TREATMENT OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

FIELD OF THE INVENTION

The present invention relates to methods and uses for (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof.

BACKGROUND

The compound (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide, is described, including methods of synthesis, in U.S. Patent No. 7,981,906 (Application Publication No. US 2009/0048290 A1), and is part of a genus described in U.S. Pat. No. 6,953,855, both of which are fully incorporated herein by reference. The compound may be referred to as TC-5619.

Schizophrenia is a chronic, severe, and disabling form of psychosis. In addition to symptoms such as delusions, hallucinations, the inability to disregard familiar stimuli (sometimes referred to as sensory gating), disorganized speech, grossly disorganized or catatonic behavior and prolonged loss of emotion, feeling, volition or drive, schizophrenia is often marked by impairment in cognitive functions, such as executive function, attention, vigilance, memory and reasoning. These cognitive impairments play a primary role in the inability of schizophrenic patients to function normally. It has been estimated that up to 75% of persons with schizophrenia are cognitively impaired (derived based on a reported prevalence of schizophrenia of 4.6 million in the world's seven major pharmaceutical markets in 2009 (*Patient Base*, a database of epidemiology available through Decision Resources, Inc., May 2010), and an estimate of 75% of schizophrenics that have cognitive dysfunction (O'Carroll, R., Cognitive impairment in schizophrenia. *Advances in Psychiatric Treatment*, 2000)). There is currently no drug approved in the United States or Europe specifically for cognitive dysfunction in schizophrenia.

As will be provided in more detail herein, one measure of clinical efficacy for cognitive dysfunction in schizophrenia includes the Schizophrenia Cognitive Test Battery. Reference is made to Collie A, Maruff P, Snyder PJ. (2006) Does atypical antipsychotic medication improve executive function in schizophrenia? Int J Neuropsychopharmacol. 9, 629-630; author reply 631-632; Falleti MG, Maruff P, Collie A, Darby DG. (2006). Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. J Clin Exp Neuropsychol. 28, 1095-1112; Snyder PJ, Piskulic D, Olver J, Norman T, Maruff P. (2006). Spatial working memory and problem solving in schizophrenia: The effect of symptom stabilization with atypical antipsychotic medication.

Psychiatry Research. In press; Snyder PJ, O'Sullivan R, Jackson C, Olver J, Norman T, Piskulic D, Collie A, Maruff P. (2006). Stability of cognitive performance in chronic schizophrenia over brief and immediate re-test intervals: Implications for studies of treatment efficacy. Human Psychopharmacology. In press; and (http://www.cogstate.com/go/clinicaltrials/our-test-batteries/schizophrenia-battery; CogState, New Haven, CT).

Schizophrenia can be divided into three major phases: the prodromal state, an active phase, and a residual phase. These phases tend to occur in sequence and appear in cycles throughout the course of the illness.

During the prodromal state it is not uncommon for a number of non-specific symptoms to be present in the weeks or months preceding the first onset of typical symptoms of schizophrenia, particularly in young people. These symptoms include:

- A general loss of interest;
- Avoidance of social interactions;
- Avoidance of work or study (e.g. dropping out of school, college or university) ;
- Being irritable and oversensitive;
- Odd beliefs (e.g. superstitiousness); and
- Odd behavior (e.g. talking to self in public).

These changes will often be incapacitating for the individual and distressing for the family. Friends or relatives may describe the individual as "no longer the same person". The length of the prodromal phase is extremely variable and prognosis is less favorable when the prodromal phase has had a lengthy course. When symptoms develop gradually, people may begin to lose interest in their usual pursuits and to withdraw from friends and family members. They may become easily confused, have trouble concentrating, and feel listless and apathetic, preferring to spend most of their days alone. They may also become intensely preoccupied with religion or philosophy. Family and friends may be upset with this behavior, believing the person is lazy rather than ill. Occasionally, these symptoms reach a plateau and do not develop further but, in most cases, an active phase of the illness follows. The prodromal period can last weeks or months. Although the symptoms described above are typical of the prodromal phase of schizophrenia, they may also be due to other causes.

During the active phase of the illness, psychotic symptoms such as delusions, odd behavior and hallucinations are prominent and are often accompanied by strong affect such as distress, anxiety, depression, and fear. If untreated, the active phase may resolve spontaneously or may continue indefinitely. With appropriate treatment (primarily medication) the active phase is usually able to be brought under control. It is during the active phase that

most individuals present for treatment, whether it is their first presentation or an exacerbation of their symptoms. During schizophrenia's active phase, people may experience delusions, hallucinations, marked distortions in thinking and disturbances in behavior and feelings. This phase most often appears after a prodromal period. On occasion, these symptoms can appear suddenly.

The active phase of the illness is usually followed by a residual phase. The residual phase is similar to the prodromal phase although during the residual phase blunted affect and impairment in role functioning are more common. While psychotic symptoms may persist into the residual phase, the psychotic symptoms are less likely to be accompanied by such strong affect as experienced during the active phase. There is great variation in the severity of the residual phase from one person to the next. Some individuals will function extremely well while others may be considerably more impaired. After an active phase, people may be listless, have trouble concentrating and be withdrawn. The symptoms in this phase are similar to those outlined under the prodromal phase. If there have been no symptoms before the first episode, few or no symptoms may be experienced afterward. During a lifetime, people with schizophrenia may become actively ill once or twice, or have many more episodes. Unfortunately, residual symptoms may increase, while ability to function normally may decrease, after each active phase. It is therefore important to try to avoid relapses by following the prescribed treatment. Currently it is difficult to predict at the onset how fully a person will recover.

Reference is made to Marder et al., Methodological Issues in Negative Symptom Trials, Schizophrenia Bulletin, 2011; and Laughren and Levin, Food and Drug Administration Commentary of Methodological Issues in Negative Symptom Trials, Schizophrenia Bulletin, 2011.

The most common course of the disorder generally involves numerous active phases of illness with residual phases of impairment between episodes. The extent of residual impairment often increases between episodes during the initial years of the disorder although may possibly become less severe during the later phases of the illness.

SUMMARY OF THE INVENTION

In one aspect, the invention relates to the treatment of cognitive dysfunction in schizophrenia by administering (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to a patient in need thereof. In an embodiment, the invention relates to treatment of cognitive dysfunction in schizophrenia by improving executive function. In another embodiment, the invention relates to treatment of cognitive dysfunction in schizophrenia by improving memory. In another

embodiment, the invention relates to treatment of cognitive dysfunction in schizophrenia by improving attention.

In another aspect, the invention relates to treatment of negative symptoms of schizophrenia by administering (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to a patient in need thereof.

In another aspect, the invention relates to the treatment of residual phase schizophrenia.

Various terms used herein, not otherwise defined, may be defined with reference to the Protocol.

BRIEF DESCRIPTION OF THE INVENTION

Figure 1 is a graphical depiction that summarizes the statistically significant results from a placebo controlled parallel group study comparing the effect of a novel alpha 7 nicotine agonist on the Simple Reaction Time (information processing), International Shopping List (verbal learning) and Groton Maze Learning Task (problem solving) tasks in patients with chronic schizophrenia (n=30 per group) who were stable on their antipsychotic medication at randomization. Improvement in performance of greater than 0.4 standard deviation units was found for each measure.

Figure 2 illustrates sensitivity of the primary outcome measures from the CogState schizophrenia battery to cognitive impairment in patients with chronic schizophrenia who were receiving antipsychotic medication in three different geographical areas. The nature and magnitude of impairment in the different cognitive domains was consistent across the three cultural groups.

DETAILED DESCRIPTION OF THE INVENTION

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof, (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide, is described, including methods of synthesis, in U.S. Patent No. 7,981,906 (previously published as Publication No. US 2009/0048290 A1), and is part of a genus described in U.S. Pat. No. 6,953,855, both of which are fully incorporated herein by reference.

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof is a selective alpha7 NNR agonist. (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof had efficacy in preclinical models of memory and was generally well tolerated in phase 1 trials in healthy volunteers, who demonstrated a robust

improvement in attention when 6.7mg (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof was administered. See, Hauser TA, Kucinski A, Jordan KG, Gatto GJ, Lippiello PM, Bencherif M: (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof: An α7 NNR selective agonist that demonstrates efficacy in animal models of schizophrenia, *Biochem. Pharmacol.* 1009; 78: 803-812, herein incorporated by reference.

A Phase 2 clinical proof of concept trial was conducted to evaluate (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof as an augmentation therapy to improve cognition in patients with schizophrenia. In the trial, (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof met the protocol criteria for a positive result on the primary efficacy outcome measure, the Groton Maze Learning Task (GMLT) of the CogState Schizophrenia Battery (CogState, New Haven, CT), and was well tolerated. The trial is Study Number PRO-05619-CRD-001, incorporated herein below.

The statistically significant and qualitatively similar effects favoring (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in the primary objective endpoint (GMLT), in a number of secondary clinician and patient-rated endpoints (SANS, CGI-Global, and SGI-Cog), and in CogState objective cognitive endpoints underscore the positive efficacy of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in Cognitive Deficits in Schizophrenia.

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof exhibited a favorable tolerability profile in the trial, and there was no clinically significant difference between the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof and placebo dose groups in discontinuations due to adverse events. The most frequent adverse event that was more common in the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof cohort than in the placebo cohort was nausea (0% placebo vs. 5% (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof), which was mild to moderate in severity and never led to patient dropout. There were two serious adverse events in the trial, one in the placebo dose group and one in the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-

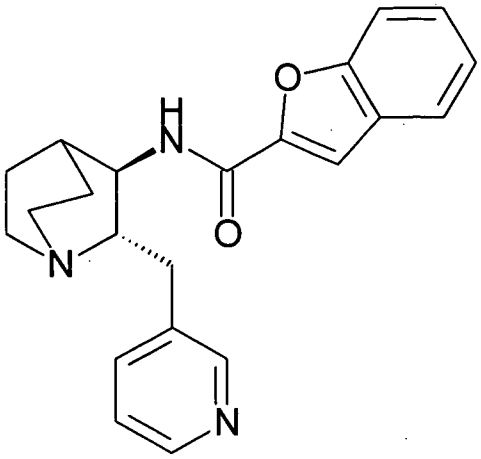
carboxamide or a pharmaceutically acceptable salt thereof dose group. Both were considered by the applicable investigator as not drug related.

The efficacy of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof against negative symptoms and cognitive symptoms is a remarkable finding due to the relative lack of effect of atypical antipsychotics upon these residual symptoms of schizophrenia. Because these residual symptoms are the primary reason that people with schizophrenia do not regain their full pre-morbid level of function, a new treatment for these symptoms fills a major unmet need. This need has been recognized by the NIMH through their MATRICS initiative (Neuchterlein et al., 2004; Gold, 2004), other initiatives with broad academic and regulatory support (Blanchard et al., 2010; Marder et al., 2011), and endorsed by the FDA (Laughren and Levin, 2011).

The MATRICS initiative has highlighted the potential for small molecules that target the alpha7 NNR receptor in the treatment for cognitive dysfunction in schizophrenia. That potential was supported by preclinical models of schizophrenia in which the alpha 7 NNR agonist, (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof, was effective; and by early clinical studies in which a variety of other alpha7 NNR agonists were effective against surrogate markers (Olincy et al., 2006; EnVivo Pharmaceuticals, 2009) and measured features of schizophrenia (Freedman et al., 2008).

I. Compound

The compound of the present invention is (2S,3R)-N(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide, represented as Compound A below, or a pharmaceutically acceptable salt forms of Compound A.



Compound A

(2S,3R)-N(2-((3-Pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide (Compound A) is a highly selective, full agonist at the α7 NNR receptor with a remarkably low EC_{50} (for activation) value and a good separation between EC_{50} and the IC_{50} (for residual inhibition), providing functional agonism over a broad range of therapeutically useful concentrations.

II. Scalable synthesis of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide

Particular synthetic steps vary in their amenability to scale-up. Reactions are found lacking in their ability to be scaled-up for a variety of reasons, including safety concerns, reagent expense, difficult work-up or purification, reaction energetics (thermodynamics or kinetics), and reaction yield.

The synthesis of (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide described herein has been used to produce kilogram quantities of material, and the component reactions have been carried out on multi-kilogram scale in high yield.

The scalable synthesis utilizes both the dynamic resolution of a racemizable ketone (2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one) and the stereoselective reduction of the (R)-α-methylbenzylamine imine derivative (reductive amination) of the resolved ketone. The synthetic sequences reported herein are readily scalable and avoid chromatographic purifications.

III. Preparation of Salt forms of (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide

(2S,3R)-N-(2-((3-Pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide as a free base is an amorphous powder with very limited water solubility. The free base will react with both inorganic and organic acids to make certain acid addition salts that have physical and chemical properties that are advantageous for the preparation of pharmaceutical compositions, including but not limited to crystallinity, water solubility, and stability. The stoichiometry of the salts of the present invention can vary.

Depending upon the manner by which the salts described herein are formed, the salts can have crystal structures that occlude solvents that are present during salt formation. Thus, the salts can occur as hydrates and other solvates of varying stoichiometry of solvent relative to the (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide.

The method for preparing the salt forms can vary. The preparation of (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide salt forms generally involves: (i) mixing the free base or a solution of the free base, namely (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide in a suitable solvent with an acid neat, or as a solution of an acids in a suitable solvent; (iia) cooling the resulting salt solution, if necessary to cause precipitation; or (iib) adding a suitable anti-solvent to cause precipitation; or (iic) evaporating the first solvent and adding a new solvent and repeating either steps (iia) or step (iib); and (iii) filtering and collecting the resulting salt. The stoichiometry, solvent mix, solute concentration, and temperature employed can vary. Representative solvents that can be used to prepare or recrystallize the salt forms include, without limitation, ethanol, methanol, isopropyl alcohol, acetone, ethyl acetate, and acetonitrile.

Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; and salts with amino acids such as aspartate and glutamate. The salts may be in some cases hydrates or ethanol solvates. Representative salts are provided as described in U.S. Patent Nos. 5,597,919 to Dull et al., 5,616,716 to Dull et al. and 5,663,356 to Ruecroft et al, each of which is incorporated by reference. Salt screening for the free base (2S,3R)-N-(2-((3-pyridinyl)methyl-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide revealed that, while many salts of pharmaceutically acceptable acids could be formed, only a few of these salts had acceptable properties for commercial manufacture. The ability to predict the characteristics exemplified by a commercially viable salt, therefore, does not exist. Acids that provided salts that were crystalline, namely salts that demonstrate some degree of crystallinity, dependent upon the

method by which they are prepared, include hydrochloric acid, sulfuric acid, phosphoric acid, p-toluenesulfonic acid, galactaric (mucic) acid, D-mandelic acid, D-tartaric acid, methanesulfonic acid, R- and S-10-camphorsulfonic acids, maleic acid, ketoglutaric acid and hippuric acid. Of these salts, the hydrochloric acid, phosphoric acid, maleic acid and p-toluenesulfonic acid salts each exhibited additional desirable properties, including high melting points, good water solubility, and low hygroscopicity.

IV. Pharmaceutical Compositions

The pharmaceutical compositions of the present invention include the salts described herein, in the pure state or in the form of a composition in which the compounds are combined with any other pharmaceutically compatible product, which can be inert or physiologically active. The resulting pharmaceutical compositions can be used to prevent a condition or disorder in a subject susceptible to such a condition or disorder, and/or to treat a subject suffering from the condition or disorder. The pharmaceutical compositions described herein include the compound of the present invention and/or pharmaceutically acceptable salts thereof.

The manner in which the compounds are administered can vary. The compositions are preferably administered orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier). Preferred compositions for oral administration include pills, tablets, capsules, caplets, syrups, and solutions, including hard gelatin capsules and time-release capsules. Standard excipients include binders, fillers, colorants, solubilizers, and the like. Compositions can be formulated in unit dose form, or in multiple or subunit doses. Preferred compositions are in liquid or semisolid form. Compositions including a liquid pharmaceutically inert carrier such as water or other pharmaceutically compatible liquids or semisolids can be used. The use of such liquids and semisolids is well known to those of skill in the art.

The compositions can also be administered via injection, i.e., intravenously, intramuscularly, subcutaneously, intraperitoneally, intraarterially, intrathecally; and intracerebroventricularly. Intravenous administration is the preferred method of injection. Suitable carriers for injection are well known to those of skill in the art and include 5% dextrose solutions, saline, and phosphate-buffered saline. The drug product can also be administered as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids).

The formulations can also be administered using other means, for example, rectal administration. Formulations useful for rectal administration, such as suppositories, are well known to those of skill in the art. The drug product can also be administered by inhalation (e.g.,

in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al., the disclosure of which is incorporated herein in its entirety); topically (e.g., in lotion form); transdermally (e.g., using a transdermal patch) or iontophoretically; or by sublingual or buccal administration. Although it is possible to administer a compound in the form of a bulk active chemical, it is preferred to present a drug product in the form of a pharmaceutical composition or formulation for efficient and effective administration.

Exemplary methods for administering compounds will be apparent to the skilled artisan. The usefulness of these formulations can depend on the particular composition used and the particular subject receiving the treatment. These formulations can contain a liquid carrier that can be oily, aqueous, emulsified or contain certain solvents suitable to the mode of administration.

The compositions can be administered intermittently or at a gradual, continuous, constant or controlled rate to a warm-blooded animal (e.g., a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey), but advantageously are administered to a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary.

Other suitable methods for administering the compounds of the present invention are described in U.S. Patent No. 5,604,231 to Smith et al., the contents of which are hereby incorporated by reference.

In an embodiment of the present invention and as will be appreciated by those skilled in the art, the compound of the present invention may be administered in combination with other therapeutic compounds or alternative, supplemental therapies.

The American Psychiatric Association's *Guideline For The Treatment Of Patients With Schizophrenia* states: "antipsychotic medications are indicated for nearly all acute psychotic episodes in patients with schizophrenia." In addition to antipsychotic medications, some patients also take anti-depressants or mood-stabilizers to help control related symptoms. One aspect of the present invention includes a combination of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof, with one or more antipsychotic medications, anti-depressants, or mood stabilizers.

One aspect of the present invention includes a combination of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof, with one or more of: Stelazine (Trifluoperazine), Flupenthixol (Fluanxol), Loxapine (Loxapac, Loxitane), Perphenazine (Etrafon, Trilafon), Chlorpromazine (Thorazine), Haldol (Haloperidol), Prolixin (Fluphenazine Decanoate, Modecate, Permitil), Atypical

Medications for Schizophrenia including but not limited to: Aripiprazole (Abilify) Clozaril (clozapine), Geodon (ziprasidone), Risperdal (resperidone), Seroquel (Quetiapine), or Zyprexa (olanzapine), or one or more new agents including but not limited to D2/5-HT2 antagonists such as iloperidone, DU 127090, or ORG 5222, D3 antagonists such as DTA 201A, neurokinin-3 antagonists such as osanetant, or another agonist of the nicotinic α7 receptor such as MEM3454.

Although an important element, medication is not the only treatment used for schizophrenia patients. Many patients and their families choose supplemental therapies (these can include psychosocial or cognitive therapy, rehabilitation day programs, peer support groups, nutritional supplements, etc) to use in conjunction with their medications. In certain severe cases, some patients also respond to electroconvulsive therapy (which has been shown to be safe and effective) or transcranial magnetic stimulation (TMS). These additional may help a person manage depression, social interactions, school, work, and the components for a full life.

In the case of therapy, some research has shown that psychotherapy and medication can be more effective than medication alone (however, the same study noted that psychotherapy alone was not a substitute for medication). The three main types of psychosocial therapy are: behavioral therapy (focuses on current behaviors), cognitive therapy (focuses on thoughts and thinking patterns), and interpersonal therapy (focuses on current relationships). For schizophrenia, cognitive-behavioral therapy has shown the most promise in conjunction with medication. Another aspect of the present invention includes a combination of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof with one or more supplemental therapy.

The compounds of the present invention may be employed alone or in combination with other therapeutic agents. Such a combination of pharmaceutically active agents may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compounds or agents and the relative timings of administration will be selected in order to achieve the desired therapeutic effect. The administration in combination may be by administration concomitantly in: (1) a unitary pharmaceutical composition including multiple compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time. The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the

compounds of the present invention may be used in combination with a variety of other suitable therapeutic agents useful in the treatment or prophylaxis of those disorders or conditions.

The appropriate dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. As noted, by "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder.

When treating a CNS disorder such as schizophrenia, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject and to modulate the activity of relevant NNR subtypes (e.g., provide neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). An example of prevention of a disorder is manifested by delaying the onset of the symptoms of the disorder. An example of treatment of a disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the recurrence of the symptoms of the disorder. Preferably, the effective amount is sufficient to obtain the desired result, but insufficient to cause appreciable side effects.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount sufficient to modulate the activity of relevant NNRs, but the amount should be insufficient to induce effects on skeletal muscles and ganglia to any significant degree. The effective dose of compounds will of course differ from patient to patient, but in general includes amounts starting where CNS effects or other desired therapeutic effects occur but below the amount where muscular effects are observed.

The compounds described herein, when employed in effective amounts in accordance with the methods described herein, can provide some degree of prevention of the progression of, ameliorate symptoms of, or ameliorate, to some degree, the recurrence of CNS or other disorders. The effective amounts of those compounds are typically below the threshold concentration required to elicit any appreciable side effects, for example those effects relating to skeletal muscle or ganglia. The compounds can be administered in a therapeutic window in which certain CNS and other disorders are treated and certain side effects are avoided. Ideally, the effective dose of the compounds described herein is sufficient to provide the desired effects upon the disorder but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, the compounds are administered at a dosage effective for treating the

CNS or other disorders but less than, often less than 1/5, and often less than 1/10, the amount required to elicit certain side effects to any significant degree.

Most preferably, effective doses are at very low concentrations, where maximal effects are observed to occur, with a minimum of side effects. Typically, the effective dose of such compounds generally requires administering the compound in an amount of less than 5 mg/kg of patient weight. Often, the compounds of the present invention are administered in an amount from less than about 1 mg/kg patent weight and usually less than about 100 µg/kg of patient weight, but frequently between about 10 µg to less than 100 µg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24-hour period. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, at least about 10, and at least about 100 mg/ 24 hr/ patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg/ 24 hr/ patient. In addition, the compositions are advantageously administered at an effective dose such that the concentration of the compound within the plasma of the patient normally does not exceed 150 ng/mL, often does not exceed 50 ng/mL, and frequently does not exceed 20 ng/mL. In one embodiment of the present invention, an effective dose is between about 1 mg and 50 mg in a 24-hour period.

Method of Using Pharmaceutical Compositions

As used herein, "intrinsic activity" or "efficacy" relates to some measure of biological effectiveness of the binding partner complex. With regard to receptor pharmacology, the context in which intrinsic activity or efficacy should be defined will depend on the context of the binding partner (*e.g.*, receptor/ligand) complex and the consideration of an activity relevant to a particular biological outcome. For example, in some circumstances, intrinsic activity may vary depending on the particular second messenger system involved. See Hoyer, D. and Boddeke, H., *Trends Pharmacol. Sci.* 14(7): 270-5 (1993), herein incorporated by reference with regard to such teaching.

As used herein, neurotransmitters whose release is mediated by the compounds described herein include, but are not limited to, acetylcholine, dopamine, norepinephrine, serotonin, and glutamate, and the compounds described herein function as modulators at the α7 subtype of the CNS NNRs.

As used herein, the terms "prevention" or "prophylaxis" include any degree of reducing the progression of or delaying the onset of a disease, disorder, or condition. The term includes

providing protective effects against a particular disease, disorder, or condition as well as amelioration of the recurrence of the disease, disorder, or condition. Thus, in another aspect, the invention provides a method for treating a subject having or at risk of developing or experiencing a recurrence of a NNR or nAChR mediated disorder. The compounds and pharmaceutical compositions of the invention may be used to achieve a beneficial therapeutic or prophylactic effect, for example, in a subject with a CNS dysfunction.

As noted above, the free base and salt compounds of the present invention modulate the α7 NNR subtype, characteristic of the CNS, and can be used for preventing or treating various conditions or disorders, including those of the CNS, in subjects which have or are susceptible to such conditions or disorders, by modulation of the α7 NNR. The compounds have the ability to selectively bind to the α7 NNR and express nicotinic pharmacology. For example, compounds of the present invention, when administered in effective amounts to patients in need thereof, provide some degree of prevention of the progression of the CNS disorder, namely, providing protective effects, amelioration of the symptoms of the CNS disorder, or amelioration of the reoccurrence of the CNS disorder, or a combination thereof.

The compounds of the present invention can be used to treat or prevent those types of conditions and disorders for which other types of nicotinic compounds have been proposed or are shown to be useful as therapeutics. See, for example, the references previously listed hereinabove, as well as Williams et al., *Drug News Perspec.* 7(4): 205 (1994), Arneric et al., *CNS Drug Rev.* 1(1): 1-26 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* 5(1): 79-100 (1996), Bencherif et al., *J. Pharmacol. Exp. Ther.* 279: 1413 (1996), Lippiello et al., *J. Pharmacol. Exp. Ther.* 279: 1422 (1996), Damaj et al., *J. Pharmacol. Exp. Ther.* 291: 390 (1999); Chiari et al., *Anesthesiology* 91: 1447 (1999), Lavand'homme and Eisenbach, *Anesthesiology* 91: 1455 (1999), Holladay et al., *J. Med. Chem.* 40(28): 4169-94 (1997), Bannon et al., *Science* 279: 77 (1998), PCT WO 94/08992, PCT WO 96/31475, PCT WO 96/40682, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., 5,604,231 to Smith et al. and 5,852,041 to Cosford et al., the disclosures of which are incorporated herein by reference with regard to such therapeutic teaching.

The compounds and their pharmaceutical compositions are useful in the treatment or prevention of a variety of CNS disorders, including cognitive deficits and dysfunctions, age-related and otherwise and attentional disorders and, in particular schizophrenia.

As noted, schizophrenia can be divided into three major phases: the prodromal state, an active phase, and a residual phase. These phases tend to occur in sequence and appear in cycles throughout the course of the illness. The residual phase is similar to the prodromal

phase although during the residual phase blunted affect and impairment in role functioning are more common. While psychotic symptoms may persist into the residual phase, the psychotic symptoms are less likely to be accompanied by such strong affect as experienced during the active phase. There is great variation in the severity of the residual phase from one person to the next. Some individuals will function extremely well while others may be considerably more impaired. After an active phase, people may be listless, have trouble concentrating and be withdrawn. The symptoms in this phase are similar to those outlined under the prodromal phase. If there have been no symptoms before the first episode, few or no symptoms may be experienced afterward. During a lifetime, people with schizophrenia may become actively ill once or twice, or have many more episodes. Unfortunately, residual symptoms may increase, while ability to function normally may decrease, after each active phase. It is therefore important to try to avoid relapses by following the prescribed treatment. Currently it is difficult to predict at the onset how fully a person will recover. The most common course of the disorder generally involves numerous active phases of illness with residual phases of impairment between episodes. The extent of residual impairment often increases between episodes during the initial years of the disorder although may possibly become less severe during the later phases of the illness.

Reference is made to Marder et al., Methodological Issues in Negative Symptom Trials, Schizophrenia Bulletin, 2011; and Laughren and Levin, Food and Drug Administration Commentary of Methodological Issues in Negative Symptom Trials, Schizophrenia Bulletin, 2011, each incorporated herein with regard to such teaching.

The above conditions and disorders are discussed in further detail, for example, in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000; incorporated herein by reference with regard to defining such conditions and disorders. This Manual may also be referred to for greater detail on the symptoms and diagnostic features.

Preferably, the treatment or prevention of diseases, disorders, and conditions occurs without appreciable adverse side effects, including, for example, significant increases in blood pressure and heart rate, significant negative effects upon the gastro-intestinal tract, and significant effects upon skeletal muscle.

The compounds of the present invention, when employed in effective amounts, are believed to modulate the activity of the α7 NNR without appreciable interaction with the nicotinic subtypes that characterize the human ganglia, as demonstrated by a lack of the ability to elicit nicotinic function in adrenal chromaffin tissue, or skeletal muscle, further demonstrated by a lack

of the ability to elicit nicotinic function in cell preparations expressing muscle-type nicotinic receptors. Thus, these compounds are believed capable of treating or preventing diseases, disorders, and conditions without eliciting significant side effects associated activity at ganglionic and neuromuscular sites. Thus, administration of the compounds is believed to provide a therapeutic window in which treatment of certain diseases, disorders, and conditions is provided, and certain side effects are avoided. That is, an effective dose of the compound is believed sufficient to provide the desired effects upon the disease, disorder, or condition, but is believed insufficient, namely is not at a high enough level, to provide undesirable side effects.

Thus, the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use in therapy, such as a therapy described above.

V. Synthetic Examples

The following synthetic examples are provided to illustrate the present invention and should not be construed as limiting the scope thereof. In these examples, all parts and percentages are by weight, unless otherwise noted. All solutions are aqueous unless otherwise noted.

Example 1: Small scale synthesis of (2S, 3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide (Compound A) and its enantiomer, (2R, 3S)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide

2-((3-Pyridinyl)methylene)-1-azabicyclo[2.2.2]octan-3-one

Potassium hydroxide (56 g, 0.54 mole) was dissolved in methanol (420 mL). 3-Quinuclidinone hydrochloride (75 g, 0.49 mole) was added and the mixture was stirred for 30 min at ambient temperature. 3-Pyridinecarboxaldehyde (58 g, 0.54 mole) was added and the mixture stirred for 16 h at ambient temperature. The reaction mixture became yellow during this period, with solids caking on the walls of the flask. The solids were scraped from the walls and the chunks broken up. With rapid stirring, water (390 mL) was added. When the solids dissolved, the mixture was cooled at 4°C overnight. The crystals were collected by filtration, washed with water, and air dried to obtain 80 g of yellow solid. A second crop (8 g) was obtained by concentration of the filtrate to ~10% of its former volume and cooling at 4°C overnight. Both crops were sufficiently pure for further transformation (88 g, 82% yield).

2-((3-Pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one

2-((3-Pyridinyl)methylene)-1-azabicyclo[2.2.2]octan-3-one (20 g, 93 mmol) was suspended in methanol (200 mL) and treated with 46 mL of 6 M hydrochloric acid. 10%

Palladium on carbon (1.6 g) was added and the mixture was shaken under 25 psi hydrogen for 16 h. The mixture was filtered through diatomaceous earth, and the solvent was removed from the filtrate by rotary evaporation. This provided crude 2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one hydrochloride, as a white gum (20 g), which was subsequently treated with 2 M sodium hydroxide (50 mL) and chloroform (50 mL) and stirred for an hour. The chloroform layer was separated, and the aqueous phase was treated with 2 M sodium hydroxide (~5 mL, enough to raise the pH to 10) and saturated aqueous Sodium chloride (25 mL). This aqueous mixture was extracted with chloroform (3 x 10 mL), and the combined chloroform extracts were dried (anhydrous magnesium sulfate) and concentrated by rotary evaporation. The residue (18 g) was dissolved in warm ether (320 mL) and cooled to 4°C. The white solid was filtered off, washed with a small portion of cold ether and air dried. Concentration of the filtrate to ~10% of its former volume and cooling at 4°C produced a second crop. A combined yield 16 g (79%) was obtained.

3-Amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane

To a stirred solution of 2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one (3.00 g, 13.9 mmol) in dry methanol (20 mL), under nitrogen, was added a 1 M solution of zinc chloride in ether (2.78 mL, 2.78 mmol). After stirring at ambient temperature for 30 min, this mixture was treated with solid ammonium formate (10.4 g, 167 mmol). After stirring another hour at ambient temperature, solid sodium cyanoborohydride (1.75 g, 27.8 mmol) was added in portions. The reaction was then stirred at ambient temperature overnight and terminated by addition of water (~ 5 mL). The quenched reaction was partitioned between 5 M sodium hydroxide (10 mL) and chloroform (20 mL). The aqueous layer was extracted with chloroform (20 mL), and combined organic layers were dried (sodium sulfate), filtered and concentrated. This left 2.97 g of yellow gum. GCMS analysis indicated that the product was a 1:9 mixture of the *cis* and *trans* amines, along with a trace of the corresponding alcohol (98% total mass recovery).

(2R,3S) and (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane

Di-p-toluoyl-D-tartaric acid (5.33 g, 13.8 mmol) was added to a stirred solution of crude 3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane (6.00 g, 27.6 mmol of 1:9 *cis/trans*) in methanol (20 mL). After complete dissolution, the clear solution was then concentrated to a solid mass by rotary evaporation. The solid was dissolved in a minimum amount of boiling methanol (~5 mL). The solution was cooled slowly, first to ambient temperature (1 h), then for ~ 4 h at 5°C and finally at -5°C overnight. The precipitated salt was collected by suction filtration and recrystallized from 5 mL of methanol. Air drying left 1.4 g of white solid, which was partitioned between chloroform (5 mL) and 2 M sodium hydroxide (5 mL). The chloroform layer

and a 5 mL chloroform extract of the aqueous layer were combined, dried (anhydrous sodium sulfate) and concentrated to give a colorless oil (0.434 g). The enantiomeric purity of this free base was determined by conversion of a portion into its N-(tert-butoxycarbonyl)-L-prolinamide, which was then analyzed for diastereomeric purity (98%) using LCMS.

The mother liquor from the initial crystallization was made basic (~ pH 11) with 2 M sodium hydroxide and extracted twice with chloroform (10 mL). The chloroform extracts were dried (anhydrous sodium sulfate) and concentrated to give an oil. This amine (3.00 g, 13.8 mmol) was dissolved in methanol (10 mL) and treated with di-p-toluoyl-L-tartaric acid (2.76 g, 6.90 mmol). The mixture was warmed to aid dissolution and then cooled slowly to -5°C, where it remained overnight. The precipitate was collected by suction filtration, recrystallized from methanol and dried. This left 1.05 g of white solid. The salt was converted into the free base (yield = 0.364 g), and the enantiomeric purity (97%) was assessed using the prolinamide method, as described above for the other enantiomer.

Trans enantiomer A of N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide

Diphenylchlorophosphate (0.35 mL, 0.46 g, 1.7 mmol) was added drop-wise to a solution of benzofuran-2-carboxylic acid (0.28 g, 1.7 mmol) and triethylamine (0.24 mL, 0.17 g, 1.7 mmol) in dry dichloromethane (5 mL). After stirring at ambient temperature for 30 min, a solution of (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane (0.337 g, 1.55 mmol) (that derived from the di-p-toluoyl-D-tartaric acid salt) and triethylamine (0.24 mL, 0.17 g, 1.7 mmol) in dry dichloromethane (5 mL) was added. The reaction mixture was stirred overnight at ambient temperature, and then treated with 10% sodium hydroxide (1 mL). The biphasic mixture was separated, and the organic layer was concentrated on a Genevac centrifugal evaporator. The residue was dissolved in methanol (6 mL) and purified by HPLC on a C18 silica gel column, using an acetonitrile/water gradient, containing 0.05% trifluoroacetic acid, as eluent. Concentration of selected fractions, partitioning of the resulting residue between chloroform and saturated aqueous sodium bicarbonate, and evaporation of the chloroform gave 0.310 g (42% yield) of white powder (95% pure by GCMS). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, 1H), 8.34 (dd, 1H), 7.66 (d, 1H), 7.58 (dt, 1H), 7.49 (d, 1H), 7.44 (s, 1H), 7.40 (dd, 1H), 7.29 (t, 1H), 7.13 (dd, 1H), 6.63 (d, 1H), 3.95 (t, 1H), 3.08 (m, 1H), 2.95 (m, 4H), 2.78 (m, 2H), 2.03 (m, 1H), 1.72 (m, 3H), 1.52 (m, 1H).

This material (trans enantiomer A) was later determined to be identical, by chiral chromatogrphic analysis, to material whose absolute configuration is 2S,3R (established by x-ray crystallographic analysis).

Trans enantiomer B of N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide

Diphenylchlorophosphate (96 µL, 124 mg, 0.46 mmol) was added drop-wise to a solution of the benzofuran-2-carboxylic acid (75 mg, 0.46 mmol) and triethylamine (64 µL, 46 mg, 0.46 mmol) in dry dichloromethane (1 mL). After stirring at ambient temperature for 45 min, a solution of (2R,3S)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane (0.10 g, 0.46 mmol) (that derived from the di-p-toluoyl-L-tartaric acid salt) and triethylamine (64 µL, 46 mg, 0.46 mmol) in dry dichloromethane (1 mL) was added. The reaction mixture was stirred overnight at ambient temperature, and then treated with 10% sodium hydroxide (1 mL). The biphasic mixture was separated, and the organic layer and a chloroform extract (2 mL) of the aqueous layer was concentrated by rotary evaporation. The residue was dissolved in methanol and purified by HPLC on a C18 silica gel column, using an acetonitrile/water gradient, containing 0.05% trifluoroacetic acid, as eluent. Concentration of selected fractions, partitioning of the resulting residue between chloroform and saturated aqueous sodium bicarbonate, and evaporation of the chloroform gave 82.5 mg (50% yield) of a white powder. The NMR spectrum was identical to that obtained for the 2S,3R isomer. Since the immediate precursor of this material (trans enantiomer B) is enantiomeric to the immediate precursor of 2S,3R compound (trans enantiomer A), the absolute configuration of trans enantiomer B is presumed to be 2R,3S.

