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The present invention provides methods for treating psychiatric diseases, such as schizophrenia, in patients with certain gene polymorphisms using antipsychotic drugs, such as risperidone and paliperidone.
PSYCHIATRIC TREATMENT FOR PATIENTS WITH GENE POLYMORPHISMS

RELATED APPLICATIONS

[0001] This application claims priority to US Application No. 62/366,768 filed July 26, 2016; to US Application No. 62/302,445 filed March 2, 2016; and to US Application No. 62/235,400 filed September 30, 2015; the disclosures of each of which are incorporated by reference herein in their entirety.

FIELD

[0002] The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in patients with certain gene polymorphisms using antipsychotic drugs, such as risperidone and paliperidone.

BACKGROUND

[0003] Schizophrenia is a severe and persistent debilitating psychiatric illness that is generally associated with considerable morbidity and extreme disability. Due to the severity of this disorder, especially the negative impact of a psychotic episode on a human, and the diminishing recovery after each psychotic episode, there is a need to more conclusively identify individuals who have or are at risk of developing schizophrenia, for example, to confirm clinical diagnoses, to allow for prophylactic therapies, to determine appropriate therapies based on their genotypic subtype, and to provide genetic counseling for prospective parents with a history of the disorder.

[0004] Various genes and chromosomes have been implicated in etiology of schizophrenia. Whole genome scans for genes involved in schizophrenia and related schizophrenia-spectrum disorders (including schizotypal personality disorder and schizoaffective disorder) have implicated numerous autosomes as having a role in the genetic etiology of schizophrenia and related schizophrenia-spectrum disorders. Generally, these linkage scans are too low in resolution to identify specific genes, but increasingly, transmission disequilibrium (TOT, family-based association) and Case/Control association studies have evaluated a number of positional candidate genes.
genes with a good measure of success.

[0005] There is a need in the art to identify whether schizophrenic patients with certain gene polymorphisms and/or genotypes would benefit from treatment with antipsychotic drugs, in order to provide therapy to patients who would receive the most benefit from certain medications. The disclosure is directed to this, as well as other, important ends.

SUMMARY

[0006] The disclosure provides methods for treating psychiatric diseases in humans having a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof, by administering therapeutically effective amounts of antipsychotic drugs to treat the psychiatric diseases. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The psychiatric disease may be schizophrenia. The antipsychotic drug may be selected from the group consisting of risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0007] The disclosure provides methods for treating psychiatric diseases in humans having a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof, by administering therapeutically effective amounts of antipsychotic drugs to treat the psychiatric diseases. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The psychiatric disease may be schizophrenia. The antipsychotic drug may be selected from the group consisting of risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0008] The disclosure provides methods for treating psychiatric diseases in humans having an rs17782313 single nucleotide polymorphism in the MC4R gene, an rs3813929 single nucleotide polymorphism in the HTR2C gene, an rs6313 single nucleotide polymorphism in the HTR2A gene, or a combination thereof, by administering therapeutically effective amounts of antipsychotic drugs
to treat the psychiatric diseases. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The psychiatric disease may be schizophrenia. The antipsychotic drug may be selected from the group consisting of risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0009] The disclosure provides methods for treating schizophrenia in humans in need thereof by administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC/TT genotype and an rs17782313 single nucleotide polymorphism in the MC4R gene.

[0010] The disclosure provides methods for treating schizophrenia in humans in need thereof by administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype and an rs3813929 single nucleotide polymorphism in the HTR2C gene.

[0011] The disclosure provides methods for treating schizophrenia in humans in need thereof by administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype or a CC/TT genotype, and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0012] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof; and (iii) administering therapeutically effective amounts of antipsychotic drugs to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide polymorphism in the MC4R gene may be rs7782313. The psychiatric disease may be
schizophrenia. The antipsychotic drug may be selected from the group consisting of risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0013] The disclosure provides methods for treating psychiatric diseases in humans having a CC genotype, a TT genotype, or a CT/TT genotype, by administering therapeutically effective amounts of antipsychotic drugs to treat the psychiatric diseases. The psychiatric disease may be schizophrenia. The antipsychotic drug may be selected from the group consisting of risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0014] These and other embodiments are described herein.

BRIEF DESCRIPTION OF THE FIGURES

[0015] FIGS. 1A-C shows the PANSS total score change from baseline until the conclusion of the study for humans having the MC4R (rs17782313) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 1A), 120 mg of Formulation C (FIG. 1B), or 90 mg of Formulation C (FIG. 1C) at Days 1 and 29 in the 57 day study.

[0016] FIGS. 2A-C shows the CGI-S total score change from baseline until the conclusion of the study for humans having the MC4R (rs17782313) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 2A), 120 mg of Formulation C (FIG. 2B), or 90 mg of Formulation C (FIG. 2C) at Days 1 and 29 in the 57 day study.

[0017] FIGS. 3A-C shows the PANSS total score change from baseline until the conclusion of the study for humans having the HTR2C gene (rs3813929) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 3A), 120 mg of Formulation C (FIG. 3B), or 90 mg of Formulation C at (FIG. 3C) Days 1 and 29 in the 57 day study.

[0018] FIGS. 4A-C shows the CGI-S total score change from baseline until the conclusion of the study for humans having the HTR2C gene (rs3813929) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 4A), 120 mg of Formulation C (FIG. 4B), or 90 mg of
Formulation C (FIG. 4C) at Days 1 and 29 in the 57 day study.

[0019] FIGS. 5A-C shows the PANSS total score change from baseline until the conclusion of the study for humans having the HTR2A (rs6313) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 5A), 120 mg of Formulation C (FIG. 5B), or 90 mg of Formulation C (FIG. 5C) at Days 1 and 29 in the 57 day study.

[0020] FIGS. 6A-C shows the CGI-S total score change from baseline until the conclusion of the study for humans having the HTR2A (rs6313) gene polymorphism receiving a subcutaneous injection of placebo (FIG. 6A), 120 mg of Formulation C (FIG. 6B), or 90 mg of Formulation C (FIG. 6C) at Days 1 and 29 in the 57 day study.

[0021] FIG. 7 shows the structural PK model for Formulation C that was used for the analysis.

[0022] FIG. 8 shows the sample window-based mean plasma concentration of risperidone and 9-OH-risperidone vs. time. FIG 8A shows the mean window-based mean plasma concentration for risperidone over time, wherein the lower line represents the 90 mg dose of Formulation C, and the upper line represents the 120 mg dose of Formulation C. FIG 8B shows the mean window-based mean plasma concentration for 9-OH-risperidone over time, wherein the lower line represents the 90 mg dose of Formulation C, and the upper line represents the 120 mg dose of Formulation C.

[0023] FIG. 9 shows the pcVPC for the covariate PK model on log scale. The three lines indicated the 5th, 50th (median) and 95th percentiles of the observed data, whereas the black lines (i.e., the dotted lines and the 3rd solid line from the top of the page) represent these percentiles for the model-simulated data. The shaded regions represent the 95% confidence intervals of the simulated percentiles. FIG. 9A shows the pcVPC for the covariate PK model for risperidone, while FIG. 9B shows the pcVPC for the covariate PK model for 9-OH-risperidone.

[0024] FIG. 10 shows a comparison of mean PANSS Score across the three treatment groups through the study duration. The upper line represents the placebo group, the middle line represents the 90 mg dose of Formulation C group, and the lower line represents the 120 mg dose of Formulation C group.

[0025] FIG. 11 shows the pcVPC for final active moiety exposure - PANSS model. The solid lines indicated the 5th, 50th (median) and 95th percentiles of the observed data whereas the black
lines (i.e., the dotted lines and the second solid line from the top) represent these percentiles for the model-simulated data. The shaded regions represent the 95% confidence intervals of the simulated percentiles.

[0026] FIG. 12 shows the distribution of consolidated CGI-S scores by dose. FIG. 12A shows the placebo group where Day 1 had CGI-S scores of 4 (lower block), 5 (middle block), and 6 (upper block); and Days 15, 29, 43, and 57 had CGI-S scores of 1-3 (lower block), 4 (lower middle block), 5 (upper middle block), and 6 (upper block). FIG. 12B shows the 90 mg Formulation C group where Day 1 had CGI-S scores of 4 (lower block), 5 (middle block), and 6 (upper block); and Days 15, 29, 43, and 57 had CGI-S scores of 1-3 (lower block), 4 (lower middle block), 5 (upper middle block), and 6 (upper block). FIG. 12C shows the placebo group where Day 1 had CGI-S scores of 4 (lower block), 5 (middle block), and 6 (upper block); Days 15 and 29 had CGI-S scores of 1-3 (lower block), 4 (lower middle block), 5 (upper middle block), and 6 (upper block), and Days 43 and 57 had CGI-S scores of 1-3 (lower block), 4 (middle block), and 5 (upper block).

[0027] FIG. 13A-D show the visual predictive checks for CGI-S vs. time for marked (FIG. 13A), severe (FIG. 13B), mild (FIG. 13C), and moderate (FIG. 13D). The circles are the observed proportions, whereas the lines are the medians and the 5th and 95th percentiles of the simulation that is also shown by the shaded area.

DETAILED DESCRIPTION

[0028] "Polymorphism" refers to a DNA sequence variation which provides for the presence of two or more distinct phenotypes in a population due to the expression of different alleles for a given gene. A polymorphism can include, for example, one or more nucleotide insertions in a DNA sequence, one or more nucleotide deletions in a DNA sequence, one or more nucleotide variations in a DNA sequence, or combinations thereof.

[0029] A "single nucleotide polymorphism," or "SNP," is a DNA sequence variation occurring when a single nucleotide at a specific location in the genome differs between members of a species or between paired chromosomes in an individual. Most SNP polymorphisms have two alleles. Each individual is in this instance either homozygous for one allele of the polymorphism (i.e. both chromosomal copies of the individual have the same nucleotide at the SNP location), or the
individual is heterozygous (i.e. the two sister chromosomes of the individual contain different nucleotides). The SNP nomenclature as reported herein (e.g., rs6313, rs17782313, rs3813929) refers to the official Reference SNP (rs) ID identification tag as assigned to each unique SNP by the National Center for Biotechnological Information (NCBI) or identifies the residue change associated with the identified polymorphism. SNP genotyping arrays have become an important tool for cohort identification and stratification, phenotype-genotype association studies, discovery of disease markers, prediction of molecular phenotypes, and clinical decision support.

[0030] "HTR2A" or "HTR2A gene" refers to 5-hydroxytryptamine (serotonin) receptor 2A.

[0031] "HTR2C" or "HTR2C gene" refers to 5-hydroxytryptamine (serotonin) receptor 2C.

[0032] "MC4R" or "MC4R gene" refers to the nielanocortin 4 receptor.

[0033] "rs6313" refers to the rs6313 single nucleotide polymorphism in the HTR2A gene. rs6313 is also known as T102C or C102T.

[0034] "rs17782313" refers to the rs17782313 single nucleotide polymorphism in the MC4R gene.

[0035] "rs3813929" refers to the rs3813929 single nucleotide polymorphism in the HTR2C gene. rs3813929 is also known as -759C/T.

[0036] "Psychiatric disease" refers to any disease in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the disclosure of which is incorporated by reference herein. In embodiments, the psychiatric disease is schizophrenia. In embodiments, the psychiatric disease is bipolar disorder. In embodiments, the psychiatric disease is bipolar mania. In embodiments, the psychiatric disease is autism. In embodiments, the psychiatric disease is anxiety disorder, social phobia, attention-deficit hyperactivity disorder, depression, an eating disorder, insomnia, obsessive-compulsive disorder, personality disorder, post-traumatic stress disorder, substance abuse, or Tourette’s syndrome.

[0037] "Schizophrenia" is a psychiatric disease characterized by, e.g., delusions, hallucinations, disorganized speech, grossly disorganized or cationic behavior, and negative symptoms. Schizophrenia can be acute schizophrenia. Schizophrenia can be further classified as paranoid
schizophrenia, disorganized schizophrenia, undifferentiated schizophrenia, catatonic schizophrenia, or residual schizophrenia. Diagnostic criteria for schizophrenia are set forth in the DSM-5, the disclosure of which is incorporated by reference herein.

[0038] "Therapeutically effective amount" refers to an amount of the drug sufficient to contribute to the treatment or reduction of a symptom or symptoms of a psychiatric disease.

[0039] "Administering" refers to oral administration, administration as a suppository, topical, intravenous, parenteral, intraperitoneal, intramuscular, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device (e.g., a solid polymeric biodegradable device, a mini-osmotic pump) to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. In embodiments, parenteral administration is subcutaneous administration. Other modes of delivery include, but are not limited to, the use of microsphere formulations, liposomal formulations, intravenous infusion, transdermal patches, etc. The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the human. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucoadhesive polymers, gelling polysaccharides and finely-divided drug carrier substrates. The compositions of the invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release intramuscularly or subcutaneously; as biodegradable and injectable gel formulations; or as microspheres for oral administration. The compositions of the present invention can also be delivered as nanoparticles.
"Pharmaceutically acceptable excipient" refers to a compound or substance that aids the administration of an active agent to a patent and can be included in the compositions of the invention without causing a significant adverse toxicological effect on the human. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringers solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful. In embodiments of the methods described herein, the pharmaceutical compositions will comprise an antipsychotic drug (e.g., risperidone, paliperidone) and at least one pharmaceutically acceptable excipient.

"Pharmaceutically acceptable salt" refers to salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogenencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like.
"Treating" or "treatment" refers to any indicia of success in the treatment or amelioration of a psychiatric disease, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the condition more tolerable to the human; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a human's physical or mental well-being. The success in the treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation.

"Month" means 28 days to 31 days. In one embodiment, a month is 28 days, 29 days, 30 days, or 31 days. In one embodiment, a month is 28 days. In one embodiment, a month is 30 days. In one embodiment, a month is 31 days.

The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a CC genotype, a TT genotype, or a CT/TT genotype.

The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide polymorphism in the MC4R gene may be rs17782313.

The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a CC genotype, a TT genotype, or a CT/TT genotype by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof.
The human may have a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide polymorphism in the MC4R gene may be rs17782313.

[0047] The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a CC genotype, a TT genotype, or a CT/TT genotype.

[0048] The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide polymorphism in the MC4R gene may be rs17782313.

[0049] The disclosure provides methods for treating psychiatric diseases, such as schizophrenia, in humans having a CC genotype, a TT genotype, or a CT/TT genotype by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric disease. The human may have a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof. The human may have a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide
polymorphism in the MC4R gene may be rs17782313.

[0050] The disclosure provides methods for treating schizophrenia in humans having a polymorphism in the MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans pharmaceutical compositions comprising therapeutically effective amounts of risperidone base, a poly(lactide-co-glycolide)copolymer, and N-methyl-2-pyrrolidone, to treat the schizophrenia. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. In one embodiment, the pharmaceutical composition is Formulation A. In one embodiment, the pharmaceutical composition is Formulation B. In one embodiment, the pharmaceutical composition is Formulation C.

[0051] The disclosure provides methods for treating schizophrenia in humans having a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof, by administering to the humans pharmaceutical compositions comprising therapeutically effective amounts of risperidone base, a poly(lactide-co-glycolide)copolymer, and N-methyl-2-pyrrolidone, to treat the schizophrenia. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The single nucleotide polymorphism in the MC4R gene may be rs17782313. In one embodiment, the pharmaceutical composition is Formulation A. In one embodiment, the pharmaceutical composition is Formulation B. In one embodiment, the pharmaceutical composition is Formulation C.

[0052] The disclosure provides methods for treating schizophrenia in humans with a CT/TT genotype and a single nucleotide polymorphism in the MC4R gene by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the MC4R gene may be rs17782313.

[0053] The disclosure provides methods for treating schizophrenia in humans with a CT/TT genotype and a single nucleotide polymorphism in the MC4R gene by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the MC4R gene may be rs17782313.
[0054] The disclosure provides methods for treating schizophrenia in humans with the CC genotype and a single nucleotide polymorphism in the HTR2C gene by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the HTR2C gene may be rs3813929.

