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ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial

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ABSTRACT

BACKGROUND: An urgent need exists for new treatments of schizophrenia that are effective against a broad range of symptoms and free of limiting safety issues. ITI-007 is a new molecular entity with a pharmacologic profile that combines dose-related monoamine modulation with phosphorylation of intracellular signaling proteins.

METHODS: A phase II randomized, double-blind, placebo-controlled, and active-controlled trial was conducted at eight sites in the United States with randomization of 335 acutely psychotic adults with schizophrenia. ITI-007 (60 mg and 120 mg), placebo, and risperidone, included for assay sensitivity, were evaluated as monotherapy for 4 weeks. The primary outcome measure was the Positive and Negative Syndrome Scale total score, with secondary analyses conducted on symptom subscales.

RESULTS: ITI-007 60 mg ($p = .017$, effect size = .4) and risperidone ($p = .013$, effect size = .4) demonstrated antipsychotic efficacy superiority over placebo on the primary end point. The results of secondary analyses reflected improvements in negative and depressive symptoms by ITI-007 60 mg. ITI-007 120 mg did not separate from placebo. However, both doses of ITI-007 were well tolerated in this patient population, as evidenced by low discontinuation and adverse event rates, and were associated with a benign metabolic profile as evidenced by significantly lower levels of prolactin, fasting glucose, total cholesterol, and triglycerides than risperidone.

CONCLUSIONS: The mechanistically novel investigational drug ITI-007 was effective for the treatment of schizophrenia and comparable with placebo on safety measures in this trial. Secondary analyses indicated that ITI-007 improved negative and depression symptoms and might have expanded therapeutic efficacy in comparison with current antipsychotic drugs.

Keywords: Antipsychotic, Comorbid depression, Negative symptoms, Positive symptoms, Prosocial factor, Safety

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Schizophrenia is a debilitating psychotic illness that affects approximately 1% of the population. Current antipsychotic drugs (APDs) have therapeutic effects in patients with schizophrenia predominantly against positive symptoms, such as hallucinations and delusions (1), but leave most individuals with significant residual symptoms, diminished quality of life, and enduring functional impairment (2). Treatment early in the course of the disease and psychosocial support may improve outcome, but treatment options remain limited.

Most APDs show only modest effectiveness, if any, in treating the nonpsychotic symptoms of schizophrenia that are believed to be responsible for the poor social and academic/vocational functioning characteristics of the illness, including social withdrawal, flattened affect, depression, and cognitive impairment (3). Additionally, all currently used APDs exhibit clinically significant side effects of varying types and severity. So-called first-generation APDs are commonly associated with extrapyramidal side effects (EPS) such as bradykinesia, rigidity, akathisia, tremor, and tardive dyskinesia, while many second-generation, or atypical, APDs frequently lead to weight gain and metabolic alterations such as hyperglycemia, insulin resistance, and dyslipidemia (4). Clozapine is arguably the most efficacious APD, yet is among the most prone to the aforementioned metabolic disturbances. It is also associated with an increased incidence of seizures and potentially lethal side effects of agranulocytosis and myocarditis (5). Consequently, there is tremendous unmet medical need for safer treatments that are more effective and have a broader spectrum of efficacy across multiple symptom domains.

ITI-007 is a new molecular entity with a unique pharmacologic profile that combines dose-related monoamine modulation with phosphorylation of intracellular signaling proteins (6). While it interacts with several targets that are common to some existing APDs, its full actions are complex and unique (7). ITI-007 is a high-affinity serotonin 2A (5-HT2A) receptor