Example 2: Large scale synthesis of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide and (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)-1-benzofuran-2-carboxamide *p*-toluenesulfonate salt

2-((3-Pyridinyl)methylene)-1-azabicyclo[2.2.2]octan-3-one

3-Quinuclidinone hydrochloride (8.25 kg, 51.0 mol) and methanol (49.5 L) were added to a 100 L glass reaction flask, under an nitrogen atmosphere, equipped with a mechanical stirrer, temperature probe, and condenser. Potassium hydroxide (5.55 kg, 99.0 mol) was added via a powder funnel over an approximately 30 min period, resulting in a rise in reaction temperature from 50°C to 56°C. Over an approximately 2 h period, 3-pyridinecarboxaldehyde (4.80 kg, 44.9 mol) was added to the reaction mixture. The resulting mixture was stirred at 20°C ± 5°C for a minimum of 12 h, as the reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction, the reaction mixture was filtered through a sintered glass funnel and the filter cake was washed with methanol (74.2 L). The filtrate was concentrated, transferred to a reaction flask, and water (66.0 L) was added. The suspension was stirred for a minimum of

30 min, filtered, and the filter cake was washed with water (90.0 L) until the pH of the rinse was 7-9. The solid was dried under vacuum at 50°C ± 5°C for a minimum of 12 h to give 8.58 kg (89.3%) of 2-((3-pyridinyl)methylene)-1-azabicyclo[2.2.2]octan-3-one.

(2S)-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one di-*p*-toluoyl-D-tartrate salt

2-((3-Pyridinyl)methylene)-1-azabicyclo[2.2.2]octan-3-one (5.40 kg, 25.2 mol) and methanol (40.5 L) were added to a 72 L reaction vessel under an inert atmosphere equipped with a mechanical stirrer, temperature probe, low-pressure gas regulator system, and pressure gauge. The headspace was filled with nitrogen, and the mixture was stirred to obtain a clear yellow solution. To the flask was added 10% palladium on carbon (50% wet) (270 g). The atmosphere of the reactor was evacuated using a vacuum pump, and the headspace was replaced with hydrogen to 10 to 20 inches water pressure. The evacuation and pressurization with hydrogen were repeated 2 more times, leaving the reactor under 20 inches water pressure of hydrogen gas after the third pressurization. The reaction mixture was stirred at 20°C ± 5°C for a minimum of 12 h, and the reaction was monitored via TLC. Upon completion of the reaction, the suspension was filtered through a bed of Celite®545 (1.9 kg) on a sintered glass funnel, and the filter cake was washed with methanol (10.1 L). The filtrate was concentrated to obtain a semi-solid which was transferred, under an nitrogen atmosphere, to a 200 L reaction flask fitted with a mechanical stirrer, condenser, and temperature probe. The semi-solid was dissolved in ethanol (57.2 L), and di-*p*-toluoyl-D-tartaric acid (DTTA) (9.74 kg, 25.2 mol) was added. The stirring reaction mixture was heated at reflux for a minimum of 1 h, and for an additional minimum of 12 h while the reaction was cooled to between 15°C and 30°C. The suspension was filtered using a tabletop filter, and the filter cake was washed with ethanol (11.4 L). The product was dried under vacuum at ambient temperature to obtain 11.6 kg (76.2% yield, 59.5% factored for purity) of (2S)-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one di-*p*-toluoyl-D-tartrate salt.

(2S,3R)-3-Amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane di-*p*-toluoyl-D-tartrate salt

Water (46.25 L) and sodium bicarbonate (4.35 kg, 51.8 mol) were added to a 200 L flask. Upon complete dissolution, dichloromethane (69.4 L) was added. (2S)-2-((3-Pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one di-*p*-toluoyl-D-tartrate salt (11.56 kg, 19.19 mol) was added, and the reaction mixture was stirred for between 2 min and 10 min. The layers were allowed to separate for a minimum of 2 min (additional water (20 L) was added when necessary to partition the layers). The organic phase was removed and dried over anhydrous sodium sulfate. Dichloromethane (34.7 L) was added to the remaining aqueous phase, and the suspension was stirred for between 2 min and 10 min. The layers were allowed to separate for

between 2 min and 10 min. Again, the organic phase was removed and dried over anhydrous sodium sulfate. The extraction of the aqueous phase with dichloromethane (34.7 L) was repeated one more time, as above. Samples of each extraction were submitted for chiral HPLC analysis. The sodium sulfate was removed by filtration, and the filtrates were concentrated to obtain (2S)-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one (4.0 kg) as a solid.

The (2S)-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one (3.8 kg) was transferred to a clean 100 L glass reaction flask, under a nitrogen atmosphere, fitted with a mechanical stirrer and temperature probe. Anhydrous tetrahydrofuran (7.24 L) and (+)-(R)-α-methylbenzylamine (2.55 L, 20.1 mol) were added. Titanium(IV) isopropoxide (6.47 L, 21.8 mol) was added to the stirred reaction mixture over a 1 h period. The reaction was stirred under a nitrogen atmosphere for a minimum of 12 h. Ethanol (36.17 L) was added to the reaction mixture. The reaction mixture was cooled to below -5°C, and sodium borohydride (1.53 kg, 40.5 mol) was added in portions, keeping the reaction temperature below 15°C (this addition took several hours). The reaction mixture was then stirred at 15°C ± 10°C for a minimum of 1 h. The reaction was monitored by HPLC, and upon completion of the reaction (as indicated by less than 0.5% of (2S)-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-one remaining), 2 M sodium hydroxide (15.99 L) was added and the mixture was stirred for a minimum of 10 min. The reaction mixture was filtered through a bed of Celite®545 in a tabletop funnel. The filter cake was washed with ethanol (15.23 L), and the filtrate was concentrated to obtain an oil.

The concentrate was transferred to a clean 100 L glass reaction flask equipped with a mechanical stirrer and temperature probe under an inert atmosphere. Water (1 L) was added, and the mixture was cooled to 0°C ± 5°C. 2 M Hydrochloric acid (24 L) was added to the mixture to adjust the pH of the mixture to pH 1. The mixture was then stirred for a minimum of 10 min, and 2 M sodium hydroxide (24 L) was slowly added to adjust the pH of the mixture to pH 14. The mixture was stirred for a minimum of 10 min, and the aqueous phase was extracted with dichloromethane (3 x 15.23 L). The organic phases were dried over anhydrous sodium sulfate (2.0 kg), filtered, and concentrated to give (2S,3R)-N-((1R)-phenylethyl)-3-amino-2-((3-pyridinyl)methyl))-1-azabicyclo[2.2.2]octane (4.80 kg, 84.7% yield).

The (2S,3R)-N-((1R)-phenylethyl)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane was transferred to a 22 L glass flask equipped with a mechanical stirrer and temperature probe under an inert atmosphere. Water (4.8 L) was added, and the stirring mixture was cooled to 5°C ± 5°C. Concentrated hydrochloric acid (2.97 L) was slowly added to the reaction flask, keeping the temperature of the mixture below 25°C. The resulting solution was transferred to a 72 L reaction flask containing ethanol (18 L), equipped with a mechanical

stirrer, temperature probe, and condenser under an inert atmosphere. To the flask was added 10% palladium on carbon (50% wet) (311.1 g) and cyclohexene (14.36 L). The reaction mixture was heated at near-reflux for a minimum of 12 h, and the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to below 45°C, and it was filtered through a bed of Celite®545 (1.2 kg) on a sintered glass funnel. The filter cake was rinsed with ethanol (3 L) and the filtrate was concentrated to obtain an aqueous phase. Water (500 mL) was added to the concentrated filtrate, and this combined aqueous layer was washed with methyl tert-butyl ether (MTBE) (2 x 4.79 L). 2 M Sodium hydroxide (19.5 L) was added to the aqueous phase to adjust the pH of the mixture to pH 14. The mixture was then stirred for a minimum of 10 min. The aqueous phase was extracted with chloroform (4 x 11.96 L), and the combined organic phases were dried over anhydrous sodium sulfate (2.34 kg). The filtrate was filtered and concentrated to obtain (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane (3.49 kg, > quantitative yield) as an oil.

The (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane was transferred to a clean 100 L reaction flask equipped with a mechanical stirrer, condenser, and temperature probe under an inert atmosphere. Ethanol (38.4 L) and di-p-toluoyl-D-tartaric acid (3.58 kg, 9.27 mol) were added. The reaction mixture was heated at gentle reflux for a minimum of 1 h. The reaction mixture was then stirred for a minimum of 12 h while it was cooled to between 15°C and 30°C. The resulting suspension was filtered, and the filter cake was washed with ethanol (5.76 L). The filter cake was transferred to a clean 100 L glass reaction flask equipped with a mechanical stirrer, temperature probe, and condenser under an inert atmosphere. A 9:1 ethanol/water solution (30.7 L) was added, and the resulting slurry was heated at gentle reflux for a minimum of 1 h. The reaction mixture was then stirred for a minimum of 12 h while cooling to between 15°C and 30°C. The mixture was filtered and the filter cake was washed with ethanol (5.76 L). The product was collected and dried under vacuum at 50°C ± 5°C for a minimum of 12 h to give 5.63 kg (58.1% yield) of (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane di-*p*-toluoyl-D-tartrate salt.

(2S,3R)-N-(2-((3-Pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide

(2S,3R)-3-Amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane di-*p*-toluoyl-D-tartrate salt (3.64 kg, 5.96 mol) and 10% aqueous sodium chloride solution (14.4 L, 46.4 mol) were added to a 72 L glass reaction flask equipped with a mechanical stirrer under an inert atmosphere. 5 M Sodium hydroxide (5.09 L) was added to the stirring mixture to adjust the pH of the mixture to pH 14. The mixture was then stirred for a minimum of 10 min. The aqueous solution was extracted with chloroform (4 x 12.0 L), and the combined organic layers were dried

over anhydrous sodium sulfate (1.72 kg). The combined organic layers were filtered, and the filtrate was concentrated to obtain (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane (1.27 kg) as an oil.

The (2S,3R)-3-amino-2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octane was transferred to a 50 L glass reaction flask equipped with a mechanical stirrer under an inert atmosphere. Dichloromethane (16.5 L), triethylamine (847 mL, 6.08 mol), benzofuran-2-carboxylic acid (948 g, 5.85 mol) and O-(benzotriazol-1-yl)-N,N,N,1-tetramethyluronium hexafluorophosphate (HBTU) (2.17 kg, 5.85 mol) were added to the reaction mixture. The mixture was stirred for a minimum of 4 h at ambient temperature, and the reaction was monitored by HPLC. Upon completion of the reaction, 10% aqueous potassium carbonate (12.7 L, 17.1 mol) was added to the reaction mixture and the mixture was stirred for a minimum of 5 min. The layers were separated and the organic phase was washed with 10% brine (12.7 L). The layers were separated and the organic phase was cooled to 15°C ± 10 °C. 3 M Hydrochloric acid (8.0 L) was slowly added to the reaction mixture to adjust the pH of the mixture to pH 1. The mixture was then stirred for a minimum of 5 min, and the layers were allowed to partition for a minimum of 5 min. The solids were filtered using a table top filter. The layers of the filtrate were separated, and the aqueous phase and the solids from the funnel were transferred to the reaction flask. 3 M Sodium hydroxide (9.0 L) was slowly added to the flask in portions to adjust the pH of the mixture to pH 14. The aqueous phase was extracted with dichloromethane (2 x 16.5 L). The combined organic phases were dried over anhydrous sodium sulfate (1.71 kg). The mixture was filtered, and the filtrate was concentrated to give (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide (1.63 kg, 77.0% yield) as a yellow solid.

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl]benzofuran-2-carboxamide *p*-toluenesulfonate

(2S,3R)-N-(2-((3-Pyridinyl)methyl)-1-azabicyclo[2.2.2]octan-3-yl)benzofuran-2-carboxamide (1.62 kg, 4.48 mol) and dichloromethane (8.60 kg) were added into a carboy. The weight/weight percent of the material in solution was determined through HPLC analysis. The solution was concentrated to an oil, acetone (4 L) was added, and the mixture was concentrated to an oily solid. Additional acetone (12 L) was added to the oily solid in the rotary evaporator bulb, and the resulting slurry was transferred to a 50 L glass reaction flask with a mechanical stirrer, condenser, temperature probe, and condenser under an inert atmosphere. The reaction mixture was heated to 50°C ± 5°C. Water (80.7 g) was added to the solution, and it was stirred for a minimum of 10 min. *p*-Toluenesulfonic acid (853 g, 4.44 mol) was added to the reaction

mixture in portions over approximately 15 min. The reaction mixture was heated to reflux and held at that temperature for a minimum of 30 min to obtain a solution. The reaction was cooled to 40°C ± 5°C over approximately 2 h. Isopropyl acetate (14.1 L) was added over approximately 1.5 h. The reaction mixture was slowly cooled to ambient temperature over a minimum of 10 h. The mixture was filtered and the filter cake was washed with isopropyl acetate (3.5 L). The isolated product was dried under vacuum at 105°C ± 5°C for between 2 h and 9 h to give 2.19 kg (88.5% yield) of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide *p*-toluenesulfonate, mp 226-228°C. ^{1}H NMR (500 MHz, D_2O) δ 8.29 (s, 1H), 7.78 (m, *J* = 5.1, 1H), 7.63 (d, *J* = 7.9, 1H), 7.54 (d, *J* = 7.8, 1H), 7.49 (d, *J* = 8.1, 2H), 7.37 (m, *J* = 8.3, 1H), 7.33 (m, *J* = 8.3, 6.9, 1.0, 1H), 7.18 (m, *J* = 7.8, 6.9, 1.0, 1H), 7.14 (d, *J* = 8.1, 2H), 7.09 (s, 1H), 6.99 (dd, *J* = 7.9, 5.1, 1H), 4.05 (m, *J* = 7.7, 1H), 3.74 (m, 1H), 3.47 (m, 2H), 3.28 (m, 1H), 3.22 (m, 1H), 3.15 (dd, *J* = 13.2, 4.7, 1H), 3.02 (dd, *J* = 13.2, 11.5, 1H), 2.19 (s, 3H), 2.02 (m, 2H), 1.93 (m, 2H), 1.79 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 157.2, 154.1, 150.1, 148.2, 146.4, 145.2, 138.0, 137.0, 130.9, 128.2 (2), 126.9, 126.8, 125.5 (2), 123.7, 123.3, 122.7, 111.7, 100.7, 61.3, 50.2, 48.0, 40.9, 33.1, 26.9, 21.5, 20.8, 17.0.

Samples of this material were converted into Compound A free base (for use in salt selection studies) by treatment with aqueous sodium hydroxide and extraction with chloroform. Thorough evaporation of the chloroform left an off-white powder, mp 167-170°C, with the following spectral characteristics: Positive ion electrospray MS $[M+H]^+$ ion m/z = 362. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, *J* = 7.6 Hz, 1H), 8.43 (d, *J* = 1.7 Hz, 1H), 8.28 (dd, *J* = 1.6, 4.7 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.63 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.52 (s, 1H), 7.46 (m, *J* = 8.5, 7.5 Hz, 1H), 7.33 (m, *J* = 7.7, 7.5 Hz, 1H), 7.21 (dd, *J* = 4.7, 7.7 Hz, 1H), 3.71 (m, *J* = 7.6 Hz, 1H), 3.11 (m, 1H), 3.02 (m, 1H), 2.80 (m, 2H), 2.69 (m, 2H), 2.55 (m, 1H), 1.80 (m, 1H), 1.77 (m, 1H), 1.62 (m, 1H), 1.56 (m, 1H), 1.26 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.1, 154.1, 150.1, 149.1, 146.8, 136.4, 135.4, 127.1, 126.7, 123.6, 122.9, 122.6, 111.8, 109.3, 61.9, 53.4, 49.9, 40.3, 35.0, 28.1, 26.1, 19.6.

The monohydrochloride salt of Compound A (see Example 3) was submitted for x-ray crystallographic analysis. The resulting crystal structure established the 2S,3R absolute configuration of Compound A.

Example 3: Synthesis of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide hydrochloride salts

Monohydrochloride: A hydrochloric acid/THF solution was prepared by adding of concentrated hydrochloric acid (1.93 mL of 12M, 23.2 mmol) drop-wise to 8.5 mL of chilled THF.

The solution was warmed to ambient temperature. To a round bottom flask was added (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide (8.49 g, 23.5 mmol) and acetone (85 mL). The mixture was stirred and heated at 45-50°C until a complete solution was obtained. The hydrochloric acid/THF solution prepared above was added drop-wise over a 5 min period, with additional THF (1.5 mL) used in the transfer. Granular, white solids began to form during the addition of the acid solution. The mixture was cooled to ambient temperature, and stirred overnight (16 h). The solids were collected by suction filtration, the filter cake was washed with acetone (10 mL), and the solid was air-dried with suction for 30 min. The solid was further dried in a vacuum oven at 75°C for 2 h to give 8.79 g of the fine white crystals (94% yield), mp 255-262°C. Chiral LC analysis gave a purity of 98.8% (270 nm). ^{1}H-NMR (DMSO-d_6) shows no residual solvents and confirms mono stoichiometry. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.7 (broad s, 1H – quaternary ammonium), 8.80 (broad s, 1H – amide H), 8.54 (s, 1H), 8.23 (d, 1H), 7.78 (d, 1H), 7.74 (d, 1H), 7.60 (d, 1H), 7.47 (m, 2H), 7.33 (m, 1H), 7.19 (m, 1H), 4.19 (m, 1H), 4.08 (m, 1H), 3.05-3.55 (m, 6H), 2.00-2.10 (m, 3H), 1.90 (m, 1H), 1.70 (m, 1H). An x-ray crystallographic analysis of this salt established stereochemical assignment and stoichiometry.

Dihydrochloride: Hydrogen chloride gas was slowly bubbled into a ice cooled solution of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide (1.9 g, 5.3 mmol) in anhydrous ether (25 mL). The volatiles were removed, first in a nitrogen stream and then with high vacuum (sodium hydroxide scrubber in high vacuum line). The residue was triturated several times with small volumes of anhydrous ether (discarded), and the remaining solid was dried under high vacuum. This gave 2.17 g (94% yield) of off-white powder, mp 210-212 °C (hygroscopic). Chiral LC analysis gave a purity of 93.7% (270 nm). Positive ion electrospray MS $[M+H]^+$ ion m/z = 362. ^{1}H NMR (300 MHz, CD_3OD) δ 9.15 (s, 1H), 8.84 (d, 1H), 8.63 (d, 1H), 7.97 (t, 1H), 7.75 (d, 1H), 7.61 (d, 1H), 7.52 (m, 2H), 7.35 (t, 1H), 4.50 (m, 1H), 4.32 (m, 1H), 3.40-3.85 (m, 6H), 1.95-2.40 (m, 5H).

VI. A Double-blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess Efficacy, Safety, and Tolerability of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof as Augmentation Therapy to Improve Cognition in Outpatients with Cognitive Dysfunction in Schizophrenia

A Phase 2 clinical proof of concept trial was conducted to evaluate (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt as an augmentation therapy to improve cognition in patients with schizophrenia.

In the trial, (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or pharmaceutically acceptable salt thereof met the protocol criteria for a positive result on the primary efficacy outcome measure, the Groton Maze Learning Task (GMLT) of the CogState Schizophrenia Battery (CogState, New Haven, CT; http://www.cogstate.com/go/clinicaltrials/our-test-batteries/schizophrenia-battery), and was well tolerated.

As provided in the above-referenced brochure, CogState is a provider of cognitive testing products and services that predominantly caters to the global pharmaceutical industry. The Schizophrenia Cognitive Test Battery covers all domains identified by MATRICS initiative; requires around 35 minutes for administration; is sensitive to the effects of novel compounds and licensed medication; is sensitive to the effects of medication in groups or individual patients; and the outcome measures are related to functional status.

There is sensitivity of three measures from the CogState schizophrenia battery to change in cognitive function in schizophrenia. Figure 1 summarizes the results from a placebo controlled parallel group study comparing the effect of a novel alpha 7 nicotine agonist on the Simple Reaction Time (information processing), International Shopping List (verbal learning) and Groton Maze Learning Task (problem solving) tasks in patients with chronic schizophrenia (n=30 per group) who were stable on their antipsychotic medication at randomization. Improvement in performance of greater than 0.4 standard deviation units was found for each measure.

Figure 2 illustrates sensitivity of the primary outcome measures from the CogState schizophrenia battery to cognitive impairment in patients with chronic schizophrenia who were receiving antipsychotic medication in three different geographical areas. The nature and magnitude of impairment in the different cognitive domains was consistent across the three cultural groups.

As a result of FDA and NIH agreement that cognitive dysfunction/impairment is an important health issue in schizophrenia, the FDA confirmed that improved cognitive function would be considered as a primary outcome in schizophrenia research. Following this guidance, the MATRICS initiative, a collaboration of FDA, NIH, academic researchers, and industry, recommended a test battery for the assessment of cognition in this population. Prior to the MATRICS initiative, there was no consensus on the optimum outcome measures for evaluation of cognitive function in clinical trials in schizophrenia. The test criteria recommended by the MATRICS group was defined as:

High test-retest reliability

- Good coverage of cognitive domains
- Comparable alternative forms
- Strong internal consistency
- Well established in general population
- Demonstrated tolerability and acceptability

All CogState tasks meet the criteria set out above with regards to scientific validity, reliability and consistency. These tasks, when put together to form the CogState Schizophrenia Battery, also cover the cognitive domains stipulated by the MATRICS initiative.

The test battery is rapid. It covers all necessary domains in around 35 minutes – a benefit when working with patients suffering from schizophrenia. The user-friendly test battery allows for non-expert administration on standard computer equipment, which reduces costs and increases efficiency. The tasks utilize culture-neutral stimuli, which ensures that they can be integrated into clinical trials all around the world regardless of culture, ethnicity and socio-economic status. The test battery has high test-retest reliability, which ensures quality data.

Table 1 – The CogState Schizophrenia Battery

Domain	CogState Task	Task Description
Speed of Processing/Simple Reaction Time	Detection	The pre-task on-screen instructions ask: "Has the card turned over?" A playing card is presented in the center of the screen. The card will flip over so it is face up. As soon as it does, the subject must press the "Yes" key. The card will go to the back of the pack and the subject must press the "Yes" key as soon as the next card flips over and so on.
Attention/Vigilance	Identification	The pre-task on-screen instructions ask: "Is the card red?" A playing card is presented in the center of the screen. The card will flip over so it is face up. As soon as it does this the subject must decide whether the card is red or not. If it is red they should press "Yes", if it is not red they should press "No".
Working Memory	One-Back	The pre-task on-screen instructions ask: "Does the face up card exactly match the one before?" A playing card is presented face up in the center of the screen. The subject must decide as each card is presented whether it is identical to the one just before. If the card is identical to the card presented immediately before it, they should press "Yes" if it is not they should press "No".
Visual Learning	One Card Learning	The pre-task on-screen instructions ask: "Have you seen this card before in this task?" A playing card is presented in the center of the screen. As soon as it does the subject must decide whether or not the same card has been seen before in this task. Subjects must try to remember all the cards that have been shown previously in order to decide whether or not they have seen each card before.
Verbal Learning	International Shopping List	The subject is told by the test supervisor: "In this task, I am going to read you a shopping list. I would like you to remember as many items from this list as possible. Are you ready to start?" The test supervisor reads the list of words as they appear on the computer screen. When the test supervisor has read all the words, the subject is required to recall as many items as possible from the list.
Reasoning/Problem Solving	Groton Maze Learning	The subject is shown a 10 x 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among these 100 possible locations. The start is indicated by a blue tile at the top left and the finish location is a tile with the red circles at the bottom right of the grid. The subject is instructed to move one step from the start location and then to continue, one tile at a time, toward the end (bottom right).
Social Cognition	Social-Emotional Cognition	The pre-task on-screen instructions ask, "Tap the odd one out". In this task, the subject will see a number of pictures on the screen. One of these pictures will be different to the others in some way. The subject must decide which one of the pictures is different, then tap that picture as quickly as they can.

The double blind, placebo controlled Phase 2 trial was conducted at 7 sites in the United States and 12 sites in India. In the trial, 185 patients meeting DSM-IV criteria for schizophrenia, with stable psychotic symptoms and taking a stable dose of an approved atypical antipsychotic medication (either quetiapine, marketed as Seroquel®, or risperidone, marketed as Risperdal®) were randomized to receive either (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt or placebo, together with continued treatment with the atypical antipsychotic, for 12 weeks. Of the randomized patients, approximately 69% were male and approximately 46% were users of tobacco products. Patients who received (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt received 1mg daily dose for the first four weeks, a 5 mg daily dose for the next four weeks and a 25 mg daily dose for the last four weeks. The primary efficacy outcome measure was GMLT, and the trial included a number of other scales as secondary efficacy outcome measures.

The GMLT is a computerized test designed to assess executive function (the ability to organize cognitive processes, including the ability to plan, prioritize, stop and start activities, shift from one activity to another activity and to monitor one's own behavior). Impaired executive function is thought to be an important aspect of cognitive dysfunction in schizophrenia. The trial protocol (see hereinafter – the Protocol) defined a positive outcome on GMLT as superiority (one-sided p-value < 0.10) for the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt dose group as compared to the placebo dose group after adjusting statistically to account for 3 multiple comparisons (at Weeks 4, 8, and 12 to evaluate the 3 doses).

In the trial, the results on GMLT met the pre-defined success criteria (adjusted p-value = 0.054), as well as at two of the trial's three measurement dates (at 4 weeks, unadjusted p-value = 0.018; and at 12 weeks, unadjusted p-value = 0.041); and were favorable for tobacco users as compared to non-users and for patients at study sites in United States as compared to patients at study sites in India. It has been estimated that approximately 80% of schizophrenic patients smoke (Swan& Lessoc-Schlaggar, *Neuropsychological Review*, 17:259-273, 2007); there was no activity in non-users. Each of the p-values reported was derived after data log transformation, a commonly utilized technique where the distribution of data is skewed (not normally distributed).

In addition, encouraging efficacy signals were observed in the trial on several secondary outcome measures, including Scale for Assessment of Negative Symptoms, an investigator

assessment of improvement on the negative symptoms of schizophrenia, Clinical Global Impression – Global Improvement, an investigator assessment of overall response, and Subject Global Impression – Cognition scale, a patient self-assessment of cognitive change. Clinical Global Impression – Severity, did not demonstrate a drug effect. Further, while certain secondary outcome measures of the trial, including cognitive measures in the CogState Schizophrenia Test Battery, did not demonstrate a drug effect, several CogState objective cognitive endpoints, including but not limited to composite score, detection (psychomotor speed), identification (attention), 1-card learning (visual learning), 1-back (working memory), and International Shopping List (verbal learning), provided statistically significant results of improvement.

Table 2 provides the results of primary, secondary, and CogState analyses of the total population (tobacco users and non-users).

Table 2. Results of Primary, Secondary and CogState* analyses, total population (tobacco users and non-users)

TASK	WEEK 4**	WEEK 8**	WEEK 12**
GMLT log (10) transformed	0.05 (0.02); p = 0.018	0.02 (0.02); p = 0.131	0.04 (0.02); p = 0.041
SANS	0.78 (1.18); p = 0.255	1.71 (1.44); p = 0.118	3.70 (1.68); p = 0.015
CGI-I	0.15 (0.09); p = 0.049	0.08 (0.12); p = 0.253	0.15 (0.14); p = 0.150
SGI-Cog	0.05 (0.28); p = 0.428	0.01 (0.36); p = 0.491	0.66 (0.39); p = 0.046
CGI-S	-0.02 (0.06); p = 0.674	-0.01 (0.06); p = 0.544	0.01 (0.09); p = 0.450
CogState Composite score	- 0.066 (0.066);p = 0.838	- 0.062 .068); p = 0.821	0.030 0.067); p = 0.326
CogState Detection	0.007 (0.015); p = 0.693	0.006 (0.014) p = 0.650	0.002 (0.015) p = 0.567
CogState Identification	- 0.005 (0.011); p = 0.311	- 0.014 (0.012); p = 0.111	- 0.017 (0.011); p = 0.063
CogState 1-Card Learning	- 0.008 (0.019); P = 0.660	- 0.024 (0.019); P = 0.899	- 0.019 (0.020); P = 0.841
CogState 1-Back	0.007 (0.014); p = 0.691	0.005 (0.015); p = 0.647	- 0.024 (0.014); p = 0.042
CogState Social-Emotional Cognition	0.013 (0.020); p = 0.259	0.015 (0.020); p = 0.217	- 0.002 (0.020); p = 0.546

* Rows for CogState Composite score through Social-Emotional Cognition Task depict results in subjects meeting data integrity criteria.

** Values in each cell are: [Mean (SEM); 1-tailed p-value]

Table 3 provides the results of primary, secondary, and CogState analyses in tobacco users.

Table 3. Results of Primary, Secondary and CogState analyses* in tobacco users

	Week 4**	Week 8**	Week 12**
GMLT log (10) transformed	0.06 (.03) p=0.014	0.04 (0.03) p=0.086	0.07 (0.02) p=0.002
SANS	2.74 (2.10); p = 0.098	4.00 (2.45); p = 0.054	4.86 (2.58); p = 0.033
CGI-I	0.25 (0.14); p = 0.047	0.24 (0.16); p = 0.075	0.18 (0.20); p = 0.189
SGI-Cog	- 0.13 (0.47); p = 0.606	0.24 (0.49); p = 0.314	0.65 (0.52); p = 0.109
CGI-S	0.02 (0.09); p = 0.434	0.08 (0.10); p = 0.224	0.07 (0.14); p = 0.308
CogState Composite score	0.007 0.099); p = 0.471	- 0.029 (0.101); p = 0.614	0.129 0.100); p = 0.098
CogState Detection	- 0.014 (0.021); p = 0.254	- 0.000 (0.021); p = 0.491	-0. 013 0.021); p = 0.265
CogState Identification	- 0.021 (0.016); p = 0.097	-0 .011 (0.017); p = 0.261	- 0.026 (0.016); p = 0.057
CogState 1-Card Learning	- 0.008 (0.027); p = 0.615	- 0.021; 0.028); p = 0.778	0.012 (0.028); p = 0.338
CogState 1-Back	0.005 (0.021); p= 0.605	- 0.009 (0.021); p = 0.329	- 0.042 (0.020); p = 0.020
CogState Social-Emotional Cognition	-0.010 (0.028); p = 0.632	-0 .009 (0.029); p = 0.625	-0 .019 (0.027); p = 0.752

* All CogState results except for GMLT are in subjects meeting data integrity criteria. The methodology for GMLT does not use a data integrity criterion.
** Values in each cell are: [Mean (SE); 1-tailed p-value]

The statistically significant and qualitatively similar effects favoring (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt in the primary objective endpoint (GMLT), in a number of secondary clinician and patient-rated endpoints (SANS, CGI-Global, and SGI-Cog), and in CogState objective cognitive endpoints underscore the positive efficacy of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in Cognitive Deficits in Schizophrenia.

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof exhibited a favorable tolerability profile in the trial,

and there was no clinically significant difference between the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof and placebo dose groups in discontinuations due to adverse events. The most frequent adverse event that was more common in the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt cohort than in the placebo cohort was nausea (0% placebo vs. 5% (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt), which was mild to moderate in severity and never led to patient dropout. There were two serious adverse events in the trial, one in the placebo dose group and one in the (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt dose group. Both were considered by the applicable investigator as not drug related.

The efficacy of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof against negative symptoms and cognitive symptoms is a remarkable finding due to the relative lack of effect of atypical antipsychotics upon these residual symptoms of schizophrenia. Because these residual symptoms are the primary reason that people with schizophrenia do not regain their full pre-morbid level of function, a new treatment for these symptoms fills a major unmet need. This need has been recognized by the NIMH through their MATRICS initiative (Neuchterlein et al., 2004; Gold, 2004), other initiatives with broad academic and regulatory support (Blanchard et al., 2010; Marder et al., 2011), and endorsed by the FDA (Laughren and Levin, 2011). The MATRICS initiative has highlighted the potential for small molecules that target the alpha7 NNR receptor in the treatment for cognitive dysfunction in schizophrenia. That potential was supported by preclinical models of schizophrenia in which the alpha 7 NNR agonist, (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof, was effective; and by early clinical studies in which a variety of other alpha7 NNR agonists were effective against surrogate markers (Olincy et al., 2006; EnVivo Pharmaceuticals, 2009) and measured features of schizophrenia (Freedman et al., 2008).

(2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof showed efficacy primarily in tobacco users. Without being limited thereto, there are at least 3 hypotheses that may explain this observation. First, in schizophrenic patients who smoke, mRNA encoding the alpha7 NNR subunit was shown to be upregulated by 250% in comparison to schizophrenic patients who did not smoke;

and there were a greater number of functional alpha7 NNR receptors in the smokers (Mexal et al., 2010). This finding may suggest that there were more functionally active alpha7 receptors upon which (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof could act in the brains of the tobacco-users in this study, with a greater functional consequence. Second, nicotine has been demonstrated to make the blood-brain barrier more permeable to small molecules in preclinical models (Hawkins et al., 2004; Manda et al., 2010). If this effect of nicotine is also present in humans, then it is possible that a greater brain concentration of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof was present in tobacco-users in this study. If the doses used in the study were below the E_{max} for alpha 7 NNR activation, then this hypothetically greater brain concentration of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in tobacco-users could result in a greater amount of receptor activation. Third, subjects in this study were asked to take (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt in the morning, at least 90 minutes before first tobacco intake (if smokers). Hence (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide pharmaceutically acceptable salt may have acted upon sensitized alpha7 NNRs due to a night-time deprivation of nicotinic stimulation. Whether any of these or other factors underlie the greater effect of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in tobacco users in this study will require further preclinical and clinical research. If, however, there is confirmation that (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof or other alpha7 NNR agonists work primarily in tobacco-using patients with schizophrenia, this should not deter development of these compounds since the majority of patients with schizophrenia are smokers (Hughes et al., 1986; Goff et al., 1992; de Leon et al., 1995; Diwan et al., 1998; O'Carroll, 2000). One aspect of the invention includes a combination of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof.

There are a number of caveats that should be considered in the interpretation of this study. First, the numbers of tobacco users in the study was relatively small (46% of the enrolled population), and so the finding needs to be replicated in larger studies. Second, this study was conducted predominantly in India (approximately two-thirds of enrolled subjects), and therefore

these findings need to be replicated in larger studies in other regions to demonstrate translation into other cultures and other ways of medical practice.

Nevertheless these findings are encouraging in supporting the role of alpha7 NNR agonists like (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to treat the residual phase of schizophrenia. The effect of a reliable treatment for these symptoms could be enormous for patients with schizophrenia, for the families and caregivers who help them, and for the society and economy that could benefit from these patient's return to more productive lives.

Efficacy Results

Efficacy results are presented in Tables 4 – 8.

Table 4 – Efficacy Results: Groton Maze Learning (GML)

All Patients				GML (Total Error) LOG		
Visit	Treatment	Adjusted Mean	Standard Error of Adjusted Mean	Mean Difference ± SE between TC-5619 and Placebo (Placebo-TC5619)	One-sided 90% Confidence Interval for Mean Difference	One-sided P-Value
Week 1	Placebo	-0.02	0.01			
	TC-5619	-0.01	0.01			
				-0.01 ± 0.02	(-0.03 , ∞)	0.6709
Week 4	Placebo	0.02	0.02			
	TC-5619	-0.03	0.02			
				0.05 ± 0.02	(0.02 , ∞)	0.0180
Week 8	Placebo	-0.02	0.02			
	TC-5619	-0.05	0.02			
				0.02 ± 0.02	(-0.00 , ∞)	0.1308
Week12	Placebo	-0.02	0.02			
	TC-5619	-0.06	0.02			
				0.04 ± 0.02	(0.01 , ∞)	0.0405

Primary endpoint is statistically significant based on Hochberg adjustment for 3 comparisons (one-sided p<.1)

Table 5 – Efficacy Results – SANS Total Score

All Patients		SANS TOTAL SCORE				
Visit	Treatment	Adjusted Mean	Standard Error of Adjusted Mean	Mean Difference ± SE between TC-5619 and Placebo (Placebo-TC5619)	One-sided 90% Confidence Interval for Mean Difference	One-sided P-Value
Week 1	Placebo	-0.92	0.93			
	TC-5619	-1.20	0.93			
				0.28 ± 0.82	(-0.77 , ∞)	0.3647
Week 4	Placebo	-2.74	1.11			
	TC-5619	-3.52	1.11			
				0.78 ± 1.18	(-0.74 , ∞)	0.2547
Week 8	Placebo	-5.55	1.25			
	TC-5619	-7.25	1.25			
				1.71 ± 1.44	(-0.14 , ∞)	0.1184
Week 12	Placebo	-6.23	1.39			
	TC-5619	-9.93	1.40			
				3.70 ± 1.68	(1.53 , ∞)	0.0147

Table 6 - Efficacy Results – CGI Global Change

All Patients		CGI-Global Change				
Visit	Treatment	Adjusted Mean	Standard Error of Adjusted Mean	Mean Difference ± SE between TC-5619 and Placebo (Placebo-TC5619)	One-sided 90% Confidence Interval for Mean Difference	One-sided P-Value
Week 1	Placebo	3.80	0.15			
	TC-5619	3.77	0.15			
				0.03 ± 0.07	(-0.06 , ∞)	0.3434
Week 4	Placebo	3.64	0.15			
	TC-5619	3.49	0.16			
				0.15 ± 0.09	(0.04 , ∞)	0.0485
Week 8	Placebo	3.30	0.16			
	TC-5619	3.22	0.16			
				0.08 ± 0.12	(-0.07 , ∞)	0.2533
Week 12	Placebo	3.18	0.17			
	TC-5619	3.03	0.17			
				0.15 ± 0.14	(-0.03 , ∞)	0.1502

Table 7 – SGI – Cognition by Patient

All Patients		SGI-COGNITION TOTAL BY PATIENT				
Visit	Treatment	Adjusted Mean	Standard Error of Adjusted Mean	Mean Difference ± SE between TC-5619 and Placebo (Placebo-TC5619)	One-sided 90% Confidence Interval for Mean Difference	One-sided P-Value
Week 1	Placebo	11.37	0.19			
	TC-5619	11.18	0.19			
				0.19 ± 0.20	(-0.07 , ∞)	0.1757
Week 4	Placebo	10.65	0.24			
	TC-5619	10.60	0.24			
				0.05 ± 0.28	(-0.31 , ∞)	0.4282
Week 8	Placebo	9.80	0.28			
	TC-5619	9.79	0.29			
				0.01 ± 0.36	(-0.45 , ∞)	0.4914
Week 12	Placebo	9.61	0.30			
	TC-5619	8.95	0.31			
				0.66 ± 0.39	(0.16 , ∞)	0.0455

SGI-Cog. Composed of 3 subscales (memory, attention and speed of thinking). Effect is driven by memory (p=.055) and attention (p=.021).