[0055] The disclosure provides methods for treating schizophrenia in humans with the CC genotype and a single nucleotide polymorphism in the HTR2C gene by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the HTR2C gene may be rs3813929.

[0056] The disclosure provides methods for treating schizophrenia in humans with the CC genotype and a single nucleotide polymorphism in the HTR2A gene by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the HTR2A gene may be rs63 13.

[0057] The disclosure provides methods for treating schizophrenia in humans with the CC genotype and a single nucleotide polymorphism in the HTR2A gene by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the HTR2A gene may be rs63 13.

[0058] The disclosure provides methods for treating schizophrenia in humans with the CT/TT genotype in the HTR2A single nucleotide polymorphism by administering to the humans therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt to treat the schizophrenia. The single nucleotide polymorphism in the HTR2A gene may be rs63 13.

[0059] The disclosure provides methods for treating schizophrenia in humans with the CT/TT genotype in the HTR2A single nucleotide polymorphism by administering to the humans therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the schizophrenia. The single nucleotide polymorphism in the HTR2A gene may be rs6313.

[0060] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a polymorphism in the MC4R gene; and (iii) administering therapeutically effective amounts of
risperidone or a pharmaceutically acceptable salt thereof or paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for the polymorphism in the MC4R gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype.

[0061] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the MC4R gene; and (iii) administering therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the MC4R gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the MC4R gene may be rs177823 13. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC/TT genotype and an rs177823 13 single nucleotide polymorphism in the MC4R gene.

[0062] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the MC4R gene; and (iii) administering therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the MC4R gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the MC4R gene may be rs177823 13. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC/TT genotype and an rs177823 13 single nucleotide polymorphism in the MC4R gene.

[0063] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a polymorphism in the HTR2C gene; and (iii) administering therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof or paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for the polymorphism in the HTR2C gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype.
[0064] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the HTR2C gene, and (iii) administering therapeutically effective amounts of risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the HTR2C gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC genotype and an rs3813929 single nucleotide polymorphism in the HTR2C gene.

[0065] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the HTR2C gene; and (iii) administering therapeutically effective amounts of paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the HTR2C gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2C gene may be rs3813929. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC genotype and an rs3813929 single nucleotide polymorphism in the HTR2C gene.

[0066] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a polymorphism in the HTR2A gene; and (iii) administering therapeutically effective amounts risperidone or a pharmaceutically acceptable salt thereof or paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a polymorphism in the HTR2A gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype.

[0067] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the HTR2A gene; and (iii) administering therapeutically effective amounts risperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric
diseases when the human tests positive for a single nucleotide polymorphism in the HTR2A gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene. In embodiments, the humans have a CC/TT genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0068] The disclosure provides methods for treating psychiatric diseases in humans in need thereof by the steps of (i) obtaining a blood sample from the human; (ii) testing the sample for a single nucleotide polymorphism in the HTR2A gene; and (iii) administering therapeutically effective amounts paliperidone or a pharmaceutically acceptable salt thereof to treat the psychiatric diseases when the human tests positive for a single nucleotide polymorphism in the HTR2A gene. The human may have a CC genotype, a TT genotype, or a CT/TT genotype. The single nucleotide polymorphism in the HTR2A gene may be rs6313. The psychiatric disease may be schizophrenia. In embodiments, the humans have a CC genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene. In embodiments, the humans have a CC/TT genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0069] In embodiments, the pharmaceutical composition may contain risperidone in the form of the free base or a pharmaceutically acceptable salt. In embodiments, risperidone is in the form of the free base. In embodiments, risperidone is in the form of a pharmaceutically acceptable salt. In embodiments, the pharmaceutical composition may contain prodrugs of risperidone or metabolites of risperidone. In embodiments, the risperidone has a particle size distribution such that at least 75% of the particles have a size from about 1 micron to about 250 microns. In embodiments, the risperidone has a particle size distribution such that at least 75% of the particles have a size from about 1 micron to about 40 microns. In embodiments, the risperidone has a particle size distribution such that at least 75% of the particles have a size from about 50 microns to about 150 microns. The particle size distribution may be determined by methods known in the art, such as laser light scattering/diffraction method following the Fraunhofer diffraction theory.

[0070] In embodiments, the pharmaceutical composition may contain paliperidone in the form of the free base or a pharmaceutically acceptable salt. In embodiments, paliperidone is in the form of
the free base. In embodiments, paliperidone is in the form of a pharmaceutically acceptable salt. In embodiments, the pharmaceutical composition may contain prodms of paliperidone or metabolites of paliperidone. Paliperidone is also known as 9-hydroxy-risperidone, an active metabolite of risperidone. In embodiments, the paliperidone has a particle size distribution such that at least 75% of the particles have a size from about 1 micron to about 250 microns. In embodiments, the paliperidone has a particle size distribution such that at least 75% of the particles have a size from about 1 micron to about 40 microns. In embodiments, the paliperidone has a particle size distribution such that at least 75% of the particles have a size from about 50 microns to about 150 microns. The particle size distribution may be determined by methods known in the art, such as laser light scattering/diffraction following the Fraunhofer diffraction theory.

[0071] In embodiments, the pharmaceutical composition containing risperidone can be RISPERDAL® CONSTA® (risperidone intramuscular injection by Janssen Pharmaceuticals) or a generic equivalent thereof. Such compositions and methods of making them are described in US Patent No. 5,688,801, US Patent No. 5,792,477, US Patent No. 5,916,598, US Patent No. 6,194,006, and US Patent No. 6,667,061, the disclosures of which are incorporated by reference herein in their entirety.

[0072] In embodiments, the pharmaceutical composition containing risperidone can be an oral solution, an oral suspension, an oral capsule, or an oral tablet, such as RISPERDAL® (risperidone oral solution or oral tablet, both by Janssen Pharmaceuticals) or a generic equivalent thereof. Such compositions and methods of making them are described in US Patent No. 5,648,093 and US Patent No. 6,224,905, the disclosures of which are incorporated by reference herein in their entirety.

[0073] In embodiments, the pharmaceutical composition can be a solid implantable composition containing risperidone and a biodegradable polymer. In embodiments, the solid implantable composition contains risperidone and a polymer selected from the group consisting of a polylactic acid, a polyglycolic acid, and a combination thereof. In embodiments, the solid implantable composition contains risperidone and a poly(lactide-co-glycolide) copolymer. In embodiments, the solid implantable composition is administered to the patient by a surgical implant technique. Such solid implantable pharmaceutical compositions containing risperidone are described in US Patent No. 9,439,905, US Patent No. 8,802,127, US Patent No. 8,741,327, and US Patent No. 8,221,778,
the disclosures of which are incorporated by reference herein in their entirety.

[0074] In embodiments, the pharmaceutical composition can be an injectable depot formulation containing risperidone in the form of a base or a pharmaceutically acceptable salt; a poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 1000 Daltons to about 5000 Daltons, and an organic solvent selected from the group consisting of benzyl alcohol, benzyl benzoate, ethyl benzoate, N-methyl-2-pyrrolidone, or a combination of two thereof; wherein the risperidone has a particle size distribution such that at least 75% of the particles have a size ranging from about 1 micron to about 40 microns (or less than 38 microns) when measured by a laser light scattering/diffraction technique, such as the Fraunhofer diffraction theory. Such compositions are described in US Patent No. 9,044,450 and US Patent No. 8,852,638, the disclosures of which are incorporated by reference herein in their entirety.

[0075] In embodiments, the pharmaceutical composition containing paliperidone can be an oral capsule or tablet, such as INVEGA® (paliperidone oral tablet by Janssen Pharmaceuticals) or a generic equivalent thereof. In embodiments, the pharmaceutical composition containing paliperidone can be an injectable solution or an injectable suspension, such as INVEGA®, SUSTENNA® or INVEGA TRINZA™ (paliperidone intramuscular injection by Janssen Pharmaceuticals), or generic equivalents thereof. Such compositions and methods of making them are described in US Patent No. 6,077,843 and US Patent No. 6,555,544, the disclosures of which are incorporated by reference herein in their entirety.

[0076] In embodiments, the pharmaceutical composition can be a solid implantable composition containing paliperidone and a biodegradable polymer. In embodiments, the solid implantable composition contains paliperidone and a polymer selected from the group consisting of a polyiactic acid, a polyglycolic acid, and a combination thereof. In embodiments, the solid implantable composition contains paliperidone and a poly(lactide-co-glycolide) copolymer. In embodiments, the solid implantable composition is administered to the patient by a surgical implant technique. Such solid implantable pharmaceutical compositions containing paliperidone are described in US Patent No. 9,439,905, US Patent No. 8,802,127, US Patent No. 8,741,327, and US Patent No. 8,221,778, the disclosures of which are incorporated by reference herein in their entirety.

[0077] In embodiments, the pharmaceutical composition can be an injectable depot formulation
containing paliperidone in the form of a base or a pharmaceutically acceptable salt; a poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 1000 Daltons to about 5000 Daltons, and an organic solvent selected from the group consisting of benzyl alcohol, benzyl benzoate, ethyl benzoate, N-methyl-2-pyrrolidone, or a combination of two thereof; wherein the paliperidone has a particle size distribution such that at least 75% of the particles have a size ranging from about 1 micron to about 40 microns (or less than 38 microns) when measured by a laser light scattering/diffraction technique, such as the Fraunhofer diffraction theory. Such compositions are described in US Patent No. 9,044,450 and US Patent No. 8,852,638, the disclosures of which are incorporated by reference herein in their entirety.

[0078] In embodiments, the pharmaceutical composition may contain any antipsychotic agent. Exemplary antipsychotic agents that can be used in the methods of treatment described herein include risperidone, paliperidone, clozapine, loxapine, olanzapine, thioridazine, perphenazine, aripiprazole, iloperidone, ziprasidone, lurasidone, molindone, asenapine, mesoridazine, quetiapine, trifluoperazine, or a pharmaceutically acceptable salt of any of the foregoing.

[0079] In embodiments, the pharmaceutical composition containing risperidone or paliperidone is in a form suitable for subcutaneous injection, such formulations and methods of making them are described in US Patent No. 9,180,197, the disclosure of which is incorporated by reference herein in its entirety.

[0080] In embodiments, the pharmaceutical composition containing risperidone is Formulation A, wherein Formulation A comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide) copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrrolidone. Formulation A can be prepared by processes known in the art and described, for example, in US Patent No. 9,180,197, the disclosure of which is incorporated by reference herein in its entirety. In embodiments, Formulation A is parenterally administered to a human from about once every 2 weeks to about once every 8 weeks. In embodiments, Formulation A is parenterally administered to a human from about once a month to about once every 6 weeks. In embodiments, Formulation A is parenterally administered to a human about once a month. In embodiments, parenteral administration is subcutaneous administration. In embodiments, risperidone is present in Formulation A in an amount from about 25 mg to about 200 mg; from about 50 mg to about 150
nig; from about 60 mg to about 150 mg; from about 80 mg to about 140 mg; from about 90 mg to about 120 mg. In embodiments, risperidone is present in Formulation A in an amount of about 60 mg. In embodiments, risperidone is present in Formulation A in an amount of about 90 mg. In embodiments, risperidone is present in Formulation A in an amount of about 120 mg.

[0081] In embodiments, the pharmaceutical composition containing risperidone is Formulation B, wherein Formulation B comprises about 10 wt% to about 20 wt% risperidone base; about 35 wt% to about 45 wt% of a 50:50 to 90:10 poly(lactide-co-glycolide)copolymer; and about 40 wt% to about 50 wt% N-methyl-2-pyrrolidone. Formulation B can be prepared by processes known in the art and described, for example, in US Patent No. 9,180,197, the disclosure of which is incorporated by reference herein in its entirety. In embodiments, Formulation B is parenterally administered to a human from about once every 2 weeks to about once every 8 weeks. In embodiments, Formulation B is parenterally administered to a human from about once a month to about once every 6 weeks. In embodiments, Formulation B is parenterally administered to a human about once a month. In embodiments, parenteral administration is subcutaneous administration. In embodiments, risperidone is present in Formulation B in an amount from about 25 mg to about 200 mg; from about 50 mg to about 150 mg; from about 60 mg to about 150 mg; from about 80 mg to about 140 mg; from about 90 mg to about 120 mg. In embodiments, risperidone is present in Formulation B in an amount of about 60 mg. In embodiments, risperidone is present in Formulation B in an amount of about 90 mg. In embodiments, risperidone is present in Formulation B in an amount of about 120 mg.

[0082] In embodiments, the pharmaceutical composition containing risperidone is Formulation C, wherein Formulation C comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone. Formulation C can be prepared by processes known in the art and described, for example, in US Patent No. 9,180,197, the disclosure of which is incorporated by reference herein in its entirety. In embodiments, Formulation C is parenterally administered to a human from about once every 2 weeks to about once every 8 weeks. In embodiments, Formulation C is parenterally administered to a human from about once a month to about once every 6 weeks. In embodiments, Formulation C is parenterally administered to
a human about once a month. In embodiments, parenteral administration is subcutaneous administration. In embodiments, risperidone is present in Formulation C in an amount from about 25 mg to about 200 mg; from about 50 mg to about 150 mg, from about 60 mg to about 150 mg; from about 80 mg to about 140 mg; from about 90 mg to about 120 mg. In embodiments, risperidone is present in Formulation C in an amount of about 60 mg. In embodiments, risperidone is present in Formulation C in an amount of about 90 mg. In embodiments, risperidone is present in Formulation C in an amount of about 120 mg. Formulation C is also known as RBP-7000.

[0083] "Number average molecular weight" refers to the total weight of all the polymer molecules in a sample, divided by the total number of polymer molecules in a sample. Number average molecular weight can be determined by methods known in the art, such as by gel permeation chromatography/size exclusion chromatography (e.g., available from Agilent Technologies).

[0084] In embodiments, the pharmaceutical composition containing risperidone is Formulation D, wherein Formulation D comprises about 1 wt% to about 30 wt% of risperidone, a pharmaceutically acceptable salt of risperidone, paliperidone, or a pharmaceutically acceptable salt of paliperidone; about 10 wt% to about 80 wt% of a biodegradable polymer; and about 10 wt% to about 80 wt% of an organic solvent. In embodiments, the biodegradable polymer is a polylactide, a polyglycolide, a polyisocaprolactone, a copolymer thereof, a terpolymer thereof, or any combination thereof. In embodiments, the organic solvent is N-methyl-2-pyrrolidone, 2-pyrrolidone, acetic acid, lactic acid, methyl lactate, ethyl lactate, monomethyl succinate acid, monomethyl citric acid, glycofurol, glycerol formal, isopropylidene glycol, 2,2-dimethyl-1,3-dioxolone-4-methanol, solketal, dimethylformamide, dimethylacetamide, dimethysulfoxide, dimethylsulfone, epsilon-caprolactone, butyrolactone, caprolactam, or a mixture of two or more thereof. Formulation D can be prepared by processes known in the art and described, for example, in US Patent No. 9,180,197, the disclosure of which is incorporated by reference herein in its entirety. In embodiments, Formulation D is parenterally administered to a human from about once every 2 weeks to about once every 8 weeks. In embodiments, Formulation D is parenterally administered to a human from about once a month to about once every 6 weeks. In embodiments, Formulation D is parenterally administered to a human about once a month. In embodiments, parenteral administration is subcutaneous administration. In embodiments, risperidone, a pharmaceutically acceptable salt of risperidone, paliperidone, or a
pharmaceutically acceptable salt of paliperidone is present in Formulation D in an amount from about 1 mg to about 500 mg; from about 25 mg to about 200 mg; from about 50 mg to about 150 mg; from about 60 mg to about 150 mg; from about 80 mg to about 140 mg; from about 90 mg to about 120 mg. In embodiments, risperidone, a pharmaceutically acceptable salt of risperidone, paliperidone, or a pharmaceutically acceptable salt of paliperidone is present in Formulation D in an amount of about 60 mg. In embodiments, risperidone, a pharmaceutically acceptable salt of risperidone, paliperidone, or a pharmaceutically acceptable salt of paliperidone is present in Formulation D in an amount of about 90 mg. In embodiments, risperidone, a pharmaceutically acceptable salt of risperidone, paliperidone, or a pharmaceutically acceptable salt of paliperidone is present in Formulation D in an amount of about 120 mg.

