Safety and Efficacy of Fingolimod in Schizophrenia Patients who have Suboptimal Responses to Antipsychotic Drug Treatment

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1.0 Background

Schizophrenia is a severe brain disorder that begins during the teenage years and early twenties and typically progresses to a life-long chronic illness marked by psychotic symptoms, cognitive impairment and poor functioning. A leading hypothesis to account for the symptoms and cognitive dysfunction of this disorder is that abnormalities exist in cortical circuits, particularly in frontal and temporal areas. An interest in cortical circuitry has led to a focus on the integrity of cortical white matter tracts as possibly contributing to the pathophysiology of this illness. Indeed, several lines of evidence have supported abnormalities in white matter structure and function in schizophrenia (1). Numerous myelin-related genes and their functional expression have been associated with schizophrenia (1, 2). Moreover, quantitative and qualitative abnormalities in prefrontal cortical oligodendrocytes have been found in postmortem studies (3, 4). MRI-determined volumetric reductions in prefrontal white matter have been reported in schizophrenia (5). Advances in MRI technology have enhanced the ability to study white matter pathology in vivo. Diffusion tensor imaging (DTI) and fractional anisotropy (FA) provides an assessment of the density and integrity of white matter tracts (6). Decreased FA has been reported in many de-myelinating diseases including multiple sclerosis (MS), leukodystrophies, and HIV (1). Numerous studies using DTI have reported decrements in FA in schizophrenia with the most consistent abnormalities occurring in frontal cortical white matter (7). Also, FA has been shown to be sensitive to therapeutic drug effects in MS which supports DTI-derived FA as an outcome measure in clinical trials of neuroprotective agents (8).

The etiopathophysiological mechanisms that have been proposed to account for white matter abnormalities in schizophrenia include oxidative stress, altered apoptosis and autoimmune mechanisms (9, 10). The possibility that brain abnormalities in schizophrenia may be secondary to autoimmune factors has been supported by a large literature that includes signs of inflammation and microglia activation in postmortem tissue and CSF (11), altered cytokine levels (12) and association of HLA genotypes and schizophrenia (13-15). Based on the above literature, agents that increase myelin density and integrity through autoimmune mechanisms would be intriguing therapeutic candidates to consider for proof of principle trials in schizophrenia.

Fingolimod (FTY720, approved as Gilenya™) is a sphingosine-1-phosphate (S1P) receptor modulator and recently licensed in the USA and several other countries for relapsing forms of multiple sclerosis (MS). It is administered as a once per day oral preparation. In registration clinical trials, it had positive effects on brain atrophy, MRI-determined axonal lesions and relapse rates (16-18). Significant improvement in the mean number of MRI assessed T1 gadolinium (Gd) enhanced lesions/patient and the percentage of patients free of T1 Gd-enhanced lesions was observed within 6 months of treatment and there was evidence of clinical improvement as early as 2 months after treatment initiation (16). In a one year trial, it reduced the number of MS relapses by 52%. Eighty three percent of patients taking fingolimod remained relapse free compared to 70% taking interferon beta-1a, an MS standard of care. In a two year trial, 70% of patient taking fingolimod remained relapse free compared to 46% for placebo treated

patients. In these studies, there was a significantly lower number of new or enlarged white matter lesions compared to interferon beta-1a and placebo (16).

Although not fully understood, fingolimod may have multiple mechanisms by which it prevents relapses in MS (19). It is metabolized to fingolimod-phosphate which blocks the capacity of lymphocytes to egress from lymph nodes. This results in a reduced number of peripherally circulating lymphocytes. It is hypothesized that fingolimod attenuates the number of lymphocytes entering the CNS and thereby imparts protection from autoimmune-induced neuropathology (20). In addition, there is evidence that fingolimod has direct effects on brain tissue. It is highly lipophilic and readily crosses the blood-brain barrier resulting in substantial CNS concentration with particularly high levels found in myelin tissue (20). S1P receptors are located on all brain cell types. S1P signaling in oligodendrocytes has been shown to play roles in cell survival (21) and proliferation (22). Stimulation of S1P receptor by fingolimod demonstrated neuroprotective properties by preserving oligodendrocytes against apoptosis mediated by growth factor deprivation and in models of glial-derived oxidative stress (21). In addition, fingolimod has been shown to enhance oligodendrocyte precursor cell mitogenesis and to produce re-myelination (23, 24). Further, anti-inflammatory properties are supported by the decreased gadolinium enhancing lesions found in the clinical trials of MS (16). Thus, this compound appears to have multiple actions including immunomodulatory, neuroprotective, myelin replenishing and anti-inflammatory properties that may mediate its therapeutic effects. Because white matter abnormalities may underlie the pathophysiology of schizophrenia and the possibility that these alterations may arise from autoimmune and/or oxidative stress mechanisms, we propose to assess the effects of fingolimod on measures of white matter density and clinical outcomes in patients with schizophrenia.

2.0 Rationale

Safety of Fingolimod

To date (May, 2015), more than 36,000 patients have been treated with fingolimod for MS. The most serious side effects associated with fingolimod are reduced heart rate, atroventricular conduction deficits, risks of infections, posterior reversible encephalopathy syndrome, decreased pulmonary function, elevated liver enzymes, fetal risk and macular edema.

