METHODS OF TREATING NEGATIVE SYMPTOMS OF SCHIZOPHRENIA USING DEUTERATED DEXTROMETHORPHAN AND QUINIDINE

[01] This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/820,142, filed March 18, 2019, which is incorporated herein by reference in its entirety.

[02] The present disclosure relates to the treatment of negative symptoms of schizophrenia. The present disclosure provides methods of treating negative symptoms of schizophrenia in a patient having schizophrenia by administering effective amounts of deuterated [d6]-dextromethorphan hydrobromide and quinidine sulfate.

[03] Schizophrenia is a severe mental disorder that has a prevalence of approximately 1% of the world's population and is a leading cause of disability (Switaj et al. BMC Psychiatry. 2012;12(1):193; World Health Organization. Mental Health: Schizophrenia. 2012). Onset of the illness is usually during adolescence or early adulthood and tends to begin earlier in men. Schizophrenia rarely occurs in children, but awareness of childhood-onset schizophrenia is increasing (World Health Organization. Mental Health: Schizophrenia. 2012).

[04] Symptoms of schizophrenia are typically described as “positive” or “negative.” Positive symptoms include delusions, disturbances in the process of thinking, hallucinations, incoherence, hostility, and impulsive behaviors. Negative symptoms include deficits in motivation and emotional expressiveness, blunted affect, avolition, lack of motivation, apathy, and lack of desire to form social relationships. Negative symptoms can also manifest as severe expressive deficits in both verbal and non-verbal communication. This impairment in communication skills can cause severe functional deficits that result in diminished adaptive prosocial behaviors, social isolation, and withdrawal (Del-Monte et al. Psychia Res. 2013;210:29-35; Adamczyk et al. Schizophr Res. 2016;176(2-3):331-339). Furthermore, patients suffering from expression deficits may turn away from social interactions and become increasingly withdrawn or isolated, further adding to the severity

of their illness. Communication is a key feature of an individual's ability to integrate into society – to form and keep relationships, to go to school, to find and maintain employment (Del-Monte et al. Psychia Res. 2013;210:29-35; Adamczyk et al. Schizophr Res. 2016;176(2-3):331-339). It is believed that the deficits in communication are a core feature of negative symptoms and key contributors to the long-term poor outcomes for patients.

[05] Negative symptoms are estimated to affect between 20% and 40% of individuals with schizophrenia (Pai, Nitte Univ J Health Sci. 2015;5(2):104-115). Nearly 60% of stable outpatients with schizophrenia have at least one negative symptom, and 41% have two or more negative symptoms (Bobes et al. J Clin Psychiatry. 2010;71(3):280-6). Negative symptoms can impact the course of schizophrenia and account for much of patients' long-term morbidity (Fervaha et al. Eur Psychiatry. 2014;29(7):449-55; Rabinowitz et al. Schizophr Res. 2012;137(1-3):147-150; Sicras-Mainar et al. BMC Psychiatry. 2014;14:225). Patients with more prominent negative symptoms of schizophrenia have consistently shown worse functional outcomes (Alphs et al. Schizophr Bull. 2006;32(2):225-230; Barnes et al. Health Technol Assess. 2016;20(29); Blanchard et al. Schizophr Res. 2005;77(2-3):151-165; Milev et al. Am J Psychiatry. 2005;162(3):495-506; Ho et al. Am J Psychiatry. 1998;155(9):1196-1201). Negative symptoms are also associated with greater reductions in quality of life and greater family/caregiver burdens than positive symptoms (Gonfrier et al. J Nutr Health Aging. 2012;16(2):134-137; Kirkpatrick and Fischer, Schizophr Bull. 2006;32(2):246-249; Rofail et al. Qual Life Res. 2016;25(1):201-211; Velligan et al. Schizophr Res. 1997;25(1):21-31; Mantovani et al. Trends Psychiatry Psychother. 2016;38(2):96-99). As such, negative symptoms of schizophrenia represent an important component of illness management and a clinically important target for pharmacologic treatment (Laughren and Levin, Schizophr Bull. 2006;32(2):220-222; Marder et al. Schizophren Bull. 2011;37(2):250-254; Foussias, Schizophr Bull. 2010;36(2):359-369; Strauss et al. J Psychiatr Res. 2013;47(6):783-790). Treatments that decrease the severity

of these expression and communication deficits have the potential to fundamentally improve patients' functional ability and quality of life.

[06] The International Society for Central Nervous System Clinical Trials and Methodology (ISCTM) Workshop panel considers use of the subscales of the Positive and Negative Syndrome Scale (PANSS, e.g., negative factors score) and the Negative Symptom Assessment-16 (NSA-16) scale as reliable and valid measures of negative symptoms, with the severity of these being reflective of patients' functional impairment (Marder et al. Schizophren Bull. 2011;37(2):250-254; Daniel et al. Clin Schizophr Relat Psychoses. 2011;5(2):87-94; Velligan et al. Psychiatry Res. 2009;169(2):97-100). Furthermore, a 2009 ISCTM consensus statement expressed preference for the PANSS negative factors (e.g., the PANSS Marder negative factors) over the original PANSS negative subscale, as the original subscale includes N5, difficulty with abstract thinking and N7, stereotyped thinking, which are felt to be outside the accepted domains of negative symptoms of schizophrenia (Laughren and Levin, Schizophr Bull. 2006;32(2):220-222).

[07] Multiple interventions for the treatment of negative symptoms of schizophrenia have been the subject of investigation, including pharmacological strategies using dextromethorphan (Remington et al. Curr Treat Options Psychiatry. 2016;3:133-150; Veerman et al. Drugs. 2017;77(13):1423-1459; Lee et al. J Psychiatr Res. 2015;69:50-56). "The array and diversity of strategies currently under investigation highlight the lack of evidence-based treatments and our limited understanding regarding negative symptoms underlying etiology and pathophysiology" (Remington et al. Curr Treat Options Psychiatry. 2016;3:133-150 at 134). "There is insufficient evidence at present to support a specific treatment for negative symptoms." *Id*. at 144. "This is despite a tremendous increase in the topic, as well as studies where negative symptoms are the identified primary outcome." *Id*. There is currently no U.S. Food and Drug Administration (FDA)-approved treatment for negative symptoms of schizophrenia.

[08] Thus, there remains an unmet need for a safe and effective pharmacologic intervention for treating negative symptoms of schizophrenia. “This is undoubtedly driven, at least in part, by evidence that negative symptoms play a critical role in functional decline that is not necessarily addressed with adequate control of positive symptoms” (Remington et al. Curr Treat Options Psychiatry. 2016;3:133-150 at 145). An effective treatment for patients with negative symptoms of schizophrenia could profoundly improve patients’ mental health, quality of life, caregiver burden, and reduce healthcare costs.

[09] This disclosure provides, in some embodiments, methods of treating negative symptoms in patients with schizophrenia using deuterated [d6]-dextromethorphan, or a salt thereof, in combination with quinidine, or a salt thereof. In some embodiments, this disclosure provides methods of treating negative symptoms in patients with schizophrenia using deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in combination with quinidine sulfate (Q). As used herein, the term “d6-DM” means deuterated [d6]-dextromethorphan hydrobromide. As used herein, the term “Q” means quinidine sulfate.

[10] More specifically, in some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q. In some embodiments, the d6-DM is administered in a 27 mg to 54 mg dose twice daily and the Q is administered in a 4 mg to 7.5 mg dose twice daily. In some embodiments, the d6-DM is administered in a 30 mg to 45 mg dose twice daily and the Q is administered in a 4 mg to 6 mg dose twice daily. In some embodiments, the d6-DM is administered in a 34 mg to 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some embodiments, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some embodiments, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[11] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia and having clinically stable positive symptoms, comprising administering to the patient therapeutically effective amounts of d6-DM and Q.

[12] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

[13] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

[14] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility. In some embodiments, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some embodiments, that patient has been assessed as having a total PANSS negative subscale score (N1 to N7) of greater than or equal to 18.

[15] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising

administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility. In some embodiments, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some embodiments, the patient has been assessed as having a total PANSS Marder negative factors score (N1:blunted effect; N2: emotional withdrawal; N3: poor rapport; N4: passive/apathetic social withdrawal; N6: lack of spontaneity/flow of conversation; G7: motor retardation; and G16: active social avoidance) of greater than or equal to 20.

[16] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an atypical antipsychotic. In some embodiments, the patient has been treated with the atypical antipsychotic for at least 3 months, the dose of the atypical antipsychotic has been stable for at least 1 month. In some embodiments, the patient has not had an inpatient psychiatric hospitalization within 4 months, prior to treatment with d6-DM and Q.

[17] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an antidepressant. In some embodiments, the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to treatment with d6-DM and Q.

[18] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with a hypnotic. In some embodiments, the dose of the hypnotic has been stable for at least 1 month prior to treatment with d6-DM and Q.

[19] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with lorazepam up to a total dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation. In some embodiments, the dose of the lorazepam has been stable for at least 1 month prior to treatment with d6-DM and Q.

[20] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs).

[21] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with clozapine.

[22] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

[23] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with levodopa.

[24] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a typical antipsychotic.

[25] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an agent that:

(a) increases plasma levels of quinidine;

(b) is metabolized by CYP2D6;

(c) is related to quinidine;

(d) produces serotonin syndrome when co-administered with dextromethorphan;

(e) decreases plasma levels of dextromethorphan and quinidine;

(f) is clozapine; or

(g) is a typical antipsychotic.

[26] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an anticholinergic medication.

[27] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

[28] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have myasthenia gravis.

[29] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have schizoaffective disorder.

[30] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have bipolar disorder.

[31] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

[32] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

[33] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a concurrent clinically significant or unstable systemic

disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

[34] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a suicide risk. In some embodiments, suicide risk is determined by one or more of the following:

(a) judgment of the prescribing doctor;

(b) the patient answers yes on the Columbia Suicide Severity Rating Scale (C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without a specific plan) and the patient's most recent episode meeting this C-SSRS Item 4 occurred within six months;

(c) the patient answers yes on the C-SSRS Suicidal Behavior Item 5 (active suicidal ideation with specific plan and intent) and the patient's most recent episode meeting this C-SSRS Item 5 occurred within six months; and

(d) the patient answers yes on any of the 5 on the C-SSRS Suicidal Behavior Items (active attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and the patient's most recent episode meeting any of these C-SSRS Items occurred within two years prior to treatment. For example, in some such embodiments, suicide risk is determined by all of (a), (b), (c), and (d). For example, in some such embodiments, suicide risk is determined by (a), (b), and (c). For example, in some such embodiments, suicide risk is determined by (a) and (b). For example, in some such embodiments, suicide risk is determined by any one of (a), (b), (c), or (d).

[35] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a cardiovascular history of any one or more of:

(a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes;

(b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing;

(c) family history of congenital QT interval prolongation syndrome; and

(d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia. For example, in some such embodiments, the patient does not have a history of all of (a), (b), (c), and (d). For example, in some such embodiments, the patient does not have a history of (a), (b), and (c). For example, in some such embodiments, the patient does not have a history of (a) and (b). For example, in some such embodiments, does not have a history of any one of (a), (b), (c), or (d).

[36] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

[37] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

[38] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

[39] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

[40] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first week of treatment, the d6-DM is administered in a 24 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the second week of treatment, the d6-DM is administered in a 24 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[41] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first three days of treatment, the d6-DM is administered in a 28 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the next four days of treatment, the d6-DM is administered in a 28 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[42] In some embodiments of the methods disclosed herein, the patient is further administered an atypical antipsychotic other than clozapine.

[43] In some embodiments of the methods disclosed herein, the patient is a male or female patient from 18 to 60 years of age.

[44] In some embodiments of the methods disclosed herein, the patient is a female of childbearing potential. In some embodiments, the patient: (a) has a negative urine pregnancy test; (b) is not nursing or planning a pregnancy for the duration of treatment through 30 days after the last dose; and (c) is abstinent or willing to use a method of birth control prior to treatment, and to continue with the same method until 28 days after the last dose.

[45] In some embodiments of the methods disclosed herein, the patient does not have hypersensitivity to dextromethorphan, quinidine, an opiate drug, d6-DM, Q, or any ingredient thereof.

[46] In some embodiments of the methods disclosed herein, the patient does not have allergy or hypersensitivity to one or more medications.

[47] In some embodiments of the methods disclosed herein, the patient does not have one or more clinically significant laboratory abnormalities, one or more safety values of clinical concern, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper limit of normal, as determined by the prescribing doctor.

[48] In some embodiments of the methods disclosed herein, the patient has been diagnosed as having schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia. In some embodiments, the diagnosis based on the DSM criteria has been confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.).

[49] In some embodiments of the methods disclosed herein, the patient does not have schizoaffective disorder. In some embodiments, the patient does not have bipolar disorder.

[50] In some embodiments of the methods disclosed herein, the treatment results in an at least 20% decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment. In some embodiments, the treatment results in an at least 2 point decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

[51] The methods disclosed herein may also, optionally, include administration of the d6-DM and the Q in conjunction with other therapeutic agents, such as, for example, one or more therapeutic agents useful for the treatment of schizophrenia. In some embodiments, the d6-DM and the Q may be administered in combination with an atypical antipsychotic other than clozapine (e.g., a second-generation atypical antipsychotic drug (SGA)).

[52] Also provided herein are therapeutic uses of d6-DM and Q. In some embodiments, the present disclosure provides d6-DM and Q for use in specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. In some embodiments, the present disclosure provides the use of d6-DM and Q in specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. In some embodiments, the present disclosure provides the use of d6-DM and Q in a method of manufacturing a medicament for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. Compositions useful for treating negative symptoms of schizophrenia are also provided.

[53] In some embodiments, the present disclosure provides a medicament comprising a therapeutically effective amount of d6-DM for use in the treatment of negative symptoms of schizophrenia in a patient having schizophrenia, which is used in combination with a therapeutically effective amount of Q simultaneously, separately, or sequentially.

