A 12 WEEK RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL INVESTIGATING THE EFFECTS OF ADD-ON LEVETIRACETAM IN EARLY PSYCHOSIS

Abbreviated Title: *Levetiracetam in Early Psychosis*

Version #: *1.6*
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List of Abbreviations

AD: Alzheimer's disease
ASL: arterial spin labeling
BPAQ: Buss-Perry Aggression Questionnaire
BPRS: Brief Psychiatric Rating Scale
bSSFP: balanced steady-state free precession
CBF: cerebral blood flow
CDSS: Calgary Depression Scale for Schizophrenia
CGI: Clinical Global Impression
C-SSRS: Columbia Suicide Severity Rating Scale
CSF: cerebrospinal fluid
CSSRS: Columbia Suicide Severity Rating Scale
DUP: duration of untreated psychosis
EP: early psychosis
EHI: Edinburgh Handedness Inventory
GM: gray matter
HVI: hippocampal volumetric integrity
ICC: intraclass correlation coefficient
MCCB: Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery
mITT: modified Intent-to-Treat
MCI: mild cognitive impairment
MRI: magnetic resonance imaging
SAFTEE: Systematic Assessment for Treatment Emergent Side Effects
SANS: Scale for Assessment of Negative Symptoms
SCID: Structured Clinical Interview for DSM-V
SMHC: Shanghai Mental Health Center
TLE: temporal lobe epilepsy
UHR: ultra-high risk
VTA: ventral tegmental area
WM: white matter

Study Summary

Title	A 12 week randomized, double-blind, placebo-controlled trial investigating the effects of levetiracetam in early psychosis
Protocol Number	S19-01820
Study Duration	Months 1-6: Complete regulatory requirements for the R33 trial, train staff at both sites, verify inter-rater reliability and calibrate MRI morphometry between sites. Complete initiation visit at Shanghai Mental Health Center (SMHC). Complete data collection and data management systems. Months 6-29: Enroll 3 subjects per month at SMHC and 1.5 subjects per month at NYUMC to complete the enrollment target of 84 participants in month 26 and last participant completed in month 29. Repeat inter-rater reliability testing and training every 6 months and site visits annually. Months 30-36: Data analysis and manuscript preparation.
Study Center(s)	Multicenter Study: New York University Langone Medical Center /Bellevue Shanghai Mental Health Center (SMHC)
Objectives	The objectives of this study are to evaluate the efficacy of 12 weeks of Levetiracetam (500 mg) twice daily versus placebo on clinical symptoms, hippocampal volume and cognition and tolerability when added to antipsychotic in early psychosis (EP) patients with treatment-resistant symptoms and to assess the association between hippocampal cerebral blood flow (CBF) and markers of oxidative stress and inflammation with outcomes.
Endpoints / Outcome Measures	84 treatment resistant early psychosis (EP) subjects will be studied in a two-site, 12-week, double-blind, placebo-controlled trial of levetiracetam 500 mg twice daily added to a stable dose of clinician-determined antipsychotic.. - Change in BPRS total score at 12 weeks is the primary outcome; - Hippocampal volume change measured by MRI prior to the first dose and after 12 weeks and hippocampal CBF measured by arterial spin labeling (ASL) are the secondary outcomes. - In addition, we will measure other clinical symptoms and cognition and will analyze levetiracetam blood levels and biomarkers for oxidative stress and glial injury that predicted hippocampal volume loss in our previous study.
Number of Subjects	We aim to enroll a total of 84 participants: 28 EP participants at NYU Langone Medical Center and 56 at Shanghai Mental Health Center.

Inclusion/Exclusion Criteria	Inclusion Criteria 1. Males and females 16 to 40 years of age, inclusive, at time of informed consent 2. Must have experienced a first episode of nonaffective psychosis within 5 years and exhibit current psychosis, as defined by a score of ≥ 4 on one of the following psychosis items on the BPRS: conceptual disorganization, suspiciousness, hallucinations, unusual thought content, or grandiosity, for at least 4 days per week for at least 4 weeks 3. Must have a diagnosis of either schizophrenia, schizoaffective disorder or schizophreniform disorder as established by a Structured Clinical Interview for DSM-V(SCID) 4. Must have taken antipsychotic medication for a minimum of 8 weeks and at a stable dose for at least 4 weeks prior to randomization. 5. If assigned female at birth and of childbearing potential, patients must: a. Have a negative urine pregnancy test (all participants assigned female at birth regardless of childbearing potential will be required to submit a pregnancy test) and b. Not be nursing or planning a pregnancy for the duration of the study through 30 days after the last dosing visit and c. Be abstinent or willing to use a reliable method of birth control from the screening visit and continue with the same method until termination from the study. Exclusion Criteria 1. Current substance abuse or dependence for substances other than nicotine and THC (i.e. alcohol, amphetamines, barbiturates). a. A positive urine toxic screen (excluding THC, tricyclic antidepressants, or benzodiazepines (if prescribed)). b. Moderate or severe cannabis use disorder. 2. Diagnosis of major mood disorder or other Axis I disorder other than Schizophrenia, Schizoaffective Disorder or Schizophreniform Disorder. 3. Current suicidal ideation. Suicidal ideation with intent or plan (indicated by affirmative answers to items 4 or 5 of the suicidal ideation section of the baseline C-SSRS) in the 6 months prior to screening or subjects who represent a significant risk of suicide in the opinion of the Principal Investigator 4. Pregnant, nursing or positive urine pregnancy test. 5. Significant medical or neurological illness by history or physical exam including seizure disorder, history of loss of consciousness related to head trauma or developmental disorder including mental retardation.

	6. Renal insufficiency (if serum creatinine is greater than laboratory limits for normal, estimated creatinine clearance must be greater than 80) 7. Contraindications to MRI: metal implants, pacemaker, or other metal in the body, or claustrophobia. Individuals with tattoos will be excluded from imaging if tattoos cover more than 5% of the body surface, if a tattoo is greater than 20 cm, or if the tattoo is located on the face, neck or genitals. (Individuals with a contraindication to MRI may participate in the trial but will be excluded from the elective MRI component) 8. Significant history of serious violence a. For both inpatient and outpatient subjects, a history of serious violence as assessed by the Buss-Perry Aggression Questionnaire b. For outpatient subjects only, a score of 5 (moderately severe) or higher on the BPRS hostility item at screening or baseline
Study Product, Dose, Route, Regimen	84 EP subjects will be randomized in a 2:1 ratio stratified by site in a 12-week, double-blind, placebo-controlled trial of levetiracetam 500 mg bid added to clinician-determined antipsychotic treatment.

1 Introduction

Title: A 12 week randomized, double-blind, placebo-controlled trial investigating the effects of add-on levetiracetam in early treatment-resistant psychosis

1.1 Background

Pharmacologic treatment of schizophrenia has made little progress since clozapine was introduced 25 years ago. Antipsychotics are only partially effective for psychosis in many patients and are generally ineffective for negative symptoms and cognitive deficits. It is increasingly clear that dopamine D2 receptor blockade does not target core deficits in most individuals with schizophrenia. In addition, our recent work suggests that antipsychotics may cause additional injury by increasing hippocampal dopamine release, which results in neurotoxic metabolites. As will be outlined in this proposal, we are proposing to test a new approach based on converging animal and clinical evidence that targets a key dysregulation of hippocampal glutamate transmission in early psychosis. This approach is based on a specific mechanistic model for psychosis onset and progression of illness, involves a well-tolerated drug that targets a molecule that is genetically linked to schizophrenia, has highly specific and reliable imaging biomarkers for target engagement and clinical outcome and, if successful, could fundamentally alter the early course of illness.

A model for illness onset and progression: It is well-established that individuals with schizophrenia display hippocampal hyperactivity at rest and fail to recruit hippocampal networks during cognitive activation [1-3]. This increased hippocampal activity at rest has been associated with cognitive deficits, negative symptoms and psychosis [4, 5] and is believed to result from a deficit in GABAergic input from inhibitory interneurons [6, 7]. The hippocampus is particularly vulnerable to hypoxia, stress and inflammation due to the low ratio of inhibitory interneurons to neurons [8]; intrauterine exposure to inflammation, which is a risk factor for schizophrenia, has been demonstrated in mice to reduce hippocampal inhibitory interneuron density and disrupt CA1 oscillatory activity [9]. Furthermore, lesions of the ventral hippocampus in mice produce a neurodevelopmental model for schizophrenia that includes prefrontal cortical deficits and impairment of prepulse inhibition [10]. Hippocampal hyperactivity, demonstrated by magnetic resonance imaging (MRI) with gadolinium measurement of blood volume in the CA1 subfield [11], or by arterial spin labeling (ASL) [12], is an early biomarker that correlates with psychosis, predicts progression from “ultra-high risk” (UHR) status to schizophrenia, predicts hippocampal volume loss, and differentiates individuals with schizophrenia from healthy controls [11]. Spontaneous improvement of psychotic symptoms in unmedicated UHR subjects was associated with a decrease in hippocampal perfusion measured by ASL [12]. In addition, hippocampal glutamate concentrations measured by magnetic resonance spectroscopy (MRS) are elevated in EP and increased glutamate concentrations predict subsequent hippocampal volume loss [5] believed to result from excitotoxicity produced by excessive glutamatergic transmission. A decrease in hippocampal volume in schizophrenia subjects is a strong predictor of poor outcome over a 5-7 year follow-up [13, 14]. Excessive activity of the CA1 subfield also results in increased excitatory input to the ventral tegmental area (VTA) dopamine neurons which may drive psychosis via aberrant dopamine release in striatum and hippocampus [15].

While this model is now well-established by animal experiments and clinical imaging studies, no experimental therapeutic intervention has tested it. However, excessive glutamatergic transmission producing excitotoxic injury to the hippocampus is well established as a factor contributing to cognitive deficits and illness progression in mild cognitive impairment (MCI), Alzheimer’s disease (AD) and in temporal lobe epilepsy (TLE). In MCI, elevated hippocampal activity and glutamate transmission are associated with hippocampal volume loss and progression to Alzheimer’s disease [16, 17]. In healthy elderly subjects, age-related increased hippocampal activity predicts cognitive decline at 3-8 year follow-up [18].

In summary, hippocampal hyperactivity drives early psychosis and produces excitotoxic injury resulting in hippocampal volume loss which is associated with negative symptoms, cognitive deficits and poor outcome.

Antipsychotic effects on hippocampus: D2 receptors are found in only two locations in the hippocampus: post-synaptic D2 receptors are located on mossy cells in the hilum (efferents from dentate gyrus to CA3) and presynaptic D2 autoreceptors are located on dopamine fibers in the CA1 subfield [19]. Antipsychotics decrease hippocampal activity [20], most likely via blockade of D2 receptors on mossy cells. The reduction in hippocampal activity following a single dose of risperidone strongly predicted antipsychotic response at six weeks [21]. In subjects treated with either haloperidol or olanzapine, a reduction of hippocampal activation after one week predicted antipsychotic response at 6 weeks [22]. A failure of D2 blockade to reduce hippocampal activity is associated with poor antipsychotic response [22]. Activity of the CA2 and CA3 subfields is not elevated in medicated patients with early psychosis, whereas CA1 activity remains elevated, but not to the degree reported in unmedicated EP patients [23]; these findings are consistent with a primary antipsychotic effect "upstream" on mossy fibers. Blockade of D2 presynaptic autoreceptors in the CA1 subfield markedly increases the number of dopamine fibers and dopamine concentration in CA1 over a period of several weeks and is associated with memory impairment [19]. Excessive dopamine release increases production of free radical dopamine metabolites [24] and of homocysteine, a neurotoxic by-product of dopamine metabolism by COMT in the hippocampus [25, 26]. A proteomic study of hippocampus in mice found that 28 days of haloperidol administration increased proteins associated with mitochondrial injury, consistent with oxidative stress [27].