The most common side effects are headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity.

In clinical trials following initial dosing, bradycardia occurred commonly and symptomatic bradycardia occurred in 0.6% of patient treated with fingolimod and 0.1% treated with placebo. In controlled clinical trials, first-degree AV bock after the first dose occurred in 4.7% of patients receiving fingolimod and 1.6% of patients on placebo. In a study of 697 patients with available 24-hour Holter monitoring data after their first dose (N=351 receiving fingolimod and N=346 on placebo), second-degree AV blocks (Mobitz Types I [Wenckebach] or 2:1 AV blocks) occurred in 4% (N=14) of patients receiving

fingolimod and 2% (N=7) of patients on placebo. Of the 14 patients receiving fingolimod, 7 pateints had 2:1 AV block (5 patients within the first 6 hours postdose and 2 patients after 6 hours postdose). Reduced heart rate is most pronounced six hours after the initial dose of fingolimod and normalizes within one month of treatment, though there have been cases of delayed cardiac effects. Because of these cardiac effects, all patients are required to remain in the clinic for cardiac monitoring for six hours following the initial dose of fingolimod, when used for MS. Concomitant drugs that lower heart rate (e.g., beta blockers) are to be avoided and patients with pre-existing cardiac conduction deficits may not be appropriate for fingolimod treatment.

Fingolimod also causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. Fingolimod may therefore increase the risk of infections, some serious in nature. Additionally, in clinical trials there have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in patients receiving fingolimod. Dyspnea was reported in 9% of patients receiving fingolimod 0.5 mg and 7% of patients receiving placebo in MS placebo-controlled trials. Also, in 2-year placebo-controlled clinical trials, elevation of liver transaminases to 3-fold the upper limit of normal (ULN) or greater occurred in 14% of patients treated with fingolimod 0.5 mg and 3% of patients on placebo. Elevations 5-fold the ULN or greater occurred in 4.5% of patients on fingolimod and 1% of patients on placebo. Based on animal studies, fingolimod may cause fetal harm. Fingolimod also increases the risk of macular edema, the risk of which is increased in patients with a history of uveitis and patients with diabetes mellitus. In 2-year, double-blind, placebo-controlled studies in patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 1.5% of patients (11/799) treated with fingolimod 1.25 mg, 0.5% of patients (4/783) treated with fingolimod 0.5 mg and 0.4% of patients (3/773) treated with placebo.

Rationale of Study Period

Two months was chosen as the treatment period because it is an adequate duration for an initial safety assessment in schizophrenia of early emerging adverse events. In addition, significant effects in MS patients were observed as early as two months post randomization (16). Further, Garver et al (25) reported improvement in DTI-determined white matter integrity in patients with schizophrenia who responded to antipsychotic drug therapy in only 28 days. Thus, if fingolimod has a large effect in improving the symptoms of schizophrenia, it may be detected in a two month study of 40 subjects.

3.0 Specific Aims

The **primary aims** of this clinical study are to 1) assess the safety of fingolimod in subjects with schizophrenia being treated with antipsychotic drugs, and 2) determine if fingolimod compared to placebo results in symptomatic improvement as measured by reductions in PANSS total score.

Secondary aims include assessment of the effects of fingolimod versus placebo on memory, cognition, positive and negative symptoms, and plasma cytokine levels in addition to gathering preliminary data on the effects of fingolimod on DTI-derived FA and other MRI indices.

4.0 Study Design

This will be a single site safety and proof of concept study conducted at the Indiana University Psychotic Disorders Program. Forty subjects with schizophrenia or schizoaffective disorders with suboptimally treated symptoms (despite previous and/or current antipsychotic medication exposure) (39) will be randomized 1:1 to double-blind treatment with fingolimod or matched placebo for duration of 8 weeks.

All subjects will be admitted to the Indiana Clinical and Translational Sciences Institute Clinical Research Center (CRC) and remain hospitalized for the first 24 (+/- 2) hours post initial dose of study medication. The CRC is located in Indiana University Hospital and has 24 hour staffing with nurses skilled in conducting Phase 1 and Phase 2 investigational drug studies.

5.0 Study Population (Inclusion/Exclusion Criteria)

Inclusion criteria:

1. 18 to 65 years of age at study entry
2. Male or female
3. DSM IV-TR Diagnosis of schizophrenia or schizoaffective disorder as confirmed by Structured Clinical Interview for DSM-IV-TR (SCID)
4. Previous and/or current exposure to *one* of the following antipsychotic medication (clozapine, olanzapine, risperidone, paliperidone, haloperidol, and quetiapine) as defined by a minimum of 8 weeks in duration greater than or equal to the Food and Drug Administration approved therapeutic range for schizophrenia at time of study entry OR previous and/or current exposure to *two* antipsychotic medications as defined by a minimum of 4 weeks in duration greater than or equal to the Food and Drug Administration approved therapeutic range for schizophrenia at time of study entry
5. Able to give informed consent (or has an active guardian or LAR who is willing to consent on behalf of the subject)
6. Subjects must be willing to participate in a minimum of 1 day of inpatient hospitalization
7. Inpatient or outpatient
8. Clinical stability as defined by:
    a. CGI-S score of less than or equal to 4 (moderately ill) at randomization AND
    b. Subjects must not have experienced an exacerbation of their illness within 4 weeks prior to randomization, leading to an intensification of psychiatric care in the opinion of the investigator. Examples of intensification of care

include, but are not limited to: inpatient hospitalization, day/partial hospitalization, outpatient crisis management, or psychiatric treatment in an emergency room AND

c. Antipsychotic treatment stability for at least 4 weeks prior to randomization (no change in antipsychotic dosing or addition of any new antipsychotic medication)

