Official Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL INVESTIGATING THE EFFECTS OF LEVETIRACETAM IN EARLY PSYCHOSIS
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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL INVESTIGATING THE EFFECTS OF LEVETIRACETAM IN EARLY PSYCHOSIS

Abbreviated Title: *Levetiracetam in Early Psychosis*

Version #: *1.19*
Version Date: *07/28/2020*

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Protocol Number: *S17-00266*

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List of Abbreviations

AD: Alzheimer's disease
ASL: arterial spin labeling
BPRS: Brief Psychiatric Rating Scale
CAARMS: Comprehensive Assessment of At-Risk Mental States
CBF: cerebral blood flow
CSF: cerebrospinal fluid
CSSRS: Columbia Suicide Severity Rating Scale
EP: early psychosis
HVI: hippocampal volumetric integrity
MCI: mild cognitive impairment
MRI: magnetic resonance imaging
MRS: magnetic resonance spectroscopy
SAFTEE: Systematic Assessment for Treatment Emergent Side Effects
SCID: Structured Clinical Interview for DSMIV TR
SIPS: Structured Interview for Prodromal Syndromes
TLE: temporal lobe epilepsy
UHR: ultra-high risk
VTA: ventral tegmental area

Study Summary

Title	A randomized, double-blind, placebo-controlled trial investigating the effects of levetiracetam in early psychosis
Protocol Number	S17-00266
Study Duration	Months 1-2: Complete all staff training and regulatory requirements for levetiracetam administration. Months 3-24: Enroll 46 EP subjects to meet randomization target of at least 8 eligible FEP completers in each treatment group (placebo, low- and high-dose levetiracetam). Randomize 1.5 medication-naïve EP subjects each month and perform a single-dose placebo-controlled levetiracetam trial with ASL and spectroscopy. Enroll 12 healthy controls to meet randomization target of 10 healthy controls and study with ASL and spectroscopy. Months 24-28: Complete analysis of R61 data to determine if target engagement and tolerability goals have been achieved. If achieved, select levetiracetam dose and begin preparations for the R33 trial.
Study Center(s)	Single-center
Objectives	A placebo-controlled single-dose parallel group trial of levetiracetam 185 mg and 500 mg in medication-naïve EP patients will be conducted to establish target engagement and identify an effective dose. Hippocampal activity by pulsed arterial spin labeling (ASL) pre-dose and 2 hours post-dose will also be measured and compared to the hippocampal activity of 10 healthy controls. If this pilot trial is successful, we will proceed to the R33 placebo-controlled 12 week add-on trial of levetiracetam in 84 EP subjects using a dose selected on the basis of the results of this study. We are not requesting approval of the R33 trial.

Number of Subjects	We aim to enroll a total of 58 participants: 46 EP participants, 12 healthy controls. In anticipation of screen failures or study drop outs enrollment of 58 will allow us to reach our target goal of at least 8 EP completers in each treatment group (placebo, low- and high-dose levetiracetam) and 10 healthy controls. Due to drop-outs and participants who are disqualified from data analysis due to diagnostic ineligibility or technical problems with the MRI arterial spin labelling scan, recruitment will continue until all three EP treatment groups have 8 eligible completers.

Inclusion/Exclusion Criteria	Inclusion Criteria 1. Males and females 16 to 35 years of age, inclusive, at time of informed consent 2. Must have experienced a first episode of non-affective psychosis within 5 years and exhibit current psychosis, as defined by a score of ≥ 2 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 DSMIV TR (SCID) 4. Must not have taken an oral antipsychotic medication within the past 4 weeks prior to study enrollment or received a long acting injectable antipsychotic within 3 times the dosing interval. 5. If female and of childbearing potential, patients must: a. Have a negative urine pregnancy test (all females regardless of childbearing potential will be required to submit a pregnancy test) b. Not be nursing or planning a pregnancy for the duration of the study through 30 days after the last dosing visit 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. c. use of marijuana within the 72 hours prior to MRI scanning by self report. 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 and/or PhD or MD level clinician completing screening visit. 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. Metal implants, pacemaker, or other metal in the body or medicinal patch.7. History of claustrophobia. 8. Currently taking any antipsychotic medication (within 4 weeks).
Study Product, Dose, Route, Regimen	Non-affective early psychosis patients will be randomized to a single oral dose of levetiracetam 185 mg, 500 mg or placebo. Subjects will have MRI brain imaging at baseline and 2 hours after administration of study drug. 10 healthy subjects will have brain imaging without being administered any medication.

1 Introduction

Title: A randomized, double-blind, placebo-controlled trial investigating the effects of levetiracetam in early 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 7 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, levitiracetam 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). Higher doses typical of anticonvulsant activity were not effective (35). In patients with MCI, levetiracetam 62.5 mg bid and 125 mg bid improved performance and normalized hippocampal BOLD hyperactivation during a pattern separation task (16). In addition, levetiracetam normalized left and right hippocampal activation patterns during verbal and visual memory tasks in patients with temporal lobe epilepsy (TLE) (36). 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 (consistent with anticonvulsant treatment) 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. Levetiracetam is approved at doses up to 3,000 mg/d administered twice-daily for epilepsy and oral loading doses of 3,000 mg are well-tolerated (29).

Whereas levetiracetam is now generic, the manufacturer, UCB, has recently received FDA approval for a levetiracetam analogue, brivarecitam, which is more potent and more rapidly crosses the blood brain barrier (20 minutes vs 1 hour). The rapidity of CNS penetrance is an advantage for status epilepticus; however, because brivaracetam is less selective for SVP2A than levetiracetam (37) and because data on dosing for neuroprotection of hippocampus is only available for levetiracetam, we will study levetiracetam rather than brivaracetam, although it is a potential option for future studies.

