Fycompa titration intervals and effects on retention rates

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IIS PROTOCOL SYNOPSIS

Protocol Title:	Fycompa titration intervals and effects on retention rates
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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:

With its novel mechanism of AMPA receptor blockade, Fycompa is efficacious for seizure reduction in both partial onset seizures and generalized tonic-clonic seizures. As only a few of antiepileptic medications have this capability, it is important to elucidate the ideal methods of avoiding complications and improving retention rates.

Recent studies find real-world rates currently range from 44-89% (Trinka et al 2016). Personal clinical experience has revealed difficulty in maintaining patients on Fycompa due to adverse effects. However, certain studies find correlations between slower titration schedules and lower side effect percentages (Trinka et al 2016, Lawthom et al, 2014).

We therefore propose to test whether a slower initial upward titration (2mg increase every 3 weeks) improves 1-year retention rates as compared to those of a more typical titration every 2 weeks. As any retention rate may be affected by adverse effects and/or seizure frequency, these will be followed as secondary endpoints.

Study Design:

A total of 60 patients with a confirmed diagnosis of either partial onset or primary generalized epilepsy will be recruited into the trial. 30 patients will initiate Fycompa at a dose of 2 mg/day and titrate upward every 2 weeks to a target dose of 6 mg/day. Patients in this group will be designated Group A. The remaining 30 patients will also begin Fycompa at a dose of 2 mg/day but will titrate upwards every 3 weeks to a target dose of 6 mg/day and will be designated Group B. Initial study visits will occur every two weeks for the first 2 months in order to assess for titration related adverse effects. Long term evaluation of retention rates will be calculated at 3, 6, 9 and 12 months after enrollment.

Objectives:

Primary:

To evaluate the differences in retention rate between patients using a more conventional upward titration schedule (Group A) vs. those using a slower up-titration schedule (Group B).

Secondary:

1. To compare the adverse effects reported in patients up-titrating Fycompa at a slower titration rate (Group B) to those titrating at a more conventional rate (Group A).
2. To evaluate the short term and long term efficacy of perampanel between the two treatment groups.

Subjects and Centers:

A total of 60 epilepsy patients will be recruited from the Epilepsy Center at Banner University Medicine Neuroscience Institute. 30 patients will be randomly assigned to treatment group A, up-titrating Fycompa every 2 weeks while the remaining 30 being assigned to group B, up-titrating Fycompa every 3 weeks.

Inclusion Criteria:

1. Must provide written informed consent signed by the subject or legal guardian prior to entering the study in accordance with the ICH, GCP guidelines if the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained.
2. Subject has a confirmed diagnosis of medically refractory epilepsy with or without secondary generalization for at least 12 months prior to visit 1.
3. Subjects currently being treated with 1 to 3 antiepileptic medications with or without VNS (does not count as an AED).
4. Subjects aged 18 to 75.
5. Subject's requiring an additional epilepsy medication due to either uncontrolled seizure and/or lack of tolerability with current epilepsy medications
6. Can be safely treated, in the opinion of the investigator with Fycompa.
7. Able and agrees to follow specified titration schedule
8. Subjects or a legal guardian who is able to communicate effectively with study personnel and considered reliable, able, willing and cooperative with regard to complying with protocol-defined requirements, including completion of the study diary.

Exclusion Criteria:

1. Any history of non-epileptic or psychogenic seizures.
2. Women who are currently pregnant, lactating or have plans to become pregnant in the immediate future.
3. Subjects with active suicidal ideation or behavior as evidenced by positive answers on the Columbia Suicide Severity Rating Scale (C-SSRS) or subject's with a history of suicidal ideation or attempt within 12 months.
4. Subjects with a suicidal attempt in the 12 months prior to Visit 1
5. Any clinically significant medical or psychiatric illness, psychological or behavioral problems, which in the opinion of the investigator would interfere with the subject's ability to participate in the study.
6. Subjects with severe hepatic impairment or severe renal impairment or on hemodialysis.
7. Any use of concomitant medication as listed in the drug insert, including medications known to be inducers of cytochrome P450 (CYP3A).

IIS PROTOCOL SYNOPSIS

Other Therapy:

Concomitant antiepileptic and medical treatment will be allowed as deemed necessary by the Principle investigator and/or sub-investigators. .

Efficacy Measures:

Patient diaries containing seizure types and frequencies along with adverse effects experienced will be maintained. Seizure diaries will be reviewed in Epilepsy Clinic during study visits occurring at the following intervals: weeks 0, 2, 4, 6, 8 then months 3, 6, 9, and 12. Data point collation at study visits will include:

1. Fycompa dose taken and duration at this dose
2. Adverse effects experienced
3. Alterations to Fycompa dose once in maintenance phase.
4. Interim seizure types and number of each
5. Interim changes in other medication during maintenance phase.

Safety Measures:

Adverse effects and seizure frequency will be assessed at each clinic visit along with vital sign measurements and brief neurological exams. Dosage adjustments of the Fycompa and other concomitant medications will be done at the discretion of the Investigator during the maintenance phase.

Correlative Science:

Data collected will be based on the patient's seizure/adverse effect diary as well as patient/caregiver reports at each study visit.

Statistical Analysis:

The study will target a total size of 60 patients (30 per group). This sample size will allow for a power of 0.85 to determine significant difference of 30% retention in group A and 70% retention in group B.

Primary endpoint will be Fycompa retention rate at the end of 1 year with Kaplan-Meier survival curves created for both groups. Log rank testing will be done to determine significant difference ($p<0.05$). Cox proportional hazard test will be done to quantify the odds of retention in each arm.

Secondary endpoint analysis will be done to tabulated side effects experienced in each group and the percentages of patients reporting the effects. Seizure frequency per 28 days during initial titration and final maintenance will be calculated for each group. Comparison within groups will be made by ANOVA.

Data Collection:

Data will be collected at each study visit through patient interview and the use of a seizure/adverse effect diary.

Study Drug Regimens:	Group A will have Fycompa 2mg qD for 2 weeks, then 4mg qD for 2 weeks, then 6mg qD for at least 2 weeks. Further adjustments upward or downward in the maintenance phase will be allowed as per Investigator's discretion. We anticipate 15 will continue at 6mg, 8 will decrease to 4mg, and 7 will increase to 8mg during the next 46 weeks of maintenance. Group B will have Fycompa 2mg qD for 3 weeks, then 4mg qD for 3 weeks, then 6mg qD for at least 3 weeks. Further adjustments upward or downward in the maintenance phase will be allowed as per the Investigator's discretion. We anticipate 15 will continue at 6mg, 8 will decrease to 4mg, and 7 will increase to 8mg for the remaining 40 weeks of maintenance.
Study Drug Requested Per Patient:	TOTAL: 2mg tablets = 11,550 4mg tablets = 24,794

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

Total study drug amount in units (tablets, capsules, vials, etc.):

Total Active Drug	**36,344 tablets**
Amount of Pure Substance (if applicable)	

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Estimated Study Start Date:	February 1, 2017
Estimated Length of Enrollment:	2 years
Description of Site Enrollment Capabilities:	The Banner University Medicine Neuroscience Institute, Epilepsy Center includes 3 full-time epileptologists, each with weekly outpatient clinics for epilepsy patients. It also employs a full-time study coordinator.
Estimated Study Duration:	24 months from study initiation to data analysis and paper completion, allowing for a 12 month enrollment period.
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):	Epilepsia, submission in August 2020.

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