9. Female subjects of childbearing potential must test negative for pregnancy at screening visit and agree to use a single, effective, medically acceptable method of birth control for the duration of the study and for two months following cessation of study medication
10. Subjects must agree not to consume tonic water for the duration of the study and for two months following cessation of study medication.
11. Sub-optimally treated positive symptoms OR negative symptoms at the time of study entry as defined by the Brief Psychiatric Rating Scale (BPRS):
    a. BPRS positive symptom factor (conceptual disorganization, hallucinations, suspiciousness, and unusual thought content) score of greater than or equal to 4 on any one item or a sum greater than or equal to 8 on the factor.
    b. BPRS negative symptom factor (motor retardation, blunted affect, and inappropriate affect) score of greater than or equal to 4 on any one item or a sum greater than or equal to 6 on the factor.

Exclusion criteria:

1. Subjects who are considered prisoners per the Indiana University Standard Operating Procedures for Research Involving Human Subjects.
2. Subjects with current acute, serious, or unstable medical conditions, including, but not limited to: inadequately controlled diabetes, asthma, COPD, severe hypertriglyceridemia, recent cerebrovascular accidents, acute systemic infection or immunologic disease, unstable cardiovascular disorders, malnutrition, or hepatic, renal gastroenterologic, respiratory, endocrinologic, neurologic, hematologic, or infectious diseases
3. Clinically significant electrocardiogram (ECG) abnormality prior to randomization as defined by: subjects with a corrected QT interval (Bazett's; QTcB) >450 msec (male) or >470 msec (female) prior to randomization (based on the cardiologist overread) OR sinus bradycardia (resting heart rate < 50 beats per min). Repeat ECGs will be conducted at the discretion of the principal investigator or medical designee
4. Subjects with hypokalemia, hypomagnesemia, or congenital long-QT syndrome
5. Subjects with known medical history of Human Immunodeficiency Virus positive (HIV+) status or tuberculosis
6. Subjects with an active seizure disorder
7. Pregnant or lactating women or women who plan to become pregnant or will be lactating within two months after cessation of study drug
8. Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculoperitoneal shunt, or other contraindication to undergoing an MRI scan..

9. Subjects taking class1a or class 3 antiarrhythmic agents, beta blockers, diltiazem, verapamil, digoxin, tricyclic antidepressants, warfarin, ketoconazole, ketamine.
10. Subjects who will be likely to need a live attenuated vaccine during the course of the study or within two months after stopping study medication
11. Subjects with no history of chicken pox or chicken pox vaccination, or with a negative VZV titer
12. Active herpes simplex outbreak, mononucleosis, or zoster.
13. Subjects with histories of ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrest, cerebrovascular disease, unexplained or recurrent syncope, cardiac conduction prolongations (prolonged P-R interval), cardiac arrhythmias, symptomatic bradycardia, decompensated heart failure requiring hospitalization or Class III/IV heart failure, or severe untreated sleep apnea
14. Subjects receiving antineoplastic, immunosuppressive, or immune modulating therapies
15. Subjects with history of macular edema or uveitis based on medical history
16. Known IQ less than 70 based on medical history
17. Subjects with current active fungal or viral infection based on history and physical examination
18. Current DSM IV-TR diagnosis of substance dependence (excluding caffeine and nicotine)
19. Positive urine toxicology screen for the following: cocaine, barbiturates, methamphetamine, opiate, methadone, phencyclidine, or amphetamine prior to randomization
20. Test positive for (1) Hepatitis C virus antibody, (2) Hepatitis B surface antigen (HBsAg) with or without positive Hepatitis B core total antibody, or (3) HIV 1 or 2 antibodies
21. Subjects with moderate to severe renal impairment as defined by creatinine clearance (CrCl) < 60 ml/min (measured by the Cockcroft-Gault equation) at screening
22. Subjects with hepatic impairment as defined by liver transaminases or total bilirubin > 3 × upper limit of normal (ULN)
23. Subjects considered a high risk for suicidal acts – active suicidal ideation as determined by clinical interview OR any suicide attempt in 90 days prior to screening
24. Subjects who have participated in a clinical trial with any pharmacological treatment intervention for which they received study-related medication in the 4 weeks prior to screening OR Subjects currently receiving treatment (within 1 dosing interval plus 4 weeks) with an investigational depot formulation of an antipsychotic medication
25. Subjects who demonstrate overtly aggressive behavior or who are deemed to pose a homicidal risk in the investigator's opinion

6.0 Subject Recruitment

Subjects will be recruited through referring community mental health centers, treatment providers, invited to participate if they are included in our registry, and self-referrals through advertisement and word-of-mouth.

7.0 Study Procedures

See Study Procedures Table Attachment 1

8.0 Clinical Assessments and Procedures

The following assessments will be administered at one or more visits during the duration of the study according to the study procedures tables (Attachment 1). All assessments will be completed by study personnel based on interviews with the subject or based on questionnaires completed by the subject (i.e. EuroQol).