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. 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 (38) and open-label trials (39) 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 (40) and affective disorders (41) but have not been observed in patients with cognitive or anxiety disorders (40).

Antipsychotic-associated excitotoxicity and oxidative stress: Twenty years ago we found that treatment with first generation antipsychotics elevated cerebrospinal fluid (CSF) concentrations of

alanine, consistent with free radical injury to mitochondrial function (42). Using tardive dyskinesia as a model of antipsychotic toxicity, we also found elevated CSF levels of aspartate and products of oxidative stress (43). Aspartate crosses the blood brain barrier more readily than glutamate and preferentially binds to extra-synaptic NMDA receptors which mediate excitotoxicity (44). Hence, our results were consistent with antipsychotic toxicity mediated via excitotoxicity and oxidative stress resulting in injury to mitochondria.

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 elevation of serum aspartate levels (Cohen's d=0.43, p=0.02) and significantly decreased hippocampal volumetric integrity bilaterally (Right: Cohen's d= 0.57, p=.001; Left: Cohen's d= 0.91, p=.0001) with the left side significantly more affected than the right (p=.005) 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 6.5% 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 and did not significantly correlate with serum biomarkers (p>0.1). 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 (45). 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 (46), 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.

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) (47). The fully automated, fast, reliable and robust process is based on 3D T1-weighted structural MRI and involves identification of the mid-sagittal plane (48) and the anterior and posterior commissures (49) 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) (50) 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.

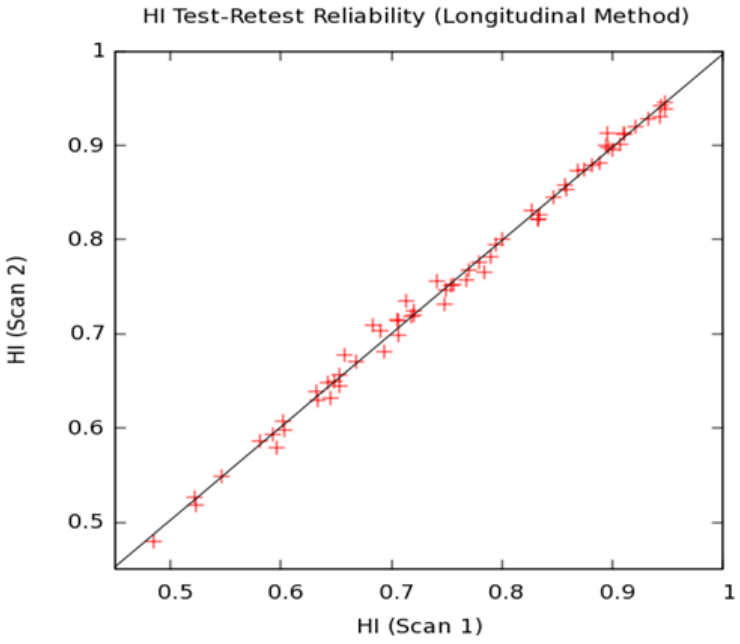

Figure 1. Hippocampal volumetric integrity measurement. ICC = 0.998

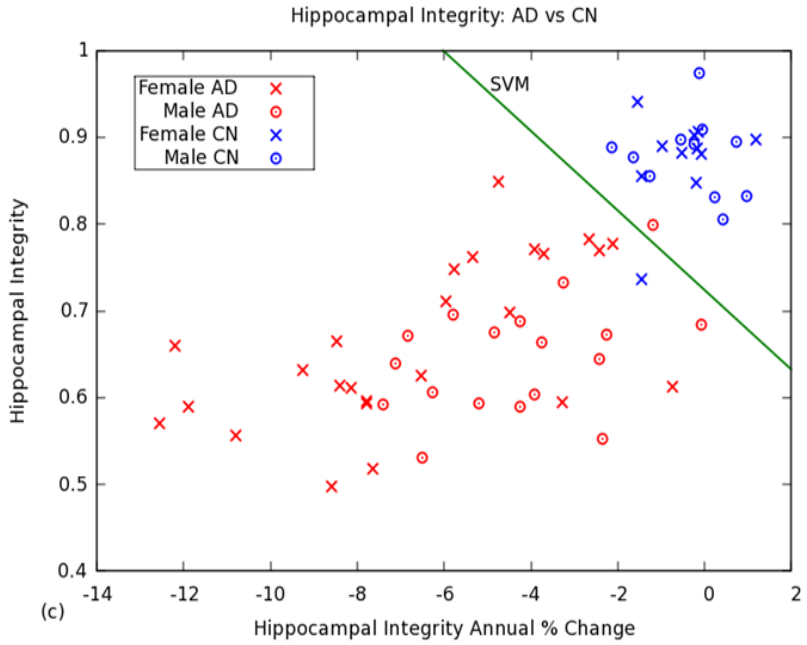

Figure 2. Hippocampal volumetric integrity, Alzheimers subjects and healthy controls.

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) (51). 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 (52).