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antagonist with lower, but clinically relevant, affinity for other neurobiological targets, including D_2 receptors. While 5-HT2A receptor antagonism in addition to D_2 receptor antagonism has been the hallmark of atypical APDs (8), ITI-007 has a wider separation (sixtyfold) between its affinity for 5-HT2A receptors and D_2 receptors than other APDs, allowing full saturation of 5-HT2A receptors, even at modest levels of dopamine receptor occupancies (7). Moreover, unlike most other antipsychotics that are antagonists at D_2 receptors both presynaptically and postsynaptically and unlike aripiprazole and related compounds that are partial agonists at D_2 receptors both presynaptically and postsynaptically, ITI-007 interacts with dopamine receptors in a unique way. At D_2 receptors, ITI-007 is a presynaptic partial agonist and postsynaptic antagonist with functional mesolimbic/mesocortical selectivity (7). This allows for functional blockade of dopamine without increasing dopamine turnover and corresponds to antipsychotic efficacy without motor side effects (7). Above and beyond 5-HT2A and D_2 receptor interactions, ITI-007 increases phosphorylation of mesolimbic GluN2B subunits of *N*-methyl-D-aspartate (NMDA) receptors (7). An increase in GluN2B increases synaptic NMDA activity via subcellular trafficking to plasma membranes (9). To the extent that a deficit in glutamatergic function contributes to schizophrenia symptoms (10,11), indirect enhancement of glutamatergic NMDA function is predicted to reduce psychosis and improve cognitive function and negative symptoms. Although investigational therapeutics targeted solely at direct interaction with glutamate receptors or glycine transporters have not successfully translated into clear clinical benefit, it is recognized that the interaction between glutamate and dopamine modulation is important in schizophrenia (12). At serotonin transporters, ITI-007 inhibits the serotonin transporter (7), an effect associated with many antidepressant drugs (13). ITI-007 lacks significant activity at many receptors (e.g., H1, muscarinic, serotonin 2C) that are associated with deleterious effects experienced with many other APDs (i.e., clinically significant sleep induction, cognitive impairment, weight gain). Thus, by acting through serotonergic, dopaminergic, and glutamatergic signaling systems in a mechanistically and neuroanatomically selective manner, ITI-007 represents a novel approach to the treatment of schizophrenia and other neuropsychiatric disorders.

This study evaluated the efficacy of ITI-007 in schizophrenia patients and included secondary outcomes of positive, negative, and depressive symptoms and symptoms associated with social function. We hypothesized that based on its pharmacologic profile and preliminary data that ITI-007 would be an effective APD with efficacy across a broader range of symptoms in patients presenting with an acute exacerbation of schizophrenia and excellent tolerability as compared with placebo and risperidone (one of the most commonly prescribed APDs).

METHODS AND MATERIALS

Study Design

This was a randomized, double-blind, placebo- and active-controlled, multicenter phase II clinical trial (ITI-007-005) conducted at eight sites in the United States from December 2011 to November 2013. Subjects ($n = 335$) were randomized in a 1:1:1:1 ratio across parallel groups to receive ITI-007 (60 mg, 120 mg), placebo, or risperidone (4 mg) as oral monotherapy once daily in the morning for 4 weeks. Individuals randomized to 120 mg ITI-007 or risperidone received a single day dose titration (60 mg to 120 mg ITI-007 on day 2; 2 mg to 4 mg risperidone on day 2); 60 mg ITI-007 required no dose titration. Doses of 60 mg and 120 mg ITI-007 were selected based on estimated striatal D_2 receptor occupancy of approximately 50% and 70%, respectively, modeled from the D_2 receptor occupancies determined in a positron emission tomography study at lower doses in healthy volunteers (14). A dose of risperidone of 4 mg was selected as a positive control for assay sensitivity based on its mean modal effective dose determined by the Clinical Antipsychotic Trials of Intervention Effectiveness (15) and its well-characterized efficacy and safety profile as one of the most prescribed antipsychotics in the United States. The risperidone dose and titration schedule are also within the recommendations of the US Food and Drug Administration approved label for this drug. Assignment of a randomization number across the study was via an automated central randomization and trial supply management system using a computer-generated sequence. The randomization assigned a numbered kit containing visually matched capsules to keep subjects, clinical site staff, and study oversight team blinded.

Participants

Patients, 18 to 55 years of age, with a diagnosis of schizophrenia confirmed by a Structured Clinical Interview for DSM Disorders–Clinical Trials Version (16) were eligible for participation if experiencing an acute exacerbation of psychosis defined as a score of ≥40 on the 18-item Brief Psychiatric Rating Scale (item range 1–7) with a score of ≥4 on ≥2 of the positive symptom items: suspiciousness, conceptual disorganization, hallucinatory behavior, or unusual thought content. The current acute episode was required to have started within 4 weeks of screening with an independent informant verifying that symptom severity represented an acute exacerbation for a given individual. Individuals were required to have shown previous treatment response to APD therapy and thus be neither treatment-naïve nor treatment-resistant. Diagnosis and symptom severity at screening were rated by study investigators and confirmed by independent psychiatrists or clinical psychologists to ensure inclusion of an appropriate patient population (Clintara LLC, Boston, Massachusetts) (17). Patients who met any of the following exclusion criteria were not included in the study: unable to provide informed consent; pregnant/breastfeeding; dementia/delirium/mental retardation/epilepsy/drug-induced psychosis/brain trauma; schizoaffective disorder/bipolar disorder/acute mania/major depression with psychotic features; imminent danger to self or others; suicidal ideation/behavior; unstable living environment; use of depot antipsychotic within one treatment cycle before baseline; use of any APD within screening period; use of specific agents with known interaction with 5-HT2A receptors; clinically significant abnormal laboratory values or clinical findings; uncontrolled angina/recent history of myocardial