Diagnostic Interview
The Structured Clinical Interview for DSM-IV-TR (SCID-I/P Patient Edition) will be used to confirm the diagnosis of a psychotic disorder and/or rule out other diagnoses. The SCID-IP is a semi-structured interview designed to evaluate DSM-IV-TR Axis I diagnoses.

The Brief Psychiatric Rating Scale (BPRS)
The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms (38). Some of the items (eg mannerisms and posturing) can be rated simply on observation of the subject; other items (eg anxiety) involve an element of self-reporting by the subject.

Clinical Global Impressions Severity Scale (CGI-S)
The CGI-S will be used for repeated evaluations of global psychopathology (34-35). The CGI-S scale is widely used in schizophrenia research and is a single 7-point Likert scale rating severity of psychopathology on a scale of 1 (normal, not ill) to 7 (very severely ill).

Clinical Global Impressions Severity Improvement Scale (CGI-I)
The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point Likert scale, ranging from very much improved (1) to very much worse (7) (34-35).

The Positive and Negative Syndrome Scale (PANSS)
The PANSS will be the primary assessment instrument for psychopathology (27). The PANSS contains 30 items that assess symptoms of psychotic disorders including positive, negative and general psychopathology. The PANSS was chosen because of its widespread use in clinical studies of psychosis, and its demonstrated reliability in assessing psychopathology across diverse patient populations.

Personal and Social Performance Scale (PSP)
The PSP scale (32) is a 100-point, single item, clinician rated scale to assess 4 domains of functioning, including personal and social relationships, socially useful activities, self-care and disturbing and aggressive behaviors.

EuroQol Questionaire-5 dimensions (EQ-5D)
The EQ-5D (30) is a generic, multidimensional, health-related, quality-of-life instrument that contains two parts: a health status profile, and a visual analog scale to rate global health-related quality of life.

Quality of Life Scale (QLS)
Quality of Life Scale (QLS), a 21-item scale based on a semistructured interview designed to assess deficit symptoms.

Abnormal Involuntary Movement Scale (AIMS)
The AIMS is a 12-item scale designed to records the occurrence of dyskinetic movements (29). Items 1 to 10 are rated on a 5-point scale, with 0 being no dyskinetic movements and 4 being severe dyskinetic movements. Items 11 and 12 are yes/no questions regarding the dental condition of as subject.

Barnes Akathisia Scale (BARS)
The BARS is used to rate drug-induced akathisia (31). Symptoms are rated on a 4-point scale, with 0 being no akathisia and 3 being severe akathisia. A global clinical assessment of akathisia is then scored on a 6-point scale, with 0 being no evidence of akathisia and 5 being severe akathisia.

Simpson Angus Scale (SAS)
The SAS is a 10-item scale used to evaluate the presence and severity of drug induced Parkinsonism (33). Each item is rated from 0 to 4.

Busch Francis Catatonia Rating Scale (BFCRS) Evaluation
The BFCRS consists of 23 sections supplemented by specific instructions to standardize the evaluation (26). Seventeen sections are scored on a 0 to 3 scale while the last 6 sections are rated as either absent (“0”) or present (“3”). The total score ranges from 0 to 69.

Brief Assessment of Cognition in Schizophrenia (BACS)
The BACS (Keefe et al, 2004) is a battery specifically designed to measure treatment-related changes in cognition, and has alternate forms, thus minimizing practice effects. The battery includes brief assessments of executive functions, verbal fluency, attention, verbal memory, working memory and motor speed, and generates a composite score that is calculated by summing *z*-scores derived by comparisons with a normative sample of 400 healthy controls. The reliability, validity and comparability of forms has been established empirically (Keefe et al, 2004). The composite score have high test–retest reliability in people with schizophrenia and healthy controls (intraclass correlation coefficients>0.80).

Trail Making Test-Part B

The Trail Making Test is a neuropsychological test of visual attention and task switching (28). The subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. The test provides information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning and sensitive to detecting several cognitive impairments. The task requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper. In Part B version the subject alternates between numbers and letters (1, A, 2, B, etc.) The goal of the test is for the subject is to finish part B as quickly as possible, the time taken to complete the test is used as the primary performance metric. Error rate is not recorded in the paper and pencil version of the test, however, it is assumed that if errors are made it will be reflected in the completion time.

Magnetic Resonance (MR) Measures

The MR work of this project will be conducted at Indiana University Center for Neuroimaging. A Siemens 3T Trio MR system equipped with a novel 32-channel head coil will be used. This study will use an MR imaging protocol optimized for 3T to provide optimal contrast between grey matter, white matter and CSF. The MR imaging protocol is designed to assess brain changes that may be associated with both white matter and grey matter as well as functional changes associated with duration of illness. Subjects will receive a high-resolution, isotropic 1 mm^3 T1-weighted gradient echo MRI (MPRAGE) for brain segmentation into gray matter, white matter and cerebrospinal fluid (CSF) and for highly sensitive visualization of T1-signal changes in the brain due to Mn deposition. The diffusion tensor images are collected with a 2mm isotropic resolution to study white matter changes. Functional images will be acquired with T2*-weighted gradient echo-planar imaging (EPI) scans with a resolution of 2.5x2.5x3.5mm to assess brain activity during resting state and task paradigms. Quantitative measurement of cortical thickness and potential atrophy using automated Freesurfer and VBM parcellation methods will be conducted, as well as fronto-temporal axonal tract integrity (cingulum, arcuate and uncinate fasciculi) assessed by DTI tractography; and cortical activation with fMRI coupled with working and semantic memory tasks.