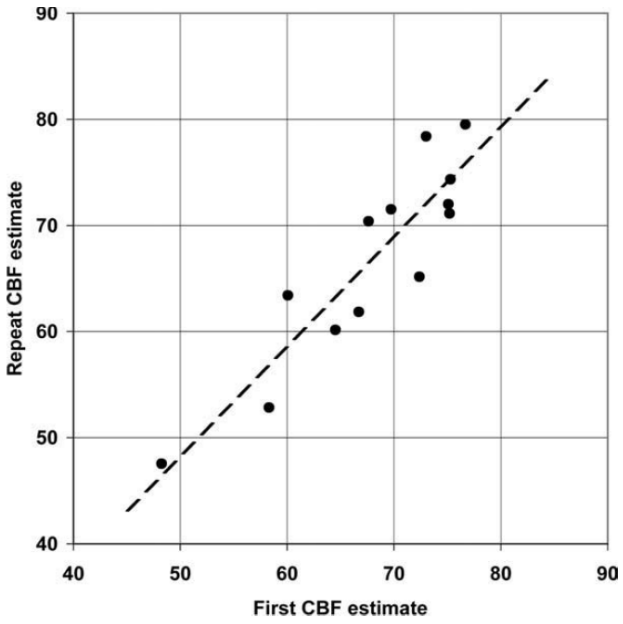

Figure 3. Measurement of hippocampal perfusion. ICC = 0.90

In summary, levetiracetam at low, well-tolerated doses 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.

<u>Measurement of glutamatergic transmission using proton MR spectroscopy:</u>

^{1}H MRS is the study of compounds other than water whose ^{1}H signal is high enough to be reliably detected. A brain ^{1}H MRS spectrum is usually dominated by three major singlets: the *N*-acetyl groups of *N*-acetyl-aspartate (NAA) at 2.01 ppm; creatine and phosphocreatine (Cr) at 3.03 ppm; and the tetra methylamines of choline-containing compounds (Cho) at 3.19 ppm. At short echo time (*TE*), also observable are the *pseudo*-singlets of *myo*-inositol (mI) at 3.56 ppm, glutamate (Glu) at 2.35 ppm and glutamine (Gln) at 2.43 ppm (74, 75) (figure 4). These metabolites are widely used as surrogate markers for neuronal dysfunction (NAA); cellular energy/density (Cr); membrane turnover (Cho); glial activation (mI); and Glu+Gln, or Glx, for changes in the glutamate cycle between neurons and astrocytes (74). For this project, special emphasis is placed on Glx, since levetiracetam is thought to exert its effects through decrease of glutamate release. Because of the proximity of their major resonances around 2.4 ppm (figure 4), Glu and Gln are usually not reliably distinguished at clinical magnetic field strengths (≤ 3 T) (76). Their sum, however, referred to as Glx (76), can be quantified with high accuracy, especially when *TE*=108 ms, as employed in this study (figure 5). Importantly, abnormally high Glx has been previously found in the hippocampus of schizophrenia patients (77), likely reflecting excessive glutamatergic transmission.

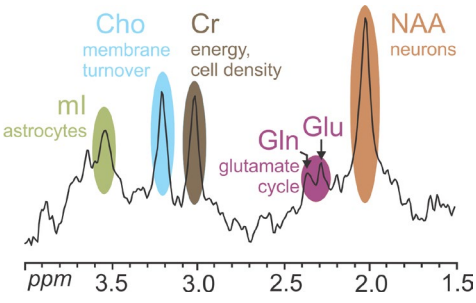

Figure 4. ^{1}H MRS. Short *TE*, brain *in vivo* spectrum showing the major resonances in healthy tissue and their general specificities.

Single voxel ^{1}H MRS. Prior to the ^{1}H MRS, scanner manufacturer's "advanced shimming" procedure will be employed to adjust the first- and second-order currents, reducing the full-width-at-half maximum water linewidth to ~20 Hz. Next, a ^{1}H MRS single voxel with the following parameters will be placed on the left hippocampus: 3×1.5 ×1.5 cm^3, *TR*=1800 ms, *TE*=105 ms, 192 averages, (figure 5). The duration of the ^{1}H MRS sequence will be around 7 minutes. Finally, a reference scan (< 1 min) with the water suppression turned off, will be obtained for quantification purposes. Absolute quantification of metabolite levels will be done off-line using in-house software, as previously described (78).

Measurement of corneal temperature and hand temperature. (Optional Procedure)
Evidence suggests that unmedicated patients with schizophrenia may have elevated body (core) temperature [79], accompanied by decreased peripheral (hand) temperature [80]. In addition, medications used to treat schizophrenia may reduce temperature [81-82]. Given neuronal activity is known to be strongly influenced by temperature [83], changes in brain temperature that accompany disease states or medication effects may interact with brain activity relevant to this study and inform outcomes. Measurement of corneal and hand temperature by infrared, using a portable infrared camera, is non-invasive, with no known risks to patient safety. Measurement of core temperature with a temporal artery forehead scan takes seconds and is routinely used in outpatient clinical settings.

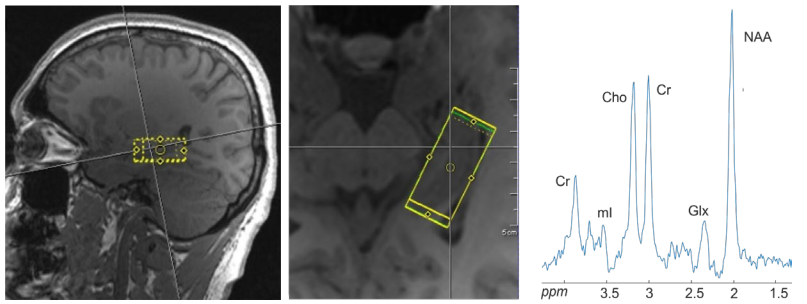

Figure 5. Single voxel ^{1}H MRS of the hippocampus.
MP-RAGE superimposed with the 3×1.5×1.5 cm^3 PRESS VOI placed on the left hippocampus and the corresponding spectrum obtained at *TE*=105 ms. Note: (1) the choice of *TE*, at which the Glx multiplet (*e.g.* Fig. 4) appears as a pseudo-singlet, enabling easier quantification; (2) the excellent SNR consequent to the large size voxel, which enables the quantification of mI even at this intermediate *TE*; (3) the additional resonance of Cr, at 3.9 ppm, which would be included in the modelling algorithm used for quantification.