Table 8 – CGI – Severity

All Patients		CGI-SEVERITY				
Visit	Treatment	Adjusted Mean	Standard Error of Adjusted Mean	Mean Difference ± SE between TC-5619 and Placebo (Placebo-TC5619)	One-sided 90% Confidence Interval for Mean Difference	One-sided P-Value
Week 1	Placebo	-0.05	0.03			
	TC-5619	-0.03	0.03			
				-0.02 ± 0.03	(-0.07 , ∞)	0.7588
Week 4	Placebo	-0.09	0.05			
	TC-5619	-0.06	0.05			
				-0.02 ± 0.06	(-0.10 , ∞)	0.6737
Week 8	Placebo	-0.24	0.05			
	TC-5619	-0.23	0.05			
				-0.01 ± 0.06	(-0.09 , ∞)	0.5440
Week 12	Placebo	-0.29	0.07			
	TC-5619	-0.31	0.07			
				0.01 ± 0.09	(-0.11 , ∞)	0.4495

SGI-Cog. Composed of 3 subscales (memory, attention and speed of thinking). Effect is driven by memory (p=.055) and attention (p=.021).

TARGACEPT

Protocol Document Control Number: PRO-05619-CRD-001

Version: 02

Effective Date: 21 Dec 2009

Study Number: PRO-05619-CRD-001

A Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess Efficacy, Safety, and Tolerability of TC-5619 as Augmentation Therapy to Improve Cognition in Outpatients with Cognitive Dysfunction in Schizophrenia.

TARGACEPT PRO-05619-CRD-001(02) Effective Date: 21 Dec 2009

TARGACEPT SIGNATURE PAGE

Author(s):	Signature:	Date:
[redacted] Medical Director/Safety Officer	[redacted]	21 DEC 2009
[redacted] Study Manager		21 Dec 2009
[redacted] Study Pharmacokinetic Scientist		21 DEC 2009

Approver(s):	Signature:	Date:
[redacted] Head of Clinical Development and Regulatory Affairs	[redacted]	21-Dec-09
[redacted] Head of Clinical Operations		21 Dec 2009

TARGACEPT PRO-05619-CRD-001(02) Effective Date: 21 Dec 2009

TARGACEPT CLINICAL STUDY PROTOCOL

A Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess Efficacy, Safety, and Tolerability of TC-5619 as Augmentation Therapy to Improve Cognition in Outpatients with Cognitive Dysfunction in Schizophrenia.

Study Number: PRO-05619-CRD-001

CONTACT INFORMATION

Sponsor:	Targacept, Inc. 200 East First Street, Suite 300 Winston-Salem, North Carolina 27101-4165 Tel: [redacted] Fax:
Sponsor Contact:	[redacted]
Targacept Medical Contact:	
Principal Investigator:	
Contract Research Organization:	

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

TARGACEPT PRO-05619-CRD-001(02) Effective Date: 21 Dec 2009

PROTOCOL AMENDMENT

This version (02) was written by making change to Version 01, as follows:

Section:	**Contact Information**
Previously read:	TBD
Now reads:	[redacted]
Reason for change:	To identify the Principal Investigator for the study.
Section:	**Table of Contents, List of Appendices**
Previously read:	Appendix 13. Signed and Dated Investigator Protocol
Now reads:	Appendix 13. Fagerstrom Test for Nicotine Dependence .....
Reason for change:	To add copy of test to the protocol and insert appendix.
Section:	**Table of Contents, List of Appendices**
Previously read:	Text not previously present.
Now reads:	Appendix 14. Signed and Dated Investigator Protocol .....
Reason for change:	To adjust the numbering of Appendices for the insertion of Fagerstrom Test for Nicotine Dependence.
Section:	**Clinical Protocol Synopsis, Title of Study**
Previously read:	A double-blind, randomized, placebo-controlled, multicenter, fixed dose titration study to assess efficacy, safety, and tolerability of TC-5619 as augmentation therapy to improve cognition in outpatients with cognitive dysfunction in schizophrenia. *PRO-05619-CRD-001*
Now reads:	A Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess Efficacy, Safety, and Tolerability of TC-5619 as Augmentation Therapy to Improve Cognition in Outpatients with Cognitive Dysfunction in Schizophrenia. *PRO-05619-CRD-001* Phase 2
Reason for change:	To correct the title of the study.
Section:	**Clinical Protocol Synopsis, Investigators**
Previously read:	TBD
Now reads:	[redacted]
Reason for change:	To list the Principal Investigator for the study.
Section:	**Clinical Protocol Synopsis, Clinical Laboratories**
Previously read:	QECG (ECGs); CogState (computerized test battery); Clinigene (labs)
Now reads:	QECG (ECGs); CogState (computerized test battery); ICON and Tandem (labs)
Reason for change:	To correctly list the laboratories utilized for the study.

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Section:	**Clinical Protocol Synopsis, Inclusion Criteria**
Previously read:	2. Controlled schizophrenia, on same dose of quetiapine or risperidone for no less than 2 months prior to screening
Now reads:	2. Controlled schizophrenia, on stable dose of quetiapine or risperidone for at least 2 months prior to screening
Reason for change:	To ensure that more subjects meet or exceed the 2-month requirement
Section:	**Clinical Protocol Synopsis, Inclusion Criteria**
Previously read:	4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening
Now reads:	4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening (social admissions allowed)
Reason for change:	Social admissions in India are common preceding a clinic visit if a subject has traveled for a long distance. These admissions are allowed, because they are not for psychiatric management.
Section:	**Clinical Protocol Synopsis, Exclusion Criteria**
Previously read:	2. Patients at imminent risk of suicide or of danger to themselves or others
Now reads:	2. Patients at significant risk of suicide or of danger to themselves or others
Reason for change:	To clarify exclusion criteria
Section:	**Clinical Protocol Synopsis, Exclusion Criteria**
Previously read:	10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level
Now reads:	10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level > than 50ng/ml (urine cotinine level between 50ng/ml and 500ng/ml will be excluded).
Reason for change:	To account for the high sensitivity of the test for secondary exposure to nicotine
Section:	**Clinical Protocol Synopsis, Exclusion Criteria**
Previously read:	13. Myocardial infarction
Now reads:	13. History of myocardial infarction
Reason for change:	To clarify exclusion criteria
Section:	**Clinical Protocol Synopsis, Exclusion Criteria**
Previously read:	14. Seizure disorder
Now reads:	14. History of seizure disorder
Reason for change:	To clarify exclusion criteria
Section:	**Clinical Protocol Synopsis, Exclusion Criteria**
Previously read:	Text previously not present
Now reads:	26. Body Mass Index (BMI) < 15 and > 31
Reason for change:	To add exclusion criteria
Section:	**Clinical Protocol Synopsis, Test Product(s), Dose, and Mode of Administration, Batch Number(s)**
Previously read:	TBD
Now reads:	1mg: B090229

5mg: B090245
25mg: B090253
Placebo: B090222

Reason for change: To clarify the batch numbers of study drug.

Section: **Clinical Protocol Synopsis, Efficacy analysis**

Previously read: The primary endpoint will be change in CogState Schizophrenia Test Battery GML from Baseline to Week 4, Week 8, and Week 12 or EW. This change from Baseline will be analyzed using Analysis of Covariance (ANCOVA) techniques with an alpha of 0.10 (one-tailed), to examine differences between the TC-5619 and placebo treatment cohorts (entire cohorts, tobacco-users and non-users combined). The ANCOVA model will include treatment as a main factor and baseline values, country, time, tobacco use status, and interaction of tobacco use status with treatment as covariates. Other covariates may be used as delineated in the Statistical Analysis Plan. Since the primary outcome (GML) is assessed on 3 occasions (Week 4, Week 8, and Week 12) that may result in the rejection of the null hypothesis, the Hommel-Hochberg method will be used to control for multiple comparisons.

Now Reads: The primary endpoint will be change in CogState Schizophrenia Test Battery GML from Baseline to Week 4, Week 8, and Week 12 or EW. This change from Baseline will be analyzed using Analysis of Covariance (ANCOVA) techniques with an alpha of 0.10 (one-tailed), to examine differences between the TC-5619 and placebo treatment cohorts (entire cohorts, tobacco-users and non-users combined). The ANCOVA model will include treatment as a main factor and baseline values, country, time, tobacco use status, and interaction of tobacco use status with treatment as covariates. Other covariates may be used as delineated in the Statistical Analysis Plan. Since the primary outcome (GML) is assessed on 3 occasions (Week 4, Week 8, and Week 12) that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons.

Reason for change: To clarify that the method used will be the Hochberg method.

Section: **Clinical Protocol Synopsis, Secondary Efficacy Endpoints**

Previously read: Composite CSTB score; at Week 1, Week 4, Week 8, Week 12 or EW, and Week 14 (Follow-Up Visit).

Now reads: Composite CSTB score; at Week 1, Week 4, Week 8, Week 12 or EW compared to Baseline.

Reason for change: To specify the measurements used in the statistical analysis.

Section: **Clinical Protocol Synopsis, Secondary Efficacy Endpoints**

Previously read: Continuous Paired Associate Learning (CPAL) task; at Week 1, Week 4, Week 8, and Week 12 or EW.

Now reads: Deleted

Reason for change: To remove CPAL task.

Section: **Clinical Protocol Synopsis, Statistical Methods, Secondary Endpoints**

Previously read: The endpoints examined will include change from Baseline to Weeks 4, 8 and 12 in: SGI-Cognition total score; CPAL item score of the CSTB; CSTB composite score; SANS total score; CGI-S; and CGI-I.

Now reads:	The endpoints examined will include change from Baseline to Weeks 4, 8 and 12 in: SGI-Cognition total score; CSTB composite score; SANS total score; CGI-S; and CGI-I.
Reason for change:	To remove CPAL task.
Section:	**Clinical Protocol Synopsis, Statistical Methods, Exploratory Analysis**
Previously read:	mRNA expression in a subset of subjects will be measured and correlated with change from Baseline in GML, CPAL, CSTB composite score, SANS, P50, P300, MMN, CGI-S, CGI-I, and SGI-Cog scores.
Now reads:	mRNA expression in a subset of subjects will be measured and correlated with change from Baseline in GML, CSTB composite score, SANS, P50, P300, MMN, CGI-S, CGI-I, and SGI-Cog scores.
Reason for change:	To remove CPAL task.
Section:	**Time and Events Schedule**
Previously read:	[2] Laboratory samples on Day 1 and F/U visit will be collected only for subjects with abnormal values from the Screening or Week 12 assessments, respectively.
Now reads:	[2] Laboratory samples on Day 1 and F/U visit will be collected only for subjects with abnormal values from the Screening or Week 12 assessments, respectively. Screening laboratory results must be received by the site before the subject can be randomized on Day 1.
Reason for change:	to clarify that the repeat of screening laboratory results must be available prior to randomization.
Section:	**Time and Events Schedule**
Previously read:	[3] Serial blood samples for pharmacokinetic assessments will be obtained from a subset of subjects at a single US site on Day 1, Week 4, Week 8 and Week 12 at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose.
Now reads:	[3] Serial blood samples for pharmacokinetic assessments will be obtained from a subset of subjects at selected US site(s) on Day 1, Week 4, Week 8 and Week 12 at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose
Reason for change:	To allow flexibility to include additional sites in the collecting of serial PK samples to ensure adequate number of subjects are included.
Section:	**Time and Events Schedule**
Previously read:	Text not previously present
Now reads:	Addition of columns in the double-blind treatment phase for telephone contact at Week 2, Week 6 and Week 10
Reason for change:	To align table with new study procedures in Section 3.3.1.
Section:	**Time and Events Schedule**
Previously read:	Text not previously present
Now reads:	Addition of event line "Telephone contact to assess drug compliance and tolerability"
Reason for change:	To align table with new study procedures in Section 3.3.1.
Section:	**Time and Events Schedule**
Previously read:	Footnote text not previously present

Now reads:	[7] CogState Battery at Screening will include two assessments, one to train the subject on the battery and one for baseline measurement. [8] P50, P300 and MMN at Baseline will include two assessments, one for the subject to become comfortable with test procedures and one for baseline measurement. [8] At Screening, the Baseline version of CSSRS assessment will be completed. At all subsequent visits, the Since Last Visit version of CSSRS assessment will be completed.
Reason for change:	To align table with study procedures in Section 3.3.1.
Section:	**Time and Events Schedule**
Previously read:	Urine pregnancy test
Now reads:	Urine pregnancy test for WOCBP
Reason for change:	Clarify who should have pregnancy test performed.
Section:	**Time and Events Schedule**
Previously read:	Text not previously present
Now reads:	Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To clarify that the Trails A & B and Symbol-Digit paper and pencil tests while supplies by CogState are separate from the CogState Battery.
Section:	**List of Abbreviations**
Previously read:	ANOVA Analysis of Variance
Now reads:	Analysis of Covariance
Reason for change:	Correction of model being used.
Section:	**List of Abbreviations**
Previously read:	CPAL: Continuous Paired Associate Learning test
Now reads:	Deleted
Reason for change:	To remove CPAL abbreviation
Section:	**List of Abbreviations**
Previously read:	Text previously not present
Now reads:	BMI: Body Mass Index
Reason for change:	To add BMI abbreviation
Section:	**1.5. Conduct of the Trial**
Previously read:	This study will be conducted according to the ICH guidelines for Good Clinical Practice, to the Declaration of Helsinki (1996 version), and to applicable regulatory requirements.
Now reads:	This study will be conducted according to the ICH guidelines for Good Clinical Practice, to the Declaration of Helsinki (2008 version), and to applicable regulatory requirements.
Reason for change:	To correct the reference date.
Section:	**1.6. Study Population**
Previously read:	This study will consider for inclusion outpatient subjects aged 18-55 years who meet a diagnosis of schizophrenia per DSM-IV TR criteria, as assessed using the MINI International Neuropsychiatric Interview (MINI).

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Now reads:	This study will consider for inclusion outpatient subjects aged 18-60 years who meet a diagnosis of schizophrenia per DSM-IV TR criteria, as assessed using the MINI International Neuropsychiatric Interview (MINI).
Reason for change:	To correct age range of eligible participants.
Section:	**1.6. Study Population**
Previously read:	Patients will not have more than a minimal level of extra-pyramidal signs (a score of ≤6 on the Simpson-Angus Scale).
Now reads:	Deleted
Reason for change:	To remove reference to Simpson Angus Scale because the AIMS is being used in its place.
Section:	**3.1. Study Design**
Previously read:	At Screening, subjects will be assessed for stable schizophrenia as documented by lack of hospitalization for the preceding 8 weeks beforehand, as well as stable dosing of quetiapine or of risperidone for at least 8 weeks beforehand.
Now reads:	At Screening, subjects will be assessed for stable schizophrenia as documented by lack of psychiatric hospitalization for the preceding 8 weeks beforehand, as well as stable dosing of quetiapine or of risperidone for at least 8 weeks beforehand.
Reason for change:	To clarify the type of hospitalization in the determination of stable schizophrenia.
Section:	**3.1. Study Design**
Previously read:	Blood samples for pharmacokinetic evaluation will be collected in a subset of subjects in this population. Serial samples will be collected at one US site on Day 1 (1 mg single-dose), Week 4 (1 mg qd at steady-state), Week 8 (5 mg qd at steady-state) and Week 12 (25 mg qd at steady-state). Sparse samples will be collected at the other US sites on Day 1, Week 4, Week 8 and Week 12.
Now reads:	Blood samples for pharmacokinetic evaluation will be collected in a subset of subjects in this population. Serial samples will be collected at select US sites on Day 1 (1 mg single-dose), Week 4 (1 mg qd at steady-state), Week 8 (5 mg qd at steady-state) and Week 12 (25 mg qd at steady-state). Sparse samples will be collected at the other US sites on Day 1, Week 4, Week 8 and Week 12.
Reason for change:	To allow flexibility to include additional sites in the collecting of serial PK samples to ensure adequate number of subjects are included.
Section:	**3.1.1.2. Secondary Endpoints**
Previously read:	Continuous Paired Associate Learning (CPAL) at Weeks 1, 4, 8 and 12 or EW compared to Baseline.
Now reads:	Deleted
Reason for change:	To remove CPAL task
Section:	**3.1.1.2. Secondary Endpoints**
Previously read:	Alpha-7 mRNA expression as a function of:

- GML, CPAL, CSTB composite score, CGI-I, SGI-Cog, SANS, and P50/P300/MMN scores: change at Week 4, Week 8 and week 12 or EW compared to Baseline;

Now reads: Alpha-7 mRNA expression as a function of:

- GML, CSTB composite score, CGI-I, SGI-Cog, SANS, and P50/P300/MMN scores: change at Week 4, Week 8 and week 12 or EW compared to Baseline;

Reason for change: To remove CPAL task

Section: **3.3. Study Procedures, Approximate Volume of Blood to be Collected From Each Subject**

Previously read:

Approximate Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample	No. of Samples per Subject	Total Volume of Blood[a]
Safety (including screening, double-blind phase and follow-up assessments)			
- Hematology	5 mL	4	20 mL
- Serum chemistry	10 mL	4	40 mL
- HbA1C	10 mL	1	10 mL
Pharmacokinetic samples[b]	7 mL	32	224 mL
Blood sample for mRNA expression	5 mL	1	5 mL
Total			**299 mL**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Maximum number of samples obtained from a subset of the subjects randomized.

Now reads:

Approximate Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample	No. of Samples per Subject	Total Volume of Blood[a]
Safety (including screening, double-blind phase and follow-up assessments)			
- Hematology	5 mL	4	20 mL
- Serum chemistry	10 mL	4	40 mL
- HbA1C	10 mL	1	10 mL
Pharmacokinetic samples[b]	6 mL	32	192 mL
Blood sample for mRNA expression	5 mL	1	5 mL
Total			**267 mL**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Maximum number of samples obtained from a subset of the subjects randomized.

Reason for change: To correct the volume per sample for PK.

Section: **3.3.1.1. Screening (Week -4)**

Previously read:	8. Training on and completion of CogState Schizophrenia test battery (at least 1 hr after prior tobacco use, if applicable).
Now reads:	8. Training on and completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable). Two assessments will be completed, one to train the subject on the battery and one for the baseline measurements.
Reason for change:	To obtain 2 measurements, one for training and one for actual baseline assessment and to clarify when to perform the battery in relationship to tobacco use.
Section:	**3.3.1.1. Screening (Week -4)**
Previously read:	Text previously not present
Now reads:	19. Repeat hematology, clinical chemistry, bilirubin, LFTs, or urinalysis will be performed prior to randomization (Day 1), if any abnormal values were detected in the screening tests.
Reason for change:	To allow time for repeat lab test results to be reviewed prior to randomization
Section:	**3.3.1.1. Screening (Week -4)**
Previously read:	Text previously not present
Now reads:	20. Completion of Trails A&B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	3.3.1.1. Screening (Week -4)
Previously read:	Text previously not present
Now reads:	21. Blood samples will be obtained for measurement of alpha 7 mRNA expression.
Reason for change:	To combine blood draws for the subjects not participating in the PK substudy while providing consistency for the sampling of the alpha 7 mRNA.
Section:	**3.3.1.2. Baseline Assessments (Day 1)**
Previously read:	The Baseline Visit will be held approximately 28 days after screening, with a window of +3 days, as required to continue to assess stability of schizophrenic symptoms and of quetiapine / risperidone dose, in an outpatient setting.
Now reads:	The Baseline Visit will be held at least 28 days after screening, with a window of +3 days, as required to continue to assess stability of schizophrenic symptoms and of quetiapine / risperidone dose, in an outpatient setting.
Reason for change:	To ensure that the period between Screening and Day 1 is not less than 28 days.
Section:	**3.3.1.2. Baseline Assessments (Day 1)**
Previously read:	11. Completion of CogState Schizophrenia test battery (at least 1 hour after prior tobacco use, if applicable).
Now reads:	11. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable).
Reason for change:	To clarify when to perform the battery in relationship to tobacco use.
Section:	**3.3.1.2. Baseline Assessments (Day 1)**
Previously read:	12. Acquisition of P50, P300 and MMN data at selected sites.

Now reads:	12. Acquisition of P50, P300 and MMN data at selected sites. Two assessments will be completed, one for the subject to become comfortable with test procedures and one for the baseline measurements.
Reason for change:	To obtain 2 measurements, one for the subject to become comfortable with the test procedure and one for actual baseline assessment.
Section:	**3.3.1.2. Baseline Assessments (Day 1)**
Previously read:	7. Repeat hematology, clinical chemistry, bilirubin, LFTs, or urinalysis will be performed, if any abnormal values were detected in the screening tests.
Now reads:	7. Repeat hematology, clinical chemistry, bilirubin, LFTs, or urinalysis will be performed prior to randomization (Day 1) assessments, if any abnormal values were detected in the screening tests.
Reason for change:	To clarify that repeat lab tests for abnormal screening laboratory results must be reviewed prior to randomization.
Section:	3.3.1.2. **Baseline Assessments (Day 1)**
Previously read:	8. Blood samples will be obtained for measurement of alpha 7 mRNA expression.
Now reads:	Deleted
Reason for change:	Deleted at Baseline Assessments (Day 1) but added to Screening (Week -4) in order to combine blood draws for the subjects not participating in the PK substudy while providing consistency for the sampling of the alpha 7 mRNA.
Section:	**3.3.1.2. Baseline Assessments (Day 1)**
Previously read:	Text previously not present
Now reads:	22. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	**3.3.1.3. Week 1**
Previously read:	6. CSTB and SGI-Cog will be completed.
Now reads:	6. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable) and SGI-Cog.
Reason for change:	To clarify when to perform the battery in relationship to tobacco use.
Section:	**3.3.1.3. Week 1**
Previously read:	Text previously not present
Now reads:	15. Acquisition of P50, P300 and MMN data at selected sites.
Reason for change:	To align text with the Table & Event Schedule
Section:	**3.3.1.3. Week 1**
Previously read:	Text previously not present
Now reads:	16. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	**New 3.3.1.4. Week 2 (Telephone Contact)**
Previously read:	Text previously not present

Now reads:	1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.
Reason for change:	To assess study drug tolerability and compliance between study visits.
Section:	**New 3.3.1.5. Week 4 (old 3.3.1.4.)**
Previously read:	10. Completion of CogState Schizophrenia test battery (at least 1 hour after prior tobacco use, if applicable) and SGI-Cog
Now reads:	10. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable) and SGI-Cog.
Reason for change:	To clarify when to perform the battery in relationship to tobacco use.
Section:	**New 3.3.1.5. Week 4 (old 3.3.1.4.)**
Previously read:	17. An in-clinic dose of study drug will be administered (5mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
Now reads:	17. An in-clinic dose of study drug will be administered (1mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
Reason for change:	To correct study drug dose administered at this visit.
Section:	**New 3.3.1.5. Week 4 (old 3.3.1.4.)**
Previously read:	Text previously not present
Now reads:	21. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	**New 3.3.1.6. Week 6 (Telephone Contact)**
Previously read:	Text previously not present
Now reads:	1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.
Reason for change:	To assess study drug tolerability and compliance between study visits.
Section:	**New 3.3.1.7. Week 8 (old 3.3.1.5.)**
Previously read:	10. Completion of CogState Schizophrenia test battery (at least 1 hour after prior tobacco use, if applicable) and SGI-Cog
Now reads:	10. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable) and SGI-Cog.
Reason for change:	To clarify when to perform the battery in relationship to tobacco use.
Section:	**New 3.3.1.7. Week 8 (old 3.3.1.5.)**
Previously read:	17. An in-clinic dose of study drug will be administered (25mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
Now reads:	17. An in-clinic dose of study drug will be administered (5mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
Reason for change:	To correct study drug dose administered at this visit.
Section:	**New 3.3.1.7. Week 8 (old 3.3.1.5.)**
Previously read:	Text previously not present
Now reads:	21. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.

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Section:	**3.3.1.8. Week 10 (Telephone Contact)**
Previously read:	Text previously not present
Now reads:	1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.
Reason for change:	To assess study drug tolerability and compliance between study visits.
Section:	**New 3.3.1.9. Week 12 or Early Withdrawal Visit (old 3.3.1.6.)**
Previously read:	11. Completion of CogState Schizophrenia test battery (at least 1 hour after prior tobacco use, if applicable) and SGI-Cog
Now reads:	11. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable) and SGI-Cog.
Reason for change:	To clarify when to perform the battery in relationship to tobacco use.
Section:	**New 3.3.1.9. Week 12 or Early Withdrawal Visit (old 3.3.1.6.)**
Previously read:	Text previously not present
Now reads:	22. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	**New 3.3.1.10. Follow Up Visit, Week 14 (old 3.3.1.7.)**
Previously read:	Text previously not present
Now reads:	12. Completion of Trails A & B and Symbol-Digit paper and pencil tests.
Reason for change:	To include new assessment in study procedures.
Section:	**3.4. Study Restrictions**
Previously read:	1. If tobacco users (50% of subjects), subjects should not vary their smoking habits during the study. If tobacco non-users (50% of subjects), subjects should not begin to smoke during the study.
Now reads:	1. Tobacco users (50% of subjects) should not vary their tobacco use during the study. Tobacco non-users (50% of subjects) should not begin to use tobacco during the study.
Reason for change:	To clarify that use of any tobacco products (smoking, snuff, etc.) falls into the definition of nicotine use.
Section:	**3.4. Study Restrictions**
Previously read:	2. Subject may not use any new prescription or nonprescription medication (including vitamins and herbal supplements) except for acetaminophen (not exceeding 1gm/day) throughout the study duration.
Now reads:	2. Subjects may not use any new prescription or nonprescription medication (including vitamins and herbal supplements) except for acetaminophen (not exceeding 1.5gm/day), or other short-term use medications as permitted by the Medical Monitor (e.g. antibiotics) throughout the study duration.
Reason for change:	To align acetaminophen amount with Appendix 3 and allow the use of short-term use medications.

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Section:	**3.4. Study Restrictions**
Previously read:	3. Subjects with a positive urine drug screen will be discontinued from the trial, unless ascribed to appropriate use of a prescribed medication (e.g. benzodiazepine for sleep), and after discussion with the medical monitor.
Now reads:	3. Subjects with a positive urine drug screen will be discontinued from the trial, unless ascribed to appropriate use of a prescribed medication (e.g. benzodiazepine for sleep), and after discussion and approval of the Medical Monitor.
Reason for change:	To clarify that approval from the Medical Monitor must also be obtained.
Section:	**3.4. Study Restrictions**
Previously read:	5. If a subject has had a recent febrile illness within 7 days of scheduled drug intake, the start of study drug intake should be postponed until the body temperature is normal for at least 72 hours.
Now reads:	Deleted
Reason for change:	The decision of inclusion of a subject with a recent febrile illness will be made at the discretion of the investigator after the nature of the illness is considered (e.g. a short-lived URI would not normally be grounds for exclusion).
Section:	**3.4. Study Restrictions (old 8, new 7)**
Previously read:	8. Be willing to use acceptable methods of contraception (e.g. IUD, spermicidal agent, oral contraceptive) throughout the study period.
Now reads:	7. Be willing to use acceptable methods of contraception (e.g. IUD, spermicidal agent, oral contraceptive) throughout the study period and for 7 days after study completion
Reason for change:	To align text with the restrictions for male participants and renumber as item 5 was removed.
Section:	**3.7.3. Dosage and Dosage Regimen**
Previously read:	Subjects taking 1mg TC-5619 will take a single 1mg capsule TC-5619 p.o. qd. Subjects taking 5mg TC-5619 will take a single 5mg capsule of 5mg TC-5619 p.o. qd. Subjects taking 25mg TC-5619 will take a single capsule of 25mg TC-5619 p.o. qd. Subjects taking placebo will take a single capsule of matching placebo p.o. qd. Study drug should be taken as soon after awakening as possible, at least 30 minutes before the morning quetiapine or risperidone dose, and at least 90 minutes before the first tobacco use, if applicable
Now reads:	TC-5619-238 will be provided as hard gelatin capsules in strengths of 1mg, 5mg, and 25mg (as free base). Subjects will take 1mg TC-5619, 5mg TC-5619, 25mg TC-5619, or matching placebo – one capsule once daily p.o., as soon as possible after awakening, at least 90 min before first tobacco use in tobacco users, and at least 30 min before first dose of quetiapine or risperidone in all subjects
Reason for change:	To align with the protocol synopsis.

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Section:	**3.7.4. Drug Storage**
Previously read:	The study drug must be stored under controlled room temperature, 15 to 30°C (59 – 86°F) and under controlled humidity (<70%), within an appropriately secured facility.
Now reads:	The study drug must be stored under controlled room temperature, 15 to 30°C (59 – 86°F), within an appropriately secured facility..
Reason for change:	To remove the humidity restriction for drug storage at the sites. This requirement for tracking humidity levels is for formal stability testing.
Section:	**3.11. Procedures for Breaking Randomization Codes**
Previously read:	**Only** when knowledge of the investigational product is essential for the clinical management or welfare of the subject, can the Investigator unblind a subject's treatment assignment after approval is granted by the Targacept Medical Director or designee.
Now reads:	**Only** when knowledge of the investigational product is essential for the clinical management or welfare of the subject, can the Investigator unblind a subject's treatment assignment after approval is granted by the Targacept Medical Monitor or designee.
Reason for change:	Correct term should be Medical Monitor rather then Medical Director
Section:	**4.1. Inclusion Criteria**
Previously read:	2. Controlled schizophrenia, on same dose of quetiapine or risperidone for no less than 2 months prior to screening
Now reads:	2. Controlled schizophrenia, on stable dose of quetiapine or risperidone for at least 2 months prior to screening
Reason for change:	To ensure that more subjects meet or exceed the 2-month requirement
Section:	**4.1. Inclusion Criteria**
Previously read:	4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening
Now reads:	4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening (social admissions allowed)
Reason for change:	Social admissions in India are common preceding a clinic visit if a subject has traveled for a long distance. These admissions are allowed, because they are not for psychiatric management.
Section:	**4.2. Exclusion Criteria**
Previously read:	2. Patients at imminent risk of suicide or of danger to themselves or others
Now reads:	2. Patients at significant risk of suicide or of danger to themselves or others
Reason for change:	To clarify exclusion criteria
Section:	**4.2. Exclusion Criteria**
Previously read:	10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level
Now reads:	10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level > than 50ng/mL (urine cotinine level between 50ng/ml and 500ng/ml will be excluded)
Reason for change:	To account for the high sensitivity of the test for secondary exposure to nicotine

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Section:	**4.2. Exclusion Criteria**
Previously read:	13. Myocardial infarction
Now reads:	13. History of myocardial infarction
Reason for change:	To clarify exclusion criteria

Section:	**4.2. Exclusion Criteria**
Previously read:	14. Seizure disorder
Now reads:	14. History of seizure disorder
Reason for change:	To clarify exclusion criteria

Section:	**4.2. Exclusion Criteria**
Previously read:	Text previously not present
Now reads:	26. Body Mass Index (BMI) < 15 and > 31
Reason for change:	To add exclusion criteria

Section:	**5.1. Dosage and Administration**
Previously read:	TC-5619-238 will be initiated at a dose of 1mg; titrated to 5mg at Week 4; and titrated to 25mg at Week 4, or matching placebo.
Now reads:	TC-5619-238 will be initiated at a dose of 1mg; titrated to 5mg at Week 4; and titrated to 25mg at Week 8, or matching placebo.
Reason for change:	To correct the week that the dose is titrated to 25mg.

Section:	**New 5.3.3. Prohibited and Restricted Medications (old Prohibited Medications)**
Previously read:	Text previously not present
Now reads:	Drugs with restricted use: must have must have written prior approval from the Medical Monitor.
Reason for change:	To provide additional clarification regarding the use of restricted medications.

Section:	**6.1. Sample Collection and Handling**
Previously read;	Pharmacokinetic evaluation will be performed in a subset of the total study population. Twenty subjects (ten in each cohort) will be enrolled in the serial sample pharmacokinetic evaluation at one US site. Subjects enrolled for pharmacokinetic evaluation will also include 50% tobacco users and 50% non-tobacco users. Blood sample collection and pharmacokinetic assessments for this subset of the study population are described below.
Now reads:	Pharmacokinetic evaluation will be performed in a subset of the total study population. Approximately twenty (20) subjects (ten in each cohort) will be enrolled in the serial sample pharmacokinetic evaluation at select US sites. Subjects enrolled for pharmacokinetic evaluation will also include approximately 50% tobacco users and 50% non-tobacco users. Blood sample collection and pharmacokinetic assessments for this subset of the study population are described below.
Reason for change:	To allow flexibility to include additional sites in the collecting of serial PK samples to ensure adequate number of subjects are included.

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Section:	**6.1. Sample Collection and Handling**
Previously read:	Serial blood samples (7 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose.
Now reads:	Serial blood samples (6 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose.
Reason for change:	To correct the volume per sample for PK.

Section:	**6.1. Sample Collection and Handling**
Previously read:	Sparse blood samples (7 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 1 and 3 hours post-dose.
Now reads:	Sparse blood samples (6 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 1 and 3 hours post-dose.
Reason for change:	To correct the volume per sample for PK.

Section:	**7.1.1. CogState Schizophrenia Test Battery**
Previously read:	Text not previously present
Now reads:	The Trail Making Test is a two-part neuropsychological test that measures visual attention and task switching. It assesses cognition in the following domains: psychomotor speed, visual scanning, and executive functioning (sequence alternation and flexibility/set shifting). The subject is required to draw lines to connect consecutively numbered circles on Part A, and on Part B to connect consecutively numbered and lettered circles, alternating between numbers and letters (1-A-2-B, etc.) as quickly as possible. Two scores for each part are obtained, the total time and number of errors, with the total time score being the predominantly used measure. The Digit Symbol Substitution Test assesses psychomotor processing and attention. It is a code-substitution test that has often been included in non-language intelligence scales. In this test, subjects are asked to substitute geometric figures for randomized presentations of numbers. The correct pairing is shown in a key containing the numbers 1 through 9, each of which is paired with a different geometric symbol. The key is placed in front of the subject, and the subject has a specified amount of time to fill in as many symbols as possible under the numbers on the answer sheet. The score on this test is the number of correct symbols drawn within the allowed time.
Reason for change:	To describe the paper and pencil tests, Trails A & B and Symbol-Digit.

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Section:	**7.1.6. Alpha 7mRNA expression**
Previously read:	The level of expression will be correlated with primary (GML) and secondary (CPAL, CSTB composite score; SANS, SGI-Cog, CGI-I, CGI-S) efficacy endpoints.
Now reads:	The level of expression will be correlated with primary (GML) and secondary (CSTB composite score; SANS, SGI-Cog, CGI-I, CGI-S) efficacy endpoints.
Reason for change:	To remove CPAL from secondary endpoint listing.
Section:	**8.1. Safety Parameters, Physical Examination**
Previously read:	The physical exams conducted after the Screening visit may be abbreviated exams (psychiatric, neurologic, cardiovascular and GI), although each must include use of the AIMS.
Now reads:	Deleted
Reason for change:	To correct the type of physical exam conducted at each visit.
Section:	**8.1. Safety Parameters, Vital Signs**
Previously read:	Blood pressure, pulse and respiratory rate will be assessed at times indicated in the Time and Events Schedule.
Now reads:	Blood pressure, pulse, respiratory rate, height and weight will be assessed at times indicated in the Time and Events Schedule.
Reason for change:	To list all vital sign measurements being taken.
Section:	**8.1. Safety Parameters, ECG**
Previously read:	Digital twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured manually. These ECGs will be recorded in triplicate at each visit except the Follow-up Visit (unless an abnormality was detected at Week 12). The ECG will be recorded with the subject in a sitting position after at least 5 minutes of rest until 4 regular consecutive complexes are available.
Now reads:	Digital twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured manually. These ECGs will be recorded in triplicate at each visit except the Follow-up Visit (unless an abnormality was detected at Week 12). The ECG will be recorded with the subject in a supine of semi-recumbent position after at least 5 minutes of rest until 4 regular consecutive complexes are available.
Reason for change:	To clarify that ECGs should be done in a supine of semi-recumbent position.
Section:	**8.1.1. Blood Samples**
Previously read:	Blood samples for hematology and biochemistry will be taken at Screening (and Baseline if indicated), Week 4, Week 8, and Week 12. Samples will be fasting at Screening and Week 12, so that samples for fasting lipids may be obtained in addition to the other hematology and biochemistry labs.
Now reads:	Blood samples for hematology and biochemistry will be taken at Screening (an additional time at Screening and Baseline if indicated), Week 4, Week 8, and Week 12. Samples will be fasting at Screening and Week 12, or at repeats, so

	that samples for fasting lipids may be obtained in addition to the other hematology and biochemistry labs.
Reason for change:	To allow one repeat screening lab testing so that results may be received prior to randomization on Day 1.
Section:	**8.1.4. Pregnancy**
Previously read:	The investigator, or his/her designee, will collect pregnancy information on every female who becomes pregnant while participating in this study.
Now reads:	The investigator, or his/her designee, will collect pregnancy information using the Targacept Serious Event/Important Event Reporting Form on every female who becomes pregnant while participating in this study.
Reason for change:	To clarify how the investigators will collect pregnancy information.
Section:	**8.2.1.4. Adverse Event of Special Interest**
Previously read:	LFT abnormalities leading to withdrawal
Now reads:	LFT abnormalities leading to withdrawal (e.g. lab values of 3 times greater limit)
Reason for change:	To specify events that is of interest to the sponsor because they are relevant to the molecule or to the therapeutic area, even if the events are neither severe, serious, nor lead to withdrawal.
Section:	**8.2.1.4. Adverse Event of Special Interest**
Previously read:	Tardive dyskinesia Rigidity or Bradykinesia
Now reads:	Clinically significant change, if present in screening, or emergence of tardive dyskinesia Clinically significant change, if present in screening, or emergence of rigidity or bradykinesia
Reason for change:	To specify events that is of interest to the sponsor because they are relevant to the molecule or to the therapeutic area, even if the events are neither severe, serious, nor lead to withdrawal.
Section:	**8.2.1.4. Adverse Event of Special Interest**
Previously read:	Text not previously present.
Now reads:	Overdose Suicide
Reason for change:	To add the overdose and suicide to the list of collected AEs of special interest.
Section:	**8.2.5. Assessment of Causality**
Previously read:	However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE MedWatch form to Sponsor or CRO. The investigator may change his/her opinion of causality in light of follow-up information, amending the eCRF and SAE MedWatch forms accordingly.
Now reads:	However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the Targacept Serious Event/Important Event Reporting Forms to Sponsor or CRO. The investigator may change his/her opinion of causality in light of follow-up information, amending the eCRF and Targacept Serious Event/Important Event Reporting Forms accordingly.