The MRI scanning procedure will last approximately 60 minutes and follows the order described below:

1. Written informed consent and MRI Safety Screening will be obtained and documented.
2. Prior to MRI scanning, female subjects who have begun to menstruate and have not undergone menopause or a hysterectomy will take a urine pregnancy test. The pregnancy test will be administered by research staff and there will be no charge to the subject. Subjects who are found to be pregnant will be informed
3. Prior to scanning all subjects will first empty their bladder and remove any metal objects or if required, change into a hospital gown.
4. Subjects will be placed in supine on the scanner table. All scans will be completed in the Siemens Magnetom Trio 3.0T magnet
5. As needed for a particular scan sequence, noninvasive physiological monitoring devices will be put in place, potentially including: pulse oximeter and respiratory bellows.

Artifact due to cardiac and respiratory factors can be a problem for MRI and information on these sources can be used to minimize and correct for them.

6. Peripheral audio devices will be put in place, including ear plugs and sound dampening headphones, to enable the subject to hear auditory instructions and protect hearing against scanner noise, and goggles to allow subjects to see stimuli for visual fMRI tasks.
7. The RF imaging coil will be slid down over the subject's head and the scanner table will be inserted into the bore of the magnet such that the head is at the geometric center of the magnet tube.
8. Preliminary scout images will be obtained to evaluate head position. High resolution anatomic images may be acquired with which to co-register the sequences being tested (e.g., MPRAGE, T1, PD/T2, B0, or FLAIR images), and to use for radiological review of any incidental or known structural abnormalities.
9. Depending upon the sequences/tasks to be evaluated, other MR scans will be obtained, potentially to include fMRI, DTI, and ASL series. Any changes made to a sequence, including self-programmed sequences, will fulfill the safety limitations of the Siemens Scanner (e.g., limitations on power deposition).
10. fMRI stimulation paradigms may include tasks of memory, language, attention and executive functions, affect, and/or sensorimotor processing (i.e., visual, olfactory, gustatory, auditory, or tactile stimuli).
11. Subjects will be removed from the scanner following imaging.

9.0 Safety Assessments and Procedures

Dosing Safety

First dose monitoring

- The first dose of study medication will be administered at the CRC
- All subjects will be placed on continuous telemetry during the first 24 (+/- 2) hours following administration of the first dose of study medication
- Blood pressure measurements will be completed hourly during the first 6 hours post initial dose of study medication and every 4 (+/- 1) hours thereafter unless study doctor determines a different schedule based on safety.

Second dose monitoring

- For subjects who require pharmacologic intervention for symptomatic bradycardia at any time within the first 24 (+/-2) hours, whose electrocardiogram shows new onset second degree or higher AV block at any time within the first 24 (+/-2) hours or who continue to have bradycardia (resting heart rate < 50 beats per min) after 24 (+/- 2) hours (with or without pharmacologic intervention), first dose monitoring procedures will be reinstituted following the second dose

Ophthalmologic Examination

Ophthalmologic examination will be performed before initiating study medication and at 4 (+/-1) months after treatment initiation. For subjects who report visual changes, an additional examination will be completed

Vitals
Vital signs will be assessed at study visits per Study Procedures Table (Attachment 1). Blood pressure, heart rate, and oxygen saturation will be taken in a seated position after a rest period of five minutes. Oxygen saturation will be taken via a finger mounted pulse oximeter.

Medical History
The subject's lifetime medical history will be taken during the screening period. Medical history includes previous and current diseases.

Physical Examination
A physical examination including a neurological examination.

Electrocardiograph (ECG)
A supine, 12 lead ECG will be performed according to the Study Procedures Table (Attachment 1). ECGs will be interpreted by a local cardiologist.

Telemetry
Cardiac telemetry, monitoring of the cardiac rhythm and transmission of signals or data from one electronic unit to another by radio waves using a device that provides real-time measurement of a subject's ECG for various lengths of time, will be performed according to the Study Procedures Table (Attachment 1). Subjects will be outfitted with measuring, recording, and transmitting devices. An alerting function will alert CRC staff if the subject is suffering from an acute condition.

Other Safety Assessments
- Unexplained dyspnea has been reported in clinical trials of this study medication; therefore, subjects who develop unexplained dyspnea during the study will complete an assessment of pulmonary function (spirometric testing) and assessment of diffusion lung capacity for carbon monoxide (DLCO).
- Subjects will be assessed for active infectious disease by clinical history (and physical exam, if necessary) at each study visit.
- Liver enzymes will be monitored at baseline (Visit 1), 4 weeks (Visit 7), and 8 weeks (Visit 11) as well as at the two month follow up visit (Visit 13) and in subjects who develop signs or symptoms of liver dysfunction including unexplained nausea and/or vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine.

