PROTOCOL TITLE: *Lamotrigine for Ménière's disease: a double-blind, placebo-controlled pilot study*

INSTRUCTIONS: Complete Research Protocol (HRP-503)

- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable for the response. For example, most behavioral studies would answer all questions in section 30 with words to the effect of "drugs and medical devices are not used in this study."*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it will not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Include the full protocol title.

Response:

Lamotrigine for Ménière's disease: a double-blind, placebo-controlled pilot study

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VERSION NUMBER:

Include the version number of this protocol.

Response:

7

DATE:

Include the date of submission or revision.

Response: 6/4/2015

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Response:

Not funded by a grant

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1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

Response:

The purpose of this study is:

- Primary objective: To determine if lamotrigine, a sodium channel blocker, can reduce the frequency of Ménière's vertigo attacks greater than a placebo treatment
- Secondary objective: To determine if lamotrigine can improve other Ménière's disease symptoms, like tinnitus and hearing loss, and improve patients' quality of life greater than a placebo treatment

1.2 State the hypotheses to be tested.

Response:

Lamotrigine, a sodium channel blocker, can reduce the frequency of Ménière's vertigo attacks greater than a placebo treatment and it can improve other Ménière's disease symptoms, like tinnitus and hearing loss, and improve patients' quality of life greater than a placebo treatment

2.0 Background

2.1 Describe the relevant prior experience and gaps in current knowledge.

Response:

Prosper Ménière first described an inner ear disorder that caused vertigo and hearing loss (Baloh, Halmagyi, & Zee, 2012; Gates, Green, Tucci, & Telian, 2004). Today the disorder, known as Ménière's disease (MD), is reported to affect 20 to 200 individuals per 100,000. MD continues to be characterized by the same symptoms described in 1861. The 1995 American Academy of Otolaryngology- Head and Neck Surgery's (AAO-HNS) criteria include recurrent spontaneous and episodic vertigo with hearing loss, aural fullness and/or tinnitus. The vertigo episodes can last from 20 minutes up to several days (Committee on Hearing and Equilibrium, 1995; Gates et al., 2004). Additionally, many individuals develop related anxiety and depression symptoms, and a poorer quality of life (Balaban, Jacob, & Furman, 2011; de Moraes, Soares, Ferriolli, & Perracini, 2013; Van Cruijsen, Jaspers, Van de Wiel, Wite & Albers, 2006). Those diagnosed with Ménière's disease are severely impacted and treatment of the vestibular disorder is challenging. The disease's idiopathic nature is one hindrance to developing an efficacious therapy.

It is commonly thought that endolymphatic hydrops (EH) causes Ménière's disease (Sajjadi & Paparella, 2008). The buildup of endolymph fluid within the cochlear and saccular ducts, from either failed absorption or excess production, cause the structures to expand into the

endolymphatic space (Syed & Aldren, 2012; Thai-Van, Bounaix & Fraysse, 2001). The subsequent increased inner ear pressure may cause damage to hair cells and the vestibular labyrinth, prompting vertigo attacks and an aural fullness sensation. These symptoms are characteristic of Ménière's disease; however, hydrops may instead be an epiphenomenon rather than the primary cause (Lempert, 2012). EH has an earlier age of onset than Ménière's disease and not every patient with EH develops Ménière's symptoms (Foster & Breeze, 2013). Additionally, studies have shown that animals induced with hydrops did not develop vertiginous spells and did not present differences in hydrostatic pressures in the perilymph and endolymph (Berlinger, 2011; Kimura, 1982). This suggests that the mechanism of hydrops is not fully understood and that EH is likely a predisposing factor, but not a sufficient primary cause.

It has been hypothesized that Ménière's disease is an autoimmune disorder. Some viruses are well known for affecting the inner ear (Davis & Johnson, 1976) and the chemical damage caused by an immune reaction could cause labyrinthitis. This leads to fibrosis in the vestibular cistern and endolymphatic hydrops (Greco et al., 2012). Supporters of this theory cite the presence of lymphatic vascularization, various immunocompetent cells located close to the endolymphatic sac and biological signs of immune reactions in Ménière's disease patients (Evans, Baldwin, Bainbridge & Morrison, 1988; Dornhoffer, Wagner, Arenberg, & Montague, 1993; Soliman, 1996). The theory's major inconsistency is that autoimmune disorders are systemic and should thus affect both ears rather than the commonly seen unilateral MD presentation (Foster & Breeze, 2013).

A more recent etiology theory involves ischemia. The stria vascularis within the inner ear is particularly sensitive to ischemia and when affected the ear loses endocochlear potential. This results in tinnitus and low frequency hearing loss. Furthermore, vertigo can occur when a significant amount of the calyces or boutons of sensory neurons in at least one of the cristae or maculae becomes ischemic. Repeat destruction of calyces and boutons and hair cell ischemia cause sensory neuron death and degeneration of hair cells, which manifests as progressive hearing loss and vestibular impairment (Foster & Breeze, 2013). Whether ischemia causes endolymphatic hydrops to occur or vice versa is disputed. One belief is that cerebrovascular problems cause the perfusion pressure to lower to just above the ischemic threshold of an ear with endolymphatic hydrops, causing the Ménière's symptoms. An alternative argument is that cerebrovascular impairments cause altered hemodynamics, which then cause endolymphatic hydrops. Although the involvement of endolymphatic hydrops in Ménière's disease is a shared feature among various theories, there is still much to be discovered. The unknown etiology has led to several treatment approaches with various success.

A low salt diet is frequently recommended based on the belief that sodium increases inner ear fluid and causes the integral hydrops (Gates et al.,

2004). Patients are instructed to avoid adding salt to food, make a habit of reading food labels, and avoid processed food. Increasing water intake has also been used to further reduce sodium levels. These restrictions can be very difficult to maintain long-term and compliance is often an issue (Gates, 2005). Even though limiting sugar, monosodium glutamate, caffeine, and alcohol has been reported to help decrease the frequency of MD attacks, there is no substantial evidence that dietary considerations can significantly affect the fluid composition in the inner ear or address Ménière's symptoms (Berlinger, 2011; Gates, 2004; Quaranta, Aloisi, De Benedittis & Scaringi, 1999).

Pharmacological treatments have routinely been symptomatic, focusing on eliminating dizziness with vestibular suppressants and relieving nausea, vomiting, and anxiety (Strupp et al., 2008). Benzodiazepines, like Diazepam, have a central vestibular sedative effect and can be useful in helping with anxiety, but can interfere with vestibular compensation and cause side effects of dependence, impaired memory, and incoordination with ataxia (Thai-Van, Bounaix, & Fraysse, 2001). Antiemetic agents are used to control the vertigo and anxiety associated with MD. Meclizine, a well-known antiemetic, is believed to decrease the excitability in the middle ear labyrinth and reduce the strength of the middle ear vestibular-cerebellar pathways (Thai-Van, Bounaix, & Fraysse, 2001). However, negative side effects include drowsiness and increased toxicity of antipsychotics and anticholinergics (Quaranta et al., 1999).

Drug therapies grounded in etiology theories of ischemia and hydrops include vasodilators and diuretics. Betahistine, a vasodilator, blocks H1 and H3 receptors and increases vestibular and cochlear blood flow to facilitate vestibular compensation and control vertigo (Strupp et al., 2008). Although Betahistine is able to control vertigo, it has not been shown to address any other MD symptoms (Kaylie, Jackson & Gardner, 2005). The drug has not been US FDA approved and side effects include stomach fullness and discomfort, diarrhea, nausea, and headaches (Sampson, 2003; Monzani, 2012; Quaranta et al., 1999). Alternatively, diuretics are prescribed to reabsorb the endolymph fluid causing endolymphatic hydrops. Long term, non-blind trials showed up to a 79% improvement in vertiginous symptoms with some improvement in hearing, but this may reflect the natural history of the disease (Thai-Van, Bounaix, & Fraysse, 2001). Other doubts about the benefits of diuretics arise from methodology flaws in many of the studies (Quaranta et al., 1999).

Aminoglycosides reduce the sensitivity of the vestibular system by damaging the vestibular sensory hair cells. The injection treatment claims to preserve hearing because vestibular sensory hair cells are more sensitive to damage than cochlear hair cells. Gentamicin is the most commonly used aminoglycoside due to its availability, large therapeutic window before becoming cochleotoxic, and less pain experienced during injection (Silverstein, Wazen, Van Ess, Daugherty & Alameda, 2010). Studies have

had success with gentamicin, including complete resolution of vertigo attacks (Steenerson, Hardin, & Cronin 2008), minor improvements in tinnitus and aural fullness (Quaranta, Aloisi, Benedittis, & Scaringi, 1999), reduction in disability and anxiety (Boleas-Aguirre Sanchez-Ferrandiz, Guillen-Grima, & Perez, 2007), and increased perceived quality of life (Postema, Kingma, Wit, Albers & Wan Der Laan, 2008). However, some patients still suffered hearing loss (Kaylee, Jackson, & Gardner, 2005; Posema et al., 2008). It is unclear whether this is due to the gentamicin therapy, natural history of the disease or inconsistent procedures (Brinson, Chen & Arriaga, 2007). The treatment lacks a standard dosage, number of treatments, and time between treatments, or indicators for ending treatment. Aminoglycosides therapy also excludes bilateral MD patients, who would experience bilateral hypofunction and induced disequilibrium and oscillopsia (Coelho & Lalwani, 2008).

Corticosteroids therapeutic usage aligns with the autoimmune etiology. Success rates vary across literature and, similarly to gentamicin treatment, there is a wide variety of recommended doses and frequency of administration (Hamill, 2006). Complications reported include pain, short-lasting vertigo, otitis media, perforations in the tympanic membrane, and hearing loss. Corticosteroids have recently had great success with treating sudden sensorineural hearing loss, but there is no strong evidence to support its use for Ménière's disease (Gottsball, Hoffer, Moore & Balough, 2005). Prospective studies have shown an improvement in vertigo with no significant changes with hearing and tinnitus (Coelho & Lalwani, 2008). Since there is no effect on hearing, it is believed that the pathophysiology of Ménière's is different from sudden sensorineural hearing loss (Gottsball, 2005). The decision to use a specific drug for MD is based on what the physician believes is causing the disease, whether it is endolymphatic hydrops, ischemia, or autoimmune disease. However, evidence is lacking for many of these pharmacotherapies and negative side effects are a major concern.