In summary, antipsychotics may improve psychotic symptoms by reducing hippocampal hyperactivity via blockade of D2 receptors on mossy cells, but also produce neurotoxic metabolites via blockade of D2 autoreceptors in CA1.

1.2 Investigational Agent

Levetiracetam is an atypical anticonvulsant that is frequently used in children and adults due to its superior tolerability, ease of use and excellent safety profile [28]. It is rapidly absorbed and rapidly crosses the blood-brain barrier. Maximal blood levels, brain concentrations and antiepileptic efficacy occur approximately 1 hour after oral administration in rodents and in humans [29, 30]. Levetiracetam exhibits linear pharmacokinetics, is not plasma bound, has approximately 100% absorption, and is not metabolized in the liver; it has no reported drug-drug interactions [29]. The half-life of levetiracetam is 6-8 hours; clearance may be slowed in individuals with severe renal impairment [29]. The mechanism of action of levetiracetam is unlike any other anticonvulsant; it binds to synaptic vesicle glycoprotein 2A (SVP2A) [31] which modulates release of neurotransmitter vesicles under conditions of sustained high activation [32]. SVP2A has been genetically linked to schizophrenia [33]. In the hippocampus, levetiracetam reduces neuronal glutamate and dopamine release and enhances GABA release from inhibitory interneurons [32, 34]. Levetiracetam normalized hippocampal hyperactivity and improved hippocampus-dependent memory in aged rats at doses of 5 mg/kg and 10 mg/kg given 40 minutes before testing [35]. In patients with mild cognitive impairment (MCI), levetiracetam 62.5 mg bid and 125 mg bid improved performance and normalized hippocampal BOLD hyperactivation during a pattern separation task [16]. At typical anticonvulsant doses, levetiracetam normalized left and right hippocampal activation patterns during verbal and visual memory tasks in patients with temporal lobe epilepsy (TLE) [36].

The most common side effects reported with levetiracetam are drowsiness, weakness, dizziness and infection (pharyngitis). Mood and behavioral problems have also been reported, including aggression, anxiety, anger, depression, apathy and hostility—these responses appear to be most

common in patients with epilepsy and pre-existing mood disorders. Rare cases of suicidality and of serious dermatologic reactions have also been reported. The median levetiracetam dose in registration trials was 3,000 mg/d administered as a split dose (twice daily) for epilepsy; oral loading doses of 3,000 mg are well-tolerated [29]. Treatment guidelines recommend testing for pregnancy and obtaining a serum creatinine level prior to initiating levetiracetam. Monitoring for behavioral effects (aggression, depression and suicidality) is also recommended—no other laboratory or medical monitoring are recommended.

In summary, levetiracetam is a well-tolerated agent that does not affect metabolism of antipsychotic drugs and normalizes hippocampal hyperactivity by decreasing excessive glutamatergic and dopaminergic transmission, thereby making it an ideal agent to enhance treatment of early psychosis and to prevent antipsychotic toxicity.

1.2.1 Innovative approaches for the measurement of brain atrophy, perfusion and temperature:

Hippocampal volumetric integrity measurement: Our collaborator, Dr. Babak Ardekani, has developed an automated measure of hippocampal volumetric integrity expressed as the fraction of the volume of a region that is expected to encompass the hippocampus in a normal brain that is occupied by tissue (rather than CSF) [37]. The fully automated, fast, reliable and robust process is based on 3D T1-weighted structural MRI and involves identification of the mid-sagittal plane [38] and the anterior and posterior commissures [39] on the MRI scan, from which a rigid-body transformation is performed to a standard orientation. Once in standard space, based on a priori training, 230 landmarks in the vicinity of the hippocampi are detected by template matching from which two (one for each hemisphere) 12-parameters affine transformations are computed. The composite (rigid-body + affine) transformations are applied to probabilistic left and right hippocampi labels determined based on manual tracings of hippocampi on scans from 65 normal subjects. Thus, a volume is determined (separately for each hemisphere) that is expected to encompass the hippocampus in a normal brain. Finally, an automated histogram analysis method using the expectation maximization (EM) algorithm is used to determine the partial fraction of this region that is occupied by brain tissue (rather than CSF). The ratio is termed the *hippocampal volumetric integrity* (HVI). This procedure has been well-validated and has demonstrated excellent test-retest reliability of ICC=0.998 using two independent structural MRI scans acquired on the same day on multiple subjects (figure 1) [40] and demonstrated superior discrimination of Alzheimer's disease subjects from healthy controls (figure 2) with significantly greater accuracy than achieved by using the FreeSurfer measure of hippocampal volume. This approach requires no pre-processing of the MRI scan, is very simple to apply, and volumetric analysis requires less than one minute per scan—making this a biomarker with wide potential clinical applicability. Due to the affine transformation step, the HVI is a scale-invariant measure which, unlike the absolute hippocampal volume, does not require correction for intra-cranial volume and can be used across 3T imaging platforms.

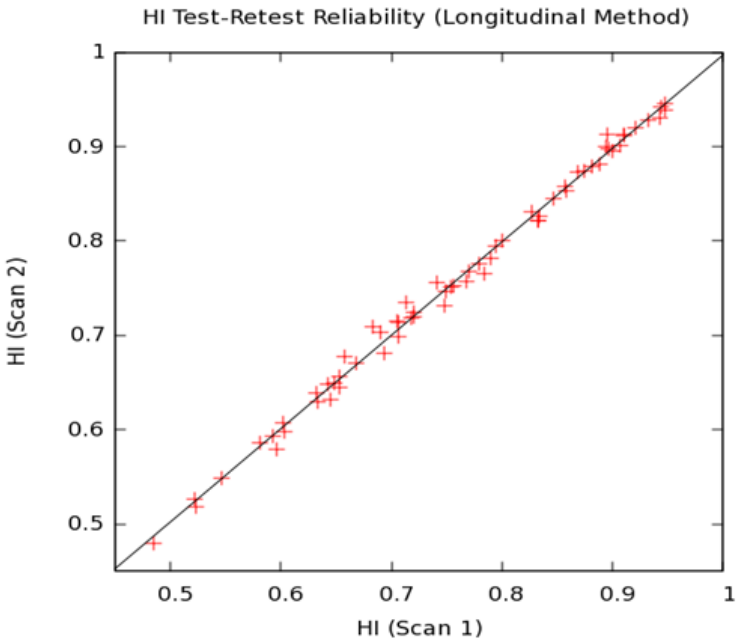

Figure 1. Hippocampal volumetric integrity measurement. ICC = 0.998

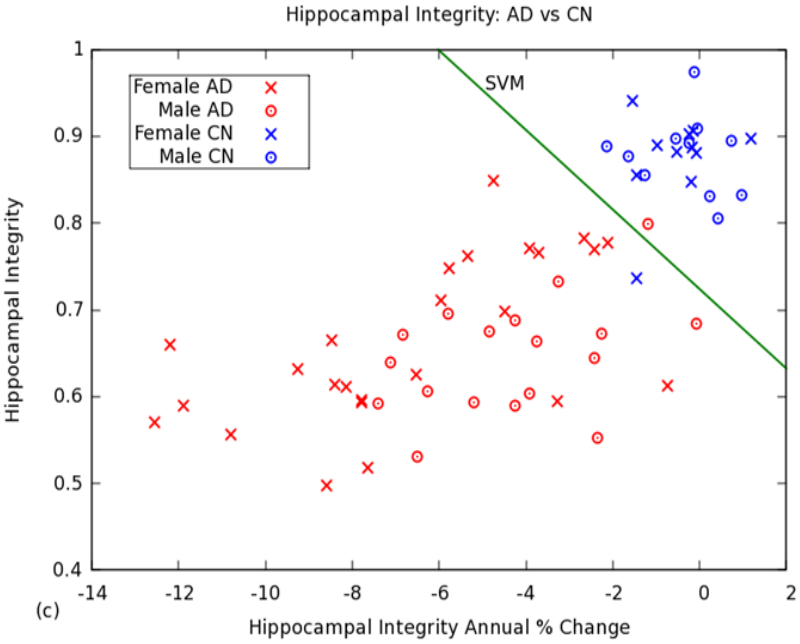

Figure 2. Hippocampal volumetric integrity, Alzheimers subjects and healthy controls.

Measurement of hippocampal perfusion using ASL: Our collaborator, Dr. Henry Rusinek, has developed an approach for measurement of hippocampal perfusion using a pulsed arterial spin labeling sequence with excellent spatial resolution, sensitivity and test-retest reliability (ICC = 0.90; figure 3) [41]. This approach is based on multi-shot true fast imaging in steady precession and is calibrated by subtraction of cerebral blood flow (CBF) in cortical white matter, which is approximately

3 times lower than CBF in gray matter. A co-registered 3D MPRAGE is used to eliminate all voxels with less than 75% gray matter and all large blood vessels. This method will allow us to measure a change in hippocampal blood flow with sufficient sensitivity and reliability to detect changes with levetiracetam. A similar approach has been used successfully to measure region-specific changes in CBF after single-dose antipsychotic administration [42].

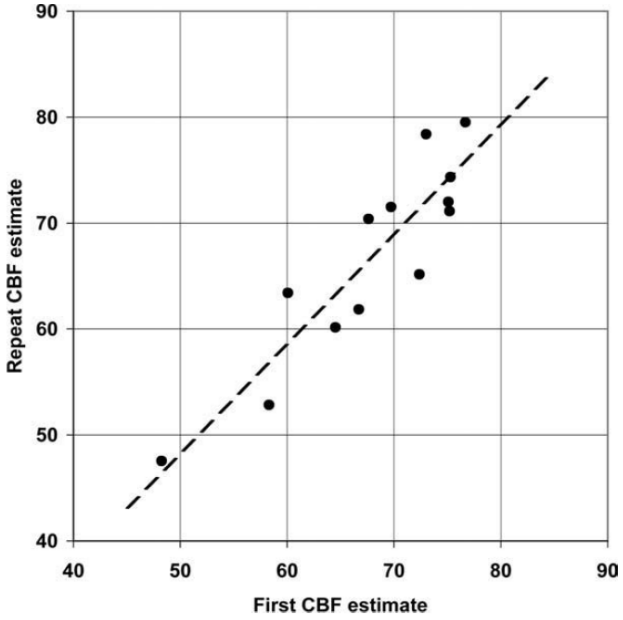

Figure 3. Measurement of hippocampal perfusion. ICC = 0.90

This is a 3T ASL method with balanced steady-state free precession (bSSFP) readout. bSSFP is chosen instead of the more conventional echo planar sequence to reduce susceptibility artifacts and to allow for higher spatial resolution without image distortion. The 64 channel Siemens Prisma head coil that is used at NYU Langone Medical Center and SMHC yields excellent S/N and tagging efficiency. The slice-selective FAIR inversion pulse is applied in a slab encompassing the imaging slice, but 2.5 times thicker. The 1.2 s inversion time allows for blood outside the slab to flow into the imaging slice and to estimate tissue perfusion. Data are acquired in a single shot using parallel imaging, with an acceleration factor of 2 to reduce the echo train duration. Other parameters are: TE=1.4 ms, flip angle = 360^{O}, receiver bandwidth = 977 Hz/pixel, slice thickness = 6 mm, 320 x 210 matrix, voxel size 0.9 x 0.9 mm (fine enough to resolve small blood vessels). 48 repetitions are performed, alternating between nonselective and slice-selective inversions. The repetition time (TR) between successive inversion pulses is 3 s. Since this is not long enough to ensure complete recovery of magnetization, the first 4 repetitions are excluded.