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Reason for change: To correct the name of the form used in reporting serious adverse events and AEs of special interest.

Section: **8.2.8. SAE Reporting Procedures**

Previously read: The SAE MedWatch form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to Sponsor or CRO within the designated time frames.

Now reads: The Targacept Serious Event/Important Event Reporting Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to Sponsor or CRO within the designated time frames.

Reason for change: To correct the name of the form used in reporting serious adverse events and AEs of special interest.

Section: **8.2.8. Table 1. Timeframes for Submitting SAE Reports to Sponsor or CRO**

Previously read:

Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Time Frame	Documents	Time Frame	Documents
24 hrs	MedWatch form	24 hrs	Updated MedWatch form

Now reads:

Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Time Frame	Documents	Time Frame	Documents
24 hrs	Targacept Serious Event/Important Event Reporting Form	24 hrs	Updated Targacept Serious Event/Important Event Reporting Form

Reason for change: To correct the name of the form used in reporting serious adverse events and AEs of special interest.

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Section:	**8.2.8. SAE Reporting Procedures**
Previously read:	Facsimile transmission of the MedWatch form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the MedWatch form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the MedWatch form within 24 hours.
Now reads:	Facsimile transmission of the Targacept Serious Event/Important Event Reporting Form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the Targacept Serious Event/Important Event Reporting Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the Targacept Serious Event/Important Event Reporting Form within 24 hours.
Reason for change:	To correct the name of the form used in reporting serious adverse events and AEs of special interest.

Section:	**8.2.8. SAE Reporting Procedures**
Previously read:	Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.
Now reads:	Sponsor will provide a list of project contacts for SAE receipt, e-mail addresses, fax numbers, telephone numbers, and mailing addresses.
Reason for change:	To add contact information by e-mail.

Section:	**8.2.8.2 Management of an SAE and Events of Special Interest**
Previously read:	Text not previously present
Now reads:	A 6 ml PK plasma sample will be obtained at the earliest opportunity immediately following the occurrence of an SAE or Event of Special Interest.
Reason for change:	To correlate the SAE or ESI with levels of study drug.

Section:	**8.2.9. Management of Overdose**
Previously read:	In the event a study subject takes an overdose of study medication, the investigator may obtain the identity of the subject's medication by contacting the Targacept Medical Monitor or other designee. A detailed description of the treatment administered for the overdose and the subject's clinical course will be recorded on the special case report forms provided.
Now reads:	In the event a study subject takes an overdose of study medication, the investigator may obtain the identity of the subject's medication, however, the Targacept Medical Monitor or other designee must be notified if not before breaking the blind, within g24 hours after breaking the blind. A detailed description of the treatment administered for the overdose and the subject's clinical course will be recorded on the Targacept Serious Event/Important Event Reporting Form provided.
Reason for change:	To clarify the process of breaking the blind and documentation of treatment for overdose.

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Section: 8.2.9. Management of Overdose

Previously read:

- A 10 ml plasma sample for TC-5619 assay on admission, 1 hour after admission, 4 hours after admission and then every 8 hours for a minimum of 24 hours and until all signs and symptoms of the overdose have resolved. If possible, an additional plasma sample should be obtained at the time of occurrence of any major clinical event such as seizure or hypotensive crises.
- A drug screen on admission to the hospital to detect other drugs taken during the overdose.
- A detailed listing of clinical signs and symptoms such as the occurrence of anticholinergic effects (e.g., urinary retention, ileus, etc.), arrhythmias, seizures, respiratory depression and depressed level of consciousness.
- Frequent vital signs (initially hourly, or more frequently if clinically indicated) including supine blood pressure, standing blood pressure if possible, supine pulse, temperature and respiratory rate.
- An ECG on admission and every 8 hours thereafter until 3 consecutive ECGs that are normal or the same as the pre-study ECG have been obtained. Particular attention should be paid to the PR, QRS, and QTc intervals.
- Continuous monitoring of cardiac rhythm with representative tracings of any arrhythmias until no abnormalities of cardiac rhythm have been observed for 24 hours (therefore the minimum period of cardiac monitoring should be 24 hours).
- Hematological and blood chemistry tests and a urinalysis on admission and once daily for a minimum of 48 hours.

Now reads:

- A 6 ml plasma sample for TC-5619 assay immediately upon becoming aware of the overdose, 1 hour later, 4 hours later and then every 8 hours for a minimum of 24 hours and until all signs and symptoms of the overdose have resolved. If possible, an additional plasma sample should be obtained at the time of occurrence of any major clinical event such as seizure or hypotensive crises.
- A drug screen immediately upon becoming aware of the overdose to detect other drugs taken during the overdose.
- A detailed listing of clinical signs and symptoms such as the occurrence of anticholinergic effects (e.g., urinary retention, ileus, etc.), arrhythmias, seizures, respiratory depression and depressed level of consciousness.
- Frequent vital signs (initially hourly, or more frequently if clinically indicated) including supine blood pressure, standing blood pressure if possible, supine pulse, temperature and respiratory rate.
- An ECG immediately upon becoming aware of the overdose and every 8 hours thereafter until 3 consecutive ECGs that are normal or the same as the pre-study ECG have been obtained. Particular attention should be paid to the PR, QRS, and QTc intervals.

- Continuous monitoring of cardiac rhythm with representative tracings of any arrhythmias until no abnormalities of cardiac rhythm have been observed for 24 hours (therefore the minimum period of cardiac monitoring should be 24 hours).

Reason for change: To clarify amount of plasma required for the TC5619 assay and the timing of the assessments.

Section: **8.2.9. Management of Overdose**
Previously read: Hematological and blood chemistry tests and a urinalysis on admission and once daily for a minimum of 48 hours.
Now reads: Hematological and blood chemistry tests (including LFTs) and a urinalysis immediately and once daily for a minimum of 48 hours.
Reason for change: To clarify that liver function tests will also need to be conducted in the event of an overdose and that the samples should be drawn immediately upon becoming aware of the overdose.

Section: **New 8.2.10. Management of Suicide Attempt**
Previously read: Text previously not present.
Now Reads: All suicide attempts must be reported as an SAE/ESI whether the attempt was serious attempt or not. A detailed history regarding the circumstances of the suicide attempt including what lead up to the suicide attempt and the method used in the suicide attempt A. description of the treatment administered for the suicide attempt and the participant's clinical course will be reported on the Targacept Serious Event/Important Event Reporting Form

The evaluation outlined for an overdose should also be followed for an apparent suicide attempt regardless of whether method of the attempt was an overdose.

Any possible suicide-attempts will result in immediate withdrawal of the participant from the study. Appropriate medical and psychiatric management of the suicide attempt and/or related AEs/SAEs must be provided to the participant.
Reason for change: Provide additional guidance to the management of a suicide attempt.

Section: **New 8.2.11. Management of Increase Liver Function Tests**
Previously read: Text previously not present.
Now reads: Any increase in liver function tests of > 3 times the upper limit of the reference range should be reported on the Targacept Serious Event/Important Event Reporting Form

A detailed history including all possible explanations for the elevations of Liver Function tests including a list of all concomitant medications the subject has taken in the last 30 days.

- Blood chemistry tests including LFTs should be repeated to confirm the results.
- A 6 ml plasma sample for TC-5619 assay should be obtained
- Repeat LFTs should be performed weekly until the levels return to baseline.
- Management of the elevated LFTs should be discussed with the Medical Director or Medical Safety Monitor.

TARGACEPT PRO-05619-CRD-001(02) Effective Date: 21 Dec 2009

Reason for change: Provide additional guidance to the management of elevated liver function tests

Section: **New 8.2.12. Management of Prolonged QTc Fridericia**
Previously read: Text previously not present.
Now reads: A QTc prolongation is defined as a QTcF $\geq$ 500 msec on the automated report, or a mean QTcF of > 450 msec (males), QTcF > 480 msec (females), or an increase > 60 msec on the cardiologist read ECG. The Medical Monitor must be notified and the Targacept Serious Event/Important Event Reporting Form must be completed

- The participant should be contacted and requested to come to the clinical site for repeat ECGs (in triplicate)
- A 6 ml plasma sample for TC-5619 assay (unscheduled PK sample) should be obtained.
- Appropriate medical management shall be performed as required by the subject's clinical signs and symptoms.
- The following information should be obtained from the participant and confirmed with the informant:
  - Was he/she symptomatic?
  - What medications (prescription and OTC) is the participant taking?
  - Does the participant have a history of heart disease?
  - Is there a familial history of heart disease?

Reason for change: Provide additional guidance to the management of Prolonged QTcF

Section: **8.3. Follow-Up of Adverse Events**
Previously read: Once resolved, the appropriate eCRF entries and MedWatch forms will be updated....New or updated information will be recorded on the originally completed MedWatch form, with all changes signed and dated by the investigator.
Now reads: Once resolved, the appropriate eCRF entries and Targacept Serious Event/Important Event Reporting Form will be updated....New or updated information will be recorded on the originally completed Targacept Serious Event/Important Event Reporting Form, with all changes signed and dated by the investigator.
Reason for change: To correct the name of the form used in reporting serious adverse events and AEs of special interest.

Section: **9.1.4. Primary Efficacy Endpoint Analysis**
Previously read: Since there are three dose comparisons (Week 4 [1mg]; Week 8 [5mg]; and Week 12 [25mg] that may result in the rejection of the null hypothesis, the Hommel-Hochberg method will be used to control for multiple comparisons.
Now reads: Since there are three dose comparisons (Week 4 [1mg]; Week 8 [5mg]; and Week 12 [25mg] that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons.
Reason for change: To clarify that the method used will be the Hochberg method.

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Section:	**9.3. Level of Significance**
Previously read:	The level of significance used for all efficacy variables will be defined by an alpha of 0.10 in one-tailed tests. For the primary efficacy endpoint, because there are three dose comparisons that may result in the rejection of the null hypothesis, the Hommel-Hochberg method will be used to control for multiple comparisons. The level of significance used for all efficacy variables will be defined by an alpha of 0.10 in one-tailed tests. For the primary efficacy endpoint, because there are three dose comparisons that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons.
Reason for change:	To clarify that the method used will be the Hochberg method.
Section:	**12.1. Ethical Principles**
Previously read:	This study will be conducted in accordance with International Conference of Harmonization, Good Clinical Practice and all applicable regulatory requirements, including, where applicable, the 1997 version of the Declaration of Helsinki.
Now reads:	This study will be conducted in accordance with International Conference of Harmonization, Good Clinical Practice and all applicable regulatory requirements, including, where applicable, the 2008 version of the Declaration of Helsinki.
Reason for change:	Correct the reference date.
Section:	**12.3. Institutional Review Board**
Previously read:	This study will be conducted in full compliance with the Institutional Review Board (IRB) regulations in 21 CFR 56 and applicable local regulatory guidance, in accordance with the Declaration of Helsinki (1997).
Now Reads:	This study will be conducted in full compliance with the Institutional Review Board (IRB) regulations in 21 CFR 56 and applicable local regulatory guidance, in accordance with the Declaration of Helsinki (2008).
Reason for change:	Correct reference date.
Section:	**14. References**
Previously read:	23. ECDEU Assessment Manual for Psychopharmacology. Revised 1976 Ed. Guy W. 218. 24. Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schiz Bull 13: 261-276. 25. Perl O, Strous RD, Dranikov A, Chen R, and Fuchs S (2006). Low levels of alpha7-nicotinic acetylcholine receptor mRNA on peripheral blood lymphocytes in schizophrenia and its association with illness severity. Neuropsychobiol 53: 88-93. 26. Andreasen N (1981) The Scale for the Assessment of Negative Symptoms (SANS). University of Iowa Press, Iowa City, Iowa.
Now reads:	22. ECDEU Assessment Manual for Psychopharmacology. Revised 1976 Ed. Guy W. 218. 23. Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schiz Bull 13: 261-276. 24. Perl O, Strous RD, Dranikov A, Chen R, and Fuchs S (2006). Low levels of alpha7-nicotinic acetylcholine receptor mRNA on peripheral blood

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lymphocytes in schizophrenia and its association with illness severity. Neuropsychobiol 53: 88-93.
25. Andreasen N (1981) The Scale for the Assessment of Negative Symptoms (SANS). University of Iowa Press, Iowa City, Iowa.

Reason for change: To correct the numeration of the references as original 22 was taken out in Version 01.

Section: **Appendix 1. Pharmacokinetic Sample Collection, Handling and Shipping, Materials and Labeling:**

Previously read: Blood must be collected in glass or plastic K_3EDTA containing blood collection tubes (e.g., Vacutainer®). Resulting plasma samples must be stored in polypropylene storage tubes. No tubes with separation gel should be used.

Now reads: Blood must be collected in glass or plastic K_2EDTA containing blood collection tubes (e.g., Vacutainer®). Resulting plasma samples must be stored in polypropylene storage tubes. No tubes with separation gel should be used.

Reason for change: Clarify the type of collection tube used.

Section: **Appendix 1. Pharmacokinetic Sample Collection, Handling and Shipping**

Previously read: Collect 7 mL of blood into the appropriate K_3EDTA containing collection tube (e.g., Vacutainer®) at each time point.

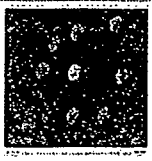
Now reads: Collect 6 mL of blood into the appropriate K_2EDTA containing collection tube (e.g., Vacutainer®) at each time point.

Reason for change: To clarify the type of collection tube and to correct the volume per sample for PK.

Section: **Appendix 2. CogState Schizophrenia Test Battery (CSTB)**

Previously read:
b. Continuous Paired Associate Learning Task (CPAL)
Administration Time (in healthy volunteers): 5 Minutes
Cognitive Domain Usually Measured: Visual Learning & Memory
Task Description:
Stage 1
The pre-task on-screen instructions ask: "In what locations do these pictures belong"
In this task, the subject must learn and remember the pictures hidden beneath different locations on the screen. The subject must tap the target on the central location to begin. As each picture to be learned is revealed, the subject must tap each location and remember where the picture was located.
Stage 2
The pre-task on-screen instructions ask: "In what locations do these pictures belong"
Now the same pictures will be presented in the center of the screen, and the subject must tap on the peripheral location where that picture previously appeared.

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Now reads:	Deleted
Reason for change:	To remove CPAL task
Section:	**Appendix 3. Prohibited and Restricted Concomitant Medications**
Previously read:	Tricyclic antidepressants (TCA) (e.g., amitriptyline, clomipramine, imipramine, ofepramine, maprotiline, nortriptyline, trimipramine); maximal dose allowed is the lowest therapeutic dose according to the U.S. labeling text
Now reads:	Deleted from drugs with narrow therapeutic range and prohibited use from Day 1 and during the study section
Reason for change:	As tricyclic antidepressants was listed in two sections in this appendix, the text was retained in the more restrictive section, drugs with restricted use 4 weeks prior to Day 1 and during the study.
Section:	**Appendix 13.**
Previously read:	Appendix 13. Signed and Dated Investigator Protocol Agreement Page
Now reads:	Appendix 13. Fagerstrom Test for Nicotine Dependence
Reason for change:	To add copy of test to the protocol and insert appendix.
Section:	**Appendix 14.**
Previously read:	Appendix not previously present
Now reads:	Appendix 14. Signed and Dated Investigator Protocol Agreement Page
Reason for change:	To adjust the numbering of Appendices for the insertion of Fagerstrom Test for Nicotine Dependence.

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TARGACEPT

CLINICAL PROTOCOL SYNOPSIS

Name of Company: Targacept	Name of Finished Product: TC-5619-238	Name of Active Substance: TC-5619

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess Efficacy, Safety, and Tolerability of TC-5619 as Augmentation Therapy to Improve Cognition in Outpatients with Cognitive Dysfunction in Schizophrenia.
PRO-05619-CRD-001, Phase 2

Investigators: [redacted]

Clinical Laboratories: QECG (ECGs); CogState (computerized test battery); ICON and Tandem (labs)

Study Period: 18 weeks, including a 4-week screening period, a 12-week treatment period, and a 2-week follow-up period

Objective(s):

Primary:

- To assess the efficacy of TC-5619 as augmentation therapy to quetiapine or risperidone, to improve cognition in stable outpatients with Cognitive Dysfunction in Schizophrenia (CDS).

Secondary:

- To further assess the efficacy, and the safety and tolerability of TC-5619 administered adjunctively with quetiapine or risperidone in outpatients with CDS.
- To evaluate the pharmacokinetics of TC-5619 in this population through serial and sparse sampling in a subset of subjects in the study and to assess plasma levels of quetiapine and risperidone/9-OH-risperidone.

Exploratory:

- To correlate mRNA expression of the alpha-7 neuronal nicotinic receptor (NNR) with study drug response
- To assess the response to study drug of P50, P300, and Mismatch Negativity (MMN) in a subset of subjects

Methodology: This is a double blind, randomized, placebo-controlled, fixed dose titration, add-on study.

Number of Subjects: No more than 200 subjects will be enrolled, divided into 2 cohorts, to ensure that at least 120 subjects complete (60 per cohort); this assumes a 40% drop-out rate. Randomization will be stratified so that one-half of the subjects in each cohort will be tobacco users (30 per cohort), and one-half will be non-users (30 per cohort).

The number of study subjects is based upon the following sample size calculation. This study is powered to demonstrate a statistically significant difference in each of the stratified sub-cohorts (tobacco users or tobacco non-users) between TC-5619 and placebo in the change from Baseline (Day 1) to the end of the fourth week of dosing with each of 3 doses of TC-5619 (1mg, 5mg, and 25mg) in the primary endpoint (Groton Maze Learning [GML]), which is an item in the CogState Schizophrenia test battery. The number of subjects per sub-cohort needed for GML is 29, to detect a difference of 18.0 points with 80% power using a one-sided test and a significance level of 10% ($p < 0.10$), assuming a standard deviation (SD) of 32.2 and normally distributed errors. Hence the number of subjects required in the entire cohort (tobacco users plus non-users) is 60.

Study Design: Following a 4-week screening period, subjects on prior treatment with quetiapine or risperidone will be randomized in double-blind fashion into 1 of 2 cohorts: placebo or TC-5619-238. Subjects will undergo fixed dose titration every 4 weeks: a 1mg p.o. qd starting dose for 4 weeks (Day 1 – Week 4); then a 5mg p.o. qd dose for 4 weeks (Week 4 – Week 8); and finally a 25mg p.o. qd dose for 4 weeks (Week 8 – Week 12). All doses are expressed as free base equivalents. The double-blind treatment period will therefore last for 12 weeks. There will be a 2-week follow-up period following the end of the treatment period. Pharmacokinetic evaluation will be performed in subset of the study population.

Inclusion Criteria

1. Diagnosis of schizophrenia, per DSM-IV TR criteria, as aided by the MINI International Neuropsychiatric Interview (MINI)
2. Controlled schizophrenia, on stable dose of quetiapine or risperidone for at least 2 months prior to screening
3. Age 18 – 60, male or female
4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening (social

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admissions allowed)
5. Clinical history of stable psychotic symptoms for 1 month prior to Screening.
6. Stable positive symptoms of schizophrenia for 4 weeks prior to Day 1, as shown by score </= 4 on PANSS for items related to delusion, hallucination, conceptual disorganization, and unusual thought content, at Screening and at Day 1
7. Calgary Depression Scale for Schizophrenia score < 6
8. Outpatient with stable housing, and presence of an informant who sees the subject at least 4 times weekly
9. Able to understand and sign informed consent

Exclusion Criteria:

1. Diagnosis of schizoaffective or schizophreniform disorders 1 year prior to Screening
2. Patients at significant risk of suicide or of danger to themselves or others
3. Antipsychotics other than quetiapine or risperidone, or a change in dosing of these within 2 months of Screening
4. Treatment with mood stabilizers, antidepressants, or anxiolytics (short-acting hypnotics permitted)
5. Treatment within 1 month using cognition-affecting agents other than the above, as listed in Appendix 3 (e.g. CNS stimulants)
6. Use of other prohibited concomitant medications
7. Other concomitant medications that have been changed within 1 month prior to Screening
8. History within past 6 months of alcohol or illicit drug abuse
9. Use of smoking cessation therapy within 1 month prior to Screening
10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level > than 50ng/mL (urine cotinine level between 50ng/ml and 500ng/ml will be excluded)
11. Unable to comply with study procedures in opinion of investigator, including CogState battery
12. History of significant other major or unstable neurological, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, or urological disorder
13. History of myocardial infarction
14. History of seizure disorder
15. Type 1 diabetes mellitus (DM); type 2 DM that requires medication (diet-controlled allowed, with HbA1C < 7.3)
16. Electroconvulsive therapy within 2 months prior to Screening
17. Uncontrolled hypothyroidism, vitamin B12 or folic acid deficiency
18. Current TB or known systemic infection (HBV, HCV, HIV)
19. Clinically significant finding on physical exam that could be a safety issue in the study
20. ALT or AST levels > 2.5 times the upper limits of the laboratory reference range
21. Clinically significant lab or ECG abnormality that could be a safety issue in the study, including QTcF > 450 (males) or QTcF > 480msec (females)
22. Women of child-bearing potential and men unwilling or unable to use accepted methods of birth control
23. Women with a positive pregnancy test, or who are lactating
24. Participation in another clinical trial in last 3 months prior to Screening
25. Involvement in planning or conduct of the study by site staff
26. Body Mass Index (BMI) < 15 and > 31

Test Product(s), Dose, and Mode of Administration, Batch Number(s):

Investigational: TC-5619-238 will be provided as hard gelatin capsules in strengths of 1mg, 5mg, and 25mg (as free base). Subjects will take 1mg TC-5619, 5mg TC-5619, 25mg TC-5619, or matching placebo – one capsule once daily p.o., as soon as possible after awakening, at least 90 min before first tobacco use in tobacco users, and at least 30 min before first dose of quetiapine or risperidone in all subjects

Control: Placebo will be provided with exactly the same shape, size and appearance.

Batch Numbers: 1mg: B090229
5mg: B090245
25mg: B090253
Placebo: B090222

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Duration of Treatment:
Treatment period lasts for 12 weeks, with a 4-week screening period, and a 2-week follow-up period after treatment ends.

Concomitant Medication Restrictions:
Subjects must be on stable dose of quetiapine or risperidone for at least 2 months prior to Screening and enrollment.

Efficacy endpoints:

- Primary efficacy endpoint is an item in the CogState Schizophrenia Test Battery (CSTB): Groton Maze Learning (GML), comparing TC-5619 vs. placebo, at each of three occasions vs. Baseline (Day1): Week 4, Week 8, and Week 12 or Early Withdrawal (EW). CSTB is to be administered at least 90 minutes after last tobacco use if applicable.
- Secondary efficacy endpoints are (each testing TC-5619 vs. placebo, and compared to Baseline):
  - GML item at Week 1
  - Composite CSTB score; at Week 1, Week 4, Week 8, Week 12 or EW compared to baseline.
  - Subjective Global Impression-Cognition (SGI-Cognition), patient and informant versions; at Week 1, Week 4, Week 8 & Week 12 or EW.
  - Clinical Global Impression of Severity (CGI-S); at Day 1, Week 1, Week 4, Week 8, Week 12 or EW, and Week 14 (Follow-up Visit).
  - Clinical Global Impression-Global Improvement (CGI-I); at Week 1, Week 4, Week 8, Week 12 or EW, and Week 14.
  - Scale for Assessment of Negative Symptoms (SANS) total score; at Week 1, Week 4, Week 8, and Week 12 or EW.
- Other (for tobacco users only):
  - Tobacco use: estimated by patient at Baseline and Week 12 or EW.
  - Fagerstrom test score: at Baseline and Week 12 or EW.

Safety Endpoints:

- Physical examination at Week -4, Day 1, Week 1, Week 4, Week 8, Week 12 or EW, and Week 14.
- Abnormal Involuntary Movement Scale (AIMS) at Week -4, Day 1, Week 1, Week 4, Week 8, and Week 12 or EW.
- Calgary Depression Scale for Schizophrenia (CDSS) total scores at Week -4, Day 1, Week 4, Week 8, and Week 12 or EW.
- Assessment of AEs at Week -4, Day 1, Week 1, Week 4, Week 8, Week 12 or EW, and Week 14
- Completion of Columbia Suicide Severity Rating Scale (CSSRS) at Week -4, Day 1, Week 1, Week 4, Week 8, Week 12 or EW, and Week 14.
- Sitting and orthostatic vital signs at Week -4, Day 1, Week 1, Week 4, Week 8, Week 12 or EW and Week 14; and additional orthostatic vital signs pre-dose and post-dose (1 and 3 hours after in-clinic dose), at Day 1, Week 4, Week 8, and Week 12 or EW. When collecting sitting vital signs, BP and heart rate will be recorded after the subject sits for at least 5 minutes. When orthostatic vital signs are collected, BP and heart rate will be recorded following at least 2 and not more than 3 minutes standing.
- 12 Lead digital ECG performed in triplicate at Week -4, Week 1, Week 4, Week 8, Week 12 or EW; and at Week 14 if an abnormality was identified at Week 12; and additional pre-dose and post-dose ECGs (1 & 3 hrs after in-clinic dosing) at Day 1, Week 4, Week 8, and Week 12 or EW.
- Clinical laboratory tests (hematology, plasma biochemistry, liver function tests [LFTs], bilirubin, and urinalysis) at Week -4, Day 1, Week 4, Week 8, Week 12 or EW, and Week 14. A lipid panel will be added at Screening and Week 12 or EW, and labs on these days will be fasting.
- Urine drug screen at Screening, Day 1, Week 4, Week 8, and Week 12 or EW.
- Pregnancy test for pre-menopausal females at Week –4, Day 1 and Week 12 or EW.

PK endpoints:

- Changes in plasma levels of quetiapine or risperidone/9-OH-risperidone at Day 1, Week 4, Week 8 and Week 12.
- Appropriate pharmacokinetic parameters for TC-5619 will be estimated on Day 1, Week 4, Week 8 and Week 12.

Exploratory endpoints:

- mRNA expression of the alpha 7 NNR gene in lymphocytes and its correlation with primary and secondary

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efficacy endpoints.

- P50, P300, and Mismatch Negativity evoked potentials in a subset of subjects; at Day 1, Week 4, Week 8, and Week 12 or EW.

Statistical Methods:

General Statistical considerations: Categorical variables will be summarized by presenting the number and percent of subjects in each category. Continuous variables will be summarized by presenting n, mean, median, standard error (SE), standard deviation (SD), minimum, and maximum values. To evaluate possible treatment differences, binary and ordinal categorical measures will be analyzed using Chi-square test; all continuous measures will be analyzed using an ANCOVA model. All statistical tests for the analyses will be performed using one-tailed tests at the $p < 0.10$ level of significance, except as noted below.

Efficacy analysis

- The primary endpoint will be change in CogState Schizophrenia Test Battery GML from Baseline to Week 4, Week 8, and Week 12 or EW. This change from Baseline will be analyzed using Analysis of Covariance (ANCOVA) techniques with an alpha of 0.10 (one-tailed), to examine differences between the TC-5619 and placebo treatment cohorts (entire cohorts, tobacco-users and non-users combined). The ANCOVA model will include treatment as a main factor and baseline values, country, time, tobacco use status, and interaction of tobacco use status with treatment as covariates. Other covariates may be used as delineated in the Statistical Analysis Plan. Since the primary outcome (GML) is assessed on 3 occasions (Week 4, Week 8, and Week 12) that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons. To ensure that the significance level over the three independent tests is 10%, should the first P value be worse than the 10% level of significance, then the second P value will be assessed using the 5% level of significance; and should the second P value not reach significance, then the third P value will be assessed using the 3.33% level of significance. Rejection of the null hypothesis for GML at any of the 3 occasions will constitute trial success.
- The primary efficacy analysis will be performed using the primary efficacy endpoint for the Intent-to-Treat (ITT) population and the Per Protocol (PP) population. The results of the ITT population efficacy analysis comprise the pre-specified measure of trial success for the primary endpoint. To account for missing data, the last-observation-carried-forward (LOCF) method will be used, i.e. the last available on-therapy observation for a subject will be used to estimate subsequent missing data.
- Secondary endpoints will be examined to measure differences between TC-5619 and placebo in the entire cohorts (tobacco-users and non-users combined); and in tobacco-users alone; and in non-users alone. The endpoints examined will include change from Baseline to Weeks 4, 8 and 12 in: SGI-Cognition total score; CSTB composite score; SANS total score; CGI-S; and CGI-I. All secondary analyses will be performed for the ITT and PP populations. The results of the ITT population efficacy analysis comprise the pre-specified measure of trial success for secondary endpoints.
- Other efficacy analysis will examine (tobacco users only):
  - tobacco use, as estimated by patients at Baseline and Week 12 or EW;
  - nicotine dependence (Fagerstrom Test of Nicotine Dependence), Week 12 or EW vs. Baseline;

  Descriptive statistics without formal statistical testing will be used for the other efficacy results.

Safety analysis:

All safety analyses will be performed for the ITT Population. Adverse events will be coded by system organ class and preferred term using MedDRA. Treatment emergent adverse events (TEAE) will be tabulated and summarized to show the number and percentage of patients in each treatment group.

- ECG parameters, vital signs, and lab data will be tabulated and then interpreted using descriptive statistics. No inferential statistical analysis will be performed.
- Change from Baseline to Week 4, Week 8 and Week 12 in the AIMS scores, Calgary Depression Scale for Schizophrenia total score, and CSSRS total score will be analyzed using an ANCOVA model with treatment as main factor and baseline values as covariate.

Pharmacokinetic analysis:

Individual and descriptive statistics for quetiapine and risperidone/9-OH-risperidoane will be presented. Individual

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plasma TC-5619 concentration data and estimated PK parameters will be listed and summarized using descriptive statistics. Graphical representations of individual, mean, median and composite concentration-time profiles for TC-5619 will be presented according to dose level. Exploratory analysis: mRNA expression in a subset of subjects will be measured and correlated with change from Baseline in GML, CSTB composite score, SANS, P50, P300, MMN, CGI-S, CGI-I, and SGI-Cog scores. ▪ P50, P300 and MMN will be measured and compared between TC-5619 and placebo cohorts.		

TIME AND EVENTS SCHEDULE

Phase	Screening	Double-Blind Treatment								Follow-Up
Event	Visit 1 Week -4 Screening	Visit 2 Day 1 Baseline	Visit 3 Wk 1	TC Wk 2	Visit 4 Wk 4	TC Wk 6	Visit 5 Wk 8	TC Wk 10	Visit 6 Wk 12	Visit 7 Wk 14 Follow-Up
Informed Consent	X									
Social Habits	X	X	X		X		X		X	
DSM-IV Evaluation inc MINI	X									
PANSS	X	X								
SANS	X	X	X		X		X		X	
Inclusion/exclusion criteria	X	X								
CDSS	X	X	X		X		X		X	
Medical/Psychiatric History	X									
Medication History	X									
Compliance with quetiapine / risperidone assessed	X	X	X		X		X		X	X
Concomitant Medications	X	X	X		X		X		X	X
Birth control counseling, WOCBP & men	X	X	X		X		X		X	X
Adverse Events history inc CSSRS[9]	X	X	X		X		X		X	X
Physical Exam	X	X	X		X		X		X	X
AIMS	X	X	X		X		X		X	X
Vital Signs (incl. orthostatic BP)[1]	X	X	X		X		X		X	X
Labs (Chem7, CBC, LFTs, bilirubin, fasting lipids[6])	X	X[2]			X		X		X	X[2]
Hemoglobin A1C (HbA1C)	X								X	
Urinalysis	X	X[2]							X	X[2]
Urine drug screen	X	X			X		X		X	
Urine pregnancy test for WOCBP	X	X							X	
Urinary cotinine, creatinine	X	X			X		X		X	
PK, antipsychotic levels[3]		X			X		X		X	
ECG[4]	X	X	X		X		X		X	X[5]

CogState Battery	X[7]	X	X		X		X		X	X
SGI-Cognition, subject and informant versions			X		X		X		X	
CGI-I			X		X		X		X	X
CGI-S	X	X	X		X		X		X	X
P50, P300, MMN		X[8]	X		X		X		X	
Fagerstrom Test for Nicotine Dependence		X							X	
Blood sample for alpha-7 mRNA expression		X								
Drug Dispensation		X			X		X			
Initiation of dose		X								
In-clinic dosing		X			X		X		X	
Telephone contact to assess drug compliance and tolerability				X		X		X		
Completion of Trails A & B and Symbol-Digit paper and pencil tests.	X	X	X		X		X		X	X

[1]Sitting vital signs will be obtained at each visit, by recording BP and heart rate after the subject has been sitting for at least 5 minutes. On each occasion that sitting vital signs are obtained, orthostatic vital signs will also be obtained, by recording BP and heart rate following at least 2 and not more than 3 minutes standing. In addition to these measurements, on Day 1, Week 4, Week 8, and Week 12, sitting and orthostatic vital signs will be performed pre-dose and approximately 3hrs post-dose. Weight and height will be obtained at Screening. Weight will also be obtained at Week 12.

[2] Laboratory samples on Day 1 and F/U visit will be collected only for subjects with abnormal values from the Screening or Week 12 assessments, respectively. Repeat screening laboratory results must be received by the site before the subject can be randomized on Day 1.

[3] Serial blood samples for pharmacokinetic assessments will be obtained from a subset of subjects at selected US site(s) on Day 1, Week 4, Week 8 and Week 12 at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose. In the other US sites sparse blood samples will be obtained on Day 1, Week 4, Week 8 and Week 12 at the following time points: pre-dose, 1 and 3 hours post-dose.

[4]ECG will be recorded digitally in triplicate, after the subject has rested for 5 minutes in a supine position. These ECGs will be obtained both pre-dose and 3 hours post-dose on Day 1, Week 4, Week 8, and Week 12 visits.

[5] ECG will be obtained at F/U visit only if an abnormality was found in the Week 12 ECG.

[6] Labs at baseline and at week 12 will be obtained after an overnight fast so that a fasting lipid panel can be obtained. Lab assessments at other visits are not fasting, and do not include lipid panel testing.

[7] CogState Battery at Screening will include two assessments, one to train the subject on the battery and one for baseline measurement.

[8] P50, P300 and MMN at Baseline will include two assessments, one for the subject to become comfortable with test procedures and one for baseline measurement.

[9] At Screening, the Baseline version of CSSRS assessment will be completed. At all subsequent visits, the Since Last Visit version of CSSRS assessment will be completed.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of Co-variance
API	Active Pharmaceutical Ingredient
BMI	Body Mass Index
CDS	Cognitive Dysfunction in Schizophrenia
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression scale – Global Improvement
CGI-S	Clinical Global Impression scale – Severity
CLP	Clinical Pharmacology
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CSSRS	Columbia Suicide Severity Rating Scale
CSTB	CogState Schizophrenia Test Battery
DBP	Diastolic Blood Pressure
DET	Detection test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GML	Groton Maze Learning test
HbA1C	Hemoglobin A1C
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonization
IDN	Identification task
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
MINI	Mini International Neuropsychiatric Inventory
MMN	Mismatch Negativity
NNR	Neuronal Nicotinic Receptor
NOAEL	No Observable Adverse Effect Level
NTEAE	Non Treatment-Emergent Adverse Event
P50	Positive wave 50msec after Event

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P300	Positive wave 300msec after Event
PANSS	Positive and Negative Symptoms of Schizophrenia
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
SANS	Scale for Assessment of Negative Symptoms
SD	Standard Deviation
SEM	Standard Error of the Mean
SGI-Cog	Subject Global Impression – Cognition scale
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
WOCBP	Women of Childbearing Potential

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1. INTRODUCTION

1.1. Description of Investigational Product

TC-5619 is a new chemical entity that targets α7 neuronal nicotinic receptors (NNRs). Highly specific for the α7 nicotinic receptor, TC-5619 exhibits more than a thousand-fold selectivity for α7 versus α4β2 receptor subtypes.[1] In nonclinical studies, TC-5619 produced no detectable effects on muscle or ganglionic nicotinic receptor sub-types, indicating marked selectivity for the central nervous system (CNS) over the peripheral nervous system (PNS).[2] In toxicology studies, TC-5619 was well tolerated in rodents and dogs. In humans, TC-5619 demonstrated excellent tolerability up to and including administration of a single oral dose of 600mg (tosylate salt; Study TC-5619-238-CLP-001)[3] and multiple oral doses of 300mg per day (tosylate salt; Study TC-5619-238-CLP-002)[4]. In studies of behavioral pharmacology, TC-5619 was effective in a rodent model of cognition with doses as low as 0.3 mg/kg, indicating the potential for a wide therapeutic index. In the Multiple Rising Dose study (TC-5619-238-CLP-002)[4], following the administration of TC-5619 at doses of 10mg (tosylate salt), subjects exhibited statistically significant increases in the Power of Attention measurement using the Cognitive Drug Research (CDR) test battery. Therefore, TC-5619 is being developed for use as an adjunctive therapy in combination with atypical antipsychotics to treat cognitive dysfunction in schizophrenia (CDS).