[54] In some embodiments, the present disclosure provides a therapeutically effective amount of d6-DM for use in treating negative symptoms of schizophrenia in a patient having schizophrenia, characterized in that the d6-DM is administered in combination with a therapeutically effective amount of Q, wherein both medicaments are administered simultaneously, separately, or sequentially.

[55] In some embodiments, the present disclosure provides a combination of a therapeutically effective amount of d6-DM and a therapeutically effective amount of Q for use in treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein both medicaments are administered simultaneously, separately, or sequentially.

[56] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of d6-DM, which is used in combination with a therapeutically effective amount of Q simultaneously, separately, or sequentially, for treating negative symptoms of schizophrenia in a patient having schizophrenia.

BRIEF DESCRIPTION OF THE DRAWINGS

[57] **FIG. 1** shows the chemical structure of deuterated [d6]-dextromethorphan hydrobromide (d6-DM).

[58] **FIG. 2** shows the study design and schedule of assessments in the study from Example 1. Study medication (active or placebo) was administered as 1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart. M: Morning Dose (in mg d6-DM/mg Q); E: Evening Dose (in mg d6-DM/mg Q); *: Visit 4 (Day 43) stratification was based on treatment response criteria followed by Re-Randomization (1:1).

[59] **FIG. 3** shows disposition of patients in the modified intent-to-treat (mITT) population in the study from Example 1.

[60] **FIG. 4** shows NSA-16 Total Mean Scores by visit (sequential parallel comparison design (SPCD), mITT population) in the study from Example 1.

[61] **FIG. 5** shows PANSS Total Mean Scores by visit (SPCD, mITT population) in the study from Example 1.

[62] **FIG. 6** shows PANSS Negative Subscale Mean Scores by visit (SPCD, mITT population) in the study from Example 1.

[63] **FIG. 7** shows PANSS Marder Negative Factors Mean Scores by visit (SPCD, mITT population) in the study from Example 1.

[64] **FIG. 8** shows PANSS Prosocial Factors Mean Scores by visit (SPCD, mITT population) in the study from Example 1.

[65] **FIG. 9** shows NSA-16 Global Negative Symptoms Ratings by visit (SPCD, mITT population) in the study from Example 1.

[66] **FIG. 10** shows PGI-C Ratings of “Much” or “Very Much” Improved: Stage 1 (Baseline to Week 6) and Stage 2 (Week 6 to Week 12) in the study from Example 1.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[67] The following detailed description and examples illustrate certain embodiments of the present disclosure. Those of skill in the art will recognize that there are numerous variations and modifications of this disclosure that are encompassed by its scope. Accordingly, the description of certain embodiments should not be deemed to limit the scope of the present disclosure.

[68] In order that the disclosure may be more readily understood, certain terms are defined throughout the detailed description. Unless defined otherwise herein, all scientific and technical terms used in connection with the present disclosure have the same meaning as commonly understood by those of ordinary skill in the art.

[69] All references cited herein, including, but not limited to, published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent a cited reference conflicts with the disclosure herein, the specification shall control.

[70] As used herein, the singular forms of a word also include the plural form, unless the context clearly dictates otherwise; as examples, the terms “a,” “an,” and “the” are understood to be singular or plural. By way of example, “an element” means one or more element. The term “or” shall mean “and/or” unless the specific context indicates otherwise.

[71] The present disclosure, in some embodiments, provides methods of treating negative symptoms of schizophrenia in a patient having schizophrenia by administering to the patient deuterated [d6]-dextromethorphan hydrobromide (d6-DM) and quinidine sulfate (Q). Uses of d6-DM and Q, e.g., in treating negative symptoms of schizophrenia, are also provided. Compositions (e.g., pharmaceutical compositions) comprising d6-DM and Q are also disclosed and are useful in the therapeutic methods and uses described herein.

[72] As used herein, the term “d6-DM” means deuterated [d6]-dextromethorphan hydrobromide. As used herein, the term “Q” means quinidine sulfate.

[73] As used herein, the term “a patient having schizophrenia” means a patient that has been diagnosed as having schizophrenia.

[74] “Negative symptoms of schizophrenia” include one or more of blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, motor retardation, active social avoidance, difficultly in abstract thinking, stereotyped thinking, alogia, asociality, anhedonia, and avolition. In some embodiments, the negative symptom of schizophrenia is blunted affect. In some embodiments, the negative symptom of schizophrenia is emotional withdrawal. In some embodiments, the negative symptom of schizophrenia is poor rapport. In some embodiments, the negative symptom of schizophrenia is passive/apathetic social withdrawal. In some embodiments, the negative symptom of schizophrenia is lack of spontaneity and flow of conversation. In some embodiments, the negative symptom of schizophrenia is motor retardation. In some embodiments, the negative symptom of schizophrenia is active social avoidance. In some embodiments, the negative symptom of

schizophrenia is difficulty in abstract thinking. In some embodiments, the negative symptom of schizophrenia is stereotyped thinking. In some embodiments, the negative symptom of schizophrenia is alogia. In some embodiments, the negative symptom of schizophrenia is asociality. In some embodiments, the negative symptom of schizophrenia is anhedonia. In some embodiments, the negative symptom of schizophrenia is avolition.

[75] In addition to negative symptoms, schizophrenia patients can also exhibit one or more positive symptoms. Exemplary positive symptoms of schizophrenia include delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspicious/persecution, and hostility.

[76] As used herein, the term "treating negative symptoms of schizophrenia" means improving one or more negative symptoms of schizophrenia.

[77] As used herein, the term "treating prosocial factors" means improving one or more prosocial factors.

[78] As used herein, the term "specifically treating negative symptoms of schizophrenia" means improving one or more negative symptoms of schizophrenia irrespective of the effect on one or more of: any positive symptom of schizophrenia; depression; and any extrapyramidal symptom.

[79] The term "therapeutically effective amounts of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) and quinidine sulfate (Q)" refers to the amount of d6-DM and the amount of Q that are sufficient to improve one or more negative symptoms of schizophrenia when administered in combination. As used herein, the term "combination" applied to d6-DM and Q means a single pharmaceutical composition (formulation) comprising both d6-DM and Q or two separate pharmaceutical compositions (formulations), each comprising d6-DM or Q, to be administered in combination.

[80] Administered "in combination" or "co-administration," as used herein, refers to administration of d6-DM and Q simultaneously in one composition, or simultaneously in different compositions, or sequentially. For sequential administration to be considered

administration “in combination” or “co-administration,” the d6-DM and the Q are administered separated by a time interval that permits the resultant beneficial effect for treating one or more negative symptoms of schizophrenia in a patient.

[81] The term “patient” and “subject” means a human. In some embodiments, the patient is a human having schizophrenia.

[82] In certain alternative embodiments, salt forms of deuterated [d6]-dextromethorphan other than hydrobromide and salt forms of quinidine other than sulfate may be used in the embodiments described herein.

[83] Unless otherwise specified, the doses described herein refer to the hydrobromide and sulfate salt forms of deuterated [d6]-dextromethorphan and quinidine (i.e., d6-DM and Q), respectively. Based on such information, those skilled in the art can calculate corresponding dosages for the respective free-base forms of the active ingredient. A person of skill in the art can calculate the molecular weight for the salt of dextromethorphan and the molecular weight for free base of dextromethorphan and use the ratio to calculate appropriate dosages for the free base as well as for the salt.

Therapeutic Methods

[84] The present disclosure provides, in some embodiments, methods of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) and quinidine sulfate (Q).

[85] In some embodiments, the specification provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the d6-DM is administered in a 27 mg to 54 mg dose twice daily and the Q is administered in a 4 mg to 7.5 mg dose twice daily.

[86] In some embodiments, the specification provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the d6-DM is administered in a 30 mg to 45 mg dose twice daily and the Q is administered in a 4 mg to 6 mg dose twice daily.

[87] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the d6-DM is administered in a 34 mg to 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some embodiments, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some embodiments, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[88] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia and having clinically stable positive symptoms, comprising administering to the patient therapeutically effective amounts of d6-DM and Q.

[89] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

[90] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

[91] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility. In some embodiments, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some embodiments, the patient has been assessed as having a total PANSS negative subscale score (N1 to N7) of greater than or equal to 18.

[92] In some embodiments, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility. In some embodiments, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some embodiments, the patient has been assessed as having a total PANSS Marder negative factors score (N1:blunted effect; N2: emotional withdrawal; N3: poor rapport; N4: passive/apathetic social withdrawal; N6: lack of spontaneity/flow of conversation; G7: motor retardation; and G16: active social avoidance) of greater than or equal to 20.

[93] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an atypical antipsychotic, wherein the patient has been treated with the atypical antipsychotic for at least 3 months, the dose of the atypical antipsychotic has been stable for at least 1 month. In some embodiments, the patient has not had an inpatient psychiatric hospitalization within 4 months, prior to treatment with d6-DM and Q.

[94] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an antidepressant, wherein the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to treatment with d6-DM and Q.

[95] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with a hypnotic, wherein the dose of the hypnotic has been stable for at least 1 month prior to treatment with d6-DM and Q.

[96] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with lorazepam up to a total dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation, wherein the dose of the lorazepam has been stable for at least 1 month prior to treatment with d6-DM and Q.

[97] In some embodiments of the methods disclosed herein, the patient is not being treated with certain additional therapeutic agents concomitantly with the d6-DM and the Q. In some embodiments, the patient has not taken certain additional therapeutic

agent(s) within 2 weeks or 5 half-lives of the additional therapeutic agent(s), whichever is longer, prior to the start of treatment with the d6-DM and the Q.

[98] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs). Exemplary MAOIs include carbamazepine, cyproterone, hyperforin, oxcarbazepine, phenobarbital, phenytoin, rifampicin, and St. John's Wort.

[99] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with clozapine.

[100] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

[101] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with levodopa.

[102] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a typical antipsychotic. Exemplary typical antipsychotics include but are not limited to haloperidol, loxapine, thioridazine, molindone, thiothixene, fluphenazine, mesoridazine, trifluoperazine, perphenazine, and chlorpromazine.

[103] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an agent that:

(a) increases plasma levels of quinidine;

(b) is metabolized by CYP2D6;

(c) is related to quinidine;

(d) produces serotonin syndrome when co-administered with dextromethorphan;

(e) decreases plasma levels of dextromethorphan and quinidine;

(f) is clozapine; or

(g) is a typical antipsychotic.

[104] In some embodiments, the patient is not being treated with an agent that may increase plasma levels of quinidine. Exemplary agents that may increase plasma levels of quinidine include but are not limited to amiodarone, a carbonic anhydrase inhibitor, cimetidine, diltiazem, itraconazole, ketoconazole, a macrolide antibiotic, a protease inhibitor, and voriconazole. Non-limiting examples of macrolide antibiotics include erythromycin, azithromycin, clarithromycin, dirithromycin, and roxithromycin. Non-limiting examples of protease inhibitors include saquinavir, ritonavir, atazanavir, and indinavir.

[105] In some embodiments, the patient is not being treated with an agent that is metabolized by CYP2D6 and may have increased plasma levels if co-administered with quinidine. Exemplary agents that are metabolized by CYP2D6 and may have increased plasma levels if co-administered with quinidine include but are not limited to dextromethorphan (over-the-counter or prescription), a tricyclic antidepressant (TCA), and atomoxetine. Non-limiting examples of TCAs include imipramine, desipramine, amitriptyline, and nortriptyline.

[106] In some embodiments, the patient is not being treated with an agent that is related to quinidine. Exemplary agents that are related to quinidine include but are not limited to quinine and mefloquine.

[107] In some embodiments, the patient is not being treated with an agent that might produce serotonin syndrome when co-administered with dextromethorphan. Exemplary agents that produce serotonin syndrome when co-administered with dextromethorphan include MAOIs. Non-limiting examples of MAOIs include carbamazepine, cyproterone, hyperforin, oxcarbazepine, phenobarbital, phenytoin, rifampicin, and St. John's Wort.

[108] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an anticholinergic medication.

[109] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

[110] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have myasthenia gravis.

[111] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

[112] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

[113] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a concurrent clinically significant or unstable systemic disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

[114] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have schizoaffective disorder.

[115] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have bipolar disorder.

[116] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a suicide risk. In some embodiments, suicide risk is determined by one or more of the following:

(a) judgment of the prescribing doctor;

(b) the patient answers yes on the Columbia Suicide Severity Rating Scale (C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without a specific plan) and the patient's most recent episode meeting this C-SSRS Item 4 occurred within six months;

(c) the patient answers yes on the C-SSRS Suicidal Behavior Item 5 (active suicidal ideation with specific plan and intent) and the patient's most recent episode meeting this C-SSRS Item 5 occurred within six months; and

(d) the patient answers yes on any of the 5 on the C-SSRS Suicidal Behavior Items (active attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and the patient's most recent episode meeting any of these C-SSRS Items occurred within two years prior to treatment. For example, in some such embodiments, suicide risk is determined by all of (a), (b), (c), and (d). For example, in some such embodiments, suicide risk is determined by (a), (b), and (c). For example, in some such embodiments, suicide risk is determined by (a) and (b). For example, in some such embodiments, suicide risk is determined by any one of (a), (b), (c), or (d).