1.4 Study/Dose Rationale

We are proposing a 2-year R61 project in which we will examine the effects of a placebo-controlled trial of single dose administration of levetiracetam 185 mg and 500 mg on hippocampal CBF measured by ASL in up to 48 EP participants in order to collect data in at least 8 eligible completers per treatment group ((placebo, low-dose levetiracetam and high-dose levetiracetam)
to establish target engagement, assess tolerability, and guide dose selection. Due to drop-outs and participants who are disqualified from data analysis due to diagnostic ineligibility or technical problems with the MRI arterial spin labelling scan, recruitment will continue until all three EP treatment groups have 8 eligible completers.

We will verify the elevation of hippocampal CBF at baseline in our sample by also studying 10 healthy controls group-matched on age and gender. Healthy controls will not be randomized to receive study drug or placebo, but will only have brain imaging.

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.

The neurodevelopmental model for early schizophrenia upon which this proposal is based, the pharmacologic agent and its target, and the imaging biomarkers are all well-validated. However, 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.

In the study of hippocampal CBF measured by ASL in UHR and EP subjects by Allen and colleagues (12), the elevation in left hippocampal CBF compared to healthy controls was a very large effect (Z statistic = 4.35). In addition, repeated measurements of hippocampal CBF in subjects who remained psychotic were highly reliable (12). Bakker and colleagues (58) found that levetiracetam decreased elevated hippocampal activation in patients with MCI to levels below those observed in healthy controls (from 0.8 to -0.2 in MCI patients vs. 0.0 in healthy controls). The magnitude of reduction of hippocampal hyperactivation with levetiracetam was highly consistent between trials involving two patient samples (58). Furthermore, the method of ASL that we will use to measure hippocampal CBF has very high reliability (ICC=0.90) (51). Therefore, based on previous studies, the elevation of hippocampal activation in our sample should be large, the reduction by levetiracetam should also be large, and our method for measurement is highly reliable, so we are confident that our proposed approach for verifying target engagement is quite valid and feasible. In addition, two hours post-dose should be sufficient to measure levetiracetam effects with ASL since maximal blood levels are achieved within one hour and, within one hour of oral levetiracetam administration, abolishment of seizures has been demonstrated in humans with photosensitive epilepsy {Kasteleijn-Nolst Trenite, 1996 #6357} and within one hour a reduction of corticospinal excitability measured by transcranial magnetic stimulation (TMS) has been demonstrated in healthy human subjects {Kasteleijn-Nolst Trenite, 1996 #6357}. Because a single dose can treat epilepsy within the two hour time frame of our R61 study and because perfusion as measured by

ASL should reflect hippocampal activation acutely, we believe that a single dose will provide us valid information about the range of levetiracetam concentrations that will correct hyper-perfusion associated with first episode psychosis. If we fail to observe a reduction in hippocampal perfusion with either of the two doses, we would recommend repeating the R61 study with a two-week repeated dosing trial in FEP subjects who have been stabilized on medication but remain symptomatic. We would make this decision in consultation with NIMH staff.

We will use a method developed and validated by our collaborator, Henry Rusinek (51) and recently adopted by our imaging team (Rusinek & Convit) in the study of insulin resistance on brain CBF (60). 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 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 (51). 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 (51), likely due to the use of WM as reference. The tissue perfusion computation uses a general kinetic model (61). 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 (51).

In a two-week trial, levetiracetam doses of 62.5 mg bid and 125 mg bid reduced hippocampal activation and improved cognition in a sample of MCI patients with a mean age of 70 years whereas a dose of 250 mg bid was not effective {Bakker, 2015 #6213}. Due to an estimated 30% reduction in renal clearance in the elderly {Contin, #6359}, these effective doses would be equivalent to 84 mg bid and 167 mg bid in young EP patients. We selected an intermediate value of 125 mg bid (half-way between 84 mg and 167 mg); a single dose of 185 mg is calculated to produce blood levels equivalent to blood levels achieved at steady state following repeated dosing of 125 mg bid. Therefore, we will administer a single levetiracetam dose of 185 mg to achieve blood levels within the range of steady state blood levels that were effective in elderly patients with MCI. The 500 mg levetiracetam dose is a standard antiepileptic dose for partial (temporal

lobe) epilepsy. We expect that both doses of levetiracetam will be well-tolerated; in the treatment of epilepsy, levetiracetam doses up to 3 g are routinely administered without serious side effects.

It is possible that a low dose of levetiracetam "optimizes" synaptic transmission and is preferable to a higher antiepileptic dose in MCI, but we cannot be certain that this will also hold true for first episode psychosis. We thus selected two doses: a dose that achieves blood levels within the range that was effective for MCI (correcting for age and calculating a single dose that will produce blood levels equivalent to steady state concentrations achieved by repeated dosing) and a typical anticonvulsant dose for which we can be confident of full target engagement. Since it is a trade-off between the number of doses examined and the sample size in each dose group, we believe it is better to perform a definitive test of these two doses than to risk having an under-powered test of multiple doses.

1.5 Research Risks & Benefits

1.5.1 Risk of Study Drug

The most common side effects reported with levetiracetam are drowsiness, weakness, dizziness and infection. 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.

Drug Interactions

There are no known interactions between tetrahydrocannabinol (THC), cannabidiol (CBD) or other phytocannabinoids and levetiracetam. Levetiractam 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. 1.5.2 Other Risks of Study Participation

Phlebotomy

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

Privacy

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. During the Baseline scan, we will monitor adverse effects for 3 hours after administration of levetiracetam; subjects will be psychiatrically cleared by a psychiatrist prior to release from the imaging center. Subjects will be contacted the following day to assess safety.

