METHODS FOR THE ADMINISTRATION OF CERTAIN VMAT2 INHIBITORS

BACKGROUND

[0001] Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. The onset of the disease is usually in late adolescence or early adulthood. Schizophrenia presents with a heterogeneous combination of symptoms typically categorized into positive, negative, and cognitive symptoms.

[0002] While no definitive single etiology has been identified, schizophrenia has multifactorial etiological underpinnings including strong genetic contributions and prominent gene environment interactions. Schizophrenia manifests with subtle structural and functional abnormalities of various brain structures, such as the striatum, hippocampus, and prefrontal cortex. Although schizophrenia is highly heritable, as indicated by epidemiological studies, it is not a purely genetic disorder nor is it caused by a single gene. Rather, it likely results from a combination of both rare and common genetic variants, environmental risk factors, and their interactions.

[0003] Overall, patients with schizophrenia have higher mortality and morbidity rates, with a reduced expected lifespan that is nearly 20 years shorter than that of the general population.

[0004] Pharmacotherapy is the mainstay of schizophrenia management and antipsychotics are generally employed for the treatment of schizophrenia and associated symptoms; however, some patients fail to respond to antipsychotics. Additionally, antipsychotics can have a wide range of side effects and poor compliance with drug treatment is a frequent problem among schizophrenia patients. Non-compliance with antipsychotic medication can lead to relapse for patients in remission and persistent symptoms for those with existing symptoms.

SUMMARY

[0005] In an example, provided herein is a method for the add-on treatment of schizophrenia, comprising administering to a subject in need thereof a therapeutically effective amount of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, wherein the subject is also being administered at least one co-therapeutic agent for the treatment of schizophrenia. In one aspect, the present disclosure refers to use of a therapeutically effective amount of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the add-on treatment of schizophrenia in a subject in need thereof, wherein the subject is also being administered at least one co-therapeutic agent for the treatment of schizophrenia.

[0006] In an example, provided herein is a method for the add-on treatment of schizophrenia, comprising administering to a subject in need thereof a therapeutically effective amount of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-

hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, wherein the subject has at least one symptom chosen from the following symptoms in Positive and Negative Symptom Scale (PANSS): P1 (delusions), P3 (hallucinations), P6 (suspiciousness), and G9 (unusual thought content), and further wherein the subject is also being administered at least one co-therapeutic agent for the treatment of schizophrenia. In one aspect, the present disclosure refers to use of a therapeutically effective amount of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the add-on treatment of schizophrenia in a subject in need thereof, wherein the subject has at least one symptom chosen from the following symptoms in Positive and Negative Symptom Scale (PANSS): P1 (delusions), P3 (hallucinations), P6 (suspiciousness), and G9 (unusual thought content), and further wherein the subject is also being administered at least one co-therapeutic agent for the treatment of schizophrenia.

[0007] In certain examples, the subject has at least one sign or symptom of schizophrenia.

[0008] In certain examples, the subject has at least one positive, negative, and/or cognitive sign or symptom of schizophrenia.

[0009] In certain examples, the at least one sign or symptom is delusions, hallucinations, disorganized speech, disorganized behavior or attention, anhedonia, catatonic behavior, affective flattening, alogia, avolition, conceptual disorganization, or any combination thereof.

[0010] In certain examples, the subject has a total PANSS score ≥70.

[0011] In certain examples, the subject has Clinical Global Impression of Severity (CGI-S) score ≥ 4.

[0012] In certain examples, the subject has a stable background antipsychotic medication dose.

[0013] In certain examples, the subject has a stable PANSS total score.

[0014] In certain examples, the subject is residually symptomatic or has at least one residual sign or symptom after first- or second-line treatment of schizophrenia.

[0015] In certain examples, the subject is residually symptomatic or has at least one residual sign or symptom after mono- or combination therapy for schizophrenia.

[0016] In certain examples, the mono- or combination therapy is initial therapy.

[0017] In certain examples, the at least one co-therapeutic agent is least one antipsychotic agent.

[0018] In certain examples, the antipsychotic agent is a typical antipsychotic agent.

[0019] In certain examples, the typical antipsychotic agent is benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, molindone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, thiothixene, trifluoperazine, thioridazine, zuclopenthixol, or any combination thereof.

[0020] In certain examples, the antipsychotic agent is an atypical antipsychotic agent.

