

Use of visual contrast sensitivity and cholestyramine in diagnosis and treatment of indoor air acquired, chronic, neurotoxin-mediated illness

Background Summary

The use of visual contrast sensitivity testing (VCS) testing in patients with neurotoxin-mediated illnesses is relatively new. Pioneering work by Dr. Ken Hudnell of the US EPA National Health and Environmental Effects Research Laboratory has shown that exposure to estuaries with toxin forming dinoflagellates and fish kills can cause a distinctive mid-frequency deficit in contrast sensitivity. Work by Turf and others in Virginia has confirmed this finding. Work by the author in collaboration with Hudnell has shown that the VCS deficit resolves when symptomatic, exposed patients are treated with cholestyramine (CSM). Improvement in VCS following therapy matches abatement of clinical symptoms. Additional work by Shoemaker and Hudnell, with a variety of co-workers, has shown promise that the VCS-CSM approach may generalize to other illnesses known to be caused by low molecular weight, biologically produced neurotoxins including *Pfiesteria* and related toxic complex organisms, ciguatera, chattonella, cylindrospermopsis and microcystis. In a paper that is entering the peer review process, Hudnell and Shoemaker extend their work to include exposure to indoor environments with resident *Stachybotrys* species of fungi. Because it is not likely that an affected indoor environment will have only one species of resident toxin forming fungus present, we wish to generalize our approach to indoor air environments. When we can document the presence of species specific neurotoxins as causative agents in human illness, then we can specify which organism is responsible for the illness. Toxin identification in patients can currently only be accomplished by showing a non-specific deficit in a physiologic test, like VCS, as no reliable serologic tests are available.

VCS has been used successfully to screen patients with residential and recreational exposure to affected waterways in the absence of fish kills. In a tightly controlled study (manuscript in preparation) the combination of VCS and CSM successfully corrected a clinical syndrome of a chronic, neurotoxin-mediated illness that met all the CDC criteria for Possible Estuarine Associated Syndrome (PEAS). If VCS could be established as being an effective screening test in patients with unknown exposure, in addition to being a reliable test to detect the presence of the effect of neurotoxins in patients known to be exposed, then we would have a rapid, portable, non-invasive and inexpensive test that would have utility in screening patients in large buildings (for example), with large numbers of potentially exposed people.

The FDA issued a letter of exemption to Shoemaker (6/99), when he petitioned the agency to permit use of CSM in other chronic illnesses caused by neurotoxins including *pfiesteria*, ciguatera and cylindrospermopsis. In multiple studies since then, including a FDA, IRB approved study on patients with Lyme Disease coinfecting with *Babesia*, side effects of CSM have been minimal, with bloating, reflux and constipation having been reported. The opinion of the FDA, that they saw no reason why patients with environmental exposures would be more at risk for untoward side effects than patients for whom the medication was FDA approved, has been confirmed by our experience.

Because VCS is non-invasive, there is no risk to taking the test greater than holding a book, for example.

The mechanism causing the VCS deficit and its correction by CSM is not delineated, but is thought to be due to hypoperfusion of the optic nerve head similar to deficit associated with the hypoperfusion due to glaucoma. None of the patients in the studies of Hudnell and Shoemaker had untreated glaucoma.

In an attempt to validate the premise that hypoperfusion of the optic nerve head is indeed present with the VCS deficit and that the hypoperfusion resolves at the same time that VCS deficits abate and symptoms resolve, a special device, also FDA approved, the Heidelberg Retinal Flowmeter will be used to record velocity of capillary blood flow in the retina, neural rim of the optic nerve and lamina cribosa, the deepest layer of the optic nerve. In the Stachybotrys study, Shoemaker showed that retinal capillary flow rates were the same as unexposed controls but that neural rim flow rates were markedly diminished in exposed, symptomatic patients.

Contrast sensitivity: The ability to separate black from gray from white is measured by a neurotoxicological test of contrast sensitivity. As opposed to visual acuity, a measure that reflects 100% contrast between black and white, contrast testing isolates the functioning of neurons of the optic nerve and optic radiation that enable a visual image to include an edge. Previous work by Ginsburg and others has shown that deficits in contrast are associated with abnormalities in visually evoked potentials. A large number of normal patients have been studied, providing a reference distribution of normal contrast sensitivity. Deficits in contrast may be permanent, resulting from ophthalmologic diseases, neurodegenerative diseases, and occupational exposure to known neurotoxic substances, including organic solvents, heavy metals and petroleum products. Deficits in contrast that are not durable have been shown by Hudnell and Shoemaker to be present in chronic illnesses associated with exposure to toxin forming organisms, including *pfisteria* and ciguatera (both dinoflagellates), chronic fungal syndromes, cylindrospermopsis (blue green algae) and Lyme Disease. There are no data showing that *resident indoor fungal* organisms make a neurotoxin(s), but the preliminary study suggests that Stachybotrys may not be the only fungus that is neurotoxic and pathogenic.

