Study Protocol

An open-label, feasibility trial of adjunctive telmisartan in patients with treatment resistant schizophrenia

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A. BACKGROUND

1. Treatment resistant schizophrenia (TRS): TRS, which affects approximately 1/3 of patients with schizophrenia (Meltzer 1997). Currently available antipsychotic agents all fall into the “D2, me too" category. However, the abnormal presynaptic dopamine transmission usually seen in schizophrenia are absent in TRS (Demjaha et al 2012). Novel treatment approaches targeting alternative neural circuits or pathways are urgently needed.

Increased glutamate levels have been reported in antipsychotic-naïve or free patients with schizophrenia (de la Fuente-Sandoval et al 2013, Kraguljac et al 2013). Some studies suggested that antipsychotic treatment may reduce brain glutamate to the levels similar as in healthy controls (de la Fuente-Sandoval et al 2013, Kegeles et al 2012). However, recent studies found higher glutamate levels in the anterior cingulate cortex of antipsychotic-treated first episode patients with unremitted psychotic symptoms, and in treatment-resistant patients than in medication responders (Demjaha et al 2014, Egerton et al 2012). Abnormal glutamatergic signaling secondary to excessive stimulation of non-NMDA glutamate receptors (i.e., AMPA and kainate) may result in calcium influx and neuronal injury, which likely lead to clinical symptoms including cognitive impairment in patients with schizophrenia (Deutsch et al 2001).

3. Telmisartan, inflammation and oxidative stress: Studies have demonstrated that blockade of AT1R by telmisartan reduces inflammation, apoptosis, and oxidative stress (Jung et al 2007, Sato et al 2014). In addition, telmisartan activates the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), which regulates multiple pathways to counteract inflammation and oxidative stress, and promote neuroprotection (Min et al 2012, Pang et al 2012).

4. Potential benefit of telmisartan in schizophrenia: We recently reported that adjunctive treatment with telmisartan improves schizophrenia symptoms (Fan et al 2017). We now further propose to examine whether telmisartan targets glutamatergic signaling in the brain with neuroimaging to measure concentrations of cerebral glutamate metabolites in patients with TRS.

We propose a 4-week, open-label, feasibility trial of adjunctive telmisartan in adult patients with TRS. We plan to recruit 10 patients. All patients will receive telmisartan 80mg daily for 4 weeks.

B. SPECIFIC AIMS

Primary

1. Evaluate changes in blood biomarkers for inflammation and oxidative stress.

C. STUDY DESIGN

Screening visit: After signing a HIPAA compliant informed consent form, subjects will undergo a review of medical history and concomitant medications, and a physical exam. The MINI International Neuropsychiatric Interview will be performed to confirm the psychiatric diagnosis. Subjects will also have a urine drug screen, urine pregnancy test, a complete blood count (CBC), complete metabolic panel (CMP), vital signs, 12-lead ECG.

Baseline visit: After the screening visit, eligible subjects will undergo: 1) vital signs; 2) efficacy assessment battery; 3) safety assessment battery; 4) blood biomarkers for inflammation and oxidative stress, including glutathione (GSH), glutathione disulfide (GSSG), high sensitivity C reactive protein (hsCRP), interleukin 6 (IL-6) and tumor necrosis factor α (TNFα).

Week 1, 2, 3 visits: Vital signs will be assessed. Treatment compliance and possible adverse effects will be evaluated. Subjects will receive one week supply of study medication. Urine drug screen will be repeated at week 2 only.

Week 4 visit: Subjects will undergo: 1) vital signs; 2) efficacy assessment battery; 3) safety assessment battery; 4) blood biomarkers for inflammation and oxidative stress, including GSH, GSSG, hsCRP, IL-6 and TNFα. Lab samples for CBC and CMP will also be collected.

Early termination visit: Subjects will undergo: 1) vital signs; 2) safety assessment battery; 3) CBC and CMP.

