated signs and symptoms including but not limited to changes in HR or BP will not be an AE for this study. The oral and

gastric discomfort from the sublingual administration of the CPC study drug is expected and will not be recorded as an AE.

6.2.1 Adverse Event (AE) Definition

Adverse event (AE) means any untoward or unfavorable medical occurrence in a human subject or others that happens during participation in a research study.

6.2.2 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of the investigator, meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires an inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly/birth defect
- Constitutes, based upon appropriate medical judgment, an event that may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed above

6.2.3 Unanticipated Problem (UP) Definition

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to research participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents.
- The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places participants or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized

6.2.4 Classification of an Adverse Event

Severity of the AE: The investigator will classify all AE's related to the following scale:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **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. For this protocol, providing milk and/or bread to reduce oral discomfort will not be considered treatment or infer severe toxicity.

- **Life threatening** - The patient was at risk of death at the time of the event.
- **Fatal** - The event caused death.

6.2.5 Relationship of AE to Investigation Product: The investigator will determine the relationship of all AE's based on the following scale:

- **Definitely Related** – Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
- **Probably Related** – Likely related to the study procedures/intervention and the influence of other factors is unlikely.
- **Possibly Related** – Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
- **Unlikely to be related** – Doubtfully related to the study procedures/intervention and there is another likely cause.
- **Unrelated** – Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in this clinical protocol and/or the investigational brochure.

6.3 Reporting of AE's, SAE's and UP's

AE/SAEs that meet the definition of an unanticipated problem will be reported to the HSIRB within 14 business days of learning of the event. Events that are immediately life threatening, severely debilitating to other current participants or resulted in a death will be reported to the IRB Chair or IRB Director via telephone or email within 24 hours (1 business day) of site awareness.

Events that are determined to be meet the FDA safety reporting requirements will be submitted by the sponsor-investigator within the timeframes described in following table.

Adverse Events that include all of the following:	**Notify in the time specified below based on date study team learned of event.**
• Serious (SAE) • Suspected/Related* • Unexpected	**HSIRB:** Within 14 business days **DMC**: Within 15 calendar days **FDA:** Within15 calendar days
• Life threatening or Fatal • Suspected/Related* • Unexpected	**HSIRB:** Within 1 business day **DMC:** Within 7 calendar days **FDA:** Within 7 calendar days
*Events that are possibly, probably, or definitely related meet the criteria for "Suspected/Related"	

6.4 Study and Participant Stopping Rules:

Study Stopping Rules:

Study Accrual will be paused if a participant experiences a SAE while the investigator reviews the case to determine if it meets the definition on an unanticipated problem.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the investigator will inform the IRB and regulatory authorities, including the reason(s) for the termination or suspension.

Participant Stopping Rules:
Participants may choose to discontinue participation at any time. If the investigator determines that study participation is not in participant's best interest, study participation may be stopped.

7.0 Study Analysis

7.1 Statistical Analyses

The **primary outcome** of the proportion of patients who experience hypotensive syncope or near syncope with SBP ≤ 70 mmHg during the tilt test will be compared between active and placebo arms via the two-sample z-test for population proportions. Given this primary outcome, we acknowledge the possibility that a subject may be randomized and participate in the protocol, but blood pressure measurement may not be available throughout the study period due technical problems. A subject who experiences near syncope without a known concurrent blood pressure measure would be unevaluable for the primary outcome. Thus, we define randomized subjects into two categories. First, randomized – evaluable patients are patients who are randomized and have complete blood pressure measurements that are sufficient to make a determination on the primary outcome. And second, we define randomized – unevaluable patients as those randomized patients whom, because of a lack of blood pressure measurement, we would be unable to determine if they had a primary outcome. Specifically, we define x_a and x_p to be the number of randomized – evaluable patients in the active and placebo arms, respectively, who experience hypotensive syncope or near syncope with SBP ≤ 70 mmHg from the n_a and n_p patients that are randomized – evaluable patients in each group, then the z-test statistic is given by

$$\boldsymbol{z} = \frac{\frac{\boldsymbol{x_a}}{\boldsymbol{n_a}} - \frac{\boldsymbol{x_p}}{\boldsymbol{n_p}}}{\sqrt{\bar{\boldsymbol{p}}\,(\boldsymbol{1}-\bar{\boldsymbol{p}})\left(\frac{\boldsymbol{1}}{\boldsymbol{n_a}}+\frac{\boldsymbol{1}}{\boldsymbol{n_p}}\right)}}$$

where $\bar{p} = (\boldsymbol{x_a} + \boldsymbol{x_p})/(\boldsymbol{n_a} + \boldsymbol{n_p})$. The test statistic will be evaluated against the Pocock boundaries at the interim and possible final analysis.