We will use the signal difference in healthy white matter (WM) as reference. This approach, justified by animal evidence, exploits the fact that cerebral blood flow (CBF) is ~3x lower in WM compared to gray matter (GM). Deviations from this assumption introduce a relatively minor bias on cerebral GM flow [41]. Our measurements of the resting cortical CBF agree with CBF measured using O^{15} PET. However, the precision of our technique is double that of competing methods [41], likely due to the use of WM as reference. The tissue perfusion computation uses a general kinetic model [43]. WM and GM segmentation is done directly from bSSFP images. To avoid blood vessel contamination, we use only cortical voxels with CBF values < 150 mL/(100 g min). Although this will exclude only the largest blood vessels, smaller vessels likely do not to contribute to the “through flow” artifact [41].

1.3 Clinical Data to Date

There are compelling reasons to study levetiracetam in early schizophrenia, since it is expected to decrease the neurotoxic excessive release of glutamate associated with psychosis and the neurotoxic excessive dopamine release associated with early antipsychotic treatment and, unlike most other anticonvulsants, does not have pharmacokinetic interactions with antipsychotic medication. However, the only studies of levetiracetam in schizophrenia were in later-stage patients for the treatment of tardive dyskinesia-- levetiracetam significantly reduced tardive dyskinesia compared to placebo, producing response rates of 44% vs 19%. A total of 58 patients with psychotic disorders received levetiracetam in placebo-controlled [44] and open-label trials [45] in subjects with tardive dyskinesia and no adverse effects were observed. One reason for the relative lack of experience with levetiracetam in schizophrenia is the warning against using it in patients with psychiatric illness due to reports of aggression and hostility. However, adverse behavioral effects have been largely limited to patients with epilepsy [46] and affective disorders [47] but have not been observed in patients with cognitive or anxiety disorders [46].

Hippocampal volume loss in early psychosis:
With our collaborators in Shanghai (Dr. Jijun Wang, M.D.), we recently completed a biomarker study of 64 medication-naïve EP patients and 58 healthy matched controls; 24 patients were subsequently treated with second generation antipsychotics and both the treated patients and 32 matched controls were re-examined after 8 weeks by MRI measurement of hippocampal volumetric integrity (defined below). At baseline there was a significant decrease in hippocampal volumetric integrity bilaterally (Right: Cohen's d= 0.57, p=.001; Left: Cohen's d= 0.91, p=.0001) in medication-naïve patients compared to age and gender-matched controls. From baseline to week 8, hippocampal volumetric integrity was significantly reduced in patients bilaterally compared to controls (Right: Cohen's d=1.3, p=.05; Left: Cohen's d= 1.1, p <.01); left hippocampal volume loss occurred at a mean annualized rate of 6.0% and significantly correlated with duration of untreated psychosis (DUP) (r= -.61,p=.002), with baseline concentration of S100B (a marker of glial injury) (r= -.50, p=.01), and with a treatment-related increase in thioredoxin (a marker of oxidative stress) (r=-.54, p=.01). Right hippocampal volume decreased at a rate of 4.8% per year. Left hippocampal volume at baseline correlated with symptom severity at baseline (BPRS total, r=-.34, p=.01) and the change in left hippocampal volume correlated inversely with response of negative symptoms at week 8 (r=.-.41, p=.05). In addition, concentrations of homocysteine increased with treatment (Cohen's d=0.52, p=.01). The increase in homocysteine concentration was predicted by COMT genotype (p<.05) and correlated with an increase in S100B (r= .54, p=.01), consistent with the hypothesis that COMT metabolism of dopamine produces homocysteine, which is toxic to glia. Overall, these results are consistent with a model of glutamatergic excitotoxicity associated with early psychosis, early hippocampal injury and with an interaction between DUP, illness-related glial injury, and antipsychotic-related oxidative injury producing hippocampal volume loss during the early phase of treatment. The treatment-related oxidative injury may result from dopamine metabolism which produces free radical metabolites and homocysteine. This process appears to be clinically significant since hippocampal volume correlated with psychotic symptoms at baseline and hippocampal volume loss during the first 8 weeks of treatment was associated with negative symptom severity at week 8, consistent with previous reports that hippocampal volume loss was associated with severity of psychosis and cognitive impairment across psychotic diagnostic groups [48]. The rapid rate of volume loss that we observed could not be sustained long-term, given the absence of evidence for volume loss greater than 10% in post-mortem studies. The rapid volume loss resulting from excessive dopamine release may be time-limited, since antipsychotics produce "depolarization blockade" of VTA dopamine neurons after 2-3 months [49], and so hippocampal exposure to high levels of treatment-related oxidative stress may be time-limited, potentially making it critically important to treat prophylactically with levetiracetam early in the course

of antipsychotic treatment. We have recently found an absence of hippocampal volume loss during 12 months after initial stabilization (mean 10.3 weeks) on antipsychotics in 65 early psychosis patients (manuscript in preparation).

Results of the preliminary (R61) dose-finding study:

We recently completed a placebo-controlled, randomized, single-dose trial comparing levetiracetam 185 mg and 500 mg administered to 20 medication-free early psychosis patients studied at NYU Langone Medical Center. Hippocampal cerebral blood flow (CBF) was measured by arterial spin labelling (ASL) performed prior to study drug administration and two hours after study drug administration. Side effects were recorded in all 20 participants, whereas hippocampal CBF measured by ASL before and after study drug administration was analyzed in 17 participants; two participants were excluded from analysis due to poor quality scans and one participant was found to not meet entry criteria based on additional diagnostic information. Compared to placebo, levetiracetam 500 mg significantly reduced hippocampal perfusion (-6.8% $\pm$ 2.6 vs -1.9% $\pm$ 2.4, p= 0.02, effect size = 2.0); levetiracetam 185 mg did not significantly reduce hippocampal perfusion compared to placebo (-3.3% $\pm$ 4.9 vs -1.9% $\pm$ 2.4, effect size = 0.35). Neither levetiracetam 185 mg nor 500 mg significantly reduced prefrontal cortical perfusion (selected as a test of hippocampal selectivity) compared to placebo (placebo = 1.1% $\pm$ 2.6, levetiracetam 185 mg = 0.6% $\pm$ 4.4, levetiracetam 500 mg= -1.3% $\pm$ 4.4; p = 0.80 and p = 0.32, respectively). The change in hippocampal perfusion significantly correlated with blood concentrations of levetiracetam (r= -0.51, p= 0.04). There were no serious adverse events. Side effects included mildly decreased appetite in one participant (16%) and increased sedation / drowsiness in one participant in the levetiracetam 500 mg group, and increased sedation / drowsiness in one participant (14%) in the levetiracetam 185 mg group; side effects were mild and the incidence of side effects did not differ between levetiracetam and placebo (p=0.64 Fisher's exact test). Based on these results, we have received approval from the NIMH to proceed to the R33 study using a dose of levetiracetam 500 mg bid.

1.4 Study Rationale

This 3-year R33 project will examine the effects of a placebo-controlled administration of levetiracetam 500 mg bid added to clinician-determined antipsychotic treatment on clinical symptoms and hippocampal volumetric integrity (HVI) and cerebral blood flow (CBF) in 84 medication-free EP participants. NIMH funding (R33) for this clinical trial follows from our successful demonstration of target engagement (reduction in hippocampal CBF) and good tolerability with levetiracetam 500 mg in our pilot trial (R61). This protocol is to approve the R33 phase of the study, the R61 phase of the study has previously been approved by the NYU Human Research Committee (i17-00266).

The evidence for hippocampal dysfunction in schizophrenia is quite strong and the model of CA1 hyperactivity in early psychosis is supported by imaging studies using multiple modalities (PET, fMRI, MRI with gadolinium contrast, ASL). Evidence for early hippocampal volume loss is also consistent across studies; our finding of hippocampal volume loss during the first 8 weeks of antipsychotic treatment was a large effect size and was highly statistically significant. Levetiracetam is clearly the best agent to test this model since it is well-established that levetiracetam targets SVP2A, reduces excessive glutamatergic and dopaminergic neurotransmission, and is neuroprotective. Furthermore, studies similar to our proposed approach have been successful in MCI and in temporal lobe epilepsy.

This proposed study is highly innovative in several ways. It is the first intervention study to directly test the model of hippocampal hyperactivity and neurodegeneration in early psychosis. It also is the first to study levetiracetam and the SVP2A target in early psychosis. This study is also the first to employ ASL and an MRI measure of hippocampal volumetric integrity as biomarkers for target engagement and clinical outcome. Our collaborators developed and validated new methods for both

of these imaging biomarkers that are far more sensitive and reliable than prior approaches. The automated measurement of hippocampal volumetric integrity is user-friendly, fast and potentially could become widely employed for monitoring of illness progression. Furthermore, the method of ASL that we will use to measure hippocampal CBF has very high reliability (ICC=0.90) [41].

The selection of a levetiracetam dose of 500 mg is based on the results of our dose finding trial (i17-00266), in which levetiracetam 500 mg significantly reduced hippocampal CBF and was well-tolerated, whereas levetiracetam 185 mg did not significantly reduce hippocampal CBF. The 500 mg levetiracetam dose is a standard starting antiepileptic dose for partial (temporal lobe) epilepsy; administration of levetiracetam twice-daily will produce mean blood levels similar to those produced two hours after a single dose of levetiracetam 500 mg in our pilot study which were well-tolerated and associated with a reduction in hippocampal CBF. Levetiracetam doses up to 3 g/day are routinely administered in individuals with epilepsy.

1.5 Research Risks & Benefits

1.5.1 Risk of Study Drug

In a randomized, placebo-controlled cross-over trial in 20 healthy subjects (mean age 29 years, range 20-49 years), levetiracetam 500 mg administered twice at an interval of 12 hours produced side effects in 50% of subjects compared to 44% with placebo and 83% with lorazepam 2 mg. Unlike lorazepam, levetiracetam 500 mg did not adversely affect cognition but, compared to placebo, was associated with somnolence (40%), balance disorder (20%), dizziness (15%) but no psychiatric adverse effects. Side effects with levetiracetam are usually mild and include: somnolence, fatigue, mood swings, headache, agitation, irritability, aggression, depression, memory loss, confusion, vomiting, abdominal pain, nausea, anorexia, pharyngitis and paresthesia. Uncommon but potentially serious side effects that occur in less than 1% of patients include: psychosis, suicidal thoughts, hypersensitivity reactions and leukopenia. In our dose-finding trial we observed mild decreased appetite in 1 of 6 participants and drowsiness in 1 of 6 participants randomized to levetiracetam 500 mg.

There is increased risk of seizures with rapid withdrawal of levetiracetam. All participants will be made aware of this risk. After the 12-week study, participants will be tapered off of the medication for 9 additional days. Participants will return within 3 days of finishing the tapering for a final visit. During the first week, participants in the levetiracetam arm will have their dose lowered to 250 mg levetiracetam AM and 500 mg levetiracetam PM for 3 days, then 250 mg twice daily for 3 days, and then 250 mgs once daily for three days. The tapering regimen will be provided in a blister pack to the research participants. Participants in the placebo arm will also receive a blister pack with placebo pills. Participants who choose to withdraw from the study early (after more than 7 days of medication administration) will be reminded of this risk and will be asked to return for two visits. The first will consist of a clinical assessment and dispensation of the tapering regimen. The second visit (within 3 days of completing the tapering regimen) will consist of an abbreviated clinical assessment and study termination form.