Surgical treatment, aimed to either relieve endolymphatic hydrops or deafferent the affected ear, is typically used for Ménière's disease patients who haven't had success with medications (Gates et al., 2004). Observed improvement of MD symptoms in higher elevations or with weather changes proposed the idea that the relative positive pressure in the middle ear was responsible for the relief (Gates et al., 2004). In an attempt to replicate the effect, a portable low-intensity alternating pressure generator was created to apply pulsed pressure into the ear via a surgically implanted tympanostomy tube. The machine is now marketed in the United States as the Meniett device (Gottshall, 2008). The Meniett device is well tolerated and able to reduce vertigo, at least in the short term (Thai-Van, Bounaix & Fraysse, 2001; Shojaku et al., 2011; Boudewyns et al., 2005; Buchanan, 2010). Researchers are cautious about its use because it is difficult to comprehend why pulsed pressure would benefit Ménière's patients. It instead might be treating patients who have a perilymphatic fistula and are

misdiagnosed with Ménière's (Hain, 2010). Middle and external ear infections have also been reported (Coehlo & Lalwani, 2008). Acceptance of this treatment is especially slow because of its high cost and uncertainty about its long-term effectiveness (Gates et al., 2004). U.S. insurers do not recognize Tympanostomy tube placement for Ménière's disease as an indication and few insurers have made provisions for payment.

Conservative endolymphatic sac surgery decompresses the endolymphatic sac from the overlying bone and drains the endolymph to keep the innervation intact and restore normal endolymphatic pressure (Hamill, 2006). Although publicized as a placebo effect 20 years ago (Thomsen, Bretlau, Tos & Johnsen, 1981), endolymphatic sac surgery is still the most commonly used initial surgical treatment for Ménière's (Ghossaini & Wazen, 2006). There is very little risk involved (Hamill, 2006). And this treatment is especially useful for bilateral Ménière's disease because it conserves hearing and does not rely on later compensation. The short-term rate of vertigo control is as high as 80-90% (Huang, 2002). However, the surgery's long-term efficacy is unclear (Silverstein, Lewis, Jackson, Rosenberg, Thompson & Hoffmann, 2003; Telischi & Luxford, 1993).

Vestibular nerve section surgery cuts the vestibular portion of the 8th nerve while the cochlear portion remains intact (Hamill, 2006). Ghossaini & Wazen (2006) reported that this surgery has comparable results to gentamicin when examining vertigo control rates. The surgery virtually eliminates vertigo and preserves hearing (Hamill, 2006). Unfortunately, because the intracranial cavity is opened during this surgery, it requires a several day hospitalization and complications during the procedure are higher than other surgical options. This includes risk of facial nerve paralysis, hearing loss, cerebrospinal fluid leak and headache (Gates, 2006; Gates et al., 2004). This surgical option is contraindicated for bilateral Ménière's disease patients, similarly to gentamicin, (Hamill, 2004), older patients, individuals with MS and with cerebellar dysfunction (Gates, 2006). So, although vestibular nerve section can eliminate vertigo, it is still an invasive procedure that should not be used with all Ménière's patients.

Surgical labyrinthectomy is a treatment option for Ménière's disease patients with very little usable hearing remaining (Hamill, 2004). The outpatient procedure removes the entire labyrinth to eliminate vertigo and allow vestibular compensation to occur. It has superior vertigo control rates over any other method, but also destroys all hearing function. This surgical treatment option is seen as a last resort for unilateral Ménière's patients with virtually no usable hearing on the affected side.

Consequently, there is an absence of effective treatments. Treatment has moved away from surgical procedures and more towards therapies that are non-invasive, such as dietary considerations and pharmacotherapy. The decision of which treatment to use varies and there are no strict protocols for many of the procedures, including aspects of treatment duration and

intensity. In addition, the majority of treatment options for MD have not had controlled experimental testing completed (Hamill, 2006). An effective oral medical treatment of Ménière's disease will revolutionize treatment options. It will be cheaper, avoid surgical treatment, and prevent hearing loss from cochlear damage, unlike other treatments.

The idea to use lamotrigine to treat Ménière's disease was a completely incidental finding. As a certified epileptologist, Dr. Lixin Zhang frequently uses antiepileptic medications. Dr. Zhang especially liked lamotrigine due to the favorable side effect profile, which includes fewer cognitive side effects and less sedation. Lamotrigine has already been shown to have an effect on migraines and visual auras during migraine attacks, a symptom believed to be caused by cortical spreading depression (Bogdanov et al., 2011). The Dizziness and Balance Center also observed that lamotrigine could effectively treat patients with Migraine-associated vertigo. Migraine has been frequently associated with Ménière's disease and the two disorders share several likenesses. A study on the comorbidity of migraine and Ménière's disease found a significantly higher lifetime prevalence of migraine for both men and women in the MD group compared to an age- and sex-matched control group (Radtke, Lempert, Gretsy, Brookes, Bronstein & Neuhauser, 2002). Both vestibular disorders have a similar non-drug treatment, including avoidance of caffeine, chocolate, alcohol, tobacco and salt (Sajjadi & Paparella, 2008). Additionally, Ménière's disease and migraines have significant genetic components and it is possible that patients are inheriting a brain and inner ear abnormality that causes both disorders (Baloh, Halmagyi & Zee, 2012). These commonalities suggest that MD patients with migraine may find relief with anti-migrainous medication. Lamotrigine was first used to treat a Ménière's patient because the patient also suffered from migraine. During the treatment, the patient's typical Ménière's vertigo attacks were completely under control. From that point, any patient who was diagnosed with Ménière's disease and had frequent attacks (three or more vertigo attacks over the last three months) was prescribed lamotrigine and monitored.

The most popular theories for migraine are cortical spreading depression (CSD) or vasoconstriction and dilation. Cortical spreading depression is self-generated cortical neuronal depolarization, which then spreads slowly (Dodick & Gargus, 2008). The cortical neuronal activities may cause vasoconstriction and dilation of deep subcortical white matter vessels (Brennan, Beltran-Parrazal, Lopez-Valdes, Theriot, Toga & Charles, 2007). If the vasoconstriction continuously lasts for longer periods of time, it may cause ischemic changes in the white matter and gray matter (Bashir, Lipton, Ashina & Ashina, 2013; Messina et al., 2013).

If lamotrigine is an effective treatment for Migraine-associated vertigo and Ménière's vertigo attacks, it suggests that Ménière's disease may be like an "inner ear migraine". We propose that similar neuronal activities found

in CSD, or self-generated neuronal depolarization, in the ear may spread from either the vestibular organ to the cochlear or vice versa. Spreading depression is a slow process and may explain why a true Ménière's vertigo attack is at least 20 minutes and a migraine is usually defined as four hours or longer (Committee on Hearing and Equilibrium, 1995; Headache Classification Committee, 2004; Porooshani, Porooshani, Gannon & Kyle, 2002). These neuronal activities may cause vasoconstriction and dilation, and repeated prolonged attacks may lead to ischemic damages to vestibular organs and the cochlear. This damage could then cause lymphatic hydrops, permanent vestibular imbalance and hearing loss. Another possibility is that a patient may have preexisting unilateral lymphatic hydrops, which is able to generate spreading depression and then leads to vertigo attacks, tinnitus and hearing loss. The preexisting condition may be a better explanation of the initial unilateral process in most Ménière's patients (Foster & Breeze, 2013) and the spreading depression theory may best explain the episodic presentation, slow progression, and variable course of Ménière's disease. If this theory holds true, it will completely revolutionize the understanding of this devastating vestibular disease and will open a new trajectory of research in terms of developing animal models and new medical treatments. Our preliminary data already shows promising findings to support this new theory.

2.2 Describe any relevant preliminary data.

Response:

Between January 2011 and November 2013, 48 patients in the Dent Dizziness and Balance Center were diagnosed with Ménière's disease and were prescribed lamotrigine as an off-label treatment. These patients were given a definitive or probable diagnosis based on the AAO-HNS 1995 criteria and had experienced at least three attacks in the three months prior to treatment. Almost all patients had been previously seen by ENT or other specialists and had tried conventional treatments like an improved life style, a low-sodium diet and diuretics. Some patients even attempted surgical treatments. Dosages varied from 50-300mg daily; most patients experienced a reduction of vertigo attacks during titration, but if another attack occurred the dose was increased further. We found that 13 of the 48 patients (27.1%) were also diagnosed with some form of anxiety, six individuals (12.5%) with only migraine and 21 individuals (43.8%) with an anxiety disorder and migraine. Out of these 48 individuals, ten were lost to follow-up and four patients had side effects like rash and had to discontinue the medication. After removing the above 14 patients, 94.1% (32/34) of remaining individuals reported improvement in symptoms, especially a reduction of Ménière's vertigo attacks. Furthermore, 50% (16/32) of improved patients experienced complete vertigo attack remission. Before initiation of lamotrigine therapy, 48 patients reported a mean of 13.5 (SD=12.5) vertigo attacks in the preceding three months (Figure 1). Thirty-five of the patients completed the initial follow-up and

reported a mean of 4.9 (SD=7.2) vertigo attacks in the three months after starting lamotrigine, *p<0.0001 (Wilcoxon signed rank test). Twenty-eight patients reported a mean of 2.5 (SD=5.5) vertigo attacks after completion of a three-month maintenance dose, *p<0.0001 (compared to before lamotrigine). Vertigo attack reduction and remission was not affected by migraine comorbidity.