Contrast sensitivity is tested using a standardized measure, FACT® (Stereo-Optical, Chicago, Illinois, a Gerber Coburn company). This noninvasive, rapid, portable, bedside test is reproducibly reliable when used according to a protocol. Prior, well-controlled studies have shown that the mid frequency deficit, greatest at 6 cycles per degree of visual arc, when associated with known exposure and presence of 4 of 8 categories of symptoms, is a statistically validated measure confirming the presence of a neurotoxin.

Optic nerve head imaging: The mechanism of development of the deficit in the FACT likely is due to local hypoperfusion of neurons of the optic nerve at the capillary level. Until recently, there has been no optical mechanism to demonstrate localized hypoperfusion. A new FDA licensed device, the Heidelberg retinal flow meter (HRF) can show the deficit in perfusion in affected patients, not seen in control patients.

Treatment: Treatment of indoor air acquired illness (IAAI), variously termed sick building syndrome and building related illness, with antibiotics, removal from the affected environment, asthma and allergy medications does not clear the clinical syndrome in a significant number of patients. Adjuvant therapy with cholestyramine (CSM) in patients with IAAI and symptoms refractory to standard medications and modalities who have a specific deficit in contrast sensitivity (an indicator of the presence of a biological neurotoxin) results in significant improvement in many, but not all of these patients. In the pilot study of *Stachybotrys* exposed patients, CSM treatment resulted in prompt clinical improvement, with resolution both of symptoms and the deficit on standardized contrast sensitivity testing.

Toxin binding therapy with CSM, at doses FDA labeled for treatment of hypercholesterolemia, results in a measurable improvement in FACT scores that matches symptomatic improvement in patients in all of the diseases mentioned above. The mechanism of benefit is thought to be an electrostatic interaction of the quaternary ammonium side chains of CSM with a molecular dipole (ion sink) created by the molecular structure of the toxins. The electrostatic interaction holds the toxins in the gut, preventing enterohepatic recirculation, much as CSM binds cholesterol. The FDA issued an exemption letter 6/28/99 regarding use of CSM in toxin mediated illnesses mentioned previously, stating that there was no obvious reason to think that CSM would be unsafe in this population compared to patients who take CSM to treat elevated cholesterol. Elevated cholesterol levels do not cause a deficit in FACT; treatment of high cholesterol patients who aren't affected by toxins does not result in an improvement in FACT. In prior studies, improvement in symptoms and FACT scores was durable with no relapse in the absence of re-exposure. Re-exposure can result in reacquisition of symptoms and FACT deficit that respond to repeat CSM therapy.

This study is intended to show that patients with undetermined exposure to indoor air environments with potential residence of toxin forming fungal species or other unknown sources of a chronic, neurotoxin mediated illness can be detected by a screening process, validated by sophisticated neuroophthalmological technology, treated with a benign, nonabsorbable anion binding resin, with the benefit of treatment measured by improvement in symptoms, VCS, and retinal or neural rim flow rates. The double-blinded protocol design will provide statistical certainty of benefit in patients.

Benefits of the study: According to a recent OSHA report, as many as 15% of our work sites and 10% of our schools are potentially sick buildings. Both are increasing in frequency. There are no FDA labeled medication protocols available for treatment of IAAI. By identifying an inexpensive biomarker and providing inexpensive, reliable therapy for IAAI patients, their health will improve. Perhaps of greater importance is the ability to define vague syndromes like SBS and identify the true nature of the illness as a chronic, neurotoxin –mediated illness. The FACT and HRF scores will become validated clinical tools for use in these conditions. The use of a

standardized symptom-recording instrument will help clinicians separate chronic, neurotoxin-mediated illness from other conditions, such as depression, stress, allergy, deconditioning, irritable bowel syndrome and fibromyalgia, for example.

An additional benefit for patients will be return to normal health. A benefit for clinicians will be a standardized approach to this challenging clinical problem in which older methods of laboratory testing are unreliable, expensive and controversial. By employing a physiological test and not a serological test, the clinician can document the effect of a pathogenic organism independent of the limited ability to detect the presence of the organism. Once the FACT and HRF are validated as useful screening tools, then clinicians in endemic areas can begin to detect a cohort of patients who have acquired a subclinical illness from contaminated indoor air environments. Enhanced detection will result in earlier, more effective treatment of the illness.