[0021] In certain examples, the atypical antipsychotic agent is clozapine, olanzapine, risperidone, sertindole, quetiapine, paliperidone, asenapine, ziprasidone, surmontil, iloperidone, aripiprazole, or any combination thereof.

[0022] In certain examples, the subject is receiving concomitant treatment with a subtherapeutic dose of a second antipsychotic agent.

[0023] In certain examples, the concomitant treatment with a subtherapeutic dose of a second antipsychotic is used to treat insomnia or anxiety.

[0024] In certain examples, the concomitant treatment with a subtherapeutic dose of a second antipsychotic is used to treat symptoms other than refractory positive psychosis symptoms.

[0025] In certain examples, the subject has an inadequate response to the at least one antipsychotic agent.

[0026] In certain examples, the subject is on at least a second clinical use of the at least one antipsychotic agent.

[0027] In certain examples, the subject is also being administered risperidone and/or a risperidone equivalent.

[0028] In certain examples, the subject is also being administered a total daily dose of from about 4 mg to about 8 mg of risperidone and/or risperidone equivalents.

[0029] In certain examples, the subject is receiving background antipsychotic therapy at a total daily dose of from about 4 mg to about 8 mg of risperidone equivalents according to Table 2.

[0030] In certain examples, the subject has a stable antipsychotic agent dose.

[0031] In certain examples, the stable antipsychotic agent dose is defined as ≤25% change in risperidone equivalent total daily dose.

[0032] In certain examples, the subject is also being administered up to two antipsychotic agents.

[0033] In certain examples, the total combined antipsychotic dose is from about 4 mg to about 8 mg daily dose of risperidone equivalents according to Table 2.

[0034] In certain examples, the antipsychotic agent is other than clozapine.

[0035] In certain examples, the subject is treated with a stable regimen of antipsychotic agent(s) with no clinically meaningful change in the prescribed dose.

[0036] In certain examples, the no clinically meaningful change in the prescribed dose is no increase in dose or ≤25% decrease in dose for tolerability.

[0037] In certain examples, no dose adjustment is anticipated.

[0038] In certain examples, the subject is also being administered a long-acting injectable antipsychotic.

[0039] In certain examples, there is no dose change in the long-acting injectable antipsychotic.

[0040] In certain examples, the inadequate response comprises at least one baseline criterion selected from:

Positive and Negative Symptom Scale (PANSS) total score of ≥70;

PANSS score of ≥4 on at least one symptom selected from P1 (delusions), P3 (hallucinations), P6 (suspiciousness), and G9 (unusual thought content);

Clinical Global Impression of Severity (CGI-S) score of ≥4;

stable background antipsychotic medication dose of ≤25% change in risperidone equivalent total daily dose according to Table 2; and

a stable PANSS total score of ≤15% change.

[0041] In certain examples, the subject has a confirmed diagnosis of schizophrenia as defined by the MINI Version 7.0.2 for Psychotic Disorders for the Psychotic Disorders for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) for a subject ≥18 years of age or K-SADS-PL for a subject 13 to 17 years of age.

[0042] In certain examples, the subject has a confirmed initial diagnosis of schizophrenia for at least one year.

[0043] In certain examples, the subject is at least 13 years of age with a body weight of at least 50 kg.

[0044] In certain examples, the subject is an outpatient with stable symptomatology

[0045] In certain examples, the subject does not have comorbid Parkinsonism and/or does not or exhibit more than a minimal level of extrapyramidal signs or symptoms as defined by a score on the modified Simpson Angus Scale (SAS; excluding #10, akathisia) >6.

[0046] In certain examples, the subject does not have treatment-resistant schizophrenia, as defined by at least one of the following criteria:

a history of clozapine treatment for treatment-resistant psychosis; and/or

a history of multiple adequate and failed antipsychotic medication trials, wherein the subject demonstrated minimal or no improvement.

[0047] In certain examples, the subject does not have a diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; a lifetime diagnosis of obsessive-compulsive disorder; a recent occurrence of panic disorder, a depressive episode, and/or other

comorbid psychiatric condition(s) requiring clinical attention based on the MINI Version 7.0.2.

[0048] In certain examples, the subject does not have evidence of depression as measured by a Calgary Depression Scale for Schizophrenia (CDSS) score >8.

[0049] In certain examples, the subject has not attempted suicide and/or does not have positive answers on item numbers 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS).