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Response:

Please refer to 2.1

2.4 Include complete specific citations/references.

Response:

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3.0 Inclusion and Exclusion Criteria

3.1 Describe the criteria that define who will be included or excluded in your final study sample.

Respons Inclusion Criteria:

•Male and female participants aged 18 years or older

•Diagnosed with unilateral definite Ménière's disease according to the AAO-HNS 1995 criteria, confirmed by an ENT

•Active vertigo: at least two Ménière's vertigo attacks (defined as lasting 20 minutes or longer and associated with tinnitus, ear fullness, or low frequency hearing loss and nausea/vomiting) every four weeks during the eight-week qualification period and at least two or more Ménière's vertigo attacks during the lead-in phase prior to randomization

•Documented unilateral lower frequency hearing loss defined as the four-tone average (arithmetic mean rounded to the nearest whole number) of the pure-tone thresholds at 0.25, 0.5, 1 and 2 kHz more than or equal to 25 dB of the worse audiogram during the six months before screening

•Have tried diuretics for at least one month and discontinued treatment due to continued vertigo attacks

•All other co-existing medical or psychiatric conditions are stable, and no greater than moderate severity

•Willing to avoid pregnancy during the entirety of the study (abstinence or two forms of acceptable birth control, such as condoms and oral contraceptives)

Exclusion Criteria:

•Bilateral Ménière's disease

•Current or past history of migraine

•Any other neuro-otologic disease or major vestibular abnormality found during screening that could confound the evaluation of Ménière's symptoms

•Previous intolerance or sensitivity to lamotrigine

•On any prohibited medication within four weeks prior to the study

•History of tympanostomy tubes with evidence of perforation or lack of closure

•IT gentamicin injections or endolymphatic sac surgery within the last year

•History of or current immunodeficiency disease, nephrolithiasis, hypertension, cardiac disease, arrhythmia, hypercholesterolemia, hemiplegic/basilar migraine, stroke, diabetes, vascular disease or kidney disease

•Family history of unexplained deafness

•Pregnant or breastfeeding

•Current diseases or conditions that may be associated with an altered perception of processing stimuli

•Current severe medical condition(s) that in the view of the investigator prohibits participation

•Previously used the investigational drug

•Current non-vertiginous dizziness (orthostatic or panic disorder) unless it could be clearly differentiated from Ménière's attacks by the participante:

3.2 Describe how individuals will be screened for eligibility.

Response:
Dr. Zhang conducts and orders a physical exam and relevant testing to assure subjects meet criteria outlined.
Participants who are diagnosed with Ménière's disease, as determined by clinical history, ENT confirmation and an audiogram, will qualify if they also have had two or more Ménière's vertigo attacks in a four-week span for two consecutive four-week periods (the qualification period). Those who meet these criteria will then need two or more Ménière's vertigo attacks during a four-week lead-in period to further establish a baseline and verify randomization eligibility. Participants are allowed from the beginning of the lead-in to take their choice of a symptomatic abortive medication according to its package instructions for Ménière's vertigo attacks that last longer than 30 minutes with nausea and/or vomiting. Symptomatic abortive medications include, but are not limited to, meclizine (Antivert), Valium, diazepam, or Zofran.

A total of 25 participants will be enrolled for the pre-randomization stage. Those who do not wish to continue to the next stage or who no longer meet inclusion/exclusion criteria will be replaced. At screening, participants will be asked to undergo a urine pregnancy for women of reproductive age (≤50yrs) to ensure that they are eligible to continue. If a complete blood count (CBC), comprehensive metabolic profile (CMP), and creatinine clearance has not been conducted within the past three months, the participant will have blood drawn into tubes that will be centrifuged and shipped to Kaleida Health's labs to be analyzed. A urine sample will be obtained for the 24 hour creatinine clearance analysis as a screening measure for healthy kidney and liver function. As part of the patient's routine medical care, the blinded PI will conduct a full neurological and physical exam, review prior and current medications and request all medical history of the participant's Ménière's disease. This includes any results from vestibular testing that confirm the Ménière's diagnosis and rule out other causes (e.g. a basic vestibular exam, four calorics, rotary chair, and posturography testing). If participants have not undergone a comprehensive audiogram (including electrocochleaography and tympanometry subtests) and an electrocardiogram within the past three months, they will undergo all of the missing tests at the Dent Neurologic Institute before enrollment. These tests are test for other disorders that may require treatment as part of the patient's standard medical care and to also function to verify eligibility and establish a baseline for improvement and possible adverse events during the study. Participants will be asked to complete a series of questionnaires that include the Dizziness Handicap Inventory (DHI), Ménière's Disease Patients-Oriented Severity Index (MDPOSI), Ménière's disease Self-Assessment, Tinnitus Handicap Inventory (THI), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder (GAD-7) and the baseline Columbia-Suicide Severity Rating Scale (C-SSRS). These assessments will provide a baseline of the participant's symptom severity, frequency and duration of vertigo attacks and quality of life.

Following the screening visit, participants will enter a four week lead-in period. They are responsible for recording vertigo and other symptom severity, and abortive medication use with the Ménière's daily survey. During this period any uncompleted audiogram or EKG testing can take place. This lead-in period will provide a more accurate representation of the Ménière's disease vertigo frequency and allow for screening tests to be completed at the participant's convenience. If the participant is on any prohibited medication at the screening, the medications will be discontinued if the participant wishes to continue in the study and it is deemed safe by the PI and the prescribing doctor. The lead-in period will also be used as a wash-out.

At Visit 2, after the four week lead-in, inclusion/exclusion criteria will be re-evaluated. This includes a review of any concomitant

medications. Participants will be asked to hand in their Ménière's survey if they opted for the paper document. The surveys will be reviewed to ensure that abortive measures were only used during the severe attacks, as instructed. The Principal Investigator will assess any possible adverse events and then staff will administer the questionnaire batch. If the participant is eligible for randomization, he/she will be assigned to either a placebo or lamotrigine treatment group. Assignment will be based on a randomization conducted by UBSoPPS Research pharmacists, and the participant will be considered "enrolled" in the study at this point, and from this point on, all medical services, except abortive medication(s) of the patient's choice) are study-related and are not billed to the patient's insurance.

3.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response:

Exclude all

3.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

Response:

N/A- no non-English speaking subjects

4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

Response:

N/A – not a multicenter study

5.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

5.1 Describe when, where, and how potential subjects will be recruited.

Response:

N/A – not a multicenter study

5.2 Describe the methods that will be used to identify potential subjects.

Response:

N/A – not a multicenter study

5.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response:

The study hopes to recruit from the patient population at the Dent Dizziness and Balance Center and Buffalo ENT Specialists, LLP. In doing so, the PI and staff will have to access medical charts/records to verify eligibility and diagnosis of Meniere's disease prior to obtaining consent of potential participants. A referral letter will also be sent to area physicians and ENT specialists informing them of the study design and inclusion/exclusion criteria. Those receiving the letter are encouraged to notify eligible patients of the opportunity to participate and how to contact the study staff if they are interested. If enrollment numbers are not met, another letter will be sent out to remind the physicians and specialists. If enrollment numbers are still not met through this method, recruitment strategies will include an advertisement in the once monthly issue of an After 50 free newspaper, Buffalo Healthy Living magazine, 32 sixty-second radio advertisements and 50 sixty-second streaming commercials for two weeks. The study has requested funds for this purpose, but is hoping to exhaust all other potential participants within the Dizziness and

Balance Center and Buffalo ENT Specialists first. Therefore, the additional newspaper and radio advertisement recruitment materials will be submitted as an addendum at a later date.

6.0 Multi-Site Research (Multisite/Multicenter Only)

6.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Response:

N/A – not a multicenter study

6.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response:

N/A – not a multicenter study

7.0 Study Timelines

7.1 Describe the duration of an individual subject's participation in the study.

Response:

The study is composed of five phases: medical history qualification (eight weeks), lead-in (four weeks), titration (six weeks), study period (12 weeks), and taper (two weeks).

7.2 Describe the duration anticipated to enroll all study subjects.

Response:

1-2 years

7.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Response:

06/2016

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Response:

The endpoints of this study are:

Primary Efficacy Endpoint:

- Comparison between lamotrigine and placebo groups of the reduction of Ménière's vertigo attacks from baseline

Secondary Efficacy Endpoints:

- Comparison between lamotrigine and placebo groups of vertigo attacks:
- Responder rate: Percentage of patients with > 50% reduction in vertigo attack frequency during treatment vs. baseline
- Vertigo attack free rate analysis: Length of vertigo attack-free intervals, number and percentage of vertigo attack-free days per 28 days period, number and percentage of patients who are vertigo attack-free during the double blind phase
- Comparison between lamotrigine and placebo groups of hearing loss:
- Analysis of audiograms between baseline and end of the study
- Comparison between lamotrigine and placebo groups of symptom severity:
- Ménière's Disease Patients-Oriented Severity Index (MDPOSI)
- Tinnitus Handicap Inventory (THI) questionnaire
- Clinical Global Impression-Severity & Change
- Comparison between lamotrigine and placebo groups of quality of life:
- Dizziness Handicap Inventory (DHI) questionnaire
- AAO-HNS Ménière's disease self-assessment

- Patient Health Questionnaire-9 (PHQ-9)
- Generalized Anxiety Disorder 7-item scale (GAD-7)

8.2 Describe any primary or secondary safety endpoints.

Response:

N/A – no such endpoints

9.0 Procedures Involved

9.1 Describe and explain the study design.

Response:

This is a randomized double-blind pilot proof-of-concept clinical trial. The principal investigator and all staff involved in clinic visits will remain blinded until the blind is scheduled to be broken or there is an emergency.

Participants who are diagnosed with Ménière's disease, as determined by clinical history, ENT confirmation and an audiogram, will qualify if they also have had two or more Ménière's vertigo attacks in a four-week span for two consecutive four-week periods (the qualification period). Those who meet these criteria will then need two or more Ménière's vertigo attacks during a four-week lead-in period to further establish a baseline and verify randomization eligibility. Participants are allowed from the beginning of the lead-in to take their choice of a symptomatic abortive medication according to its package instructions for Ménière's vertigo attacks that last longer than 30 minutes with nausea and/or vomiting. Symptomatic abortive medications include, but are not limited to, meclizine (Antivert), Valium, diazepam, or Zofran. The abortive medication can be used throughout the study regardless of treatment assignment and its use will be recorded. Twelve eligible participants, with a minimum total of six attacks during the qualification and lead-in periods, will be randomly assigned to either a placebo or lamotrigine treatment group. Randomization will be conducted by UBSoPPS Research Pharmacy. The study drug and matching placebo will be titrated from 25mg twice a day (BID) up to 150mg BID over a six week period. During titration, clinic visits are scheduled every two weeks to assess any adverse events, symptoms, quality of life, and compliance. Those who cannot tolerate the 150mg BID dose may return to a 100mg BID dose during an unplanned visit. However, if a participant is unable to tolerate the 100mg BID dose they will be withdrawn from the study. Participants will maintain the 150mg BID or 100mg BID dose for a 12-week period with clinic visits every four weeks to assess their progress. Between all study visits, participants are asked to complete a daily survey describing their symptoms. This survey is hosted by polleverywhere.com and can be completed through text message, an online website, or with a paper document- whatever method is preferred by the participant. At the conclusion of the 12-week study period, a study staff will be un-blinded

and will give participants assigned to the lamotrigine group the option to continue the study medication as a long-term open-label use outside of the study or to begin a two-week taper off. The number of participants who decide to continue the study medication will be noted, but the participant will be terminated from the study and thus responsible for all following costs. Those assigned to the placebo treatment will be informed of their treatment assignment and terminated from the study.