There are no known interactions between tetrahydrocannabinol (THC), cannabidiol (CBD) or other phytocannabinoids and levetiracetam. Levetiracetam is not metabolized by the hepatic cytochrome P450 system, so pharmacokinetic interactions are unlikely. THC may transiently worsen psychosis in some patients and CBD may improve psychosis; whether THC-associated worsening of psychosis responds to antipsychotics is unclear—the data are inconsistent. Similarly, it is not known whether THC-associated worsening of psychosis will improve with levetiracetam. Participants using THC will be notified of this risk.

1.5.2 Risks of MRI:

There are no known radiation risks associated with MRI. However, individuals with metal implants, such as surgical clips or pacemakers should not have an MRI. Additionally, given that the MRI takes places in a confined space, and there are loud banging noises associated with the procedure, individuals may feel anxious during the procedures. Earplugs will be offered to subjects in an effort to help reduce the MRI related noise and subjects will be told that the MRI can be stopped at any time at his/her request. Some subjects may experience muscle twitches or tingling sensations and/or a slight increase in body temperature during some types of scan activity. These are very unlikely under current MR guidelines. The FDA has determined that the most common injury associated with MRIs were burns to the skin, most commonly caused by devices that conduct electrical energy, such as metallic objects, pulse oximeters, or EKG leads. While skin tattoos may, in theory, be conductive, the first systematic study of risks of tattoos in individuals undergoing MRI scans was recently published in the New England Journal of Medicine and found minimal risk [50]. The investigators studied a sample of 330 patients who had a total of 933 unique tattoos, including both professional and self-applied tattoos, and were imaged using a 3T MRI for a total of 585 imaging sessions. They excluded individuals with greater than 5% of their body surface covered by tattoos, with tattoos larger than 20 cm, or with tattoos on face, neck or genitals. One participant reported a “tingling” sensation and one reported a sensation of warmth—no persistent adverse effects were observed. On the basis of this evidence, we will allow individuals to participate in the imaging portion of the study if they have less than 5% of their body covered with tattoos, no individual tattoo larger than 20 cm, and no tattoos located on the face, neck or genitals. Participants with tattoos will be instructed to notify the technician if they experience warmth in the location of a tattoo and the imaging session will be immediately terminated. All participants will be screened for metal objects and tattoos by both the research staff and the technicians at the imaging center to ensure that no unsafe conductive materials are present in or on the patient’s body.

In extremely rare cases, a magnet can lose its magnetism, in which case cooling fluids may be released noisily through escape valves and may collect in gas form in the scan room. The gas is not harmful in itself as long as fresh air is available. In this very remote event, participants will immediately be brought out of the magnet room.

Contrast will not be used during the MRI scans for this study.

1.5.3 Other Risks of Study Participation

Phlebotomy may cause soreness, bruising, bleeding and rarely, infection.

Loss of confidentiality regarding psychiatric or medical information is a possible risk for which precautions will be taken. Participants will be assigned a study identification code that will be used for all study documents. All identifiers will be redacted from records from this study. Study documents collected in this study will be kept in a locked cabinet. Only research staff who are directly involved in this study will have access to that file.

Several measures have been taken to protect subjects against risks incurred by participation in this protocol. We will screen out potential subjects with medical vulnerabilities, including epilepsy or unstable medical illness and will exclude individuals with a history of suicidality or violence. Participants will be closely observed for 3 hours after their first dose of study drug and will be assessed daily for the first 5 days after initiating study drug and then once weekly for the first 4 weeks.

1.5.4 Potential benefits

There are potential direct benefits from participating in this study. All subjects will receive a comprehensive psychiatric and medical evaluation and optimal clinical treatment as part of participation. Additionally, it is possible that participants randomized to levetiracetam may experience improvements in their psychosis while taking the medication, although this potential benefit has not been established by prior research.

Incidental Findings:
Study participants will be informed at the time of screening if urine tests are positive for pregnancy or drugs of abuse (excluding tricyclics and benzodiazepines (if prescribed). No other laboratory tests will be performed. MRI scans will be reviewed by a neuroradiologist at the Center for Brain Imaging (CBI) and at SMHC the results reviewed by Dr. Goff and Dr. Wang. If clinical readings of MRI scans show unanticipated abnormalities that require medical follow-up Dr. Goff or Dr. Wang will contact participants and their clinicians if participants are outpatients, study staff will telephone participants and send a follow up letter signed by the study PI via mail to advise participants that scans findings require medical follow up. The MRI and/or laboratory reports and a copy of the letter, if applicable, will be maintained with source documents. Otherwise, no research information will be shared with participants.

2 Study Objectives

The objectives of this study are to evaluate the efficacy of levetiracetam (500 mg) on clinical symptoms, hippocampal volume and perfusion and cognition and tolerability over 12 weeks when added to antipsychotic treatment in treatment-resistant EP patients and to assess the association between hippocampal CBF and markers of oxidative stress and inflammation with outcomes. The primary outcome is the change in BPRS total at week 12.

Study Hypotheses:

Primary:
1. Compared to placebo, levetiracetam will improve symptoms measured by the BPRS total score.

Secondary:
1. Compared to placebo, levetiracetam will improve psychotic symptoms measured by the BPRS psychosis subscale.
2. Compared to placebo, levetiracetam will be associated with less hippocampal volume loss and reduced hippocampal CBF over 12 weeks.
3. Compared to placebo, levetiracetam will improve negative symptoms measured by the modified SANS total score.
4. Compared to placebo, levetiracetam will improve cognitive functioning measured by the MATRICS composite score.

Tertiary:
5. Levetiracetam's effects on cognition and symptoms will be associated with its effects on hippocampal volume.
6. Levetiracetam's effects on cognition and symptoms will be associated with baseline hippocampal CBF and change from baseline in hippocampal CBF
7. Duration of untreated psychosis and serum biomarkers for oxidative stress (thioredoxin) and astroglial injury (S100B) will predict hippocampal volume loss.

8. Change from baseline to week 12 in hippocampal CBF will be associated with week 6 levetiracetam blood level and change in BPRS total score.

3 Study Design

3.1 General Design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study. The study consists of an up to 4-week Screening period, one Baseline visit, weekly visits on Weeks 2-4, and then bi-weekly visits (weeks 6,8) and a week 12 visit. Additionally, there will be 1 additional follow up visit after Week 12 after the participants complete the tapering regimen. The Screening visit and Baseline visit may occur on the same day.

Screening, Visit 1	Baseline	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	Follow-Up
Days -28 to 0	Day 1	Day 6 - 10	Day 13 - 17	Day 20 - 24	Day 34-38	Day 48-52	Day 76 – 80	Day 85 - 93

3.2 Primary Study Endpoints

The primary efficacy outcome is the change from baseline to week 12 in BPRS total score. Change in hippocampal volumetric integrity and change in hippocampal perfusion (CBF) are the secondary outcomes. Additional secondary outcomes are change in the BPRS psychosis subscale, SANS total score and MATRICS composite score.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Males and females 16 to 40 years of age, inclusive, at time of informed consent
2. Must have experienced a first episode of nonaffective psychosis within 5 years and exhibit current psychosis, as defined by a score of $\geq$ 4 on one of the following psychosis items on the BPRS: conceptual disorganization, suspiciousness, hallucinations, unusual thought content, or grandiosity, for at least 4 days per week for at least 4 weeks.
3. Must have a diagnosis of either schizophrenia, schizoaffective disorder or schizophreniform disorder as established by a Structured Clinical Interview for DSM-V (SCID)
4. Must have taken antipsychotic medication for a minimum of 8 weeks and at a stable dose for at least 4 weeks prior to randomization.
5. If assigned female at birth and of childbearing potential, patients must
    a. have a negative urine pregnancy test (all participants assigned female at birth regardless of childbearing potential will be required to submit a pregnancy test), and
    b. not be nursing or planning a pregnancy for the duration of the study through 30 days after the last dosing visit, and
    c. be abstinent or willing to use a reliable method of birth control from the Screening Visit and continue with the same method until termination from the study.

4.2 Exclusion Criteria

1. Current substance abuse / dependence for substances other than nicotine and THC, (i.e. alcohol, amphetamines, barbiturates, etc.)
   a. A positive urine toxic screen (excluding THC, tricyclic antidepressants, or benzodiazepines (if prescribed)).
   b. Moderate or severe cannabis use disorder.
2. Diagnosis of major mood disorder or other Axis I disorder other than schizophrenia, schizoaffective disorder or schizophreniform disorder.
3. Current or recent suicidal ideation-- suicidal ideation with intent or plan (indicated by affirmative answers to items 4 or 5 of the Suicidal Ideation section of the baseline C-SSRS) in the 6 months prior to screening or subjects who represent a significant risk of suicide in the opinion of the investigator.
4. Pregnant or nursing or positive urine pregnancy test.
5. Significant medical or neurological illness by history or physical exam, including seizure disorder, history of loss of consciousness related to head trauma or developmental disorder including mental retardation.
6. Renal insufficiency (if serum creatinine greater than laboratory limits for normal, estimated creatinine clearance must be greater than 80).
7. Contraindication to MRI: Metal implants, pacemaker, or other metal in the body or claustrophobia. Individuals with tattoos will be excluded from imaging if tattoos cover more than 5% of the body surface, if a tattoo is greater than 20 cm, or if a tattoo is located on the face, neck or genitals. Individuals with a contraindication to MRI may participate in the trial but will be excluded from the elective MRI component.
8. Significant history of serious violence
   a. For both inpatient and outpatient subjects, a history of serious violence as assessed by the Buss-Perry Aggression Questionnaire
   b. For outpatient subjects only, a score of 5 (moderately severe) or higher on the BPRS hostility item at screening or baseline

4.3 Inclusion of Subjects using Marijuana

The incidence of cannabis use in early psychosis patients in the US is estimated at 40% to 60% and a serious concern has been raised that excluding individuals who use cannabis may bias samples and make results less generalizable to clinical populations [51]. There is no reason to expect a negative interaction between cannabis and levetiracetam (no pharmacokinetic or pharmacodynamic interaction). Because treatment is randomized, the two treatment groups should be balanced in terms of cannabis use. We will record past use of cannabis and urine toxic screen results for cannabis at screening in addition to self-report of cannabis during the trial and will include this as a factor in our analysis to assess whether cannabis use influences response to levetiracetam.

We sought consultation from other investigators working in the area of early psychosis and from our DSMB and have adopted exclusionary criteria for cannabis use consistent with their recommendations. These new criteria are based on the Diagnostic and Statistical Manual (DSM) 5 which revised the classification for cannabis use from abuse & dependence to cannabis use disorder, mild, moderate or severe. Criteria are provided for each category. We would like to adopt these criteria for the current study and future studies:

1. Exclude individuals with moderate or severe cannabis use disorder.

2. Exclude individuals who report having used cannabis within 72 hours of the MRI scan.
3. Include individuals with mild cannabis use disorder

4.4 Vulnerable Populations

The inclusion of children for this research is necessary as early psychosis often affects individuals under the age of 18. For underage individuals, the treating clinicians will ask the potential subjects and their guardians if they would like to speak to a researcher and both will be required to complete the consenting process. Patients and/or their guardians will have an opportunity to discuss involvement in the study with their treating clinician prior to enrollment. The clinician obtaining the informed consent will take steps to ensure that the participant and his/her guardian are capable of consenting and participating in the study. The clinician will ensure that the individual understands the content and procedures of the study, their rights as a participant, and their right to discontinue participation at any time. Individuals who are not able to demonstrate this level of comprehension will be excluded from participation. As described previously, the potential subject must also achieve a perfect score on a ten-item true/false quiz that asks questions about the study procedure and potential risks. Those who are deemed to lack the capacity to consent will not be enrolled in the study. Minors who turn 18 while in the study will be re-consented as adults.

Students will be informed that if they elect to participate in this study, they can choose to/not to participate or withdraw at any time without any impact on their grades or academic standing.

