INVESTIGATOR INITIATED STUDIES (IIS) APPLICATION FORM

Protocol Title:	Pilot Study of Add-On Fycompa (perampanel) Treatment for Catamenial Epilepsy
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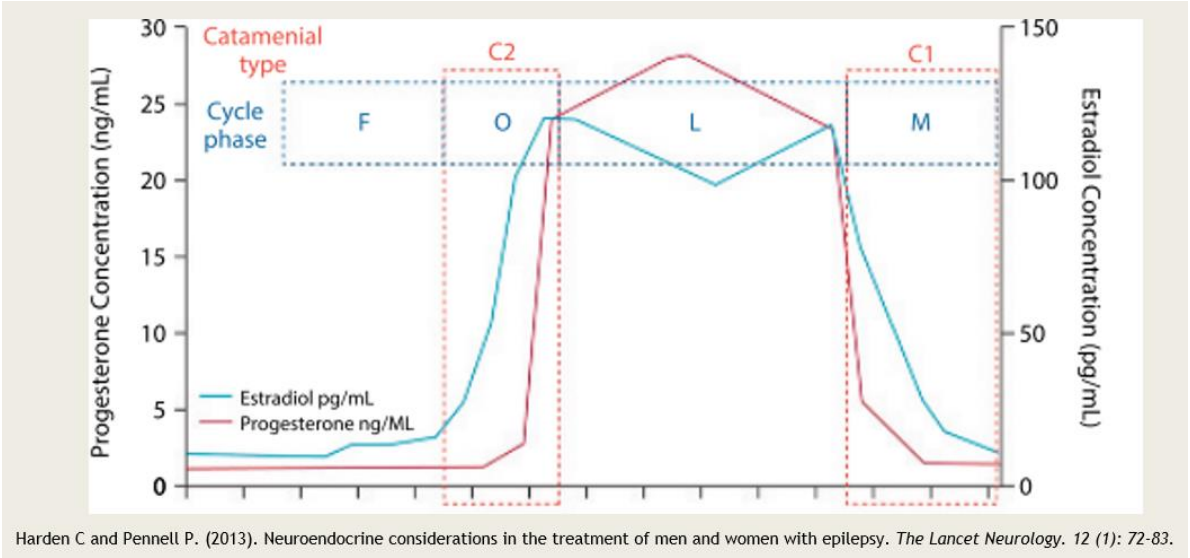
Institution Name(s):	University of Florida-Jacksonville
Sub-Investigator Name, if applicable:	Ramon Bautista MD MBA, Suparna Krishnaiengar MD
Do you plan on using other Institutions or centers to conduct study?	☐ YES ☒ NO
If yes, please list name(s) and address(es):	N/A

Rationale:

Approximately one-third of WWE have catamenial epilepsy, or cyclic seizure exacerbations in relation to the menstrual cycle. In women with ovulatory cycles, catamenial seizure exacerbations can occur either during the perimenstrual (catamenial 1, C1) or the preovulatory (catamenial 2, C2) phases of the menstrual cycle (Herzog et al., 1997; Herzog 2008).

C1 seizure exacerbations are thought be related to the rapid premenstrual withdrawal of progesterone (Herzog 2008) (Figure 1). Progesterone has been found to have dual actions on the brain. First, the progesterone neurosteroid metabolite allopregnanolone exerts an anticonvulsant effect by binding to the gamma-amino-butyric acid (GABA) type A receptor to enhance GABA action (Herzog et al., 1997; Joshi at al., 2013). The rapid withdrawal of allopregnanolone premenstrually may impair GABAergic inhibition and therefore precipitate seizures. Second, progesterone has recently also been found to exert a proconvulsant effect. Shiono et al. (2019) found that progesterone receptor activation increased seizure frequency in epileptic animals. Joshi et al. (2018) discovered that progesterone receptor activation increased excitatory transmission by upregulating a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor GluA1 and GluA2 subunit expression in the rat model. The use of a progesterone and glucocorticoid receptor blocker then attenuated neurosteroid withdrawal seizures.

