Statistical Analysis Plan

(SAP)

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

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Participants

Adult outpatients with schizophrenia were recruited from the UMass Memorial Healthcare System an in Central Massachusetts. Psychiatric diagnosis was determined using the structured psychiatric evaluation (MINI) based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) criteria. Other inclusion criteria included: 1) age 18-65 years; 2) 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; 3) A score of ≥4 on the Clinical Global Impression—Severity (CGI-S) (Guy, 1976); 4) 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; 5) Female subjects of childbearing potential must have a negative pregnancy test performed at screening visit prior to randomization. Female subjects enrolled in this trial must use adequate birth control; 6) Understands and is able, willing, and (in the opinion of the investigator) likely to fully comply with the study procedures and restrictions. Exclusion criteria were: 1) Psychiatrically unstable; 2) Current insulin treatment for diabetes; 3) 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; 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. The study was approved by the institutional review board of the University of Massachusetts Medical School and followed the Good Clinical Practice guideline.

Procedures:

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.

Statistical Analysis: A paired t-test was performed.