4.5 Subject Recruitment and Screening

Participants will be help-seeking males or females, ages 16-40, with early psychosis within 5 years of onset, meeting diagnostic criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder and currently exhibiting at least moderate psychotic symptoms defined by a score of 4 or greater on at least one psychosis item of the BPRS (conceptual disorganization, suspiciousness, hallucinations, unusual thought content, grandiosity) with persistence of at least 4 days per week for at least 4 weeks despite antipsychotic treatment for at least 8 weeks and in the absence of psychotomimetic substance use or other potential organic etiologies, or major mood disorder, and in the absence of suicidal ideation, pregnancy, or significant medical illness (including epilepsy).

Referring clinicians will receive the “Information for Clinicians” document, which contains information about the study as well as contact information for the study team.

At the Bellevue Comprehensive Psychiatry Emergency Program (CPEP) or Inpatient Psychiatry Units or Adult Outpatient Psychiatry Clinic as well as the Children’s Comprehensive Psychiatric Emergency Program (CCPEP) and Child and Adolescent Psychiatry Inpatient Unit, the staff will identify patients with early psychosis who are appropriate for study participation and willing to speak to an investigator. The study team will access EPIC to determine the participant’s initial eligibility. A psychiatrist, psychologist or nurse practitioner on the clinical team will assess the clinical appropriateness of the individual to participate in research and will assess the individual’s capacity to consent. A study MD or NP will also perform an assessment of clinical appropriateness and capacity to consent for any individuals interested in participating and will document this assessment. After a potential study participant agrees to sign consent, the remaining screening procedures will take place in the Bellevue CPEP, CCPEP, or on the Bellevue adult or child psychiatry inpatient unit or outpatient clinics. Following the screening procedures, individuals who qualify to participate and who are judged by their clinicians to be safe and appropriate for

transportation and imaging, will be transported to the NYU Center for Biomedical Imaging (at 660 1st Avenue) or the NYU CBI (at Washington Square) for the imaging procedures via ambulance or ambulet as per the existing protocol to transport patients within Bellevue for clinical procedures if the patient is inpatient; if the patient is an outpatient a car service will be provided to them at no cost.

Additionally, patients will also be recruited at NYU Langone Health medical centers in Manhattan and Brooklyn, and NYU student health. For participants referred from the Tisch emergency room and the Tisch inpatient psychiatry unit (HCC-10), study staff will follow the same protocols outlined above for Bellevue. Clinicians will be asked to only refer individuals who they believe are appropriate for the study and who are capable of deciding to participate. Once referrals are given, the study team will access EPIC to determine the participant's initial eligibility. Additionally, the study team will use NYU's DataCore service to gather information from EPIC for current NYU patients who may be eligible. Dr. Goff and the study coordinator will maintain relationships with clinicians at these institutions in order to generate referrals.

We will include individuals who speak Spanish as potential participants. In order to recruit Spanish speaking patients, our team will receive referrals from clinicians from our network of NYU-affiliated institutions. Clinicians who refer Spanish speaking patients will initially determine if the subject will be eligible to participate our study. If the patient qualifies and agrees to participate in our study, our team will provide a native Spanish speaking interpreter with training and understanding in medical terminology during the study visits.

In China, First Episode Psychosis participants will be recruited from the First Episode Psychosis Program of Shanghai Mental Health Center under the direction of Dr. Dengtang Liu. Clinicians will be asked to only refer individuals who they believe are appropriate for the study and who are capable of deciding to participate. Potential subjects identified by the initial treating clinicians will be asked whether they would like to speak to a researcher. If the patient agrees, the initial treating clinician will then contact the study psychologist or trained study team member and they will determine whether the study clinician (psychologist or psychiatrist) will go and meet with the patient at that time or whether the patient will be scheduled to return for a screening visit with the research team.

Shanghai Mental Health Center was established in 1935 and has 1875 psychiatric inpatient beds of which 80 are dedicated to medication naïve first episode schizophrenia and is staffed by 258 psychiatrists and 581 psychiatric nurses. More than 200,000 psychiatric outpatient visits are recorded each year.

4.6 Subject Consent and Assent

All subjects will be evaluated by a NP or MD for capacity to consent and safety / appropriateness to participate. In order to further ensure protection of privacy for this patient population, patients will not be contacted by any member of the research team unless they have agreed to hear about the research process beforehand from the initial treating clinician. Clinicians in the NYU Medical Center Emergency Psychiatric Service and Adult Inpatient Psychiatry Unit, Bellevue Hospital CPEP and CCPEP, Bellevue Hospital Child and Adolescent Psychiatry Inpatient Unit Walk-in Clinic and Inpatient Units, NYU Student Health Clinic, NYU-Brooklyn (Lutheran) Hospital Emergency Service and Outpatient Psychiatry Clinics (Sunset Terrace), Inpatient Psychiatry Units and the Comprehensive Psychiatry Emergency Program at Bellevue Hospital will be provided with study information as well as a document listing the inclusion/exclusion criteria in order to facilitate recruitment. This will allow the treating clinicians to help identify potential subjects as well as provide interested individuals with basic study-related information. Potential subjects identified by

the treating clinicians will be asked whether they would like to speak to a researcher. If the patient agrees, the treating clinician will then contact the study psychologist or trained study team member and they will determine whether the study clinician (psychologist or psychiatrist) or research data associate will go and meet with the patient at that time or whether the patient will be scheduled for a screening. During this meeting, the study will be explained to the potential participant and in the event that the individual is interested in participating, s/he will then be given the consent form to read and review.

Bellevue Psychiatry Adult and Child Inpatient Units and CPEP and CCPEP only: A Bellevue Hospital psychiatrist, psychologist or nurse practitioner will assess the clinical appropriateness of the individual to participate in research and will assess the individual's capacity to consent. A study MD or NP will also perform an assessment of clinical appropriateness and capacity to consent for any individuals interested in participating. After a potential study participant agrees to sign consent, the remaining screening procedures, including the informed consent process (as outlined below), as well as any subsequent study visits will take place on the inpatient unit at Bellevue.

Tisch emergency room / inpatient psychiatry unit (HCC-10): Study staff will receive referrals from NYU clinicians in the emergency room and inpatient psychiatry unit. Study staff will be responsible for assessing the clinical appropriateness of these individuals. After a potential study participant agrees to sign consent, the remaining screening procedures, including the informed consent process (as outlined below), will take place in the emergency room or on the unit. Some outpatients may choose to be electively admitted to HCC-10 at the beginning of the study. Participants choosing to be electively admitted will be allowed to continue participating in the study, and all visits and assessments will take place on the unit.

Process of Consent: Patients who are interested in participating in the study will meet with one of the study MDs or NPs, who will review the consent form and assess the patient's capacity for participation in research in accordance with our standardized research procedures (See CRF for "Assessment of Capacity"). After signing consent, participants will be assessed for eligibility. The study team member will ensure that the individual understands the content and procedures of the study, their rights as a participant, and their right to discontinue participation at any time. Individuals who are not able to demonstrate this level of comprehension will be excluded from participation. In addition, the potential subject must also achieve a perfect score on a ten-item true/false quiz that asks questions about the study procedures and potential risks. After the consent form has been signed, the subject will be provided with a letter detailing study-related information and contact information for key study staff.

Participants who lose capacity during the study will be assessed by the site PI (Dr. Goff and Dr. Wang) to determine if they should be excluded from the study or if they can safely continue in the study. The PIs will consult with their respective IRBs when making this decision. These decisions will also be reported to the Chair of the DSMB (Dr. Buchanan).

For Spanish Speaking Subjects: Spanish speaking subjects will be provided with certified translated consent forms and assent forms accompanied by a native Spanish speaking interpreter with training and understanding in medical terminology during study visits. The Spanish consent form will be translated and submitted after IRB approval of the study and the English consent form.

Consent Forms: Consent forms will be stored in a locked file cabinet in folders labeled with the patient's study identification number. This file will be separate from any of the subject's study data in order to separate their data from any identifying information.

4.7 Early Withdrawal of Subjects

Participants will be advised verbally and in the ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. Participants may withdraw from the study at any time and for any reason and are not obligated to provide the reason.

The Investigator may discontinue a patient from the study in the event of an inter-current illness, AE, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

Participants choosing to withdraw from the study early will be asked to return for 2 additional study visits as outlined above and will be provided the 9-day study drug tapering blister-pack and warned of the risk of seizures with abrupt discontinuation. The first visit will consist of a clinical assessment (consisting of Assessments in the Week 12 visit) and dispensation of the tapering regimen. The second visit (completed within 3 days of completing the tapering regimen) will consist of an abbreviated clinical assessment and study termination form (see Appendix: Follow up visit).

Any reason for withdrawal given (or the failure to provide a reason) must be recorded in the source documentation and on the patient's electronic case report form (eCRF).

4.8 Virtual Study Visits

4.8.1 Screening and Baseline Procedures

In light of the coronavirus pandemic, each study site (NYU and SMHC) will outline a participant protection plan in accordance with their local hospital's guidelines. The NYU plan is outlined below.

The NYU Langone study team will minimize in-person contact with study participants. All assessments that can be completed remotely can, optionally, take place via WebEx, a secure video conferencing platform. For participants in the inpatient units and emergency departments at Bellevue and Tisch, study staff will follow the social distancing guidelines and personal protective equipment requirements outlined by the unit. This may include using remote Webex based assessments.

For inpatients and outpatients, consent can take place remotely, in which a MD or NP will review the electronic consent form and consent quiz with the participant over WebEx. Participants will be provided an electronic consent form to sign (in REDCap), and a copy will be sent to their email.

For outpatients, all screening assessments that can be conducted remotely will be completed via WebEx. If participants meet eligibility criteria according to those assessments, participants will be scheduled for an in-person visit at One Park Avenue with careful adherence to all institutional safety precautions and social distancing. The assessments that must be completed in-person include the following: vital signs, anthropometrics, physical exam, phlebotomy, collection of a urine specimen, and study drug dispensation.

If the participant appears to be eligible for the study during the remote screening visit, study staff will also complete the baseline assessments that can be completed virtually (the SANS, CDSS and CGI) during the virtual screening visit. This will allow us to streamline the screening and baseline visits, minimizing the time that participants need to be at One Park during the baseline visit. Conducting these assessments alongside the screening visit does not increase the risk to the participant.

We will allow a window of 48 hours between the time of virtual assessments and in-person study visits. If more than 48 hours passes, the assessments that were completed virtually will be repeated.

At the in-person visit for outpatients, the study staff will first complete the in-person assessments from the screening visit (including the physical exam, drug screen and pregnancy tests). Once these assessments have been reviewed by a Study MD/NP, and it has been determined that participants meet all IEC for the study, study staff will proceed with the baseline visit assessments. For participants admitted to Bellevue Hospital or Tisch Hospital, physical examinations, blood samples, urine samples performed by clinicians will be used to avoid unnecessary contact by research staff.

Optional baseline assessments (Brain Imaging and the MCCB) will be conducted with participants following all safety precautions and after verifying that the participant understands that these procedures involve additional potential exposure to COVID-19 and are optional.

4.8.2 Other study visits

For the remaining 7 visits, from Week 2 through Follow-Up, we will minimize in-person study visits. Similar to the precautions outlined above, assessments that can be completed virtually can be completed via WebEx for both outpatients and inpatients. Assessments that need to be completed in person include the following: vitals, phlebotomy for clinical laboratory assessments, urine collection for pregnancy tests, medication dispensation, imaging(optional) and the MATRICS Cognitive Battery (optional).

When possible, we will mail study medication to participants to allow for Week 3, Week 4, and Week 8 to be completed completely remotely.