C2 seizure exacerbations, alternatively, may be secondary to the preovulatory estrogen surge (Figure 1). In the animal model, estradiol has been found to act as proconvulsant by potentiating excitatory synaptic transmission by increasing the probability of glutamate release; this may be enhanced via AMPA mediated conductance (Smith, 1989; Smejkalova and Woolley, 2010). Estradiol has also been found to increase neuronal metabolism and discharge rates (Smith, 1989; Hardy, 1970).



Harden C and Pennell P. (2013). Neuroendocrine considerations in the treatment of men and women with epilepsy. *The Lancet Neurology. 12 (1): 72-83.*

Figure 1. Illustration of how fluctuations in progesterone and estradiol concentration contribute to perimenstrual (catamenial 1, C1) and preovulatory (catamenial 2, C2) cyclic seizure exacerbations.

The role of hormonal treatment of catamenial epilepsy was previously investigated in the NIH Progesterone Trial, a randomized, double-blinded clinical trial of progesterone versus placebo therapy in the treatment of intractable focal seizures in ovulatory women with and without catamenial epilepsy (Herzog et al., 2012). The principal outcomes were the proportion of ≥50% responders and the change in seizure frequency between the 3-month baseline and 3-month treatment phases. Unfortunately, no significant differences were found between progesterone and placebo therapy, though women with both C1 and C2 seizure exacerbations were included in the catamenial arm. Of note, on post hoc analysis, women with high levels of perimenstrual seizure exacerbation were found to be responsive.

Apart from trial design issues (the level of catameniality may have been insufficient for inclusion in the catamenial arm and women with C2 seizure exacerbations were also in the catamenial arm), the lack of effectiveness of progesterone suggests that the anticonvulsant effects of progesterone alone are insufficient in preventing catamenial seizure exacerbations. As previously described by Joshi et al. (2018), progesterone receptor activation may contribute to excitotoxicity by increasing AMPA receptor mediated glutamatergic transmission. The rapid withdrawal of allopregnanolone may therefore provoke seizures by disrupting the homeostatic balance of excitatory and inhibitory regulation, as in vivo and in vitro studies suggest that central neurons regulate excitatory and inhibitory balance slowly, over hours to days (Turrigiano 2011). Therefore, limiting the excitotoxicity of progesterone receptor activation may be particularly efficacious in treating perimenstrual catamenial seizure exacerbations.

The purpose of the proposed investigation is to carry out a pilot study of add-on perampanel (Fycompa) in women with perimenstrual (C1) catamenial epilepsy. Perampanel, a noncompetitive AMPA receptor antagonist, is uniquely positioned to decrease progesterone receptor mediated excitotoxicity. This mechanism of action would allow a novel use of perampanel as an effective treatment of C1 catamenial epilepsy.

Of note: Future studies should investigate the use of perampanel in women with preovulatory (C2) catamenial epilepsy, as estradiol's proconvulsant effect is potentially being mediated through the enhancement of AMPA. This population is not included in this study. Women in clinic typically report clustering of seizures specifically around their menses (perimenstrual) so I chose to target this population (C1 pattern) first as I find this more clinically relevant.

Study Design:

This is an unblinded pilot study enrolling women with C1 catamenial focal epilepsy. Subjects will chart menses and seizures for a 2 month baseline period and then be randomized into 2 parallel arms: (1) Fycompa 4 mg daily and (2) Fycompa 4 mg daily to be increased to 6 mg daily peri-menstrually (Day -7 until Day 4 of menstruation where Day 1 is the first day of menstrual flow). During this treatment phase, subjects will continue to chart menses and seizures. Other anticonvulsant medication doses will not be changed during the baseline or treatment study period.