[0050] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is administered via a titration scheme that comprises the up-titration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2, 1-a]isoquinolin-2-yl ester over a period of no more than about six weeks until an optimized dose is administered.

[0051] In certain examples, the titration scheme comprises administering the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof at an initial dose equivalent to about 40 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily for about two weeks, provided that the subject tolerates the initial dose and that the subject has not had an adequate response, increasing the dose and administering the increased dose to the subject.

[0052] In certain examples, the increased dose is equivalent to about 60 mg of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

[0053] In certain examples, the increased dose is equivalent to about 80 mg of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

[0054] In certain examples, the titration scheme further comprises administering the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof at the increased dose for about two weeks.

[0055] In certain examples, if the subject does not tolerate the increased dose, the optimized dose is the initial dose.

[0056] In certain examples, if the subject tolerates the increased dose and if the subject has had an adequate response, the optimized dose is the increased dose.

[0057] In certain examples, the methods of the present disclosure further comprise administering the optimized dose of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof to the subject.

[0058] In certain examples, if the subject tolerates the increased dose and if the subject has not had an adequate response, the method further comprises increasing the dose.

[0059] In certain examples, the further increased dose is equivalent to about 80 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

[0060] In certain examples, if the subject does not tolerate the further increased dose, the optimized dose is the increased dose.

[0061] In certain examples, if the subject tolerates the further increased dose and if the subject has had an adequate response, the optimized dose is the further increased dose.

[0062] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is administered in the afternoon or evening.

[0063] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject is treated with a stable regimen of antipsychotic agent(s) with ≤25% change in risperidone equivalent total daily dose.

[0064] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject is treated with a stable regimen of antipsychotic agent(s) with no clinically meaningful change in the prescribed dose.

[0065] In certain examples, the no clinically meaningful change in the prescribed dose is no increase in dose or a ≤25% decrease in dose for tolerability in the prescribed dose for ≥3 weeks.

[0066] In certain examples, no dose adjustment is anticipated.

[0067] In certain examples, the subject is also being administered a long-acting injectable antipsychotic with no dose change within 8 weeks prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof.

[0068] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnosis of schizophrenia.

[0069] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a confirmed diagnosis of schizophrenia as defined by the MINI Version 7.0.2 for Psychotic Disorders for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) for a subject ≥18 years of age or K-SADS-PL for a subject 13 to 17 years of age.

[0070] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a confirmed initial diagnosis of schizophrenia for at least one year.

[0071] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has at least one symptom chosen from the following symptoms in Positive and Negative Symptom Scale (PANSS): P1 (delusions), P3 (hallucinations), P6 (suspiciousness), and G9 (unusual thought content).

[0072] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a total PANSS score ≥70.

[0073] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-

a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a stable PANSS total score with ≤15% change.

[0074] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a Clinical Global Impression of Severity (CGI-S) score ≥ 4.

[0075] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has a stable background antipsychotic medication dose with ≤25% change in risperidone equivalent total daily dose according to Table 2.

[0076] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject is an outpatient with stable symptomatology for ≥3 weeks.

[0077] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject does not have treatment-resistant schizophrenia, as defined by at least one of the following criteria:

a history of clozapine treatment for treatment-resistant psychosis; and/or

a history of multiple adequate and failed antipsychotic medication trials, wherein the subject demonstrated minimal or no improvement.

[0078] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject does not have a diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; a lifetime diagnosis of obsessive-compulsive disorder; a recent occurrence of panic disorder, a depressive episode, and/or other comorbid psychiatric condition requiring clinical attention based on the MINI Version 7.0.2.

[0079] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt

thereof, the subject does not have evidence of depression as measured by a Calgary Depression Scale for Schizophrenia (CDSS) score >8.

[0080] In certain examples, prior to administration of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof, the subject has not attempted suicide within one year and/or does not have positive answers on item numbers 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS).

[0081] In certain examples, the add-on treatment results in a change in total PANSS score from Analysis Baseline to Week 10; a change in CGI-S of illness from Analysis Baseline to Week 10, a change in Personal and Social Performance (PSP) score from Analysis Baseline to Week 10, a change in VAS scores for the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L; subjects ≥18 years old) or EQ-5D Youth (EQ-5D-Y; subjects 13 to 17 years old) from baseline to Week 10; and/or a change in Sheehan Disability Score (SDS) from baseline to Week 10.