D. STUDY POPULATION

Subject eligibility

Inclusion Criteria

Each subject must meet all of the following criteria to be eligible for this study:

1. Age 18-65 years inclusive.
2. Primary diagnosis of Schizophrenia established by a structured psychiatric evaluation (MINI) based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) criteria.
3. A Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987) total score ≥ 70 with a score of ≥ 4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.
4. A score of ≥4 on the Clinical Global Impression—Severity (CGI-S) (Guy, 1976).
5. Must have ongoing antipsychotic treatment for at least 8 weeks, with a stable dose for at least 4 weeks. Subjects who have failed to achieve clinically-recognized symptom reduction to at least 1 marketed antipsychotic agent, given at a Physician Desk Reference (PDR)-defined therapeutic dose for ≥ 8 weeks during the past 12 months, will be eligible.
6. Women of childbearing potential must have a negative pregnancy test performed at screening visit prior to randomization. Women enrolled in this trial must use adequate birth control.
7. Understands and is able, willing, and (in the opinion of the investigator) likely to fully comply with the study procedures and restrictions.

Exclusionary Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Psychiatrically unstable.
2. Subjects with any clinically significant abnormalities as determined by medical history, physical exam, clinical and lab evaluation suggestive of an underlying disease state that may, in the opinion of the investigator, confound the results of study, increase risk to the subject, or lead to difficulty complying with the protocol.
3. Current insulin treatment for diabetes.
4. History of immunosuppression.
5. Current or recent radiation or chemotherapy treatment for cancer.
6. Chronic use of steroids (except local use or inhaler).
7. Pregnancy or breastfeeding.
8. Use of diuretics, ACE inhibitors, spironolactone, potassium supplements, digoxin or warfarin because the possible drug-drug interaction with telmisartan.
9. Tested positive for the urine drug screen.

10. Subjects at imminent risk of suicide or injury to self or others, as per the opinion of the investigator, or history of significant suicide attempt within the last 6 months as per the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Subjects that have taken an investigational drug or taken part in a clinical trial within 30 days prior to screening.
12. Subjects with a current (within the last 3 months) DSM-V diagnosis of alcohol or substance use disorder (excluding nicotine and caffeine) as established by the clinical assessment (MINI) at the screening visit will be excluded.
13. Any other reason that, in the opinion of the investigator, would compromise patient safety or integrity of the study.
14. Subjects with the lab values defined as exclusionary safety values in Table 1.

Table 1. Exclusionary Safety Values of Potential Clinical Concern

Complete Blood Count	
Leukocytes	<2 or >17.5 x 10^3/mm^3
Platelets	<75 or >700 x 10^3/mm^3
Comprehensive Metabolic Panel	
Sodium	<1.1 times the lower limit or >1.1 times upper limit of the reference
Potassium	<1.1 times the lower limit or >1.1 times upper limit of the reference
Blood Urea Nitrogen (BUN)	>1.3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
Glomerular Filtration Rate	< 60
Aspartate amino transferase (AST)	>3 times upper limit of the reference range
Alanine amino transferase (ALT)	>3 times upper limit of the reference range

E. ASSESSMENT PROCEDURES

Medical history
A detailed medical history will be obtained by the PI or designee during the screening visit. This will include information regarding the subject' full history of medical and psychiatric conditions, diagnoses, procedures, treatments, demographic information, and any other noteworthy medical information, including suicidality, with dates of start and finish. Any updates to medical history information that the PI or designee becomes aware of will be captured throughout the study.

Physical exam
The PI, or medically qualified designee, will perform the physical exam at the screening visit. If any clinically significant change is noted from screening, it will be reported as an adverse event and will be followed up to resolution or upon reaching a stable endpoint.

Vital signs
Evaluation of vital signs will be performed by qualified personnel after the subject has been supine for 5 minutes, and will include a measurement of systolic and diastolic blood pressure, pulse rate, and oral temperature. Systolic and diastolic blood pressure should be then measured from supine to standing to assess orthostatic hypotension. Vital sign measurements will be obtained at the time points indicated in the schedule of events (SOE).

If clinically significant findings, as determined by the PI or medically qualified designee, occur in any vital sign measurement, that measurement should be captured as an adverse event and will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

Laboratory assays
Fasting blood samples will be obtained and laboratory tests will be performed at the time points indicated in the SOE.

Complete blood count (CBC): White blood cell (WBC) count with differential (absolute neutrophil count, lymphocytes, monocytes, basophils, and eosinophils), red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), and platelet count.

Comprehensive metabolic panel (CMP): glucose, sodium, potassium, calcium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, calculated glomerular filtration rate, uric acid, phosphorus, magnesium, total protein, albumin, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), total bilirubin.

Blood levels of GSH, GSSG, hsCRP, IL-6, TNFα: Blood samples for GSH, GSSG, hsCRP, IL6 and TNF-alpha will be run at the UMass Memorial labs.