[0085] As is well known in the art, therapeutically effective amounts for use in humans can be determined from animal models and from commercially available pharmaceutical formulations that are used to treat psychiatric diseases, such as schizophrenia, bipolar disorder, and autism. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals or humans. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. In embodiments, oral dosages of antipsychotic agents, such as risperidone or paliperidone, may be from about 0.5 mg to about 10 mg, or from about 0.5 mg to about 5 mg. In embodiments, intramuscular injectable dosages of antipsychotic agents, such as paliperidone, may be from about 50 mg to about 900 mg. In embodiments, intramuscular injectable dosages of antipsychotic agents, such as risperidone, may be from about 10 mg to about 50 mg. In embodiments, subcutaneous injectable dosages of antipsychotic agents, such as risperidone, may be from about 90 mg to about 120 mg.

[0086] Embodiments of the Description.

[0087] In the following embodiments, any reference to a single embodiment encompasses a reference to each embodiment therein (e.g., a reference to Embodiment 42 encompasses a reference
to Embodiment 42A and Embodiment 42B).

[0088] Embodiment 1. A method for treating a psychiatric disease in a human having an MC4R gene polymorphism comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the MC4R gene polymorphism to treat the psychiatric disease.

[0089] Embodiment 2. A method for treating a psychiatric disease in a human having an HTR2C gene polymorphism comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the HTR2C gene polymorphism to treat the psychiatric disease.

[0090] Embodiment 3. A method for treating a psychiatric disease in a human having an HTR2A gene polymorphism comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the HTR2A gene polymorphism to treat the psychiatric disease.

[0091] Embodiment 4. A method for treating a psychiatric disease in a human having an MC4R gene polymorphism, an HTR2C gene polymorphism, an HTR2A gene polymorphism, or a combination thereof comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the MC4R gene polymorphism, the HTR2C gene polymorphism, the HTR2A gene polymorphism, or the combination thereof to treat the psychiatric disease.

[0092] Embodiment 5. The method of any one of Embodiments 1-4, wherein the human has a TT genotype.

[0093] Embodiment 6. The method of any one of Embodiments 1-4, wherein the human has a CC genotype.

[0094] Embodiment 7. The method of any one of Embodiments 1-4, wherein the human has a
CT/TT genotype.

[0095] Embodiment 8A. The method of any one of Embodiments 1 and 4-7, wherein the MC4R gene polymorphism is a single nucleotide polymorphism.

[0096] Embodiment 8B. The method of Embodiment 8A, wherein the single nucleotide polymorphism is an rs17782313 single nucleotide polymorphism.

[0097] Embodiment 9A. The method of any one of Embodiments 2 and 4-7, wherein the HTR2C gene polymorphism is a single nucleotide polymorphism.

[0098] Embodiment 9B. The method of Embodiment 9A, wherein the single nucleotide polymorphism is an rs3813929 single nucleotide polymorphism.

[0099] Embodiment 10A. The method of any one of Embodiments 3-7, wherein the HTR2A gene polymorphism is a single nucleotide polymorphism.

[0100] Embodiment 10B. The method of Embodiment 10A, wherein the single nucleotide polymorphism is an rs6313 single nucleotide polymorphism.

[0101] Embodiment 11. The method of any one of Embodiments 1-10, wherein the psychiatric disease is schizophrenia.

[0102] Embodiment 12A. The method of Embodiment 11, wherein the schizophrenia is acute schizophrenia.

[0103] Embodiment 12B. The method of Embodiment 11, wherein the schizophrenia is an acute psychotic state.

[0104] Embodiment 12C. The method of Embodiment 11, wherein the schizophrenia is a relapse with acute schizophrenic symptoms.

[0105] Embodiment 13. The method of any one of Embodiments 1-10, wherein the psychiatric disease is bipolar disorder.

[0106] Embodiment 14. The method of any one of Embodiments 1-10, wherein the psychiatric disease is autism.
[0107] Embodiment 15. The method of any one of Embodiments 1-14, wherein the human is an African-American human.

[0108] Embodiment 16. The method of any one of Embodiments 1-15, wherein the pharmaceutical composition is an oral tablet or an oral capsule.

[0109] Embodiment 17. The method of any one of Embodiments 1-15, wherein the method comprises administering the pharmaceutical composition to the human by oral administration or by parenteral administration.

[0110] Embodiment 18. The method of any one of Embodiments 1-15, wherein the method comprises administering the pharmaceutical composition by intramuscular administration or by subcutaneous administration.

[0111] Embodiment 19. The method of any one of Embodiments 1-18, wherein the pharmaceutical composition further comprises a poly(lactide-co-glycolide) copolymer.

[0112] Embodiment 20. The method of Embodiment 19, wherein the poly(lactide-co-glycolide) copolymer is a 50:50 to 95:5 poly(lactide-co-glycolide) copolymer.


[0114] Embodiment 22. The method of Embodiment 19 or 20, wherein the poly(lactide-co-glycolide) copolymer is in the form of microspheres.

[0115] Embodiment 23. The method of any one of Embodiments 1-22, wherein the pharmaceutical composition comprises risperidone or the pharmaceutically acceptable salt thereof.

[0116] Embodiment 24. The method of any one of Embodiments 1-22, wherein the pharmaceutical composition comprises risperidone in the form of a free base.

[0117] Embodiment 25. The method of any one of Embodiments 1-22, wherein the pharmaceutical composition comprises risperidone in the form of the pharmaceutically acceptable salt.

[0118] Embodiment 26. The method of any one of Embodiments 1-22, wherein the
pharmaceutical composition comprises paliperidone in the form of a free base.

[0119] Embodiment 27. The method of any one of Embodiments 1-22, wherein the pharmaceutical composition comprises paliperidone in the form of a pharmaceutically acceptable salt.

[0120] Embodiment 28. The method of any one of Embodiments 1-25, wherein the pharmaceutical composition comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide)copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrroloidone.

[0121] Embodiment 29. The method of any one of Embodiments 1-25, wherein the pharmaceutical composition comprises about 10 wt% to about 20 wt% risperidone base, about 35 wt% to about 45 wt% of a 50:50 to 90:10 poly(lactide-co-glycolide)copolymer; and about 40 wt% to about 50 wt% N-methyl-2-pyrroloidone.

[0122] Embodiment 30A. The method of any one of Embodiments 1-25, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 37 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrroloidone.

[0123] Embodiment 30B. The method of any one of Embodiments 1-25, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrroloidone.

[0124] Embodiment 31. A method for treating schizophrenia in a human having an MC4R gene polymorphism, an HTR2C gene polymorphism, an HTR2A gene polymorphism, or a combination thereof comprising subcutaneously administering once per month a pharmaceutical composition comprising: a therapeutically effective amount of risperidone base, a poly(lactide-co-glycolide)copolymer, and N-methyl-2-pyrroloidone to the human having the MC4R gene polymorphism, the HTR2C gene polymorphism, the HTR2A gene polymorphism, or the combination thereof, to treat the schizophrenia.

[0125] Embodiment 32. The method of Embodiment 31, wherein the human has a TT genotype, a
CC genotype, or a CT/TT genotype.

[0126] Embodiment 33. The method of Embodiment 32, wherein the human has the MC4R gene polymorphism and the TT genotype.

[0127] Embodiment 34. The method of Embodiment 32, wherein the human has the MC4R gene polymorphism and the CC genotype.

[0128] Embodiment 35. The method of Embodiment 32, wherein the human has the MC4R gene polymorphism and the CT/TT genotype.

[0129] Embodiment 36. The method of Embodiment 32, wherein the human has the HTR2C gene polymorphism and the TT genotype.


[0131] Embodiment 38. The method of Embodiment 32, wherein the human has the HTR2C gene polymorphism and the CT/TT genotype.


[0133] Embodiment 40. The method of Embodiment 32, wherein the human has the HTR2A gene polymorphism and the CC genotype.

[0134] Embodiment 41. The method of Embodiment 32, wherein the human has the HTR2A gene polymorphism and the CT/TT genotype.

[0135] Embodiment 42A. The method of any one of Embodiments 31-35, wherein the MC4R gene polymorphism is a single nucleotide polymorphism.

[0136] Embodiment 42B. The method of Embodiment 42A, wherein the single nucleotide polymorphism is an rs7782313 single nucleotide polymorphism.

[0137] Embodiment 43A. The method of any one of Embodiments 31, 32, and 36-38, wherein the HTR2C gene polymorphism is a single nucleotide polymorphism.
[0138] Embodiment 43B. The method of Embodiment 43A, wherein the single nucleotide polymorphism is an rs3813929 single nucleotide polymorphism.

[0139] Embodiment 44A. The method of any one of Embodiments 31, 32, and 39-41, wherein the HTR2A gene polymorphism is a single nucleotide polymorphism.

[0140] Embodiment 44B. The method of Embodiment 44A, wherein the single nucleotide polymorphism is an rs6313 single nucleotide polymorphism.

[0141] Embodiment 45. The method of any one of Embodiments 31-44, wherein the human is an African-American human.

[0142] Embodiment 46A. The method of any one of Embodiments 31-45, wherein the schizophrenia is acute schizophrenia.

[0143] Embodiment 46B. The method of any one of Embodiments 31-45, wherein the schizophrenia is an acute psychotic state.

[0144] Embodiment 46C. The method of any one of Embodiments 31-45, wherein the schizophrenia is a relapse with acute schizophrenic symptoms.

[0145] Embodiment 47. The method of any one of Embodiments 31-46, wherein the pharmaceutical composition comprises from about 60 grams to about 150 grams of risperidone base.

[0146] Embodiment 48. The method of any one of Embodiments 31-47, wherein the pharmaceutical composition comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide) copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrrolidone.

[0147] Embodiment 49. The method of any one of Embodiments 31-47, wherein the pharmaceutical composition comprises about 10 wt% to about 20 wt% risperidone base; about 35 wt% to about 45 wt% of a 50:50 to 90:10 poly(lactide-co-glycolide) copolymer; and about 40 wt% to about 50 wt% N-methyl-2-pyrrolidone.

[0148] Embodiment 50A. The method of any one of Embodiments 31-47, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 37 wt% of an 80:20
poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone.

[0149] Embodiment SOB. The method of any one of Embodiments 31-47, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone.

[0150] Embodiment 51. A method for treating a psychiatric disease in a human having a TT genotype, a CC genotype, or a CT/TT genotype comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the TT genotype, the CC genotype, or the CT/TT genotype to treat the psychiatric disease.

[0151] Embodiment 52. The method of Embodiment 51, wherein the psychiatric disease is schizophrenia.

[0152] Embodiment 53A. The method of Embodiment 52, wherein the schizophrenia is acute schizophrenia.

[0153] Embodiment 53B. The method of Embodiment 52, wherein the schizophrenia is an acute psychotic state.

[0154] Embodiment 53C. The method of Embodiment 52, wherein the schizophrenia is a relapse with acute schizophrenic symptoms.

[0155] Embodiment 54. The method of Embodiment 51, wherein the psychiatric disease is bipolar disorder.

[0156] Embodiment 55. The method of Embodiment 51, wherein the psychiatric disease is autism.

Embodiment 57. The method of any one of Embodiments 51-56, wherein the pharmaceutical composition is an oral tablet or an oral capsule.

Embodiment 58. The method of any one of Embodiments 51-56, wherein the method comprises administering the pharmaceutical composition to the human by oral administration or by parenteral administration.

Embodiment 59. The method of any one of Embodiments 51-56, wherein the method comprises administering the pharmaceutical composition by intramuscular administration.

Embodiment 60. The method of any one of Embodiments 51-56, wherein the method comprises administering the pharmaceutical composition by subcutaneous administration.

Embodiment 61. The method of Embodiment 60, wherein the poly(lactide-co-glycolide) copolymer is a 50:50 to 95:5 poly(lactide-co-glycolide) copolymer.

Embodiment 62. The method of any one of Embodiments 51-56, wherein the pharmaceutical composition further comprises N-methyl-2-pyrrolidone.

Embodiment 63. The method of Embodiment 60 or 61, wherein the poly(lactide-co-glycolide) copolymer is in the form of microspheres.

Embodiment 64. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises risperidone or the pharmaceutically acceptable salt thereof.

Embodiment 65. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises risperidone in the form of a free base.

Embodiment 66. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises risperidone in the form of the pharmaceutically acceptable salt.

Embodiment 67. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises paliperidone or the pharmaceutically acceptable salt thereof.

Embodiment 68. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises paliperidone in the form of a free base.
[0170] Embodiment 69. The method of any one of Embodiments 51-63, wherein the pharmaceutical composition comprises paliperidone in the form of a pharmaceutically acceptable salt.

[0171] Embodiment 70. The method of any one of Embodiments 51-56, 58, and 59, wherein the pharmaceutical composition comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide)copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrroloidone.

[0172] Embodiment 71. The method of any one of Embodiments 51-56, 58, and 59, wherein the pharmaceutical composition comprises about 10 wt% to about 20 wt% risperidone base, about 35 wt% to about 45 wt% of a 50:50 to 90:10 poly(lactide-co-glycolide)copolymer; and about 40 wt% to about 50 wt% N-methyl-2-pyrroloidone.

[0173] Embodiment 72A. The method of any one of Embodiments 51-56, 58, and 59, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 37 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrroloidone.

[0174] Embodiment 72B. The method of any one of Embodiments 51-56, 58, and 59, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrroloidone.

[0175] Embodiment 73. A method for treating a psychiatric disease in a human having a single nucleotide polymorphism in the MC4R gene, a single nucleotide polymorphism in the HTR2C gene, a single nucleotide polymorphism in the HTR2A gene, or a combination thereof, comprising administering to the human a therapeutically effective amount of an antipsychotic drug to treat the psychiatric disease.

[0176] Embodiment 74. The method of Embodiment 73, wherein the psychiatric disease is schizophrenia.

[0177] Embodiment 75. The method of Embodiment 73 or Embodiment 74, wherein the human has a CC genotype, a TT genotype, or a CT/TT genotype.
[0178] Embodiment 76. The method of Embodiment 73 or Embodiment 74, wherein the human has a CC genotype, a TT genotype, or a CT/TT genotype.

[0179] Embodiment 77. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is clozapine or a pharmaceutically acceptable salt thereof.

[0180] Embodiment 78. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is loxapine or a pharmaceutically acceptable salt thereof.

[0181] Embodiment 79. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is olanzapine or a pharmaceutically acceptable salt thereof.

[0182] Embodiment 80. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is thioridazine or a pharmaceutically acceptable salt thereof.

[0183] Embodiment 81. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is perphenazine or a pharmaceutically acceptable salt thereof.

[0184] Embodiment 82. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is aripiprazole or a pharmaceutically acceptable salt thereof.

[0185] Embodiment 83. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is iloperidone or a pharmaceutically acceptable salt thereof.

[0186] Embodiment 84. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is ziprasidone or a pharmaceutically acceptable salt thereof.

[0187] Embodiment 85. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is lurasidone or a pharmaceutically acceptable salt thereof.

[0188] Embodiment 86. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is molindone or a pharmaceutically acceptable salt thereof.

[0189] Embodiment 87. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is asenapine or a pharmaceutically acceptable salt thereof.

[0190] Embodiment 88. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is mesoridazine or a pharmaceutically acceptable salt thereof.
[0191] Embodiment 89. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is quetiapine or a pharmaceutically acceptable salt thereof.

[0192] Embodiment 90. The method of any one of Embodiments 73-76, wherein the antipsychotic drug is trifluoperazine or a pharmaceutically acceptable salt thereof.

[0193] Embodiment 91. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC/TT genotype and an rs177823 13 single nucleotide polymorphism in the MC4R gene.

[0194] Embodiment 92. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of paliperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC/TT genotype and an rs17782313 single nucleotide polymorphism in the MC4R gene.

[0195] Embodiment 93. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype and an rs3813929 single nucleotide polymorphism in the HTR2C gene.

[0196] Embodiment 94. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of paliperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype and an rs3813929 single nucleotide polymorphism in the HTR2C gene.