Given that there are many unknowns about IAAI, this study will provide a comprehensive approach useful to the practicing physician and researcher alike.

Study Objectives

Primary Objectives

- To determine the efficacy of CSM in the treatment of IAAI, when used in combination with VCS monitoring, in adult subjects with symptoms possibly due to exposure to neurotoxins in indoor air environments.

Secondary Objectives

- To evaluate the efficacy of VCS as a screening tool to detect IAAI
- To show that change in blood flow in the capillaries of the optic nerve head is a reliable marker for the presence of IAAI.
- To determine the efficacy of CSM when taken prophylactically in patients with a prior neurotoxin mediated illness, associated with exposure to an implicated indoor environment, when re-exposed to the suspected indoor environment

Study Endpoints

Primary Endpoints

- Clinical improvement as measured by symptoms
- Corrected visual contrast sensitivity (VCS) score as measured by FACT®

Secondary Endpoints

- Safety and tolerability

- Corrected capillary perfusion rate of the optic nerve head as measured through optic nerve imaging using a Heidelberg retinal flow meter
- Failure to develop a recrudescent illness when taking CSM, despite re-exposure with a history of illness acquisition previously associated with exposure when not taking CSM

Study Design

The study design is based on observed clinical benefit in less than 14 days in patients exposed to toxin-forming indoor fungal species, including *Stachybotrys*. By using 21 days of therapy, this study will likely reproduce previously observed benefit, but with an additional week of treatment to ensure benefit. By providing up to six additional weeks of therapy in the open label phase of treatment, our goal of resolution of symptoms has a better chance to analyze additional possibly confounding factors.

This is a single-center, randomized, double-blinded, placebo-controlled study. The initial phase of the study will use symptom lists and prior environmental and chemical exposure lists to identify patterns of illness in users of the indoor environments. All patients will be screened with VCS. Patients with deficits will then be analyzed for symptoms and confounding environmental factors.

Patients with VCS deficits, presence of symptoms from 4 of 8 categories of neurotoxic symptoms and no confounding exposures will be enrolled in the initial arm of the trial. CSM or placebo will be provided in a double-blinded manner, with randomization done by the staff of the study coordinator, for 21 days. Symptoms and VCS scores will be recorded for both groups at completion of the 21 day efficacy study. Patients will be crossed-over to the other treatment arm for an additional 21 days. Symptoms and VCS will be recorded. The double blind will be broken at this stage. If patients have persistent symptoms or VCS deficits, they will be offered CSM or placebo (at the patients request, depending on which blinded medication helped them, in their opinion, more than the other), provided in an open-label fashion. The second arm of the study will enroll successfully treated patients with normal VCS. They will return to their indoor environment, but without CSM. Possible confounding exposures will be recorded daily. VCS will be recorded daily and symptoms recorded every two days. At the end of 3 weeks of exposure, all patients will be analyzed for possible relapse. Those patients who relapse, with deficits in VCS and symptoms will be retreated with CSM for 21 days or until VCS and symptoms are again corrected. The third arm of the trial will involve patients with reexposure who relapsed. Once asymptomatic, or at the end of the 21 day CSM treatment, but before returning to the indoor environment, these patients will be treated with a prophylactic dose of CSM, one scoop taken twice a day. These patients will again monitor their VCS scores and symptoms. These patients will be evaluated 3 weeks later. Patients who successfully avoided reacquisition of their previously known, environmentally acquired illness will be provided the opportunity to continue CSM or not. These patients will be allowed to enroll in a long-term follow-up study that is the fourth arm of this trial which attempts to confirm long term prevention of relapse, despite re-exposure. These patients will have VCS and symptom recording monthly. This arm of the trial will continue for 6 months.

HRF measurements will be performed at entry into the study, completion of the 21 days of both placebo and CSM therapy, following 21 days of reexposure, following 21 days of retreatment and 21 days of the prevention arm. The HRF is much less portable than VCS and cannot be used for daily measurements on all patients.

Planned Sample Size

A total of 50 subjects at one study site will be enrolled into the study. The sample size was based on experience gathered in previous studies rather than statistical considerations. However, the number of subjects is expected to provide adequate information to evaluate the study objectives.

Study Population

Subjects regardless of gender may be enrolled into the clinical trial if they are ≥ 18 years of age and have been diagnosed with IAAI. Subjects must meet the following entry criteria within 28 days prior to study enrollment.