For more detailed information, refer to the Investigator's Brochure for TC-5619.

1.2. Summary of Findings

1.2.1. Nonclinical Studies

Nonclinical studies provide data to support the safe administration of TC-5619 to humans. In vitro studies were conducted to characterize the pharmacology, electrophysiological effects, and potential for genotoxicity of TC-5619, while in-vivo studies were conducted to investigate the safety, pharmacokinetics / metabolism, and toxicology of TC-5619. GLP safety pharmacology studies have been completed to evaluate the effects of TC-5619 on gastrointestinal and respiratory function as well as locomotor effects in rats. Additional GLP studies completed include: acute single oral and intravenous doses in rats and dogs; 30-day and 90-day repeat dosing studies in rats and dogs; a hERG (human ether-a-go-go related gene) channel inhibition study, a telemetry study in dogs; and in-vitro / in-vivo genotoxicity studies.

Receptor screening indicates that TC-5619 is highly selective for the α7 NNR, with inhibitory constants (Ki) for α7, opioid, sodium site 2 and 5-hydroxytryptamine ($5HT_3$) receptors of 1nM, 13μM, 13μM, and > 10 μM, respectively. TC-5619 exhibited competitive binding selectivity for M1, M2, nonselective central and nonselective peripheral muscarinic receptors.

In human embryonic kidney (HEK293) cells, TC-5619 exhibited an EC_{50} of approximately 50μM for hERG channel inhibition. TC-5619 produced no significant changes in cardiovascular function and no effects on the QT interval following doses of 10, 25, and 100 mg/kg in telemeterized dogs. All doses in this section are expressed as free base equivalents.

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No observed effect levels (NOELs) of 25 mg/kg for the gastrointestinal system and 100 mg/kg for the neurological and respiratory systems were noted in GLP safety pharmacology studies.

In rats, the acute no observable effect level following single oral administration was 100 mg/kg while the acute NOEL following single intravenous administration was 15mg/kg. In dogs, the acute no observable effect level following single oral administration was 20 mg/kg while the acute NOEL following intravenous administration was 2 mg/kg.

Among rats dosed with TC-5619 at 16.9, 67.7, and 338.5 mg/kg/day for 30 days, the NOEL was 67.7 mg/kg/day. At the high dose, tremors, partially closed eyelids, and hunched posture were observed. Among dogs dosed with TC-5619 at 10, 30, or 100/80 mg/kg/day for 30 days, the NOEL was 10 mg/kg/day in males and slightly less than 10 mg/kg/day in females. In the intermediate and high dose treatment groups, dogs displayed tremors and partially closed eyelids. These effects were noted in one female dog in the low-dose group as well. In the 100-mg/kg group, dogs exhibited markedly reduced food consumption and body weight loss during the first week of dosing, necessitating a reduction in the daily dose from 100 to 80 mg/kg.

TC-5619-238 was well tolerated in 90-day repeat-dose toxicity studies with a 28-day recovery period in rats and dogs. In rats, the NOEL was 50 mg/kg/day. Ptosis, head tilt, mydriasis, and waddling gait were observed at 150 and 350 mg/kg/day as well as decreased activity at 350 mg/kg/day. Increased turnover of red blood cells at 150 and 350 mg/kg/day was correlated with increased spleen weights and extramedullary hematopoiesis. Increased kidney weights at 350 mg/kg/day were associated with multifocal tubular degeneration/regeneration at 150 and 350 mg/kg/day, and hyaline casts at 350 mg/kg/day. Increased serum potassium, calcium and phosphorus and urine protein levels were also seen. Increased liver weights at 150 and 350 mg/kg/day were associated with centrilobular hypertrophy and elevated serum lactate dehydrogenase, alanine aminotransferase, alkaline phosphatase, cholesterol, triglycerides and/or phospholipids. Bile duct epithelial hypertrophy/vacuolation and follicular cell hypertrophy in thyroid gland was seen at 350 mg/kg/day. In the lungs, alveolar histiocytosis occurred at 350 mg/kg/day accompanied by elevation of monocytes at 150 and 350 mg/kg/day. Except for the bile duct epithelial hypertrophy/vacuolation, renal tubular degeneration/regeneration, and increased urine protein, all findings were reversible. In dogs, the NOAEL was 5 mg/kg/day. Mydriasis was observed at all doses. Salivation, tremor, prolapse of the nictitating membrane, ptosis, and vomiting was observed at 30 and 60 mg/kg/day. Tremor was observed in one animal at 5 mg/kg/day. Reduced food consumption and body weight were observed during the first two weeks at 60 mg/kg/day. Reduced direct and consensual pupillary reflexes and reddened mucous membranes were recorded at 60 mg/kg/day. Liver weights were slightly increased in the males at 60 mg/kg/day and correlated with minimal hepatocellular hypertrophy. Except for reddened mucous membranes, all findings were reversible

No remarkable adverse effect was observed in reproductive toxicity studies. The parental NOAEL was 150 mg/kg/day and the NOEL for reproduction was 350 mg/kg/day in fertility or early embryonic development study in rats. The embryo-fetal development studies were conducted in rats and rabbits. In rats, both maternal NOEL and fetal developmental NOAEL were 50 mg/kg/day and no teratogenic potential was revealed up to 450 mg/kg/day. In rabbits, the maternal NOAEL was 35 mg/kg/day, the embryonic and fetal developmental NOEL was 70 mg/kg/day, and no teratogenic potential was revealed up to 150 mg/kg/day.

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Three GLP studies have been completed to evaluate the mutagenic potential of TC-5619 when administered as the tosylate salt: the Ames test, the in vivo mouse erythrocyte micronucleus assay, and an evaluation of chromosomal aberrations in Chinese hamster ovary (CHO) cells. The results of the Ames test and the in vivo mouse erythrocyte micronucleus assay were negative. The compound was also negative in the in vitro CHO chromosome aberration assay at a concentration of 500 μg/mL, but it was positive at 1000 and 1500 μg/mL with and without metabolic activation. Additional testing conducted in the in vivo peripheral rat lymphocyte test indicated no evidence of genotoxicity. Daily administration of TC-5619 to humans at a dose of 300mg should produce mean maximal concentrations of approximately 1μg/mL at steady state, providing at least a 500 fold margin of safety for maximal exposures expected in the proposed study. Collectively, these data indicate that the genotoxic risk associated with TC-5619 is minimal.

For more detailed information, refer to the Investigator's Brochure for TC-5619.

1.2.2. Clinical Studies.

To date, TC-5619 has been administered to normal subjects in a Single Rising Dose (SRD) Study (TC-5619-238-CLP-001)[3] and in a Multiple Rising Dose (MRD) Study (TC-5619-238-CLP-002)[4]. All doses cited in these studies were administered as tosylate salt. The free base equivalent of these doses is 0.677 times the cited salt dose.

1.2.2.1.SRD Study Findings

In the SRD study, TC-5619 (n = 65 subjects) or placebo (n = 18 subjects) was administered to normal healthy males as a single oral administration at doses (tosylate salt) of 10mg, 20mg, 50mg, 100mg, 200mg, 300mg, 400mg, 600mg and 900mg.

At all doses up to and including 600mg, TC-5619-238 was well tolerated. Following a single dose of 900mg, 3 of 5 subjects exhibited one or more of the following moderate to severe adverse events: nausea, orthostatic hypotension/tachycardia, vomiting and/or headache. There were no serious adverse events reported. Few vital signs were outside of the normal range, and the observed abnormalities were transient and judged to be not clinically significant. There were no clinically significant changes in ECG parameters including QTcB (Bazett's correction) and QTcF (Frederica's correction). Both the EEG and Bond & Lader VAS effects indicated brain availability and some sedating potential of TC-5619 in most of the explored doses, though the effects were only sporadically of statistical significance. There were no clinically significant changes in hematology, clinical chemistry, or urinalysis parameters.

TC-5619-238 exhibited dose related and linear increases in C_{max} and AUC across a 90-fold dosing range of 10mg to 900mg. The half-life of elimination was approximately 15 - 20 hrs.

Based upon the findings in this study, a maximum tolerated dose (MTD) was defined as a dose between 600mg and 900mg TC-5619-238.

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1.2.2.2. MRD Study Findings

Thirty-two subjects, divided into 4 cohorts of 8 subjects (6 active, 2 placebo), received study drug once daily for 10 days. Dosing was initiated at 10mg (tosylate salt) and progressed sequentially to doses of 50mg, 150mg and finally to 300mg daily (tosylate salt). Safety, tolerability and PK were assessed at each dose, while cognition assessments (Cognitive Drug Research test battery: CDR) were completed at the two lower doses (10mg and 50mg daily).

TC-5619-238 exhibited excellent tolerability at all administered doses. Dosing was halted following completion of the 300mg dose largely due to exposure limits defined in the Single Rising Dose (SRD) study; any meaningful increase in dosing above the daily 300mg dose would have produced exposures that approached or exceeded the MTD defined in the SRD study. AEs were generally mild in nature, and there was no unusual constellation of AEs in any particular organ system. Observed laboratory and cardiovascular parameters were generally unremarkable. One subject in the 50 mg cohort, who was a weightlifter with an abnormal creatine kinase value at baseline, developed minor increases (<2xULN) in ALT and AST. Elevation of these 3 parameters (AST, ALT & CK) is known to occur for at least 7 days following weightlifting[5]. No other significant alterations were noted in CK or in transaminases during the study. One subject in the 300mg cohort developed transient T-wave inversions in the inferior and anterolateral leads on study day 10. Follow-up by a cardiologist indicated the most likely cause to be a change in autonomic tone, possibly associated with sudden wakening just prior to the recording of the EKG, and of no clinical significance. No other significant changes in EKGs were noted during the study.

Evaluation of cognition, using the CDR computerized battery of tests, revealed statistically significant changes in power of attention (mean maximal placebo-corrected change approximately -200 msec) and simple reaction time (mean maximal placebo-corrected change approximately -125 msec) at Day 1 and Day 10, with associated beneficial trends for continuity of attention, quality of working memory, digit vigilance speed and information processing speed at the 10mg dose. Most dramatic changes occurred approximately 2 to 6 hours post dose, which corresponds most closely with the estimated CNS Tmax. Some trends were observed at the 50mg dose, although not to the same degree of magnitude or consistency noted at the 10mg dose.

Exposure parameters (Cmax and AUC) increased in a near linear fashion with increasing doses across a range of 10mg to 300mg. Tmax (~2 hrs) and half-life (~24 hrs) were independent of dose. Approximately 20% of TC-5619 is excreted unchanged in the urine across all doses - 30 to 50% of TC-5619 appears unbound to plasma proteins. As expected for a compound with an approximate 24 hour half-life, multiple dosing produced an approximate 1.8 fold accumulation by study day 10.

Based upon the findings of this study, TC-5619-238 was well-tolerated following daily administration of 300mg.

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1.2.3. Background Information

Schizophrenia affects approximately 1% of the population worldwide, and in about 80% of cases, it is a lifelong, disabling illness.[6] It is a multi-dimensional disease that is associated with symptoms that have been characterized as positive, negative, and cognitive. CDS is a core feature of schizophrenia,[7,8] and most individuals with schizophrenia exhibit cognitive impairment. Attention disorders, slow information processing, working memory disorders, difficulty with executive functions, and lack of flexibility for adaptive strategies are symptoms of cognitive impairment that have a devastating impact on the function, employment, and social status of patients with schizophrenia.

Older typical neuroleptic medications (e.g., haloperidol, fluphenazine) do not improve cognition.[9] In fact haloperidol has been shown to induce cognitive impairment in schizophrenic patients.

Novel atypical antipsychotics, such as risperidone, clozapine, and olanzapine, seem to produce gains in cognition.[10,11] This improvement may reflect a diminution of extrapyramidal side effects of the typical high potency neuroleptics.[10,11] Alternatively, it might reflect more effective symptom reduction by the novel antipsychotics, or direct cognitive enhancement through the effects of the newer agents on a variety of neurotransmitters, their receptors, and gene expression. Even when the newer antipsychotic medications improve cognition, they do not normalize it.

Presently, there are no approved therapies for CDS.[12,13] However, in schizophrenic patients, nicotine improves multiple cognitive domains, including working memory and attention. Furthermore, based on a strong body of evidence ranging from genetic mapping to clinical trials, the α7 NNR subtype has emerged as a primary therapeutic target relevant to CDS and other core symptoms of schizophrenia (see section 1.7).

1.3. Potential Risks and Benefits

The tosylate salt of TC-5619 (TC-5619-238) has been administered to 65 healthy volunteers in a single rising dose study (TC-5619-238-CLP-001)[3] and to 28 healthy volunteers in a multiple rising dose study (TC-5619-238-CLP-002).[4] The following adverse reactions were reported by subjects in these studies up through 600mg, and they were mild to moderate in intensity: rhinorrhea, influenza, abdominal erythematous rash (non-pruritic), feeling warm, vagal malaise, dizziness, epigastric pain, orthostatic hypotension, orthostatic tachycardia, hypertension, abdominal pain, elevated ALT/AST/CK, ECG changes, nausea, headache, and rhinitis. At a dose of 900mg, which is above the maximum tolerated dose defined by the single rising dose study, severe adverse events of orthostatic malaise, orthostatic hypotension, and pallor were reported.

Potential benefits include new information for the medical and scientific fields that will result from the study, regarding effects of TC-5619 on cognitive deficits in schizophrenia. Individual subjects may benefit from study drug, but the extent of this potential benefit is unknown at this time.

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1.4. Rationale for Dose Selection

Oral doses of 1mg, 5mg, and 25mg (free base equivalents) of the tosylate salt of TC-5619 (TC-5619-238) will be administered, based upon the results from the SRD study[3] and from the MRD study (TC-5619-238-CLP-002).[4] Doses in this range and much higher (through 600mg tosylate salt [406mg free base equivalent] after single doses, and through 300mg tosylate salt per day [203mg free base equivalent] after multiple doses) were well-tolerated. Pre-clinical safety and efficacy data support the evaluation of the selected doses, and robust improvements were observed in cognitive measures (CDR) in the MRD study at a dose of 10mg (tosylate salt, or 6.77mg free base equivalent). The highest dose utilized in this study will be a daily dose of 25mg (free base), providing at least an 8-fold tolerability margin.

1.5. Conduct of the Trial

This study will be conducted according to the ICH guidelines for Good Clinical Practice, to the Declaration of Helsinki (2008 version), and to applicable regulatory requirements.

1.6. Study Population

This study will consider for inclusion outpatient subjects aged 18-60 years who meet a diagnosis of schizophrenia per DSM-IV TR criteria, as assessed using the MINI International Neuropsychiatric Interview (MINI). Eligible patients may have any of the following subtype diagnoses of schizophrenia: disorganized (DSM-IV code 295.10), paranoid (DSM-IV code 295.30), residual (DSMIV code 295.60), or undifferentiated (DSM-IV code 295.90). Patients will have no more than "moderate" ratings ($\leq$4) on delusions (P1), conceptual disorganization (P2), hallucinations (P3) and unusual thought content (G9) items on the positive and negative symptom scale for schizophrenia (PANSS). Patients will have a minimal level of depressive symptoms (Calgary Depression Scale <6). Patients will be taking only a single atypical antipsychotic medication (either quetiapine or risperidone) for control of psychotic symptoms for a minimum of 8 weeks prior to screening and at a stable dose ($\pm$25% of the dose at the time of enrollment) for at least 8 weeks prior to the time of screening. Both tobacco users (50% of subjects) and non-users (50% of subjects) will be enrolled. At least 200 subjects will be enrolled to ensure that at least 120 subjects complete Week 12 (assuming a 40% drop-out rate).

1.7. Rationale for the Study

There is an increasingly strong rationale for alpha7 NNR involvement in schizophrenia (positive, negative, and cognitive symptoms).[14] Alpha7 NNRs are located in the hippocampus, lateral and medial geniculate nuclei, and reticular nucleus of the thalamus. They modulate neurotransmitter release (i.e., glutamate, gamma-aminobutyric acid, and dopamine) and are involved in long-term potentiation, sensory processing, and neuroprotection.[15] In animal studies, blockade of the alpha7 NNRs induces gating deficits similar to those in schizophrenia, and alpha7-selective compounds improve sensory gating deficits in several models of psychosis. Recent findings indicate that clozapine normalization of sensory gating may be mediated by the alpha7 NNR.[15] Postmortem studies on brain tissue from schizophrenic patients showed a marked decrease in the number of alpha7 hippocampal NNRs (~50%). This observation also accords with lower alpha 7 mRNA expression on peripheral blood lymphocytes from patients with schizophrenia compared to

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healthy controls, and an inverse correlation between the mRNA expression and the severity of the illness.[25] The functional polymorphisms in the CHRNA7 promoter and the human alpha7 receptor gene, located on chromosome-15, have been linked to sensory inhibition deficits and familial schizophrenia. In DBA/2 mice, two alpha7 ligands have been reported to improve deficits: DMXB (or GTS-21) reversed sensory gating deficits, and AR-R17779 restored prepulse inhibition (PPI).[15]

In the object recognition model of cognition, administration of TC-5619 (0.3mg/kg and 1mg/kg i.p., and 0.3mg/kg - 10mg/kg p.o.) significantly facilitated working memory in rats.[16-19] In the win-shift radial arm maze task, TC-5619 (0.1mg/kg – 1mg/kg) significantly improved performance in rats.[20] These results further support the cognitive-enhancing properties of TC-5619 in general. Together with the ability of alpha7 NNRs to reverse sensory gating deficits and to restore PPI,[15] these findings support the use of TC-5619 in CDS specifically.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the efficacy of TC-5619 as augmentation therapy to quetiapine or risperidone, to improve cognition in stable outpatients with Cognitive Dysfunction in Schizophrenia (CDS), using the CogState Schizophrenia Test Battery (CSTB).

2.2. Secondary Objectives

Secondary objectives include:

- To further assess efficacy of TC-5619 in this population using Symptom Assessment of Negative Scores (SANS), Subject Global Impression-Cognition score (SGI-Cog), Clinical Global Impression of Improvement (CGI-I) and Clinical Global Impression of Severity (CGI-S).
- To assess the safety and tolerability of TC-5619 as augmentation therapy to quetiapine or risperidone, in outpatients with CDS.
- To evaluate the pharmacokinetics of TC-5619 in this population through serial and sparse sampling in a subset of subjects in the study.
- To assess plasma levels of quetiapine and risperidone/9-OH-risperidone.
- To assess the relationship between the expression of alpha7 mRNA and measures of efficacy.
- To assess drug response in surrogate markers of P50, P300, and Mismatch Negativity (MMN) in a subset of subjects

3. OVERVIEW OF STUDY DESIGN

3.1. Study Design

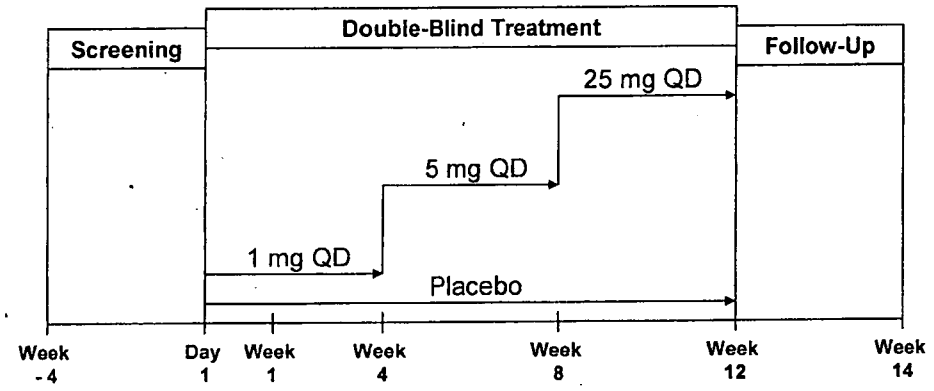
This is a multi-center, double blind, randomized, placebo-controlled, parallel group, fixed dose titration study conducted in multiple centers in the US and other countries. No more than 200

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subjects will be enrolled in the study (to ensure 120 complete) with 50% of the subjects being tobacco users and 50% being non-tobacco users. Since there is no approved treatment for CDS, a placebo-controlled study is appropriate. There will be 3 phases of the study: Screening (Week -4 to Day 1); Treatment (Day 1 – Week 12); and Follow-up (Week 12- Week 14).

At Screening, subjects will be assessed for stable schizophrenia as documented by lack of psychiatric hospitalization for the preceding 8 weeks beforehand, as well as stable dosing of quetiapine or of risperidone for at least 8 weeks beforehand. Other eligibility criteria will be verified per sections below.

For subjects meeting all eligibility criteria, TC-5619-238 or placebo will be started at Baseline (Day 1), p.o. once daily. Study drug will be increased every 4 weeks, from a starting dose of 1 mg qd for 4 weeks; then a second dose of 5 mg qd for 4 weeks; and finally a dose of 25 mg qd for 4 weeks (see study diagram below).. All doses are expressed as free base equivalent.



Four weeks on each dose (12 weeks total) should be sufficient to detect positive effects on cognition, based upon the procognitive effects of TC-5619 in rodents; the procognitive effects after 8 weeks of administration of the alpha4beta2 NNR agonist, TC-1734, in subjects with age-associated memory impairment (Study TC-1734-112-CRD-004); and the cognitive improvement after both a 1-day and a 10-day administration of TC-5619 to normal volunteers in the MRD study (TC-5619-238-CLP-002). If a subject is prematurely discontinued from the study between Baseline and Week 12 for any reason, the investigator will make every effort to perform all evaluations as per protocol, assuming the subject had reached the end of the double blind add-on treatment phase. These evaluations are to be made as soon as possible but within 2 weeks of discontinuation.

Blood samples for pharmacokinetic evaluation will be collected in a subset of subjects in this population. Serial samples will be collected at select US sites on Day 1 (1 mg single-dose), Week 4 (1 mg qd at steady-state), Week 8 (5 mg qd at steady-state) and Week 12 (25 mg qd at steady-state). Sparse samples will be collected at the other US sites on Day 1, Week 4, Week 8 and Week 12.

For the subjects completing the treatment period, there will be a Follow-up visit at Week 14, two weeks after the last dose of trial medication. At this follow-up, any signs or symptoms of relapse

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will be evaluated. A follow-up visit 2 weeks following the last dose of study drug (Week 12) is appropriate, given the approximately 20-hour half-life of TC-5619 in human subjects.

3.1.1. Study Endpoints

3.1.1.1. Primary Endpoint

The primary endpoint is the comparison in the entire cohort (tobacco-users and non-users combined) between TC-5619 and placebo on an item in the CSTB: Groton Maze Learning (GML) at Week 4, Week 8, and Week 12 or Early Withdrawal (EW) compared to Baseline.

3.1.1.2. Secondary Endpoints

Unless otherwise specified, secondary efficacy endpoints include comparisons between TC-5619 and placebo, both in the entire cohort (tobacco users and non-tobacco users), and in tobacco users separately and non-tobacco users separately, in:

- GML at Weeks 1, 4, 8 and 12 or EW compared to Baseline, in tobacco-users, and in non-users.
- CSTB Composite Score at Week 1, Week 4, Week 8, and Week 12 or EW compared to Baseline.
- SGI-Cog scores, subject and informant versions, at Week 1, Week 4, Week 8 and Week 12 or EW compared to Baseline.
- Clinical Global Impression of Severity (CGI-S); at Week 1, Week 4, Week 8, Week 12 or EW, and Week 14.
- Clinical Global Impression of Improvement (CGI-I); at Week 1, Week 4, Week 8, Week 12 or EW, and Week 14.
- Scale for Assessment of Negative Symptoms (SANS) total score; at Week 1, Week 4, Week 8, and Week 12 or EW, compared to Baseline.

Safety Endpoints:

- Change from baseline in vital signs (including weight), ECG and routine clinical laboratory parameters (biochemistry, hematology and urinalysis). Proportion of values outside of the Targacept reference ranges will be determined.
- Change from baseline in fasting lipids.
- Frequency of volunteered non-serious adverse events (AEs) and serious adverse events (SAEs).
- Clinically significant changes in physical exam
- Changes in Abnormal Involuntary Movements Scale (AIMS) scores.
- Changes in Columbia Suicide Severity Rating Scale (CSSRS) scores.
- Changes in Calgary Depression Scale for Schizophrenia (CDSS).
- Positive drug screens.
- Positive pregnancy tests.

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PK endpoints:

- Changes in plasma levels of quetiapine or risperidone/9-OH-risperidone at Day 1, Week 4, Week 8 and Week 12.
- Appropriate pharmacokinetic parameters for TC-5619 will be estimated on Day 1, Week 4, Week 8 and Week 12.

Exploratory endpoints:

- Changes in Fagerstrom Test for Nicotine Dependence scores at Week 12 compared to Baseline.
- Changes in tobacco use as judged by the subject at Week 12 compared to Baseline.
- Change in primary or secondary endpoints as a function of risperidone vs. quetiapine treatment.
- P50, P300, and MMN at Week 1, Week 4, Week 8, and Week 12 compared to Baseline, in a subset of subjects.
- Alpha-7 mRNA expression as a function of:
    - GML, CSTB composite score, CGI-I, SGI-Cog, SANS, and P50/P300/MMN scores: change at Week 4, Week 8 and week 12 or EW compared to Baseline;
    - SANS, SGI-Cog, and CGI-S scores at Baseline

3.2. Rationale for Study Design

A randomized parallel group design is being used to assess effects of dose on efficacy. A parallel group design allows the effects of doses to be clearly established, and the randomized nature of the design allows minimization of observer and subject bias.

The doses chosen (1mg, 5mg, and 25mg) reflect an appropriate range around the anticipated efficacious dose (3-10 mg), based upon preclinical extrapolations to the human, and upon the CDR findings in the MRD study (TC-5619-238-CLP-002).

50% of subjects will be tobacco users and 50% will be non-tobacco users, to evaluate the effect of TC-5619 in both populations. It is possible that tobacco (nicotine) interferes with the alpha7 NNR-mediated effects.

Quetiapine and risperidone were chosen as concomitant antipsychotic medications, to explore the effect of TC-5619 against a background of differential binding to muscarinic cholinergic receptors.

3.3. Study Procedures

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, safety, pharmacokinetic, pharmacodynamic, and other measurements.

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Approximate Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample	No. of Samples per Subject	Total Volume of Blood[a]
Safety (including screening, double-blind phase and follow-up assessments)			
- Hematology	5 mL	4	20 mL
- Serum chemistry	10 mL	4	40 mL
- HbA1C	10 mL	1	10 mL
Pharmacokinetic samples[b]	6 mL	32	192 mL
Blood sample for mRNA expression	5 mL	1	5 mL
Total			**267 mL**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Maximum number of samples obtained from a subset of the subjects randomized.

The maximum amount of blood drawn in this study will not exceed 300 mL. Repeat or unscheduled samples may be taken for safety reasons.

3.3.1. Procedures at Each Visit

Prior to signing an informed consent for the study, prospective study candidates will be pre-screened by interview to determine their eligibility and willingness to enter the study. If, after this interview, they appear to meet the study entry criteria, a signed informed consent will be obtained before any screening assessments are performed. Any subject who has signed a consent form and subsequently fails to meet all the inclusion/exclusion criteria, withdraws consent, or fails to return prior to being randomized is considered a screen failure. The investigator will maintain a list of all screened subjects. For screen failures, data including initials, gender, date of birth, date of screening and reason and date for not starting the study will be recorded in the CRF.

3.3.1.1. Screening (Week -4)

Once informed consent has been obtained:

1. Medical, social habits and psychiatric histories will be recorded (including evaluation of DSM-IV-TR criteria as assessed using the MINI). Psychiatric history to include details of previous schizophrenic illnesses, of current illness and responsiveness to previous treatment, and of stable schizophrenia as assessed by lack of hospitalization for at least the preceding 2 months.
2. Stable dosing for at least the preceding 2 months with either quetiapine or risperidone will be verified. Compliance with quetiapine or risperidone will be assessed. Subjects will be counseled to take their quetiapine or risperidone as prescribed, at the same time(s) each day during the study.
3. Other concomitant medications will be recorded.
4. Completion of PANSS, with scores less than or equal to 4 on items related to delusion, hallucination, conceptual disorganization, and unusual thought content.

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5. Tobacco use will be assessed; 50% of subjects will be tobacco users, and 50% will be non-tobacco users.
6. Urinary cotinine and urinary creatinine levels will be obtained.
7. Completion of Calgary Depression Scale for Schizophrenia (CDSS), with score < 6.
8. Training on and completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable). Two assessments will be completed, one to train the subject on the battery and one for the baseline measurements.
9. Assessment of CGI-S.
10. Completion of SANS.
11. Completion of AIMS.
12. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
13. Physical examination.
14. Triplicate 12 lead digital ECG.
15. Vital signs will be recorded including systolic and diastolic blood pressure (BP) and heart rate (HR) while in the sitting position (5 minutes) and standing position (at least 2 and less than 3 minutes). Height, weight and oral temperature will be measured.
16. Fasting blood samples for safety laboratory evaluations consisting of hematology, clinical chemistry, bilirubin, liver function tests (LFTs), and lipid panel will be drawn, processed and sent for analysis. HbA1C levels will also be obtained using these blood samples.
17. Urine will be tested for drug abuse screen, urinalysis, and cotinine/creatinine.
18. Urine pregnancy test will be performed for women of child-bearing potential (WOCBP). WOCBP and men will be counseled on use of adequate birth control.
19. Repeat hematology, clinical chemistry, bilirubin, LFTs, or urinalysis will be performed prior to randomization (Day 1) assessments, if any abnormal values were detected in the screening tests.
20. Completion of Trails A&B and Symbol-Digit paper and pencil tests.
21. Blood samples will be obtained for measurement of alpha 7 mRNA expression.

3.3.1.2. Baseline Assessments (Day 1)

The Baseline Visit will be held at least 28 days after screening, with a window of +3 days, as required to continue to assess stability of schizophrenic symptoms and of quetiapine / risperidone dose, in an outpatient setting.

1. Confirm eligibility criteria, including use of PANSS (see Section 4.1).
2. Complete the SANS.
3. Complete Social Habits Questionnaire.
4. Assess compliance with quetiapine or risperidone.
5. Perform a physical examination.
6. Vital signs (including orthostatic BP and HR) will be recorded.

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7. Repeat hematology, clinical chemistry, bilirubin, LFTs, or urinalysis will be performed, if any abnormal values were detected in the screening tests.
8. Urine will be collected for urinalysis, drug screen, cotinine and creatinine measurements, and pregnancy test.
9. Completion of AIMS.
10. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use if applicable),
11. Acquisition of P50, P300 and MMN data at selected sites. Two assessments will be completed, one for the subject to become comfortable with test procedures and one for the baseline measurements.
12. Assessment of CGI-S.
13. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
14. CDSS will be completed.
15. Concomitant medications will be recorded.
16. WOCBP and men will be counseled on use of adequate birth control.
17. The Fagerstrom Test for Nicotine Dependence will be administered.
18. An in-clinic dose of study drug will be administered (1mg study drug), at least 90 minutes before first tobacco use (if tobacco users).
19. Serial/sparse blood samples for pharmacokinetic evaluations will be collected in a subset of the subjects.
20. Triplicate 12-lead digital ECG recordings will be performed pre-dose and again approximately 3 hrs post-dose (approximate T_{max}). ECG tracings and blood sampling for PK at 3 hours post-dose should be performed no more than 30 minutes apart.
21. Study drug will be dispensed for the next 4 weeks, only if all baseline evaluations in the inclusion/exclusion criteria have been met. An additional 1-week supply of study drug will be provided to cover scheduling anomalies for the Week 4 visit or lost medication. Study drug should be brought to clinic at the Week 1 visit for compliance monitoring.
22. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.3.1.3. Week 1

Every attempt will be made to have assessments undertaken on the day indicated. A window of + 3 days is permitted.

1. All remaining study drug from the prior visit will be returned for compliance monitoring, and it will be re-issued to the subject at completion of the visit.
2. Complete Social Habits Questionnaire.
3. Assess quetiapine or risperidone compliance.
4. AIMS will be performed.
5. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
6. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use, if applicable).and SGI-Cog.

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7. SANS will be assessed.
8. CDSS will be completed.
9. Concomitant medications will be recorded.
10. Physical examination will be performed.
11. Vital signs including orthostatic BP will be obtained.
12. Triplicate 12-lead digital ECG will be obtained.
13. Completion of CGI-Global Improvement (CGI-I) and CGI-S.
14. WOCBP and men will be counseled on use of adequate birth control.
15. Acquisition of P50, P300 and MMN data at selected sites.
16. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.3.1.4. Week 2 (Telephone Contact)

1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.

3.3.1.5. Week 4

Every attempt will be made to have assessments undertaken on the day indicated. A window of + 3 days is permitted.

1. All remaining study drug from the prior visit will be returned and will not be re-used.
2. Complete the SANS.
3. Complete Social Habits Questionnaire.
4. Assess compliance with quetiapine or risperidone.
5. Perform a physical examination.
6. Vital signs (including orthostatic BP and HR) will be recorded.
7. Hematology, clinical chemistry, bilirubin, and LFTs will be performed.
8. Urine will be collected for drug screen, and cotinine / creatinine measurements.
9. Completion of AIMS.
10. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use if applicable), and SGI-Cog.
11. Acquisition of P50, P300 and MMN data at selected sites.
12. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
13. CDSS will be completed.
14. Completion of CGI-Global Improvement (CGI-I) and CGI-S.
15. Concomitant medications will be recorded.
16. WOCBP and men will be counseled on use of adequate birth control.
17. An in-clinic dose of study drug will be administered (1mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
18. Serial/sparse blood samples for pharmacokinetic evaluations will be collected in a subset of the subjects.
19. Triplicate 12-lead digital ECG recordings will be performed pre-dose and again approximately 3 hrs post-dose (approximate T_{max}). ECG tracings and blood

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sampling for PK at 3 hours post-dose should be performed no more than 30 minutes apart.

20. Study drug will be dispensed for 4 weeks at the end of the visit. An additional 1-week supply of study drug will be provided to cover scheduling anomalies for the next visit or lost medication. All remaining study drug is to be returned to the clinic on the next visit.
21. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.3.1.6. Week 6 (Telephone Contact)

1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.

3.3.1.7. Week 8

Every attempt will be made to have assessments undertaken on the day indicated. A window of + 3 days is permitted.

1. All remaining study drug from the prior visit will be returned and will not be re-used.
2. Complete the SANS.
3. Complete Social Habits Questionnaire.
4. Assess compliance with quetiapine or risperidone.
5. Perform a physical examination.
6. Vital signs (including orthostatic BP and HR) will be recorded.
7. Hematology, clinical chemistry, bilirubin, and LFTs will be performed.
8. Urine will be collected for drug screen, cotinine / creatinine measurements.
9. Completion of AIMS.
10. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use if applicable), and SGI-Cog.
11. Acquisition of P50, P300 and MMN data at selected sites.
12. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
13. CDSS will be completed.
14. Completion of CGI-Global Improvement (CGI-I) and CGI-S.
15. Concomitant medications will be recorded.
16. WOCBP and men will be counseled on use of adequate birth control.
17. An in-clinic dose of study drug will be administered (5mg study drug), at least 90 minutes before first tobacco use (in tobacco users).
18. Serial/sparse blood samples for pharmacokinetic evaluations will be collected in a subset of the subjects.
19. Triplicate 12-lead digital ECG recordings will be performed pre-dose and again approximately 3 hrs post-dose (approximate T_{max}). ECG tracings and blood sampling for PK at 3 hours post-dose should be performed no more than 30 minutes apart.

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20. Study drug will be dispensed for 4 weeks at the end of the visit. An additional 1-week supply of study drug will be provided to cover scheduling anomalies for the next visit or lost medication. All remaining study drug is to be returned to the clinic on the next visit.
21. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.3.1.8. Week 10 (Telephone Contact)

1. Contact subject by telephone in order to ask for subject replies to questions about the tolerability to the study drug and about compliance with self-administration of the study drug.

3.3.1.9. Week 12 or Early Withdrawal visit

Every attempt will be made to have assessments undertaken on the day indicated. A window of + 3 days is permitted.

1. All remaining study drug from the prior visit will be returned and will not be re-used.
2. Complete the SANS.
3. Complete Social Habits Questionnaire.
4. Assess compliance with quetiapine or risperidone.
5. Perform a physical examination.
6. Vital signs (including orthostatic BP and HR; and weight) will be recorded.
7. Hematology, clinical chemistry, bilirubin, LFTs, fasting lipids, HbA1C and urinalysis will be performed.
8. A urine pregnancy test will be performed.
9. Urine will also be collected for drug screen, and cotinine /creatinine measurements.
10. Completion of AIMS.
11. Completion of CogState Schizophrenia test battery (at least 90 minutes after prior tobacco use if applicable), and SGI-Cog.
12. Acquisition of P50, P300 and MMN data at selected sites.
13. Adverse events will be recorded; Columbia Suicide Severity Rating Scale (CSSRS) will be completed.
14. CDSS will be completed.
15. Completion of CGI-Global Improvement (CGI-I) and CGI-S.
16. The Fagerstrom Test for Nicotine Dependence will be administered.
17. Concomitant medications will be recorded.
18. WOCBP and men will be counseled on use of adequate birth control.
19. A final in-clinic dose of study drug will be administered (25mg study drug), at least 90 minutes before first tobacco use (in tobacco-users).
20. Serial/sparse blood samples for pharmacokinetic evaluations will be collected in a subset of the subjects.
21. Triplicate 12-lead digital ECG recordings will be performed pre-dose and again approximately 3 hrs post-dose (approximate T_{max}). ECG tracings and blood

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sampling for PK at 3 hours post-dose should be performed no more than 30 minutes apart.

22. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.3.1.10. Follow Up Visit, Week 14

A window of +3days is permitted.

1. Vital signs including orthostatic BP and HR will be obtained; weight will be measured.
2. Physical Examination will be performed.
3. AIMS will be performed.
4. Complete CogState Schizophrenia test Battery and assess CGI-I and CGI-S.
5. Adverse events will be assessed, and CSSRS will be completed.
6. CDSS will be completed.
7. Concomitant medications will be recorded.
8. Compliance with quetiapine or risperidone will be assessed.
9. Laboratory assessments (clinical chemistry, hematology, LFTs, bilirubin, and urinalysis) will be performed only if abnormality was detected in the Week 12 values.
10. Single Twelve (12) lead digital ECG will be recorded only if abnormality was detected at Week 12.
11. WOCBP and men will be counseled on use of adequate birth control.
12. Completion of Trails A & B and Symbol-Digit paper and pencil tests.

3.4. Study Restrictions

1. Tobacco users (50% of subjects) should not vary their tobacco use during the study. Tobacco non-users (50% of subjects) should not begin to use tobacco during the study. Tobacco non-users who begin using tobacco during the trial will be discontinued from the trial. Tobacco users who become tobacco non-users during the trial will also be discontinued.
2. Subjects may not use any new prescription or nonprescription medication (including vitamins and herbal supplements) except for acetaminophen (not exceeding 1.5gm/day) or other short-term use medications as permitted by the Medical Monitor (e.g. antibiotics) throughout the study duration. Subjects who use new prescription or non-prescription drugs may be discontinued from the trial after consultation with the Targacept Medical Monitor.
3. Subjects with a positive urine drug screen will be discontinued from the trial, unless ascribed to appropriate use of a prescribed medication (e.g. benzodiazepine for sleep), and after discussion and approval of the Medical Monitor.
4. Subjects should take their quetiapine or risperidone medication as prescribed, at the same time(s) each day during the study.

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5. Subjects will be advised not to donate blood for at least 2 months after completion of the study or to participate in an investigational drug study for at least 1 month after completion of the study.
6. Male subjects will be advised not to donate sperm from the first drug administration until 7 days after completion of the study. It is recommended that all male subjects use one of the following methods of contraception until 7 days after study completion:
    a. abstinence;
    b. use of a condom for males with a vasectomy;
    c. male subjects without a vasectomy must use a condom and be instructed that their female partner should use another form of contraception such as an IUD, spermicidal agent, oral contraceptive, etc.
7. Women of childbearing potential must:
    a. Have a negative urine pregnancy test
    b. Not be nursing
    c. Be willing to use acceptable methods of contraception (e.g. IUD, spermicidal agent, oral contraceptive) throughout the study period and for 7 days after study completion

3.5. Diet

There are 2 restrictions on diet:

- No grapefruit or grapefruit juice;
- Fasting from midnight until fasting lipid levels are obtained in clinic on the following morning, on the evening before Screening and on the evening before the Week 12 visit. Subjects may drink clear liquids during this fasting period.

3.6. Minimization of Bias

3.6.1. Randomization

Subjects will be assigned to study treatment in accordance with the pre-defined randomization schedule based upon blocks of 4 blinded kits assigned to each site.

3.6.2. Blinding

TC-5619-238 capsules and matching placebo in blister-packs will be used to blind subjects and study staff.

Tobacco users and non-users will be randomized separately with study drug dispensed accordingly.

All study staff will remain blinded throughout the study. The blind cannot be broken except with the permission of the Sponsor Medical Monitor, unless needed for management of a SAE.

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3.7. Study Treatment and Clinical Trial Supplies

Study drug will be shipped in blinded kits to the pharmacist or other qualified person at each site, to be dispensed to randomized patients at each study visit (see below).

3.7.1. Physical Description of Study Drug(s)

TC-5619-238 (TC-5619 tosylate salt), drug product will be provided as 1mg, 5mg, or 25mg dose strengths based upon free base equivalents. The drug product is supplied as a blend of API with excipients in a hard gelatin capsule (gelatin and titanium dioxide). The excipients used are microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

The placebo formulation consists of microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate in a hard gelatin capsule (gelatin and titanium dioxide).

Subjects will take their own supply of commercial quetiapine or risperidone, with the stipulation that the commercially supplied quetiapine or risperidone meets regulatory requirements for the country of each subject. No other investigational products will be used in this study.

3.7.2. Drug Packaging and Labeling

Both study drugs, TC-5619-238 and placebo, are packaged in blister-packs and arranged in blister cards suitable for each randomized subject's dosing regimen.

Study supplies will be maintained in the site under controlled conditions and dispensed by a pharmacist or other qualified personnel at the site. Each subject will be provided with blister cards specific to that subject's randomization on Day 1 and at each subsequent study visit during the treatment period (Week 1, Week 4, and Week 8). Each set of blister cards will contain sufficient study drug to last until the next visit, with an additional 1-week supply to cover scheduling anomalies or lost medication.

Study drug labels will contain information to meet the applicable regulatory requirements.

3.7.3. Dosage and Dosage Regimen

All dosages for this study are expressed as free base equivalents. TC-5619 will be provided as hard gelatin capsules in strengths of 1mg, 5mg, and 25mg.

TC-5619-238 will be provided as hard gelatin capsules in strengths of 1mg, 5mg, and 25mg (as free base). Subjects will take 1mg TC-5619, 5mg TC-5619, 25mg TC-5619, or matching placebo – one capsule once daily p.o., as soon as possible after awakening, at least 90 min before first tobacco use in tobacco users, and at least 30 min before first dose of quetiapine or risperidone in all subjects

3.7.4. Drug Storage

The study drug must be stored under controlled room temperature, 15 to 30°C (59 – 86°F), within an appropriately secured facility. Temperature will be monitored continuously and logged by appropriate Study Center staff for the duration of the study.

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Investigational product must be dispensed or administered according to procedures described herein and the Study Drug Procedures Manual. Only subjects enrolled in the study may receive the investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product.

3.7.5. Drug Dispensing

Medication will be dispensed at each visit sufficient to cover each dose titration (4 weeks after Day 1; 4 Weeks after Week 4; and 4 Weeks after Week 8). Each subject will be provided a sufficient supply of blister cards containing the determined dose of TC-5619 (1mg, 5mg, or 25mg) or placebo capsules that will appear to be identical to the TC-5619 capsules, plus an additional 1-week supply in the event that the next study visit is scheduled outside the prescribed timeline, or that study drug is lost. Blister cards will be designated: "A" for study drug at 1mg; "B" for study drug at 5mg; and "C" for study drug at 25mg.

The doses administered (1mg, 5mg, or 25mg p.o. qd) results in subjects taking a single capsule of the corresponding strength p.o. qd.

Labels indicating the study identifiers, subject identifiers, blinded dosage, start and stop dates, and instructions to the subject will be attached to the study drug container.

3.8. Study Duration and Follow-Up

Subjects will be in the study for up to 12 weeks of double-blind treatment following a 4-week Screening period. Subjects will have a single follow-up visit at 2 weeks after completion of the double-blind treatment phase.

3.9. Discontinuation Criteria

Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If Sponsor determines such action is needed, Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, Sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

Sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to Sponsor. In addition, arrangements will be made for all unused investigational product(s) to be destroyed or returned in accordance with the applicable sponsor procedures for the study.

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3.10. Study Drug Accountability

The Investigator is responsible for the investigational product accountability, reconciliation, and record maintenance.

3.10.1. Inventory Records

In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from Sponsor, and the amount supplied and/or administered to and returned by subjects.

3.10.2. Disposition of Unused Supplies

Unused supplies will be disposed of using appropriate documentation according to ICH-GCP, local requirements, and Targacept Standard Operating Procedures (SOPs).

3.11. Procedures for Breaking Randomization Codes

Only when knowledge of the investigational product is essential for the clinical management or welfare of the subject, can the Investigator unblind a subject's treatment assignment after approval is granted by the Targacept Medical Monitor or designee. The Investigator will record the date and reason for revealing the blinded treatment assignment for that subject on the appropriate source document and electronic case report form (eCRF) page.

If a serious adverse event (SAE; as defined in Section 8.3.1.2) is reported to Sponsor, appropriate staff within the Clinical Development Department may unblind the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, Sponsor SOPs, or both.

3.12. Case Report Form Completion

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on source documents and eCRFs for this study must be consistent with the subject's source documentation (i.e., medical records).

Data generated under the treatment protocol will be collected on source documents and then entered into eCRFs. The Sponsor will provide study sites with a study manual that will outline CRF completion. The Investigator is responsible for the accuracy of the data transcribed from all source documentation.

All eCRF entries should be made within 3 working days from the time of a subject's visit. Completed source documents and eCRFs must be ready and available for on-site review by the Sponsor or its designated representative within 14 days of a subject's termination from the study.

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Steps taken to ensure accurate, complete, and reliable data will begin with pre-study reviews of the protocol design and procedures with the Investigator and his or her study coordinator who will then review these procedures with their staff.

4. STUDY POPULATION

4.1. Inclusion Criteria

To participate in the study, subjects must meet all of the following criteria:

1. Diagnosis of schizophrenia, per DSM-IV TR criteria, as aided by the MINI International Neuropsychiatric Interview (MINI)
2. Controlled schizophrenia, on same dose of quetiapine or risperidone for at least 2 months prior to screening
3. Age 18 – 60, male or female
4. Stable schizophrenia as documented by lack of psychiatric hospitalization for 2 months prior to Screening (social admissions allowed)
5. Clinical history of stable psychotic symptoms for 1 month prior to Screening.
6. Stable positive symptoms of schizophrenia for 4 weeks prior to Day 1, as shown by score </= 4 on PANSS for items related to delusion, hallucination, conceptual disorganization, and unusual thought content, at Screening and at Day 1
7. Calgary Depression Scale for Schizophrenia score < 6
8. Outpatient with stable housing, and presence of an informant who sees the subject at least 4 times weekly
9. Able to understand and sign informed consent

4.2. Exclusion Criteria

To participate in the study, subjects must not meet any of the following criteria:

1. Diagnosis of schizoaffective or schizophreniform disorders 1 year prior to Screening
2. Patients at significant risk of suicide or of danger to themselves or others
3. Antipsychotics other than quetiapine or risperidone, or a change in dosing of these within 2 months of Screening
4. Treatment with mood stabilizers, antidepressants, or anxiolytics (short-acting hypnotics permitted)
5. Treatment within 1 month using cognition-affecting agents other than the above, as listed in Appendix 3 (e.g. CNS stimulants)
6. Use of other prohibited concomitant medications
7. Other concomitant medications that have been changed within 1 month prior to Screening

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8. History within past 6 months of alcohol or illicit drug abuse
9. Use of smoking cessation therapy within 1 month prior to Screening
10. Tobacco users with no detectable urine cotinine level; and tobacco non-users with a detectable urine cotinine level > than 50ng/mL (urine cotinine level between 50ng/ml and 500ng/ml will be excluded)
11. Unable to comply with study procedures in opinion of investigator, including CogState battery
12. History of significant other major or unstable neurological, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, or urological disorder
13. History of myocardial infarction
14. History of seizure disorder
15. Type 1 diabetes mellitus (DM); type 2 DM that requires medication (diet-controlled allowed, with HbA1C < 7.3)
16. Electroconvulsive therapy within 2 months prior to Screening
17. Uncontrolled hypothyroidism, vitamin B12 or folic acid deficiency
18. Current TB or known systemic infection (HBV, HCV, HIV)
19. Clinically significant finding on physical exam that could be a safety issue in the study
20. ALT or AST levels > 2.5 times the upper limits of the laboratory reference range
21. Clinically significant lab or ECG abnormality that could be a safety issue in the study, including QTcF > 450 (males) or QTcF > 480msec (females)
22. Women of child-bearing potential and men unwilling or unable to use accepted methods of birth control
23. Women with a positive pregnancy test, or who are lactating
24. Participation in another clinical trial in last 3 months prior to Screening
25. Involvement in planning or conduct of the study by site staff
26. Body Mass Index (BMI) < 15 and > 31

4.3. Subject Completion and Withdrawal

4.3.1. Subject Completion

A subject will be considered to have completed the study if he has completed all required assessments at the end of the double blind phase (Week 12). Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be considered to have completed the study and will be treated as outlined in the following sections.

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4.3.2. Patient Withdrawal (Premature Discontinuation from the Study)

An effort must be made to determine why a subject fails to return for the necessary visits or is dropped from the study, and the reason for withdrawal must be recorded in the eCRF. A subject may withdraw or be removed from the study for any of the following reasons:

- Subject request (for any reason)
- In the opinion of the investigator, continuation is not in the best interest of the subject.
- A serious or unexpected adverse event occurs such that continuation in the study is inappropriate.
- Lack of efficacy, if this places the subject at risk.

These subjects will be treated as considered appropriate by the investigator.

If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform all evaluations as per protocol assuming the subject had reached the end of treatment phase. These evaluations will be made as soon as possible but within two weeks of discontinuation. Also, the investigator is to:

- Follow up on all ongoing adverse events (if any);
- Collect all unused study medication.

These data should be recorded, as they comprise an essential evaluation that should be done before discharging any subject from the study.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 8.2.1.1) or SAE (as defined in Section 8.2.1.3), the procedures stated in Section 8.2 must be followed.

4.3.3. Reporting Discontinuations

Reasons for discontinuation from the study must be documented on the source document and in the eCRF. Study drug assigned to the withdrawn subject may not be assigned to another subject.

4.3.4. Replacement of Patients

Subjects who drop out of the study after randomization into the double blind phase of the study ("drop-outs") will not be replaced.

5. TREATMENT OF SUBJECTS

5.1. Dosage and Administration

TC-5619-238 will be initiated at a dose of 1mg; titrated to 5mg at Week 4; and titrated to 25mg at Week 8, or matching placebo. Doses are expressed as free base equivalents. If the subject experiences intolerance to study medication, the subject will be withdrawn from the study.

All doses (TC-5619 and placebo) will be administered p.o. once a day in the morning.

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Except for clinic visits at Week 4, Week 8 and Week12, all subjects will take study drug as soon as possible after awakening, and at least 30 minutes before morning dose of quetiapine or risperidone, and at least 90 minutes before a first tobacco use, if applicable.

On days of clinic visits at Week 4, Week 8, and Week 12, all subjects will refrain from taking study drug, until instructed to do so during the visit. On these visits, subjects will still refrain from taking quetiapine or risperidone until at least 30 minutes after taking study drug, and from tobacco use (if applicable) until at least 90 minutes after study drug.

5.2. Treatment Assignment

Subjects will be enrolled into one of two cohorts of up to 100 subjects each (to ensure 60 subjects per cohort complete: 50% tobacco users and 50% tobacco non-users). One cohort will be administered TC-5214, and the other will be administered matching placebo.

5.3. Concomitant Therapy

5.3.1. Quetiapine or Risperidone

All subjects will self-administer either quetiapine or risperidone at the same stable dose that they administered over at least an 8-week period prior to study randomization. Commercially available quetiapine and risperidone will be used; this concomitant medication will be obtained by the subject's usual method of prescription, and will not be supplied by the study. This commercially supplied quetiapine or risperidone must meet regulatory requirements for the country of each subject. These medications can be taken in the morning or in the evening, but preferably in the morning. However, for a given subject, the time of dosing should be constant during the study.

If the subject experiences intolerance to quetiapine or risperidone during the study or if the dose of quetiapine or risperidone is changed for any reason during the study, then the subject will be withdrawn from the study.

5.3.2. Permitted Medications

All concomitant medications taken during the study will be recorded on the source document and in the eCRF with indication, dose information, and dates of administration.

Use of short-acting hypnotics will be permitted until 2 nights before neuropsychological assessments are performed.

5.3.3. Prohibited and Restricted Medications

Several medications are prohibited and are summarized in Appendix 3.

Drugs with restricted use: must have must have written prior approval from the Medical Monitor.

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5.3.4. Non-Drug Therapies

Psychotherapy, analytical, cognitive or behavioral, is prohibited during the subject's participation in this trial as it may interfere with efficacy assessments.

5.4. Compliance

Only subjects who consume at least 80% of the prescribed daily dose during the treatment period will be considered compliant in the context of this protocol.

6. ASSESSMENT OF PHARMACOKINETICS

6.1. Sample Collection and Handling

Pharmacokinetic evaluation will be performed in a subset of the total study population. Approximately twenty(20) subjects (ten in each cohort) will be enrolled in the serial sample pharmacokinetic evaluation at select US sites. Subjects enrolled for pharmacokinetic evaluation will also include approximately 50% tobacco users and 50% non-tobacco users. Blood sample collection and pharmacokinetic assessments for this subset of the study population are described below.

Serial blood samples (6 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose. The exact dates and times of blood sample collection must be recorded on the source document and the laboratory requisition form.

An additional twenty subjects (ten in each cohort) will be enrolled in the sparse sample pharmacokinetic evaluation at selected US sites. Subjects enrolled for pharmacokinetic evaluation will also include 50% tobacco users and 50% non-tobacco users. Blood sample collection and pharmacokinetic assessments for this subset of the study population are described below.

Sparse blood samples (6 mL each) will be collected on Day 1 (1 mg) and at Week 4 (1 mg at steady-state), Week 8 (5 mg at steady-state) and Week 12 (25 mg at steady-state) visits at the following time points: pre-dose, 1 and 3 hours post-dose. The exact dates and times of blood sample collection must be recorded on the source document and the laboratory requisition form.

All plasma samples collected will be analyzed for TC-5619 concentrations. Only pre-dose samples will be analyzed for levels of antipsychotics, quetiapine and risperidone and 9-hydroxy metabolite (9-OH-risperidone).

The date and time of study drug administration (TC-5619-238 or placebo) as well as the date and time of the previous dose of risperidone or quetiapine will be recorded on the source document and in the eCRF.

Blood samples will be prepared and plasma stored according to Sponsor instructions, at -20°C (or lower temperature), until end of study. Appendix 1 details further information regarding collection, handling and shipment of plasma samples.

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6.2. Analytical Procedures

All plasma samples will be analyzed to determine concentrations of TC-5619 and select plasma samples (pre-dose only) will be analyzed for antipsychotic levels using validated, specific and sensitive LC-MS/MS methods under the supervision of the sponsor at a contracted bioanalytical laboratory.

If required, select plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile.

6.3. Pharmacokinetic Parameters

Pharmacokinetic analysis will be performed under the supervision of the sponsor. Plasma pharmacokinetic parameters for TC-5619 to be estimated using non-compartmental methods for TC-5619 include:

C_{max}	maximum plasma concentration
T_{max}	time to reach the maximum plasma concentration
AUC_{8h}	area under the plasma concentration-time curve from time 0 to time 8 hours post-dose
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
$t_{1/2,\lambda}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
λ_z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve

Additional pharmacokinetic parameters for TC-5619 may be estimated as appropriate. Pharmacokinetic data collected under the sparse sampling paradigm will be summarized using descriptive statistics by dose level and scheduled collection time. The pharmacokinetic data collected in the present study may be subject to a cross study population PK analysis at a later date. Those results will be presented in a separate report.

Pre-dose levels of antipsychotics will be summarized using descriptive statistics.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy Measures

7.1.1. CogState Schizophrenia Test Battery

This computerized battery of neuropsychological tests was developed by CogState.[21] It includes a number of factors that assess specific cognitive domains, including Motor Speed, Processing Speed, Working Memory, Executive function, and Episodic Memory. Subjects will be trained on the instrument during their Screening Visit.

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The Trail Making Test is a two-part neuropsychological test that measures visual attention and task switching. It assesses cognition in the following domains: psychomotor speed, visual scanning, and executive functioning (sequence alternation and flexibility/set shifting). The subject is required to draw lines to connect consecutively numbered circles on Part A, and on Part B to connect consecutively numbered and lettered circles, alternating between numbers and letters (1-A-2-B, etc.) as quickly as possible. Two scores for each part are obtained, the total time and number of errors, with the total time score being the predominantly used measure.

The Digit Symbol Substitution Test assesses psychomotor processing and attention. It is a code-substitution test that has often been included in non-language intelligence scales. In this test, subjects are asked to substitute geometric figures for randomized presentations of numbers. The correct pairing is shown in a key containing the numbers 1 through 9, each of which is paired with a different geometric symbol. The key is placed in front of the subject, and the subject has a specified amount of time to fill in as many symbols as possible under the numbers on the answer sheet. The score on this test is the number of correct symbols drawn within the allowed time.

7.1.2. Subject Global Impression (SGI)– Cognition (Subject and Informant versions)

This scale is the total score of 3 subscales: SGI for memory; SGI for attention; and SGI for speed of thinking. Each of these scales consists of a 7-point Likert scale, on which is indicated the informant's (for Informant version) or subject's (for subject version) impression of performance on that item since Baseline. Clinical Global Impression (CGI)

7.1.3. Clinical Global Impression (CGI) scales

CGI[23] is a 3-part scale consisting of: (1) CGI-severity of illness [CGI-S], (2) CGI-global improvement [CGI-I], and CGI-efficacy (or therapeutic) index [CGI-E].

In this study, only the CGI-S and CGI-I are used.

The CGI severity of illness (CGI-S) scores range from 0-7. CGI-S assesses how ill a subject is in terms of the investigator's total clinical experience. Possible values represent: 0=not assessed, 1=normal, not ill at all, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill and 7=amongst the most extremely ill subjects.

CGI global improvement (CGI-I) scores range from 0-7. CGI-I assesses how much, overall, the subject has improved since entering the study (present state vs. baseline state). Possible values represent: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

7.1.4. Positive and Negative Symptom Scale for Schizophrenia (PANSS)

This instrument is a 30-item rating scale that assesses specific symptoms from the positive and negative syndromes, as well as on general psychopathology, that together comprise the

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spectrum of schizophrenic symptoms.[24] The PANSS scores are derived from a semi-structured interview of the subject, along with accessory information from other sources (caregiver, medical records, etc.). Each item is rated on a scale of 1-7, with higher scores indicating more extreme symptoms. The items are divided among domains that include positive symptoms, negative symptoms, depression, a composite index, and general psychopathology.

7.1.5. Scale for Assessment of Negative symptoms (SANS)

The instrument is a 25-item scale, designed to assess negative symptoms in domains such as blunted affect, alogia, apathy, anhedonia, and inattentiveness.[26] SANS scores are derived from a clinical interview, direct observation, and other sources of information (e.g. from medical records, caregivers, etc.). Each item in each domain is rated on a scale of 0 – 5, with a score of 0 reflecting a lack of any deficit, and a score of 5 reflecting severe deficit.

7.1.6 Alpha 7 mRNA expression

A blood sample stabilized for mRNA expression (PreAnalytics tubes) will be used to measure alpha 7 mRNA expression in peripheral blood lymphocytes.[25] The level of expression will be correlated with primary (GML) and secondary (CSTB composite score; SANS, SGI-Cog, CGI-I, CGI-S) efficacy endpoints.

7.2. Analysis of Efficacy Measures

The baseline used for these analyses will be the last planned observation before randomization into the double blind treatment plan. In each scale, the score of cohorts treated with active drug will be compared to the placebo cohort, using the Week 4, Week 8, and Week 12 score compared to Baseline. Additional comparisons of TC-5619 to placebo will be made using Day 1, Week 1, or Week 12 scores compared to Baseline (see Study Endpoints, section 3.1.1, for details).

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

- **Adverse Events**
  Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study, defined as from time of informed consent until the end of the Follow-Up Visit (Week 14) (see Section 8.2, Adverse Event Reporting).

- **Physical Examinations**
  Physical examinations will be conducted at times indicated in the Time and Events Schedule. The physical exam at Screening should be complete, including use of the Abnormal Involuntary Movement Scale (AIMS). The AIMS is a structured examination for involuntary movements such as tardive dyskinesia.[23]

- **Vital Signs**
  Blood pressure, pulse, respiratory rate, height and weight will be assessed at times indicated in the Time and Events Schedule. Blood pressure and heart rate will be

recorded after at least 5 minutes rest in a sitting position and after standing for at least 2 and no more than 3 minutes.

- **ECG**
  Digital twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured manually. These ECGs will be recorded in triplicate at each visit except the Follow-up Visit (unless an abnormality was detected at Week 12). The ECG will be recorded with the subject in a supine of semi-recumbent position after at least 5 minutes of rest until 4 regular consecutive complexes are available. ECG interval estimates taken from the ECG recorder will be recorded, and a central ECG reader will verify all values and readings. QTcB and QTcF will be calculated from each ECG tracing; when triplicate ECGs are obtained, the mean QTc will be calculated.

- **Clinical Laboratory tests**
  Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be taken for evaluation of laboratory safety parameters. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Tests will be performed by the central laboratory. A summary of tests is included in Appendix 2.

8.1.1. Blood Samples

Blood samples for hematology and biochemistry will be taken at Screening (an additional time at Screening and Baseline if indicated), Week 4, Week 8, and Week 12. Samples will be fasting at Screening and Week 12, so that samples for fasting lipids may be obtained in addition to the other hematology and biochemistry labs. If any values at Week 12 are clinically abnormal, then further blood samples should be taken at the Week 14 Follow-Up Visit and/or until the abnormality resolves.

8.1.2. Urinalysis

Urinalysis will be performed at Screening and Week 12.

8.1.3. Adverse Events

Adverse events volunteered after a non leading question or observed, will be recorded at Screening and at all subsequent visits.

The Columbia Suicide Severity Rating Scale (CSSRS) will be administered at each visit from Baseline onwards. Any evidence of suicidality must be managed immediately and as appropriate by site investigator or other qualified medical personnel.

The Calgary Depression Scale for Schizophrenia (CDSS) will also be administered at each visit from Screening onwards. Evidence of clinically meaningful worsening of depression must be managed immediately and as appropriate by site investigator or other qualified medical personnel.

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8.1.4. Pregnancy

The investigator, or his/her designee, will collect pregnancy information using the Targacept Serious Event/Important Event Reporting Form on every female who becomes pregnant while participating in this study. The investigator, or his/her designee, will report to Sponsor within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Sponsor. Follow-up on the child will be for 1 year following the delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 8.2, and will be followed as described in Section 8.3.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.2. Furthermore, any SAE occurring as a result of a post-study pregnancy **and** is considered reasonably related to the investigational product by the investigator, will be reported to Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

8.1.5. Analysis of Safety Parameters

Safety analysis will be performed on the safety data set. Descriptive statistics will be performed by time of evaluation.

- Physical examination at the end of treatment (or at termination if the subject withdraws from the study): Clinically significant changes from Screening will be listed; frequencies tables will be computed. AIMS results will be summarized.
- Vital signs: Blood pressure and heart rate measurements and respiratory frequency: Descriptive statistics will be calculated on actual values as well as on changes from baseline values. Values outside the reference ranges will be counted, and also illustrated using shift tables. Plot of means and standard errors will be provided.
- Body temperature: Descriptive statistics will be calculated on actual body temperature values.
- Laboratory parameters: Descriptive statistics will be calculated on actual values as well as on changes from Screening values for all lab parameters. Values outside the reference ranges will be listed, and also tabulated using shift tables.
- Adverse experiences: AEs and SAEs will be coded by MedDRA and summarized (number of events, number and % of subjects having or experiencing at least one event) by dose, organ class and preferred term.
- Columbia Suicide Severity Rating Scale scores and Calgary Depression Scale for Schizophrenia scores will be tabulated and summary statistics will be shown.
- Concomitant medication, coded using WHO Drug Dictionary, will be listed.

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- ECG: Descriptive statistics on heart rate, PQ interval, QRS duration, QT and QTc intervals (QTcB and QTcF) will be calculated on actual values as well as on changes from baseline values. Values outside the reference ranges will be counted. Plot of means and standard errors will be provided.

8.2. Adverse Event Reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of a non-serious AE or SAE as provided in this protocol. During the study, as defined from the time of informed consent until the end of the follow-Up Visit (Week 14), the investigator or site staff will be responsible for detecting and following AEs and SAEs, as detailed in this section of the protocol.

8.2.1. Definitions

8.2.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.2.1.2. Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

8.2.1.3. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that occurs at any dose, if it satisfies any of these criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacity; or if the event is a congenital anomaly or birth defect.

8.2.1.4. Adverse Event of Special Interest

An AE of Special Interest is any AE that includes the following term:

- QTcF prolongation
- LFT abnormalities leading to withdrawal (e.g. lab values of 3 times greater limit)

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- Clinically significant change, if present at Screening, or emergence of Tardive dyskinesia
- Clinically significant change, if present at Screening, or emergence of Rigidity or bradykinesia
- Overdose
- Suicide

8.2.2. Adverse Event Reporting

Subjects will be encouraged to spontaneously report any changes in baseline health from the time the subject enters the study on through discharge. Study staff will also inquire about adverse events on each visit while the subject is in the research center. All AEs will be recorded in the source document and the eCRF.

In addition, AEs of Special Interest will be reported to Sponsor and CRO within 24 hours after they are reported or identified at a clinical site.

8.2.3. Laboratory Abnormalities as Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., ECGs, vital signs, etc.) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.2.1.1, or SAE, as defined in Section 8.2.1.3. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Screening and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2.4. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

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- Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

8.2.5. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Product Information for marketed products in the determination of his/her assessment.

The investigator will determine the relationship of the study treatment to an AE based on the following definitions:

- Not Related (the AE was more likely explained by causes other than the study treatment).
- Related (the study treatment and AE were closely related in time and the AE may be explained by exposure to study product: e.g. known pharmacological effect or recurrence on re-challenge).

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or CRO. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the Targacept Serious Event/Important Event Reporting Form to Sponsor or CRO. The investigator may change his/her opinion of causality in light of follow-up information, amending the eCRF and Targacept Serious Event/Important Event Reporting Forms accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality.

Because of its importance, any assessment of causality should also be documented in the subject's source medical record.

8.2.6. Adverse Event Recording

When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE in the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate AE eCRF entries.

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However, there may be instances when Sponsor or CRO requests copies of medical records for certain cases. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.7. Eliciting Adverse Event Reports

At each visit, subjects will be asked about AEs by means of a non leading question, such as "how have you been since your last visit?" or 'how has the medication been?" In this way, possible more mild, but clinically important, side effects of the medication can be detected. SAEs will be reported promptly to Sponsor or CRO as described in the following table once the investigator determines that the event meets the protocol definition of a SAE.

8.2.8. SAE Reporting Procedures

Once an investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information to Sponsor or CRO within 24 hours. The Targacept Serious Event/Important Event Reporting Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to Sponsor or CRO within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Sponsor or CRO of the event and completing the form. The form will be updated when additional information is received.

Table 1. Timeframes for Submitting SAE Reports to Sponsor or CRO

Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Time Frame	Documents	Time Frame	Documents
24 hrs	Targacept Serious Event/Important Event Reporting Form	24 hrs	Updated Targacept Serious Event/Important Event Reporting Form

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.2.4.

Facsimile transmission of the Targacept Serious Event/Important Event Reporting Form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the Targacept Serious Event/Important Event Reporting Form sent by overnight mail. Initial notification via the telephone does not replace the need for

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the investigator to complete and sign the Targacept Serious Event/Important Event Reporting Form within 24 hours.

Sponsor will provide a list of project contacts for SAE receipt, e-mail addresses, fax numbers, telephone numbers, and mailing addresses.

8.2.8.1. Regulatory Reporting Requirements For SAEs

Sponsor or CRO has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

8.2.8.2. Management of an SAE and Events of Special Interest

A 6 ml PK plasma sample will be obtained at the earliest opportunity immediately following the occurrence of an SAE or Event of Special Interest.

8.2.9. Management of Overdose

Any single dose of TC-5619 greater than 25mg or any dose of TC-5619 taken in a suicide attempt or gesture will be considered to be an overdose. In the event a study subject takes an overdose of study medication, the investigator may obtain the identity of the subject's medication, however, the Targacept Medical Monitor or other designee must be notified if not before breaking the blind, within 24 hours after breaking the blind. A detailed description of the treatment administered for the overdose and the subject's clinical course will be recorded on the Targacept Serious Event/Important Event Reporting Form provided.

In the event the subject has taken an overdose of TC-5619, when possible, the following determinations will be made in order to evaluate the safety of TC-5619.

A detailed history regarding the circumstances of the overdose including the time of the overdose, drugs and amounts taken will be recorded.

- A 6 ml plasma sample for TC-5619 assay immediately upon becoming aware of the overdose, 1 hour later, 4 hours later and then every 8 hours for a minimum of 24 hours and until all signs and symptoms of the overdose have resolved. If possible, an additional plasma sample should be obtained at the time of occurrence of any major clinical event such as seizure or hypotensive crises.
- A drug screen immediately upon becoming aware of the overdose to detect other drugs taken during the overdose.
- A detailed listing of clinical signs and symptoms such as the occurrence of anticholinergic effects (e.g., urinary retention, ileus, etc.), arrhythmias, seizures, respiratory depression and depressed level of consciousness.

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- Frequent vital signs (initially hourly, or more frequently if clinically indicated) including supine blood pressure, standing blood pressure if possible, supine pulse, temperature and respiratory rate.
- An ECG immediately upon becoming aware of the overdose and every 8 hours thereafter until 3 consecutive ECGs that are normal or the same as the pre-study ECG have been obtained. Particular attention should be paid to the PR, QRS, and QTc intervals.
- Continuous monitoring of cardiac rhythm with representative tracings of any arrhythmias until no abnormalities of cardiac rhythm have been observed for 24 hours (therefore the minimum period of cardiac monitoring should be 24 hours).
- Hematological and blood chemistry tests (including LFTs) and a urinalysis immediately and once daily for a minimum of 48 hours.

The physician managing the overdose may order any additional tests he or she thinks are necessary to manage the safety of the subject.

8.2.10. Management of Suicide Attempt

All suicide attempts must be reported as an SAE/ESI whether the attempt was serious attempt or not. A detailed history regarding the circumstances of the suicide attempt including what lead up to the suicide attempt and the method used in the suicide attempt A. description of the treatment administered for the suicide attempt and the participant's clinical course will be reported on the Targacept Serious Event/Important Event Reporting Form

The evaluation outlined for an overdose should also be followed for an apparent suicide attempt regardless of whether method of the attempt was an overdose.

Any possible suicide-attempts will result in immediate withdrawal of the participant from the study. Appropriate medical and psychiatric management of the suicide attempt and/or related AEs/SAEs must be provided to the participant.

8.2.11. Management of Increase Liver Function Tests

Any increase in liver function tests of > 3 times the upper limit of the reference range should be reported on the Targacept Serious Event/Important Event Reporting Form

A detailed history including all possible explanations for the elevations of Liver Function tests including a list of all concomitant medications the subject has taken in the last 30 days..

- Blood chemistry tests including LFTs should be repeated to confirm the results.
- A 6 ml plasma sample for TC-5619 assay should be obtained
- Repeat LFTs should be performed weekly until the levels return to baseline.
- Management of the elevated LFTs should be discussed with the Medical Monitor or Medical Safety Monitor.

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8.2.12. Management of Prolonged QTc Fridericia

A QTc prolongation is defined as a QTcF $\geq$ 500 msec on the automated report, or a mean QTcF of > 450 msec (males), QTcF > 480 msec (females), or an increase > 60 msec on the cardiologist read ECG. The Medical Monitor must be notified and the Targacept Serious Event/Important Event Reporting Form must be completed

- The participant should be contacted and requested to come to the clinical site for repeat ECGs (in triplicate)
- A 6 ml plasma sample for TC-5619 assay (unscheduled PK sample) should be obtained.
- Appropriate medical management shall be performed as required by the subject's clinical signs and symptoms.
- The following information should be obtained from the participant and confirmed with the informant:
  - Was he/she symptomatic?
  - What medications (prescription and OTC) is the participant taking?
  - Does the participant have a history of heart disease?
  - Is there a familial history of heart disease?

8.2.13. Reporting Safety Information to the IRB

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB) / Institutional Ethics Committee (IEC).

A given SAE may qualify for a Safety Report if the SAE is both attributable to the investigational product and unexpected. In this case, all investigators involved in studies with this drug will receive a copy of the Safety Report.

When a site receives an Initial or Follow-up safety report or other safety information (e.g., revised Clinical Investigator's Brochure/Investigator's Brochure) from Targacept, the responsible person according to local requirements is required to promptly notify his or her IRB.

8.2.14. Protocol Deviations Due to an Emergency or Adverse Event

Any subject experiencing an emergency or adverse event requiring immediate medical attention, will receive appropriate medical management by medical staff at the site and at other clinical sites as indicated. These events will be reported to the Medical Monitor of the sponsor as soon as possible. If the medical management results in departure from the study protocol, the Medical Monitor will be responsible for granting permission for the subject to continue in the trial if the subject is able to return to study protocol adherence in a timely fashion. If the subject cannot return to the study protocol in a timely fashion, then the subject will be discontinued from the study.

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8.3. Follow-Up of Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to Sponsor on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate eCRF entries and Targacept Serious Event/Important Event Reporting Forms will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed Targacept Serious Event/Important Event Reporting Form, with all changes signed and dated by the investigator. This information will also be entered into the eCRF.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator would promptly notify Sponsor.

A SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to Sponsor.