9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Response:

Please note: these procedures are a continuation from section 3.2, where section 3.2 outlines the screening procedures that are also part of standard medical care, and this section, section 9.2, is specific to research-only procedures.

At Visit 2, after the four week lead-in, inclusion/exclusion criteria will be re-evaluated. This includes a review of any concomitant medications. Participants will be asked to hand in their Ménière's survey if they opted for the paper document. The surveys will be reviewed to ensure that abortive measures were only used during the severe attacks, as instructed. The Principal Investigator will assess any possible adverse events and then staff will administer the questionnaire batch. If the participant is eligible for randomization, he/she will be assigned to either a placebo or lamotrigine treatment group. Assignment will be based on a randomization conducted by UBSoPPS Research pharmacists, and the participant will be considered "enrolled" in the study at this point, and from this point on, all medical services, except abortive medication(s) of the patient's choice) are study-related and are not billed to the patient's insurance. Both groups will receive an amber vial of 28 pills with instructions to take one pill twice a day. Those in the lamotrigine group will be taking 25mg BID while those in the placebo group will be taking encapsulated microcrystalline cellulose. A drug dosage log will also be given to participants and they will be asked to write down the number of pills taken. Participants will be advised to notify the Principal Investigator or study staff if they develop rashes or other side effects. If the principal investigator decides that the rash is medication related, the participant will immediately stop the medication, return for an early termination visit and be terminated early from the study. Serious adverse events requiring withdrawal and unrelated to rash will return for an early termination visit and begin a two-week taper. If at any visit a participant is found to be non-compliant with dosing instructions, the Principal Investigator will assess the situation and determine if early termination is required. If the participant is terminated, they will follow the same taper schedule and early termination visit required for those withdrawing due to adverse events other than rash. Staff members will also remind participants to complete the daily survey and how to do so.

Two weeks later at Visit 3, current medications and adverse events will be reviewed by the Principal Investigator. A staff member will collect the medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. If the participant is determined to be compliant the staff member will

administer the questionnaire batch. Continuing participants will receive an amber vial of 28 pills with instructions to take one pill twice a day. The medication will either be lamotrigine 50mg BID or the matching placebo. Staff members will then hand out another dosage log and remind participants to complete the daily survey. Participants are asked to return in two weeks.

At Visit 4, current medications and adverse events will be reviewed by the Principal Investigator. A staff member will collect the medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. If the participant is determined to be compliant the staff member will administer the questionnaire batch. Continuing participants will receive an amber vial of 28 pills with instructions to take one pill twice a day. The medication will either be lamotrigine 100mg BID or the matching placebo. Staff members will then hand out another dosage log and remind participants to complete the daily survey. Participants are asked to return in two weeks.

At Visit 5, current medications and adverse events will be reviewed by the Principal Investigator. Participants will complete another physical and neurological exam, a comprehensive audiogram with tympanometry, and a urine pregnancy test for females of reproductive age (≤50yrs). Blood will be drawn, centrifuged and shipped to Kaleida Health's labs to analyze study drug levels. Additionally, a urine sample will be obtained for 24 hour creatinine clearance analysis as a screening measure for healthy kidney and liver function, to verify participants' ability to continue in the study. Study drug level results will be separated from other testing results and sent to UBSoPP Research Pharmacy to hold until the blind is broken and compliance can be reviewed. A staff member will collect the medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. If the participant is determined to be compliant, the staff member will administer the questionnaire batch. Continuing participants will receive an amber vial of 56 pills with instructions to take one pill twice a day. Participants' clinical response and tolerability will be assessed and if a participant reports no serious side effects from medications, the study drug will be further titrated to 150 mg BID or the matching placebo. If the participant finds that they cannot tolerate the 150mg BID dose, they are able to come into the clinic for an unscheduled visit and decrease to 100mg BID. Staff members will then hand out another dosage log and remind participants to complete the daily survey. Participants are asked to return in four weeks.

At Visit 6, current medications and adverse events will be reviewed by the Principal Investigator. A staff member will collect medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. If the participant is determined to be compliant the staff member will administer the questionnaire batch. Continuing participants will receive an amber vial of 56 pills of the same dosage, either 150mg BID or 100mg BID, with instructions to take one pill twice a day. Staff members will then hand out another dosage log and remind participants to complete the daily survey. Participants are asked to return in four weeks.

At Visit 7, current medications and adverse events will be reviewed by the Principal Investigator. A staff member will collect medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. If the participant is determined to be compliant the staff member will administer the

questionnaire batch. Continuing participants will receive an amber vial of 56 pills of the same dosage, either 150mg BID or 100mg BID, with instructions to take one pill twice a day. Staff members will then hand out another dosage log and remind participants to complete the daily survey.

Four weeks later participants return to the clinic for Visit 8, current medications and adverse events will be reviewed by the Principal Investigator. The Principal Investigator will also administer a neurological and physical exam and complete the Clinical Global Impression-Severity and Change assessment. A staff member will collect medication containers, conduct a pill count and collect and review the dosage log and daily Ménière's survey responses. Participants will complete the questionnaire batch, and undergo a comprehensive audiogram with tympanometry. Blood will be drawn, centrifuged and shipped to Kaleida Health's labs to analyze study drug levels, CMP, CBC, and a urine pregnancy test will be conducted for female participants of reproductive age (≤50yrs). Additionally, a urine sample will be obtained for 24 hour creatinine clearance analysis as a screening measure for healthy kidney and liver function. At the conclusion of the visit a staff member will be un-blinded by unsealing an envelope that contains treatment code and participant number. Those in the lamotrigine group will be given the option to be terminated from the study, but to continue the study medication at their own cost. Alternatively, they can continue in the study and begin to taper off the study drug. Those who decide to continue the study medication will be noted, but no further study participation is required. Participants continuing lamotrigine will be free to follow up on their treatment through the Dizziness and Balance Clinic or through a physician of their choice. Participants who decide to discontinue the study drug will begin a two-week taper consisting of one week at their current dosage QD and then one week of half the current dosage QD, and be paid for these 2 remaining study visits 9 and 10. Those assigned to the placebo group will be terminated from the study and are informed that they are allowed to seek treatment for their Ménière's disease at the Dizziness and Balance Clinic or elsewhere.

At both of the taper visits, participants will be given the tapered dose and asked to continue their dosage log. Staff will collect medication containers, conduct a pill count and review the dosage log to verify that participants are stopping the study drug in a safe manner. Any adverse events will continue to be reviewed by the Principal Investigator. At the last visit, participants will undergo one last physical and neurological exam and be notified of their termination from the study. At this point participants are informed that they are allowed to seek treatment for their Ménière's disease at the Dizziness and Balance Clinic or elsewhere.

9.3 Describe procedures performed to lessen the probability or magnitude of risks.

Response: Procedures to minimize risk of adverse events due to the drug are outlined in sections 9.2 and 12.7.

To provide detail sufficient detail on study procedures in reducing risk associated with the blood draws, I will copy Dent Neurologic Institute's official Blood Draw Policy here, which is adhered to by all employees of Dent who draw blood, including the research staff member assigned on our study team to draw blood.

POLICY & PROCEDURE

Title: Blood Draws Policy Number: CLN - 037
Category: Clinic Reference Statute, If one exists:
Standard: Approved By: CEO: Joseph V. Fritz, PhD, CEO

PURPOSE:

To provide accurate and complete instructions for safe blood drawing technique.

POLICY:

It is the policy of the DNI to provide DENT staff with complete and accurate instructions for drawing blood.

RESPONSIBILITY:

It is the responsibility of the Clinic Managers to create and maintain the procedure. The DNI Clinic Staff need to be trained on this procedure.

PROCEDURE:

1.) Gather all necessary equipment;
a.) Alcohol prep pads
b.) Clean tourniquet
c.) Clean disposal gloves – sized appropriately
d.) 4x4 gauze
e.) Band-Aid or tape
f.) Tubes
g.) Vacuum holder or syringe
h.) Appropriate size blood draw needle or butterfly
i.) Specimen labels
j.) Plastic specimen bag
2.) Meet and greet patient

3.) Escort patient into phlebotomy room
4.) Identify patient by three identifiers – name, DOB, address
5.) Explain procedure to patient
6.) Check with patient regarding possible allergy to latex .(If positive – see additional information)
7.) Wash your hands
8.) Inspect both arms of the patient for possible venipunture site.
9.) Apply tourniquet to arm as per instructions
10.) Prep skin with one alcohol prep
11.) Don clean gloves
12.) Palpate possible venipunture sites as per instructions
13.) Place needle to vacuum holder or attach butterfly to syringe.
14.) With bevel up insert needle into vein at 15 degree angle. Gently push appropriate vial
onto needle hub or draw back on syringe.
15.) Allow blood to flow into blood collection tube
a.) Lavender tubes drawn prior to blue tubes due to additive and air in tubing.
b.) Invert each tube a total of at least three times to insure proper mixing of blood and additive.
16.) When blood has reached the appropriate level, gently remove tube and place second
tube on to needle hub. Continue to do this until all blood specimens have been collected. Draw enough blood in syringe if using butterfly to fill tubes.
17.) As last specimen is being obtained, remove tourniquet and complete the blood collection.