[117] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a cardiovascular history of any one or more of:

(a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes;

(b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing;

(c) family history of congenital QT interval prolongation syndrome; and

(d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia. For example, in some such embodiments, the patient does not have a history of all of (a), (b), (c), and (d). For example, in some such embodiments, the patient does not have a history of (a), (b), and (c). For example, in some such embodiments, the patient does not have a history of (a) and (b). For example, in some such embodiments, does not have a history of any one of (a), (b), (c), or (d)

[118] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

[119] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

[120] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

[121] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

[122] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first week of treatment, the d6-DM is administered in a 24 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the second week of treatment, the d6-DM is administered in a 24 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[123] In some embodiments, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first three days of treatment, the d6-DM is administered in a 28 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the next four days of treatment, the d6-DM is administered in a 28 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[124] In some embodiments, the present disclosure provides a method of treating prosocial factors in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q. Prosocial factors include the following PANSS factors: G16 (active social avoidance); N2 (emotional withdrawal); N4 (passive/apathetic social withdrawal); N7 (stereotyped thinking); P3 (hallucinatory behavior); and P6 (suspiciousness/persecution).

[125] In some embodiments of the methods disclosed herein, the patient has been diagnosed as having schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia. In some embodiments, the DSM criteria

are the criteria set forth in the American Psychiatric Association's (2000) *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision (DSM-IV-TR), which is incorporated herein by reference for the disclosure of such criteria. In some embodiments, the DSM criteria are the criteria set forth in the American Psychiatric Association's (2013) *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (DSM-V), which is incorporated herein by reference for the disclosure of such criteria.

[126] In some embodiments, the patient's diagnosis of schizophrenia based on the DSM criteria has been confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.). The M.I.N.I. is a brief structured diagnostic interview for psychiatric disorders, including those in DSM-IV and DSM-5. In some embodiments, the M.I.N.I. used to confirm the diagnosis of schizophrenia is M.I.N.I. Version 6.0, based on the DSM-IV-TR criteria. In some embodiments, the M.I.N.I. used to confirm the diagnosis of schizophrenia is M.I.N.I. Version 7.0.2, based on the DSM-V criteria.

[127] In some embodiments of the methods disclosed herein, the patient satisfies one, more than one, or all of the exemplary inclusion criteria described in Section 1.3.1 of the study from Example 1. In some embodiments, the patient satisfies one, more than one, or all of the exemplary inclusion criteria described in Section 2.1 of the study from Example 2.

[128] In some embodiments of the methods disclosed herein, the patient does not have one or more of the exemplary exclusion criteria described in Section 1.3.2 of the study from Example 1. In some embodiments, the patient does not have one or more of the exemplary exclusion criteria described in Section 2.2 of the study from Example 2.

[129] In some embodiments of the methods disclosed herein, the patient is a male or female patient from 18 to 60 years of age.

[130] In some embodiments of the methods disclosed herein, the patient is a female of childbearing potential. In some embodiments, the patient: (a) has a negative urine pregnancy test; (b) is not nursing or planning a pregnancy for the duration of treatment

through 30 days after the last dose; and (c) is abstinent or willing to use a method of birth control prior to treatment, and to continue with the same method until 28 days after the last dose.

[131] In some embodiments of the methods disclosed herein, the patient does not have hypersensitivity to dextromethorphan, quinidine, an opiate drug, d6-DM, Q, or any ingredient thereof.

[132] In some embodiments of the methods disclosed herein, the patient does not have allergy or hypersensitivity to one or more medications.

[133] In some embodiments of the methods disclosed herein, the patient does not have one or more clinically significant laboratory abnormalities, one or more safety values of clinical concern, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper limit of normal, as determined by the prescribing doctor.

[134] In some embodiments of the methods disclosed herein, the patient is administered the d6-DM and the Q irrespective of the patient's ALDH2 genotype.

[135] Lee at al. (Psychiatr Res. 2015;69:50-56) evaluated dextromethorphan as an add-on to treatment with the antipsychotic risperidone. In that study, Lee et al. assessed patients using the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). *Id*. at 52. No significant differences in the PANSS and SANS scores were reported between patients treated with risperidone and dextromethorphan and patients treated with risperidone and placebo. *Id*.

[136] Lee at al. (Psychiatr Res. 2015;69:50) also evaluated a subgroup of 13 patients that had the ALDH2*2 allele of the ALDH2 gene (7 administered risperidone and dextromethorphan; 6 administered risperidone and placebo). *Id*. at 52-53, including Table 2. The ALDH2 allele is carried by about 50% of the Asian population, but is rarely seen in Caucasians. *Id*. at 54. No significant difference in the two groups (dextromethorphan vs. placebo) was reported in the PANSS scores, including the PANSS negative symptom

subscale, but a significant difference was reported in the total SANS scores. *Id*. at 52-53. According to Lee et al., these results indicate that the ALDH2 gene might affect changes in SANS total scores. *Id*. at 54. Lee et al. also mentioned several limitations of the study and questioned whether the results were applicable to Western populations. *Id*. It is not evident that any subsequent studies have further evaluated this subgroup of patients with the ALDH2*2 allele.

[137] In studies described and exemplified herein, patients' ALDH2 genotype was not determined. A composition comprising d6-DM and Q (d6-DM/Q) was administered to treat negative symptoms of schizophrenia irrespective of the ALDH2 genotype of the patient (see, e.g., the study from Example 1; see also the study from Example 2).

[138] In some embodiments of the methods disclosed herein, the patient is administered the d6-DM and the Q in conjunction with other therapeutic agents, such as, for example, one or more therapeutic agents known or identified for the treatment of schizophrenia.

[139] In some embodiments of the methods disclosed herein, the patient is further administered an atypical antipsychotic other than clozapine. In some embodiments, the atypical antipsychotic is administered within the dose guidance from its U.S. package insert for the treatment of schizophrenia. In some embodiments, the atypical antipsychotic is an oral and long-acting intramuscular injectable. In some embodiments, the atypical antipsychotic is a second-generation atypical antipsychotic drug (SGA). Exemplary SGAs include but are not limited to olanzapine, risperidone, paliperidone, quetiapine, aripiprazole, and lurasidone. In some embodiments, the patient is not being treated with more than one SGA. In some embodiments, the patient is not being treated with more than one SGA with the exception of low dose quetiapine (e.g., up to 50 mg at night) for insomnia.

[140] In some embodiments, the d6-DM is administered in a 24 mg, 28 mg, 34 mg, or 42.63 mg dose, e.g., once or twice daily. In some embodiments, the d6-DM is administered in a 24 mg dose, e.g., once or twice daily. In some embodiments, the d6-DM

is administered in a 28 mg dose, e.g., once or twice daily. In some embodiments, the d6-DM is administered in a 34 mg dose, e.g., once or twice daily. In some embodiments, the d6-DM is administered in a 42.63 mg dose, e.g., once or twice daily. In some embodiments, the d6-DM is administered in a 34 mg dose twice daily. In some embodiments, the d6-DM is administered in a 42.63 mg dose twice daily.

[141] In some embodiments, the Q is administered in a 4.9 mg dose, e.g., once or twice daily.

[142] In some embodiments, the d6-DM and the Q are administered or used in a unit dosage form. In some embodiments, the unit dosage form includes 24 mg, 28 mg, 34 mg, or 42.63 mg of d6-DM and 4.9 mg of Q. In some embodiments, the unit dosage form includes 24 mg of d6-DM and 4.9 mg of Q. In some embodiments, the unit dosage form includes 28 mg of d6-DM and 4.9 mg of Q. In some embodiments, the unit dosage form includes 34 mg of d6-DM and 4.9 mg of Q. In some embodiments, the unit dosage form includes 42.63 mg of d6-DM and 4.9 mg of Q. In some embodiments, the unit dosage forms of the d6-DM and the Q are in the form of a tablet or a capsule. In some embodiments, the unit dosage forms of the d6-DM and the Q are in the form of a capsule.

[143] In some embodiments, the d6-DM and the Q are administered or used in a combined dose, or in separate doses. In some embodiments, the separate doses are administered substantially simultaneously. In some embodiments, the combined dose of the d6-DM and the Q (or separate doses simultaneously administered) is administered once daily, twice daily, three times daily, four times daily, or more frequently. For example: 24 mg d6-DM and 4.9 mg Q per day provided in a single dose; 48 mg d6-DM and 9.8 mg Q per day provided in two doses, each dose containing 24 mg d6-DM and 4.9 mg Q; 68 mg d6-DM and 9.8 mg Q per day provided in two doses, each dose containing 34 mg d6-DM and 4.9 mg Q; 28 mg d6-DM and 4.9 mg Q per day provided in a single dose; 56 mg d6-DM and 9.8 mg Q per day provided in two doses, each dose containing 28 mg d6-DM and 4.9 mg Q; or 85.26 mg d6-DM and 9.8 mg Q per day provided in two doses, each dose

containing 42.63 mg d6-DM and 4.9 mg Q. In some embodiments, the total amount of d6-DM and Q in a combined dose may be adjusted, depending upon the number of doses to be administered per day, so as to provide a suitable daily total dosage to the patient.

[144] In some embodiments, 68 mg d6-DM and 9.8 mg Q per day are provided in two doses, each dose containing 34 mg d6-DM and 4.9 mg Q. In some embodiments, the two doses are administered 6, 8, 10, 12, 14, or 16 hours apart. In some embodiments, the two doses are administered 12 hours apart (e.g., morning and evening).

[145] In some embodiments, 85.26 mg d6-DM and 9.8 mg Q per day are provided in two doses, each dose containing 42.63 mg d6-DM and 4.9 mg Q. In some embodiments, the two doses are administered about 6, about 8, about 10, about 12, about 14, or about 16 hours apart. In some embodiments, the two doses are administered about 12 hours apart (e.g., morning and evening).

[146] In some embodiments, the treatment is initiated at a lower daily dose, for example 24 mg or 28 mg d6-DM in combination with 4.9 mg Q per day, and increased up to 85.26 mg d6-DM in combination with 9.8 mg Q per day.

[147] For example, in some embodiments, during the first week of treatment, the d6-DM is administered in a 24 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the second week of treatment, the d6-DM is administered in a 24 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[148] In some embodiments, during the first three days of treatment, the d6-DM is administered in a 28 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the next four days of treatment, the d6-DM is administered in a 28 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[149] As will be apparent to those skilled in the art, dosages outside of these disclosed dosages and ranges may be administered in some cases. Further, it is noted that the ordinary skilled clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in consideration of individual response.

[150] Oral administration can be employed for providing the patient with an effective dosage of d6-DM in combination with Q for treating negative symptoms of schizophrenia in a patient having schizophrenia. In some embodiments, the formulations can contain a combination of d6-DM and Q with pharmaceutically acceptable carriers or diluents known to those of skill in the art. In some embodiments, the d6-DM and the Q are administered orally. In some embodiments, the d6-DM and the Q are administered orally in a unit dosage form. In some embodiments, the unit dosage forms of the d6-DM and the Q are in the form of a capsule.

[151] d6-DM and Q may be formulated as active ingredients in one or more pharmaceutical compositions. Such pharmaceutical compositions may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

[152] Pharmaceutical compositions can be prepared in forms such as powders, capsules, tablets, suspensions, sachets, cachets, solutions, and elixirs. Carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used in oral solid preparations. In some embodiments, the compositions are prepared as oral solid preparations (such as powders, capsules, and tablets). In some embodiments, the compositions are prepared as oral liquid preparations. In some embodiments, the oral solid preparations are capsules or tablets. If desired, capsules or tablets can be coated by standard aqueous or nonaqueous techniques.

[153] Pharmaceutical compositions suitable for oral administration can be provided as discrete units such as capsules, cachets, sachets, patches, tablets, and aerosol sprays, each containing predetermined amounts of the active ingredients, as

powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions can be prepared by any of the conventional methods of pharmacy, but the majority of the methods typically include the step of bringing into association the active ingredients with a carrier that constitutes one or more ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then, optionally, shaping the product into the desired presentation.

[154] For example, a tablet can be prepared by compression or molding, optionally, with one or more additional ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active, or dispersing agent. Molded tablets can be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[155] In some embodiments, the d6-DM and the Q are administered together in the form of a capsule. In some embodiments, the capsule comprising the d6-DM and the Q is an immediate release capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is size 3.

[156] In some embodiments, each capsule contains 24 mg, 28 mg, 34 mg, or 42.63 mg of d6-DM and 4.9 mg of Q. In some embodiments, each capsule contains 24 mg of d6-DM and 4.9 mg of Q. In some embodiments, each capsule contains 28 mg of d6-DM and 4.9 mg of Q. In some embodiments, each capsule contains 34 mg of d6-DM and 4.9 mg of Q. In some embodiments, each capsule contains 42.63 mg of d6-DM and 4.9 mg of Q. In some embodiments, each capsule is administered once daily. In some embodiments, each capsule is administered twice daily.

[157] In some embodiments, each capsule contains 34 mg of d6-DM and 4.9 mg of Q, and is administered twice daily.

[158] In some embodiments, each capsule contains 42.63 mg of d6-DM and 4.9 mg of Q, and is administered twice daily.

[159] In some embodiments, each capsule (or other composition comprising d6-DM and Q as active ingredients) also contains inactive ingredients. In some embodiments, the inactive ingredients may include croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and/or magnesium stearate. In some embodiments, the inactive ingredients consist of or comprise croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate.

Deuterated Dextromethorphan Hydrobromide

[160] Dextromethorphan (DM) is the common name for (+)-3-methoxy-N-methylmorphinan, one of a class of molecules that are dextrorotatory analogs of morphine-like opioids. FIG. 1 shows the structure of deuterated [d6]-dextromethorphan hydrobromide (d6-DM), which is a deuterated isotope of DM in which deuterium replaces 6 hydrogen atoms at locations shown in FIG. 1.

[161] In some embodiments, d6-DM is isolated or purified, e.g., d6-DM is present at a purity of at least 50% by weight (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, 99.5%, or 99.9%) of the total amount of isotopologues of d6-DM present, respectively. Thus, in some embodiments, a composition comprising d6-DM can include a distribution of isotopologues of the compound, provided at least 50% of the isotopologues by weight are d6-DM.

