PROTOCOL TITLE: Effects of Perampanel on Neurophysiology Test Perimeters

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IRB Protocol #: 1704018150

ClinicalTrials.gov Identifier: #NCT03653741

Current Version 6/1/2018

Prior Version Dates:
Version December 8, 2017

BACKGROUND

Neurophysiology tests such as EEG, VEP, BAER, and SEP are used to evaluate the functional status of the neuroaxis from the periphery all the way to the cortex. Many anti-epileptic drugs have been shown to affect these tests. Anti-epileptic medications such as phenytoin, carbamazepine, and oxcarbazepine have been shown to cause background slowing on EEG. Anti-epileptic medications have also been shown to prolong latency values in VEP, SSEP and BAER. One small study demonstrated that the AMPA receptor antagonist talampanel was associated with dose-dependent increase in beta activity. To date, there have been no published data on whether FDA approved anti-epileptic medication perampanel (same mechanism of action as talampanel) affects EEG, VEP, SSEP, or

BAER. As for anticipated side effects of perampanel, in a small study of 6 patients that received a single dose of perampanel at 6mg (the dose we will be using), the most common side effects was headache, fatigue, somnolence, and dizziness.

STUDY DESIGN

We hypothesize that perampanel, a FDA approved drug for epilepsy, will affect commonly performed neurophysiology tests: electroencephalogram (EEG), somatosensory evoked potential (SEP), brainstem auditory evoked potential (BAEP), and visual evoked potential (VEP). More specifically, we hypothesize it will decrease background frequency content in EEG and increase latency in VEP, SEP, and BAEP. We plan to recruit 12 healthy normal male subjects. All subjects will have VEP, SSEP, EEG, and BAER performed before and 1 hour (when Cmax is reached) after receiving 6mg of perampanel. Subjects will also receive a blood draw 1 hour after ingestion of perampanel for serum perampanel level for correlation with any changes seen in the neurophysiology test data. There is no placebo nor randomization. Subject's participation concludes after completion of post-perampanel ingestion neurophysiology tests.

Primary: Quantify the effects of perampanel on electroencephalography, visual evoked potential, somatosensory evoked potential, and brainstem auditory evoked potential to guide interpretation of test results for patients taking perampanel.

Secondary: 1) Correlate effects on neurophysiology test perimeters with known drug side effects. 2) Pinpoint where in neuroaxis perampanel exerts maximal effects, which may shed light on where it exerts its anti-seizure effects.

Based on similar studies, we will recruit 12 subjects. Each subject will undergo 4 neurophysiology tests. Then each subject will ingest perampanel and then repeat the 4 neurophysiology tests. We will compare the pre-ingestion to the post-ingestion values in the 4 tests using a Wilcoxon signed-rank test, which is more appropriate for small samples than a standard paired t-test. We do not expect any dropouts, but if they occur we will perform sensitivity analysis by providing results for different imputed values for the dropouts.

INCLUSION AND EXCLUSION CRITERIA

Healthy subjects between the ages of 18 to 50 years old with a body mass index of 19-29 kg/m2 will be recruited. Subjects would be excluded if they use recreational drugs and have any neurologic disease, psychiatric condition or any other condition that may affect outcome and risk subject safety.

Furthermore, anyone that would not be able to participate in neurophysiology tests will also be excluded. Subject will also be excluded should they take any over the counter medication or consume caffeine or alcohol 12 hours prior to the study.

DATA AND SAFETY MONITORING PLAN

The risk to subjects is minimal risk for all tests involved. Blood levels of perampanel will be drawn 1 hour after drug administration. Additionally, the 4 tests (VEP, EEG, SEP, BAEP) will be completed both prior to and following study drug administration. This study does not have interim and complete stopping rules. This is a small study and we do not expect to encounter any major adverse events since the tests we will be administering is well tolerated and the study drug, perampanel, is FDA approved and well tolerated in the way we will be administering it (single dose at 6mg). We do not expect any adverse events that would stop a subject's participation. The subject can withdraw voluntarily. The risk of taking perampanel to the subject is classified as greater than minimal risk. In a small study looking at single dose of perampanel administered to healthy volunteer at 6mg, the reported side effects were headache, dizziness (excluding vertigo), somnolence, and fatigue. These were all classified as mild to moderate in severity. Rate of side effect was reported as 16.8% while placebo was 12.6%. Serious Side Effects: Perampanel may cause new or worse aggressive behavior, homicidal thoughts or threats, hostility, anger, anxiety, irritability, being suspicious or distrustful (believing things that are not true), and other unusual or extreme changes in behavior or mood. You should contact the study doctor immediately should you experience any of the above. Antiepileptic drugs, including perampanel, may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Study subjectss should call their healthcare providers right away if they have any of the following symptoms, especially if they are new, worse, or worrisome: thoughts about suicide or dying, thoughts of self-harm, attempt to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping (insomnia), new or worse irritability, acting aggressive, being angry or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), and other unusual changes in behavior or mood. You should call your study doctor immediately if you notice any changes in mood, ideas or behavior. Most common side effects: Dizziness, fatigue, sleepiness, irritability, falls, nausea, imbalance, gait problems, vertigo, and weight gain. Less commonly seen side effects: Headache, anxiety, upset stomach, vomiting, constipation, urinary tract infection, problems with coordination, rash, bruises, muscle pain, blurry vision, swelling of arms/legs, numbness, memory problems, confusion, euphoria, low blood sodium level, increase triglyceride level, skin laceration, pain in extremities, back pain, and head trauma. Additional Risks: The U.S Drug Enforcement Agency (DEA) may classify some, but not all, medicines as controlled substances. Perampanel has been classified as schedule III. Medicines in this category have an approved medical use but have potential for abuse, physical dependence, or psychological dependence. The risk is lower compared to drugs in Schedule I and II. Some other anti-epileptic medicines have also been listed as controlled substances. It is possible that perampanel may interact with other medicines and herbal supplements that you are taking. Before starting the study, your study doctor will determine that you are not taking anything that can interact with perampanel. During the collection of blood samples, you may experience slight discomfort and a small amount of bleeding, discoloration or bruising at the site where the needle was inserted. Clot formation and infections may occur at the puncture site, but this is extremely rare. Fainting may occur during or

shortly after having blood drawn. If faintness is experienced, you should lie down immediately to avoid possible injury caused by falling and notify the site study staff. The total amount of blood taken during the study is approximately 40-60 teaspoons. Reproductive Risks: Perampanel does not affect the ability of men to father children.

Subjects will be monitored during the tests and interviewed in order to detect any adverse events. An investigator will be with the subject at all times to recognize and record any adverse events. Since the study involves only one dosing of study drug, there will not be any negative impact on subjects resulting from study closure or a subject being terminated from the study. Adverse events will be rated mild, moderate, or severe. Adverse events will be reported to the IRB and to Eisai (study sponsor). Aside from the IRB, unexpected adverse events will also be promptly reported to Eisai. The principle investigator will be monitoring the safety of the subjects.

Interim analysis will not be needed as drug is FDA approved and small study so analysis will be done after completion of all subject. Data safety monitoring board is not needed since drug is FDA approved and will be administered only once to normal subjects. It is found to be generally well tolerated in this condition.