18.) Gently remove tube from needle setup. Remove needle and secure puncture site with
gauze or cotton ball.
19.) Secure all specimens.
20.) Place Band-Aid over site.
21.) With patient still in the room: Label all specimens with correct label. Verbally verify patient's name and DOB as labels are attached to specimens.
22.) Complete appropriate paperwork, initials, time drawn.
Blood Draws
Page **2** of **3**
23.) Discharge patient
24.) Place completed specimens and paperwork into to outgoing pickup and call Quest or
LabCorp for pick up.
25.) Clean area
26.) Wash your hands
27.) Only three attempts are to be done. If unable to secure specimens after three attempts,
must have another professional attempt.
Blood Draws
Page **3** of **3**

9.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Response:

Lamotrigine is a FDA approved drug for treating epilepsy and bipolar disorder, indicated as "schedule: N" – not subject to the Controlled Substances Act. The present study is exploring a new indication for Lamotrigine. The FDA has concluded that the study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct the investigation (proof of this indication has been previously submitted to IRB)

The drug supply will be sent to the University of Buffalo's School of Pharmacy and Pharmaceutical Sciences (UBSoPPS) Research Pharmacy. Once it arrives the packing slip will be checked for completeness and then the study staff will be notified of its arrival. The invoice and inventory taken will be faxed over to the study site. The drugs will then be stored in their original containers in a room-temperature, dry and dark area of the UBSoPPS Research Pharmacy's lab, which has very limited access since it is a pharmacy. Temperature and humidity will be monitored by a UBSoPPS Research Pharmacist.

UBSoPPS Research Pharmacy will take the manufacture supplied tablet and place it inside a capsule. The capsule will be filled with methylcellulose until the entire content of the capsule is filled, decreasing the chance for un-blinding, and the capsule then closed. The encapsulated lamotrigine will then be packaged in an amber vial with a study label. Repackaging will follow NYS regulation. Repacking will be conducted by a pharmacist or under his/her immediate and personal supervision. A repacking record shall

be maintained for five years, including the name, strength, lot number, quantity and name of the manufacturer and/or distributor of the drug repacked, the date of repacking, the number of packages prepared, the number of dosage units in each package, the signature of the person performing the repacking operation, the signature of the pharmacist who supervised the repacking, and such other identifying marks added by the pharmacy for internal recordkeeping purposes. Drugs repacked shall have an expiration date 12 months, or 50 percent of the time remaining to the manufacturer's expiration date, whichever is less, from the date of repacking.

SUNY at Buffalo School of Pharmacy and Pharmaceutical Sciences (UBSoPPS) Research Pharmacy will randomize eligible participants through www.randomizer.org. An UBSoPPS pharmacist will generate 12 random sets of numbers, ranging from 1-2 for the two assignment groups, with one unique number per set. UBSoPPS Research Pharmacy will use this randomization to compile a master log with the participant number and treatment code.

Those assigned to the lamotrigine treatment will take encapsulated lamotrigine daily for the duration of 20 weeks, consisting of a six-week titration, 12-week study period, and two-week taper. Possible doses for patients are 25mg BID, 50mg BID, 100 mg BID and 150mg BID during titration; 150mg BID or 100mg BID for the 12-week study period; 150mg QD or 100mg QD for Week 1 of the taper; and 75mg QD, or 50mg QD for Week 2 of the taper. Each increase in dose will be maintained for two weeks before deciding to further increase or decrease based on tolerability. Patients who discontinue at any point of the study will have a two-week taper consisting of the current dose QD for one week followed by half the dose QD for another week.

9.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Response:

- Ménière's Disease Patients-Oriented Severity Index (MDPOSI)
- Tinnitus Handicap Inventory (THI) questionnaire
- Clinical Global Impression-Severity & Change
- Dizziness Handicap Inventory (DHI) questionnaire
- AAO-HNS Ménière's disease self-assessment
- Patient Health Questionnaire-9 (PHQ-9)
- Generalized Anxiety Disorder 7-item scale (GAD-7)
- Dosing Log
- Meniere’s daily survey

9.6 What data will be collected including long-term follow-up.

Response:

Please see 9.5, plus:

- Results of physical and neurological exams

- Audiogram
- Drug dosing
- CBC, CMP blood tests
- Lamotrigine blood levels (received from lab only after unblinding occurs)
- Urine pregnancy test results and creatinine levels
- Drug adherence information
- Medications list
- Medical history

9.7 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response: N/A

10.0 Data and Specimen Banking

10.1 *If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the* data/specimens.

Response: Blood samples will be collected, centrifuged and packed before being shipped for analysis in the Dent Neurologic Institute Infusion Clinic located within the Dent Neurologic Institute. Kaleida Health Laboratory is located only a four-minute drive away from Dent Neurologic, making the shipping and processing of blood samples simple and easy. All biologic products will be disposed of properly as biologically hazardous waste after the described testing is complete, so there will be no storage of materials for further use.

10.2 List the data to be stored or associated with each specimen.

Response: There will be no storage of materials for further use.

10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: N/A

11.0 Data Management

11.1 Describe the data analysis plan, including any statistical procedures.

Response: The primary response will be the number of vertigo attacks as measured at baseline and at the end of the study period. The secondary responses will include the percentage of vertigo free patients, audiograms, symptom severity scales and quality of life scales (listed in the Approach section). The analysis set will include all subjects who are randomized and receive at least one dose of the study medication or the placebo. Integer or continuous variables will be presented by their mean and median and their SD and IQR. Categorical variables will be summarized using counts and percentages. Demographic and baseline characteristics of the enrolled subjects will be summarized through descriptive statistics for continuous variables and through frequencies for categorical variables. Demographic and baseline characteristics of the intervention and placebo groups will be compared to assess for comparability. Continuous variables will be compared using Wilcoxon rank-sum test and categorical variables will be compared through Fisher's exact test. We will test for reduction in the Ménière's vertigo attacks from baseline through Wilcoxon's sign rank test and will compare the reduction between the two treatment groups using Wilcoxon rank-sum test. The tests will be two-tailed and the significance level will be set to 0.05. Additionally, we will perform statistical modeling of the number of vertigo attacks longitudinally through generalized linear mixed effects model using Poisson or Negative Binomial distribution as appropriate. Data analysis will be conducted using SAS (SAS Institute Inc., Cary, NC, USA) and R (http://www.r-project.org/). All data analyses will be performed by Dr. Terry Mashtare of the SUNY UB Statistical Consultant Laboratory.

11.2 Provide a power analysis.

Response: According to our preliminary data, the mean number of vertigo attacks after 3 months of treatment with Lamotrigine was 4.91 (SD=7.24), and we expect the mean number of vertigo attacks in the placebo group to be approximately 13. We assumed Negative Binomial distribution for the response, two-sided tests, level of significance 0.05 and considered various sample sizes, mean and variance of the number of attacks in the two groups. We calculated the associated power for comparison of the mean response between the two groups by utilizing Monte Carlo simulations and using Negative Binomial regression model with log link. Each simulation consisted of 1000 iterations and was conducted in R (http://www.r-project.org/). This analysis showed that a power above 80% can be obtained with a sample of 12 participants.

Table: Associated Power for Comparison of the Mean Response between Treatment Groups Calculated with Monte Carlo Simulations and Negative Binomial Regression Model with Log Link

Total N	Mean Number of Attacks in Lamotrigine group at the end of the study	Standard Deviation of the number of attacks	Mean Number of Attacks in Placebo group at the end of the study	α level	Power
12	5	7.24	13	0.05	57.6
12	5	6	13	0.05	60.6
12	5	4	13	0.05	86.6
12	6	6	13	0.05	58.2
12	6	4	13	0.05	83.5
14	5	7.24	13	0.05	60.7
14	5	6	13	0.05	70.1
14	5	4	13	0.05	92.8
20	5	7.24	13	0.05	67.6
20	5	4	13	0.05	97.6
20	5	7.24	12	0.05	60.4
20	5	4	12	0.05	94.5
20	6	7.24	12	0.05	48.8
20	6	4	12	0.05	91.9
34	5	7.24	13	0.05	82.2
34	5	6	13	0.05	92.5

Update on 6/4/2015:

As of 6/4/2015	#
Expected N complete	12
Complete	8
Currently enrolled	3
Potentially eligible, not enrolled	6
Screened & eligible but declined participation in study	1
Screened and ineligible	5
Started study but dropped out	2
TOTAL	**25**

We engage in a multi-step process to reduce drop-outs, however, this is a very long study (6 months), and some drop-outs are to be expected. Thus far, we've had 2 participants drop out of the study and 8 have completed. Therefore, our dropout rate is 25%. To compensate for drop-outs, we request to increase our enrollment by 25%, rounded to the nearest whole number attain equal numbers in each group, for a total N of 16.

11.3 Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Response: Data will be password protected and participant identity will be coded to ensure confidentiality of information. The participant code number and identifying information will be kept in a locked office in the Dent Neurologic Institute and the UBSoPPS Research Pharmacy. At the conclusion of the study only the PI, Co-Investigator, Statistician, or Research Assistant at Dent Neurologic Institute will have access to the data and participant information.

11.4 Describe any procedures that will be used for quality control of collected data.

Response: The data will be accurately entered twice in a password protected Excel Spreadsheet and checked automatically by an Excel program for accuracy. Data will only be viewed and analyzed by the research personnel.

11.5 Describe how data and specimens will be handled study-wide:

Response: Please see 11.3 and 11.4

11.6 What information will be included in that data or associated with the specimens?

- Response: Ménière's Disease Patients-Oriented Severity Index (MDPOSI)
- Tinnitus Handicap Inventory (THI) questionnaire
- Clinical Global Impression-Severity & Change
- Dizziness Handicap Inventory (DHI) questionnaire
- AAO-HNS Ménière's disease self-assessment
- Patient Health Questionnaire-9 (PHQ-9)
- Generalized Anxiety Disorder 7-item scale (GAD-7)
- Dosing Log
- Meniere's daily survey
- Pertinent results of neurological or physical exams
- Drug dosing
- CBC, CMP blood tests
- Lamotrigine blood levels

- De-identified demographics information

11.7 Where and how data or specimens will be stored?

Response: Please see 11.4. Password-protected files are located at Dent Neurologic Insititute, and study data are separate from personally identifiable information.

11.8 How long the data or specimens will be stored?

Response: Data will be stored for the duration of the study. Then, any documents or files that acted as personal identifiers for the study will be destroyed at the earliest opportunity. All documents will be placed in one of the HIPAA/Confidential Document bins which are located throughout the Dent Neurologic Institute. These secure bins are then emptied and the documents are destroyed by Cintas. Cintas is certified by the National Association for Information Destruction and also compliant with HIPAA and PCI standards.