[162] In some embodiments, any position in d6-DM designated as having D has a minimum deuterium incorporation of at least 80%, at least 85%, at least 87%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5%) at the designated position(s) in the d6-DM. Thus, in some embodiments, a composition comprising d6-DM can include a distribution of isotopologues of the compound, provided at least 80% of the isotopologues include a D at the designated position(s).

[163] In some embodiments, d6-DM is substantially free of other isotopologues of the compound, e.g., less than 20%, less than 10%, less than 5%, less than 2%, less than 1%, or less than 0.5% of other isotopologues are present.

[164] The synthesis of d6-DM can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in Kim et al. (Bioorg Med Chem Lett 2001, 11:1651) and Newman et al. (J Med Chem 1992, 35:4135).

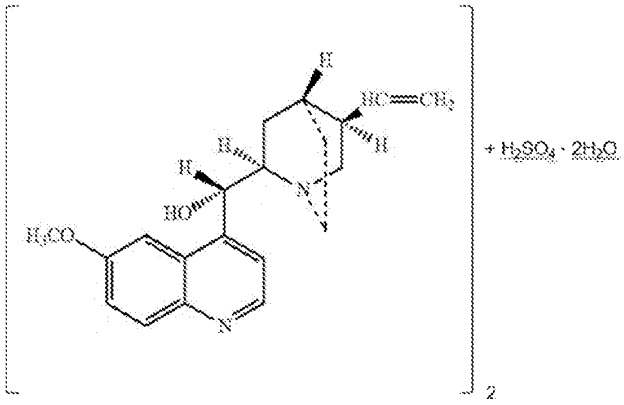
[165] A convenient method for synthesizing d6-DM according to some embodiments substitutes the appropriate deuterated intermediates and reagents in synthesis methods utilized for the preparation of dextromethorphan. These methods are described, for example, in U.S. Patent No. 7,973,049, which is incorporated by reference in its entirety.

[166] Additional methods of synthesizing d6-DM are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing d6-DM are known in the art and include, for example, those described in: Larock, Comprehensive Organic Transformations, VCH Publishers (1989); Greene et al. Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); Fieser et al. Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995); and subsequent editions thereof.

Quinidine Sulfate

[167] The present disclosure envisions the use of quinidine sulfate (Q) in combination with d6-DM. In most people (estimated to include about 90% of the general population in the U.S.), dextromethorphan undergoes extensive hepatic O-demethylation to dextrorphan that is catalyzed by CYP2D6 and is rapidly eliminated by the body

(Ramachander et al. J. Pharm. Sci. 1977;66(7):1047-1048; Vetticaden et al. Pharm. Res. 1989;6(1):13-19). However, quinidine is a potent CYP2D6 inhibitor and has been particularly studied in this use (see, e.g., U.S. Patent No. 5,206,248). The chemical structure of the sulfate salt form of quinidine, Q ($(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$), is as follows:



[168] Quinidine administration can convert subjects with extensive dextromethorphan metabolizer phenotype to poor metabolizer phenotype (Inaba et al. Br. J. Clin. Pharmacol. 1986; 22:199-200).

Exemplary Scales

[169] In some embodiments of the methods disclosed herein, one or more scales described herein, or others known in the art, may be used. Exemplary scales include the Positive and Negative Syndrome Scale (PANSS), 16-Item Negative Symptom Assessment (NSA-16), Clinical Global Impression (CGI) Scales (e.g., Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C)), Patient Global Impression of Change (PGI-C), Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), Calgary Depression Scale for Schizophrenia (CDSS), and Effort Expenditure for Reward Task (EEfRT). In some embodiments one or more of the scales is used to assess a patient's baseline status before treatment. In some embodiments, one or more of the scales is used

to assess a patient's progress at various points during treatment. In some embodiments, the patient's progress at one or more points during treatment is compared to a patient's baseline status before treatment.

Positive and Negative Syndrome Scale (PANSS)

[170] The PANSS is a validated clinical scale that has been extensively used as a reliable and valid measure of the negative and positive symptoms of schizophrenia (Daniel, Schizophr Res. 2013;150(2-3):343-345). The scale comprises 30 disparate items that collectively assess the positive and negative syndromes in schizophrenia, including their relationship to one another and to global psychopathology. Each is scored for "1" (absent) to "7" (extremely severe).

[171] The established psychometric properties of the PANSS allow for the assessment of positive, negative, and general psychopathology as part of a categorical or dimensional perspective of schizophrenia (Kay, Schizophr Bull. 1987;13(2):261-276; Kumari et al. J Addict Res Ther. 2017;8(3)). Thus, different combinations of items are generally analyzed as factor structures to score specific aspects of the negative syndrome of schizophrenia.

[172] The concept of a five-factor solution for the PANSS has been successfully used in clinical trials, and identifies five factors or dimensions of schizophrenia: 1) negative symptoms; 2) positive symptoms; 3) disorganized thought; 4) uncontrolled hostility/excitement; and 5) anxiety/depression (Lindenmayer et al. Psychopathology. 1995;28(1):22-31; Marder et al. J Clin Psychiatry. 1997;58(12):538-546). Marder investigated the five-factor solution in two controlled trials and found that risperidone produced significantly greater improvements than haloperidol on all five dimensions, with a particularly potent effect of risperidone vs. haloperidol on Factor 1 (negative symptoms). Factor 1, i.e., the PANSS Marder negative factors, has several aspects of improved content validity versus the negative subscale, meeting more consistently with the domains identified

in the 2006 NIMH-MATRICS Consensus Statement (Kirkpatrick et al. Schizophr Bull. 2006;32(2):214-219).

PANNS Marder Negative Factors Score

[173] The PANSS Marder negative factors score is a reliable and validated measure of the negative symptoms of schizophrenia, and is comprised of the following 7 items of the 30-item PANSS:

Marder Negative Factors:

- N1: Blunted affect
- N2: Emotional withdrawal
- N3: Poor rapport
- N4: Passive/apathetic social withdrawal
- N6: Lack of spontaneity and flow of conversation
- G7: Motor retardation
- G16: Active social avoidance

[174] Each of the PANSS Marder negative factors correlates with one of the five main domains of negative symptoms (Kirkpatrick et al. Schizophr Bull. 2006;32(2):214-219). PANSS item N1: blunted affect, correlates with Blunted affect; N6: lack of spontaneity and conversation flow, correlates with Alogia; and N4: passive/apathetic social withdrawal; G16: active social avoidance; and N3: poor rapport, are factors that correlate with Asociality. PANSS item N2: emotional withdrawal, correlates with Anhedonia; and G7: motor retardation, correlates with both Anhedonia and Avolition (Daniel, Schizophr Res. 2013;150(2-3):343-345).

[175] Two of the items in the PANSS Marder negative factors score (N4 and G16) are based solely on information obtained from an informant. In some embodiments, patients identify a reliable informant (e.g., case manager, social worker, family member) who spends sufficient time with them to be able to provide information to PANSS raters.

[176] In some embodiments, one or more negative symptoms of schizophrenia is evaluated based on PANSS scores. In some embodiments, only PANSS scores are determined. In some embodiments, PANSS scores are determined in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

16-Item Negative Symptom Assessment (NSA-16)

[177] The NSA-16 is considered a valid and reliable measure of the presence, severity, and range of negative symptoms associated with schizophrenia; it has high interrater and test–retest reliability across languages and cultures (Daniel, Schizophr Res. 2013;150(2-3):343-345; Axelrod et al. J Psychiatr Res. 1993;27(3):253-258). The NSA-16 uses a 5-factor model to describe negative symptoms: (1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and (5) retardation. These factors, assessed through a structured interview, are comprehensive and well-defined to help standardize assessment. As a truncated version of the 25-item NSA, the NSA-16 still captures the multidimensionality of negative symptoms but can be completed in approximately 15 to 20 minutes (Axelrod et al. J Psychiatr Res. 1993;27(3):253-258). The NSA-4 (Alphs et al. Int J Methods Psychiatr Res. 2011;20(2):e31-37) is comprised of the 4 NSA-16 items as follows: 1) restricted speech quantity, 2) emotion: reduced range, 3) reduced social drive, and 4) reduced interests, as well as an overall global rating of negative symptoms.

[178] NSA global negative symptom score rates the overall severity of negative symptoms when defined as the absence or reduction of behaviors normally present in a healthy young person. In some embodiments, ratings do not depend on any specific item or items from the NSA or any other similar instrument. Instead, in some embodiments, ratings measure the rater's gestalt of the interview and are assessed following completion of the NSA-16 interview (Alphs et al. Int J Methods Psychiatr Res. 2011;20(2):e31-37).

[179] In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the NSA-16. In some embodiments, the NSA-16 is used alone. In some

embodiments, the NSA-16 is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Clinical Global Impression (CGI) Scales

[180] The CGI was developed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a treatment (Busner and Targum, Psychiatry (Edgmont). 2007;4(7):28-37). The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI comprises 2 companion 1-item measures, the CGI-S (Severity) and CGI-C (Change).

Clinical Global Impression - Severity (CGI-S)

[181] The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy, ECDEU Assessment Manual for Psychopharmacology. 1976:76-338). Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, among the most extremely ill patients.

Clinical Global Impression - Change (CGI-C)

[182] The CGI-C is a 7-point scale that requires the clinician to rate the change of the patient's condition at the time of assessment, relative to the clinician's past experience with the patient's condition at admission. Considering total clinical experience, a patient is assessed for change of mental illness as 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse.

[183] In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the CGI (e.g., the CGI-S and/or CGI-C). In some embodiments, the CGI

(e.g., the CGI-S and/or CGI-C) is used alone. In some embodiments, the CGI (e.g., the CGI-S and/or CGI-C) is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Patient Global Impression – Severity (PGI-S)

[184] The PGI-S is a 7-point (1–7), patient-rated scale used to assess the severity of the patient's schizophrenia as follows: 1) normal, not at all ill; 2) borderline ill; 3) mildly ill; 4) moderately ill; 5) markedly ill; 6) severely ill; 7) extremely ill.

[185] In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the PGI-S. In some embodiments, the PGI-S is used alone. In some embodiments, the PGI-S is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Patient Global Impression – Change (PGI-C)

[186] The PGI-C is a 7-point (1–7), patient-rated scale used to assess treatment response with respect to the patient's schizophrenia as follows: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

[187] In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the PGI-C. In some embodiments, the PGI-C is used alone. In some embodiments, the PGI-C is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)

[188] The MCCB is the standard tool for assessing cognitive change in trials of cognitive-enhancing agents in schizophrenia. The MCCB (Nuechterlein et al. Am J Psychiatry. 2008;165(2):203-213) is intended to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders. The MCCB includes 10 tests that measure 7 cognitive domains: Speed of Processing, Attention/Vigilance, Working

Memory, Verbal Learning, Visual Learning, Reasoning, and Problem Solving and Social Cognition.

[189] In some embodiments, cognitive domains are evaluated using the MCCB. In some embodiments, the MCCB is used alone. In some embodiments, the MCCB is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Calgary Depression Scale for Schizophrenia (CDSS)

[190] The CDSS is a 9-item scale derived from the Hamilton Depression Scale (Ham-D) that is designed to assess depression specifically in patients with schizophrenia (Addington et al. Schizophr Res. 1996;19(2-3):205-12). Unlike the Ham-D, the CDSS does not contain depressive symptoms that overlap with negative symptoms of schizophrenia, such as anhedonia and social withdrawal. The CDSS has shown excellent psychometric properties. Each item on the scale is scored as 0, Absent; 1, Mild; 2, Moderate; or 3, Severe. The CDSS score is obtained by adding each of the item scores. A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

[191] In some embodiments, depression is evaluated using the CDSS. In some embodiments, the CDSS is used alone. In some embodiments, the CDSS is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

Effort Expenditure for Reward Task (EEfRT)

[192] The Effort Expenditure for Rewards Task (EEfRT) (Treadway et al. PLoS One. 2009;4(8):e6598) is a multi-trial computerized task in which patients are given an opportunity to choose between 2 tasks that differ in difficulty level and are associated with varying levels of monetary reward. This task examines probabilistic learning in response to variable reward schedules and effort expended (button pushing) for reward. Probability is manipulated in the EEfRT, because, like mobilization of effort, probability discounting

appears to be highly predictive of negative symptoms. Additionally, the inclusion of a probability manipulation improves the overall ecological validity of the task, as most real-world choices that require motivation are usually associated with some level of uncertainty in the outcome. The EEfRT reliably measures drug effects on willingness to expend effort in relation to amount of reward or probability of reward. For example, amphetamine increased effort in response to low- and moderate probability rewards (Wardle et al. J Neurosci. 2011;31(46):16597-16602). Whereas reward salience and behavioral response have been linked to dopamine release in the striatum, glutamatergic input to midbrain dopamine neurons via NMDA receptors is also required for reward conditioning (Stuber et al. Science. 2008;321(5896):1690-1692). In some embodiments, the ratio of hard task choices with moderate probability reward is used as outcome measure for negative symptoms.

[193] In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the EEfRT. In some embodiments, the EEfRT is used alone. In some embodiments, the EEfRT is used in combination with one or more additional scales (e.g., any one or more of the exemplary scales described herein).

[194] In some embodiments of the methods disclosed herein, one or more negative symptoms of schizophrenia is evaluated using the NSA-16 total score. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using any one or more the PANSS total score; PANSS subscales (e.g., positive, negative, general psychopathology, Marder negative factors, excitement component, and/or prosocial factors); the NSA-16 factor domains; the NSA-16 global symptom/functioning score; NSA-16 individual items score; the NSA-4 score; the CGI-S score; the CGI-C score; the PGI-C score; and the EEfRT score. In some such embodiments, only one of the scales is used. In some such embodiments, all of the scales are used. In some such embodiments, combinations of two or more scales are used. In some embodiments, cognition is evaluated using the MCCB composite score. In some embodiments, depression is evaluated using

the CDSS. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using any one or more of the efficacy endpoints and/or scales described in the study from Example 1.