1.5.3 Potential benefits

All subjects will receive a comprehensive psychiatric and medical evaluation and optimal clinical treatment as part of participation.

Incidental Findings:
Study participants will be informed at the time of screening if urine tests are positive for pregnancy or drugs of abuse since either is exclusionary. No other laboratory tests will be performed. MRI scans will be reviewed by a neuroradiologist at the Center for Brain Imaging (CBI) and the results reviewed by Dr. Goff. If clinical readings of MRI scans show unanticipated abnormalities that require medical follow-up Dr. Goff will contact participants via telephone and study staff will 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 subjects.

2 Study Objectives

The objectives of this study are to evaluate the tolerability and efficacy of two different doses of levetiracetam (185 or 500 mg) in medication-naïve EP patients.

3 Study Design

3.1 General Design

This is a Phase 2, single-center, randomized, double-blind, placebo-controlled study to assess the tolerability and efficacy of levetiracetam. The study consists of an up to 4-week Screening period, one Baseline visit, and a follow-up telephone call the day after, as shown below. The Screening visit and Baseline visit may occur on the same day.

Sequence	Screening	Baseline	Telephone Follow-Up
Duration	Day -28 to Day 0	Day 1	Day 2

3.2 Primary Study Endpoints

The primary efficacy outcome measure for the R61 clinical trial is the change from baseline in hippocampal CBF measured by ASL; the Go/NoGo signal will be based on the effect size magnitude rather than formal hypothesis testing.

3.3 Inclusion of Subjects using Marijuana

THC use is very common among early psychosis patients (similar to cigarette smoking) most studies of early psychosis patients in the US and in Australia have found greater than 50% of patients use cannabis. Hence, for a treatment intervention to be generalizable to typical clinical populations, the intervention must be safe and effective in individuals who use THC. There is no reason to expect a negative interaction between cannabis and levetiracetam (no pharmacokinetic or pharmacodynamics 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.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria for EP Patients

1. Males and females 16 to 35 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 $\geq$ 2 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-IV TR (SCID for DSM-IV-TR)
4. Must not have taken an oral antipsychotic medication within 4 weeks prior to study enrollment or received a long-acting injectable antipsychotic within 3x the dosing interval.
5. If female of childbearing potential, patients must
    a) have a negative urine pregnancy test (all females 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 for EP Patients

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.
   c. use of marijuana within the 72 hours prior to MRI scanning by self report.
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. Metal implants, pacemaker, or other metal in the body or medicinal patch.
7. History of claustrophobia.
8. Currently taking any antipsychotic medication (within 4 weeks).

4.3 Inclusion Criteria for Healthy Controls

1. Males and females 16 to 35 years of age, inclusive, at time of informed consent
2. No prior history or current diagnosis of either schizophrenia, , schizoaffective disorder or schizophreniform disorder as established by a Non Patient version of the Structured Clinical Interview for DSMIV TR (SCID-NP)
3. Medically healthy as assessed by study physician.
4. If female of childbearing potential, participants must
    a) have a negative urine pregnancy test (all females 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 study1. Males and females 16 to 35 years of age, inclusive, at time of informed consent

4.4 Exclusion Criteria for Healthy Controls.

1. Current substance abuse or positive urine toxic screen.
2. Current or past Axis I psychiatric history (including Substance Use Disorder/Alcohol Use Disorder, with the exception of nicotine use 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. Metal implants, pacemaker, or other metal in the body or medicinal patch.
7. History of claustrophobia.
8. History of or current treatment with any antipsychotic medication.

4.5 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 or trained research coordinator 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 or trained coordinator 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.

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.

4.6 Subject Recruitment and Screening

Participants will be antipsychotic-free (i.e. no antipsychotic medication within 4 weeks of study enrollment) help-seeking right-handed males or females, ages 16-35, with early psychosis within 5 years of onset, meeting diagnostic criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder and currently exhibiting at least mild psychotic symptoms defined by a score of 2 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 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). For this study, subjects will be recruited from our network of NYU-affiliated institutions, including the NYU Medical Center Emergency Psychiatric Service and Adult Inpatient Psychiatry Unit (which have documented 1-3 EP unique patient visits monthly over the past 12 months), Bellevue Hospital Emergency Psychiatry Service, Walk-in Clinic and Inpatient Units (8-12 EP visits monthly), NYU Student Health Clinic (1-2

EP visits monthly) and NYU-Lutheran Hospital Emergency Service and Outpatient Psychiatry Clinics (4-8 EP unique EP patient visits monthly).

At the Bellevue Inpatient Psychiatry Unit, the staff will identify patients who are refusing medication and will introduce the research study to these patients. If the patients are interested in participating, Dr. Leonardo Lopez, the Director of the Inpatient Unit, will assess the clinical appropriateness of the individual to participate in research and will assess the individual's capacity to consent. Dr. Goff, a study MD/PhD or the nurse practitioner 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 will take place on the inpatient unit at Bellevue. Following the screening procedures, individuals who qualify to participate will be transported to the NYU CBI for the Baseline procedures via ambulance as per the existing protocol at the Inpatient Unit to transport patients within NYU and Bellevue facilities for clinical procedures.

Additionally, patients will also be recruited at the Nathan Kline Institute/Rockland Psychiatric Center and Gouverneur Health. All potential study participants will be referred by clinicians – clinicians will be asked to only refer individuals who they believe are appropriate for the study, can safely delay treatment for 24 hours 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. Subjects will also be recruited through advertisements in local newspapers. Additionally, the study team will use NYU's DataCore service to gather information from EPIC for current NYU patients who may be eligible. Fliers and brochures will be distributed by clinicians to potentially interested participants. Dr. Goff and the study coordinator will maintain relationships with clinicians at these institutions in order to generate referrals.