Secondary outcome measures include time to syncope or near syncope with SBP ≤ 70 mmHg, proportions of patients who experience asystolic pauses > 3 seconds, and measures of fatigue. Time to syncope or near syncope with SBP ≤ 70 mmHg will be measured from the time of administration of sublingual CPC or Placebo. Patients who do not experience syncope will be censored at the end of the tilt test. A log-rank test statistic will be used to compare the active and placebo arms. The Chi-square test or Fisher's exact test will be used to compare the number of patients who experience asystolic pauses > 3 seconds. Measures of fatigue will be compared via the Wilcoxon rank-sum test. All tests will be two-sided using a 0.05 level of significance.

Adverse events during the tilt test will be recorded and designated as before or after administration of CPC or Placebo as well as whether the event is considered serious or not. Events will further be classified by MedDRA System Organ Class (SOC). **Safety Measures** will include whether a subject has any adverse or serious adverse events as well as the total number of each. Comparisons between treatment arms will be conducted both overall and within SOC. Chi-square or Fisher exact tests will be used to compare the proportion of patients with events, while the Wilcoxon rank-sum test will be used to compare the average number of events a patient experiences.

7.2 Interim Analysis

A single interim analysis of efficacy is planned for when 76 subjects have been randomized and completed the tilt test and determined evaluable for the primary outcome. A data safety monitoring committee will be unblinded to the interim data while the PI and the rest of the study team will remain blinded. A Pocock monitoring boundary (Pocock 1977) will be calculated so as to preserve an overall two-sided significance level of 0.05 across both the interim and possible final analysis for the primary analysis. The boundary will be calculated based on the actual number of patients randomized with data available for use at the time of the interim analysis.

7.3 Sample size

At our institution, the positivity rate i.e. induction of hypotensive syncope in patients referred for tilt table testing for VVS during the period of March 2014 through February 2015 was 61% (268 out of 438 patients), (Chaddha et al 2016). Similarly, in a cohort population of 1602 patients aged 18 to 50 years undergoing tilt test in Italy, the positivity rate was 62% (unpublished data).

Knowing that the efficacy of current therapies for VVS range between 30% and 50%, we hypothesize a 50% reduction in the primary endpoint with the CPC product. However, we anticipate that at most 10% of subjects that are randomized may not complete the treatment regimen as assigned. Examples include refusal to keep medication under their tongue, inappropriate dispensement of medication, or not experiencing a prodrome and hence not being administered CPC or placebo. Thus, while we might assume an as-treated syncope rate of 62% for the placebo group and 31% for the CPC group, we assume the potentially diluted rates in the intent-to-treat (ITT) population to be 62% for the placebo arm and 34.1% for the active arm. A single interim analysis for efficacy is planned when 76 subjects have been randomized and determined evaluable for the primary outcome. A two-sided Pocock boundary will be employed to evaluate statistical significance maintaining an overall 2-sided significance level of 0.05 across both potential analyses. Having 63 randomized evaluable subjects in each group, or 126 total subjects, results in a statistical power of 85.2% to detect this difference in the ITT population syncope or near syncope with SBP $\leq$ 70 mmHg rates. In this case the information fraction at the first interim analysis is 60.31% and thus the Pocock critical values employed are z = ± 2.1599 in order to maintain the 0.05 significance level.

We anticipate that a total of 9.4% of participants brought into the clinic for tilt testing might not actually meet the eligibility criteria and be withdrawn as a screen failure. We further estimate that 2% of the subjects that we randomized will not be evaluable for the primary endpoint. We therefore inflate our overall sample size to 143 total subjects to be enrolled in order to achieve the 126 randomized – evaluable patients to maintain our estimated statistical power.

8.0 Data Collection

8.1 Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol. Information about study participants will be kept confidential and managed according to the requirements. Data collection is the responsibility of study team members under the supervision of the principal investigator. The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

8.2 Record Retention

It is the investigator's responsibility to retain study essential documents for a minimum of period of 7 years following completion of the study per UW-Madison institutional policy, or at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes last.

9.0 Regulatory, Ethical and Study Oversight Considerations

9.1 Institutional Review Board (IRB) Information

This protocol and the informed consent/HIPAA authorization document will be reviewed and approved by the UW Health Sciences IRB before initiation of the study and enrollment of participants. All participants must provide informed consent as documented on the informed consent/HIPAA authorization document prior to participation in this study.

9.2 Data Safety Monitoring Committee

A study specific Data Monitoring Committee (DMC) with be created to oversee the study. The committee will consist of 2 Cardiologists not involved with the study and a Bio-Statistician. Based on the DMC Charter, a periodic analysis every 6 months of the study results will be performed by the DMC to independently judge whether the overall integrity and conduct of the protocol remains acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

9.3 Study Monitoring

Study monitoring will be conducted by an independent monitor to participant data and verify that the trial is in compliance with the approved protocol and applicable regulatory requirements.

9.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Noncompliance will be reported to the HSIRB as applicable and within the required time frame.

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