The PI, or medically qualified designee, should mark either "CS" for Clinically Significant or "NCS" for Not Clinically Significant in the margin of the laboratory result source document for items outside the normal range.

Urine drug screen: The test includes the following substances: opioids, cocaine, amphetamines, methadone, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine.

Urine pregnancy test: The test will be performed in female subjects of childbearing potential using a dipstick urine test during the screening visit.

12-Lead Electrocardiogram (EGG)
A 12-lead ECG will be taken at following a supine rest for 5 minutes. The ECGs will be reviewed by the PI or medically qualified designee, and a cardiologist to assess any immediate abnormalities. The findings of the ECGs will be marked as normal, abnormal-not clinically significant, or abnormal-clinically significant.

Psychiatric diagnostic assessment
Mini International Neuropsychiatric Interview (MINI v7.0): The MINI 7.0 is a short clinician administered structured diagnostic interview for major psychiatric diagnoses in DSM-5 with an administration of around 20 minutes.

Efficacy assessment battery
The Positive and Negative Syndrome Scale (PANSS) (KAY ET AL 1987): The PANSS will be used to measure symptom severity in this trial. The PANSS is a 30-item questionnaire used to evaluate schizophrenia symptoms, based on the clinical interview as well as reports of family members or primary care hospital workers. The PANSS consists of Positive Symptom subscale (7 items), Negative Symptom subscale (7 items), and General Psychopathology subscale (16 items). Each item is scored on a 7-point scale with higher scores representing increasing levels

of psychopathology: 1) Absent, 2) Minimal, 3) Mild, 4) Moderate, 5) Moderate severe, 6) Severe, and 7) Extreme.

Scale for Assessment of Negative Symptoms (SANS) (Andreasen 1989): The SANS assesses 5 domains: affective flattening, alogia, avolition/apathy, anhedonia/asociality, and attention. Within each domain, separate symptoms are related from 0 (absent) to 5 (severe).

Clinical Global Impressions–Severity (CGI-S) and Clinical Global Impressions–Improvement (CGI-I) Scales (Guy, 1976): The CGI-S is an observer-rated scale that measures illness severity. The severity is measured using a 7 point Likert scale: 1) Normal, not at all ill, 2) Borderline mentally ill, 3) Mildly ill, 4) Moderately ill, 5) Markedly ill, 6) Severely ill, and 7) Among the most extremely ill patient. The CGI-I is an observer-rated scale that measures illness improvement. Improvement is measured using a 7 point Likert scale: 1) Very much improved, 2) Much improved, 3) Minimally improved, 4) No change 5) Minimally worse, 6) Much worse, 7) Very much worse.

Safety assessment battery

Adverse Events (AE): Adverse events will be monitored at each study visit. The PI or medically qualified designee will review adverse events at every study visit. AE information is collected and recorded starting on the day the consent is signed until the end of an individual's participation in the study.

The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al 2007): The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening. The C-SSRS will be performed to assess suicidal ideation and behavior. It contains a 1-to-5 rating scale for suicidal ideation of increasing severity (from a "wish list to die" to an "active thought of killing oneself with plan and intent"). The time frame is the past six months for the Baseline/Screening scale and since the last visit for the Since Last Visit scale.

Monitoring and Reporting of Adverse Events

Continuous data and safety monitoring will be conducted by the PI. Any adverse effect reported to study personnel will be reviewed with the PI or sub-investigator who will determine whether they are mild, moderate or severe and the likelihood (definitely/possible/probable) that it is related to the study medication. All AEs will be followed until resolution, until deemed stable by the investigator or until the subject is deemed by the investigator to be lost to follow-up

Intensity	**Definition**
Mild	Causes transient or mild discomfort ; no limitation of usual activities; no medical intervention required.
Moderate	Causes mild to moderate limitation in activity; some limitation of usual activities: no or minimal medical intervention or therapy is required.
Severe	Causes marked limitation in activity; some assistance is usually required; medical intervention or therapy is required; hospitalization is probable.

The PI is ultimately responsible for assessing and reporting all adverse events as outlined in the study plan. The assessment of AEs may be delegated to a medically qualified Sub-Investigator, trained on this study plan. The PI will report adverse events to the IRB in accordance with IRB guidelines.