Inclusion Criteria

A subject will be eligible for inclusion in this study if all of the following criteria apply:

1. Male or female, at least 18 years of age.
2. History of indoor air exposure.
3. No other known causes of VCS deficits
4. Presence of 4 of 8 symptom categories of neurotoxin illness.
5. Failure to respond to standard medications, including antibiotics, lung and allergy medications.
6. If female, documentation of non- pregnant status.
7. Abnormal visual contrast sensitivity score
8. Corrected visual acuity of 20/50 or better in each eye
9. A signed and dated written informed consent is obtained for the subject or the subject's legally acceptable representative prior to study participation.

Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Participation in other investigational drug protocols within the last 28 days.
2. History of chronic solvent exposure, chronic alcoholism, occupational exposure to metal fumes, dust or petroleum products.
3. Diagnosed with complete biliary obstruction.

Study Drugs

Subjects will be randomized to receive either CSM or placebo, double blind, in combination with Questran[®], open-label, for the balance of the study.

Women who are pregnant or who are contemplating becoming pregnant should not participate in this trial unless the risk to the fetus from the illness is greater than the risk to the fetus from the medication. Nursing mothers should exercise caution even though it is not known whether or not cholestyramine is excreted into human milk. In clinical studies, the common side effects of cholestyramine are nausea, reflux, bloating, and constipation.

Questran[®] Light

Questran[®] Light (cholestyramine) is a non-absorbable anion binding resin FDA approved for the treatment of hypercholesterolemia. It is available in powder form for oral suspension. Each 5 grams of Questran Light[®] contain 4 grams of anhydrous cholestyramine resin and the inactive ingredients: aspartame, citric acid, flavor, color, propylene glycol alginate, colloidal silicon dioxide and sucrose, and xanthan gum. Cholestyramine resin is quite hydrophilic, but insoluble in water, and is not absorbed from the digestive tract. Questran[®] Light resin absorbs and combines with bile acids in the intestine, of which cholesterol is probably the sole precursor, to form an insoluble complex, which is excreted in the feces.

Questran[®] Light is contraindicated in patients with complete biliary obstruction where bile is not secreted into the intestine and in those individuals who have shown hypersensitivity to any of its components. Questran[®] Light may delay or reduce the absorption of concomitant oral medications such as phenylbutazone, warfarin, thiazide diuretics (acidic), or propranolol (basic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins, and digitalis. Because cholestyramine binds bile acids, Questran[®] Light may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E, and K. Since Questran[®] Light may bind other drugs given concurrently, it is recommended to take other drugs at least one hour before or 4 to 6 hours after Questran[®] Light to avoid impeding their absorption. The use of Questran[®] Light in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. The most common side effects of cholestyramine are constipation, nausea, bloating, and reflux. Less common side effects are abdominal discomfort and/or pain and flatulence.

For additional information, refer to the product information for Questran[®] Light.

Administration

One scoop of Questran[®] Light (5 grams) will be mixed in water or juice and swallowed four times a day on an empty stomach, 30-60 minutes before taking other medication or eating food. Questran[®] Light should not be taken in its dry form. Always mix Questran[®] Light with water or other fluids before ingesting.

Packaging and Labeling

Questran[®] Light must be obtained by a physician prescription and will have the commercial label.

Blinding

Packets of Questran Light[®] or placebo will be dispensed according to a random selection performed with no knowledge of the investigator.

Measurements and Evaluations

A Time and Events Schedule detailing the schedule of measurements and evaluations for the study are found in Table 1.

Pre-Entry (Screening) Evaluations

Written informed consent will be obtained for the subject (or his/her legal representative) by study site personnel prior to the initiation of any pre-entry or screening procedures. The consent form will be approved by the site's IRB. Following informed consent, subjects will report to the clinic within 28 days, ensuring adequate time for evaluation of the screening tests necessary to determine eligibility for the study prior to study entry. All patients will have a thorough history and physical exam performed, including demography and weight. Assessment of subject eligibility according to inclusion and exclusion criteria will be performed and included in an individual file for each patient.

Baseline (Day 0) (Study Entry) Evaluations

The following procedures will be performed:

- Assessment and recording of adverse events (only SAEs related to study participation).
- Symptoms questionnaire
- Visual contrast sensitivity using FACT
- Optic nerve imaging using HRF
- Study drug dispensation
- Laboratory evaluations (including a CBC, GGTP, and metabolic profile)
- Serum HCG in women age 10 to 55 (unless deemed unnecessary)

On Study (Days 21-84) Evaluations

The following evaluations will be performed:

- Assessment and recording of adverse events (Day 21, 42, and Day 63 and 84, if subject continues in the study)
- Symptoms questionnaire (Day 21, 42, and Day 63, 84, if subject continues in the study)
- Visual contrast sensitivity using FACT (Day 21, 42, and Day 63, 84, if subject continues in the study)
- Optic nerve imaging using HRF (Day 21, 42, and Day 63, 84, if subject continues in the study)