11.9 Who will have access to the data or specimens?

Response: Only the PI, Co-Investigator, Statistician, or Research Assistant at Dent Neurologic Institute will have access to the data and participant information.

11.10 Who is responsible for receipt or transmission of the data or specimens?

Response: Lizin Zhang, MD PhD

11.11 How data and specimens will be transported?

Response: Data are stored in password-protected files, and will be transferred electronically to the statistician if needed.

12.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

12.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Please also see section 12.7 pertaining to this question.

Adverse events (AE) will be reported to, evaluated and monitored by the PI, Dr. Zhang. Any severe adverse event (SAE) will be reported to both the PI and the HSIRB within 24 hours of the research personnel becoming aware of the event. The PI will also evaluate and monitor any severe adverse event. In the event that 20% of the participants should experience an SAE the study will be terminated. In addition to terminating the study due to the previously specified criteria, at any point if the PI should decide to

terminate the study for other reasons, such as no clear evidence of benefit from the study or arising safety concerns, all participants will receive a phone call informing them of the new findings and they will be asked to come in for an early termination visit. Their safety will be assessed, the remaining drug will be collected, and new AEs or SAEs will be recorded. Each participant will also be informed that they will be reimbursed for travel for each visit that they had completed thus far. Reports of adverse events will be continually monitored by co-investigators in order to monitor subject response, ensure subject safety, and determine the necessity for an early termination.

After signing the informed consent, each participant will be assigned a participant number that will be used as coded identification for the entire study. The study's research personnel will compile and analyze incoming data, which will be reviewed on a bi-weekly basis to minimize the risks pertaining to the study. Dr. Zhang will be responsible for data and safety oversight for the study. Data will be entered by the research personnel and verified at 100%. Data will be password protected, participant identity will be coded and access to identifying information will be limited to ensure confidentiality.

12.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Please see 12.1. Also, the ratio of side effects vs. improvements in symptoms will be specifically evaluated.

12.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Safety information is collected at every visit; participants are asked about adverse events and complete questionnaires providing feedback on symptoms every visit throughout the duration of the study. Additionally, participants are encouraged to contact study personnel with any concerns, and are required to agree to report any degree of adverse health or psychological complaints regardless of whether or not they believe it is related to the study for the duration of the study including up to 28 days after their participation has concluded.

12.4 Describe the frequency of data collection, including when safety data collection starts.

Response: Data are collected at every visit; every 2 weeks for the first 10 weeks, then every 4 weeks from weeks 10 through 22, then two more visits separated by 1 week each. As previously stated, safety data are collected at every visit.

12.5 Describe who will review the data.

Response: Only the PI, Co-Investigator, Statistician, or Research Assistant at Dent Neurologic Institute will have access to the data and participant information.

12.6 Describe the frequency or periodicity of review of cumulative data.

Response: Data will be reviewed bi-weekly.

12.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: I called IRB on 3/20/2015 to inquire about this and received verbal confirmation that the following procedures pertain to our study:

This is a small (n=12), single location pilot study on the use of Lamotrigine to treat Meniere's disease. The study employs procedures that do not provide sufficient information to conduct statistical testing for potential harm. The main reason for this is because the way in which harm is determined is through probing participants about any side effects, adverse events, or complains at every study visit, as well as providing them with a means of contacting us M-F 8am-4:30pm if they experience any side effects between study visits. Additionally, the consent form outlines specific side effects to watch for that can be associated with the drug, including the course of medical action they should take if they develop the most common allergic reaction (rash). Finally, participants are explicitly asked at the time of consent whether or not they agree to report all adverse effects to the PI or research staff throughout the duration of the study, regardless of whether they believe it is related to the drug or not. All participants must agree to this in order to be in the study. While we have not encountered any adverse events or side effects, if we did, the PI would be informed and we would complete an adverse event report and submit to IRB immediately.

12.8 Describe any conditions that trigger an immediate suspension of the research.

Response: The research will be immediately suspended if the study drug is found to be unsafe due to a drug recall or similar event, or if the safety, security, or functionality of the facilities at which the study takes place become compromised in any way.

13.0 Withdrawal of Subjects

13.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Response: Participants may be withdrawn early without their consent if they develop a rash at any point during the study and Dr. Zhang decides that it is caused by the treatment, if they develop a serious adverse event

other than rash that requires discontinuing involvement in the study, if at any visit they are found to not be following dosing instructions.

13.2 Describe any procedures for orderly termination.

Response: For rash, participants are asked to immediately stop the medication, take an antihistamine, like Benadryl, return for an early termination visit and will be removed early from the study. If a different adverse event is experienced other than a rash, the participant will be asked to return for a visit (for which they are paid as per study compensation guidelines) and begin a two-week decrease of the current study drug dose. This decrease is the current study drug dose once a day for one week followed by half of the study drug dose once a week for another week. If a participant is found to not be following dosing instructions at any visit, Dr. Zhang will review the situation and determine whether they need to be removed from the study, and if so, the participant will follow the same taper schedule and early termination visit required for those withdrawing due to adverse events other than rash.

13.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Response: Participants are informed in the consent form that if they choose to withdraw from the study, there will be no further information collected from them or about them. There isn't an instance of "partial withdrawal" in this study.

14.0 Risks to Subjects

14.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

There will be blood draws that are required for this study. Possible side effects from blood drawing include anxiety, faintness, vein inflammation, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection. Experienced medical personnel will be responsible for blood draws to minimize these risks.

There will be an electrocardiogram test. Skin irritation is rare but could occur during this test from the electrodes or gel that is used.

Participants may feel discomfort regarding questions asked in study questionnaires.

Participants will also be taking medications during the length of the study. All medications are FDA approved for use in patients. While lamotrigine is approved for use

in people who have a seizure disorder, the indication investigated during this study has not been approved.

Those assigned to the Lamotrigine treatment are at risk for rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, aseptic meningitis, hepatic and renal failure, DIC, arthritis, diplopia, sedation, dizziness, ataxia, headache, nausea and vomiting. Psychosis and depression are associated with epilepsy and occur in open label studies with all new AED's, but it is difficult to ascertain whether these relationships are causal. Incidence of rash was approximately 0.8% in adults receiving it as initial monotherapy for epilepsy and 0.08% in adults receiving it as initial monotherapy for bipolar and other mood disorders. This risk increases with concomitant valproate/divalproex use and reduces with slow titration. In order to prevent a rash, the daily dosage of lamotrigine will be slowly titrated by 50mg every two weeks. Valproate/divalproex, an anti-epileptic medication, is also prohibited from the study. If a study related rash does occur, the participant will be instructed to immediately discontinue the medication and to take an antihistamine drug. If the rash occurs with other serious symptoms associated with Stevens-Johnson syndrome and/or toxic epidermal necrolysis, such as fever, fatigue, sore throat, conjunctivitis or sores and/or ulcers in the mouth, lips or genital areas, participants are instructed to go to the emergency room. Hepatic and renal failure will be monitored with CBC andCMP blood analysis and a urine sample will be obtained for 24 hour creatinine clearance analysis as a screening, after titration and after the maintained dose period. Beginning with Visit 2, the C-SSRS will be conducted by a certified study staff to determine if there are any positive responses since last visit and whether it is safe for the participant to continue to participate in the trial. Any suicidal risk should be managed appropriately by the PI, who is a qualified mental health practitioner (MHP).

During the washout period and with placebo assignment, MD symptoms may become worse, stay the same, or improve. However, all participants are allowed to mitigate their symptoms with their choice of an abortive medication throughout the study. Common side effects from abortive medications include drowsiness, blurred vision, dry mouth, constipation or dizziness. Common serious side effects include an allergic reaction involving rash, difficulty breathing, and/or swelling of the face, lips, tongue or throat. Participants should read their specific abortive medication's package insert for a full list of side effects.

Hearing loss is another symptom of Ménière's disease currently without a treatment. During the study, participants' MD may worsen or stay the same and participants may experience fluctuating hearing loss or develop permanent hearing loss in the affected ear as a natural progression of the disorder.

All participants will be counseled on the definition of adverse events so that they may monitor for them. Additionally, participants will be asked for the presence of any adverse/serious events (specifically including those side effects associated with lamotrigine) at each visit. Dr. Zhang, as the PI, is directly responsible for assessing and monitoring all possible side effects and/or adverse events

Social risk is minimal; all measures will be taken to keep personal identifiable data confidential. Economical risk is small, but participants may have to take time off of work or find transportation in order to get to a required visit. Participants will be reimbursed for their travel up to 11 completed visits.

14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

N/A

14.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: Lamotrigine is a Category C medication, meaning that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans. To avoid the potential risk to the fetus, pregnant and breastfeeding women are excluded from the study and all female participants must be willing to avoid pregnancy during the entirety of the study.

14.4 If applicable, describe risks to others who are not subjects.

Response: N/A

15.0 Potential Benefits to Subjects

15.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Participants receiving the study drug may see improvement in their MD symptoms and quality of life. It is possible, however, that participants will receive no direct health benefit from being in this study. Others may benefit from the information learned. The results of this study could support a minimally invasive, tolerable and efficacious treatment for those who suffer from Ménière's disease. Risks to the current study's participants are reasonable in relation to the importance of the knowledge gained. Many of the current alternative treatments for Ménière's disease are much higher in risk than the treatment proposed by this study. The improvement of symptoms and quality of life could also be greater than available treatments. Although this is just a pilot-of-proof study, the evidence could argue for larger clinical studies in the future that then support FDA review of the new indication and, eventually, approval of the new indication. Subsequently, the efficient and low-risk medication would be made available to MD patients at affordable costs shared with insurance companies. Additionally, the results of the study would support research into a new etiology theory of Ménière's disease.

15.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

Response: N/A

16.0 Vulnerable Populations

16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response: N/A

17.0 Community-Based Participatory Research

17.1 Describe involvement of the community in the design and conduct of the research.

Response: N/A

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

18.0 Sharing of Results with Subjects

18.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic

tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response:

Results of screening tests that are relevant to the patient's routine medical care will be shared with the patient as they are conducted. All testing that is part of routine medical care (prior to randomization), and not specific to study-related testing, is automatically copied to the patient's primary doctor, unless the patient requests additional or alternative CCs. No study-specific testing or outcomes are communicated to the patient, their primary doctor, or anybody who is not on the protocol. The only exception to this is in the extremely unlikely event that study-specific tests reveal a risk to the participants' health, such as abnormal blood or urine test results, in which case the participant will be informed immediately.