[0197] Embodiment 95. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0198] Embodiment 96. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of paliperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.
[0199] Embodiment 97. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of risperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC/TT genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0200] Embodiment 98. A method for treating schizophrenia in a human in need thereof comprising administering a therapeutically effective amount of paliperidone or a pharmaceutically acceptable salt thereof to the human to treat the schizophrenia, wherein the human has a CC/TT genotype and an rs6313 single nucleotide polymorphism in the HTR2A gene.

[0201] Embodiment 99. The method of any one of Embodiments 1-15, 18, 51-56, 59, 60, 91, 93, 95, and 97, wherein the composition is an injectable depot formulation containing risperidone in the form of a base or a pharmaceutically acceptable salt; a poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 1000 Daltons to about 5000 Daltons, and an organic solvent selected from the group consisting of benzyl alcohol, benzyl benzoate, ethyl benzoate, N-methyl-2-pyrrolidone, or a combination of two thereof; wherein the risperidone has a particle size distribution such that at least 75% of the particles have a size ranging from about 1 micron to about 40 microns (or less than 38 microns) when measured by a laser light scattering/diffraction technique, such as the Fraunhofer diffraction theory.

[0202] Embodiment 100. The method of any one of Embodiments 1-15, 18, 51-56, 59, 60, 92, 94, 96, and 98, wherein the composition is an injectable depot formulation containing paliperidone in the form of a base or a pharmaceutically acceptable salt; a poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 1000 Daltons to about 5000 Daltons, and an organic solvent selected from the group consisting of benzyl alcohol, benzyl benzoate, ethyl benzoate, N-methyl-2-pyrrolidone, or a combination of two thereof; wherein the risperidone has a particle size distribution such that at least 75% of the particles have a size ranging from about 1 micron to about 40 microns (or less than 38 microns) when measured by a laser light scattering/diffraction technique, such as the Fraunhofer diffraction theory.

[0203] Embodiment 101. The method of any one of Embodiments 1-15, 18, 51-56, 59, 60, 91, 93, 95, and 97, wherein the composition is a solid implantable composition containing risperidone and a biodegradable polymer, and wherein the biodegradable polymer is a polylactic acid; a polyglycolic
acid, a combination of a polylactic acid and a polyglycolic acid; or a poly(lactide-co-glycolide) copolymer.

[0204] Embodiment 102. The method of any one of Embodiments 1-15, 18, 51-56, 59, 60, 92, 94, 96, and 98, wherein the composition is a solid implantable composition containing paliperidone and a biodegradable polymer, and wherein the biodegradable polymer is a polylactic acid; a polyglycolic acid, a combination of a polylactic acid and a polyglycolic acid; or a poly(lactide-co-glycolide) copolymer.


[0206] Embodiment 104. The method of any one of Embodiments 1-15, 17, 18, 23-27, 31-47, 51-56, 59, 60, 64-69, and 91-98, wherein the composition is Formulation B.


EXEMPLARY

[0209] The following examples are for purposes of illustration only and are not intended to limit the spirit or scope of the disclosure or claims.

[0210] Example 1

[0211] Formulation C is a sustained-release (28-day) formulation of risperidone for the treatment of schizophrenia, which is designed to be administered by once-monthly subcutaneous injection. Previously, it has been demonstrated that subjects with acute schizophrenia who received a 90 mg dose or a 120 mg dose of Formulation C (i.e., Formulation C containing 90 mg of risperidone, or Formulation C containing 120 mg of risperidone, respectively) showed significant improvement in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impressions severity of illness (CGI-S) score compared to placebo over an 8-week period. The aim of this study was to investigate the possible association between genetic polymorphisms in serotonin (HTR2A
and HTR2C) and melanocortin (MC4R) receptors and schizophrenia in 350 subjects with acute schizophrenia following treatment with two subcutaneous doses of Formulation C (90 mg and 120 mg) for 8 weeks. The demographics of the humans in the study are shown in Table 1.

[0212] Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n=112</th>
<th>90 mg Formulation C n=111</th>
<th>120 mg Formulation C n=114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81 (72.3%)</td>
<td>93 (83.8%)</td>
<td>84 (73.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (27.7%)</td>
<td>18 (16.2%)</td>
<td>30 (26.3%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (22.3%)</td>
<td>28 (25.2%)</td>
<td>30 (26.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>84 (75.0%)</td>
<td>79 (71.2%)</td>
<td>80 (70.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.9%)</td>
<td>2 (1.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>10 (8.9%)</td>
<td>7 (6.3%)</td>
<td>9 (7.9%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>101 (90.2%)</td>
<td>104 (93.7%)</td>
<td>104 (91.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Age at First Schizophrenia Diagnosis (years)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>26.6 ± 9.25</td>
<td>25.5 ± 8.21</td>
<td>26.9 ± 8.48</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>94.1 ± 8.89</td>
<td>95.5 ± 9.23</td>
<td>94.9 ± 8.09</td>
</tr>
<tr>
<td>Positive symptom subscale</td>
<td>25.4 ± 3.31</td>
<td>26.0 ± 3.36</td>
<td>25.9 ± 3.42</td>
</tr>
<tr>
<td>Negative symptom subscale</td>
<td>22.6 ± 3.79</td>
<td>23.5 ± 3.68</td>
<td>22.6 ± 3.96</td>
</tr>
<tr>
<td>General psychopathology subscale</td>
<td>46.2 ± 5.49</td>
<td>45.9 ± 5.94</td>
<td>46.5 ± 5.15</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.8 ± 0.59</td>
<td>4.8 ± 0.58</td>
<td>4.8 ± 0.48</td>
</tr>
</tbody>
</table>

[0213] Blood samples were collected prior to the first subcutaneous injection of 90 mg or 120 mg Formulation C or placebo on Day 1 (Visit 3). Three SNPs [HTR2C (rs3813929), HTR2A (rs6313), and MC4R (rs177823 13)] were genotyped in 350 subjects. Clinical assessments for efficacy included the PANSS total score and CGI-S score performed at screening and baseline visits and
during Visits 3 (Day 1, first injection), 5 (Day 14), 6 (Day 29, second injection), 8 (Day 43), and 9 (end of study, Day 57 or termination visit). The correlation between the genotypes and the change from baseline across study days to the end-of-study in PANSS total score and CGI-S score was evaluated. PANSS and CGI-S scores were analyzed using a mixed-effects model for repeated measures (MMRM), with difference from baseline in PANSS total score or CGI-S score as the dependent variable. Comparison of each dose group with placebo was performed using Dunnett’s procedure for controlling Type I error at 2.5% (1-sided).

Results: Melanocortin 4 Receptor - MC4R (rs17782313)

Humans with the CT/TT genotype in the MC4R gene had statistically significant improvement in total PANSS and CGI-S scores compared to humans with the CC genotype.

Humans with the CT/TT genotype in the MC4R gene (rs17782313) who received 90 mg of Formulation C (N=101) or 120 mg of Formulation C (N=100) showed significant improvement in the change from baseline in total PANSS scores compared to placebo (N=102) (LSMEAN: -6.498; 95% CI: -10.041 to -2.956; p value: 0.0004 for the 90mg Formulation C group and LSMEAN: -8.200; 95% CI: -11.748 to -4.652; p value: 0.0001 for the 120 mg Formulation C group). The detailed results are shown in Table 2 and Figure 1 for the Intent-to-Treat Population.
Table 2

<table>
<thead>
<tr>
<th>Receptor Allele</th>
<th>Treatment</th>
<th>Formulation C</th>
<th>Study Day</th>
<th>Formulation C</th>
<th>Study Day</th>
<th>Comparison</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC4R (rs17782313)</td>
<td>CC</td>
<td>90 mg (N=9)</td>
<td>-15.262 (4.4816)</td>
<td>90 mg - Placebo (N=9)</td>
<td>-3.405 (6.3267)</td>
<td>-12.657 (-16.386, -8.930)</td>
<td>0.5949</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>120 mg (N=13)</td>
<td>-12.238 (3.7751)</td>
<td>-0.381 (5.8601)</td>
<td>-17.619 (-13.405, -11.833)</td>
<td>0.9487</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>Placebo (N=9)</td>
<td>-11.857 (4.4657)</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Formulation C</td>
<td>90 mg (N=101)</td>
<td>-15.429 (1.2755)</td>
<td>90 mg - Placebo (N=101)</td>
<td>-6.498 (1.8000)</td>
<td>-10.397 (-10.491, -10.297)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>120 mg (N=100)</td>
<td>-17.130 (1.2811)</td>
<td>-8.200 (1.8078)</td>
<td>-16.330 (-11.748, -10.907)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Placebo (N=102)</td>
<td>-8.930 (1.2681)</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIG. 1A shows the PANSS total score change from baseline for humans having the MC4R (rs177823 13) gene polymorphism receiving a placebo. The lower line represents humans with the CC genotype and the upper line represents humans with the CC/TT genotype. FIG. 1B shows the PANSS total score change from baseline for humans having the MC4R (rs177823 13) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC/TT genotype and the upper line, with reference to the End of Study, represents humans with the CC genotype. FIG. 1C shows the PANSS total score change from baseline for humans having the MC4R (rs177823 13) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to Day 29, represents humans with the CC genotype and the upper line, with reference to Day 29, represents humans with the CC/TT genotype.

With reference to the description of the figures, the term "upper line" refers to the line that is closest to the top of the page, and the term "lower line" refers to the line that is closest to the bottom of the page. Stated alternatively, the term "upper line" refers to the line that is closest to the
headers of "Placebo," "RBP-7000 120 rag," and "RBP-7000 90 rag," on the graphs/figures, where all of the headers are closest to the top of the page.

Humans with the CT/TT genotype in the MC4R gene (rs17782313) who received 90 mg Formulation C (N=101) or 120 mg Formulation C (N=100) showed significant improvement in the change from baseline in CGI-S scores compared to placebo (N=102) (LSMEAN: -0.394; 95% CI: -0.586 to -0.202, p value: 0.0001 for the 90 mg Formulation C group and LSMEAN: -0.447; 95% CI: -0.639 to -0.255; p value: <0.0001 for the 120 mg Formulation C group). The detailed results are shown in Table 3 and Figure 2 for the Intent-to-Treat Population.

Table 3

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Allele</th>
<th>Treatment</th>
<th>LS Mean(SE)</th>
<th>comparison</th>
<th>Difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC4R (rs17782313)</td>
<td>cc</td>
<td>Formulation C - 90 mg (N= 9)</td>
<td>-0.819 (0.2600)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>0.076 (0.3675)</td>
<td>(-0.678, 0.830)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Formulation C - 120 mg (N= 13)</td>
<td>-0.826 (0.2193)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>0.069 (0.3387)</td>
<td>(-0.625, 0.764)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Placebo (N= 9)</td>
<td>-0.895 (0.2591)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT/TT</td>
<td>Formulation C - 90 mg (N= 101)</td>
<td>-0.878 (0.0691)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>-0.394 (0.0974)</td>
<td>(-0.586, -0.202)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CT/TT</td>
<td>Formulation C - 120 mg (N= 100)</td>
<td>-0.931 (0.0695)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>-0.447 (0.0977)</td>
<td>(-0.639, -0.255)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CT/TT</td>
<td>Placebo (N= 102)</td>
<td>-0.484 (0.0687)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIG. 2A shows the CGI-S total score change from baseline for humans having the MC4R (rs17782313) gene polymorphism receiving a placebo. The lower line represents humans with the CC genotype and the upper line represents humans with the CC/TT genotype. FIG. 2B shows the CGI-S total score change from baseline for humans having the MC4R (rs17782313) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC/TT genotype and the upper line, with reference to the End of Study, represents humans with a CC genotype. FIG. 2C

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shows the CGI-S total score change from baseline for humans having the MC4R (rs7782313) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to End of Study, represents humans with the CC/TT genotype and the upper line, with reference to End of Study, represents humans with the CC genotype.

[0223] Results: Serotonin Subtype 2C Receptor - HTR2C (rs3813929)

[0224] Humans with the CC genotype in the HTR2C gene had statistically significant improvement in total PANSS and CGI-S scores following treatment than humans with the CT/TT genotype.

[0225] Humans with the CC genotype in the HTR2C gene (rs3813929) who received 90 mg Formulation C (N=102) or 120 mg Formulation C (N=104) showed significant improvement in the change from baseline in total PANSS scores compared to placebo (N=102) (LSMEAN: -6.466; 95% CI: -10.031 to -2.901; p value: 0.0004 for the 90 mg Formulation C group and LSMEAN: -7.733; 95% CI: -11.279 to -4.186; p value: <0.0001 for the 120 mg Formulation C group). The detailed results are shown in Table 4 and Figure 3 for the Intent-to-Treat Population.

[0226] Table 4
FIG. 3A shows the PANSS total score change from baseline for humans having the HTR2C gene (rs3813929) gene polymorphism receiving a placebo. The lower line, with reference to Day 29, represents humans with the CC genotype and the upper line, with reference to Day 29, represents humans with the CC/TT genotype. FIG. 3B shows the PANSS total score change from baseline for humans having the HTR2C gene (rs3813929) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC genotype and the upper line, with reference to the End of Study, represents humans with a CC/TT genotype. FIG. 3C shows the PANSS total score change from baseline for humans having the HTR2C gene (rs3813929) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with the CC genotype and the upper line, with reference to the End of Study, represents humans with the CC/TT genotype.

Humans with the CC genotype in the HTR2C gene (rs3813929) who received 90 mg Formulation C (N=102) or 120 mg Formulation C (N=T04) showed significant improvement in the change from baseline in CGI-S scores compared to placebo (N=102) (LSMEAN: -0.352; 95% CI: -0.547 to -0.157; p value: 0.0004 for the 90 mg Formulation C group and LSMEAN: -0.414; 95% CI: -0.605 to -0.217; p value: <0.0001 for the 120 mg Formulation C group). The detailed results are shown in Table 5 and Figure 4 for the Intent-to-Treat Population.
[0229] Table 5

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Allele</th>
<th>Treatment</th>
<th>LS Mean (SE)</th>
<th>Comparison</th>
<th>Difference^t</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2C (rs3813929)</td>
<td>CC</td>
<td>Formulation C - 90 mg (N= 102)</td>
<td>-0.870 (0.0700)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>-0.352 (0.0990)</td>
<td>(-0.547, -0.157)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Formulation C - 120 mg (N= 104)</td>
<td>-0.929 (0.0694)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>-0.411 (0.0986)</td>
<td>(-0.605, -0.217)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Placebo (N= 102)</td>
<td>-0.519 (0.0701)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Formulation C - 90 mg (N= 8)</td>
<td>-0.893 (0.2333)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>-0.315 (0.3298)</td>
<td>(-0.998, 0.369)</td>
<td>0.3506</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Formulation C - 120 mg (N= 9)</td>
<td>-0.796 (0.2196)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>-0.217 (0.3133)</td>
<td>(-0.867, 0.432)</td>
<td>0.4953</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Placebo (N= 9)</td>
<td>-0.579 (0.2203)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[0230] FIG. 4A shows the CGI-S total score change from baseline for humans having the HTR2C (rs3813929) gene polymorphism receiving a placebo. The lower line, with reference to Day 29, represents humans with the CC genotype and the upper line, with reference to Day 29, represents humans with the CC/TT genotype. FIG.4B shows the CGI-S total score change from baseline for humans having the HTR2C (rs3813929) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC genotype and the upper line, with reference to the End of Study, represents humans with a CC/TT genotype. FIG. 4C shows the CGI-S total score change from baseline for humans having the HTR2C (rs3813929) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to End of Study, represents humans with the CC genotype and the upper line, with reference to End of Study, represents humans with the CC/TT genotype.

[0231] Results: Serotonin Subtype 2A Receptor - HTR2A (rs63 13)

[0232] Humans with the CC and CT/TT genotypes in the HTR2A gene had comparable total PANSS and CGI-S scores following treatment.
Humans with the CT/TT genotype in the HTR2A gene (rs6313) who received 90 mg Formulation C (N=64) or 120 mg Formulation C showed significant improvement in the change from baseline in total PANSS scores compared to placebo (N=67) (LSMEAN: -6.631; 95% CI: -10.985 to -2.277; p value: 0.0030 for the 90 mg Formulation C group and LSMEAN: -7.967; 95% CI: -12.220 to -3.713; p value: 0.0003 for the 120 mg Formulation C group). The detailed results are shown in Table 6 and Figure 5 for the Intent-to-Treat Population.