We will maintain safety precautions when working with participants visiting One Park, such as screening participants for COVID-19 related symptoms prior to their arrival at One Park, taking participants temperature before they enter the building, providing participants a mask, providing hand sanitizer, and disinfecting the study drug pill bottle. We will also provide the option for a private car to commute to and from One Park.

For outpatients, we will allow a window of 48 hours between the time of virtual assessments and in-person study visits. The assessments will need to be repeated if more than 48 hours pass.

4.8.3 NYU Langone and Bellevue In-patient Precautions

Clinical laboratory screening tests, vital signs, pregnancy tests, and drug screens are routinely performed on all individuals admitted to NYU Langone or Bellevue hospitals and are documented in EPIC. We will utilize the results of this data if they're conducted within 36 hours of the study visit. Physical exams that were performed within the last 6 months and are documented in the medical record will be used to replace the in-person physical exam for patients unless medical history obtained by the research NP or MD suggests the possibility of a new medical condition with onset after the most recent physical exam.

5 Study Drug

5.1 Description

The study drug (Levetiracetam 500mg or placebo) will be supplied in a blinded and pre-labeled package.

5.2 Treatment Regimen

84 early psychosis patients will be randomized to a 12-week twice daily oral dose of levetiracetam 500 mg bid or placebo. Additionally, participants will receive a 9-day tapering regimen either after completing the 12 weeks or upon deciding to withdraw from the study prematurely.

5.3 Method for Assigning Subjects to Treatment Groups

Randomization will be in a 2:1 ratio in blocks of random size (3 or 6), stratified by site based on the median value for each site from our previous studies.

Preparation and Administration of Study Drug:
At NYU, study drug dispensation will take place at the NYU Langone Investigational Pharmacy. In order to ensure blinding, the 500mg and placebo will be prepared in identical capsules. Once a participant passes the screening procedures, the Investigator or study MD or NP will enter the prescription information into EPIC or write a prescription order to be submitted physically to the pharmacy. The study drug will be prepared in accordance with the randomization list which will be kept by the pharmacy. Study staff will retrieve the study drug from the pharmacy and the either an inpatient MD or NP or a study MD or NP will dispense the drug. Preparation and dispensation of study drug at SMHC will be performed by the SMHC research pharmacy.

5.4 Prior and Concomitant Therapy

Concomitant medications that are permitted during the study include Benadryl for sleep. Antipsychotic medications of flexible doses are also permitted during the study. The antipsychotic regimen will be determined by the participant's independent psychiatric provider (either an inpatient or outpatient provider not associated with the study). The study staff will not specify the antipsychotic medication used. The participant's medical record will be accessed to confirm and record all concomitant medications.

5.5 Packaging

All capsules of the study drug will be received in one bulk shipment from Curis Pharmacy and Discount and will be stored at room temperature in a marked bottle at the NYU Langone Investigational Pharmacy. The SMHC research pharmacy will purchase study drug from a local compounding pharmacy. The tapering regimen will be provided to participants in a blister pack labeled by the Curis Pharmacy with the tapering protocol indicated on the blister pack.

5.6 Blinding of Study Drug

The NYU Investigational Pharmacy will maintain a randomization list for study participants. All other study staff, aside from one designated unblinded study team member, will be blinded to the treatment groups. All study drug doses and placebo will be prepared in identical capsules in order to maintain blinding. The SMHC research pharmacy will maintain the randomization list for participants at SMHC.

5.7 Receiving, Storage, Dispensing and Return

5.7.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory will be performed, and a drug receipt log filled out and signed by the person accepting the shipment at the NYU Langone Investigational Pharmacy and at the SMHC research pharmacy. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator will notify the pharmacy of any damaged or unusable study treatments that were supplied to the investigator's site.

5.7.2 Storage

All study drug will be kept at the NYU Langone Investigational Pharmacy and the SMHC research pharmacy

at room temperature. No special handling or storage requirements are necessary.

5.7.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed by the study's unblinded pharmacist to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the pharmacist. Dispensation of study drug during Baseline – Week 12 visits will be logged by study clinician or delegated site staff.

5.7.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Assessments

Delusion Classification Form (DCF): This measurement asks for a brief narrative description of the participant's delusions as well as a categorization of their delusions into 15 subtypes. This will allow us to determine if change in hippocampal circuitry after treatment with antipsychotics selectively effects specific types of delusions.

Symptom Onset in Schizophrenia (SOS): The SOS is a 16-item scale that rates the presence and date of onset for 16 general, positive, negative, and disorganized symptoms. The SOS has been used in prior work to assess the onset of schizophrenia and other psychotic disorders and can incorporate information from the patient, family members / friends, medical records and other healthcare providers. This assessment has been shown to be a reliable and time-efficient tool for assessing symptom onset.

Brief Psychiatric Rating Scale (BPRS) [52]: The BPRS is an 24-item scale that measures positive symptoms, negative symptoms, general psychopathology and affective symptoms. Individual items are scored on a seven point Likert scale. The BPRS has been extensively used in trials of antipsychotic agents and has been shown to be sensitive to change. Psychometric properties and the underlying factor structure are well-established. We will use a 1 week (7 day) lookback period for this clinical assessment.

Structured Clinical Interview for the DSM-5 (SCID): The SCID for the DSM-V (Modules A-E) will be used to assess the primary psychiatric diagnosis for patients. The other modules for the SCID will not be performed as they do not relate to the inclusion/exclusion criteria.

Scale for Assessment of Negative Symptoms (SANS) [53]*:*
The SANS will be the instrument for measurement of negative symptoms. Factor analysis has revealed good construct validity for all items of the SANS scale except the Attention subscale which clusters with measures of cognitive impairment rather than negative symptoms. Two, three and five domain models have been proposed based on factor analysis; we will utilize the total score (minus the Attention Subscale) and the two factor solution (avolition and affective expression) [54]. The SANS has been validated in FEP populations [55]. It was recommended by the MATRICS-NIMH Negative Symptom Task Force [56] and has been used extensively in trials of agents targeting

negative symptoms. We have used the SANS in previous collaborative trials with SHMC in FEP populations and have achieved and maintained excellent inter-rater reliability.

Edinburgh Handedness Inventory (EHI)[57]:
The EHI is a 10-item scale that measures laterality preferences when performing different tasks. This assessment is widely used and has recently been translated and validated in Mandarin speaking populations. Participants are asked to indicate which hand (right or left) they use when performing different actions. A laterality quotient is determined by calculating the percentage of activities that are completed solely with the right hand. A laterality score of 100 would reflect complete right-handedness. A score of 60% or greater will be used as the cutoff for right-handedness. Handedness will be recorded but is not an entry criterion.

Calgary Depression Scale for Schizophrenia (CDSS) [58]: The CDSS is a 9-item scale derived from the Hamilton Depression Scale (Ham-D) for use in patients with schizophrenia. Unlike the Ham-D, the CDSS does not contain depressive symptoms that overlap with negative symptoms of schizophrenia, such as anhedonia and social withdrawal. The CDSS has shown excellent reliability in schizophrenia patients. We will use a 1 week (7 day) lookback period for this clinical assessment.

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery [59]: The MATRICS Consensus Cognitive Battery is the standard tool for assessing cognitive change in trials of cognitive-enhancing agents in schizophrenia.

Systematic Assessment for Treatment Emergent Side Effects (SAFTEE) [60]: The SAFTEE is a well-established and validated structured interview for assessment of drug-related side effects. It consists of two components, an open-ended inquiry and a comprehensive review of all body systems.

The Columbia Suicide Severity Rating Scale (C-SSRS) [61]: The CSSRS is a clinical interview that measures the spectrum of suicidal ideation and behavior. It was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It can be administered during any evaluation or risk assessment to identify the level and type of suicidality present and can also be used during treatment to monitor clinical worsening. It contains a 1-to-5 rating scale for suicidal ideation of increasing severity. It contains a Screening scale and a Since Last Visit scale.

Clinical Global Impression (CGI):
The CGI consists of three global scales (items) that have been designed to measure the severity of illness, global improvement, and efficacy of treatment. Global Improvement is the 2nd scale in the CGI. Total overall improvement is rated on a 0-7 point weighted scale, ranging from very much improved (1) to very much worse (7) respectively.

Biomarkers: At baseline and weeks 6 & 12, blood samples will be obtained prior to the morning dose of study medication; heparinized whole blood (7-10 ml) will be centrifuged and plasma divided into 0.5 ml. aliquots and stored at -80 degrees C until assayed. Serum assays including thioredoxin, S100B, and levetiracetam levels will be performed by Wayan Laboratory in Shanghai because of the prohibition against sample exportation from China. Serum thioredoxin and S100B will be measured using ELISA kits. Levetiracetam serum concentrations will be assayed using gas chromatography mass spectroscopy. SVP2A genotype will not be analyzed as a predictor of response since it does not predict response to levetiracetam in epilepsy. Plasma or serum collected from study participants at NYU Langone Medical Center will be sent to Yale University for analysis

of autoantibodies using rapid exoproteome antigen profiling (REAP). These samples' labels will be de-identified.

Buss-Perry Aggression Questionnaire (BPAQ)[62]:
The Buss-Perry Aggression Questionnaire consists of 29 items and contains 4 subscales: Physical Aggression, Verbal Aggression, Anger, and Hostility. The BPAQ will be administered at screening to assess a history of violence.

6.2 Screening (Visit 1 – Days -28 to 0)

Study Participants will complete a Screening Visit within 28 days of Baseline (Visit 2 – Day 1) to assess eligibility for the study. EP participants will be randomized after eligibility is confirmed during Screening.

The following procedures will be performed at Screening:

1. A study MD or NP will provide potential participants with informed consent documents and will explain the rationale for the study, the procedures, risks and alternatives to participation.
2. Participants will be assessed for inclusion and exclusion criteria.
3. Medical history, including patient demographics, and any concomitant medications use (including over-the-counter medications, vitamins, and supplements) will be reviewed and recorded. The participant's medical record will be accessed to confirm and record all concomitant medications.
4. Psychiatric history will be recorded and a SCID will be conducted by a study MD or NP.
5. Physical examination will be completed by a study MD or NP, or the admission physical exam performed by an NP or MD at Bellevue or NYU Langone will be used. For outpatients, a physical exam performed within 6 months may be used only if no new medical conditions with onset since the physical exam are reported. Vital signs will also be completed by a trained study team member or by the clinical team.
6. A urine pregnancy test and questionnaire will be performed on all individuals assigned female at birth of childbearing potential.
7. A urine drug screen test and cannabis use questionnaire will be performed.
8. Routine laboratory, including electrolytes, creatinine, BUN, glucose and CBC with differential.
9. In addition, the following rating scales will be completed:
    a. Brief Psychiatric Rating Scale (BPRS) – clinical research coordinator / research assistant
    b. Columbia Suicide Severity Rating Scale (C-SSRS) – study MD or NP
    c. Edinburgh Handedness Inventory (EHI) - clinical research coordinator / research assistant
        i. note EHI can be done at any study visit
    d. Delusion Classification Form – study MD or NP / clinical research coordinator or research assistant
    e. Symptom Onset Scale for Schizophrenia – study MD or NP
    f. Buss-Perry Aggression Questionnaire (BPAQ) – clinical research coordinator / research assistant

Participants who are excluded from the study either due above-threshold scores on suicidal severity screening or a cannabis use disorder will be referred to appropriate care by the study team.