The participant will be informed in a timely manner by the investigator or research personnel when new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. This may be done in writing by letter, revised ICF or in any manner approved by the reviewing IRB. The communication of this information should be documented in the medical record along with a copy of the information provided.

19.0 Setting

19.1 Describe the sites or locations where your research team will conduct the research.

All site visits will be conducted at the Dent Neurologic Institute. The Dizziness and Balance Center (DBC) is well outfitted with the necessary audio testing equipment. This equipment is regularly maintained for clinical use. The space within the DBC will provide private exam rooms and check out areas for informed consent, questionnaires and other study procedures. The Dizziness and Balance Center will also provide access to a patient population for recruitment purposes. Blood samples will be collected, centrifuged and packed before being shipped for analysis in the Dent Neurologic Institute Infusion Clinic located within the Dent Neurologic Institute. In addition to the study space and equipment available at Dent, the organization serves as a resource for research design and implementation. Research staff has insured that all study personnel have undergone the appropriate training for human subjects research. The Dent Neuroscience Research Center, also located within the same building, is composed of experts with years of research experience that can guide and assist the study team. Other personnel at Dent include experienced pharmacists, audiologists and psychiatrists, all of whom the PI has built consultation relationships with over several years. Lastly, the Dent is funding one of the staff members to work on the execution of the study full-time.

Kaleida Health Laboratory is located only a four-minute drive away from Dent Neurologic, making the shipping and processing of blood samples simple and easy. The

clinical laboratory leads Western New York in quick and accurate testing, performing more than 4 million tests each year. Kaleida Health's experienced laboratory scientists, couriers and computer system will ensure that the blood analysis for the study is done in an exceptional manner. Although a contract will only be created once the study receives IRB and funding approval, the Dent Neurologic Institute has successfully worked with Kaleida Health in the past.

UBSoPPS Research Pharmacy is a licensed pharmacy that provides the expertise of a licensed pharmacist to assist clinicians in conducting clinical studies. The Pharmacy allows the investigating clinician to conduct blinded studies involving placebos and encapsulates drug preparations in various design patterns. The facility can compound specific drug strengths that may not be available commercially, thereby giving the clinician more control over the strengths of the drug they wish to investigate. All research is conducted in an ethical manner with its focus on protecting the human subjects and complying with all HIPAA regulations. Budget planning is provided and assistance in statistical design is available.

The UB Statistical Consulting Laboratory provides doctorate level expertise in biostatistics and clinical research. This collaboration will strengthen the design of the study and the subsequent conclusions made from the study's results.

19.2 Identify where your research team will identify and recruit potential subjects.

Response: The study hopes to recruit from the patient population at the Dent Dizziness and Balance Center and Dr. Diaz-Ordaz's patients at Buffalo ENT Specialists. In doing so, the PI and staff will have to access medical charts/records to verify eligibility and diagnosis of Meniere's disease prior to obtaining consent of potential participants. The study needs information from preexisting medical records to identify a candidate pool based on specific criteria applied to those records. Obtaining a signed authorization prior to recruitment is not practicable. If an authorization form was given to every patient seen in the Dizziness and Balance Center and every one of Dr. Diaz-Ordaz's patients, the time needed for recruitment would be dramatically increased and potential eligible participants could be overlooked due to their next appointment being scheduled for months later. Additionally, the information we are looking to capture was not collected for research purposes. This information already exists within patients' charts and patients have already consented to Dr. Zhang and the staff of the Dizziness and Balance Center or Dr. Diaz-Ordaz to have access to this information as part of their standard care. Once eligible potential participants are identified they will be sent a letter, which gives an overview of the study and contact information if they are interested in enrolling.

A referral letter will also be sent to area physicians and ENT specialists informing them of the study design and inclusion/exclusion criteria. Those receiving the letter are encouraged to notify eligible patients of the opportunity to participate and how to contact the study staff if they are interested.

If enrollment numbers are not met through this method, recruitment strategies will include an advertisement in the once monthly issue of an

After 50 free newspaper, 32 sixty-second radio advertisements and 50 sixty-second streaming commercials for two weeks. The study has requested funds for this purpose, but is hoping to exhaust all other potential participants within the Dizziness and Balance Center and Dr. Diaz-Ordaz's patients first. Therefore, the additional newspaper and radio advertisement recruitment materials will be submitted as an amendment at a later date.

19.3 Identify where research procedures will be performed.

Response: Research Procedures with participants will be performed at Dent Neurologic Institute, within the Dizziness and Balance Center (DBC).

19.4 Describe the composition and involvement of any community advisory board.

Response: N/A

19.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: Please see section 19.0 for site specific procedures/policies/regulations for the pharmacy, laboratory, and statistical computing sites.

20.0 Resources Available

20.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response:

Study coordinator: College degree or applicable technical training, Mathematics/statistics skills, prior research experience, proficiency in Microsoft Office, CITI and HIPAA training, strong interpersonal and communication skills, excellent organizational skills, problem-solving skills, high level of communication through written form.

Co-PIs: College degree or applicable technical training, proficiency in Microsoft Office, CITI and HIPAA training, strong interpersonal and communication skills, excellent organizational skills.

Other research staff: Excellent oral and written communication skills, including listening skills for participant concerns and communications, some basic knowledge of the research protocol and related literature, CITI and HIPAA training

Describe other resources available to conduct the research: For example, as appropriate:

20.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: While Meniere's Disease affects approximately 20-200 out of every 100,000 people, at this specialized institute, Dr. Zhang sees approximately 70-100 Meniere's Disease patients per year. Therefore, we believe it is reasonable to obtain the 12 participants (or approximately 5-10% of these patients) who meet eligibility criteria over the next 1-2 years.

20.3 Describe the time that you will devote to conducting and completing the research.

Response: The study coordinator will work on the study full time at 40 hours per week. The remaining research staff will spend, on average, approximately 3-5 hours per week each on the research study. The pharmacy has allocated 21 pharmacist hours, and the statistician has allocated 20 towards this pilot study.

20.4 Describe your facilities.

Response: The Dizziness and Balance Center (DBC) is well outfitted with the necessary audio testing equipment. This equipment is regularly maintained for clinical use. The space within the DBC will provide private exam rooms and check out areas for informed consent, questionnaires and other study procedures. The Dizziness and Balance Center will also provide access to a patient population for recruitment purposes. Blood samples will be collected, centrifuged and packed before being shipped for

analysis in the Dent Neurologic Institute Infusion Clinic located within the Dent Neurologic Institute. In addition to the study space and equipment available at Dent, the organization serves as a resource for research design and implementation. Research staff has insured that all study personnel have undergone the appropriate training for human subjects research. The Dent Neuroscience Research Center, also located within the same building, is composed of experts with years of research experience that can guide and assist the study team. Other personnel at Dent include experienced pharmacists, audiologists and psychiatrists, all of whom the PI has built consultation relationships with over several years.

20.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response: Routinely, the Buffalo General Hospital, Erie County Medical Center, Millard Fillmore Hospital and/or the University at Buffalo, State University of New York, Dent Neurologic Institute, their agents employees do not compensate for or provide free medical care for human subjects/participants in the event that any injury results from participation in a human research project. In the unlikely event that a participant become ill, injured, or requires psychological services as a direct result of participating in this study, they may receive the appropriate medical care at the location of their choosing.

20.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All study personnel undergo CITI, HIPAA, and other HSIRB-required training. Additionally, study personnel are required to read through the protocol and develop a good understanding of the study procedures. Additionally, study personnel work together in a collaborative environment to maintain awareness of the study procedures and any learning opportunities that may arise. Additionally, members of the research team meet weekly to discuss study progress, and clear roles as well as individual projects are defined in these meetings.

21.0 Prior Approvals

21.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response: Approval from our funding body, Dent Family Foundation, was required.

22.0 Recruitment Methods

22.1 Describe when, where, and how potential subjects will be recruited.

Response: Recruitment strategies include an advertisement in the once monthly issue of an After 50 free newspaper. If needed, the study will also be investing in 32 sixty-second radio advertisements and 50 sixty-second streaming commercials for two weeks. Additionally, the study hopes to recruit from the current patient population at the Dent Dizziness and Balance Center. However, we will avoid infringing on the privacy rights of both former and current patients by only allowing the principal investigator, who is the clinic doctor, and other study staff involved with the Dent Dizziness and Balance Center to reach out to patients. We believe this is ethical because Dr. Zhang and the clinic staff already have access to any potential participants' medical history and it would prevent other study staff from gaining access to medical information before the start of the study and without the participant's direct consent.

22.2 Describe the source of subjects.

Response: Individuals who read After 50 or are in the WNY area, already within the existing database, or in any way comes into contact with Dent or our advertisements, has Meniere's Disease and is eligible and wants to participate.

22.3 Describe the methods that will be used to identify potential subjects.

Response: Potential subjects will be identified first by Dr. Zhang if they meet criteria for a Meniere's disease diagnosis and meet basic eligibility criteria. Participants who indicate interest in participating in the study will then review the consent form and additional eligibility criteria with either the study coordinator or another member of the research team. The participant is given the option to take the form home to think about it or sign it at that time if they are certain they want to participate.

22.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: Please see 22.1

22.5 Describe the amount and timing of any payments to subjects.

Response: Participants will be reimbursed $35 per visit, up to $315 total (6-8 visits for placebo & Lamotrigine groups, respectively, plus 1 extra visit if needed for a maximum of 9 visits). Payment will be made by check and mailed to the participant's address as written on their signed Declaration of Participation form. Should the participant choose to drop out of the study or the study is terminated, a check will be mailed after

completion of the early termination visit or after completion of the most recent visit prior to dropping out.

23.0 Local Number of Subjects

23.1 Indicate the total number of subjects to be accrued locally.

Response: 12 (all)

23.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Response: 12 subjects are needed to complete research procedures. Because of the long duration of the study, and based on previous experience with patient follow-up, we anticipate approximately 2-5 dropouts. Additionally, we anticipate approximately 20 people will be consented but not enroll in the study, either due to success with other types of treatment (e.g., water pills) employed by Dr. Zhang or another provider, changing their minds or seeking treatment elsewhere, or for other unknown reasons.