[195] In some embodiments of the methods disclosed herein, one or more negative symptoms of schizophrenia is evaluated using the PANSS Marder negative factors score. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the NSA-16 global negative symptoms score. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the PGI-S score. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the PGI-C score. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using the PANSS positive subscale and depression is evaluated using the CDSS. In some embodiments, one or more negative symptoms of schizophrenia is evaluated using any one or more of the efficacy endpoints and/or scales described in the study from Example 2.

[196] In some embodiments of the methods disclosed herein, the patient has clinically stable positive symptoms. In some embodiments, the patient has been diagnosed as having clinically stable positive symptoms based on factors such as inpatient psychiatric hospitalization, psychiatric hospital admission or acute exacerbation, and/or a particular score on certain aspects of the Positive and Negative Syndrome Scale (PANSS).

[197] In some embodiments, the PANSS positive subscale (P1 - P7) indicates changes in psychotic symptoms, and includes P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P4: excitement; P5: grandiosity; P6: suspicious/persecution; and P7: hostility. In some embodiments, the patient has clinically stable positive symptoms based on the PANSS positive subscale.

Clinical Study Design

[198] In the clinical study in Example 1 below, the benefit of treating negative symptoms of schizophrenia by administering d6-DM and Q was assessed. That study included a placebo group and a group that was administered d6-DM and Q. Having a placebo group in this study was particularly informative, because high placebo responses are commonly observed in studies of psychiatric disorders (see, e.g., Fava et al. "The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach," Psychother Psychosom. 2003;72(3):115-127 at 115-116). A "placebo response represents an apparent improvement in the clinical condition of patients randomly assigned to placebo treatment …." Id. at 116. Thus, to avoid ambiguity of whether improvement in patients is provided by a therapeutic benefit of the drug or due to a placebo response, a study involving administration of a drug for treatment of a psychiatric disorder should include a placebo group.

[199] Also, the clinical study in Example 1 below considered certain other factors that can exacerbate negative symptoms of schizophrenia, such as positive symptoms, depression (evaluated with the Calgary Depression Scale for Schizophrenia), and extrapyramidal symptoms. After considering those other factors, the study concluded that the drug treatment was specifically treating the negative symptoms of schizophrenia rather than improving such other exacerbating symptoms. See, e.g., Kirkpatrick et al., "The NIMH-MATRICS Consensus Statement on Negative Symptoms," *Schizophrenia Bulletin*, 32(2):214-219 (2006) (Kirkpatrick); Arango et al., "Pharmacological approaches to treating negative symptoms: A review of clinical trials," *Schizophrenia Research*, 150(2-3):346-352 (2013). An ambiguity that arises when it is not clear if a drug has had a direct effect on negative symptoms or instead indirectly effected negative symptoms by improving exacerbating symptoms has been called a "pseudo-specificity problem." Kirkpatrick at 216. "An improvement of negative symptoms in clinically stable patients, whose psychotic

symptoms have been treated to a usual clinical standard and do not change significantly, would allow an unambiguous interpretation." *Id.*

[200] In the clinical study in Example 1 below, patients had low baseline PANSS positive scores and demonstrated little change during the study. Also, in the study in Example 1 below, patients had low baseline symptoms of depression (evaluated with the Calgary Depression Scale for Schizophrenia) and pyramidal symptoms and did not experience significant changes in these symptoms throughout the study. Such results support the conclusion that administration of d6-DM and Q specifically treated negative symptoms of schizophrenia.

[201] The following examples provide illustrative embodiments of the disclosure. One of ordinary skill in the art will recognize the numerous modifications and variations that may be performed without altering the spirit or scope of the disclosure. Such modifications and variations are encompassed within the scope of the disclosure. The examples provided do not in any way limit the disclosure.

EXAMPLES

Example 1

A multicenter, randomized, double-blind, placebo-controlled, study to assess the efficacy, safety, and tolerability of d6-DM/Q (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) as an adjunctive treatment for patients with schizophrenia

[202] To evaluate the efficacy, safety, and tolerability of d6-DM/Q when taken as adjunctive therapy in patients with negative symptoms of schizophrenia, a randomized, placebo-controlled sequential parallel comparison design (SPCD) study was performed.

[203] The patient population studied was enriched for negative symptoms of schizophrenia and the primary efficacy endpoint of the study was the 16-Item Negative Symptom Assessment (NSA-16) total score, a validated and widely-used measure of

negative symptoms of schizophrenia (Daniel, Schizophr Res. 2013;150(2-3):343-5; Axelrod et al. J Psychiatr Res. 1993;27(3):253-8). The patient population studied had clinically stable positive symptoms treated with background second-generation atypical antipsychotic medication. d6-DM/Q was tested at doses of 34 mg d6-DM/4.9 mg Q (d6-DM/Q-34/4.9) twice daily (BID).

1 INVESTIGATIONAL PLAN

1.1 Overall Study Design

[204] This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, SPCD study consisting of an up to 4-week screening period, a 12-week double-blind treatment period with 2 consecutive stages (Stage 1 and Stage 2), and a 5-day follow-up by telephone. The length of each patient's participation in the study was approximately 12 weeks with a maximum of 17 weeks including the screening phase and post study exit phone calls for 5 days.

[205] Approximately 120 patients were planned to be enrolled at 15 centers in the U.S. Patients diagnosed with schizophrenia who were clinically stable, in a residual (non-acute) phase of illness, and who met all inclusion and none of the exclusion criteria were eligible for enrollment. In Stage 1, patients were randomized in a 1:2 (active:placebo) ratio to receive either d6-DM/Q or matching placebo capsules. Patients who were randomized to the d6-DM/Q group began receiving d6-DM 24 mg/Q 4.9 mg (d6-DM/Q-24/4.9) once daily (QD) on Day 1 for the first 7 days. Scheduled dose escalations occurred on Day 8 (to d6-DM/Q-24/4.9 BID and Day 14 to d6-DM/Q-34/4.9 BID whereas patients randomized to placebo received placebo BID in Stage 1.

[206] Patients who completed Stage 1 were eligible to participate in Stage 2. Patients who received d6-DM/Q in Stage 1 continued to receive d6-DM/Q 34/4.9 BID in Stage 2 with no further dose escalations. Patients who received placebo in Stage 1 were stratified into 1 of 2 treatment-response subgroups (responders vs. non-responders) at Stage 2 baseline (Visit 4 [Day 43]) and re-randomized in a 1:1 (active:placebo) ratio within

each subgroup. Patients were considered responders if their percent of change in Positive and Negative Syndrome Scale (PANSS) total score decreased ≥ 20% from baseline, and those who did not meet this criterion were considered as non-responders. Patients who were re-randomized from placebo in Stage 1 to d6-DM/Q in Stage 2 began receiving d6-DM/Q in Stage 2 using the same dose escalation schedule used in Stage 1 whereas patients re-randomized to placebo received placebo BID for the entire duration of Stage 2. A schematic of the study is shown in FIG. 2.

[207] Patients attended a screening visit up to 4 weeks (28 days) prior to the baseline visit to determine eligibility for the study. During the study, patients attended clinic visits at baseline/Visit 1 (Day 1), Week 2/Visit 2 (Day 15), Week 3/Visit 3 (Day 22), Week 6/Visit 4 (Day 43), Week 8/Visit 5 (Day 57), Week 9/Visit 6 (Day 64) and Week 12/Visit 7/Early Termination visit (Day 85) as outlined in Table 1. Patients also received telephone follow-up calls at Days 8 and 50 to inquire about adverse events (AEs) and study drug compliance. In addition, post study exit follow-up telephone calls were made daily on Days 86 to 90 to assess any changes in health (i.e., AEs) and medication (i.e., concomitant medications).

Table 1. Study Design and Schedule of Assessments

Procedure	Visit:	Screening	Baseline Visit 1	Phone[7]	Visit 2[2]	Visit 3[1]	Visit 4[2]	Phone[7]	Visit 5[2]	Visit 6[1]	Visit 7/ ET [2,4]	Post Exit Phone[7]
	Study Day:	Day -28 to -7	Day 1	Day 8	Day 15	Day 22	Day 43	Day 50	Day 57	Day 64	Day 85	Day 86-90
	Study Week:	Week -4 to -1		Week 1	Week 2	Week 3	Week 6	Week 7	Week 8	Week 9	Week 12	
Informed Consent Form signed		X										
CTS Database		X									X	
Medical History		X										
M.I.N.I. Exam		X										
Inclusion and Exclusion		X	X									
Randomization / (re-randomization)			X				X					
Physical Examination		X										
Resting 12-lead Electrocardiogram		X[6]	X[6]				X[6]				X[6]	
Chemistry, Hematology, and Urinalysis[3]		X					X				X	
Pregnancy Test[3]		X	X			X	X			X	X	
Lab -CYP2 D6			X[5]									
Plasma Antipsychotic Levels		X					X				X	
PK and Additional Genotyping Blood Samples			X[5]				X[5]				X[5]	
Review of Adverse Events			X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Record Vital Signs/Weight[9]		X	X		X	X	X		X	X	X	
NSA-16		X	X			X	X			X	X	
PANSS		X	X			X	X			X	X	
MCCB[10]		X	X				X				X	
CGI-S			X				X				X	
CDSS		X	X			X	X			X	X	

Procedure	Visit:	Screening	Baseline Visit 1	Phone[7]	Visit 2[2]	Visit 3[1]	Visit 4[2]	Phone[7]	Visit 5[2]	Visit 6[1]	Visit 7/ ET [2,4]	Post Exit Phone[7]
	Study Day:	Day -28 to -7	Day 1	Day 8	Day 15	Day 22	Day 43	Day 50	Day 57	Day 64	Day 85	Day 86-90
	Study Week:	Week -4 to -1		Week 1	Week 2	Week 3	Week 6	Week 7	Week 8	Week 9	Week 12	
CGI-C							X				X	
PGI-C							X				X	
RDoC Task (EEfRT)			X				X				X	
Side Effects Scales (AIMS, BAS, SAS)			X				X				X	
C-SSRS		X	X		X	X	X		X	X	X	
Smoking Cessation Question			X				X				X	
Dispense Study Medication			X			X	X			X		
Dose in Clinic			X		X	X	X		X	X	X	
Review and/or Return Unused Study Medication				X[8]	X	X	X	X[8]	X	X	X	

AIMS = Abnormal Involuntary Movements Scale; BAS = Barnes Akathisia Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI- C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity of Illness; C-SSRS = Columbia Suicide Severity Rating Scale; CTS = Clinical Trial Subject (database); CYP2D6 = Cytochrome P450 isoenzyme 2D6; EEfRT = Effort Expenditure for Reward Task; MCCB = MATRICS Consensus Cognitive Battery; M.I.N.I = Mini International Neuropsychiatric Interview; NSA-16 = 16-Item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale; PGI-C = Patient Global Impression of Change.

[1] Visits 3 and 6 had a +3-day window.

[2] Visits 2, 4, 5, and 7 had a ± 3-day window.

[3] Urinary (beta-hCG) test were performed for all females regardless of childbearing potential (serum beta-hCG at screening only). Fasting glucose and lipids were measured at screening, Visits 4, and 7.

[4] Final visit or Early Termination visit for patients who withdrew prior to study completion.

[5] PK blood draws were taken 2-3 hours' post-dose for Baseline and Visits 4 and 7. Blood samples for CYP2D6 genotyping were taken before dosing at Baseline. A one-time blood sample for additional genotyping may have been taken at any visit when blood was already being drawn.

[6] Electrocardiogram were performed prior to dosing and 2-3 hours post-dosing for Visits 1 and 4. Post-dose only for Visit 7. Triplicate ECGs at screening only.

[7] Telephone call had a + 3-day window. Post study exit calls were made daily for 5 days to assess any changes in health (AEs)/concomitant medications.

[8] Patient were asked if they have taken their medications as directed during telephone calls at Days 8 and 50.

[9] Height was measured at screening only.

[10] The MCCB should have been conducted at approximately the same time of day (± 2 hours) and preferably in the AM. After the screening visit, patients who used sedatives/hypnotics or benzodiazepine medications on a prn basis should not have taken any of these medications the day of, or the day before, the assessment of

cognitive function by MCCB. Patients who were on stable dose regimens of sedatives/hypnotics or benzodiazepine medications were to take their medication as prescribed.

1.2 Discussion of the Study Design, Including the Choice of Control Groups

[208] A randomized, placebo-controlled, double-blind study design was adopted to reduce sources of bias inherent to studies of schizophrenia. In addition, an SPCD that stratified placebo-treated patients in Stage 2 according to their responder status at the end of Stage 1 was used to reduce the impact of a confounding placebo response. High placebo responses are commonly observed in studies of behavioral and psychiatric disorders and constitute a significant challenge for drug development in these indications (Fava et al. Psychother Psychosom. 2003;72(3):115-127; Chen et al. Contemp Clin Trials. 2011;32(4):592-604). The SPCD (Chen et al. Contemp Clin Trials. 2011;32(4):592-604) selected for this study attempts to overcome these challenges by stratifying placebo-treated patients according to treatment response at the end of Stage 1 in order to reduce the detrimental impact of placebo response on signal detection. As a result, this design essentially comprised of two randomized trials run one after another with the expectation that signal detection would be enhanced by including only placebo non-responders in the primary analysis. The opportunity to compare patients who have taken drug or placebo for the entire duration of the trial (a built-in parallel study comparison) was retained with this design.

[209] The 6-week durations for Stage 1 and Stage 2 were selected to ensure exposure to the targeted optimal dose of d6-DM/Q for at least 4 weeks and up to 10 weeks for patients randomized to d6-DM/Q in Stage 1. This treatment duration also allowed for sufficient time to observe a treatment response, which was expected to be within the first few weeks of study treatment, and to assess duration of response. A consensus group comprised of representatives from the National Institute of Mental Health, FDA, academic, and industry identified a 6 to 12-week duration of treatment as appropriate for designing studies of negative symptoms of schizophrenia (Laughren and Levin, Schizophr Bull. 2006;32(2):220-222).