6.3 Baseline (Visit 2 – Day 1)

The following procedures will be performed at Baseline:

1. A trained research assistant will complete the BPRS, SANS, CDSS, SAFTEE, MATRICS Cognitive Battery and MRI safety questionnaire (for participants completing the elective MRI scans). A study MD or NP will administer the CSSRS. If the participant is unable to complete MATRICS cognitive testing during the baseline assessment, this can be performed during the first week of study participation.
2. When clinically feasible, study participants will have the option to undergo a 15-30-minute MRI scan to measure blood flow in the brain and to assess brain structure (hippocampal volumetric integrity). Occasionally portions of the scan may need to be repeated due to movement. Participants will also have the option to repeat the 15-30-minute MRI scan two hours after the first dose of study drug to assess the effect of levetiracetam or placebo on hippocampal CBF.
3. Study medication will be dispensed by a study MD or NP or by clinical staff.

Participants will be monitored for 3 hours after the administration of the first dose of medication. Outpatients will be monitored by study MD or NP. Inpatients will be monitored by the clinical staff on the unit.

6.4 Follow-up (Day 2-5)

Participants will be assessed daily (inpatients) or by telephone (outpatients) for the first 5 days after initiating study drug to assess safety.

6.5 Follow-up Visits

Over the 12 weeks of medication administration and 9-day drug taper, participants will complete follow up assessments as outlined in the Appendix 1. The full assessment battery administered at the baseline visit will be repeated at weeks 6 and 12 or end of study participation. The optional MRI will be repeated at week 12 or end of study participation. Safety assessments by a study MD or NP and administration of the CSSRS and SAFTEE will occur weekly for the first 4 weeks and then at weeks 6, 8, and 12 weeks. The BPRS, SANS, and CGI will be repeated at weeks 2, 3, 4, 6, 8, and 12.

All participants will complete a tapering regimen (9 days) either after study completion (Week 12) or upon decision to withdraw from the study. Participants completing Week 12 will be given the tapering regimen (blister pack) and be asked to return for one final visit within 3 days of completing their tapering regimen. Participants choosing to withdraw early from the study will be asked to return for two subsequent visits: one to receive the tapering regimen, and a second within 3 days of completing the tapering regimen.

6.6 Visit Scheduling

Participants may complete the screening and baseline visits on the same day. If the screening and baseline visits are completed within 48 hours, then repeated assessments (BPRS and CSSRS) will not be repeated. For participants completing the baseline and screening visits on the same day, the study staff will hold dispensation of the medication until the laboratory results (drug screen, pregnancy test, clinical labs) have been completed and reviewed by a study MD / NP.

To allow for flexibility in the schedule of assessments for scheduling conflicts, holidays, etc., study visits (Weeks 2-12) can be scheduled either one day prior to the scheduled assessment date or within three days after the scheduled assessment date (-1 to +3 days). For example, if a participant completes their Week 3 visit on a Tuesday, the Week 4 visit could be scheduled Monday to Friday of the following week. Study staff will attempt to schedule the visit as close to the intended day as possible.

6.7 Assessment Administration

Due to the time commitment of the MCCB and MRI imaging, these assessments will be completed when clinically feasible. The MCCB and MRI imaging results are not used as part of the screening criteria and are not primary outcome measures. Therefore, while the study staff will attempt to complete these assessments in all participants, failure to complete these assessments will not be exclusionary from the study. Additionally, while the study staff will attempt to complete these assessments prior to the start of antipsychotic medication and of levetiracetam / placebo, these assessments may be completed within 7 days of the baseline visit.

6.8 Optional MRI Series to Assess Target Engagement

As mentioned above, the MRI imaging (including the ASL measurement of hippocampal CBF) will be completed when clinically feasible. Participants that are eligible and willing to complete the MRI imaging at Baseline will have the additional option to complete a second scan two hours after study drug administration that duplicates the assessment of target engagement conducted in the preliminary (R61) dose-finding study by measuring the effect of study drug on hippocampal CBF (perfusion).

For these participants, the following procedures will be performed:

1. Study medication will be administered by study MD or NP following baseline imaging
2. Two hours after administration of study medication, the following procedures will be performed
    a. A trained research assistant will complete the BPRS and SAFTEE assessing symptoms over the last two hours since study drug administration.
    b. Blood will be drawn (1 milliliter, or 0.25 teaspoons) for assay of levetiracetam levels.
3. Participants will complete a second structural and ASL imaging scan which will take up to 30 minutes total
4. Safety evaluation will be completed by study MD or NP three hours after study drug administration.

Participants will be allowed to smoke cigarettes ad lib prior to and after imaging. Occasionally, portions of the scan may need to be repeated due to movement.

Participants will be eligible for this assessment if they meet the inclusion exclusion criteria for the overarching study and have no contraindications for MRI. The first dose of the study medication will be administered between the two MRI scans, and the first dose of their antipsychotic.

6.9 Drug and Pregnancy Tests

A rapid urine drug screen and (for individuals assigned female at birth or with childbearing potential of childbearing age) a urine pregnancy test will be conducted by the research coordinator / research assistant or by clinical staff during the screening visit. The rapid urine pregnancy test will be repeated at the week 6 study visit. These results will be reviewed at the time of the visit with the study MD or NP. These results will be confirmed by also submitting urine samples to outpatient labs.

At each study visit, a pregnancy prevention questionnaire will be administered. At the screening, week 6 and week 12 visits, a cannabis use questionnaire will be administered to assess cannabis use.

6.10 Audio Visual Recordings

In order to create training videos for the raters, 6 patients at NYU Langone Medical Center and Shanghai Mental Health Center will be recorded (either audio or video) while interviewed with the

BPRS, SANS, and CDSS (a total of 6 patients for each scale at each site). These patients will not need to participate in the rest of the study and do not need to meet inclusion criteria for the study. Participants will sign a separate consent form (audio/video training ICF) indicating that they consent for voice or audio recording and are volunteering to complete the assessment understanding that it will be used for rater training in this study or in future studies conducted under the supervision of Dr. Goff. In addition, patients recruited at NYU Langone Medical Center will sign the "Authorization for Use and Disclosure of PHI for Academic Purposes" form found on the Compliance Policies intranet site (https://central.nyumc.org/shared/legal/compliance/Pages/Policies-and-Procedures-.aspxor in the HIPAA manual in Ellucid (https://nyumc.ellucid.com/documents/view/4582/7653), and the signed form will be maintained for a minimum of six (6) years. At NYU, participants will be recruited and consented in English or Mandarin, and assessments may be conducted in English or in Mandarin. Consenting research staff will be fluent in the language of consent (English or Mandarin) and will conduct the consent in either English or in Mandarin depending on the subject's preferred language.

If participants enrolled in the study at NYU Langone Medical Center agree to have their assessments recorded, they will need to sign the audio/video training ICF, the Institution Authorization for use and Disclosure of PHI for Academic Purposes form in addition to the main study ICF and they will be compensated $20 in addition to the compensation for the overarching study.

These recordings will be deidentified, labeled only with the subject's study ID, and kept on a shared drive that is only accessible to individuals who are study staff within Dr. Goff's lab. Only research staff who are directly involved in the study will have access to these files. Additionally, Dr. Corinne Cather PhD, an independent contractor, will also have access to the videos as she will primarily be responsible for the rater training for the study. Dr. Cather has served as the gold standard rater on previous studies for Dr. Goff and primary trainer for clinical assessments. As per Dr. Cather's agreement, she will be covered as a contractor by HIPAA confidentiality rules. Dr. Cather will review audiovisual recordings behind the NYU firewall.

7 Statistical Plan

7.1 Analysis population

The modified Intent-to-Treat (mITT) population will be used for all efficacy endpoints. The mITT population includes all randomized subjects who receive one dose of study medication and at least one evaluation post baseline.

7.2 Primary Endpoint Analyses

7.2.1 Primary analysis

The primary analysis will test the efficacy of levetiracetam 500 mg bid vs. placebo on symptoms measured by the BPRS total score. Time-normalized area under the curve (AUC) will be used as primary efficacy measurement.

A linear mixed effect model on BPRS total score will include fixed effects of treatment*visit two-way interaction where variable "visit" contains categorical indicators of study visits. BPRS assessments from baseline (week 0), week 2, 3, 4, 6, 8 and 12 will be included. A subject-level random intercept will be included in the model, and the residual matrix will be modelled using a spatial-power covariance structure based on the number of weeks apart between two visits.

The time-normalized AUC will be estimated by the trapezoidal rule. For Weeks 0, 2, 3, 4, 6, 8 and 12, the linear estimation coefficients will be [63,3,2]/12 respectively. A significantly smaller BPRS AUC estimation in the levetiracetam arm compared to placebo will be regarded as evidence of levetiracetam's efficacy on clinical symptoms.

With frequent measurements and relatively short follow-up period, drop-outs will have limited impact on study conclusions with MAR (missing at random) assumption.

7.2.2 Secondary analyses

As a sensitivity analysis to the MAR assumption, if the trial retention rate at Week 12 is below 70%, a stratified analysis based on follow-up duration will be carried out.

If the treatment arm difference in BPRS continues to diverge, a parametric model will be added using "visit" as a continuous variable. The functional form of "visit" in the model shall be selected among linear, linear + logarithm spline term, linear + exponential spline term to properly capture the trajectories. A significant interaction term will be a more effective evidence than AUC difference between treatment arms.

7.3 Secondary Endpoints Analyses

For repeatedly measured secondary endpoints, including BPRS psychosis subscale, hippocampal volume loss, hippocampal CBF, modified SANS total score, and MATRICS composite score, the same mixed effect model used in the primary analysis of BPRS total score will be used. For MATRICS composite score and hippocampal volume loss, the linear estimation coefficients to calculate AUC require updates due to less frequent measurements compared to BPRS and SANS score. For MATRICS composite score, the linear estimation coefficients will be [63]/12 for Week 0, 6 and 12 respectively. For hippocampal volume loss, the coefficients will be [63]/12 for Weeks 0 and 12.

The Spearman Correlation between pre-dose hippocampal blood flow change from baseline to Week 12, and BPRS total score change from baseline to Week 12 will be calculated and presented. If subject retention at Week 12 is below 70%, multiple imputation will be used to account for informative dropouts. This analysis will ignore subjects' treatment arm information.

Subjects' hippocampal blood flow difference at baseline and week 12 will be compared between two treatment arms with a two-sided two sample t-test.

7.4 Tertiary Endpoint Analyses

A linear regression model on hippocampal volume change from baseline to Week 12 with following predictors will be built to explore the potential mechanism: duration of untreated psychosis, levetiracetam blood level at week 6, and serum biomarkers for oxidative stress (thioredoxin) and astroglial injury (S100B).

The Spearman Correlation will be calculated for following pairs of variables with two treatment arms pooled together:

- MATRICS composite score change from baseline to Week 12, and hippocampal volume change from baseline to Week 12;
- Modified SANS total score change from baseline to Week 12, and hippocampal volume change from baseline to Week 12;

- BPRS total score change from baseline to Week 12, and hippocampal volume change from baseline to Week 12;
- MATRICS composite score change from baseline to Week 12, and pre-dose hippocampal blood flow change from baseline to Week 12;

Modified SANS total score change from baseline to Week 12, and pre-dose hippocampal blood flow change from baseline to Week 12;

7.5 Sample Size Determination

A sample size of 84 randomized in a 2:1 ratio of levetiracetam to placebo provides 80% power to detect a moderate effect size (Cohen's d of 0.65) with a two-sample t-test and two-sided level of significance at p=0.05.

With no missing data, the primary analysis is equivalent to a two-sample t-test on AUC estimates. With a 2:1 randomization ratio, the effect size can be calculated as:

$$d = \frac{\delta_{AUC}}{\sigma_{AUC}} = \sqrt{\frac{3}{2 \times N_{control}}}\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right) = \sqrt{\frac{3}{56}}(1.96 + 0.84) = 0.648$$

7.6 Subject Population(s) for Analysis

Both the incidence of adverse effects and ASL evidence of hippocampal target engagement will be analyzed in all participants who receive study drug. The primary efficacy outcome measure for this trial are described above in section 3.2.