10.0 Criteria for Rescreening, Repeat Assessments, and Discontinuation

Repeat Assessments
Screening assessments can be repeated within the screening window under the same screening number with the exception of eligibility criteria related rating scales/questionnaires. Subject diagnosis confirmation will not be repeated.

Rescreening
Subject who screen fail may be rescreened one time, under a new screening number. If a subject is rescreened, all screening assessments (with the exception of the diagnosis confirmation) must be repeated and the stability criteria timelines must be met.

Discontinuation
Subjects will be discontinued under the following circumstances:

1. Within the first two weeks of treatment, subjects with an interruption of treatment of one day or more
2. Within the third and fourth week of treatment, subjects with an interruption of treatment of more than seven days
3. Subjects who have an elevation of liver transaminase levels >3 times the ULN while on study medication
4. Subjects who develop moderate or severe renal impairment as defined by CrCl <60 ml/min (measured by the Cockcroft-Gault equation) while on study medication
5. Female subjects who become pregnant while on study medication
6. Subjects who develop a serious infectious disease while on study medication
7. Subjects who develop macular edema or uveitis while on study medication
8. Any subject who requires pharmacologic intervention for symptomatic bradycardia after the second dose of study medication or who continues to experience bradycardia or who demonstrates any other new, serious cardiac pathology 24 (+/-2) hours after the second dose of study medication will be discontinued from the study
9. Subjects who require an increase in their dose of antipsychotic medication or the addition of a new antipsychotic medication
10. Subjects who require treatment with any excluded concomitant medications (See Attachment 2)

If subjects discontinue from the study, discontinuation assessments will be at the discretion of the principal investigator.

A subject may withdraw from the study medication at any time at his/her own request, or may be withdrawn at any time at the discretion of the principal investigator for safety, behavioral, or administrative reasons.

11.0 Laboratory Assessments

Study associated laboratory assessments (blood and urine) will be collected at time points specified in Study Procedures Table (Attachment 1) and analyzed by a local laboratory with the exception of the urine dipstick assessments which will be collected and analyzed onsite.

A total of 36 mL of blood will be collected for baseline/screening assessments (Visit 1) and 30 mL of blood (at each visit) will be collected at weeks 4 and 8 (Visits 7 and 11).

Laboratory assessments to be completed:
complete blood count with differential (CBC w/diff)
comprehensive metabolic panel (CMP)
magnesium
calcium
lipid panel
hemoglobin A1c (HgbA1c)
thyroid stimulating hormone level (TSH)
pregnancy test (serum (beta HCG) and urine)
varicella zoster titer (VZV titer)
urine toxicology screen
HIV test
hepatitis panel
plasma cytokines

Plasma cytokines
Research staff members will transport the cytokine specimens to Indiana Clinical and Translational Sciences Institute (CTSI) for processing and storage. Specimen handling procedures will be performed based on the CTSI standard operating procedures.

Assay Methodology:
Plasma cytokine and soluble receptor quantifications will be performed in duplicates using pre-validated commercially available assay kits employing Luminex® x-MAP technology. With this approach, we will be able to simultaneously quantify multiple human cytokines of relevance in a single experiment using very small volume of sample (Less than 50-µl). Each of the assay kits employs 1-2 positive control(s) of known concentration and a negative control in every run. We will follow manufacturer provided established protocols for these assays. The testing panel for cytokines include IFN-γ, IL-10, IL-12p40,IL-12p70, IL-17, IL-1β, IL-1ra, IL-2, IL-4, IL-6, and TNF-α (Millipore #HCYTOMAG-60K) and the testing panel for soluble receptors include soluble IL-2Rα, soluble IL-6R, soluble TNFRI and soluble TNFRII (Millipore HSCR-32K-04).
Luminex® is an antibody-based fluorescent immunoassay performed in suspension using distinctly identifiable bead sets. This platform uses internally color-coded microspheres (up to 100 distinct bead sets are available), for coating with a capture antibody specific for a target cytokine. The capability of adding multiple conjugated beads to each sample results in the ability to obtain multiple results from each sample. After the target cytokine from a test sample is captured by the bead, a biotinylated detection antibody is introduced. The reaction mixture is then incubated with Streptavidin-Phycoerythrin conjugate, the reporter molecule, to complete the reaction on the surface of each microsphere. The microspheres are allowed to pass rapidly through a laser which excites the internal dyes marking the microsphere set. A second laser excites PE, the fluorescent dye on the reporter molecule. Finally, high-speed digital-signal processors in the special reader instrument (Bio-Plex 200 system from Bio-Rad) identify each individual microsphere and quantify the result of its bioassay based on fluorescent reporter signals. A cytokine standard mix containing all target cytokines at known calibrated levels will be used to generate separate standard curves for each of the cytokines. Concentrations of each target cytokine will then be estimated using a standard curve specific to that particular cytokine by 5-parameter logistic curve fit method.

Preservation and Specimen Storage:
At the time of specimen submission to and processing by the CTSI the specimens will be stored in the freezers in specially labeled boxes, organized by internal "grids" for easy tracking. The bar-coded ID number and location of each specimen in the freezer will be entered and tracked by the CaTissue specimen database, a CTSI-maintained, password-protected database with limited access. No personal identifiers will appear on the blood tubes stored at the CTSI. The CTSI freezers will be secured and wired to an alarm system. The daily monitoring and maintenance of the freezers will be managed by the CTSI.