[210] The safety assessments used in this study are standard in clinical research. The rating scales used to assess efficacy are well-established instruments that are clinically validated and have been widely used in clinical studies of schizophrenia and other psychiatric and behavioral disorders. The primary efficacy analysis was based on methods reviewed by Chen et al. and employed in previously conducted studies using SPCD (Chen et al. Contemp Clin Trials. 2011;32(4):592-604). Calculation of the overall effect is based on a combination of the effects observed in Stage 1 and observed in Stage 2 for placebo non-responder stratum only (Fava et al. Psychother Psychosom. 2003;72(3):115-127).

1.3 Selection of Study Population

1.3.1 Inclusion Criteria

1. Males and females 18 to 60 years of age, inclusive, at time of informed consent.
2. Patients who met DSM-IV-TR diagnostic criteria for schizophrenia using the Mini International Neuropsychiatric Interview (M.I.N.I.) version 6.0 (Appendix 11A) and who met DSM-IV-TR diagnostic criteria for residual schizophrenia.
3. Patients must have had a score of $\leq$ 4 on PANSS items of delusions, hallucinations, and hostility. Patients must have a PANSS score of $\geq$ 4 (moderate) on any 2, or $\geq$ 5 on any 1, of the following items of the PANSS: blunted affect, emotional withdrawal, passive/apathetic social withdrawal, or lack of spontaneity/flow of conversation and a total PANSS negative subscale score (N1 to N7) of $\geq$ 18 at screening and baseline.
4. If female of childbearing potential, patients' must
   a. have had a negative urine pregnancy test (all females regardless of childbearing potential are required to submit a pregnancy test), and
   b. not have been nursing or planning a pregnancy for the duration of the study through 30 days after the last dosing visit, and

c. have been abstinent or willing to use a reliable method of birth control from the screening visit, and continue with the same method until 28 days after the last dosing visit

Reliable methods of contraception that meet the study requirements were:

- Intrauterine device
- Vasectomized partner
- Surgical sterilization (have had uterus and/or both ovaries removed, and/or have had a bilateral tubal ligation)
- Hormonal contraceptives (estrogen-containing birth control pills, vaginal ring, patch, injections or implants)
- The use of 2 barrier methods of contraception (i.e., 2 of the following used together): male condom with intravaginal spermicide, diaphragm with spermicide; cervical cap with spermicide

Note: The mini pill (micro-dosed progesterone preparations that do not contain estrogen) was not an acceptable form of contraception for this study.

Females of childbearing potential who were abstinent could have enrolled in the study.

A female was considered of childbearing potential unless she was post-menopausal (i.e., history compatible with menopause [i.e., reported lack of menses for ≥ 12 months] and no other biological/surgical cause).

All male patients must have followed the same methods of birth control with partners of childbearing potential from the screening visit until 28 days after the last dosing visit, Visit 7/Early Termination visit (Day 85).

5. Patients currently receiving atypical antipsychotics (oral and long acting intramuscular injectables) within the dose guidance from the U.S. package insert for the treatment of schizophrenia disorder (e.g., second-generation antipsychotics [SGAs] like olanzapine, risperidone, paliperidone, quetiapine, aripiprazole and

lurasidone) were eligible provided they had been treated with the medication for at least 3 months (90 days), the dose had been stable for at least 1 month (30 days) prior to the screening visit (includes no change from screening to baseline/Visit 1 [Day 1]), and there had been no inpatient psychiatric hospitalization in the past 4 months prior to screening.

6. Concomitant use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, citalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone) were allowed as long as patient was on an optimized dose for 3 months (90 days), provided the dose had been stable for at least 1 month (30 days) prior to baseline and the dose used was within the guidance from the U.S. label for that drug. Paroxetine, a CYP2D6 substrate, was allowed provided the dose did not exceed 10 mg/day.
7. Concomitant use of hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 100 mg/day]) for the nighttime treatment of insomnia was allowed, provided the dose had been stable for at least 1 month (30 days) prior to baseline and remained stable throughout the study. Patients on lorazepam for anxiety, restlessness, or agitation prior to study entry should have remained on the same treatment regimen for the duration of the study. All other benzodiazepines were disallowed, except for lorazepam use for short term or prn treatment of insomnia and behavioral disturbances. The duration of dosing should not have exceeded 3 days in a 7-day period.
8. Patients who were capable, according to the Investigator, and had signed and received a copy of the patient informed consent form (ICF) after the nature and risks of study participation had been fully explained to them.
9. Patients must have had a reliable informant as deemed appropriate by the investigator.

1.3.2 Exclusion Criteria

Patients were *not* to be enrolled in the study if they met any of the following criteria:

1. Patients with myasthenia gravis.
2. Patients with current major depressive disorder at the screening visit and/or a Calgary Depression Scale for Schizophrenia (CDSS) score $\geq$6.
3. Patients with cardiovascular concerns at screening or baseline such as:
    a. History or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions as evaluated by a central reader, QTc prolongation or *torsades de pointes.*
    b. QTc using the Fridericia's formula (QTcF) at screening > 450 msec for males and > 470 msec for females based on central review at the screening visit, unless due to ventricular pacing.
    c. Any family history of congenital QT interval prolongation syndrome.
    d. History or presence of clinically significant syncope, orthostatic hypotension or postural tachycardia.
4. Patients with known hypersensitivity to DM, Q, opiate drugs (codeine, etc.), or any other ingredient of the study medication.
5. Patients with history of allergy or hypersensitivity to several classes of medications.
6. Patients who had received DM co-administered with Q within 3 months (90 days) prior to baseline.
7. Patients with pseudoparkinsonism secondary to their ongoing antipsychotic medication based on PI judgement.
8. Patients treated with any typical antipsychotic within 3 months (90 days) prior to baseline. Typical antipsychotic medications were not allowed during the study.
9. Patients with a history of clozapine use within 3 months (90 days) prior to baseline. Clozapine was not allowed during the study.

10. Patients who were currently using anticholinergic medications or within 1 month (30 days) prior to baseline for treatment of AEs associated with antipsychotic medications.
11. Patients who were currently treated with monoamine oxidase inhibitors (MAOIs) or within 2 weeks prior to baseline.
12. Patients who had been taking prohibited concomitant medications per study protocol, within 2 weeks or 5 half-lives, whichever is longer, prior to baseline.
13. Patients with concurrent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (e.g., malignancy [except skin basal-cell carcinoma or untreated prostate cancer], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease), cognitive and other neurodegenerative disorders. Some cases might have been evaluated individually with the Investigator and medical monitor.
14. Current suicide risk, as evidenced by any of the following:
    a. It is the judgment of the Investigator that the patient might have been at risk for suicide.
    b. The patient was rated a “yes” to question 4 or question 5 on the screening and baseline Columbia Suicide Severity Rating Scale (C-SSRS), and the most recent episode occurred within 6 months prior to screening and baseline.
    c. The patient had attempted suicide within 12 months prior to screening and baseline.
15. Patients who had an inpatient psychiatric hospitalization within 4 months of screening.
16. Patients with clinically significant laboratory abnormalities (hematology, chemistry, and urinalysis) or with safety values of potential clinical concern or with aspartate

aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x the upper limit of normal at the screening visit.

17. Patients who were currently participating in, or who had participated in other interventional (drug or device) clinical study within 30 days prior to baseline.
18. Unwilling or unable, in the opinion of the Investigator, to comply with study instructions.
19. Patients with a history of substance and/or alcohol abuse, not including cigarettes (cannabis use might have been allowed per Investigator discretion) within 6 months or dependence within 1 year prior to baseline.
20. Patients who had received electroconvulsive treatment, repetitive transcranial magnetic stimulation or deep brain stimulation in the past year prior to screening.
21. Patients who were found to be a virtually certain match in CTS database with a patient who had participated in another interventional drug or device study within 30 days prior to baseline.

1.3.3 Removal of Patients from Therapy or Assessment

[211] Patients were advised verbally and in the ICF that they had the right to withdraw from the study at any time without prejudice or loss of benefits to which they were otherwise entitled, and were not obligated to provide the reason.

[212] The Investigator or Sponsor may have discontinued a patient from the study for any of the following reasons:

- In case of an inter-current illness, AE, other reasons concerning the health or well-being of the patient
- In the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons.
- Patients who presented a QTcF > 500 msec (unless due to ventricular pacing) or a QTcF change from the pre-dose baseline ECG of > 60 msec at any time

after baseline. The QTcF values was recorded and assessed for clinical significance.

- Patients who started a prohibited concomitant medication, psychotherapy, or somatic therapy (light therapy, repetitive transcranial magnetic stimulation, and other non-invasive brain stimulation techniques) during the study. The decision to withdraw the patient was made on a case-by-case basis in conjunction with the medical monitor.

[213] Patients who withdrew prior to study completion for any reason were asked to return to the clinic to complete the Visit 7 (Early Termination) assessments. If a patient did not return for a scheduled visit, every effort was made to contact the patient. In any circumstance, every effort was made to document patient outcome, if possible.

[214] If the patient withdrew from the study and consent for disclosure of further information was withdrawn, then no further evaluations were performed and no additional data was collected.

[215] Patients who withdrew from the study were not replaced.

1.4 Treatments

1.4.1 Treatments Administered

[216] Clinical study medication was provided as hard, blue-colored opaque gelatin capsules (size 3). Three different capsule strengths were provided, as follows:

- d6-DM/Q-24/4.9 (d6-DM 24 mg/Q 4.9 mg)
- d6-DM/Q-34/4.9 (d6-DM 34 mg/Q 4.9 mg)
- d6-DM/Q Placebo, with the same excipients as the study medication

[217] All medication used in this study were prepared, packaged, and labeled in accordance with Good Manufacturing Practice guidelines, ICH guidelines, GCP guidelines, and applicable laws and regulations.

1.4.2 Identity of Investigational Product(s)

[218] d6-DM/Q and matching placebo were supplied as a solid oral dosage form (gelatin capsule). The composition of each investigational product is shown in Table 2.

Table 2. Composition of Study Medication

Ingredient	d6-DM/Q (d6-DM 24 mg/Q 4.9 mg) (mg)	d6-DM/Q (d6-DM 34 mg/Q 4.9 mg) (mg)	Placebo (mg)
d6-dextromethorphan hydrobromide	24.0	34.0	0
Quinidine sulfate USP, EP	4.9	4.9	0
Croscarmellose sodium NF, EP	6.6	6.6	6.6
Microcrystalline cellulose NF, EP	181.2	171.2	210.1
Colloidal silicone dioxide NF, EP	2.2	2.2	2.2
Magnesium stearate NF, EP	1.1	1.1	1.1
Total	**220.0**	**220.0**	**220.0**
Capsule: Hard gelatin capsules, opaque blue cap and body, size 3. (average weight)	48.0	48.0	48.0
Total Weight	**268.0**	**268.0**	**268.0**

EP = European Pharmacopoeia; NF = National Formulary; USP = United States Pharmacopoeia

[219] The study medication was supplied as ready-packaged, blinded, pre-labeled, individually pre-packaged blister cards. Each blister card contained enough study medication to last for 3 weeks, i.e., 48 capsules of 1 of the 2 active study medications or placebo. Each 3-week blister card was clearly labeled to identify the morning and evening doses.

1.4.3 Method of Assigning Patients to Treatment Groups

[220] Eligible patients were randomized in a 1:2 ratio of d6-DM/Q or matching placebo at Stage 1 baseline. Patients randomized to placebo at Stage 1 baseline were re-randomized at the beginning of Stage 2, in a 1:1 ratio to d6-DM/Q and placebo. The re-randomization was stratified by patient responder status (responder vs. non-responder). A responder was defined as a patient with ≥ 20% change from baseline (Stage 1) in PANSS total score. Patients assigned to placebo in Stage 1 who dropped out early in Stage 1 were also randomly assigned Stage 2 treatment in the same manner as the other placebo

patients for statistical analysis purposes; their responder status was based on the measurements at their Early Termination visit.

[221] Double-blinded study medication assignment adhered to a randomization scheme and was managed using Interactive Response Technology (IRT). Allocation was handled by an IRT, which dynamically assigned the randomization blocks to study centers as they were needed. Enrollment was centrally randomized across the study.

1.4.4 Selection of Doses in the Study

[222] The doses selected for evaluation in this study were hypothesized to be potentially efficacious in the treatment of schizophrenia based on several *in vitro* studies of d6-DM assessing receptor pharmacology. The doses of d6-DM/Q were also expected to have a good safety and tolerability profile based on data from completed Phase 1 studies of d6-DM/Q. Therefore, the doses of d6-DM/Q used in this study, d6-DM/Q-24/4.9 and d6-DM/Q-34/4.9, were selected to provide an optimal benefit-risk ratio in this patient population.

[223] Escalation to the higher dose of d6-DM/Q (d6-DM/Q-34/4.9) using a fixed titration scheme was implemented with the assumption that it may increase tolerability.

1.4.5 Selection and Timing of Dose for Each Patient

[224] Patients self-administered the study medication approximately every 12 hours, orally with water (morning and evening), except on visit days when the morning dose of study medication was administered in the presence of site personnel.

[225] Patients randomized to d6-DM/Q in Stage 1, took d6-DM/Q-24/4.9 QD in the morning and placebo in the evening during the first week (Day 1 to 7), d6-DM/Q-24/4.9 BID for the next 1 week (Day 8 to 13), and d6-DM/Q-34/4.9 BID for the remaining 10 weeks of the study (Day 14 to 85).