The modified Intent-to-Treat (mITT) population will include all randomized subjects who receive one dose of levetiracetam and at least one evaluation post baseline.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal

- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

While adverse events will not be limited to the items assessed on the SAFTEE, a two-point increase of any item on the SAFTEE (as compared to their screening visit) will be considered an adverse event.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably

be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Procedures to minimize additional risks:
As described, a psychiatric and medical evaluation will be completed as part of screening. Participants will be closely observed for 3 hours after their first dose of study drug. Inpatients will be monitored by the clinical staff on the unit. In the event of adverse reactions or other medical complications, an MD or NP will respond to the event and 911 will be called if needed.

We are studying a low dose of levetiracetam. The low dose is the standard starting dose which has been approved for almost 20 years and is not associated with medical complications. We will be monitoring closely for psychiatric reactions. Subjects will be contacted by telephone (for outpatients) or assessed in person (if inpatient) by the research assistant for the first 5 days after starting the study medication to affirm that they are stable using the medication safety assessment checklist. Any reports of worsening (symptoms or side effects) will be immediately (same day) shared with Dr. Goff (NYC) or Dr. Wang (Shanghai). Outpatients who report worsening of psychosis or new suicidal or aggressive ideation will be asked to come into the clinic for assessment within 24 hours.

Additionally, weekly safety assessments will be conducted for the first 4 weeks of study drug administration by the study MD or NP. These assessments include the CSSRS and the SAFTEE. The BPRS will also be conducted by a research coordinator or research assistant.
If a patient develops new suicidal or aggressive ideation or has a 20% or greater worsening in their BPRS total score, this information will be shared with the clinical team and with the Chair of the

DSMB (Dr. Buchanan). Either the clinical team or Dr. Buchanan can decide to discontinue study medication. After the first four weeks participants will be assessed by a research assistant and by a study MD or NP at each study visit (weeks 6, 8, and 12) using the same safety assessments as above. The participant will be assessed during weeks 5, 7, 9, 10 and 11 by phone by the research assistant who will complete the safety assessment checklist and follow the same reporting guidelines outlined above.

To minimize risk of COVI-19 exposure, all institutional guidelines will be followed, including screening of participants and staff, social distancing and use of PPE. Whenever possible, all assessments will be performed remotely or by clinicians performing them as part routine practice.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning (SAFTEE) and, as appropriate, by examination. A side effect and adverse effect of the medication is defined as a 2-point increase on any given item on the SAFTEE from baseline. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting

requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3.2 Sponsor reporting: *Notifying the NIH*

The study sponsor is required to report certain study events in an expedited fashion to the NIH. These written notifications of adverse events are referred to as Reportable Events. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 3 business days***
  Any suspension or termination of the study by IRB or DSMB recommendation.

- ***Within 5 business days***
  - Deaths related to study participation

- ***Within 10 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug or study participation
  - unexpected,
  - fatal or life-threatening
  - Results in inpatient hospitalization or prolongation of existing hospitalization

Results in a persistent or significant disability / incapacity

  - Study Events including: a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 10 calendar days from when event was deemed reportable).
  - Other unanticipated problems involving risks to subjects or others
  - Serious or continuing noncompliance

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
  -

- ***With annual progress report***
  - Protocol violations
  - AEs and SAEs that are deemed expected and / or unrelated to the study

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted in writing to the NIMH Program Official. These reports should indicate that monitoring entities (including PI, IRB, and DSMB) have been notified in accordance with the monitoring plan. The contact information for the Program Official is noted below:

- **Administration:** Program Official (PO)
- **Name:** Hillefors, Mi
- **Phone:** 301-443-1692
- **Email:** hillefom@mail.nih.gov

8.4 Unblinding Procedures

If the study MD or NP determines that unblinding is necessary for a subject's safety, the study MD or NP will contact the NYUMC Research Pharmacy and the study code will be unblinded and shared with clinicians as appropriate.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Data Monitoring Committee

Our existing data safety and monitoring board (DSMB) will monitor this study. The DSMB has monitored five clinical studies over the past 9 years and is comprised of a statistician and two psychiatrists with extensive experience conducting clinical trials and in participating on DSMBs. If specific risks emerge additional members with expertise in the area of the potential safety issue will be added to the DSMB. The DSMB will approve the protocol prior to initiation of the study. The DSMB will review site performance, including recruitment, subject retention, protocol violations, and data quality reports. The DSMB will receive an unblinded report of all safety data (adverse events as defined above, including change scores on the SAFTEE assessments or findings upon clinician assessment) after completion of the first 4 subjects in addition to reports for bi-annual meetings. The DSMB will also be provided copies of all communications with the IRB. The DSMB will meet prior to initiation of the study and a minimum of every six months and will be provided data regarding enrollment and side effects and a study summary prior to each meeting. The DSMB may request additional meetings as necessary to monitor safety or site performance. The information for safety monitoring of the Shanghai site is outlined below (Section 9). Dose selection and titration schedule can be adjusted by the DSMB. Dr. Goff and study staff will not attend the closed section of the DSMB meetings. Throughout the study, notification of any Serious Adverse Events (SAEs) as well as any proposed investigator-initiated changes in the protocol will be submitted to the DSMB. Based on its review of the revised protocol, the DSMB will identify the data parameters and format of the information to be regularly reported. All SAEs and adverse events will be tabulated and submitted to the IRB and DSMB in the bi-annual (every 6 months) data reports or at the time of continuing review. AEs will be reported to the IRB annually.

9 Site Management

9.1 Management Plan of Unanticipated Problems Involving Risks to Participants or Others

The study coordinating site will be at NYU Langone Medical Center. The Study PI and NYU Site PI, Don Goff, and the SMHC site PI, Jijun Wang, will monitor the safety of the participants. Drs. Goff and Wang have conducted bi-weekly Skype conferences for 6 years—these bi-weekly calls will continue to review study progress. Protocol violations and data quality reports will be discussed during bi-weekly meetings of study staff at both NYU and SMHC. If an unanticipated risk or a serious adverse event (as defined above) is identified at SMHC, clinicians will notify Dr. Goff and the research coordinator / research assistant at NYU within 24 hours of the event.

All clinical data will be reviewed by the NYUMC Research Coordinator / research assistant within 2 weeks of acquisition to provide ongoing quality assurance. The Research Coordinator / research assistant will conduct a Skype call with Drs. Yingying Tang, PhD (fMRI data collection) and Dr. Hu

Hao (clinical data collection) every 2 weeks.

During the first 6 months of the grant funding, the Research Coordinator, research assistant, and Dr. Goff will visit Shanghai Mental Health Center to provide training, including administration of symptom rating scales at Shanghai Mental Health Center. In addition to the site initiation visit in year one, additional site visits for training and audit of CRFs will be made by Dr. Goff, the research assistant, and the Research Coordinator in years 2 and 3. These site visits may be conducted virtually (i.e. via skype call) in the event of a national travel ban such as those relating to COVID-19.

9.2 Interim Results

Data collected from SMHC will be entered into a Acquire database and reviewed by the clinical research coordinator / research assistant within 2 weeks of acquisition. The data from SMHC will be included in the initiation and bi-annual DSMB reports along with the NYU data.

A report of the DSMB meeting will be emailed to the SMHC team after the DSMB meeting, and Dr. Wang (Site PI) will be asked to review and confirm receipt of the report. The report will also be reviewed at the next bi-weekly meeting. If Dr. Goff determines that the content of the DSMB report requires an earlier meeting, then an additional meeting will be scheduled with Dr. Wang and the team at SMHC.

9.3 Ethical Considerations / Protocol Modifications

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) at both NYU and Shanghai Mental Health Center in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

10 Data Handling and Record Keeping

10.1 Confidentiality

Subjects will be assigned a study identification code that will be used for all study documents. All patient identifiers will be redacted, and subjects will not be identified in any presentations that are given of the results of this study. Study documents collected in this study will be kept in a locked cabinet in a locked office belonging to the study staff. Only research staff who are directly involved in this study will have access to that file.

Research staff will handle data according to NIMH specifications from study grant.

10.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

A Acquire project for this study will be created to mirror the paper CRFs. Acquire will be the primary method for completing CRFs.

In the event a paper CRF is used, all entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. All CRFs completed on paper will be entered into the Acquire system using a double data entry protocol.

10.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in Section 8.5 and 8.5.1. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment [include attachment number here] for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or subject's parent/guardian (if under 18), and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is financed through a grant from the US National Institute of Health. Upon request of study participants, referrals for treatment may be provided. Study participants will be informed that they are responsible for any costs associated with referrals.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

13.3 Subject Payments

There is no cost to subjects for participating. Round trip metro cards will be provided for each study visit. For subjects traveling from further away, subjects will be reimbursed up to $20 per visit for

transportation. In the event that a car service is deemed helpful to bring the participant to the visit, study staff will arrange for a car to pick up and drop off the participant.

EP participants will receive up to $495.00 for completion of the study. Payments will be via cash, check, or gift card.

- $25 for Screening (Visit 1)
- $75 for Baseline (Visit 2)
- $25 for Weeks 2,3,4,8
- $50 for Week 6
- $85 for Week 12
- $10 for Follow-up visit post tapering regimen

Optional Assessments:

- $25 per MRI (Participants completing the R61 Target Engagement MRI Series at Baseline will be compensated $50 total for the two MRI sessions)
- $25 per MCCB assessment

Subjects will not receive remuneration for the follow-up phone calls.

Participants who request to withdraw from the study early will be asked to return for two additional study visits. These visits will consist of the content of the week 12 visit and the Follow-up visit. Participants completing those two additional visits will be paid in accordance with the amounts listed for the Week 12 and Follow up visits above.

Participants completing the audio/visual recordings will be compensated $20.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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Appendix 1: Schedule of Events *EP Participants*

	Screening, Visit 1	Baseline	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	Follow-Up
	Days -28 to 0	Day 1	Day 6-10	Day 13-17	Day 20-24	Day 34-38	Day 48-52	Day 76-80	Day 85-93
Consent	X								
Authorization Form	X								
Inclusion/Exclusion Checklist	X								
Medical History	X								
Physical Exam	X								

Psychiatric History	X								
Psychotropic Medication History	X								
DCF	X							X	
SOS	X								
Demographics	X								
EHI	X								
Concomitant Medications	X		X			X		X	
Vital signs	X		X			X		X	X
Anthropometrics	X								
Clinical laboratory assessments (Blood)	X							X	
Biomarkers^		X				X		X	
Urine Drug Screen	X								
Pregnancy Test	X					X			
Randomization		X							
Study drug dispensation		X	X	X	X	X	X	X	
SCID	X								
BPRS	X	X	X	X	X	X	X	X	
SANS		X	X	X	X	X	X	X	
CDSS		X				X		X	
C-SSRS	X	X	X	X	X	X	X	X	
CGI		X	X	X	X	X	X	X	X
BPAQ	X								
Cannabis Use Questionnaire	X					X		X	
Pregnancy Questionnaire	X	X	X	X	X	X	X	X	
SAFTEE		X	X	X	X	X	X	X	X
MCCB*		X				X		X	
Medical Monitoring		X							
Brain Imaging*		X						X	
Levetiracetam blood levels		X**				X		X	
Adverse Event Form		X	X	X	X	X	X	X	X
Study Completion Form									X

* These assessments may be completed within 7 days of the baseline visit.
** These assessments are completed only if participant opts into the optional R61 MRI imaging (see section 6.8)
^ Biomarkers should be collected prior to that day's medication dose