Table 6

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Allele</th>
<th>Treatment</th>
<th>LS Mean (SE)</th>
<th>Comparison</th>
<th>Difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2A (rs6313)</td>
<td>CC</td>
<td>Formulation C - 90 mg (N=45)</td>
<td>-15.678 (2.0173)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>-5.747 (2.8762)</td>
<td>(-11.438, -0.056)</td>
<td>0.0478</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Formulation C - 120 mg (N=43)</td>
<td>-16.275 (2.0721)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>-6.344 (2.9167)</td>
<td>(-12.115, -0.572)</td>
<td>0.0315</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Placebo (N=44)</td>
<td>-9.931 (2.0515)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Formulation C - 90 mg (N=64)</td>
<td>-15.282 (1.5791)</td>
<td>Formulation C - 90mg - Placebo</td>
<td>-6.631 (2.2077)</td>
<td>(-10.985, -2.277)</td>
<td>0.0030</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Formulation C - 120 mg (N=70)</td>
<td>-16.617 (1.5085)</td>
<td>Formulation C - 120mg - Placebo</td>
<td>-7.967 (2.1570)</td>
<td>(-12.220, -3.713)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>Placebo (N=67)</td>
<td>-8.650 (1.5371)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIG. 5A shows the PANSS total score change from baseline for humans having the HTR2A (rs6313) gene polymorphism receiving a placebo. The lower line represents humans with the CC genotype and the upper line represents humans with the CC/TT genotype. FIG. 3B shows the PANSS total score change from baseline for humans having the HTR2A (rs6313) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC/TT genotype and the upper line, with reference to the End of Study, represents humans with a CC genotype. FIG. 3C shows the PANSS total score change from baseline for humans having the HTR2A (rs6313) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000).
The lower line, with reference to End of Study, represents humans with the CC genotype and the upper line, with reference to End of Study, represents humans with the CC/TT genotype.

[0236] Humans with the CT/TT genotype in the HTR2A gene (rs63 13) who received 90 mg Formulation C (N=64) or 120 mg Formulation C (N=70) showed significant improvement in the change from baseline in CGI-S scores compared to placebo (N=67) (LSMEAN: -0.385; 95% CI: -0.624 to -0.145; p value: 0.0018 for the 90 mg Formulation C group and LSMEAN: -0.424; 95% CI: -0.658 to -0.189; p value: 0.0005 for the 120 mg Formulation C group). The detailed results are shown in Table 7 and Figure 6 for the Intent-to-Treat Population.

[0237] Table 7

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Allele</th>
<th>Treatment</th>
<th>LS Mean (SE)</th>
<th>Comparison</th>
<th>Difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR2A (rs6313)</td>
<td>cc</td>
<td>Formulation C- 90 mg (N= 45)</td>
<td>-0.870 (0.1064)</td>
<td>Formulation C- 90mg - Placebo</td>
<td>-0.305 (0.1522)</td>
<td>(-0.606, -0.004)</td>
<td>0.0471</td>
</tr>
<tr>
<td></td>
<td>cc</td>
<td>Formulation C- 120 mg (N= 43)</td>
<td>-0.917 (0.1092)</td>
<td>Formulation C- 120mg - Placebo</td>
<td>-0.352 (0.1541)</td>
<td>(-0.657, -0.047)</td>
<td>0.0240</td>
</tr>
<tr>
<td></td>
<td>cc</td>
<td>Placebo (N= 44)</td>
<td>-0.565 (0.1083)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>Formulation C- 90 mg (N= 64)</td>
<td>-0.878 (0.0870)</td>
<td>Formulation C- 90mg - Placebo</td>
<td>-0.385 (0.1215)</td>
<td>(-0.624, -0.145)</td>
<td>0.0018</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>Formulation C- 120 mg (N= 70)</td>
<td>-0.917 (0.0832)</td>
<td>Formulation C- 120mg - Placebo</td>
<td>-0.424 (0.1188)</td>
<td>(-0.658, -0.189)</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>Placebo (N= 67)</td>
<td>-0.493 (0.0847)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[0238] FIG. 6A shows the CGI-S total score change from baseline for humans having the HTR2A (rs63 13) gene polymorphism receiving a placebo. The lower line, with reference to End of Study, represents humans with the CC/TT genotype and the upper line, with reference to End of Study, represents humans with the CC genotype. FIG.6B shows the CGI-S total score change from baseline for humans having the HTR2A (rs63 13) gene polymorphism receiving a 120 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to the End of Study, represents humans with a CC/TT genotype and the upper line, with reference to the End of Study.
Study, represents humans with a CC genotype. FIG. 6C shows the CGI-S total score change from baseline for humans having the HTR2A (rs6313) gene polymorphism receiving a 90 mg dose of Formulation C (referred to in the Figure as RBP-7000). The lower line, with reference to End of Study, represents humans with the CC genotype and the upper line, with reference to End of Study, represents humans with the CC/TT genotype.

[0239] Summary of Example 1.

[0240] The results described herein show an association of HTR2C (rs3813929), HTR2A (rs6313), and MC4R (rs17782313) polymorphisms with PANSS and CGI-S scores in humans with acute schizophrenia. This study supports the hypothesis that polymorphisms in the HTR2C (rs3813929), HTR2A (rs6313), and MC4R (rs17782313) receptors may affect individual responses to risperidone, such as risperidone administered as Formulation C.

[0241] Example 2

[0242] A long-acting (28-day) subcutaneous formulation of risperidone (Formulation C) was developed for the treatment of schizophrenia to address issues of compliance and non-adherence associated with oral risperidone treatment. Using the medical ranking systems Positive and Negative Syndrome Scale (PANSS) or the Clinical Global Impression - Severity (CGI-S) scale to measure symptom severity in humans, the inventors established an exposure-response relationship between active moiety exposure (risperidone + 9-OH-risperidone) and PANSS or CGI-S scores using data from a registration trial. 9-OH-risperidone is also known as paliperidone.

[0243] The registration trial consisted of a phase 3 randomized, double-blind, placebo-controlled, multicenter study in 354 humans to evaluate the efficacy, safety and tolerability of Formulation C at two doses, 90 mg and 120 mg. Pharmacokinetic/Pharmacodynamic (PKPD) models were developed using non-linear mixed effects modeling (NONMEM) using the program NONMEM 7.3. These integrated population PKPD models included a joint PK model for risperidone and 9-OH-risperidone together with placebo and drug-effect models. Taken together, these models are necessary to establish the relationship between active moiety exposure and PANSS/CGI-S scores.

[0244] Cytochrome P450 2D6 (CYP2D6) is one of the most important enzymes involved in the metabolism of xenobiotics. Subjects classified as CYP2D6 poor and intermediate metabolizers had
lower formation rates of 9-OH risperidone (94% and 76% lower respectively) compared to subjects classified as extensive and ultra-rapid CYP2D6 metabolizers. Following Formulation C treatment, the maximum relative decrease in the PANSS score was ~ 5% above the placebo effect, half of which could be achieved at a concentration of 4.6 ng/mL of the active moiety. A proportional odds model for CGI-S score related the average concentration to probability of improving scores over time. It is noted that the CYP2D6 phenotype on metabolism of risperidone was the only relevant covariate identified.

[0245] Formulation C (also known as RBP-700Q) is a long-acting formulation of risperidone administered once monthly via subcutaneous (SC) injection for the treatment of schizophrenia. Formulation C is being developed to address issues of compliance and non-adherence associated with oral risperidone treatment. The safety, tolerability, and pharmacokinetic (PK) profile of Formulation C were evaluated in two Phase 1 single dose studies (a first-in-man study and a single ascending dose study) and in one Phase 2a multiple ascending dose study, all conducted in clinically stable schizophrenic male and female adult subjects. These studies showed that the subcutaneous injection of Formulation C resulted in sustained plasma concentrations of the active moiety over the dosing interval (28 days), and that plasma concentrations close to steady-state were reached after the first subcutaneous injection when transitioning from oral risperidone therapy.

[0246] Population PK models of Formulation C were previously developed using data from the single and multiple ascending dose studies. In the single ascending dose study, 45 clinically stable schizophrenic patients with confirmed diagnosis of paranoid, residual or undifferentiated schizophrenia were randomized to receive a single dose of one of the three Formulation C dose levels (60, 90, and 120 mg), with 15 subjects per cohort. The multiple ascending dose study recruited a similar number of patients within the same population as the single ascending dose study and evaluated the effects of three monthly doses (60, 90 and 120 mg) after switching subjects from 2, 3 or 4 mg/day oral risperidone, respectively. Risperidone and 9-OH-risperidone plasma concentration data were well described by a population PK model having the same structural model as the one used for the modeling of the single dose data. Steady-state was reached after the second or third Formulation C subcutaneous injection, but plasma concentrations close to steady state values were obtained right after the first subcutaneous injection when switching from oral
risperidone therapy. Data from these two studies were analyzed together using a single population
PK model to guide dose selection for phase 3 trials.

[0247] The purpose of the present modeling work was to establish an exposure-response
relationship between active moiety exposure (risperidone + 9-OH-risperidone) and Positive and
Negative Syndrome Scale (PANSS) or Clinical Global Impressions severity (CGI-S) scores, using
data from a phase 3 registration trial (NCT02109562). The objectives of the population analysis for
Formulation C were to (a) characterize the PK profile of Formulation C in schizophrenic patients
and to assess the effect of selected covariates on the PK of Formulation C, and (b) characterize the
PK/pharmacodynamic (PD) relationships between active moiety plasma concentrations with the
PANSS and CGI-S scales.

[0248] Methods

[0249] A phase 3, randomized, double-blind, placebo-controlled, multicenter study
(NCT02109562) was conducted to evaluate the efficacy, safety and tolerability of Formulation C (90
mg and 120 mg) as a treatment in subjects with acute schizophrenia, subjects in an acute psychotic
state, or subjects in relapse with acute schizophrenic symptoms, who had a PANSS score of at least
80-120 and a score greater than 4 on at least two of the following four items: hallucinatory behavior,
delusions, conceptual disorganization, or suspiciousness/persecution at screening. Subjects were
randomly assigned to receive 2 subcutaneous doses of either Formulation C (90 or 120 mg) or
placebo over 8 weeks. A total of 538 subjects were screened to enroll in this Phase 3 study. Only
354 subjects passed screening, of which 119 belonged to the placebo group and 116 and 119
belonged to the 90 mg and 120 mg treatment arms, respectively. Furthermore, 17 subjects (7-
placebo, 5-90 mg, 5-120 mg) failed to make it to the Intent-to-Treat (ITT) group as they either did
not receive at least one dose of Formulation C or did not have at least one assessment post-baseline
that facilitates the calculation of change from baseline.

[0250] During the screening phase all subjects received 0.25 mg of oral risperidone at Visit 1 (3 to
8 days before double-blind treatment) and a second dose of 0.25 mg oral risperidone 24 hours later
to assess their tolerability to risperidone prior to receiving Formulation C. Subjects who passed
screening were tapered off their oral anti-psychotic if applicable. Tapering rates for washout
medications were at the discretion of the investigator and were determined on an individual basis.
with consideration to patient state, dose, and known PK of the medication being tapered, provided the restricted medication was discontinued during Day -8 and Day -1, inclusive. Modifications to subject's pre-existing treatment were not made unless deemed clinically important by the investigator. Upon completion of all study participation requirements, subjects were randomized to one of the three study treatments at Visit 3 (Day 1), corresponding to the start of the 8-week double-blind treatment period: subjects received two subcutaneous injections of Formulation C (90 mg or 120 mg) or placebo at a 28-day interval, on Day 1 and on Day 29.

[0251] Pharmacokinetic Sampling

[0252] Sparse PK blood samples for analysis of risperidone and 9-OH risperidone plasma levels were collected at specific time points. A pre-dose sample of Day 1 was followed by post-injection samples on Days 1-3, 8-15, 16-22 and on Day 29 just before the second subcutaneous injection of Formulation C. Following the second injection of Formulation C, samples were collected on Days 29-31, 36-42, 43-49 and 55-57.

[0253] Pharmacogenetics Sampling

[0254] Blood samples for DNA analysis were collected before the first injection of Formulation C on Day 1. These samples were collected to assess how the genetic variation in enzymes and receptors might affect the PK, safety, and efficacy of Formulation C. Genotypes were assessed for cytochrome P450 2D6 (CYP2D6), dopamine D2 receptor (DRD2), serotonin 2C receptor (5-HT2C), serotonin 2A receptor (5-HT2A) and melanocortin 4 receptor (MCR4).

[0255] Laboratory Tests

[0256] Various laboratory tests were conducted throughout the study duration at specified time points. Tests related to liver function (aspartate aminotransferase - AST; alanine aminotransferase - ALT) and renal function (Creatinine clearance - CRCL) were used as predictors to explore and account for the variability in PK exposure.

[0257] Bioanalysis

[0258] Plasma concentrations of risperidone and 9-OH risperidone were determined using a validated method of liquid chromatography with tandem mass spectrometry (LC-MS/MS). The
analytical methodology was based on the following procedure: 0.05 mL of human plasma containing internal standards (d4-risperidone, d4-9-OH risperidone) was first acidified and then extracted using solid phase extraction. Analysis required evaporation of elute solvent before being reconstituted. An aliquot of the extract was injected onto a Sciex API 5500 LC-MS/MS equipped with an HPLC column. Quantitation was performed using $1/x^2$ weighted linear least squares regression analysis generated from fortified plasma calibration standards prepared immediately prior to each run. The method was validated for specificity, linearity, lower limit of quantitation, precision, accuracy, recovery and stability for a range of 0.1 to 100 ng/mL for both risperidone and 9-OH risperidone. The overall precision for both analytes was greater than 11.7%; the overall accuracy was within ±4.4%. The recoveries of both analytes and internal standards were greater than 91%. The established short-term and long-term stability covered the maximum sample storage time.

[0259] Efficacy Assessments

[0260] The clinical assessments for efficacy included the PANSS and the CGI-S scales. The PANSS scale consists of 30 items, where each item is scored from 1 through 7 (1 indicating the absence of the symptom, and 7 indicating extremely suffering from the symptom). These 30 items are grouped into 3 subscales; positive (7 items), negative (7 items) and general psychopathology (16 items). PANSS scores were collected at baseline on Day 1 and on Days 15+/-1, 29, 43+/-1 and 57. A total of 1571 PANSS assessments were available for analysis from this 8-week study.

[0261] CGI-S represents the overall clinical severity of illness for each subject. To perform this assessment, the rater answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices included: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. CGI-S scores were collected at the same times as those for PANSS, i.e., at baseline on Visit 3 (Day 1) and on Days 15+/-1, 29, 43+/-1 and 57. A total of 1998 CGI-S assessments were available for analysis from this 8-week study.

[0262] Model Development

[0263] A non-linear mixed effects modeling approach to describe the time course of PK, PANSS
and CGI-S scores was implemented using the NONMEM 7.3 software. Perl-speaks-NONMEM (PsN, v 4.4.0) was used to operate NONMEM. R software version 3.2.0 (www.r-project.org) was used for graphical inspection of the results. Risperidone and 9-OH risperidone plasma concentrations were used to estimate the parameters of the population PK model, while absolute PANSS scores and CGI-S scores were used for the PD and PK/PD models. The First-Order Conditional Estimation (FOCE) method with or without interaction option in NONMEM was used to estimate population PK and PK/PD model parameters and in the case of CGI-S analysis, LAPLACE method was used. Inter-individual variability (IIV) for the structural model parameters was evaluated assuming lognormal or normal distributions of subject-specific random effects:

\[
p_i = TV \times \exp^\omega \quad \text{or} \quad p_i = TV + \eta_i
\]

where TV represents the population typical value of the PK and/or PD parameter, and \( p_i \) is the value of the parameter for subject \( i \). \( \eta_i \) denotes an individual-specific random effect that distinguishes the value of the \( i^{th} \) subject from the TV. The \( \eta_i \) is normally distributed with mean zero and variance \( \omega^2 \). The IIV was expressed as percent coefficient of variation (% CV) that was calculated as \( \sqrt{e^{\omega^2} - 1} \) for exponential models; for additive models, the CV was calculated as \( \omega / TV \).