All study information will be stored in locked file cabinets and in password-protected computer files. Specimens will be stored by the Indiana CTSI on the IU campus but are not the property of the Indiana CTSI. The PI and IU will remain responsible for the specimens.

All specimens will be kept until they are used in their entirety.

12.0 Study Medication

Fingolimod (FTY720, approved as Gilenya™) a sphingosine-1-phosphate (S1P) receptor modulator and matching placebo tablets will be used as study medication for this study. Placebo tablets will look like fingolimod tablets, with matching shape, taste, and color. Study medication will be purchased directly through the Wishard pharmacy. Wishard pharmacists will over-encapsulate the fingolimod and create matching placebo capsules. Study medication will be stored according to the details on the product label.

Dosing
The dosing used in this study will follow doses recommended for MS which is 0.5 mg by mouth once daily (see package insert for more information).

Compliance
Compliance will be assessed at each visit by direct questioning and medication count of unused medication and packaging to be returned at each visit. Adequate study medication dispensing records will be obtained.

13.0 Concomitant Medication
See Concomitant Medication Table Attachment 2

14.0 Adverse Events

Adverse events (AEs), especially those for which the relationship to study medication is not "unrelated," will be followed up until they have returned to baseline status or stabilized at the discretion of the principal investigator. If after the follow-up period, return to baseline or stabilization cannot be established an explanation will be recorded in the source documentation.

15.0 Data Safety Monitoring Board

The Indiana University Adult Psychiatry Data Safety Monitoring Board (DSMB) will be responsible for data and safety monitoring. DSMB is responsible for reviewing study procedures, adverse events, safety mailings (if applicable), enrollment, active subjects, and ongoing conduct of the research. The DSMB members can ask questions and make comments and/or recommendations. The IRB is notified of significant findings by way of the DSMB meeting minutes at the time of continuing review. For a list of current DSMB members, see Psychiatry DSMB Board Members supplement. An updated DSMB member list will be provided at the time of Institutional Review Board (IRB) continuing review or upon request.

Due to the small sample size and single site design of this protocol, there is not sufficient justification for conducting interim analyses to examine trends.

Data on the number of subjects enrolled and the number of adverse events will be reviewed by the Board at least **quarterly** and more frequently if needed. The resultant report will be issued to the Indiana University IRB at least at the time of continuing review or more frequently by request.

Any unanticipated events will be immediately directed to the principal investigator who will follow the Indiana University IRB reporting procedures.

16.0 Statistical Considerations

Analyses

In terms of the power to detect a significant effect of this molecule, there are no known calculations with schizophrenia patients. However, an extension phase of a MS registration trial found that patients on fingolimod demonstrated rapid anti-inflammatory responses in relatively small samples (< 35 subjects per dosing arm) (16). In addition, Garver et al (25) examined myelin integrity in schizophrenia and found significant improvement in white matter integrity utilizing a small sample (N=8) of antipsychotic drug responsive schizophrenic patients. Given the above findings, it is reasonable to assume a medium (0.50) to large effect size (0.80) will be observed. Therefore, with a sample size of 40 patients, we could detect a significant effect of treatment (between the fingolimod and placebo groups) with statistical power (37) between .3 and .7, utilizing a two-sided independent test and a significance level of 0.05.

Preliminary analyses will consist of descriptive statistics for all outcome variables, including summary statistics, graphical displays of distributions, and spaghetti plots of individual data over time to detect possible data errors. Demographic and clinical characteristics at baseline will be compared between the two randomized groups, using parametric or nonparametric test statistics as appropriate. Variables that show significant differences will be added to the final models as covariates in order to ensure that the observed treatment effects are not spurious or due to demographic confounds. Data

analysis will be *intent to treat* with all data considered usable providing subjects have completed the randomization visit. To minimize the potential for Type I error, all treatment comparisons will be evaluated based on a two-sided significance level of 0.05. Primary and secondary measures will be examined using ANOVA and ANCOVA general linear modeling analyses for measures resulting in ratio data or the Kruskal-Wallis for those measures that produce ordinal data.

17.0 Privacy/Confidentiality Issues

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the principal investigator and research staff. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the principal investigator and research staff. Any screening information obtained from potential research subjects who subsequently do not participate in the research study will be destroyed.

18.0 Record Retention

Paper copies of medical records and source documentation will be kept for seven years after the study is closed with the IRB. One year after study closure, the documents will be shipped to the Indiana University Department of Psychiatry long-term storage facility until destruction.