- Study drug dispensation (Day 21 and Day 42, 63 , if subject continues in the study)
- Laboratory evaluations (on the subject's last study visit: Day 42 or Day 63 or 84, if subject continues in the study)
- Weight (on the subject's last study visit: Day 42 or Day 63 or 84, if subject continues in the study)
- If the patient begins the second arm (relapse with re-exposure) and the third arm, (prevention of relapse with re-exposure), the above parameters will be recorded at a clinic visit on days 105 and 126, respectively. Additional symptom and VCS recording will be performed at least every other day.
- The fourth arm of the trial, long term prevention of relapse, will include symptom and VCS recording monthly for 6 months.

Follow-Up Evaluations

At the conclusion of the study, a follow-up visit with physical exam will be scheduled within one month of study completion to assess and record any adverse events. Serious adverse events observed during the study will be followed by the investigator until these events have resolved or stabilized, the subject is lost to follow-up, or the event is otherwise explained.

Withdrawal/Premature Discontinuation

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his discretion, discontinue the subject's participation from this study at any time. An effort will be made to obtain the following evaluations:

- Assessment and recording of adverse events
- Symptoms questionnaire
- Visual contrast sensitivity using FACT
- Optic nerve imaging using HRF
- Laboratory evaluations
- Weight

Safety Assessments

Adverse events will be recorded regardless of whether the event(s) are considered related to study medication. All adverse events considered related to study medication will be followed until resolution.

Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended

sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE does include a/an:

- exacerbation of a pre-existing illness.
- increase in frequency or intensity of a pre-existing episodic event or condition.
- condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a/an:

- medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- the disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.
- overdose of either study drug or concurrent medication without any signs or symptoms.

Definition of a Serious Adverse Event

An SAE is any adverse event occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a disability/incapacity
- a congenital anomaly in the offspring of a subject who received drug
- important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event 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

Clarifications:

- "Occurring at any dose" does not imply that the subject is receiving study drug.
- Life threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.
- “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.
- With regard to the last bullet above, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

Emergency procedures

The test center is an outpatient physician’s office. IAAI patients are seen as part of the daily patient mix of a busy Family Practice office. There is no reason to expect study patients to present a greater risk for emergency care than other patients in the practice. The center is close to the local ambulance squad, with 911 response time less than 5 minutes. The office is equipped with basic life support equipment.

Data Analysis Methods

Statistical analysis of symptoms, visual contrast sensitivity scores, and HRF histograms will be performed according to standard methods. Results from before and after treatment will be reported with a *p* value reflecting probability of statistical significance.

References

Attached is a partial list of papers reviewed in support of this application.

Ritchie C. Shoemaker MD
Chronic Fatigue Center
Chronic Neurotoxin Mediated Illness Center
McCready Outpatient Systems
Pocomoke City, Maryland

Table 1: Time and Events Schedule

Event	Screenin g	Baseline	Treatment Phase					
	-28 to -1	0 ^a	Day					
			21	42	63	84	WD _b	FU ^c
Informed Consent	X							
Medical History	X							
Physical Exam	X							
Demography	X							
Weight	X			X ^d	X _d ^d	X ^d	X ^d	
Visual Acuity	X	X	X	X	X	X	X	
Symptoms questionnaire	X	X	X	X	X	X	X	
Visual Contrast Sensitivity using FACT [®]	X	X	X	X	X	X	X	
Optic Nerve Imaging using HRF		X	X	X	X	X	X	
Adverse Events		X ^e	X	X	X	X	X	X
Laboratory Evaluations ^f	X	X		X ^d	X _d ^d	X ^d	X ^d	
Quesstran [®] Dispensing: Double-Blind		X ^g	X ^g					
Quesstran [®] Dispensing: Open-Label				X ^h	X _h ^h			

WD – Study withdrawal
FU – Follow-up

HRF – Heidelberg retinal flow meter
FACT[®] - Stereo-Optical

- a Day 0 is used to indicate study entry (the day on which the first dose of study medication is administered).
- b Withdrawal evaluations must be performed if subject discontinues prematurely from the study.
- c Subjects completing or withdrawn from the study should also have a follow-up evaluation within one month.
- d Assessment will be performed on the subject’s last study visit (Day 42, 63, 84 or upon withdrawal).
- e Study-related serious adverse events
- f Laboratory evaluations will include CBC, GGTP, and metabolic profile. HCG as indicated.
- g Subjects will be randomized to receive either CSM[®] or CSM placebo in a blinded, crossover fashion
- h Subjects will continue on CSM as per protocol