[0264] The intra-individual or residual variability (RUV) describes the variability in residual error, i.e. the variability that remains unexplained and refers to, for example, dosing inaccuracies, analytical assay error, or error in recording sampling times, and structural model misspecifications. A combined proportional and additive error model was used to describe RUV in the plasma concentration, while, an additive term was used to account for the unexplained variability in PANSS score as shown in the following equations:

\[
\begin{align*}
\gamma_{ij} &= \tilde{y}_{ij} + \varepsilon_{ij} + \varepsilon_{zij} + \varepsilon_{2ij} \quad \text{for PK Model} \\
\gamma_{ij} &= \tilde{y}_{ij} + \varepsilon_{ij} \quad \text{for PANSSPD Model}
\end{align*}
\]

Where \( v_{ij} \) is the \( j^{th} \) observation in the \( i^{th} \) individual, \( \tilde{y}_{ij} \) is the expectation of \( y_{ij} \) under the model conditionally to subject \( i \), \( \varepsilon_{ij} \) and \( \varepsilon_{zij} \) and \( \varepsilon_{2ij} \) are normally-distributed random errors with mean zero and variance \( \sigma^2 \), \( \sigma_1^2 \), and \( \sigma_2^2 \), respectively. In the combined error model \( \sigma_1^2 \), and \( \sigma_2^2 \), represent the
additive and proportional variance components, respectively.

Model selection was based on comparison of the objective function values (SOFV: 3.84 for one additional estimated parameter, corresponding to a p-value of 0.05) and the goodness-of-fit (GOF) plots. GOF was assessed graphically by evaluation of the agreement between observed and predicted plasma concentrations or PANSS scores, the individual predicted profiles vs. time, the range of individual weighted residuals (IWRES), conditional weighted residuals (CWRES) and expected weighted residuals (EWRES), and the shape of the distribution of these residuals about zero across the range of the predicted concentrations or PANSS scores. The percentage relative standard errors (% RSE) of the parameter estimates and reductions in both IIV and RUV were also used to discriminate between competing models.

Influences of patient and study-specific covariates were evaluated as possible explanatory variables for the variability in the PK or PK/PD model parameters. Covariate analysis was performed in NONMEM using PsN with a step-wise forward additive approach followed by a step-wise backward elimination approach with a p-value of 0.05 and 0.001, respectively. Unrelated covariates were included in the model using different functional forms like linear, power and exponential functions.

Pharmacokinetic Model

The population PK of risperidone and 9-OH risperidone after administration of Formulation C was previously described using data from the single and multiple ascending dose studies for Formulation C. Both studies were designed to provide rich plasma concentration-time data that could be used to characterize the PK of Formulation C after single or multiple injections at various doses.

The analysis of the plasma concentration time data from the present phase 3 study was started using the base structural model developed in these two earlier studies (FIG. 7). Briefly, a joint model for risperidone and 9-OH risperidone described the PK profile of Formulation C after subcutaneous injection. A dual absorption process was modeled to account for the double peak plasma concentration-time profiles observed for risperidone and 9-OH-risperidone. This dual absorption process was described by (1) a first-order rate constant (ka1) associated with the first
peak; and (2) a transit compartment absorption model, with absorption rate constant \( ka2 \) and transit rate constant \( ktr \), associated with the second peak to mimic the slow delivery of risperidone from the formulation. Together with this absorption sub-model, a two-compartment model with two first-order elimination processes described the plasma disposition of risperidone; systemically available risperidone was partly converted into 9-OH risperidone \( (kr9) \) and partly eliminated by other routes \( (krel) \). The plasma disposition of 9-OH risperidone following Formulation C administration was described by a one-compartment model with first-order elimination \( (k9el) \). Since the volume of the 9-OH risperidone was not identifiable, it was set equal to the central volume of the parent compound.

[0270] Pharmacodynamic Model of PANS

[0271] PD models usually comprise an underlying disease progression model to capture the changing disease status of schizophrenia with time, and include treatment effects models (placebo and drug) that refer to all the underlying PK and PD processes involved in producing a treatment effect on the time course \( (t) \) of disease progression, as shown below:

\[
\text{Disease Status} (t) = \text{disease state} (t_0) + \text{disease progression} (t) + \text{placebo} (t) + \text{drug response} (t)
\]

where \( \frac{3}{4} \) is the time at the start of the trial. In the present case, it is difficult to separate the disease progression from placebo response due to the episodic nature of schizophrenia and the short duration of the study. Hence, the overall disease progression + placebo response will be referred to as the placebo model.

[0272] Placebo Response Model

[0273] Several placebo response models were investigated before picking the one that best described the time course of PANS in the placebo group of the Phase 3 study. Model exploration was conducted using only the placebo data from this study.

[0274] Note on Dropouts

[0275] Dropouts are common in schizophrenia trials and are in the upper 40-70 \%. Dropouts, if not accounted for, influence standard errors of estimated model parameters and widen the confidence intervals predicted through simulations. The dropout rates in this phase 3 trial were
about 6-9% only across each of the three arms, which is very low when compared to other trials in schizophrenia and were considered unlikely to affect the precision of the parameter estimates, and hence a sub-model to account for dropouts was not considered for this analysis.

PANSS PK/PD – Drug Effect Model

PK/PD modeling relating the time course of PANSS to the drug exposure was performed using a sequential approach. Since the pharmacological profile and potency of 9-OH-risperidone are similar to those of risperidone itself, active moiety plasma concentration was used as a predictor for efficacy. Active moiety [AM] plasma concentrations were calculated as the sum of risperidone and 9-OH-risperidone plasma concentrations, corrected by molecular weight according to the following formula: \[ AM = [\text{risperidone}] + [9-OH \text{risperidone}] \times \left( \frac{410}{426} \right), \]
where [risperidone] and [9-OH risperidone] are the population PK model-based individual predictions of concentrations.

Sequential (where the placebo response model parameters were initially fixed) and simultaneous analysis of the drug-effect model were explored. Two drug effects models were tested: a linear concentration related slope and an Emax function, both of which affect the change from baseline in PANSS by relating drug exposures.

Pharmacodynamic Model for CGI-S

The overall clinical severity of illness for each subject was rated using the CGI-S ordinal scale with 6 categories. The CGI-S scores were the secondary efficacy endpoint for the Phase 3 study. Due to the low frequency, some levels were consolidated such that the final scores were represented in four categories: (1) Levels 1-3 - mildly ill; (2) Level 4 - moderately ill; (3) Level 5 - markedly ill; and (4) Level 6 - severely ill.

As the consolidated CGI-S score is a categorical ordinal variable (taking integer values 3-6) the probability of observing each score was modeled using logistic regression. If \( Y_j \) denotes the observation in subject \( i \) at time \( t_j \) (\( j = \tau \ldots \eta \)) and \( Y_i = (Y_1, \ldots, Y^{\eta_i}) \) is the vector of CGI-S scores for subject \( i \), the probability for \( Y_j \) to be larger than or equal to the score \( m \) (\( m = 4, 5 \) and 6) can be expressed as follows:

\[
G[P(Y_j \geq m)] = \logit(p_j) = \beta_m + fp + fd + \eta_i;
\]
in which

$$\text{logit}(p_{ij}) = \log \left( \frac{p_{ij}}{1 - p_{ij}} \right)$$

and

$$p_{ij} = \frac{\exp(\beta_m + fp + fd + \eta_i)}{1 + \exp(\beta_m + fp + fd + \eta_i)}$$

where $g$ is the logit function of a probability, $p_{ij}$ is short notation for $P(Y_{ij} \geq m)$. For a $M$ category score, only $M - 1$ intercepts need to be estimated. Here, $\beta_m$ decreases with $m$ to account for the ordinal nature of the data; $fp$ represents the placebo effect estimated using placebo data only that is a function of time ($TSLP$); $fd$ is the drug effect and is a function of active moiety concentration through the parameter $CSLP$; $\eta_i$ is the subject-specific random effect introduced on the intercept.

The relation is setup such that the covariate relationship is the same for all cumulative categories on the log odds (logits).

[0282] The probability of being at a particular score was formulated as:

$$P(Y_{ij} = 3) = 1 - P(Y_{ij} \geq 4)$$

$$P(Y_{ij} = 4) = P(Y_{ij} \geq 4) - P(Y_{ij} \geq 5)$$

$$P(Y_{ij} = 5) = P(Y_{ij} \geq 5) - P(Y_{ij} \geq 6)$$

$$P(Y_{ij} = 6) = P(Y_{ij} \geq 6)$$

[0283] CGI-S PK/PD – Drag Effect Model

[0284] Using only data from placebo patients, the formulation listed above was first used to model the CGI-S scores. Subsequently, the treatment arm data was added in a next step where the CGI-S
scores were fit as a function of time. The PK/PD model between drug exposure and CGI-S score was established using the plasma concentrations of the active moiety as the predictor.

[0285] Covariate Model

[0286] Covariate exploration was conducted on each sub-model and the final joint PK/PD model. The inclusion of potential covariates in the final model was based on their clinical relevance and diagnostic plots of empirical Bayes parameter estimates (EBEs) vs. covariate values. The graphical assessment to evaluate covariate relationships looked at the predictions of subject-specific deviations from population mean estimates (n's) for the respective PK or PK/PD parameter from the base model against covariate of interest. Continuous covariates included in this analysis were body weight (BW), age, waist-to-hip ratio (WTH), body mass index (BMI), aspartate aminotransferase (AST), alanine amino transferase (ALT) and creatinine clearance (CRCL). Categorical covariates included gender (male=reference, female), race (African American=reference, Caucasian, Others), ethnicity (Not Hispanic or Latino=reference, Hispanic or Latino), CYP2D6 metabolizer status (Extensive Metabolizers (EM) and Inconclusive = reference, Poor Metabolizers (PM), Intermediate Metabolizers (IM)) and genotype classification for Dopamine D2 (DRD2), Serotonin 2A (5-HT2A), Serotonin 2C (5-HT2C) and Melanocortin 4 (MCR4) receptors. For categorical covariates, covariate effects were added as a proportional component such that the effect estimate represents the % change from the reference typical value of the estimate.

\[
P_{TV} = P_{TV} \times (1 + \text{slope} \times (\text{Cov} - \text{median}_{\text{cov}}))
\]

\[
P_{TV} = P_{TV} \times \left(\frac{\text{Cov}}{\text{median}_{\text{cov}}}\right)^{\text{pow}} \quad \text{— For continuous covariates}
\]

\[
P_{TV} = P_{TV} \quad \text{if } \text{Cot} == 0
\]

\[
P_{TV} = P_{TV} \times (1 + \text{prop}\text{actor}) \quad \text{if } \text{Cov} == 1 \quad \text{— For categorical covariates}
\]

where \(PTV\) and \(slope\), \(pow\) and \(prop/actor\) are fixed effect parameters representing the population typical value and the covariate effect respectively.

[0287] To test the covariate parameter relationship, covariates were added to structural parameters, using the stepwise covariate modeling approach (SCM), as implemented in the PsN software package (5,6). With this technique, different covariate-parameter relationships can be
tested in a forward fashion ($p < 0.05$ and $SOFV$ of 3.84) to build up the final full model, which in turn is evaluated in the backward elimination step ($p < 0.001$ and $dOFV$ of 10.8). When a correlation between covariates was found, one of them was omitted on the basis of the prior clinical preference. The resulting final model contains only covariates that meet the pre-defined statistical criteria and show an acceptable precision of related parameter estimates ($<50\%$ RSE).

[0288] Model Evaluation

[0289] A nonparametric bootstrap resampling method was used to evaluate the stability and robustness of the final PK model. Resampling with replacement generated 200 bootstrap data sets and the final population PK model was fitted repeatedly to each of the 200 bootstrap data sets. The median and 95\% confidence intervals of parameters obtained from this step were compared with the final parameter estimates. In addition, the prediction-corrected visual predictive check (pcVPC) with 1000 simulated datasets was also performed. In a pcVPC, the variability coming from binning across independent variables is removed by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. Results from the VPC were assessed using graphical comparison of the appropriate 90\% prediction interval from simulated data and was visually explored in comparison with overlaid observed data from the original dataset. pcVPC’s for the PANSS models and categorical VPC’s for the CGI-S PD and PK/PD models were used.

[0290] Formulation C Pharmacokinetic Analysis

[0291] Descriptive statistics in Table 8 provide a summary of the demographics for continuous and categorical covariates. FIG. 8 shows the mean (SD) plasma concentration-time plots for risperidone and 9-OH risperidone in the 90 mg and 120 mg Formulation C groups. The mean profiles in these plots reveal a prolonged absorption phase consistent with the slow delivery of risperidone from the depot formed from Formulation C. Rich PK sampling from the previous Phase 1 studies suggested the presence of two peaks: the first one associated with a rapid deliver}- from the injection site (first-order absorption process), and the second one associated with the slow delivery from the depot (delayed delivery process described by a transit compartment absorption model). It is difficult to visualize this double peak phenomenon in this sparse design.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group</th>
<th>90 mg Formulation C group</th>
<th>120 mg Formulation C group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number (n)</td>
<td>112</td>
<td>111</td>
<td>114</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.76±8.65</td>
<td>40.45±9.42</td>
<td>40.41±9.42</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>92.61±22.86</td>
<td>90.89±18.86</td>
<td>88.54±20.34</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>30.97±7.29</td>
<td>29.59±5.96</td>
<td>29.33±6.73</td>
</tr>
<tr>
<td>Waist-to-hip-ratio</td>
<td>0.95±0.09</td>
<td>0.95±0.08</td>
<td>0.94±0.07</td>
</tr>
<tr>
<td>Alanine transferase (ALT, U/L)</td>
<td>29.06±20.09</td>
<td>29.88±21.01</td>
<td>28.54±23.58</td>
</tr>
<tr>
<td>Aspartate transferase (AST, U/L)</td>
<td>21.65±8.5</td>
<td>23.14±12.13</td>
<td>20.99±8.66</td>
</tr>
<tr>
<td>Creatinine Clearance (CRCL, mL/min)</td>
<td>122.69±46.91</td>
<td>121.91±32.68</td>
<td>122.62±39.77</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>81 (72.3%)</td>
<td>93 (83.78)</td>
<td>84 (73.6%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>101 (90.1%)</td>
<td>104 (93.6%)</td>
<td>104 (91.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (9.8%)</td>
<td>7 (6.3%)</td>
<td>10 (8.7%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>84 (75%)</td>
<td>79 (71.1%)</td>
<td>80 (70.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (25%)</td>
<td>32 (28.8%)</td>
<td>34 (29.8%)</td>
</tr>
<tr>
<td>CYP2D6 Genotype Metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>92 (82.1%)</td>
<td>98 (88.2%)</td>
<td>97 (85.0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 (7.1%)</td>
<td>4 (3.6%)</td>
<td>7 (6.1%)</td>
</tr>
<tr>
<td>Poor</td>
<td>3 (2.6%)</td>
<td>1 (0.9%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>8 (7.1%)</td>
<td>7 (6.3%)</td>
<td>6 (5.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Dopamine D2 receptor (DRD2) genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>106 (94.6%)</td>
<td>108 (97.2%)</td>
<td>113 (99.1%)</td>
</tr>
<tr>
<td>GC</td>
<td>5 (4.4%)</td>
<td>2 (1.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Serotonin 2C receptor (5-HT2C) genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>102 (91.0%)</td>
<td>102 (91.9%)</td>
<td>104 (91.2%)</td>
</tr>
<tr>
<td>CT</td>
<td>4 (3.6%)</td>
<td>4 (3.6%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>TT</td>
<td>5 (4.4%)</td>
<td>4 (3.6%)</td>
<td>6 (5.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Serotonin 2A receptor (5-HT2A) genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>44 (39.2%)</td>
<td>45 (40.5%)</td>
<td>43 (37.7%)</td>
</tr>
<tr>
<td>CT</td>
<td>55 (49.1%)</td>
<td>49 (44.1%)</td>
<td>48 (42.1%)</td>
</tr>
<tr>
<td>TT</td>
<td>12 (10.7%)</td>
<td>15 (13.5%)</td>
<td>22 (19.2%)</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Melanocortin 4 receptor (MCR4) genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>9 (8.0%)</td>
<td>9 (8.1%)</td>
<td>11.4 (85.0%)</td>
</tr>
<tr>
<td>TC</td>
<td>48 (42.8%)</td>
<td>55 (49.5%)</td>
<td>27.1 (61.1%)</td>
</tr>
<tr>
<td>TT</td>
<td>54 (48.2%)</td>
<td>46 (41.4%)</td>
<td>60.5 (2.6%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>
Following inspection of raw data, the 234 subjects from the Formulation C treatment arms contributed to 3154 PK samples that were included in the analysis, 1577 for risperidone and 1577 for 9-OH risperidone. Drug concentrations below the lower limit of quantification (BLQ) were considered as missing. The total number of BLQ was 373 that is approximately 10.3%. However, of the 373 BLQ values, 355 were pre-dose concentrations and the remaining values were post-dose. Considering these extremely small number of BLQ values post-dose (n=18), a decision was made to not include them in the analysis. The pre-dose concentrations above the LLOQ were mainly due to the low dose oral risperidone that was given to all subjects prior to treatment. However, these exposures were insignificant compared to those from the treatment arm (data not shown) and hence were not included in the analysis.