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ATTACHMENT 1

Study Procedures Table

Visit	1a	1b	2	3a Inpatient	3b[a] Inpatient	3c[b] Inpatient	4	5	6	7	8	9	10	11[d] /ET	12	13
Day				-1 to -6 hours	0	1	7	14	21	28	35	42	49	56	84	112
Visit Window (days since last visit) [f]			0-30	0-7	NA	NA	5-9	5-9	5-9	5-9	5-9	5-9	5-9	5-9	24-32	24-32
Informed Consent	X															
SCID	X															
Med/Psych/ Medication History	X															
Demographics	X															
Physical Exam	X															
Vitals	X			X			X	X	X	X	X	X	X	X	X	X
Ophthalmology Exam		X														X
ECG (triplicate, 1 min apart)	X			X			X	X	X	X	X	X	X	X	X	X
CGI-S&I [e]	X			X			X	X	X	X	X	X	X	X	X	X
BPRS	X															
PANSS			X				X			X				X		
PSP			X				X	X	X	X	X	X	X	X	X	X
EQ-5D & Quality of Life			X							X				X		
BACS/Trails B			X							X				X		
MRI			X											X		
BFCRS				X										X		
AIMS				X										X		
SAS				X										X		
BARS				X										X		

Visit	1a	1b	2	3a Inpatient	3b[a] Inpatient	3c[b] Inpatient	4	5	6	7	8	9	10	11[d] /ET	12	13
Day				-1 to -6 hours	0	1	7	14	21	28	35	42	49	56	84	112
Visit Window (days since last visit) [f]			0-30	0-7	NA	NA	5-9	5-9	5-9	5-9	5-9	5-9	5-9	5-9	24-32	24-32
CBC w/ diff	X									X				X		X
CMP	X									X				X		X
TSH	X															
Beta HCG	X															
VZV Titer	X															
HIV test	X															
Hepatitis Panel	X															
Plasma Cytokines				X						X				X		
Magnesium & Calcium	X															
Lipid Panel	X															
HgbA1c	X															
Urine Toxicology	X		X	X			X	X	X	X	X	X	X	X		
Urine Pregnancy Test	X		X	X			X	X	X	X	X	X	X	X	X	X
Adverse Event	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Dispensation					X[c]	X	X	X	X	X	X	X	X			
Medication Accountability							X	X	X	X	X	X	X	X		
Telemetry					X	X										
Hourly Blood Pressure					X	X										

a 3b is the first 24 +/- 2 hours post dose
b 3c will be completed per dosing safety section as outlined in this protocol (if applicable)
c Initial dose will be administered before 12pm
d Visit 11 procedures may be split over a 7 day period
e Only CGI-S will be completed at visit 1a
f: All visits may be split at the discretion of the principal investigator

ATTACHMENT 2

Concomitant Medication Table

Medication	Use prior to Visit 4	Use after Visit 4
Class 1a antiarrhythmic	No	No
Class 3 antiarrhythmic	No	No
Alpha 2 agonists (eg., Clonidine)	No	No
Alpha-adrenergic blockers (eg, doxazosin, terazosin)	Stable dose, no changes or additions	Stable dose, no changes or additions
Anticoagulants	No	No
Antiemetics (eg., metoclopromide, domperidone, other dopamine receptor blockers)	No	No
Antiepileptic mood stabilizers	Stable dose, no changes or additions	Stable dose, no changes or additions
Antihistamines, nonsedating	Yes	Yes
Antihistamines, sedating	Yes[a]	Yes[a]
Antineoplastics	No	No
Antipsychotic medications	Stable dose, no changes or additions	Stable dose, no changes or additions
Antivirals (including trantadine)	No	No
Barbiturates	No	No
Belladonna	No	No
Benzodiazepines	Yes	Yes
Beta 2 agonists (eg, albuterol)	Yes-Episodic Use Only	Yes-Episodic Use Only
Beta blockers	No	No
Bupriopion	Stable dose, no changes or additions	Stable dose, no changes or additions
Calcium channel blockers (-dipines)	No	No
Cathartics and Laxatives	Yes-Episodic Use Only	Yes-Episodic Use Only
Citalopram (40mg or less)	Stable dose, no changes or additions	Stable dose, no changes or additions
Corticosteroids (except topical or inhaled)	No	No
Decongestants (eg., pseudophedrine)	No	No
Dicyclomine	Yes[a]	Yes[a]
Diltiazem	No	No
Digoxin	No	No
Ergotamine, dihydroergotamine	No	No
Gold Compounds	No	No
Herbal medications or Over the Counter Medications w/ primary CNS activity	Conditional Use [a]	Conditional Use [a]
Hyoscyamine	No	No
Ketamine	No	No
Ketoconazole	No	No
Ketorolac,	No	No
Linezolid	No	No
Lithium	Stable dose, no changes or additions	Stable dose, no changes or additions
Live attenuated vaccine	No	No
Loop and thiazide diuretics	Stable dose, no changes or additions	Stable dose, no changes or additions
MAOIs	No	No
Macrolides	No	No
Medroxyprogesterone injections	Yes	Yes
Metaproternal	No	No
Methadone	No	No

Methotrexate	No	No
Methyldopa	No	No
Midrin	Yes	Yes
Mineralocorticoids	No	No
Minocycline	No	No
Minoxidil	No	No
Niacin	No	No
Nicotine Replacement	Yes	Yes
Nitrites and nitrates	No	No
Opiates	No	Yes
Phentermine	No	No
Reserpine	No	No
Erectile dysfunction treatments	No	No
Muscle relaxants	No	No
Sleeping medications (zolpidem, etc.)	Yes	Yes
SNRIs	Stable dose, no changes or additions	Stable dose, no changes or additions
SSRIs	Stable dose, no changes or additions	Stable dose, no changes or additions
Theophylline	No	No
Tricylic antidepressants	No	No
Triptans	No	No
Varenicline	No	No
Verapamil	No	No
Warfarin	No	No

[a] Conditional Use: Will be reviewed by the principal investigator on a case by case basis.