9. STATISTICS

9.1. Description of Statistical Methods

9.1.1. Quantitative Parameters

Descriptive statistics (mean, median, standard error of the mean, standard deviation, minimum and maximum) will be calculated for quantitative parameters. In addition, to evaluate possible treatment differences, binary and ordinal categorical measures will be analyzed using Chi-square test; all continuous measures will be analyzed using an ANCOVA model. All statistical tests for the efficacy analyses will be one-sided and will be performed at the $p < 0.10$ level of significance, except where noted.

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9.1.2. Qualitative Parameters

Qualitative parameters will be summarized with the frequency and percent of categories and examined for differences between treatment and placebo using Chi-square tests.

9.1.3. Baseline Data Analysis

Demographic data and subjects' characteristics at screening will be listed and summarized using descriptive statistics.

Medical history (sorted by type of disease) will be tabulated by group and subject.

Any deviations from inclusion/exclusion criteria will be listed.

9.1.4. Primary Efficacy Endpoint Analysis

The primary endpoint will be change in the GML item of the CogState Schizophrenia Test Battery from Baseline to Week 4, Week 8, and Week 12 in the entire cohort (tobacco users plus non-users). This change from baseline will be analyzed using Analysis of Covariance (ANCOVA) techniques with an alpha of 0.10 (one-sided), to examine differences between the TC-5619 and placebo treatment groups in the entire cohort of approximately 60 completing subjects in each treatment group (tobacco users and non-tobacco users collectively; and tobacco users separately and non-tobacco users separately). The ANCOVA model will include treatment as a main factor and baseline value, country, time, tobacco use, and interaction of tobacco use with treatment as covariates. Other covariates may be used as appropriate, and these will be described in the Statistical Analysis Plan.

Since there are three dose comparisons (Week 4 [1mg]; Week 8 [5mg]; and Week 12 [25mg] that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons. To ensure that the significance level over the two independent tests is 10%, should the first P value be worse than the 10% level of significance, then the second P value will be assessed using the 5% level of significance. Should the second P value be worse than the 5% level of significance, then the third P value will be assessed using the 3.33% level of significance.

The primary efficacy analysis will be performed using the primary efficacy endpoint for the Intent-to-Treat (ITT) population and Per Protocol (PP) population. To account for missing data, the last-observation-carried-forward (LOCF) method will be used, i.e. the last available on-therapy observation for a subject will be used to estimate subsequent missing data points.

The primary efficacy endpoint will be considered to be positive if the primary endpoint is statistically significant in at least 1 of the 3 dose comparisons vs. placebo in the Intent-to-Treat (ITT) population at the $P < 0.10$ level, in the entire cohort (tobacco users and non-tobacco users).

9.1.5 Pharmacokinetic Analysis

Pre-dose plasma concentrations of risperidone/9-OH-risperidone and quetiapine will be listed, and descriptive statistics will be presented in tables as a function of visit/dose level.

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For TC-5619, plasma concentration data will be listed for all individual subjects with available plasma concentrations per visit/dose level and tobacco use. All concentrations below the limit of quantification (LOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LOQ will be treated as zero in the summary statistics and for the calculation of pharmacokinetic parameters, as appropriate. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each dose level, descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum will be calculated for the TC-5619 plasma concentrations at each sampling time and for all estimated pharmacokinetic parameters.

Graphical representations of the results will include (but are not limited to) the following graphs for TC-5619 as appropriate:

- Log-linear and linear-linear plasma concentration-time profiles for each individual
- Log-linear and linear-linear plasma concentration-time profiles for the mean values per cohort
- Log-linear and linear-linear plasma concentration-time profiles for the median values per cohort
- Log-linear and linear-linear overlay plots of the individual plasma concentration-time profiles for each cohort
- A graphical comparison of the individual and mean (± SD) primary PK parameters of each analyte for each cohort

Pharmacokinetic data collected in the present study may be subject to a cross study population PK analysis at a later date. Those results will be presented in a separate report.

9.2. Sample Size

No more than 200 subjects (50% tobacco users and 50% non-tobacco users) will be randomized, divided into 2 cohorts, to ensure that at least 120 subjects complete (60 per cohort: 30 tobacco users and 30 non-tobacco users); this assumes a 40% drop-out rate.

This is based upon the following sample size calculation. This study is powered to demonstrate a statistically significant difference in each of the stratified sub-cohorts (tobacco users or tobacco non-tobacco users) between TC-5619-238 and placebo in the change from the beginning of treatment to the end of the fourth week of dosing for each of 3 doses of TC-5619 (1mg, 5mg, and 25mg) in the primary endpoint (Groton Maze Learning [GML]), which is an item in the CogState Schizophrenia test battery. The number of subjects per sub-cohort needed for GML is 29, to detect a difference of 18.0 points with 80% power using a one-sided test and a significance level of 10% ($p < 0.10$), assuming a standard deviation (SD) of 32.2 and normally distributed errors. Hence the number of subjects required in the cohort (tobacco users plus tobacco non-tobacco users) is 60.

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9.3. Level of Significance

The level of significance used for all efficacy variables will be defined by an alpha of 0.10 in one-tailed tests. For the primary efficacy endpoint, because there are three dose comparisons that may result in the rejection of the null hypothesis, the Hochberg method will be used to control for multiple comparisons. To ensure that the significance level over the two independent tests is 10%, should the first P-value be worse than the 10% level of significance then the second P-value will be assessed using the 5% level of significance. Likewise, should the second P-value be worse than the 5% level of significance, then the third P-value will be assessed using the 3.33% level of significance.

9.4. Procedure for Accounting for Missing, Unused, and Spurious Data

The LOCF method of imputation will be employed for missing values. Detail regarding procedures for accounting for missing, unused, and spurious data will be elaborated in the study specific data management plan.

9.5. Analysis of Patients Withdrawing Prematurely from the Study

Randomized subjects who withdraw prematurely from the study should complete all necessary assessments in the early termination visit. A summary of all-cause discontinuation will be provided. All information for withdrawing subjects will be included in safety analyses.

9.6. Selection of Patients To Be Included in Analyses

The randomized data set will contain all randomized subjects.

The safety data set will contain all randomized subjects who receive at least one dose of the study medication (drug or placebo) and have at least one post-baseline assessment.

The Per Protocol data set will include only randomized subjects who complete the study, fully compliant with all aspects of the protocol, including 80% compliance with study drug administration. Secondary efficacy analysis will be performed on the Per Protocol data set.

The intention to treat (ITT) data set will include all randomized subjects who receive at least one dose of the study medication and have at least one post-dose efficacy assessment. For those subjects who drop out of the study prematurely, the last values while on therapy will be used for all subsequent (missed) visits (i.e., LOCF imputation). Primary efficacy analysis will be performed on the ITT data set.

The primary efficacy analysis will focus on the entire cohort (tobacco users and non-tobacco users); and on the 2 separate groups of tobacco users and non-tobacco users. Secondary efficacy analyses will include non-tobacco users only and both tobacco users and non-tobacco users.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Monitoring

In accordance with applicable regulations, ICH-GCP, and Sponsor procedures, Sponsor or CRO monitors will contact the site prior to the subject enrollment to review the protocol and data

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collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits at an appropriate frequency.

During these contacts, the monitor will:

1. Check the progress of the study.
2. Review study data collected.
3. Conduct source document verification and eCRF data entry.
4. Identify any issues and address their resolution.

This will be done in order to verify that the:

1. Data are authentic, accurate, and complete.
2. Safety and rights of subjects are being protected.
3. Study is conducted in accordance with the currently approved protocol (and any amendments), ICH-GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 13.3.

10.2. Review of Original Subject Records

Original patient records (source documents) will be audited or reviewed during the course of monitoring to verify the accuracy of the source documents, and accuracy of data entered from these source documents into the eCRF. This audit or review will be conducted according to the Sponsor's Standard Operating Procedures and the monitoring plan.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Regulatory Authority Approval

Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with all applicable country-specific regulatory requirements prior to a site initiating the study in that country.

To ensure compliance with ICH-GCP and all applicable regulatory requirements, Targacept may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.2. Protocol Modifications

All protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation of the amendment. The Principal Investigator must submit all protocol modifications to the IRB or applicable local regulatory authority. Sponsor or designee will submit protocol modifications to the FDA and other country regulatory agencies.

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Departures from the protocol will be determined as allowable on a case-by-case basis, only in event of an emergency. The Investigator or other physician in attendance must contact the Medical Monitor (Sponsor or CRO) as soon as possible to discuss the circumstances of the emergency. The Medical Monitor, in concurrence with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and the reason for such deviations must be noted on the source document and in the eCRF, and reported to the IRB / IEC as appropriate.

12. ETHICS

12.1. Ethical Principles

This study will be conducted in accordance with International Conference of Harmonization, Good Clinical Practice and all applicable regulatory requirements, including, where applicable, the 2008 version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IRB/IEC. The investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements. Sponsor or CRO will provide the investigator with relevant document(s)/data that are needed for IRB/IEC review and approval of the study. Before investigational product(s) and other study material can be shipped to the site, Sponsor or CRO must receive copies of the IRB/IEC approval, the approved informed consent form, and any other information that the IRB/IEC has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IRB/IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IRB/IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IRB/IEC approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IRB/IEC approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to Sponsor promptly.

12.2. Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50.

The consent form must be reviewed and approved by the Sponsor prior to submission to the IRB/IEC. The consent form must be approved by the IRB/IEC prior to initiation of the study.

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The consent form must contain a full explanation of the possible advantages, risks, alternate treatment options, and availability of treatment in the case of injury, in accordance with Title 21 of the Code of Federal Regulations. The consent should also indicate that, by signature, the patient or, where appropriate, legal guardian permits access to relevant medical records by the Sponsor and by representatives of the FDA.

The Investigator is responsible for obtaining written consent from potential subjects prior to performing any trial tests or assessments required by the protocol. A copy of the signed consent document will be given to the patient and the original retained by the Investigator with the site's copy of the case report forms.

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator may seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information given to the subject or the representative must be in a language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the Investigator, the institution, the Sponsor, or its agents from liability for negligence.

An IRB-approved consent form should inform each prospective subject or the legally authorized representative of each prospective subject of the purpose and the nature of the study, its possible hazards and benefits, and the subject's right to withdraw from the study at any time without prejudice to further treatment. 21 CRF 50.23 lists exemptions to the requirement for informed consent in the United States.

Before initiation of any screening assessments specifically for this study, each subject must sign the informed consent form. Subject thumb prints are allowed for subjects unable to write. The signed consent form must remain in the subject's file and must be available for verification by a representative of the Sponsor.

12.3. Institutional Review Board

This study will be conducted in full compliance with the Institutional Review Board (IRB) regulations in 21 CFR 56 and applicable local regulatory guidance, in accordance with the Declaration of Helsinki (2008).

This protocol will not be initiated unless it has been reviewed and approved by, and remains open to continuing review by, an IRB/IEC meeting the requirements of 21 CFR 56. The IRB/IEC shall review and have the authority to approve, require modification in (to secure approval), or disapprove the protocol. The IRB/IEC shall notify the Investigator and the institution in writing of its decision. The IRB/IEC shall require that the information given to patients as part of the informed consent is in accordance with 21 CFR 50.25. The IRB/IEC shall conduct continuing reviews of the protocol at intervals appropriate to the degree of risk, but not less than once per year. Copies of all reports to and correspondence between the Investigator and the IRB/IEC must be provided to the Sponsor. Further, at the completion or early

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termination of the trial, a final report should be made to the IRB/IEC by the Investigator within 90 days.

Any change in the protocol that significantly affects the safety of the patients, the scope of the investigation, or the scientific quality of the trial must be approved by the Sponsor and the IRB/IEC prior to implementation. However, any protocol change intended to eliminate an apparent immediate hazard to the subject may be implemented immediately if the Sponsor subsequently notifies the FDA or local regulatory body of the amendment and the Investigator informs the IRB/IEC.

The Investigator is obligated to maintain an IRB/IEC correspondence file, and to make this file available for review by the Sponsor's representatives as part of the trial monitoring process.

12.4. Investigator Reporting Requirements

As indicated in Section 8.2, the investigator (or Sponsor or CRO, where applicable) is responsible for reporting SAEs to the IRB/IEC, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IRB/IEC. Such periodic safety updates and notifications are the responsibility of the investigator and not of Sponsor.

The investigator is also responsible for notifying the IRB/IEC when any changes in the conduct of the study occur, including exceptions granted for Inclusion/Exclusion criteria, changes in study staff, laboratories or facilities, and notifying the IRB/IEC when the study is complete at their site. The Investigator's Final Report to his or her IRB/IEC must also be provided to the Sponsor.

13. DATA HANDLING AND RECORD KEEPING

13.1. Submission of Documentation

Documents that must be provided to Sponsor prior to study initiation are as follows:

- Signed and dated Form FDA 1572 plus a current curriculum vitae for the Principal Investigator;
- Signed and dated Investigator Agreement;
- Assurance that an IRB/IEC, that complies with the requirements set forth in the Code of Federal Regulations, has reviewed and approved the protocol. The required documentation will consist of the name and address of the IRB/IEC and a current list of IRB/IEC members; an assurance number from the Department of Health and Human Services may be substituted for this list for U.S. sites;
- A copy of the formal written notification to the Investigator regarding approval of the protocol and Informed Consent Form by the IRB/IEC. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB/IEC member has a known conflict of interest, abstention of that individual from voting should be documented; an Investigator (or Sub-Investigator) may be a member of the IRB/IEC, but may not vote on any research in which he or she is involved;

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- A copy of the IRB/IEC-approved informed consent form and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of IRB/IEC approval of these items.

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

The Investigator will promptly report to the IRB/IEC all changes in research activity and all unanticipated problems involving risks and will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate immediate hazards to human subjects. Those amendments that involve no more than minimal risk or minor changes in previously approved research only require submission to the IRB/IEC. Major amendments require approval of the full IRB committee and must be submitted to the FDA by Sponsor before implementation, except in an emergency situation. Documentation of all study amendment activity should be forwarded to Sponsor. The Investigator must also report to the IRB/IEC at least yearly on the progress of the investigation.

Continuing IRB review should be documented by a letter from the IRB/IEC, which should be forwarded to the Sponsor. Notification to the IRB/IEC by the Investigator within three months after completion, termination, or discontinuation of the study at the specific study center must be documented.

13.2. Case Report Forms and Source Documentation

Subjects who are screened but choose not to continue in the study or those that are found to be ineligible for the study will be considered "screen failures". The reason for the failure will be recorded on the source document and in the eCRF.

The clinical research associate (CRA) will verify the eCRF documentation for each patient against the source documents at the study center. Instances of missing or uninterpretable data will be brought to the attention of the Sponsor for resolution. A copy of the source document and eCRF (i.e. DVD-ROM containing pdf files of the eCRFs) will be placed in the Investigator's study file, and the original eCRF will be kept by the Sponsor.

The eCRF will be the sole property of the Sponsor.

13.3. Study Site Close-Out

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or site staff, as appropriate:

1. Return of all study data to Sponsor.
2. Resolution of data queries.
3. Accountability, reconciliation, and arrangements for unused investigational product(s).
4. Review of site study records for completeness.
5. Return of treatment codes to sponsor.
6. Shipment of PK samples to the central laboratory.
7. Return all study-specific equipment to the sponsor.

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Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and Sponsor.

13.4. Retention of Study Documents

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

13.5. Provision of Study Results and Information to Investigators

When a clinical study report is completed, Sponsor will provide the major findings of the study to the investigator. In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subjects.

13.6. Information Disclosure and Inventions

13.6.1. Ownership

All information provided by Sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) is the sole property of Sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of sponsor, and are hereby assigned to sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between sponsor and the study site, that contract's ownership provisions shall apply rather than this statement.

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13.6.2. Confidentiality

All information provided by sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study is executed which includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement.

In subjects consenting to measurements of alpha 7 mRNA expression, a blood sample will be obtained and de-identified using codes prepared by an unblinded statistician, so that study site staff cannot correlate the de-identification code with subject ID. Confidentiality of these mRNA blood samples will be maintained at all times during the study and after study conclusion. Identification of samples will be permitted only as required by regulatory or legal authorities. Publication of data resulting from measurement of mRNA expression will not identify the subjects.

13.6.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by Sponsor. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide sponsor with a copy of the proposed Publication and allow sponsor a reasonable period to review the proposed Publication. Proposed Publications shall not include either sponsor confidential information other than the study results or personal data on any subject, such as name or initials.

At Sponsor's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow Sponsor to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

13.6.4. Data Management

Subject data are collected by the investigator or designee using source documents that are entered into an eCRF, defined by Sponsor. Subject data necessary for analysis and reporting will be entered onto the source documents and then into the validated eCRF system. Clinical data management will be performed in accordance with applicable sponsor standards and data cleaning procedures.

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Database lock will occur when data management quality control procedures are completed. All eCRF data will be retained by Sponsor. The investigator will retain an exact copy of all source documents and eCRF data (i.e. DVD-ROM containing pdf files s of eCRFs) on site.

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15. APPENDICES

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Appendix 1. Pharmacokinetic Sample Collection, Handling and Shipping

Materials and Labeling:

Blood must be collected in glass or plastic K_2EDTA containing blood collection tubes (e.g., Vacutainer®). Resulting plasma samples must be stored in polypropylene storage tubes. No tubes with separation gel should be used.

All tubes and containers will be labeled with preprinted labels. The preprinted information will include the study number, subject identification number (eCRF I.D.#), treatment or treatment period, scheduled sampling day and time as stipulated in the protocol, and the analyte name(s) if applicable. Other information may be included on label without deviation if approved by Sponsor.

Preparation of **Plasma** Pharmacokinetic Samples:

- Collect 6 mL of blood into the appropriate K_2EDTA containing collection tube (e.g., Vacutainer®) at each time point.
- Record the exact date and time of sampling on the lab requisition form.
- Gently invert the tubes 8 to 10 times to afford mixing, before processing.
- Centrifuge blood samples at room temperature within 1 hour of collection in a clinical centrifuge at (1,300 g for 10 minutes, unless otherwise specified by the supplier).
- Transfer all separated plasma immediately with a clean, disposable glass or polyethylene pipette (use 1 new pipette per sample) to a pre-labeled storage tube.
- The approximate 3-ml of plasma (after centrifugation) will be split evenly between two storage tubes each containing approximately 1.5 mL plasma.
- Store plasma samples in an upright position, in a non-frost-free freezer (at approximately –20°C or lower) until transfer to the bioanalytical facility.
- The time between blood collection and freezing the plasma will not exceed 2 hours.

Shipment of Pharmacokinetic Samples:
All pharmacokinetic samples will be sent to the central laboratory in multiple shipments as agreed upon with the sponsor. An inventory list must be included with each shipment. The inventory list must note each specimen drawn for each subject, and note any missing specimens.

The investigator must follow the instructions below:

- Ship specimens according to the instructions provided by the bioanalytical facility, sorted by subject, by sample collection date and time.
- For all international shipments, World Courier will be used. For domestic shipments in the US, a reliable domestic courier such as Federal Express will be used. For domestic shipment originating outside the US, a reliable domestic courier will be used.
- The central laboratory will be notified by fax or email, that a shipment of samples is imminent. This notification will be made before the shipping date.

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- Notify the central laboratory and the courier, at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Unless agreements were made with the sponsor, samples will be shipped via overnight delivery only on Monday through Wednesday, excluding holidays.
- Double-bag the frozen samples for each subject in bags that can withstand dry ice conditions (e.g. cryogenic bags), and label with eCRF I.D.#. Pack the frozen samples in sufficient quantity of dry ice in appropriate containers, to maintain a frozen state for at least 3 days.
- Avoid direct contact between sample bags and dry ice by separating them with a dry ice resistant material (e.g., newspaper).
- For all biological samples, follow the International Air Transport Association (IATA) regulations for shipment. Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Ensure that the total package weight does not exceed 27.2 kg (60 pounds). Label the package with the sponsor name and study number.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.

As soon as shipment day and air bill number(s) are available, the site will call, fax or email the central laboratory. The call, fax or email must specify the study number, the number of pharmacokinetic samples, and the time of shipment pick-up.

Questions regarding handling the pharmacokinetic specimens should be addressed to the contact person of the sponsor. Alternative procedures will not result in a protocol amendment if approved by the sponsor.

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Appendix 2. CogState Schizophrenia Test Battery

CogState Schizophrenia Test Battery (CSTB)

1. General Description.

The MATRICS Initiative

As a result of an agreement between the FDA and NIH that cognitive dysfunction/impairment is an important health issue in schizophrenia, the FDA confirmed that improved cognitive function would be considered as a primary outcome in schizophrenia research. Following this guidance, the MATRICS initiative (a collaboration of the FDA, NIH, academic researchers and industry), recommended a test battery for the assessment of cognition in people with schizophrenia.

Prior to the MATRICS initiative, there was no consensus on the optimum outcome measures for evaluation of cognitive function in clinical trials in schizophrenia. The test criteria recommended by the MATRICS group was defined as:

- High test-retest reliability
- Good coverage of cognitive domains
- Comparable alternative forms
- Strong internal consistency
- Well established in general population
- Demonstrated tolerability and acceptability

The MATRICS initiative also recommended the cognitive domains to be tested in order to assess cognitive function in schizophrenic patients. This is illustrated in the table below.

The CogState Schizophrenia Battery

Domain	MATRICS test	Equivalent CogState task
Speed of Processing	Category Fluency / Symbol Coding	Detection Task
Attention / Vigilance	Continuous Performance Task	Identification Task
Working Memory	Verbal Span / Spatial Span	One-Back / Two-Back Task
Visual Learning	Object Learning	One Card Learning Task
Verbal Learning	Word List Learning	International Shopping List Task
Reasoning / Problem Solving	Mazes	Groton Maze Learning Task
Social Cognition	Managing Emotions Test	Social-Emotional Cognition Task

CogState's Schizophrenia Battery was developed with all the MATRICS criteria and recommendations in mind. All CogState tasks have been developed to meet the criteria set out above with regards to scientific validity, reliability and consistency and we have selected a set of tasks that target those cognitive domains recommended by the MATRICS initiative.

The benefits of the CogState Schizophrenia Battery

- The test battery is rapid. It covers all necessary domains in around 35 minutes - minimizing the testing burden on both patient and test administrator.
- The user-friendly test battery allows for non-expert administration on standard computer equipment, reducing costs and increasing efficiency.

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- The tasks utilize culture-neutral stimuli - which ensures that they can be integrated into clinical trials all around the world regardless of each patient's culture, ethnicity, education or socio-economic status.

2. Co-primary Efficacy Variables

a. Groton Maze Learning Test (GML)

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Executive Function / Spatial Problem Solving

Task Description:

The subject is shown a 10 x 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among these 100 possible locations. The start is indicated by the blue tile at the top left and the finish location is the tile with the red circles at the bottom right of the grid. The subject is instructed to move one step from the start location and then to continue, one tile at a time, toward the end (bottom right).

The subject moves by touching a tile next to their current location with the stylus. After each move is made, the computer indicates whether this is correct by revealing a green checkmark (i.e. this is the next step in the pathway), or incorrect by revealing a red cross (i.e. this is not the next step in the pathway, or the subject has broken a rule, see below). If a choice is incorrect (i.e. a red cross is revealed), the subject must touch the last correct location (i.e. the last green checkmark revealed) and then make a different tile choice to advance toward the end.

While moving through the hidden maze, the subject is required to adhere to two rules. Firstly, the subject cannot move diagonally or touch the same tile twice in succession. Secondly, the subject cannot move backwards along the pathway (e.g. move back to a location that displayed a green tick, but from which they have since moved on from).

If the subject chooses a tile that is not part of the hidden pathway, but the tile choice is within the rules, this is recorded as a different type of error (e.g. not a rule break). This could be due to chance (the first time through the maze) or due to misremembering the path on subsequent attempts.

The subject learns the 28-step pathway though the maze on the basis of this trial and error feedback. Once completed, they are returned to the start location and repeat the task, usually 4 more times, trying to remember the pathway they have just completed.

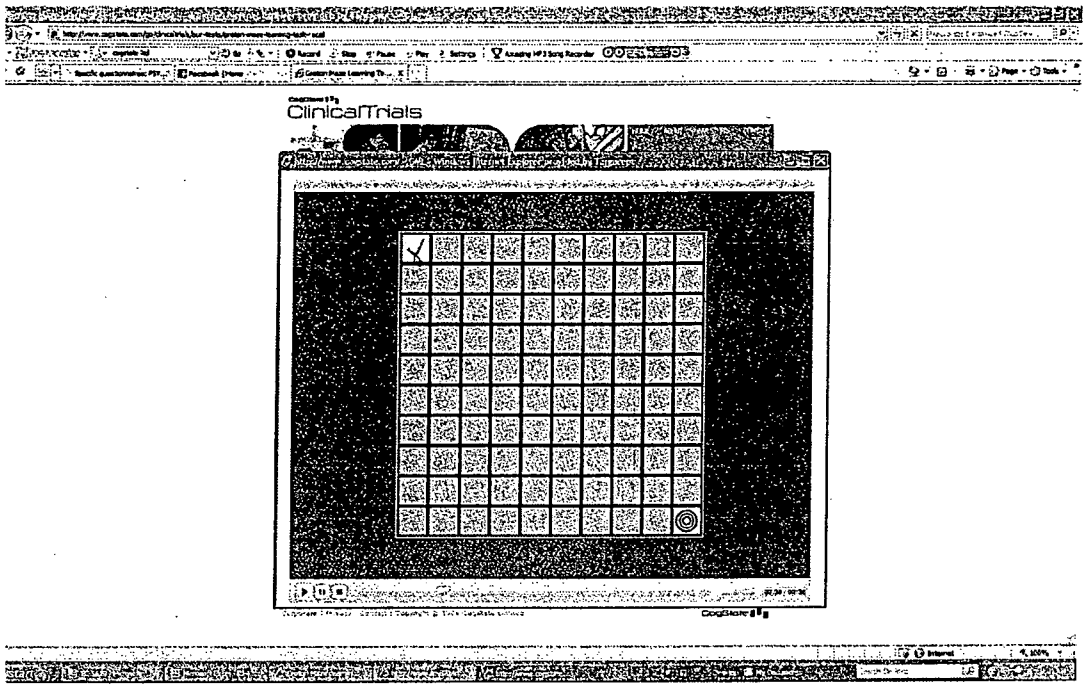
There are 20 well-matched alternate forms for this task, and these are selected in pseudo-random order to ensure that no subject will complete the same hidden path on any two different testing sessions throughout a study.

Primary Outcome measures:

Unit of measurement: Errors

Description and interpretation of scores: Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session. (Lower score = better performance)

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Appendix 3. Prohibited and Restricted Concomitant Medications

Medications affecting cognitive function:

Amphetamines
Atomoxetine
Donepezil
Duloxetine
Galantamine
Ginkgo biloba
Memantine
Methylphenidate
Modafinil
Rivastigmine
Tacrine

Drugs with narrow therapeutic range and prohibited use:

Within 10 weeks preceding Day 1 and during the study:
- Amiodarone

From Day 1 and during the Study:
- Analgesics [Alfentanil, opioids, propoxyphene (all formulations), tramadol]
- Aminoglycoside antibacterials; All (ophthalmic use permitted)
- Antiarrhythmics (eg, disopyramide, dofetilide, flecainide, ibutilide, procainamide, propafenone, quinidine, tocainide, verapamil)
- Anticoagulants [e.g., acenocoumarol, heparin (except for topical use), warfarin]
- Anticonvulsants:
  - Barbiturates (e.g., phenobarbital)
  - carboxamide derivatives (e.g., carbamazepine, oxcarbazepine)
  - fatty acid derivatives (eg,valproic acid);
  - hydantoin derivates (e.g., phenytoin)
- Antidepressives; Moclobemide
- Antihistamines; Astemizole, terfenadine
- Antipsychotics; Clozapine
- Cytostatics (e.g., methotrexate)
- Digitalis glycosides: Digitoxin, Digoxin
- Immunosuppressants (e.g., cyclosporine, sirolimus, tacrolimus)
- HIV protease inhibitors / Antiretrovirals (E.g., zidovudine)

Within 10 weeks from Day 1 and during the study:
- Amiodarone
- Hypoglycemic agents (e.g., glibenclamide, glimepiride, glipizide, insulin, metformin, tolbutamide)
- Migraine agents (e.g., Dihydroergotamine, ergotamine)
- Miscellaneous: Theophylline
- Mood Stabilizers: Lithium

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Drugs with narrow therapeutic range and restricted use:

From Day 1 and during the study:
Acetaminophen Maximal dose 0.5 g x 3/day
Acetylsalicylic acid Maximal dose: 0.5 g x 3/day

Use of these drugs is a exclusion:
Antipsychotics (e.g., chlorpromazine, chlorprothixene, flupentixol, fluphenazine, haloperidol, levomepromazine, melperone, perphenazine, pimozide, prochlorperazine, sertindole, thioridazine, ziprasidone, zuclopenthixol

Note: Patients treated with antipsychotic medications other than quetiapine or risperidone are not eligible for the study and must not be enrolled or randomized. If use of these medications is required after randomization, the patient must be withdrawn from treatment.

Drugs with prohibited use 4 weeks prior to Day 1 & during the study:

Smoking cessation therapy (e.g., Bupropion, Varenicline, or any dosage form of nicotine replacement therapy)

Drugs with restricted use 4 weeks prior to Day 1 and during the study:

Anticholinergic spasmolytics: (e.g., hyoscyamine)
Urinary spasmolytics (e.g., Darifenacin, oxybutynin, solifenacin, tolterodine)
Anti-Parkinson drugs(e.g., Benztropine, biperiden, trihexyphenidyl)
Antihistamines (eg, Alimemazine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, promethazine)
Tricyclic antidepressants (TCA) (eg, Amitriptyline, clomipramine, imipramine, lofepramine, maprotiline, nortriptyline, trimipramine)
Anti-asthmatics (eg, Ipratropium, tiotropium bromide)

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Appendix 4. Clinical Laboratory Tests

Hemoglobin A1C

Clinical Chemistry (sodium, potassium, chloride, bicarbonate, glucose, creatinine, BUN, bilirubin, liver function tests [LFTs; ALT, AST, Alkaline phosphatase, LDH])

Hematology (white blood cell count, white blood cell differentiation, red blood cell count, red blood cell MCV, red blood cell MCHC, hematocrit, hemoglobin, platelet count)

Lipid panel (total cholesterol, HDL, LDL, VLDL, triglycerides, HDL/LDL ratio)

Urinalysis (glucose, protein, bilirubin, blood, ketones, pH, specific gravity)

Urine pregnancy test

Urine drug screen

Urine cotinine level

Urine creatinine

Alpha 7 mRNA expression on peripheral blood lymphocytes

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APPENDIX 5: Calgary Depression Scale for Schizophrenia

Date of assessment |_|_|_|_|_|_|_|_| year mm
dd 24-hour clock
:

CDSS01

1. DEPRESSION

How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?

0 Absent

1 Mild Expresses some sadness or discouragement on questioning.

2 Moderate Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.

3 Severe Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

CDSS02

2. HOPELESSNESS

How do you see the future for yourself? Can you see any future? -or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0 Absent

1 Mild Has at times felt hopeless over the last 2 weeks but still has some degree of hope for the future.

2 Moderate Persistent, moderate sense of hopelessness over last 2 weeks. Can be persuaded to acknowledge possibility of things being better.

3 Severe Persisting and distressing sense of hopelessness.

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CDSS03

3. SELF DEPRECIATION

What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as other? Do you feel inferior or even worthless?

0	Absent	
1	Mild	Some inferiority; not amounting to feeling of worthlessness.
2	Moderate	Subject feels worthless, but less than 50% of the time.
3	Severe	Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

CDSS04

4. GUILTY IDEAS OF REFERENCE

Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0	Absent	
1	Mild	Subject feels blamed but not accused less that 50% of the time.
2	Moderate	Persisting sense of being blamed, and/or occasional sense of being accused.
3	Severe	Persistent sense of being accused. When challenged, acknowledges that it is not so.

CDSS05

5. PATHOLOGICAL GUILT

Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?

0	Absent	
1	Mild	Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2	Moderate	Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
3	Severe	Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

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CDSS06

6. MORNING DEPRESSION

When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

0	Absent	No depression
1	Mild	Depression present but no diurnal variation.
2	Moderate	Depression spontaneously mentioned to be worse in a.m.
3	Severe	Depression markedly worse in am, with impaired functioning which improves in pm

CDSS07

7. EARLY WAKENING

Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

0 Absent No early wakening.

1 Mild Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.

2 Moderate Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm time.

3 Severe Daily wakes 1 hour or more before normal time.

CDSS08

8. SUICIDE

Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0 Absent

1 Mild Frequent thoughts of being better off dead, or occasional thoughts of suicide.

Moderate Deliberately considered suicide with a plan, but made no attempt. 2

3 Severe Suicidal attempt apparently designed to end in death (ie: accidental discovery of inefficient means).

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CDSS09

9. OBSERVED DEPRESSION

Based on Interviewer's observations during the entire interview. The question **—Do you feel like crying?"** used at appropriate points in the interview, may elicit information useful to this observation.

0	Absent	
1	Mild	Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2	Moderate	Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3	Severe	Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that thesis present.

Total Score RATER

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Appendix 6: Subject Global Impression – Cognition scales

SGI: SUBJECT GLOBAL IMPROVEMENT: MEMORY

Compared to your condition prior to inclusion in the project has your memory changed?

Score

1. Very much improved

2. Much improved

3. Minimally improved

4. No change

5. Minimally worse

6. Much worse

7. Very much worse

SGI: SUBJECT GLOBAL IMPROVEMENT: ATTENTION

Compared to your condition prior to inclusion in the project has your attention (ability to focus) changed?

Score

1. Very much improved

2. Much improved

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3. Minimally improved

4. No change

5. Minimally worse

6. Much worse

7. Very much worse

SGI: SUBJECT GLOBAL IMPROVEMENT: SPEED OF THINKING

Compared to your condition prior to inclusion in the project has your speed of thinking changed?

Score

1. Very much improved

2. Much improved

3. Minimally improved

4. No change

5. Minimally worse

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6. Much worse

7. Very much worse

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APPENDIX 7. CLINICAL GLOBAL IMPRESSION SCALE

(a) Clinical global Impression – Global Improvement (CGI-I)

1: very much improved
2: much improved
3: minimally improved
4: no change
5: minimally worse
6: much worse
7: very much worse

Rate total improvement, whether or not it is entirely due to drug treatment. Consider time when subject entered the study and present observation.

- ☐ Not assessed
- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

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(b) Clinical Global Impression - Severity of Illness (CGI-S)

Subject No.	Subj. Initials	Visit Week	Visit Date	Targacept, Inc.
_____	_____		_____ dd MMM yyyy	TC-xxxx-yyy-CRD-zzz

CLINICAL GLOBAL IMPRESSION - SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- ☐ Not assessed
- ☐ Normal, not at all ill
- ☐ Borderline mentally ill
- ☐ Mildly ill
- ☐ Moderately ill
- ☐ Markedly ill
- ☐ Severely ill
- ☐ Among the most extremely ill patients

1: normal, not at all ill
2: borderline mentally ill
3: mildly ill
4: moderately ill
5: markedly ill
6: severely ill
7: among the most extremely ill patients

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Appendix 8: Positive and Negative Symptom Scale in Schizophrenia (PANSS)

The PANSS consists of: an Interviewer Questionnaire, containing items related to Positive, Negative, and General Psychopathological symptoms; and a Structured Clinical Interview, designed to help gather information from the informants.

These materials are copyrighted, and so they may not be included in clinical trial protocols or other documents, even with permitted use of the PANSS during clinical trials.

For this reason, the PANSS will be distributed separately as a source document.

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Appendix 9: Scale for Assessment of Negative Symptoms (SANS)

AFFECTIVE FLATTENING OR BLUNTING

Affective flattening or blunting manifests itself as a characteristic impoverishment of emotional expression, reactivity, and feeling. Affective flattening can be evaluated by observation of the subject's behavior and responsiveness during a routine interview. The rating of some items may be affected by drugs, since the Parkinsonian side-effect of phenothiazines may lead to mask-like facies and diminished associated movements. Other aspects of affect, such as responsivity or appropriateness, will not be affected, however.