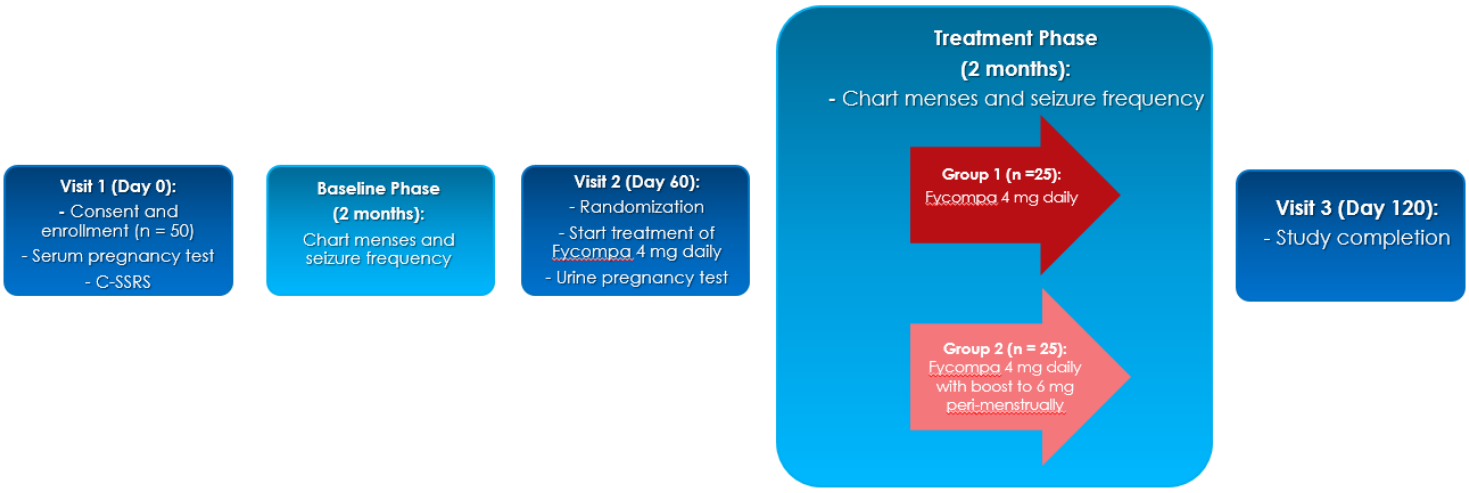
Objectives:

Primary: To determine the responder rate in each group (percent of patients experiencing a 50% or greater reduction in seizures) relative to baseline seizure frequencies.

Secondary: Changes in seizure frequency in each group relative to baseline seizure frequencies.

Tertiary: Comparisons of primary and secondary outcomes between two groups.

Study Schema:



Subjects and Centers:

This a single site study at a tertiary care academic center, the University of Florida at Jacksonville. 50 total female subjects will be enrolled.

Inclusion Criteria:

1. Female
2. Diagnosis of focal onset seizures (FOS)
   i. Established by clinical history and an EEG
   ii. Patients with a normal EEG may be included if they met other diagnostic criteria based on clinical history
3. Presumably ovulatory women based on menstrual cycles of 21-35 days from beginning of menstrual flow to the beginning of the next menses
4. ≥18-50 years old
5. ≥2 unprovoked seizures per month despite drug trials with ≥1 first-line anti-epileptic drugs (AED)
6. Seizures must show a C1 catamenial pattern in 2 of 3 documented cycles
   i. C1 pattern will be defined as a two-fold increase in average daily seizure frequency during the menstrual phase, as compared to the follicular and luteal phases of the ovulation cycle, in 2 of 3 documented cycles. The menstrual phase will be defined as days -3 to +3 of the menstrual cycle (where onset of menstruation is defined as day 1) (Herzog et al, 1997). Of note, in the NIH Progesterone Trial, the level of catameniality was 1.69 based on Herzog et al. (1997) criteria though this trial will use a level of 2 to include women only with high levels of perimenstrual catamenial exacerbation.
7. Willingness and ability to comply with scheduled visits and study procedures

Exclusion Criteria:

1. Progressive neurologic or systemic disorder
2. Use of systemic hormonal contraception during 3 months prior to enrollment (however, subjects with a progestin-releasing IUD who still have monthly periods may be enrolled)
    a. Women on system hormonal contraception will be excluded as these women are not ovulatory
3. Subject is pregnant or breastfeeding
4. Active suicidal or homicidal ideation
5. ~~Decisionally impaired or~~C ~~c~~omatose individuals.