[0082] In certain examples, the treatment results in a reduction in the subject's CGI-S positive symptoms, relative to the subject's score at baseline.

[0083] In certain examples, the treatment results in a change in EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) scores from Analysis Baseline to Week 10 and/or a change in Sheehan Disability Score (SDS) from Analysis Baseline to Week 10.

[0084] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is in a solid dosage form.

[0085] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is orally administered.

[0086] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is in the form of a capsule.

[0087] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or

an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is administered daily.

[0088] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is administered once daily or twice daily.

[0089] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt thereof is administered once daily.

[0090] In certain examples, the therapeutically effective amount is an amount equivalent to from about 10 mg to about 90 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0091] In certain examples, the therapeutically effective amount is an amount equivalent to from about 20 mg to about 80 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0092] In certain examples, the therapeutically effective amount is an amount equivalent to about 20 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0093] In certain examples, the therapeutically effective amount is an amount equivalent to about 40 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0094] In certain examples, the therapeutically effective amount is an amount equivalent to about 60 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0095] In certain examples, the therapeutically effective amount is an amount equivalent to about 80 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0096] In certain examples, the therapeutically effective amount is an amount equivalent to about 40 mg/day of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

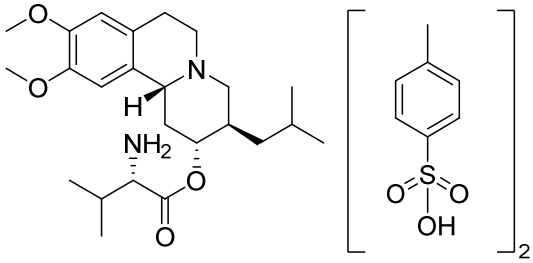
[0097] In certain examples, the therapeutically effective amount is an amount equivalent to about 60 mg/day of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0098] In certain examples, the therapeutically effective amount is an amount equivalent to about 80 mg/day of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.

[0099] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester is a free base.

[00100] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester is a salt. In certain examples, the salt is a tosylate salt.

[00101] In certain examples, the tosylate salt is (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester tosylate salt of structural Formula (I):



(I).

[00102] In certain examples, the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt, is in crystalline form.

[00103] In certain examples, the crystalline form of the (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester or an isotopic variant thereof; or a pharmaceutically acceptable salt, is Form I of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2, l-a]isoquinolin-2-yl ester tosylate salt having a differential scanning calorimetric (DSC) peak temperature within 2% of 243 °C.

[00104] In certain examples, the DSC peak temperature is within 1% of 243 °C.

[00105] In certain examples, the DSC peak temperature is within 0.5% of 243 °C.

[00106] In certain examples, the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising a peak at a two-theta angle of 6.3°±0.2°.

[00107] In certain examples, the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising a peak at a two-theta angle of 17.9°±0.2°.

[00108] In certain examples, the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising a peak at a two-theta angle of 19.7°±0.2°.

[00109] In certain examples, the crystalline form is stable upon exposure to about 25 °C and about 60% relative humidity.

[00110] In certain examples, the crystalline form has a D90 particle size of about 70 μM in length.

[00111] In certain examples, the crystalline form has a D10 particle size of about 10 μM in length.

[00112] In certain examples, the crystalline form has a purity of no less than 97% by weight of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2, l-a]isoquinolin-2-yl ester tosylate salt.

[00113] In certain examples, the crystalline form has a purity of no less than 98% by weight of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2, l-a]isoquinolin-2-yl ester tosylate salt.

[00114] In certain examples, the crystalline form has a purity of no less than 97% by weight of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2, l-a]isoquinolin-2-yl ester tosylate salt; and has an X-ray powder diffraction (XRPD) pattern comprising peaks at two-theta angles of 6.3°±0.2°, 17.9°±0.2°, and 19.7°±0.2°.

[00115] These and other aspects of the disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds, and/or compositions, and are each hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWING

[00116] FIG. 1 shows a schematic of the study design. The study includes a Screening Period of up to 4 weeks, a 2-week double-blind Placebo Run-in Period, an 8 week Randomized Double-Blind Treatment Period, and a 2-week Washout Period. DB=double-blind; V=visit; VBZ=valbenazine; Wk=week.

INCORPORATION BY REFERENCE