Unchanging Facial Expression The subject's face appears wooden, mechanical, frozen. It does not change expression, or changes less than normally expected, as the emotional content of discourse changes. Since phenothiazines may partially mimic this effect, the interviewer should be careful to note whether or not the subject is on medication, but should not try to "correct" the rating accordingly.	Not at all: Subject is normal or labile	0	SS11
	Questionable decrease	1	
	Mild: Occasionally the subject's expression is not as full as expected	2	
	Moderate: Subject's expressions are dulled overall, but not absent	3	
	Marked: Subject's face has a flat "set" look, but flickers of affect arise occasionally	4	
	Severe: Subject's face looks 'wooden" and changes little, if at all throughout the interview	5	
Decreased Spontaneous Movements The subject sits quietly throughout the interview and shows few or no spontaneous movements. He does not shift position, move his legs, move his hands, etc., or does so less than normally expected.	Not at all: Subject moves normally or is overactive	0	SS12
	Questionable decrease	1	
	Mild: Some decrease in spontaneous movements	2	
	Moderate: Subject moves three or four times during the interview	3	
	Marked: Subject moves once or twice during the interview	4	
	Severe: Subject sits immobile throughout the interview	5	

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Paucity of Expressive Gestures The subject does not use his body as an aid in expressing his ideas, through such means as hand gestures, sitting forward in his chair when intent on a subject, leaning back when relaxed, etc. This may occur in addition to decreased spontaneous movements.	Not at all: Subject uses expressive gestures normally or excessively	0	SS13
	Questionable decrease	1	
	Mild: Some decrease in expressive gestures	2	
	Moderate: Subject uses body as an aid in expression at least three or four times	3	
	Marked: Subject uses body as an aid in expression only once or twice	4	
	Severe: Subject never uses body as an aid in expression	5	
Poor Eye Contact The subject avoids looking at others or using his eyes as an aid in expression. He appears to be staring into space even when he is talking.	Not at all: Good eye contact and expression	0	SS14
	Questionable decrease	1	
	Mild: Some decrease in eye contact and eye expression	2	
	Moderate: Subject's eye contact is decreased by at least half of normal	3	
	Marked: Subject's eye contact is very infrequent	4	
	Severe: Subject almost never looks at interviewer	5	
Affective Nonresponsivity Failure to smile or laugh when prompted may be tested by smiling or joking in a way which would usually elicit a smile from a normal individual. The examiner may also ask, "Have you forgotten how to smile?" while smiling himself.	Not at all	0	SS15
	Questionable decrease	1	
	Mild: Slight but definite lack in responsivity	2	
	Moderate: Subject occasionally seems to miss the cues to respond	3	
	Marked: Subject seems to miss the cues to respond most of the time	4	
	Severe: Subject is essentially unresponsive, even on prompting	5	

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Lack of Vocal Inflections While speaking the subject fails to show normal vocal emphasis patterns. Speech has a monotonic quality, and important words are not emphasized through changes in pitch or volume. Subject also may fail to change volume with changes of subject so that he does not drop his voice when discussing private topics nor raise it as he discusses things which are exciting or for which louder speech might be appropriate.	Not all all: Normal vocal inflections	0	SS16
	Questionable decrease	1	
	Mild: Slight decrease in vocal inflections	2	
	Moderate: Interviewer notices several instances of flattened vocal inflections	3	
	Marked: Obvious decrease in vocal inflections	4	
	Severe: Subject's speech is a continuous monotone	5	
Global Rating of Affective Flattening The global rating should focus on overall severity of affective flattening or blunting. Special emphasis should be given to such core features as unresponsiveness, inappropriateness, and an overall decrease in emotional intensity.	No flattening: Normal affect	0	SS17
	Questionable affective flattening	1	
	Mild affective flattening	2	
	Moderate affective flattening	3	
	Marked affective flattening	4	
	Severe affective flattening	5	
Inappropriate Affect Affect expressed is inappropriate or incongruous, not simply flat or blunted. Most typically, this manifestation of affective disturbance takes the form of smiling or assuming a silly facial expression while talking about a serious or sad subject. (Occasionally subjects may smile or laugh when talking about a serious subject which they find uncomfortable or embarrassing. Although their smiling may seem inappropriate, it is due to anxiety and therefore should not be rated as inappropriate affect.) Do not rate affective flattening or blunting as inappropriate.	Not at all: Affect is not inappropriate	0	SS18
	Questionable	1	
	Mild: At least one instance of inappropriate smiling or other inappropriate affect	2	
	Moderate: Subject exhibits two to four instances of inappropriate affect	3	
	Marked: Subject exhibits five to ten instances of inappropriate affect	4	
	Severe: Subject's affect is inappropriate most of the time	5	

TARGACEPT

ALOGIA

Alogia is a general term coined to refer to the impoverished thinking and cognition that often occur in subjects with schizophrenia (Greek a = no, none; logos = mind, thought). Subjects with alogia have thinking processes that seem empty, turgid, or slow. Since thinking cannot be observed directly, it is inferred from the subject's speech. The two major manifestations of alogia are nonfluent empty speech (poverty of speech) and fluent empty speech (poverty of content of speech). Blocking and increased latency or response may also reflect alogia.

Poverty of Speech

Restriction in the amount of spontaneous speech, so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with this speech pattern, the interviewer may find himself frequently prompting the subject in order to encourage elaboration of replies. To elicit this finding, the examiner must allow the subject adequate time to answer and to elaborate his answer.

No poverty of speech: A substantial and appropriate number of replies to questions include additional information	0	SS19
Questionable poverty of speech	1	
Mild: Occasional replies do not include elaborated information even though this is appropriate	2	
Moderate: Some replies do not include appropriately elaborated information, and some replies are monosyllabic or very brief--("Yes." "No." "Maybe." "I don't know." "Last week.")	3	
Marked: Answers are rarely more than a sentence or a few words in length	4	
Severe: Subject says almost nothing and occasionally fails to answer questions	5	

TARGACEPT

Poverty of Content of Speech Although replies are long enough so that speech is adequate in amount, it conveys little information. Language tends to be vague, often over-abstract or over-concrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the subject has spoken at some length but has not given adequate information to answer the question. Alternatively, the subject may provide enough information, but require many words to do so, so that a lengthy reply can be summarized in a sentence or two. Sometimes the interviewer may characterize the speech as "empty philosophizing." Exclusions: This finding differs from circumstantiality in that the circumstantial subject tends to provide a wealth of detail. Example: Interviewer: "Why is it, do you think, that people believe in God?" Subject: "Well, first of all because he uh, he are the person that is their personal savior. He walks with me and talks with me. And uh, the understanding that I have, um, a lot of peoples, they don't really, uh, know they own personal self. Because, uh, they ain't, they all, just don't know they personal self. They don't, know that he uh, seemed like to me, a lot of 'em don't understand that he walks and talks with them."	No poverty of content	0	SS20
	Questionable	1	
	Mild: Occasional replies are too vague to be comprehensible or can be markedly condensed	2	
	Moderate: Frequent replies which are vague or can be markedly condensed to make up at least a quarter of the interview	3	
	Marked: At least half of the subject's speech is composed of vague or incomprehensible replies	4	
	Severe: Nearly all the speech is vague, incomprehensible, or can be markedly condensed	5	
Blocking Interruption of a train of speech before a thought or idea has been completed. After a period of silence which may last from a few seconds to minutes, the person indicates that she/he cannot recall what he had been saying or meant to say. Blocking should only be judged to be present if a person voluntarily describes losing his thought or if, upon questioning by the interviewer, the person indicates that that was the reason for pausing.	No blocking	0	SS21
	Questionable	1	
	Mild: A single instance noted during a forty-five minute period	2	
	Moderate: Occurs twice during forty-five minutes	3	
	Marked: Occurs three or four times during forty-five minutes	4	
	Severe: Occurs more than four times in forty-five minutes	5	

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Increased Latency of Response The subject takes a longer time to reply to questions than is usually considered normal. He may seem "distant" and sometimes the examiner may wonder if he has even heard the question. Prompting usually indicates that the subject is aware of the question, but has been having difficulty in formulating his thoughts in order to make an appropriate reply.	Not at all	0	SS22
	Questionable	1	
	Mild: Occasional brief pauses before replying	2	
	Moderate: Often pauses several seconds before replying	3	
	Marked: Usually pauses at least ten to fifteen seconds before replying	4	
	Severe: Long pauses prior to nearly all replies.	5	
Global Rating of Alogia Since the core features of alogia are poverty of speech and poverty of content of speech, the global rating should place particular emphasis on them.	No alogia	0	SS23
	Questionable	1	
	Mild: Mild but definite impoverishment in thinking	2	
	Moderate: Significant evidence for impoverished thinking	3	
	Marked: Subject's thinking seems impoverished much of the time	4	
	Severe: Subject's thinking seems impoverished nearly all of the time	5	

AVOLITION-APATHY

Avolition manifests itself as a characteristic lack of energy, drive, and interest. Subjects are unable to mobilize themselves to initiate or persist in completing many different kinds of tasks. Unlike the diminished energy or interest of depression, the avolitional symptom complex in schizophrenia is usually not accompanied by saddened or depressed affect. The avolitional symptom complex often leads to severe social and economic impairment.

Grooming and Hygiene The subject displays less attention to grooming and hygiene than normal. Clothing may appear sloppy, outdated, or soiled. The subject may bathe infrequently and not care for hair, nails, or teeth--leading to such manifestations as greasy or uncombed hair, dirty hands, body odor, or unclean teeth and bad breath. Overall, the appearance is dilapidated and disheveled. In extreme cases, the subject may even have poor toilet habits. *How often do you bathe or shower?* *Do you change your clothes every day?* *How often do you do laundry?*	No evidence of poor grooming and hygiene	0	SS24
	Questionable	1	
	Mild: Some slight but definite indication of inattention to appearance, i.e., messy hair or disheveled clothes	2	
	Moderate: Appearance is somewhat disheveled, i.e., greasy hair, dirty clothes	3	
	Marked: Subject's attempts to keep up grooming or hygiene are minimal	4	
	Severe: Subject's clothes, body and environment are dirty and smelly	5	
Impersistence at Work or School The subject has had difficulty in seeking or maintaining	No evidence of impersistence at work		

TARGACEPT

employment (or schoolwork) as appropriate for his or her age and sex. If a student, he/she does not do homework and may even fail to attend class. Grades will tend to reflect this. If a college student, there may be a pattern of registering for courses, but having to drop several or all of them before the semester is completed. If of working age, the subject may have found it difficult to work at a job because of inability to persist in completing tasks and apparent irresponsibility. He may go to work irregularly, wander away early, complete them in a disorganized manner. He may simply sit around the house and not seek any employment or seek it only in an infrequent and desultory manner. If a housewife or retired person, the subject may fail to complete chores, such as shopping or cleaning, or complete them in an apparently careless and half-hearted way.	or school	0	SS25
	Questionable	1	
	Mild: Slight indications of impersistence, i.e., missing a couple days of school or work	2	
	Moderate: Subject often has poor performance at work or school	3	
	Marked: Subject has much difficulty maintaining even a below normal level of work or school	4	
	Severe: Subject consistently fails to maintain a record at work or school	5	
Have you been having any problems at (work, school)?			
Do you ever start some project and just never get around to finishing it?			
Physical Anergia The subject tends to be physically inert. He may sit in a chair for hours at a time and not initiate any spontaneous activity. If encouraged to become involved in an activity, he may participate only briefly and then wander away or disengage himself and return to sitting alone. He may spend large amounts of time in some relatively mindless and physically inactive task such as watching TV or playing solitaire. His family may report that he spends most of his time at home "doing nothing except sitting around". Either at home or in an inpatient setting he may spend much of his time sitting in his room.	No Evidence of Physical Anergia	0	SS28
	Questionable	1	
	Mild Anergia	2	
	Moderate: Subject lies in bed or sits immobile at least a quarter of normal waking hours	3	
	Marked: Subject lies in bed or sits immobile at least half of normal waking hours	4	
	Severe: Subject lies in bed or sits immobile for most of the day	5	
Are there times when you lie or sit around most of the day?			
(Does this ever last longer than one day?)			
Global Rating of Avolition - Apathy The global rating should reflect the overall severity of the avolition symptoms, given expectational norms for the subject's age and social status or origin. In making the global rating, strong weight may be given to only one or two prominent symptoms if they are particularly striking.	No Avolition	0	SS27
	Questionable	1	
	Mild, But Definitely Present	2	
	Moderate Avolition	3	
	Marked Avolition	4	
	Severe Avolition	5	

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ANHEDONIA-ASOCIALITY

This symptom complex encompasses the schizophrenic subject's difficulties in experiencing interest or pleasure. It may express itself as a loss of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds.

Recreational Interests and Activities The subject may have few or no interests, activities, or hobbies. Although this symptom may begin insidiously or slowly, there will usually be some obvious decline from an earlier level of interest and activity. Subjects with relatively milder loss of interest will engage in some activities which are passive or non-demanding, such as watching TV, or will show only occasional or sporadic interest. Subjects with the most extreme loss will appear to have a complete and intractible inability to become involved in or enjoy activities. The rating in this area should take both the quality and quantity of recreational interests into account. *Have you felt interested in the things you usually enjoy?* *(Have they been as fun as usual?)* *Have you been watching TV or listening to the radio?*	No Inability to Enjoy Recreational Interests or Activities	0 SS28
	Questionable	1
	Mild Inability to Enjoy Recreational Activities	2
	Moderate: Subject often is not "up" for recreational activities	3
	Marked: Subject has little interest in and derives only mild pleasure from recreational activities	4
	Severe: Subject has no interest in and derives no pleasure from recreational activities	5
Sexual Interest and Activity The subject may show a decrement in sexual interest and activity, as judged by what would be normal for the subject's age and marital status. Individuals who are married may manifest disinterest in sex or may engage in intercourse only at the partner's request. In extreme cases, the subject may not engage in any sex at all. Single subjects may go for long periods of time without sexual involvement and make no effort to satisfy this drive. Whether married or single, they may report that they subjectively feel only minimal sex drive or that they take little enjoyment in sexual intercourse or in masturbatory activity even when they engage in it. *Have you noticed any changes in your sex drive?*	No Inability to Enjoy Sexual Activities	0 SS29
	Questionable Decrement in Sexual Interest and Activity	1
	Mild Decrement in Sexual Interest and Activity	2
	Moderate: Subject occasionally has noticed decreased interests in and/or enjoyment from sexual activities	3
	Marked: Subject has little interest in and/or derives little pleasure from sexual activities	4
	Severe: Subject has no interest in and/or derives no pleasure from sexual activities	5

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Ability to Feel Intimacy and Closeness The subject may display an inability to form close and intimate relationships of a type appropriate for his age, sex, and family status. In the case of a younger person, this area should be rated in terms of relationships with the opposite sex and with parents and siblings. In the case of an older person who is married, the relationship with spouse and with children should be evaluated, while older unmarried individuals should be judged in terms of relationships with the opposite sex and any family members who live nearby. Subjects may display few or no feelings of affection to available family members. Or they may have arranged their lives so that they are completely isolated from any intimate relationships, living alone and making no effort to initiate contacts with family or members of the opposite sex. *Have you been having any problems with your (family, spouse)?* *How would you feel about visiting with your (family, parents, spouse, etc.)?*	No Inability to Feel Intimacy and Closeness	0 ss30
	Questionable Inability	1
	Mild, But Definite Inability to Feel Intimacy and Closeness	2
	Moderate: Subject appears to enjoy family or significant others but does not appear to "look forward" to visits	3
	Marked: Subject appears neutral toward visits from family or significant others. Brightens only mildly	4
	Severe: Subject prefers no contact with or is hostile toward family or significant others	5
Relationships with Friends and Peers Subjects may also be relatively restricted in their relationships with friends and peers of either sex. They may have few or no friends, make little or no effort to develop such relationships, and choose to spend all or most of their time alone. *Have you been spending much time with friends?* *Do you enjoy spending time alone, or would you rather have more friends?*	No Inability to Form Close Friendships	0 ss31
	Questionable Inability to Form Friendships	1
	Mild, But Definite Inability to Form Friendships	2
	Moderate: Subject able to interact, but sees friends/acquaintances only two to three times per month	3
	Marked: Subject has difficulty forming and/or keeping friendships. Sees friends/acquaintances only one to two times per month	4
	Severe: Subject has no friends and no interest in developing any social ties	5
Global Rating of Anhedonia-Asociality The global rating should reflect the overall severity of the anhedonia-asociality complex, taking into account the norms appropriate for the subject's age, sex, and family status.	No Evidence of Anhedonia-Asociality	0 ss32
	Questionable Evidence of Anhedonia-Asociality	1
	Mild, But Definite Evidence of Anhedonia-Asociality	2
	Moderate Evidence of Anhedonia-Asociality	3
	Marked Evidence of Anhedonia-Asociality	4
	Severe Evidence of Anhedonia-Asociality	5

TARGACEPT

Appendix 10. Columbia Suicide Severity Rating Scale
A. Columbia Suicide Severity Rating Scale: Baseline Visit

Columbia-Suicide Severity Rating Scale, Baseline CSSRSB

SUICIDAL IDEATION	Lifetime: Time He/She Felt Most Suicidal
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If Yes, describe: CSI1DESC	Yes ☐1 No ☐0 CSIDEAT1
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If Yes, describe: CSI2DESC	Yes ☐1 No ☐0 CSIDEAT2
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If Yes, describe: CSI3DESC	Yes ☐1 No ☐0 CSIDEAT3
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and Subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If Yes, describe: CSI4DESC	Yes ☐1 No ☐0 CSIDEAT4
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and Subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If Yes, describe: CSI5DESC	Yes ☐1 No ☐0 CSIDEAT5

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Columbia-Suicide Severity Rating Scale, Baseline, continued CSSRSB

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. *Most Severe Ideation:* CSMSI _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	CSMSIFRQ _____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	CSMSIDUR _____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	CSMSICTL _____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	CSMSIDTR _____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	CSMSIREA _____

TARGACEPT

Columbia-Suicide Severity Rating Scale, Baseline, continued CSSRSB

SUICIDAL BEHAVIOR (Check all that apply; so long as these are separate events, must ask about all types)	Lifetime
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you ____?*** ***Were you trying to end your life when you ____?*** ***Or did you think it was possible you could have died from ____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: CSACTDES **Has Subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐1 No ☐0 CSACTATT Total # of attempts ____ CSACTN CSNSSI Yes ☐1 No ☐0
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe: CSINTDES	Yes ☐1 No ☐0 CSINTATT Total # of interrupted CSINTN ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe: CSABTDES	Yes ☐1 No ☐0 CSABTATT Total # of aborted CSABTN ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe: CSPRPDES	Yes ☐1 No ☐0 CSPREP
Suicidal Behavior: Suicidal behavior was present during the assessment period? CSSUICID	Yes ☐1 No ☐0

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Columbia-Suicide Severity Rating Scale, Baseline, continued CSSRSB

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* CSMRAAL	*Enter Code* CSMLAAL	*Enter Code* CSIFAAL
Potential Lethality: Only Answer If Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* CSMRAPL	*Enter Code* CSMLAPL	*Enter Code* CSIFAPL

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B. Columbia Suicide Severity Rating Scale - Since Last Visit

This scale is nearly identical to the scale for the baseline visit, and will not be reproduced here.

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Appendix 11: MINI International Neuropsychiatric Interview

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

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M.I.N.I. 5.0.0 (July 1, 2003)

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

Patient Name:		*Patient Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Recurrent	☐ ☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
	MDE WITH MELANCHOLIC FEATURES Optional	Current (2 weeks)	☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1
C	SUICIDALITY	Current (Past Month) Risk: ☐ Low ☐ Medium ☐ High	☐		
D	MANIC EPISODE	Current Past	☐ ☐	296.00-296.06	F30.x-F31.9
	HYPOMANIC EPISODE	Current Past	☐ ☐	296.80-296.89	F31.8-F31.9/F34.0
E	PANIC DISORDER	Current (Past Month) Lifetime	☐ ☐	300.01/300.21	F40.01-F41.0
F	AGORAPHOBIA	Current	☐	300.22	F40.00
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8
I	POSTTRAUMATIC STRESS DISORDER Optional	Current (Past Month)	☐	309.81	F43.1
J	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months	☐ ☐	303.9 305.00	F10.2x F10.1
K	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months	☐ ☐	304.00-.90/305.20-.90 304.00-.90/305.20-.90	F11.1-F19.1 F11.1-F19.1
L	PSYCHOTIC DISORDERS	Lifetime Current	☐ ☐	295.10-295.90/297.1/ 297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	☐	296.24	F32.3/F33.3
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0
O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➨) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « NO » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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M.I.N.I. 5.0.0 (July 1, 2003)

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

A. MAJOR DEPRESSIVE EPISODE

(➨ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS A1 OR A2 CODED YES? ➨	NO	YES
A3	**Over the past two weeks, when you felt depressed or uninterested:**		
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE YES.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES?

NO	YES *
MAJOR DEPRESSIVE EPISODE, CURRENT	

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:

A4	a During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? ➨	NO	YES
	b Did you ever have an interval of at least 2 months without any depression and any loss of interest between 2 episodes of depression?		

NO	YES
MAJOR DEPRESSIVE EPISODE, RECURRENT	

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? IF NO: When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER A5a OR A5b CODED YES?	➡ NO	YES
A6		**Over the past two week period, when you felt depressed and uninterested:**		
	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS A3c CODED YES (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS A3a CODED YES FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE 3 OR MORE A6 ANSWERS CODED YES?

NO	YES
Major Depressive Episode with *Melancholic Features Current*	

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

B. DYSTHYMIA

(➨ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	➨ NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	➨ YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE 2 OR MORE B3 ANSWERS CODED YES?	➨ NO	YES
B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	➨ NO	YES
	IS B4 CODED YES?	NO	YES

DYSTHYMIA CURRENT

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

C. SUICIDALITY

				Points
	In the past month did you:			
C1	Think that you would be better off dead or wish you were dead?	NO	YES	1
C2	Want to harm yourself?	NO	YES	2
C3	Think about suicide?	NO	YES	6
C4	Have a suicide plan?	NO	YES	10
C5	Attempt suicide?	NO	YES	10
	In your lifetime:			
C6	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST 1 OF THE ABOVE CODED YES?

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C6) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS:

NO	YES

SUICIDE RISK CURRENT

1-5 points	Low	☐
6-9 points	Moderate	☐
≥ 10 points	High	☐

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

D. (HYPO) MANIC EPISODE

(➨ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you ever had a period of time when you were feeling 'up' or 'high' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH', CLARIFY AS FOLLOWS: By 'up' or 'high' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF YES:	NO	YES
	b	Are you currently feeling 'up' or 'high' or full of energy?	NO	YES
D2	a	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF YES:	NO	YES
	b	Are you currently feeling persistently irritable?	NO ➨	YES
		IS D1a OR D2a CODED YES?	NO	YES

D3		IF D1b OR D2b = YES: EXPLORE ONLY CURRENT EPISODE, OTHERWISE IF D1b AND D2b = NO: EXPLORE THE MOST SYMPTOMATIC PAST EPISODE **During the times when you felt high, full of energy, or irritable did you:**		
	a	Feel that you could do things others couldn't do, or that you were an especially important person?	NO	YES
	b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES
	c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES
	d	Have racing thoughts?	NO	YES
	e	Become easily distracted so that any little interruption could distract you?	NO	YES
	f	Become so active or physically restless that others were worried about you?	NO	YES
	g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES
		ARE 3 OR MORE D3 ANSWERS CODED YES (OR 4 OR MORE IF D1a IS NO (IN RATING PAST EPISODE) OR IF D1b IS NO (IN RATING CURRENT EPISODE))?	NO ➨	YES

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

D4 Did these symptoms last at least a week and cause significant problems at home, at work, socially, or at school, or were you hospitalized for these problems?

NO YES

THE EPISODE EXPLORED WAS A: ☐ HYPOMANIC EPISODE ☐ MANIC EPISODE

IS D4 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	YES
HYPOMANIC EPISODE	
CURRENT	☐
PAST	☐

IS D4 CODED YES?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	YES
MANIC EPISODE	
CURRENT	☐
PAST	☐

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

E. PANIC DISORDER

(➡ MEANS: CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells peak within 10 minutes?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent fear of having another attack, or worries about the consequences of the attack?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH E3, AND 4 OR MORE E4 ANSWERS, CODED YES?	NO	YES *PANIC DISORDER LIFETIME*
		IF YES TO E5, SKIP TO E7.		
E6		IF E5 = NO, ARE ANY E4 ANSWERS CODED YES?	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*
		THEN SKIP TO F1.		
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent fear of having another attack?	NO	YES *PANIC DISORDER CURRENT*

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF F1 = NO, CIRCLE NO IN F2.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS F2 (CURRENT AGORAPHOBIA) CODED NO

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO YES

PANIC DISORDER without Agoraphobia CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO YES

PANIC DISORDER with Agoraphobia CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E5 (PANIC DISORDER LIFETIME) CODED NO?

NO YES

AGORAPHOBIA, CURRENT without history of Panic Disorder

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➨ NO	YES
G2	Is this fear excessive or unreasonable?	➨ NO	YES
G3	Do you fear these situations so much that you avoid them or suffer through them?	➨ NO	YES
G4	Does this fear disrupt your normal work or social functioning or cause you significant distress?		

NO	YES
SOCIAL PHOBIA (Social Anxiety Disorder) CURRENT	

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

H. OBSESSIVE-COMPULSIVE DISORDER

(➨ ABOVE A NO MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ➨ to H4
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ➨ to H4
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES obsessions
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES compulsions
	IS H3 OR H4 CODED YES?	➨ NO YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➨ NO YES
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, occupational functioning, usual social activities, or relationships, or did they take more than one hour a day?	NO YES *O.C.D. CURRENT*

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➨ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➨ NO	YES
I2	Did you respond with intense fear, helplessness or horror?	➨ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➨ NO	YES

I4	**In the past month:**		
a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	ARE 3 OR MORE I4 ANSWERS CODED YES?	➨ NO	YES
I5	**In the past month:**		
a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	ARE 2 OR MORE I5 ANSWERS CODED YES?	➨ NO	YES

I6	During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?	NO YES *POSTTRAUMATIC STRESS DISORDER CURRENT*

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

		➡ NO	YES
J1	In the past 12 months, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?		

J2 **In the past 12 months:**

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF YES TO EITHER, CODE YES.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE 3 OR MORE J2 ANSWERS CODED YES?

NO YES*

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN ABUSE BOX AND MOVE TO NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE

ALCOHOL DEPENDENCE
CURRENT

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE 1 OR MORE J3 ANSWERS CODED YES?

NO N/A YES

ALCOHOL ABUSE
CURRENT

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➨ NO	YES
K1	a	In the past 12 months, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?		

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel Dust", "peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, or MDMA.

Inhalants: "glue", ethyl chloride, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown.

Miscellaneous: steroids, nonprescription sleep or diet pills, GHB. Any others?

SPECIFY MOST USED DRUG(S): _____

	CHECK ONE BOX
ONLY ONE DRUG / DRUG CLASS HAS BEEN USED	☐
ONLY THE MOST USED DRUG CLASS IS INVESTIGATED.	☐
EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED)	☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:_____

			NO	YES
K2		**Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**		
	a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? IF YES TO EITHER, CODE YES.	NO	YES
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO YES
	g	Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems?	NO YES

ARE 3 OR MORE K2 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO ➨ YES

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3	a	Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO YES
	b	Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)?	NO YES
	c	Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct?	NO YES
	d	Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people?	NO YES

ARE 1 OR MORE K3 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO YES

SUBSTANCE ABUSE
CURRENT

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Appendix 11. MINI International Neuropsychiatric Interview, continued

L. PSYCHOTIC DISORDERS

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

					BIZARRE
		Now I am going to ask you about unusual experiences that some people have.			
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	IF YES: do you currently believe these things?	NO	YES	YES →L6
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	IF YES: do you currently believe these things?	NO	YES	YES →L6
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	IF YES: do you currently believe these things?	NO	YES	YES →L6
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	IF YES: do you currently believe these things?	NO	YES	YES →L6
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO	YES	YES
	b	IF YES: do they currently consider your beliefs strange?	NO	YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:	NO	YES	
		IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?			YES
	b	IF YES: have you heard these things in the past month?	NO	YES	YES →L8b

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Appendix 11. MINI International Neuropsychiatric Interview, continued

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b IF YES: have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 ARE 1 OR MORE « b » QUESTIONS CODED YES BIZARRE?

OR

ARE 2 OR MORE « b » QUESTIONS CODED YES (RATHER THAN YES BIZARRE)?

NO YES

PSYCHOTIC DISORDER CURRENT

L12 ARE 1 OR MORE « a » QUESTIONS CODED YES BIZARRE?

OR

ARE 2 OR MORE « a » QUESTIONS CODED YES (RATHER THAN YES BIZARRE)?

CHECK THAT THE TWO SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

OR IS L11 CODED YES?

NO YES

PSYCHOTIC DISORDER LIFETIME

L13 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED YES AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC EPISODE, (CURRENT OR PAST) CODED YES? NO YES

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).
Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM L1b TO L7b) restricted exclusively to times when you were feeling depressed/high/irritable?

NO YES

MOOD DISORDER WITH PSYCHOTIC FEATURES CURRENT

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

M. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1	a	How tall are you?	☐☐ ft ☐☐ in. ☐☐☐ cm.	
	b	What was your lowest weight in the past 3 months?	☐☐☐ lbs. ☐☐☐ kgs.	
	c	IS PATIENT'S WEIGHT LOWER THAN THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO	YES

In the past 3 months:

M2		In spite of this low weight, have you tried not to gain weight?	➡ NO	YES
M3		Have you feared gaining weight or becoming fat, even though you were underweight?	➡ NO	YES
M4	a	Have you considered yourself fat or that part of your body was too fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
M5		ARE 1 OR MORE ITEMS FROM M4 CODED YES?	➡ NO	YES
M6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO	YES

FOR WOMEN: ARE M5 AND M6 CODED YES?

FOR MEN: IS M5 CODED YES?

NO	YES
ANOREXIA NERVOSA CURRENT	

TABLE HEIGHT / WEIGHT THRESHOLD (height-without shoes; weight-without clothing)

Female Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	84	85	86	87	89	92	94	97	99	102	104	107	110	112
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Male Height/Weight														
ft/in	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10	5'11	6'0	6'1	6'2	6'3
lbs.	105	106	108	110	111	113	115	116	118	120	122	125	127	130	133
cm	155	156	160	163	165	168	170	173	175	178	180	183	185	188	191
kgs	47	48	49	50	51	51	52	53	54	55	56	57	58	59	61

The weight thresholds above are calculated as a 15% reduction below the normal range for the patient's height and gender as required by DSM-IV. This table reflects weights that are 15% lower than the low end of the normal distribution range in the Metropolitan Life Insurance Table of Weights.

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Appendix 11. MINI International Neuropsychiatric Interview, continued

N. BULIMIA NERVOSA

(➨ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➨ NO YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	➨ NO YES
N3	During these binges, did you feel that your eating was out of control?	➨ NO YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➨ NO YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	➨ NO YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO YES ↓ Skip to N8
N7	Do these binges occur only when you are under (_____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO YES
N8	IS N5 CODED YES AND N7 CODED NO OR SKIPPED?	NO YES *BULIMIA NERVOSA* CURRENT
	IS N7 CODED YES?	NO YES *ANOREXIA NERVOSA* *Binge Eating/Purging Type* CURRENT

TARGACEPT

Appendix 11. MINI International Neuropsychiatric Interview, continued

O. GENERALIZED ANXIETY DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO ➨	YES
	b	Are these worries present most days?	NO ➨	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES ➨
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO ➨	YES
O3		FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE 3 OR MORE O3 ANSWERS CODED YES?

NO	YES
GENERALIZED ANXIETY DISORDER CURRENT	

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Appendix 11. MINI International Neuropsychiatric Interview, continued

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➨ MEANS: GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1	**Before you were 15 years old, did you:**		
a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	ARE 2 OR MORE P1 ANSWERS CODED YES?	NO	YES
	DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.		
P2	**Since you were 15 years old, have you:**		
a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES
	ARE 3 OR MORE P2 QUESTIONS CODED YES?	NO	YES

ANTISOCIAL PERSONALITY DISORDER LIFETIME

THIS CONCLUDES THE INTERVIEW

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Appendix 11. MINI International Neuropsychiatric Interview, continued

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Translations	M.I.N.I. 4.4 or earlier versions	M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Croatian		In preparation
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis
Gujarati		M. Patel, B. Patel
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima
Korean		In preparation, Anxiety Disorder Association of Korea
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky
Serbian	I. Timotijevic	I. Timotijevic
Setswana		K. Ketlogetswe
Slovenian	M. Kocmur	M. Kocmur
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, M. Waern, A. Brimse, M. Humble, H. Agren
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner
Urdu		A. Taj, S. Gambhir

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Appendix 12: Abnormal Involuntary Movement Scale (AIMS)

Examination Procedure

Either before or after completing the examination procedure, observe the patient unobtrusively at rest (e.g., in the waiting room).
The chair to be used in this examination should be a hard, firm one without arms.

Ask the patient whether there is anything in his or her mouth (such as gum or candy) and, if so, to remove it.

Ask about the *current* condition of the patient's teeth. Ask if he or she wears dentures. Ask whether teeth or dentures bother the patient *now*.

Ask whether the patient notices any movements in his or her mouth, face, hands, or feet. If yes, ask the patient to describe them and to indicate to what extent they *currently* bother the patient or interfere with activities.

Have the patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at the entire body for movements while the patient is in this position.)

Ask the patient to sit with hands hanging unsupported -- if male, between his legs, if female and wearing a dress, hanging over her knees. (Observe hands and other body areas).

Ask the patient to open his or her mouth. (Observe the tongue at rest within the mouth.) Do this twice.

Ask the patient to protrude his or her tongue. (Observe abnormalities of tongue movement.) Do this twice.

Ask the patient to tap his or her thumb with each finger as rapidly as possible for 10 to 15 seconds, first with right hand, then with left hand. (Observe facial and leg movements.)

Flex and extend the patient's left and right arms, one at a time.

Ask the patient to stand up. (Observe the patient in profile. Observe all body areas again, hips included.)

Ask the patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth.)

Have the patient walk a few paces, turn, and walk back to the chair. (Observe hands and gait.) Do this twice.

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Scoring Procedure

Complete the examination procedure before making ratings.
For the movement ratings (the first three categories below), rate the highest severity observed.
0 = none, 1 = minimal (may be extreme normal), 2 = mild, 3 = moderate, 4 = severe.
According to the original AIMS instructions, one point is subtracted if movements are seen **only on activation**, but not all investigators follow that convention.

Facial and Oral Movements	
1. Muscles of facial expression,	0 1
e.g., movements of forehead, eyebrows, periorbital area, cheeks. Include frowning, blinking, grimacing of upper face.	2 3 4
2. Lips and perioral area,	0 1
e.g., puckering, pouting, smacking.	2 3 4
3. Jaw,	0 1
e.g., biting, clenching, chewing, mouth opening, lateral movement.	2 3 4
4. Tongue.	0 1
Rate only increase in movement both in and out of mouth, not inability to sustain movement.	2 3 4

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Extremity Movements

5. Upper (arms, wrists, hands, fingers).	0 1
Include movements that are choreic (rapid, objectively purposeless, irregular, spontaneous) or athetoid (slow, irregular, complex, serpentine). Do not include tremor (repetitive, regular, rhythmic movements).	2 3 4
6. Lower (legs, knees, ankles, toes),	0 1
e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	2 3 4

Trunk Movements

7. Neck, shoulders, hips,	0
e.g., rocking, twisting, squirming,	1
pelvic gyrations. Include	2
diaphragmatic movements.	3
	4

Global Judgements

8. Severity of abnormal movements.	0 1
Based on the highest single score on the above items.	2 3 4
9. Incapacitation due to abnormal movements.	none, normal minimal mild moderate severe
10. Patient's awareness of abnormal movements.	no awareness aware, no distress aware, mild distress aware, moderate distress aware, severe distress

Dental status	
11. Current problems with teeth and/or dentures.	no yes
12. Does patient usually wear dentures?	no yes

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APPENDIX 13. FAGERSTROM TEST FOR NICOTINE DEPENDENCE

FAGERSTROM TEST FOR NICOTINE DEPENDENCE (for smokers only)				
Point scale	**0 Points** ▼	**1 Point** ▼	**2 Points** ▼	**3 Points** ▼
1. How soon after you wake up do you smoke your first cigarette?	☐ 0 After 60 minutes	☐ 1 31-60 minutes	☐ 2 6-30 minutes	☐ 3 Within 5 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?	☐ 0 No	☐ 1 Yes		
3. Which cigarette would you hate most to give up?	☐ 0 All others	☐ 1 The first one in the morning		
4. How many cigarettes per day do you smoke?	☐ 0 10 or less	☐ 1 11-20	☐ 2 21-30	☐ 3 31 or more
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	☐ 0 No	☐ 1 Yes		
6. Do you smoke if you are so ill that you are in bed most of the day?	☐ 0 No	☐ 1 Yes		

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RATER'S INITIALS:_____

FTND- UK/English- Feb. 16, 2007
ID 3265

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APPENDIX 14. SIGNED AND DATED INVESTIGATOR PROTOCOL AGREEMENT PAGE

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Investigator Name: _____

_____ _____

Investigator Signature Date

The following co-signature is required only when the investigator is not a licensed physician.

Physician Name: _____

_____ _____

Physician Signature Date

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for the treatment of cognitive dysfunction in schizophrenia comprising administering (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to a patient in need thereof.
2. Use of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of cognitive dysfunction in schizophrenia.
3. A compound (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof for use in the treatment of cognitive dysfunction in schizophrenia.
4. The method, use, or compound of claim 1, 2, or 3, wherein the treatment provides an improvement in executive function.
5. The method, use, or compound of claims 1 – 4, wherein the treatment provides an improvement in memory.
6. The method, use, or compound of claims 1 – 5, wherein the treatment provides an improvement in attention.
7. A method for the treatment of negative symptoms of schizophrenia comprising administering (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to a patient in need thereof.
8. Use of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of negative symptoms of schizophrenia.
9. A compound (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof for use in the treatment of negative symptoms of schizophrenia.
10. A method for the treatment of residual phase schizophrenia comprising administering (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof to a patient in need thereof.
11. Use of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of residual phase schizophrenia.

12. A compound (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof for use in the treatment of residual phase schizophrenia.
13. A pharmaceutical composition for the treatment of one or more of cognitive dysfunction in schizophrenia, negative symptoms of schizophrenia, or residual phase schizophrenia comprising (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.
14. The pharmaceutical composition of claim 13, wherein the composition further comprises one or more antipsychotic medications, anti-depressants, or mood stabilizers.
15. The pharmaceutical composition of claim 14, wherein the one or more antipsychotic medication is one or more of: Stelazine (Trifluoperazine), Flupenthixol (Fluanxol), Loxapine (Loxapac, Loxitane), Perphenazine (Etrafon, Trilafon), Chlorpromazine (Thorazine), Haldol (Haloperidol), Prolixin (Fluphenazine Decanoate, Modecate, Permitil), Aripiprazole (Abilify), Clozaril (clozapine), Geodon (ziprasidone), Risperdal (resperidone), Seroquel (Quetiapine), Zyprexa (olanzapine), or an agonist of the nicotinic α7 receptor.