A combined additive and proportional residual error model common to risperidone and 9-OH-risperidone was used in the base model. There were no correlations between the random effects at the subject level. This model provided a reasonable fit of the data and was thus retained for subsequent covariate model development. The exploratory analysis on individual PK parameter predictions (EBEs) vs. covariates identified CYP2D6 phenotype as potential covariate with a strong correlation to the formation of metabolite from the parent. In addition, race was correlated, although to a lesser extent, to both the fast (ka1) and slow (ka2) absorption rate constants. So, based on EBE's, CYP2D6 phenotype on metabolite formation and race on ka1 and ka2 were selected for testing in NONMEM. BMI was a significant predictor in the previous work, and hence BMI was also taken forward for covariate testing along with CYP2D6 phenotype and race.

Non-parametric bootstrap-based parameter estimates for the final covariate model are presented in Table 9. Stepwise covariate search showed that BMI was not a significant covariate on the absorption rate constants, confirming the lack of correlation in the visual diagnostics of absorption rate constant EBE's vs. BMI. Race was also not significant. Regarding CYP2D6 phenotype, intermediate metabolizers had a 76% lower metabolite formation than extensive/inconclusive metabolizers, while poor metabolizers had a 94% lower metabolite formation.
Table 9

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Estimate [95 % CI]</th>
<th>IIV [95 % CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ka1</td>
<td>Rapid abs (h⁻¹)</td>
<td>0.005 [0.004, 0.007]</td>
<td>41.8 [35.5, 50.7]</td>
</tr>
<tr>
<td>ka2</td>
<td>Slow abs (h⁻¹)</td>
<td>0.016 [0.01, 0.022]</td>
<td>32.1 [0.3, 49.9]</td>
</tr>
<tr>
<td>krel</td>
<td>Elimination (h⁻¹)</td>
<td>0.043 [0.026, 0.074]</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>App. Vol of Risp (L)</td>
<td>129 [96, 158]</td>
<td>38.6 [32.4, 44.8]</td>
</tr>
<tr>
<td>ktr</td>
<td>Transit Rate Constants (h⁻¹)</td>
<td>0.023 [0.021, 0.025]</td>
<td>42.3 [31.8, 52.7]</td>
</tr>
<tr>
<td>krkp</td>
<td>Cen to Per (h⁻¹)</td>
<td>0.841 [0.652, 1.143]</td>
<td>45.1 [28.4, 57.1]</td>
</tr>
<tr>
<td>krpr</td>
<td>Per to Cen (h⁻¹)</td>
<td>0.006 [0.005, 0.008]</td>
<td>67.9 [47.9, 81.3]</td>
</tr>
<tr>
<td>kr9</td>
<td>Met Formation (h⁻¹)</td>
<td>0.221 [0.179, 0.278]</td>
<td>49.3 [37.8, 60.1]</td>
</tr>
<tr>
<td>K9el</td>
<td>Met Elimination (h⁻¹)</td>
<td>0.069 [0.056, 0.088]</td>
<td>18.8 [0.2, 29.5]</td>
</tr>
<tr>
<td>σadd</td>
<td>Additive RUV (ng/mL)</td>
<td>0.137 [0.003, 0.214]</td>
<td></td>
</tr>
<tr>
<td>σprop</td>
<td>Proportional RUV</td>
<td>0.297 [0.278, 0.321]</td>
<td></td>
</tr>
<tr>
<td>CYP2Dt intermediate</td>
<td>Effect on Metabolite Formation</td>
<td>-0.76 [-0.858, -0.567]</td>
<td></td>
</tr>
<tr>
<td>CYP2D6 Poor</td>
<td>Effect on Metabolite Formation</td>
<td>-0.942 [-0.968, -0.886]</td>
<td></td>
</tr>
</tbody>
</table>

Standard diagnostic plots and representative model fits for the individual PK profiles for risperidone and 9-OH risperidone indicate that the model captured the data very well. Further, a pcVPC stratified by analyte for the final covariate model (FIG. 9) shows that the variability in the data (quantified by 5th and 95th percentiles) was well predicted, with the exception of the upper 95th percentiles which was under- and over- predicted for the parent and metabolite respectively. This was a direct consequence of the presence of some extremely high levels contributed by poor and intermediate metabolizers for CYP2D6.

Pharmacodynamic Model for PANS S

FIG. 10 shows the mean PANSS score over time across the dose groups. There is a clear
separation in change from baseline between placebo and treatment arms. There were 527, 526 and 518 PANSS observations in the placebo, 90 mg and 120 mg groups, respectively. It is clear from the plots that on average, PANSS decreased over time in all three treatment groups. Based on the model selection criteria as described in the methods, the Weibull model was chosen over the exponential models even though they had similar OFV, as it provided better individual fits than the exponential model. Further, a linear drift parameter with associated IIV was added to the Weibull model to account for potential individual relapses.

[0300] The baseline demographic covariates (age, BMI, WTH, BW, sex, race, ethnicity), CYP2D6 phenotype and the receptor genotypes (5-HT2C, 5-HT2A, MC4R, DRD2) were tested in NONMEM as predictors on this model (Table 8). A stepwise covariate approach found no significant covariates on the placebo model. GOF plots and pcVPC for the placebo model shows that the model captured the data very well.

[0301] PK/PD Analysis for PANSS Score

[0302] The treatment arm data was then added to the placebo data. Treatment (placebo vs. 90 mg and 120 mg) as a predictor on placebo effect, MDS, was the only expected significant covariate with Formulation C eliciting a maximum change in baseline of about 11.6% as opposed to 5% in the placebo arm. In order to investigate the exposure-response relationship at the subject level, active moiety plasma concentrations were calculated from the individual predictions of risperidone and 9-OH risperidone plasma concentrations as indicated in the methods section. An \( E_{\text{max}} \) model best quantified the drug effect, and the parameter estimates of the overall PK/PD model are shown in Table 10. The final exposure response model is depicted by the following equations:

\[
\text{DrugEff} = \frac{E_{\text{max}} \times AM}{EC_{50} + AM}
\]

\[
\text{PredictedPANSS} = \text{ESL} \times \left[ 1 - \text{MDS} \times \left( 1 - \exp \left( \frac{T}{T_{\text{PROG}}} \right)^{\text{POW}} \right) - \text{DmgEff} \right]^{0.5} \times \text{DRIFT} \times T
\]
The placebo effect (MDS) for the average schizophrenic patient in this population was estimated to be 0.066 (i.e. the maximum relative decrease in PANSS from the baseline PANSS score was 6.6%). Similarly, the maximum drug effect ($E_{\text{max}}$) of active moiety (AM) was found to be 0.054 (i.e., the maximum relative decrease in PANSS score from baseline following Formulation C treatment on top of the placebo effect was ~ 5.5%). The typical $EC_{50}$ value for PANSS total score was found to be 4.6 ng/mL. The IIV in $EC_{50}$ could not be estimated, probably due to the sparseness in this design, and was set to zero. Time when 63.2% of the maximum change from baseline was reached was about 1.7 weeks (~ 12 days). The linear drift parameter describes the worsening of the disease in some patients after initial improvement or vice versa. Typical model diagnostics and bootstrap results in Table 10 show that the PK/PD model parameters were well estimated with good precision, except for $EC_{50}$.

Inspection of Empirical Bayes estimate's relation with covariates did not identify any major trends. Further, a stepwise covariate analysis confirmed that no covariates were significant in this model. Concomitant medications and clinical study site were not tested for their effects, due to the large number of missing data and low number of subjects across the 33 clinical sites to achieve a
meaningful effect.

[0306] A pcVPC shown in FIG. 11 shows that the model captured both the mean and variability well, although there seemed to be a small under-prediction with regards to change from baseline PANSS. However, the overall trend was well captured.

[0307] Pharmacodynamic model for CGI-S

[0308] FIG. 12 shows that the proportion of patients with a CGI-S score of 3 (mildly ill) increased over time in all treatment groups, while the proportion of patients with score 5 (markedly ill) decreased. While such trends were expected in Formulation C treatment groups, they were also observed in the placebo group, suggesting the presence of a placebo effect.

[0309] There were 518, 516 and 515 CGI-S observations in the placebo, 90 mg and 120 mg treatment group respectively. A placebo model with a time course effect (TSLP x 1 \( \text{M}^{3/4} \)) was statistically superior to the base model without the time course (data not shown).

[0310] PK/PD Analysis for CGI-S Score

[0311] Models with and without a relationship between CGI-S score and Formulation C exposure [dose, active moiety plasma concentration] were tested on top of the placebo model that included a time course on placebo effect. The model that included Formulation C dose as a predictor did not show any significant effect (\( d \ OFV = -1.02 \)); however, the model including active moiety plasma concentration as predictor was significantly better than the model that excluded it (\( \delta \ OFV = -14.92 \)). No significant improvement was observed in any of the models when the linear relation of concentration (on a logit scale) was replaced by a maximal effect (\( E_{\text{max}} \)) model. Significant improvements were observed when IIIV was added on the slope for active moiety plasma concentration. FIG. 13 shows a VPC of the time course of the predicted probabilities of different CGI-S scores over time after accounting for active moiety effect. The population estimates of these parameters are listed in Table 11.
Table 1

<table>
<thead>
<tr>
<th>Description</th>
<th>Placebo Data</th>
<th>All Data</th>
<th>Drug Effect Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Estimate</td>
</tr>
<tr>
<td>α4</td>
<td>7.86</td>
<td>1.08</td>
<td>8.46</td>
</tr>
<tr>
<td>α5</td>
<td>-6.33</td>
<td>0.98</td>
<td>-6.64</td>
</tr>
<tr>
<td>α6</td>
<td>-5.79</td>
<td>0.73</td>
<td>-6.25</td>
</tr>
<tr>
<td>TSLP</td>
<td>-0.296</td>
<td>0.08</td>
<td>-0.74</td>
</tr>
<tr>
<td>CSLP</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ω_{ai}</td>
<td>8.9</td>
<td>3.19</td>
<td>7.82</td>
</tr>
<tr>
<td>ω_{TSLP}</td>
<td>1.84</td>
<td>0.49</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Discussion

Formulation C is being developed as a long-acting subcutaneous injectable formulation of risperidone given once a month to patients for the treatment of schizophrenia. The long-acting injectable formulation of risperidone currently available in the market (Risperdal® Consta®, risperidone by Janssen Pharmaceuticals, Inc.) is given every 2 weeks intramuscularly and requires supplementation with oral risperidone for 3 weeks after the first injection to ensure that adequate therapeutic plasma concentrations are reached. Formulation C has been developed for subcutaneous injection once per month.

The present data originated from a phase 3, placebo-controlled trial comparing 2 doses of Formulation C (90 mg and 120 mg) to placebo in patients with acute schizophrenia. The main objective of this analysis was to establish an exposure-response relationship between the total active moiety concentrations (risperidone + 9-OFI-risperidone) and PANSS/CGI-S scores. The integrated population PK/PD model developed here was a combination of the following sub-models: (1) a joint PK model for the parent drug and the active metabolite; (2) a PK/PD model for PANSS score; and (3) a PK/PD model for CGI-S score.
The structural PK model was well established from two previous single dose and multiple dose studies where rich data were collected, and hence no effort was made to refine the model for this sparse sampling design. An evaluation of this model provided reasonable fits in most PK profiles from the Phase 3 study and was used for estimating the parameters of this structural model using the Phase 3 study data. Comparison of parameter estimates between the current analysis and previous combined analysis of single dose and multiple dose studies shows consistency, which provides a good external validation to the current PK model. The design of the phase 3 study allowed the collection of PK samples in specific sampling windows that covered the complete time course in the population. Such a design, even with sparse sampling, may have facilitated collection of data that resulted in a population PK model where the parameters were well estimated with reasonable precision.

In the previous single and multiple dose studies, BMI was identified as a significant covariate. This most likely reflects the influence of fat abdominal tissues on the absorption of risperidone which is a lipophilic drug. Hence, in this Phase 3 sparse sampling design, BMI was assessed as a covariate on absorption rate constants, as well as WTH ratio. None of them was identified as significant. The precision of the absorption parameters was good due to the use of sampling time windows in this sparse design. The effect of CYP2D6 phenotype on conversion of risperidone to 9-OH-risperidone has been well established in the literature. In a previous combined analysis by Laffont et al., this effect could not be estimated well due to the low number (n=3) of poor metabolizers. In this study however, even though only 7 poor metabolizers were available in the ITT group, the covariate effect was estimated with statistical significance and the inclusion of the covariate was associated in a 20% drop in IV on the formation rate constant of the metabolite. Intermediate and poor metabolizers for CYP2D6 had 74% and 96% lower metabolite formation, respectively, than extensive metabolizers. The concentration of the active moiety was however similar across these phenotypes, supporting no need in dose adjustment.

The pcVPC plots shown in FIG. 9 for the covariate PK model well captured the median of the entire time course, but there was marginal underestimation in the upper percentiles. Standard diagnostic plots (not shown) did not show any apparent bias. Overall, the population PK model was considered to adequately describe the data.
The primary endpoint in this phase 3 trial was to assess the efficacy of Formulation C (90 mg and 120 mg) compared with placebo on the symptoms of acute schizophrenia over an 8-week treatment period using the change from baseline to end of treatment in the total PANSS score, which is the sum of all 30 PANSS items. The base placebo model development results for PANSS showed that the Weibull model with a linear slope to account for late relapses, appeared to be adequate to characterize the PANSS data in this 8-week study and was thus selected. This is an empirical placebo model that provided good fits to the data and the pcVPC’s showed the good predictive nature of the model. A limitation of such an empirical model is that parameter estimates are based on the study design and duration. A semi-mechanistic or mechanistic model would have been more robust and independent of the study design and duration. However, there are not many semi-mechanistic models due to the complexity and lack of understanding of the disease. This work can be considered for extension to such mechanism based models in the future.

Nevertheless, the empirical base model chosen here to model the placebo PANSS data described the data well with good precision of parameter estimates and excellent simulation properties. The estimates agree well with those reported by Pilla Reddy, with nearly identical numbers for the Weibull parameters, specifically the time to 63.2% of disease progression and the maximum placebo effect. In the present analysis, no covariates were identified on the placebo model to carry forward to the PK/PD model.