[226] Patients randomized to placebo in Stage 1, took placebo BID for the 6-week duration of Stage 1 (Day 1 to 42). Those who were re-randomized to placebo continued taking placebo BID for the 6-week duration of Stage 2 (Day 43 to 85) and those who were

re-randomized to d6-DM/Q took d6-DM/Q using the same dose escalation schedule in Stage 1, i.e., d6-DM/Q-24/4.9 QD in the morning and placebo in the evening during the first week of Stage 2 (Day 43 to 50), d6-DM/Q-24/4.9 BID for the next 1 week (Day 51 to 58), and d6-DM/Q-34/4.9 BID for the remaining 4 weeks of Stage 2 (Day 59 to 85).

1.4.6 Blinding

[227] All study medication, including d6-DM/Q capsules and placebo capsules, were of identical appearance in order to maintain the integrity of the blind, including during dose escalation. Neither the Sponsor, patients, investigators, nor other study personnel were aware of a patient's treatment assignment. In the event that it became medically necessary to identify which treatment a patient had received, the blind could be broken. In that event, the investigator was to make all attempts to contact the medical monitor or representative to request the unblinding of a patient. The IRT manager was not required to be blinded, and he or she had access to the study medication list and the randomization code.

1.4.7 Prior and Concomitant Therapy

1.4.7.1 Allowed Concomitant Medications

[228] Allowed concomitant medications were to be evaluated by the Investigator and discussed with the medical monitor as necessary to determine if there was any concern for use during the study.

[229] Concomitant use of hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 100 mg/day]) for the nighttime treatment of insomnia was allowed, provided the dose had been stable for at least 1 month prior to baseline and remained stable throughout the study. Patients on lorazepam for anxiety, restlessness, or agitation prior to study entry remained on the same treatment regimen for the duration of the study.

[230] All other benzodiazepines were disallowed, except for lorazepam use for short term or prn treatment of insomnia and behavioral disturbances. Dosing was not to exceed 3 days in a 7-day period.

1.4.7.2 Prohibited Medications

[231] Patients were not allowed to take any of the prohibited medications during the study or 2 weeks or 5 half-lives, whichever was longer, prior to the start of dosing on Day 1. Examples of the prohibited medications are listed in Table 3. At each visit, patients were queried as to whether they took any concomitant medications and, if so, the Investigator recorded the medications taken and the reasons for their use. After the screening visit, patients who were using sedatives/hypnotics or benzodiazepine medications on a prn basis were not allowed to take any of these medications the day of, or the day before, the assessment of cognitive function by MCCB. Patients who were on stable dose regimens of sedatives/hypnotics or benzodiazepine medications were to take their medication as prescribed.

Table 3. Prohibited Medications

Classes	Prohibited Concomitant Medications
May increase Q plasma levels[1]	Amiodarone Carbonic anhydrase inhibitors Cimetidine Diltiazem Itraconazole Ketoconazole Macrolide antibiotics[2] Protease inhibitors[3] Voriconazole
Metabolized by CYP2D6 and might have increased plasma levels if co-administered with Q	Dextromethorphan[4] TCA[5] Atomoxetine
Related to Q	Quinine Mefloquine
Might produce serotonin syndrome when co-administered with DM	MAOIs[6]
Might decrease DM and Q plasma levels	Carbamazepine Cyproterone Hyperforin Oxcarbazepine Phenobarbital

	Phenytoin Rifampicin St. John's Wort
Other	Clozapine[7]
Typical antipsychotic medications[7]	

These are examples of disallowed medications and not a comprehensive list.
CYP2D6 = cytochrome P450 isoenzyme 2D6; DM = dextromethorphan; MAOI = monoamine oxidase inhibitor; Q = quinidine sulfate; TCA = tricyclic antidepressants.
[1] Topical preparations were permitted unless applied under occlusive dressing or other technique that was intended to increase systemic absorption.
[2] Examples included erythromycin, azithromycin, clarithromycin, dirithromycin, and roxithromycin.
[3] Examples included saquinavir, ritonavir, atazanavir, and indinavir.
[4] Over-the-counter and prescription.
[5] Examples included imipramine, desipramine, amitriptyline, and nortriptyline.
[6] Patients were to allow at least 14 days after stopping study medication before starting an MAOI.
[7] Not allowed during the study or within 3 months (90 days) prior to baseline.

1.5 Efficacy and Safety Variables

1.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

[232] The schedule of procedures and assessments is presented in Table 1.

1.5.1.1 Efficacy Measures

[233] The primary efficacy measure was the 16-Item NSA-16 total score. Secondary measures included scores from the PANSS, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), Patient Global Impression of Change (PGI-C), MCCB, CDSS, EEfRT, and Smoking Cessation Question. Descriptions of the scales used to measure efficacy are provided below.

1.5.1.1.1 16-Item Negative Symptom Assessment (NSA-16)

[234] The NSA-16 (Appendix 3A) is considered a valid and reliable measure of the presence, severity, and range of negative symptoms associated with schizophrenia; it has high interrater and test–retest reliability across languages and cultures (Daniel, Schizophr Res. 2013;150(2-3):343-345; Axelrod et al. J Psychiatr Res. 1993;27(3):253-258). The NSA-16 uses a 5-factor model to describe negative symptoms: (1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and (5) retardation. These factors, assessed through a structured interview, are comprehensive and well-defined to help standardize assessment. As a truncated version of the 25-item

NSA, the NSA-16 still captures the multidimensionality of negative symptoms but can be completed in approximately 15 to 20 minutes (Axelrod et al. J Psychiatr Res. 1993;27(3):253-258). The NSA-4 (Alphs et al. Int J Methods Psychiatr Res. 2011;20(2):e31-37) is comprised of the 4 NSA-16 items as follows: 1) restricted speech quantity, 2) emotion: reduced range, 3) reduced social drive, and 4) reduced interests, as well as an overall global rating of negative symptoms.

[235] The NSA-16 evaluation was performed at screening (Day –28 to Day –1), baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination visit (Day 85).

1.5.1.1.2 Positive and Negative Syndrome Scale (PANSS)

[236] The PANSS (Appendix 2) is a 30-item clinical scale that has been extensively used as a reliable and valid measure for negative symptom trials (Daniel, Schizophr Res. 2013;150(2-3):343-345). Each item is scored for “1” (absent) to “7” (extremely severe). Subscales of the PANSS include:

- Positive subscale (P1-P7),
- Negative subscale (N1-N7),
- General psychopathology subscale (G1-G16),
- Prosocial factors (G16. active social avoidance, N2. emotional withdrawal, N4. passive/apathetic social withdrawal, N7. stereotyped thinking, P3. hallucinatory behavior, P6. suspiciousness/persecution),
- Marder negative factors (N1. blunted affect, N2. emotional withdrawal, N3. poor rapport, N4. passive/apathetic social withdrawal, N6. lack of spontaneity and flow of conversation, G7. motor retardation, G16. active social avoidance),
- Excitement component (P4. excitement, P7. hostility, G4. tension, G8. uncooperativeness, G14. poor impulse control).

[237] The PANSS evaluation was performed at screening (Day –28 to Day –1), baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination visit (Day 85).

1.5.1.1.3 Clinical Global Impression (CGI) Scales

[238] The CGI was developed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication (Busner and Targum, Psychiatry (Edgmont). 2007;4(7):28-37). The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI comprises 2 companion 1-item measures, the CGI-S (Severity) and CGI-C (Change). The CGI forms can be completed in less than 1 minute by an experienced rater.

Clinical Global Impression - Severity (CGI-S)

[239] The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy W. ECDEU Assessment Manual for Psychopharmacology. 1976:76-338). Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, among the most extremely ill patients.

[240] The CGI-S evaluation was performed at baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

Clinical Global Impression - Change (CGI-C)

[241] The CGI-C is a 7-point scale that requires the clinician to rate the change of the patient's condition at the time of assessment, relative to the clinician's past experience with the patient's condition at admission. Considering total clinical experience, a patient is

assessed for change of mental illness as 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse.

[242] The CGI-C evaluation was performed at Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85). At Day 43 (Visit 4), the CGI-C was completed to assess change from the baseline visit (Day 1). At Day 85 (Visit 7), the CGI-C was completed to assess change from Day 43 (Visit 4) and change from the baseline visit (Day 1).

1.5.1.1.4 Patient Global Impression – Change (PGI-C)

[243] The PGI-C (Appendix 5A) is a 7-point (1–7), patient-rated scale used to assess treatment response as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

[244] The PGI-C evaluation was performed at Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

1.5.1.1.5 Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)

[245] The MCCB is the standard tool for assessing cognitive change in trials of cognitive-enhancing agents in schizophrenia. The MCCB (Nuechterlein et al. Am J Psychiatry. 2008;165(2):203-213) is intended to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders. The MCCB includes 10 tests that measure 7 cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning, and Problem Solving and Social Cognition.

[246] The MCCB evaluation was performed at screening (Day –28 to Day –1), baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85). The MCCB was to be conducted at approximately the same time of day (+/- 2 hours) and preferably in the AM. Alternate versions of the battery were used at different visits to decrease the learning confound.

1.5.1.1.6 Calgary Depression Scale for Schizophrenia (CDSS)

[247] The CDSS (Appendix 6) is a 9-item scale derived from the Hamilton Depression Scale (Ham-D) that is designed to assess depression specifically in patients with schizophrenia (Addington et al. Schizophr Res. 1996;19(2-3):205-212). Unlike the Ham-D, the CDSS does not contain depressive symptoms that overlap with negative symptoms of schizophrenia, such as anhedonia and social withdrawal. The CDSS has shown excellent psychometric properties. Each item on the scale is scored as 0, Absent; 1, Mild; 2, Moderate; or 3, Severe. The CDSS score is obtained by adding each of the item scores. A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

[248] The CDSS evaluation was performed at screening (Day –28 to Day –1), baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination visit (Day 85).

1.5.1.1.7 Effort Expenditure for Reward Task (EEfRT)

[249] The Effort Expenditure for Rewards Task (EEfRT) (Treadway et al. PLoS One. 2009;4(8):e6598) is a multi-trial computerized task in which participants are given an opportunity on each trial to choose between 2 tasks that differ in difficulty level and are associated with varying levels of monetary reward. This task examines probabilistic learning in response to variable reward schedules and effort expended (button pushing) for reward. Probability is manipulated in the EEfRT, because, like mobilization of effort, probability discounting appears to be highly predictive of negative symptoms. Additionally, the inclusion of a probability manipulation improves the overall ecological validity of the task, as most real-world choices that require motivation are usually associated with some level of uncertainty in the outcome. The EEfRT reliably measures drug effects on willingness to expend effort in relation to amount of reward or probability of reward. For example, amphetamine increased effort in response to low- and moderate probability rewards (Wardle et al. J Neurosci. 2011;31(46):16597-16602). Whereas reward salience

and behavioral response have been linked to dopamine release in the striatum, glutamatergic input to midbrain dopamine neurons via NMDA receptors is also required for reward conditioning (Stuber et al. Science. 2008;321(5896):1690-1692). The ratio of hard task choices with moderate probability reward was used as outcome measure for negative symptoms.

[250] The EEfRT evaluation was performed at baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

1.5.1.1.8 Smoking Cessation Question

[251] A smoking cessation question was asked at baseline/Visit 1 (Day 1), Visit 4 (Day 43), and Visit 7/Early Termination visit (Day 85). At the baseline visit, patients were asked about their usage of tobacco (cigarettes); for example, never, current, former. They were then asked about the number of cigarettes and what frequency. At visit 4 and visit 7, subjects were asked if there had been any change in usage.

1.5.1.2 Efficacy Variables

[252] The primary efficacy variable was the change from baseline/Visit 1 to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7(Day 85, Stage 2) on the NSA-16 total score analyzed based on the SPCD method using a weighted ordinary least square test statistics combining treatment effects from Stage 1 and 2.

[253] The secondary efficacy variables included change from baseline to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7 (Day 85, Stage 2) for the following efficacy measures:

- PANSS total score
- PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and prosocial factors)
- NSA-16 (factor domains, global score, individual items, and NSA-4 factors)
- Proportion of patients with ≥ 20% reduction in PANSS total score
- MCCB composite score

- CGI-S score
- CGI-C scores (measures change at post baseline visits)
- PGI-C scores (measures change at post baseline visits)
- CDSS
- EEfRT

1.5.1.3 Safety Measures

[254] Safety was assessed by reported AEs, serious AEs (SAEs), physical examinations (scheduled for screening visit only), vital signs, weight, pregnancy tests, clinical laboratory assessments, and resting 12-lead ECGs. In addition, the following scales were used to assess safety:

- Columbia Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movements Scale (AIMS)
- Barnes Akathisia Scale (BAS)
- Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

1.5.1.3.1 Adverse Events

[255] An AE was defined as any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time the ICF was signed, including inter-current illness, which occurred during the course of a clinical trial after treatment was started, whether considered related to treatment or not. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

[256] Treatment-emergent adverse events (TEAEs) were defined as AEs that first occurred, or worsened, after the first dose of study medication and within 30 days after the permanent discontinuation of the study medication (first dose date on or before AE start date which was on or before the date of last dose + 30 days). Changes associated with

normal physiology that did not vary in frequency or magnitude from what was ordinarily anticipated clinically were not considered AEs (e.g., onset of menstruation occurring at a physiologically appropriate time). A deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses was considered an overdose. Overdoses were reported irrespective of outcome (even if toxic effects were not observed).

[257] Any AE reported after a patient received the last dose of study medication and up until 30 days after receiving the last dose of study medication was followed up until resolution (patient's health returned to his/her baseline status or all variables returned to normal) or until stabilization of the event occurred (the investigators did not expect any further improvement or worsening of the event).