24.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

24.1 Where and how data or specimens will be stored locally?

Response: Data will be password protected and participant identity will be coded to ensure confidentiality of information. The participant code number and identifying information will be kept in a locked filing cabinet in the Dent Neurologic Institute and in a locked office at the UBSoPPS Research Pharmacy. Study data are separate from personally identifiable information. Any documents or files that acted as personal identifiers for the study will be destroyed at the earliest opportunity. All documents will be placed in one of the HIPAA/Confidential Document bins which are located throughout the Dent Neurologic Institute. These secure bins are then emptied and the documents are destroyed by Cintas. Cintas is certified by the National Association for Information Destruction and also compliant with HIPAA and PCI standards.

24.2 How long the data or specimens will be stored locally?

Response: Data will be stored for the duration of the study. Then, any documents or files that acted as personal identifiers for the study will be destroyed at the earliest opportunity. All documents will be placed in one of the HIPAA/Confidential Document

24.3 Who will have access to the data or specimens locally?

Response: Only the PI, Co-Investigator, Statistician, or Research Assistant at Dent Neurologic Institute will have access to the data and participant information.

24.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response: Dr. Zhang and the study coordinator share this responsibility.

24.5 How data and specimens will be transported locally?

Response: Dr. Zhang, the study coordinator and the research staff team share this responsibility.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response: Only the PI, Co-Investigator, Statistician, or Research Assistant at Dent Neurologic Institute will have access to study-related data and participant information. The participant code number and identifying information will be kept in a locked office in the Dent Neurologic Institute and the UBSoPPS Research Pharmacy. At the conclusion of the study only the PI, Co-Investigator, or Research Assistant at Dent Neurologic Institute will have access to the data and participant information. All personnel have completed CITI human research training, various clinical trial trainings and have an educational background in human subjects research and HIPAA regulations. Any documents or files that acted as personal identifiers for the study will be destroyed at the earliest opportunity. All documents will be placed in one of the HIPAA/Confidential Document bins which are located throughout the Dent Neurologic Institute. These secure bins are then emptied and the documents are destroyed by Cintas. Cintas is certified by the National Association for Information Destruction and also compliant with HIPAA and PCI standards.

25.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response:

Participants are greeted in a friendly manner, and maximal effort is made to build a courteous, respectful, and pleasant rapport with all study participants. At the consent visit, participants are encouraged to ask any questions as the research staff member reviews the form with them.

Participants are explicitly told they are welcome to take the form home to think about and discuss with family members.

To reduce pressure on participants at each visit, they are given time alone to complete the questionnaires. Additionally, appointments are scheduled at the participants' convenience to the best of the study personnel's availability.

When the urine container is given to participants for visits 1, 5, and 8, it is placed in a large bag for privacy as they leave the building.

25.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response: Please see 25.1

26.0 Compensation for Research-Related Injury

26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response: No available compensation (please see 26.2)

26.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response:

REIMBURSEMENT FOR MEDICAL TREATMENT

Routinely, the Buffalo General Hospital, Erie County Medical Center, Millard Fillmore Hospital and/or the University at Buffalo, State University of New York, its agents, or its employees do not compensate for or provide free medical care for human subjects/participants in the event that any injury results from participation in a human research project. In the unlikely event that you become ill or injured as a direct result of participating in this study, you may receive medical care, but it will not be free of charge even if the injury is a direct result of your participation.

27.0 Economic Burden to Subjects

27.1 Describe any costs that subjects may be responsible for because of participation in the research.

Response: Participants may take time off work to attend the appointments, which last approximately 20-60 minutes. In the unlikely event of a medical or psychological complication from the research, participants will seek treatment from a provider of their choice, which is not paid for by the PI or study funds. Participants are paid $35 per visit to cover travel (and related) costs.

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent

Response: Written consent will be obtained for all participants. The consent form is enclosed in this package submission.

28.2 Describe where the consent process take place

Response: Consents will be obtained from all individuals in private exam rooms or private check-out areas. The exam room and the check-out desk are designed as a private space to ensure confidentiality during day-to-day clinical practice and will provide the same confidentiality and privacy for consenting participants.

The PI or designee will fully inform the participant of all pertinent aspects of the study including the written information as approved by the IRB. The process includes: giving the participant adequate information concerning the study; providing ample time and opportunity for the participant to inquire about the details and to decide whether or not to participate; responding to participant's questions to the satisfaction of the participant. Participants also have the choice to sign the form at the initial visit or to take the form home to review independently or with their primary physician and return to sign it. The Principal Investigator is not the subjects' primary care physician. It will be stressed that a patient's participation is completely voluntary, that they may withdraw at any time and that their decision to participate or not to participate will not affect their standard of care at the Dent Dizziness and Balance Center or Buffalo ENT Specialists. Before signatures are obtained, the staff member obtaining consent will confirm that the patient has no further questions and understands fully. Each person's signature and date must be in his / her own handwriting; no other person may fill in missing dates or times. All Informed consent signatures must be obtained on the same date, beginning with the participant's signature. The investigator or designee will file the original signed consent form with the study records and a copy of the signed consent form will be provided to the participant at the time of consent. Any alternative treatments will be discussed before the participant signs the informed consent. The participant will be informed in a timely manner by the investigator or research personnel when new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. This may be done in writing by letter, revised ICF or in any manner approved by the reviewing IRB. The communication of this information should be documented in the medical record along with a copy of the information provided. If the written consent form is revised during the course of a participant's duration in the study, then the participant shall be re consented by the principal investigator or designee with the revised IRB approved consent form. The investigator or designee will file the newly obtained original signed consent form with the participant's study record.

28.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response: Participants are allowed to take as much or as little time as they would like to decide if they want to participate in the study. Subjects may decide to sign the consent form immediately after reviewing it with the research staff member or they may take it home with them to think about it. Participants decide how long they would like to wait.

28.4 Describe any process to ensure ongoing consent.

Response: Only a current IRB-approved and stamped form may be used to consent a research participant. If/when the consent document is revised or updated, a the most recent copy of the consent form is provided and explained to all current participants.

28.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: The consent form enclosed in this package adheres to guidelines in the HRP090 form. The research staff member invites and encourages questions from the participant, explicitly gives them the option to decline participation, sign the consent, or take it home to think about it with friends and family. Potential participants are given the phone number of the study coordinator and Dr. Zhang to discuss any further questions they might have after leaving. Additionally, potential participants are given as much time as they need to read through the consent form either in a private exam room or at home.

Non-English Speaking Subjects

28.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: N/A

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Response: N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

28.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: N/A

28.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: N/A

Subjects who are not yet adults (infants, children, teenagers)

28.10 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response: N/A

28.11 For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: N/A

28.12 Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: N/A

28.13 Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response: N/A

28.14 Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response: N/A

28.15 When assent of children is obtained describe whether and how it will be documented.

Response: N/A

Cognitively Impaired Adults

28.16 Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response: As per phone conversation with Alyssa at IRB 4/10/2015: We are unsure why this question was flagged for editing. This study does not recruit or enroll cognitively impaired adults and Meniere's Disease is not a cognitively degenerative disease. It's an inner ear disorder that can cause vertigo, tinnitus/hearing loss, nausea and headaches.

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

28.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

Response: N/A

28.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: N/A

28.19Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: N/A

28.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: N/A

29.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

29.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response: The consent form for this study adheres to guidelines in form HRP091, and is enclosed in this package.

30.0 Drugs or Devices

30.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: Lamotrigine is a FDA approved drug, but the study is exploring a new indication. The FDA has concluded that the study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct the investigation.

The drug supply will be sent to the University of Buffalo's School of Pharmacy and Pharmaceutical Sciences (UBSoPPS) Research Pharmacy. Once it arrives the packing slip will be checked for completeness and then the study staff will be notified of its arrival. The invoice and inventory taken will be faxed over to the study site. The drugs will then be stored in their original containers in a room-temperature, dry and dark area of the UBSoPPS Research Pharmacy's lab, which has very limited access since it is a pharmacy. Temperature and humidity will be monitored by a UBSoPPS Research Pharmacist.

UBSoPPS Research Pharmacy will take the manufacture supplied tablet and place it inside a capsule. The capsule will be filled with methylcellulose until the entire content of the capsule is filled, decreasing the chance for un-blinding, and the capsule then closed. The encapsulated lamotrigine will then be packaged in an amber vial with a study label. Repackaging will follow NYS regulation. Repacking will be conducted by a pharmacist or under his/her immediate and personal supervision. A repacking record shall

be maintained for five years, including the name, strength, lot number, quantity and name of the manufacturer and/or distributor of the drug repacked, the date of repacking, the number of packages prepared, the number of dosage units in each package, the signature of the person performing the repacking operation, the signature of the pharmacist who supervised the repacking, and such other identifying marks added by the pharmacy for internal recordkeeping purposes. Drugs repacked shall have an expiration date 12 months, or 50 percent of the time remaining to the manufacturer's expiration date, whichever is less, from the date of repacking.

SUNY at Buffalo School of Pharmacy and Pharmaceutical Sciences (UBSoPPS) Research Pharmacy will randomize eligible participants through www.randomizer.org. An UBSoPPS pharmacist will generate 12 random sets of numbers, ranging from 1-2 for the two assignment groups, with one unique number per set. UBSoPPS Research Pharmacy will use this randomization to compile a master log with the participant number and treatment code.

Those assigned to the lamotrigine treatment will take encapsulated lamotrigine daily for the duration of 20 weeks, consisting of a six-week titration, 12-week study period, and two-week taper. Possible doses for patients are 25mg BID, 50mg BID, 100 mg BID and 150mg BID during titration; 150mg BID or 100mg BID for the 12-week study period; 150mg QD or 100mg QD for Week 1 of the taper; and 75mg QD, or 50mg QD for Week 2 of the taper. Each increase in dose will be maintained for two weeks before deciding to further increase or decrease based on tolerability. Patients who discontinue at any point of the study will have a two-week taper consisting of the current dose QD for one week followed by half the dose QD for another week.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

30.2 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: N/A

30.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: N/A