The next step was to integrate the PK and the PANSS PD models to establish an exposure-response relationship using a drug-effect model. This integration of critical sub-models such as disease-progression models, placebo-response models, drug-effect models, covariate models and dropout models enables reliable prediction of the outcome of future trials through model-based simulation with consideration of various predictors of the placebo response and dropout. The dropout rate in this phase 3 study was just about 8% and hence a decision was made to not include a dropout sub-model for data description. The parameters estimates of the drug-effect model, $E_{max}$ and $EC50$, differ from previous literature mostly because of the choice of independent variable. In this analysis, the active moiety plasma concentration was linked to the effect while other studies used either risperidone concentrations as a predictor, or used a summary statistic of the active moiety PK over the dosing interval. Here, the active moiety concentration was considered more
representative of the actual exposure as 9-OH risperidone and risperidone are equally active. The choice of the active moiety plasma concentration in place of any PK summary statistics is explained by the 28-day dosing schedule for Formulation C, i.e., summarizing a 28-day exposure by a few average statistics to correlate to a weekly PD assessment would not be as informative as using the actual concentrations. Moreover, one expects that active moiety concentrations will be correlated with the cumulative average concentrations.

[0322] The PK/PD model developed here described the data adequately. The pcVPC's of this integrated model (FIG. 11) show that the PANSS score was predicted well over the range of active moiety concentrations. There were no covariates identified for the PANSS PK/PD model.

[0323] The CGI-S scores that range from 1 to 7 had to be consolidated in this study to fewer categories as the number of individual with scores 0 to 2 and 7 was extremely small resulting in just 4 categories of scores. As the data are ordinal in nature, a proportional odds model was selected to model the probability of observing any given score. The placebo model that estimated the baseline probability of being at each score was augmented with a component that explained the time course of the probability that captured the data well. The addition of active moiety plasma concentration as a predictor on the logit of the probabilities significantly improved the model fit and captured the relationship between observed frequency and exposures as seen in FIG. 13. Similar to the PANSS score analysis, no significant covariates were found for the CGI-S placebo model or CGI-S exposure-response model.

[0324] The 90 mg and 120 mg doses of Formulation C used in this study were selected as they were expected to provide D2 receptor occupancy levels within the targeted range of 65 to 80%. The results for the Phase 3 study confirm the dose selection with respect to clinical endpoints (PANSS and CGI-S), showing an expected relationship between exposure and response. The PK/PD modeling approach also provides additional insight in evaluating the net effect of the drug (on top of placebo) and relating this effect to the active moiety plasma concentration.

[0325] Conclusions

[0326] Exposure-response analysis of this phase 3 registration trial for Formulation C established a good relationship between the concentrations of active moiety (risperidone + 9-OH-risperidone)
and PANSS and CGI-S scores. The PK sub-model captured the data well where the parameters were estimated with good precision and consistent with previous knowledge. CYP2D6 phenotype on metabolism of risperidone was the only identified covariate. PANSS and CGI-S models were correlated with the active moiety exposures through a PK/PD model.

References

CLAIMS

What is claimed is:

1. A method for treating a psychiatric disease in a human having an MC4R gene polymorphism, an HTR2C gene polymorphism, an HTR2A gene polymorphism, or a combination thereof, comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the MC4R gene polymorphism, the HTR2C gene polymorphism, the HTR2A gene polymorphism, or the combination thereof, to treat the psychiatric disease.

2. The method of claim 1, wherein the human has a TT genotype; a CC genotype, or a CT/TT genotype.

3. The method of claim 1 or 2, wherein the MC4R gene polymorphism is a single nucleotide polymorphism; wherein the HTR2C gene polymorphism is a single nucleotide polymorphism; and wherein the HTR2A gene polymorphism is a single nucleotide polymorphism.

4. The method of claim 1 or 2, wherein the MC4R gene polymorphism is an rs17782313 single nucleotide polymorphism; wherein the HTR2C gene polymorphism is an rs3813929 single nucleotide polymorphism; and wherein the HTR2A gene polymorphism is an rs6313 single nucleotide polymorphism.

5. The method of any one of Claims 1-4, wherein the psychiatric disease is schizophrenia, bipolar disorder, or autism.

6. The method of claim 5, wherein the schizophrenia is acute schizophrenia.

7. The method of any one of claims 1-6, wherein the method comprises administering the pharmaceutical composition to the human by oral administration, parenteral administration, or surgical implantation.

8. The method of any one of claims 1-6, wherein the method comprises administering the pharmaceutical composition by intramuscular administration or by subcutaneous administration.
9. The method of any one of claims 1-8, wherein the pharmaceutical composition further comprises a poly(lactide-co-glycolide) copolymer.

10. The method of claim 9, wherein the poly(lactide-co-glycolide) copolymer is a 50:50 to 95:5 poly(lactide-co-glycolide) copolymer.

11. The method of any one of claims 1-10, wherein the pharmaceutical composition further comprises N-methyl-2-pyrrolidone.

12. The method of claim 9 or 10, wherein the poly(lactide-co-glycolide) copolymer is in the form of microspheres.

13. The method of any one of claims 1-8, wherein the pharmaceutical composition comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide) copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrrolidone.

14. The method of any one of claims 1-8, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide) copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone.

15. A method for treating schizophrenia in a human having an MC4R gene polymorphism, an HTR2C gene polymorphism, an HTR2A gene polymorphism, or a combination thereof comprising subcutaneously administering once per month a pharmaceutical composition comprising a therapeutically effective amount of risperidone base, a poly(lactide-co-glycolide) copolymer, and N-methyl-2-pyrrolidone, to the human having the MC4R gene polymorphism, the HTR2C gene polymorphism, the HTR2A gene polymorphism, or the combination thereof, to treat the schizophrenia.

16. The method of claim 15, wherein the human has a TT genotype, a CC genotype, or a CT/TT genotype.

17. The method of claim 15 or 16, wherein the MC4R gene polymorphism is a single
2 nucleotide polymorphism; wherein the HTR2C gene polymorphism is a single nucleotide polymorphism; and wherein the HTR2A gene polymorphism is a single nucleotide polymorphism.

18. The method of claim 15 or 16, wherein the MC4R gene polymorphism is an rs17782313 single nucleotide polymorphism; wherein the HTR2C gene polymorphism is an rs3813929 single nucleotide polymorphism; and wherein the HTR2A gene polymorphism is an rs6313 single nucleotide polymorphism.

19. The method of any one of claims 15-18, wherein the schizophrenia is acute schizophrenia.

20. The method of any one of claims 15-18, wherein the pharmaceutical composition comprises from about 60 grams to about 150 grams of risperidone base.

21. The method of any one of claims 15-18, wherein the pharmaceutical composition comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a poly(lactide-co-glycolide)copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrrolidone.

22. The method of any one of claims 15-18, wherein the pharmaceutical composition comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone.

23. A method for treating a psychiatric disease in a human having a TT genotype, a CC genotype, or a CT/TT genotype comprising administering a pharmaceutical composition comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the TT genotype, the CC genotype, or the CT/TT genotype to treat the psychiatric disease.

24. The method of Claim 23, wherein the psychiatric disease is schizophrenia, bipolar disorder, or autism.

25. The method of claim 24, wherein the schizophrenia is acute schizophrenia.
26. The method of any one of claims 23-25, wherein the method comprises administering
the pharmaceutical composition to the human by oral administration, by parenteral administration,
or by surgical implantation.

27. The method of any one of claims 23-25, wherein the method comprises administering
the pharmaceutical composition by intramuscular administration or by subcutaneous administration.

28. The method of any one of claims 23-27, wherein the pharmaceutical composition
further comprises a poly(lactide-co-glycolide) copolymer.

29. The method of claim 28, wherein the poly(lactide-co-glycolide) copolymer is a 50:50
to 95:5 poly(lactide-co-glycolide) copolymer.

30. The method of any one of claims 23-29, wherein the pharmaceutical composition
further comprises N-methyl-2-pyrrolidone.

31. The method of any one of claims 28-30, wherein the poly(lactide-co-glycolide)
copolymer is in the form of microspheres.

32. The method of any one of claims 23-27, wherein the pharmaceutical composition
comprises about 5 wt% to about 25 wt% risperidone base; about 25 wt% to about 50 wt% of a
poly(lactide-co-glycolide)copolymer; and about 35 wt% to about 60 wt% N-methyl-2-pyrrolidone.

33. The method of any one of claims 23-27, wherein the pharmaceutical composition
comprises about 15 wt% risperidone base; about 38 wt% of an 80:20 poly(lactide-co-
glycolide)copolymer having a number average molecular weight from about 20,000 Daltons to
about 30,000 Daltons; and about 47 wt% N-methyl-2-pyrrolidone.

34. A method for treating a psychiatric disease in a human having a polymorphism in the
MC4R gene, a polymorphism in the HTR2C gene, a polymorphism in the HTR2A gene, or a
combination thereof, comprising administering to the human a therapeutically effective amount of
an antipsychotic drug to treat the psychiatric disease.
35. The method of claim 34, wherein the psychiatric disease is schizophrenia.

36. The method of claim 34 or 35, wherein the human has a CC genotype, a TT genotype, or a CT/TT genotype.

37. The method of any one of claims 34-36, wherein the HTR2C gene has a single nucleotide polymorphism; the HTR2A gene has a single nucleotide polymorphism; and the MC4R gene has a single nucleotide polymorphism.

38. The method of any one of claims 34-36, wherein the HTR2C gene has an rs3813929 single nucleotide polymorphism; the HTR2A gene has an rs6313 single nucleotide polymorphism; and the MC4R gene has an rs17782313 single nucleotide polymorphism.

39. The method of any one of claims 34-38, wherein the antipsychotic drug is clozapine or a pharmaceutically acceptable salt thereof; loxapine or a pharmaceutically acceptable salt thereof; olanzapine or a pharmaceutically acceptable salt thereof; thioridazine or a pharmaceutically acceptable salt thereof; perphenazine or a pharmaceutically acceptable salt thereof; aripiprazole or a pharmaceutically acceptable salt thereof; iloperidone or a pharmaceutically acceptable salt thereof; ziprasidone or a pharmaceutically acceptable salt thereof; lurasidone or a pharmaceutically acceptable salt thereof; molindone or a pharmaceutically acceptable salt thereof; asenapine or a pharmaceutically acceptable salt thereof; risperidone or a pharmaceutically acceptable salt thereof; quetiapine or a pharmaceutically acceptable salt thereof; or trifluoperazine or a pharmaceutically acceptable salt thereof.
FIG. 2

Placebo

RBP-7000 120mg

RBP-7000 90mg

2A

2B

2C

MC4R(rs17782313) - CC - CT/TT

Baseline - Day15 - Day29 - Day43 - End of study

Baseline - Day15 - Day20 Visit [Days] - Day29 - Day43 - End of study

Baseline - Day15 - Day29 - Day43 - End of study

CO-8 TOTAL SCORE CHANGE FROM BASELINE

-1.2 -0.8 -0.4 0.0 0.4 0.8 1.2

2/13
FIG. 6

6/13

Placebo

RBP-7000 120mg

RBP-7000 90mg

Visit [Days]

HTR2A(rs3313) CC CT/TT

Baseline Day15 Day29 Day43

Baseline Day15 Day29 Day43

Baseline Day15 Day29 Day43

End of study

End of study

End of study

CGI'S TOTAL SCORE CHANGE FROM BASELINE

-1.25 -1.00 -0.75 -0.50 -0.25 0.00

6A 6B 6C
FIG. 7
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/519 A61P25/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>
| X        | KASTELIC M ET AL: “MDR1 gene polymorphisms and response to acute risperidone treatment”.
PROGRESS IN NEURO-Psychopharmacology & Biological Psychiatry, ELSEVIER, GB,
vol. 34, no. 2, 17 March 2010 (2010-03-17), pages 387-392, XP026909032,
ISSN: 0278-5846, DOI: 10.1016/j.pnpbp.2010.01.005
[retrieved on 2010-02-16]
page 388
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D. See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

14 December 2016

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Date of mailing of the international search report

27/02/2017

Authorized officer

Hars, Jesko
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<td>X</td>
<td>TATSUHIKO YAGIHASHI ET AL: &quot;Effects of the CYP2D6*10 alleles and co-medications with CYP2D6-dependent drugs on risperidone metabolism in patients with schizophrenia&quot;, HUMAN PSYCHOPHARMACOLOGY. CLINICAL AND EXPERIMENTAL., vol. 24, no. 4, 1 June 2009 (2009-06-01), pages 301-308, XP055323041, XX.</td>
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<td>ANIL K. MALHOTRA: “Association Between Common Variants Near the Melanocortin 4 Receptor Gene and Severe Antipsychotic Drug-Induced Weight Gain”, ARCHIVES OF GENERAL PSYCHIATRY, vol. 69, no. 9, 1 September 2012 (2012-09-01), pages 904-912; XP055323884, ISSN: 0003-990X, DOI: 10.1001/archgenpsychiatry.2012.191</td>
<td>1-3, 5-7</td>
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<td>wo 2015/127557 Al (CAMH [CA]) 3 September 2015 (2015-09-03) claims 3, 21</td>
<td>1-3, 5-7</td>
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### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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see additional sheet
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1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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Impartially)
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#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☑ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7 (partially)

A method for treating schizophrenia in a human having at least one MC4R gene polymorphic sm, comprising administering a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the gene polymorphic sm, to treat schizophrenia, where n the pharmaceutically acceptable copolymer.

2. claims: 7-22 (partially)

A method for treating schizophrenia in a human having at least one MC4R gene polymorphic sm, comprising administering a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the gene polymorphic sm, to treat schizophrenia, where n the pharmaceutically acceptable copolymer.

3-10. claims: 1-33 (partially)

A method for treating a psychiatric disease in a human having at least one gene polymorphic sm, comprising administering a pharmaceutically acceptable copolymer, comprising a therapeutically effective amount of (i) risperidone or a pharmaceutically acceptable salt thereof or (ii) paliperidone or a pharmaceutically acceptable salt thereof, to the human having the gene polymorphic sm, to treat the psychiatric disease, where n the at least one gene polymorphic sm and the psychiatric disease are, respectively (inventor on number in brackets):
- MC4R and bipolar disorder (3),
- MC4R and autism (4),
- HTR2C and schizophrenia (5),
- HTR2C and bipolar disorder (6),
- HTR2C and autism (7),
- HTR2A and schizophrenia (8),
- HTR2A and bipolar disorder (9),
- HTR2A and autism (10).

11-13. claims: 23-33 (partially)

A method for treating a psychiatric disease in a human having a TT genotype, a CC genotype, or a CT/TT genotype
compri sing admini steri ng a pharmaceuti cal composition compri sing a therapeuti cal ly effecti ve amount of (i) risperi done or a pharmaceuti cal ly acceptabl e salt thereof or (ii) paliperi done or a pharmaceuti cal ly acceptabl e salt thereof, to the human having the TT genotype, the CC genotype, or the CT/TT genotype to treat the psychi atric disease, whereby the genotype affects a gene other than MC4R, HTR2C or HTR2A, and the psychiatric disease is (inventi on number in brackets):
- schi zophreni a (11),
- bi pol ar di sorder (12),
- auti sm (13).

14-55. Claims: 34-39

A method for treating a psychiatric disease in a human having at least one gene polymorphi sm, compri sing administering to the human a therapeutically effective amount of an anti psychot i c drug to treat the psychiatric disease, whereby the at least one gene polymorphi sm, the anti psychot i c drug and the psychiatric disease are, respectively (inventi on number in brackets):
- MC4R, a psychiatric disease and the drug clozapine (14), loxapine (15), olanzapine (16), thi oridazine (17), perphenazine (18), are p i prazol e (19), iloperi done (20), zi prasi done (21), lurasi done (22), molindone (23), asenapine (24), mesoridazine (25), quetiapine (26), or trifluoperazine (27);
- HTR2C, a psychiatric disease and the drug clozapine (28), loxapine (29), olanzapine (30), thi oridazine (31), perphenazine (32), are p i prazol e (33), iloperi done (34), zi prasi done (35), lurasi done (36), molindone (37), asenapine (38), mesoridazine (39), quetiapine (40), or trifluoperazine (41);
- HTR2A, a psychiatric disease and the drug clozapine (42), loxapine (43), olanzapine (44), thi oridazine (45), perphenazine (46), are p i prazol e (47), iloperi done (48), zi prasi done (49), lurasi done (50), molindone (51), asenapine (52), mesoridazine (53), quetiapine (54), or trifluoperazine (55).
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