Other Therapy: **N/A**

Efficacy Measures:

1. Primary: To determine the responder rate (percent of patients experiencing a 50% or greater reduction in seizures) relative to baseline seizure frequencies.
2. Secondary: Changes in seizure frequency relative to baseline seizure frequencies.
3. Tertiary: Comparisons of primary and secondary outcomes between two groups.

Safety Measures:

1. We do not plan to have an internal Data Safety Monitoring Board. PI and study coordinator to be in charge of safety measures.
2. There will be a baseline Columbia-Suicide Severity Rating Scale (C-SSRS) at enrollment to screen for suicidal ideation and behaviors. If suicidal ideation or behaviors are present, subjects will not be enrolled in the study. At each follow-up visit, we will screen for changes in this scale. During each telephone call, we will screen for depressive symptoms and suicidality by asking patients if they are suicidal.
    1. Suicidality plan:
        a. C-SSRS will be performed at each visit by study coordinator. Study coordinator to contact PI if there is a change in the C-SSRS.
        b. For suicidal ideation and/or behaviors, we will refer subject to the Emergency Department for emergent evaluation and treatment. Phone number for suicide hotline will also be provided. Will also discontinue enrollment in trial and study drug.
3. We will screen for behavioral changes at each visit and during each telephone call.
    1. Will screen by asking specifically if patient is having:
        a. Thoughts of harming others, physical assault, or threating behavior
        b. Worsening anger, aggression, or irritability

2. If thoughts of harming others, physical assault, or threating behavior develops in a subject, will discontinue enrollment in trial and study drug. Subject will be referred to the Emergency Department.
3. If worsening anger, aggression, or irritability is mild or moderate, will continue enrollment and continue monitoring subject.
4. If worsening anger, aggression, or irritability is severe, will discontinue enrollment in trial and study drug.

4. We will check a serum pregnancy prior to enrollment in baseline phase and then a urine pregnancy test prior to enrollment in treatment phase to ensure pregnant women are excluded.
5. Subjects who are not status post tubal ligation or who do not have an IUD must agree to use a double barrier contraceptive method while enrolled in study (e.g. condom +spermicide OR condom + diaphragm/cervical cap).
   a. During monthly telephone calls while enrolled in the study (see "Data Collection" below), subjects will be reminded to utilize the double barrier contraceptive method while enrolled in the study.

Adverse Events:

1. Serious FDA definition: A serious adverse event results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, results in a congenital anomaly / birth defect.
2. Severity: Severity describes the intensity of a specific event and will be graded as:
   a. Mild: easily tolerated, causing minimal discomfort.
   b. Moderate: sufficiently discomforting to interfere with every day activities.
   c. Severe: prevents normal every day activities.
3. Relationship will be detailed as:
   a. Unrelated: There is no association between the study intervention and the reported event.
   b. Related: A definite causal relationship exists between the event and the study, and other conditions (concurrent illness, progression of disease or concomitant medication use do not appear to explain the event).
   c. Cannot be ruled out: The event might be related to the intervention, but could also have been produced by other factors.

Correlative Science: N/A

Statistical Analysis: The primary outcome (50% responder rate) will be analyzed using Chi square analysis. The secondary outcome, changes in seizure frequency from baseline to treatment, will be analyzed using paired t-test or ANCOVA.

The pilot should provide data for calculation of the required sample size for demonstration of a significant difference or equivalence between the two groups with 80% power.