We will also be recruiting Spanish speaking subjects for our study. In order to recruit for 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.

Our goal is to recruit and randomize 1.5 subjects per month out of 14-25 potential subjects who are identified in our referral network monthly. In addition, we will study 10 healthy controls meeting the same exclusionary criteria as EP participants and group-matched on age and gender. To recruit healthy controls, the study team will utilize an existing study database that is locked and password protected. The study database contains contact information of well-screened healthy volunteers who can be selected based on relevant demographic and medical information meeting study inclusion criteria; this approach is the preferred approach since subjects have been pre-screened by trained study staff and a representative sample can be selected based on demographic information. Additional healthy control study participants will be recruited through advertisements in local newspapers, on research websites such as ResearchMatch, or on sites such as Craigslist. "Umbrella" approaches, such as listing this study on ClinicalTrials.gov, will also be used. All

recruitment materials will be approved by the IRB prior to distribution. Initial recruitment procedures via telephone will be performed by trained study staff.

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 (Manseau & Goff, 2015) In addition, a recent study found that effects of cannabis on cognition are small and after 72 hours are essentially nondetectable, whereas urine toxic screens may remain positive for 2 weeks due to THC absorption in adipose tissue.(Scott et al., 2018) Most studies of THC effects in healthy individuals and individuals with early psychosis have found transient increases of paranoia and memory impairment that return to normal within 6 hours. We selected a 72 hour period of cannabis abstinence based on self-report because in our experience self-report of research subjects has been quite reliable and confirmed by urine toxic screen, 72 hours is a conservative threshold to ensure that cognitive effects are unlikely to persist, and reliance on urine toxic screen is not reliable since it can remain positive for weeks after brain effects are no longer detectable. 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 who have not used cannabis within 72 hours prior to the MRI scan.

4.7 Remote Study Visits

4.7.1 Screening and Baseline Procedures

In light of the coronavirus pandemic, we have outlined a plan to protect patients and staff during study visits.

The NYU Langone study team will minimize in-person contact with study participants. All assessments that can be completed remotely will, optionally, take place via WebEx, a secure video conferencing platform. Participants without access to a computer or stable internet will be able to come to One Park for screening visits, and all department outlined precautions for in-person visits will be followed.

If consent can take place remotely, study staff 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 / the Center for Brain Imaging at 660 1st Avenue, with careful adherence to all institutional safety precautions and social distancing. The screening assessments that must be completed in-person include the following: vital signs, anthropometrics, physical exam, and collection of a urine specimen for toxicology analysis/pregnancy screening.

At the in-person Baseline visit, study staff will first complete the in-person assessments from the screening visits. 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 procedures.

4.7.2 Physical Exams / Laboratory Tests

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.

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 or prior to the baseline visit if the screening visit was conducted remotely. 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.

4.8 Subject Consent and Assent

All subjects will be evaluated by trained research coordinator or the nurse practitioner for capacity to consent and will be further evaluated by a licensed psychiatrist for safety and appropriateness to participate. Consent and assent will be completed by a trained coordinator or study clinician at One Park Avenue. 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 Emergency Psychiatry Service, Walk-in Clinic and Inpatient Units, NYU Student Health Clinic, NYU-Lutheran Hospital Emergency Service and Outpatient Psychiatry Clinics Outpatient Psychiatry Clinic, 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 initial treating clinicians to help identify potential subjects as well as provide interested individuals with basic study-related information. 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 for a screening visit at One Park Avenue. 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 Inpatient Unit only: Dr. Leonardo Lopez, the Director of the Inpatient Unit, will assess the clinical appropriateness of the individual to participate in research and will assess the individual's capacity to consent. Dr. Goff or the MD/PhD level clinician / nurse practitioner 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), will take place on the inpatient unit at Bellevue.

Process of Consent: Patients who are interested in participating in the study will meet with a trained research coordinator, an MD/PhD level clinician, or the nurse practitioner, who will review the consent form and assess the patient's capacity for participation in research in accordance with our standardized research procedures. After signing consent, participants will be assessed for eligibility. Subjects' capacity for participation in research will be reviewed by the coordinators in addition to an MD/PhD level clinician or a nurse practitioner during the screening process. The study team member obtaining the informed consent will take steps to ensure that the participant is capable of consenting and participating in the study. 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 procedure 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.

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.

Consent Forms: Consent forms will be stored in a locked file cabinet in folders labeled with the patients 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.

4.9 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 or Sponsor 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.

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).

5 Study Drug

5.1 Description

The study drug (Levetiracetam 185mg, 500mg, or placebo) will be supplied in a blinded and pre-labeled package.

5.2 Treatment Regimen

At least 24 and maximum of 46 early psychosis patients will be randomized to a single oral dose of levetiracetam 185 mg, 500 mg or placebo, which will be administered at Baseline (Visit 2).

5.3 Method for Assigning Subjects to Treatment Groups

Randomization will be in a 1:1:1 ratio in blocks of random size (3 or 6), stratified by diagnosis (schizoaffective vs. schizophreniform/schizophrenia).

5.4 Preparation and Administration of Study Drug

Study drug dispensation will take place at the NYU Langone Investigational Pharmacy. In order to ensure blinding, the 185mg, 500mg and placebo will be prepared in identical capsules. Once a participant passes the screening procedures, the Investigator, study physician, or nurse practitioner 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 a study physician or nurse practitioner will administer the drug.