Reporting of Serious Adverse Events

The PI will report all SAEs to UMass IRB. The PI will inform the IRB regarding any AE (does not have to be causally related) that is both serious and unexpected; or that represents a series of AEs that, on analysis, is unanticipated, or occurs at an unanticipated frequency, or otherwise represents an unanticipated safety risk to the study subject in accordance with UMass IRB reporting guidelines.

F. TREATMENT

Dosing
Subjects will start telmisartan 40mg once a day during week 1; the dose will be increased to 80mg (target dose) or as tolerated during the remaining weeks.

Study medication Supplies and Administration
Telmisartan has 20mg, 40mg and 80mg dose strengths. Subjects will be given one 40mg pill per day during week 1, and one 40mg pill plus two 20mg pills per day for the remaining weeks.

Potential risks of telmisartan
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is therefore recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan. Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR). Telmisartan can cause fetal and neonatal morbidity and death when administered to pregnant women. In volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan. Adverse events occurring at an incidence of 1% or more in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, include upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis. Common adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. In placebo-controlled trials involving 1,041 patients treated with various doses of telmisartan (20-160mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed. (Micardis® package insert, revised, February 2018).

For the proposed study, patients will be excluded if they are on diuretics, ACE inhibitors, digoxin or warfarin because the possible drug-drug interaction with telmisartan. Subjects will be excluded from the study if they have an abnormal potassium blood level out of the defined cutoff range at screening. Subjects will be terminated from the study if they have an abnormal potassium blood level at screening. For female patients of childbearing potential, a urine pregnancy test must be negative at screening. These patients must agree to practice appropriate birth control methods during the study.

Discontinuation from Study Treatment

The reasons for early discontinuation include the following: 1) request of patient, 2) decision of the PI, 3) serious adverse event.

Procedures for discontinuation from study

If a patient discontinues from the study before randomization, then no further follow-up will be expected. However, if the patient discontinues after randomization, but before receiving any study treatment, the patient will be asked to return for a final study visit, during which the procedures outlined in the early termination visit procedures will be completed, including AEs and concomitant medication assessments.

If a patient discontinues from the study before completion and has received the dose of study drug, the patient will be asked to return for a final study visit, at which the procedures outlined in the early termination visit will be completed. Every effort will be made to follow up with patients who discontinue from the study. If the patient refuses follow-up, the reason for the refusal and last contact date should be documented in the CRF.

G. ETHICAL CONSIDERATION

Informed consent

The investigator must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

All subjects will receive the consent form for the study. Any questions, concerns, or ambiguities will be clarified by the PI or medically qualified designee prior to the patient signing consent. Subjects will sign informed consent and only then will begin participation in the study.

IRB review

Before study initiation, the investigator will have written and dated approval from the UMass IRB for the protocol, consent form, patient recruitment materials and process (e.g., advertisements), and any other written information to be provided to subjects.

The investigator will provide the IRB with reports, updates, and other information (e.g., safety updates, amendments) according to regulatory requirements and institution procedures.

H. DATA ANALYSIS

There are no published data yet about the effect of telmisartan treatment on the levels of glutamate and GABA in the brain in patients with schizophrenia. The study is intended to provide preliminary evidence of target engagement in the brain, as well as an indication of effect size for the purpose of designing future studies. Paired sample t tests will be used to examine the difference in outcome measures between week 4 and baseline. In addition, Pearson correlation analysis or partial correlation analysis will be used to examine the relationship between changes in biomarkers and changes in symptom outcome measures.

INVESTIGATOR STUDY PLAN- REQUIRED

SCHEDULE OF EVENTS

Procedure	Visit	Screening	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Early Termination (ET) Visit
	Study Week		Week 0	Week 1	Week 2	Week 3	Week 4	
Medical History		X						
Physical Exam		X						
MINI		X						
Pregnancy Test (Females only)		X						
ECG		X						
Labs (CMP, CBC)		X					X	X
Labs (GSH, GSSG, hsCRP, IL-6, TNFα)			X				X	
Vital Signs		X	X	X	X	X	X	X
Urine Drug Screen		X			X			
Adverse Events			X	X	X	X	X	X
PANSS			X				X	
SANS			X				X	
CGI-S and CGI-I			X	X	X	X	X	
CSSRS			X				X	X
Drug dispensing			X	X	X	X		
Patient Medication Log			X	X	X	X		X
Pill Count				X	X	X	X	X

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