Data Collection:	Subjects will be seen in the clinical trial clinic for three separate visits. Subjects will be seen at enrollment and then also after the completion of baseline (first 2 months of charting) and treatment phases (second 2 months of charting). Subjects will also be contacted by phone on a monthly basis to verify compliance with charting and treatment and to monitor for any adverse effects. [Subjects will also be reminded to utilize double barrier contraceptive methods during these phone calls]. Data will be obtained via paper charting on printed calendar and then entered into an electronic database (REDCap) for analysis. All adverse events will be reported to the IRB.
Study Drug Regimens:	During the treatment phase, subjects will be randomized into 2 parallel arms: (1) Fycompa 4 mg daily and (2) Fycompa 4 mg daily to be increased to 6 mg (4-mg pill and 2 mg pill) daily peri-menstrually (from Day -7 until Day 4 of menstruation where Day 1 is the first day of menstrual flow). This treatment phase will last for two menstrual cycles.
Study Drug Requested Per Patient:	Group 1 (n=25), to take 4 mg daily for 2 menstrual cycles or 60 days, 1500 tablets (25 subjects x 60 days). Group 2 (n=25), to take 4 mg daily (1 tablet) with6 mg daily (1 4-mg tablet and 1 2-mg tablet) for 11 days around menses for 60 days. This would be 1500 tablets (25 subjects x 60 days) of 4 mg tablets and 550 tablets (25 subject x 22 days) of 2 mg tablets.

Are Clinical/Drug Supplies Requested? (check only 1 box**):** ☒ **'YES'** ☐ **'NO'**

Total study drug amount in units (tablets, capsules, vials, etc.):	
Total Active Drug	**3000 tablets of 4 mg tablets needed** **550 tablets of 2 mg tablets needed**
Amount of Pure Substance (if applicable)	

Estimated Length of Enrollment:	I plan to enroll 50 patients within a 6 month time period.

Description of Site Enrollment Capabilities:	University of Florida-Jacksonville is a busy Level 4 National Association of Epilepsy Center (NAEC) with thousands of epilepsy patients seen per year. Patients seek care at three differential UF locations within the Jacksonville area covering a large catchment area that includes southern Georgia.
Estimated Study Duration:	~ 1 year
Potential written outcomes of this study (check all that apply):	☐ Final Study Report ☒ Submit for Presentation at scientific conference ☒ Submit for Publication ☒ Submit Abstract/Poster at scientific conference
Publication Plan (if applicable):	Goal of being published in either Neurology or Epilepsia, to be submitted for publication within 1-1.5 years of contract execution.

Manuscript Publication Assistance:

DO YOU REQUIRE MANUSCRIPT PUBLICATION ASSISTANCE, AS OUTLINED BELOW?: ☐☒ YES ☐☐ NO ☐

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Other sources of funding:	Other sources of funding for this study are: None The following are other pending sources of funding: None
Other sources of study drug:	None
Intellectual Property Disclosure:	None
Research Team Members/Co-Investigators and all others' Responsibilities:	Ramon Bautista MD MBA, sub-investigator, Ramon.bautista@jax.ufl.edu Suparna Krishnaiengar MD, sub-investigator, Suparna.krishnaiengar@jax.ufl.edu Felicia Smith, Epilepsy Research/Clinical Coordinator, Felicia.smith3@jax.ufl.edu Yasmeen Shabbir, Research Coordinator, Yasmeen.shabbir@jax.ufl.edu
Insurance:	As a University of Florida faculty member, I am protected by the University of Florida Self-Insurance Program (UFSIP). No additional insurance will be purchased for this study.
Past History and Experience:	I have never been a Principal Investigator on an IIS prior, though I have assisted during residency and fellowship with creation of IIS proposals and with ongoing IIS. I have never had any disciplinary actions against my medical license.

References:

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IND:

☒ IND Exemption ☐ IND Number