5.5 Prior and Concomitant Therapy

Concomitant medications that are permitted during the study include Benadryl for sleep. Antipsychotics are not permitted due to interactions with neurotransmitters affected by levetiracetam.

5.6 Packaging

All capsules of the study drug will be received in one bulk shipment from Sentrix Pharmacy and Discount and will be stored at room temperature in a marked bottle at the NYU Langone Investigational Pharmacy.

5.7 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.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment at the NYU Langone Investigational 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 must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.8.2 Storage

All study drug will be kept at the NYU Langone Investigational Pharmacy at room temperature. No special handling or storage requirements are indicated.

5.8.3 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. Administration of study drug during Baseline (Visit 2) will be logged by study clinician or delegated site staff.

5.8.4 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

Study Participants will be seen in the clinic for 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. During the screening visit, healthy controls will complete the non-patient version of the SCID while EP participants will complete the patient version of the SCID for DSM-IV-TR. In addition, EP participants will complete the BPRS rating scale per inclusion criteria and both EP participants and health controls will complete the C-SSRS. During the baseline visit, EP participants will complete all procedures. Healthy controls will receive the second ASL scan but will not receive levetiracetam, and will not have blood drawn for levetiracetam levels.

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

The following procedures will be performed at Screening:

1. The Investigator, Study MD, trained research coordinator, or the nurse practitioner will provide the participants with informed consent documents and will explain the rationale for the study.
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.
4. Psychiatric history will be recorded and a SCID will be conducted by the study MD or nurse practitioner. The SCID for the DSM-IV (Modules A-D) will be used to assess the primary psychiatric diagnosis for patients. Module E of the SCID for the DSM-IV will be used to assess alcohol and substance dependence/abuse (except for cannabis). Cannabis use disorder will be assessed using Module E from the SCID for the DSM-5. The other modules for the SCID will not be performed as they do not relate to the inclusion/exclusion criteria. Healthy controls will complete the non-patient version of the SCID; EP participants will complete the patient version of the SCID for DSM-IV-TR.
5. Physical examination will be completed by study MD or health nurse practitioner. Vital signs will also be completed by a trained study team member.
6. A urine pregnancy test will be performed on all females of childbearing potential.
7. A urine drug screen test will be performed.
8. In addition, the following rating scales will be completed:
    a. Brief Psychiatric Rating Scale (BPRS) – EP Participants only.
    b. Columbia Suicide Severity Rating Scale (CSSR-S)

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

6.2 Baseline (Visit 2 – Day 1)

The following procedures will be performed at Baseline:

1. A trained research assistant will complete the BPRS (EP participants only), SAFTEE and MRI safety questionnaire.
2. Optional: EP participants may decide to complete the Matrics Consensus Cognitive Battery (MCCB) to evaluate cognition.
3. Study participants will undergo a 15-minute ASL imaging scan to measure blood flow in the brain. If time permits, study participants will undergo additional ASL imaging, up to 30 minutes total, and a spectroscopy scan, up to 30 minutes, to measure chemical activity in the brain.
4. Study medication will be administered by study MD or nurse practitioner (EP participants only).
5. HC participants will also complete an additional 15-minute ASL imaging scan, and an additional spectroscopy scan, up to 30 minutes. 2 hours after the first scan is completed.
1. All participants will have their corneal, hand and temporal artery (forehead) temperature measured while seated in a chair (1 minute procedure). (optional)

Two hours after administration of study medication, the following procedures will be performed in EP participants only:

2. A trained research assistant will complete the BPRS and SAFTEE.
3. Blood will be drawn (1 milliliter, or 0.25 teaspoons) for assay of levetiracetam levels.
4. Participants will complete a second 15-minute ASL imaging scan. If time permits, study participants will undergo additional ASL imaging, up to 30 minutes total, and an additional spectroscopy scan, up to 30 minutes.
5. Safety evaluation will be completed by study psychiatrist or nurse practitioner prior to discharge.
6. Participants will have their corneal, hand and temporal artery (forehead) temperature measured while seated in a chair (1 minute procedure). (optional)

Participants will be allowed to smoke cigarettes ad lib prior to and after imaging.

6.3 Follow-up Telephone Call (Day 2)

A study clinician or trained research assistant will contact the participant via telephone the following day to assess safety.

6.4 Optional follow up procedure:

Participants may undergo a second session of imaging and study drug administration following approximately 8 weeks of exposure to antipsychotic medication. They will receive the same study drug (placebo, low dose levetiracetam or higher dose levetiracetam) that they received at their first session. This follow-up imaging may provide important information about possible changes in brain activation following medication compared to healthy controls and whether levetiracetam is likely to benefit individuals when added to antipsychotic medication. If subjects elect to remain medication-free, after a delay of at least 2 weeks they may return for a second session of imaging and administration of levetiracetam or placebo. They will also receive the same study drug (placebo, low dose levetiracetam or higher dose levetiracetam) that they received at their first session. This will provide important information about whether hippocampal ASL changes with severity of psychosis and whether the effect of levetiracetam on hippocampal ASL changes with severity of psychosis. Individuals will receive the same remuneration for all three sessions (initial session, session following initiation of antipsychotic medication and session following a progression of psychotic symptom severity off-medication). Thus, participants are not incentivized to remain medication free—they will have an opportunity to repeat the procedure regardless of their decision about medication.

The follow-up procedure will include the following assessments:

1. Medical history, including patient demographics, and any concomitant medications use (including over-the-counter medications, vitamins, and supplements) will be reviewed and recorded.

2. Physical examination will be completed by study MD or nurse practitioner. Vital signs will also be completed by a trained study team member.
3. A urine pregnancy test will be performed on all females of childbearing potential.
4. A urine drug screen test will be performed.
5. In addition, the following rating scales will be completed:
    a. Columbia Suicide Severity Rating Scale (CSSR-S)
6. Subsequently, participants will complete the imaging section of the visit, which will include all procedures outlined above under Baseline (Visit 2 – Day 1)

7 Statistical Plan

7.1 Sample Size Determination

We are not testing for statistical significance and are not powering the study based on estimates of statistical significance. This is a pilot study to determine whether we have an adequate signal to proceed to a fully-powered clinical trial (R33). In keeping with the NIMH "fast fail" guidelines, we are selecting a threshold which will provide reasonable evidence to support continuing to the next phase of development. The decision to proceed to the R33 trial will be based on the demonstration of target engagement, defined by an effect size (Cohen's d) of .5 or greater in the mean reduction by levetiracetam of hippocampal perfusion measured by ASL compared to placebo, plus the demonstration of adequate tolerability defined by the absence of serious adverse events and confirmed by review of safety and tolerability data with the DSMB and NIMH staff. The decision whether to proceed and the selection of the optimal dose will be made in conjunction with NIMH staff.

7.2 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.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- <u>Related or possibly related to participation in the research</u> (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***.

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 <u>any one of the following</u> 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 psychiatrist will provide a psychiatric and medical evaluation as part of screening. A study MD or nurse practitioner will be present at the imaging center during the procedure and will evaluate the participant after completion of the scanning procedure to affirm that the participant is safe to leave after completing the study. Subjects will also be contacted by telephone the following day to affirm that they are stable. We will follow the same emergency procedures that are followed at the imaging center in the event of adverse reactions to contrast agents or other medical complications—the study physician (Dr. Goff or Urban) will respond to the event along with other CBI staff (including a nurse) and 911 will be called if needed. We are studying a low dose and an extremely 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. Psychiatric reactions occur but usually only after 1 week of daily dosing—we will be monitoring closely for psychiatric reactions to the single dose, even though this is highly unlikely to occur.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. 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 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 FDA*

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

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

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

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 on FDA Form 3500A (MEDWATCH Form; see Attachment XXXX), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

[Include the FDA Division, contact person, telephone number and fax number here]

8.4 Unblinding Procedures

If the study psychiatrist determines that unblinding is necessary for a subject's safety, the study psychiatrist 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 7 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 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 study will be halted by the PI if any serious safety issues arise pending review by the DSMB. Dose selection and titration schedule can be adjusted by the DSMB. Dr. Goff will not attend meetings of the DSMB. 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 quarterly data reports or at the time of continuing review. AEs will be reported to the IRB annually.

9 Data Handling and Record Keeping

9.1 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.

9.2 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.

9.3 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.

9.4 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. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". 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.

9.5 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.

10 Study Monitoring, Auditing, and Inspecting

10.1 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.

10.2 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.

11 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.

12 Study Finances

12.1 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.

12.2 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.

12.3 Subject Payments

There is no cost to subjects for participating. Round trip metro cards will be provided for each study visit.

EP participants will receive $200.00 for completion of the study and up to $150 for completion of optional study procedures.

- $50 for Screening (Visit 1)
- $150 for Baseline (Visit 2)
- Optional: $150 for follow-up imaging sessions
- Optional: $25 for MCCB at Baseline

Healthy controls will receive $100.00 for completion of the study and up to $175.00 for completion of the optional study procedures.

- $25 for Screening (Visit 1)
- $100 for Baseline (Visit 2)
- Optional: $75 for follow-up imaging

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

13 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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15 Attachments

Schedule of Events – EP Participants

	Screening, Visit 1	Baseline, Visit 2	Follow-up Phone Call	Follow-up, Visit 3 (Optional)	Follow-up Phone Call (Optional)
	Days -28 to 0	Day 1	Day 2	Day 3 (Week 8)	Day 4
Consent	X				
Authorization Form	X				
Inclusion/Exclusion Checklist	X				
Medical History	X				
Physical Exam	X				
Psychiatric History	X				
Demographics	X				
Concomitant Medications	X				
Vital signs	X				
Anthropometrics	X				
Urinalysis	X				
Urine Drug Screen	X				
Pregnancy Test	X				
Randomization	X				
Study drug dispensation		X			
SCID for DSM-IV-TR	X				
BPRS	X	X			
C-SSRS	X				
SAFTEE		X		X	
MCCB (optional)		X			
ASL Imaging		X		X	
Spectroscopy Imaging		X		X	
Levetiracetam blood levels		X			
Safety evaluation		X		X	
Adverse Event Form		X	X	X	X
Phone Call			X		X
Study Completion Form			X		

Schedule of Events – Healthy Controls

	Screening, Visit 1	Baseline, Visit 2	Follow-up Phone Call	Follow-up, Visit 3 (Optional)	Follow-up Phone Call (Optional)
	Days -28 to 0	Day 1	Day 2	Day 3 (Week 8)	Day 4
Consent	X				
Authorization Form	X				
Inclusion/Exclusion Checklist	X				
Medical History	X				
Physical Exam	X				
Psychiatric History					
Demographics	X				
Concomitant Medications	X				
Vital signs	X				
Anthropometrics	X				
Urinalysis	X				
Urine Drug Screen	X				
Pregnancy Test	X				
Randomization	X				
Study drug dispensation					
SCID-NP	X				
BPRS					
C-SSRS	X				
SAFTEE		X		X	
MCCB (optional)					
ASL Imaging		X		X	
Spectroscopy Imaging		X		X	
Levetiracetam blood levels					
Safety evaluation		X		X	
Adverse Event Form		X	X	X	X
Phone Call			X		X
Study Completion Form			X		