[258] All AEs were graded on a 3-point scale and reported in detail as indicated on the electronic Case Report Form (eCRF) as follows:

Rating	Definition
Mild	Easily tolerated, causing minimal discomfort and not interfering with normal everyday activities
Moderate	Sufficiently discomforting to interfere with normal everyday activities
Severe	Incapacitating and/or preventing normal everyday activities

[259] The relationship of each AE to study medication was determined by the investigators using the following explanations:

- Not related: this category was applicable to those AEs that were clearly related to other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
- Unlikely related: this category was applicable to those AEs that were most likely produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient; and did not follow a known response pattern to the study medication.

- Possibly related: this category was applicable to those AEs that followed a reasonable temporal sequence from the time of drug administration; and/or followed a known response pattern to the study medication; but could have been produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
- Related: this category was applicable to those AEs that followed a reasonable temporal sequence from the time of drug administration; and followed a known response pattern to the study medication; and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.

1.5.1.3.2 Serious Adverse Events

[260] An SAE was defined as any AE occurring at any dose that resulted in any of the following outcomes:

- Death;
- Life-threatening experience (one that placed the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred; i.e., it did not include an AE that, had it occurred in a more severe form, might have caused death);
- Persistent or significant disability/incapacity (disability was a substantial disruption of a person's ability to conduct normal life functions);
- In-patient hospitalization or prolongation of hospitalization;
- Congenital anomaly/birth defect.

[261] Important medical events that did not result in death, were not life-threatening, or did not require hospitalization were considered an SAE when, based upon appropriate medical judgment, they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in the definition. The medical monitor

had to be contacted immediately (within 24 hours) for any SAE (including an abnormal laboratory test value).

[262] A death that occurred during the study, or that came to the attention of the investigators within 30 days after stopping the treatment whether considered treatment-related or not, was to be reported. Pregnancy was not considered an AE or SAE, unless a complication occurred that met the requirements for an AE or SAE; however, it was reported on a pregnancy report form. The terms “cancer” and “overdose” were not considered SAEs unless the other criteria for SAE were met; however, cancer and overdose were reported as AEs.

1.5.1.3.3 Physical and Neurological Examination

[263] Physical and neurological examinations were performed at screening (Day –28 to Day –1) and at the discretion of the Investigator at the subsequent visits. It included assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. Physical and neurological examinations were performed by the same person each time, whenever possible.

[264] Physical and neurological examination abnormalities determined by the investigators to be clinically significant at screening were recorded as medical history. Any clinically significant changes in physical and neurological examination findings from the screening examination were recorded as AEs.

1.5.1.3.4 Vital Signs and Weight

[265] At screening (Day –28 to Day –1), orthostatic blood pressure (BP) and heart rate (HR) measurements were performed. Supine BP and HR were measured after a patient rested for at least 5 minutes in the supine position. Each measurement was taken and recorded twice. After the measurement of supine BP and HR, the patient stood still for up to 3 minutes and a single measurement of standing BP and HR was recorded within

these 3 minutes of standing. Respiratory rate (breaths/minute), body temperature, height, and weight were also recorded.

[266] Patients presenting with orthostatic hypotension (decrease of ≥ 20 mm Hg in systolic blood pressure [SBP] or ≥ 10 mm Hg in diastolic blood pressure [DBP] upon postural change from supine to standing measured within 3 minutes) and/or postural tachycardia (HR increase ≥ 30 beats per minute (bpm) from the supine measurements or HR ≥ 120 bpm on standing) met exclusion criteria 3.

[267] At all subsequent visits, the supine/semi-recumbent systolic and diastolic BP and HR (beats/minute), after at least 5 minutes of rest, were taken and recorded twice. Respiratory rate (breaths/minute), body temperature, and weight were also recorded.

[268] The vital signs and weight were captured at all visits as indicated in Table 1.

1.5.1.3.5 Pregnancy Test

[269] All female patients of childbearing potential were instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication.

[270] Urine pregnancy tests (beta-hCG) were performed on all females regardless of childbearing potential at all clinic visits except at the screening visit where serum beta-hCG test was performed.

1.5.1.3.6 Clinical Laboratory Assessments

[271] The clinical laboratory assessments which included blood chemistry, hematology, and urinalyses were performed at the visits presented in Table 1. The clinical laboratory assessments included:

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase

[AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], creatine kinase, gamma-glutamyl transferase, triglycerides, total protein, total cholesterol, and glycosylated hemoglobin [HbA1c, at screening and Visit 7]).

- Hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology).
- Urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, urobilinogen, nitrites, leucocytes, and blood). Microscopic analysis is performed on those samples that are positive for blood, protein, leucocyte esterase or nitrates.
- Urine screen for presence of alcohol and substances of abuse – pheneyelidine, PCP, benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, and opiates. (screening visit only).
- Thyroid function tests TSH, T3, T4 (screening visit only).
- Plasma antipsychotic levels were measured at Screening, Week 6, and Week 12.

[272] Any patients with clinically significant abnormal laboratory test results were required by the medical monitor to have a repeat test 1 week later or sooner, if medically indicated. Clinically significant laboratory abnormalities could have been a basis for exclusion from study entry. Non-eCRF data including, but not limited to, laboratory tests and results, were sent to the contract research organization (CRO) by data transfer from the central laboratory for assimilation into the database.

1.5.1.3.7 Electrocardiograms

[273] ECG equipment was provided by the central reader. ECG data was recorded at the study center and included general findings, HR (beats/minute), QRS complex and PR and QTc intervals (milliseconds). Results were provided by the central reader to the investigators within 72 hours and any significant findings were reported within

24 hours. ECG abnormalities present at screening were recorded as medical history. Any changes from the ECG status at screening that were deemed to be clinically significant by the investigators were recorded as AEs. Any clinically significant abnormal ECG was discussed with the study medical monitor and if necessary was repeated within a 1-week period. Non-eCRF data including, but not limited to, ECG tests and results, were sent to the CRO by data transfer from the central reader for assimilation into the database. A resting 12-lead ECG was performed at all visits as indicated in Table 1. At Stage 1 baseline (Day 1), and Stage 2 baseline visit 4 (Day 43), 2 ECGs were performed; 1 prior to study medication dosing, and another 2-3 hours after dosing. Triplicate ECGs were performed at screening.

1.5.1.3.8 Columbia Suicide Severity Rating Scale (C-SSRS)

[274] The C-SSRS (Appendix 10) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening. The C-SSRS rating was performed at all clinic visits.

1.5.1.3.9 Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

[275] The SAS (Appendix 9A) is composed of 10 items and is used to assess pseudoparkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Signs assessed include gait, arm-dropping, shoulder-shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The SAS evaluation was performed at baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

1.5.1.3.10 Barnes Akathisia Scale (BAS)

[276] The BAS (Appendix 8) consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The BAS is scored as follows: Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0-3 and are summed yielding a total score ranging from 0 to 9. The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0-4. The BAS evaluation was performed at baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

1.5.1.3.11 Abnormal Involuntary Movements Scale (AIMS)

[277] The AIMS (Appendix 7A) is composed of 12 items and was used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness were rated using a 5-point scale (0 = none to 4 = severe). Two items related to dental status were scored using "yes" or "no" responses. The AIMS evaluation was performed at baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85).

1.5.2 Drug Concentration Measurements

[278] All patients had plasma samples collected for analysis of d6-DM, d3-DX, d3-3-MM, and Q plasma concentrations at baseline/Visit 1 (Day 1, post-dose), Visit 4 (Day 43) and Visit 7/Early Termination visit (Day 85), 2 to 3 hours after the morning dose of study medication. Maximum concentration (C_{max}) and area under the curve (AUC) were estimated based on a PK model for d6-DM, its metabolite deuterated (d3)-dextrorphan (d3-DX), and Q for those patients taking d6-DM/Q. Drug concentrations and estimated PK parameters were summarized by visit, treatment group and metabolizer type.

[279] Plasma samples were separated by centrifugation and then frozen at -20°C until assayed at the analytical unit.

1.5.3 Cytochrome P450 2D6 and Genotype Assessments

[280] A blood sample for CYP2D6 genotyping was collected at the baseline visit (Day 1) prior to study medication administration.

[281] A sample of whole blood was also collected at any visit when blood was already being drawn, for exploratory biomarker analyses. The samples were processed and stored in a biobank in aliquots for up to 5 years (or until the aliquots were depleted).

1.5.4 Appropriateness of Measurements

[282] The rating scales used to assess efficacy of the study medication are well-established instruments that are clinically validated and widely used in clinical studies of schizophrenia and other psychiatric and behavioral disorders. The safety assessments used in this study are standard in clinical research and are generally recognized as reliable, accurate, and relevant.

1.6 Data Quality Assurance

1.6.1 Study Administration and Conduct

[283] The study was routinely monitored to ensure compliance with the study protocol and the overall quality of data collected.

[284] For each patient enrolled in the study, an eCRF was completed and electronically signed by the investigators to certify that the data within each eCRF was completed and correct. This also applied to those patients who failed to complete the study. If a patient was withdrawn from the study because of a treatment-limiting AE, thorough efforts were to be made to document the outcome. The eCRFs were reviewed by the study monitor at the study site for completeness and adherence to protocol. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors, and the changes were documented and approved by the investigators.

[285] Any site personnel with the responsibility for data entry, query resolution, or eCRF approval completed training prior to accessing the eCRF. The electronic data capture vendor provided a username once training completion was confirmed, and the account was

then approved. A change to the data once initially saved was tracked via audit trail, and the reason for change was mandatory. The audit trail also included information of who made the change and a date/time stamp.

[286] Investigator meetings and site initiation visits (Initial Site Study Protocol and Procedures Training) took place to prepare investigators and standardize performance. Investigators and study staff were kept up to date and reminded of important study updates, such as protocol amendments, via Web-Ex trainings and quarterly newsletters, and field monitors reviewed the quarterly newsletters with study sites during interim monitoring visits. In-house clinical research associates (CRAs), overseen by a clinical study manager, called study sites on a regular basis to review important study updates, patient screening, and enrollment status and to answer any site questions. In-house CRAs were also available for any site and monitor support on an ad-hoc basis.

1.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

[287] Statistical analyses were performed using statistical analysis software (SAS®) version 9.3 or higher.

1.7.1 Endpoints

1.7.1.1 Efficacy Endpoints

[288] The primary efficacy endpoint was the change from baseline in the NSA-16 total score.

[289] Secondary endpoints were the change from baseline (or actual scores for the CGI-C and PGI-C) in the scores of the assessments listed below:

- PANSS total score, PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and prosocial factors)
- NSA-16 factor domains, global symptom/functioning score, individual items, and NSA-4

- MCCB composite score
- CGI-S, CGI-C, and PGI-C scores
- CDSS total score
- EEfRT score
- Proportion of patients with a reduction of 20% or greater in the PANSS total score
- Smoking cessation question

1.7.1.2 Safety Endpoints

[290] Safety endpoints in this study included frequency and nature of AEs reported, changes over time in vital signs, weight, urine pregnancy tests, clinical laboratory assessments, resting 12-lead ECGs, C-SSRS, AIMS, BAS, and SAS.

1.7.2 Analysis Populations

1.7.2.1 Modified Intent-to-treat Population

[291] The modified intent-to treat (mITT) population was the primary efficacy analysis population for SPCD analyses. Patients included in this population were determined separately for Stage 1 and Stage 2. Patients included in the Stage 2 analyses of the mITT population were a subset of those included in the Stage 1 analyses. The mITT population was defined as follows:

- Stage 1: All patients randomized in Stage 1 who had at least 1 post-baseline NSA-16 total score assessment in Stage 1.
- Stage 2: All patients who were re-randomized into Stage 2 (regardless of Stage 1 treatment group) and had at least 1 NSA-16 total score assessment in Stage 2 (after Visit 4 [Week 6]).

[292] When implementing changes in Protocol Amendment 4, the IRT vendor who carried out the IVRS found that approximately 14 Stage 1 Placebo patients were re-randomized for Stage 2 at Week 3 instead of Week 6. Patients with randomization error (13 patients) were excluded from the mITT analysis population.

[293] The Stage 2 mITT population subsets used in SPCD analyses were determined by Stage 1 placebo responder status:

- Stage 1 placebo non-responders (this was the primary efficacy Stage 2 mITT subset for SPCD analyses)
- Stage 1 placebo responders
- Stage 1 placebo responders and non-responders.

1.7.2.2 Per-Protocol Population

[294] The per-protocol (PP) population included those mITT patients who had no major protocol violations which may have substantially impacted efficacy assessments. The following criteria was used as a guide to exclude patients from the per protocol analysis population.

- Violation of inclusion and exclusion criteria which may have substantially impacted efficacy assessment.
- Study medication compliance < 80%
- Received incorrect treatment during the study. Specifically, active treatment group patient received placebo or placebo treatment group patient received active re-treatment.
- Took disallowed medication(s) post baseline which may have substantially impacted efficacy assessment.
- d6-DM or Q concentrations that were below the limit of quantification at Week 6 or 12 when receiving active treatment.

1.7.2.3 Intent-to-treat Population

[295] The intent-to-treat (ITT) population was used for sensitivity analysis of the SPCD methodology. It included all patients randomized in Stage 1 and all patients who were correctly re-randomized into Stage 2. The 13 patients with randomization error were excluded from this ITT population.

1.7.2.4 Safety Population

[296] The safety population was used for all safety analyses. It included all patients who received at least one dose of study medication.

1.7.2.5 12-week Parallel Group Population

[297] The 12-week parallel group population comprised patients who were randomized into placebo/placebo or d6-DM/Q/d6-DM/Q (randomized to d6-DM/Q in Stage 1). It was intended to assess efficacy or safety under a 12-week study duration, as would be done if the study had been a parallel group design. Note that patients randomized to Placebo/d6-DM/Q, whether or not they dropped out in Stage 1, were not part of this population.

[298] mITT 12-week Parallel Group Population: This population comprised patients in the 12-week parallel group population who had at least one post-baseline NSA-16 total score.

[299] Safety 12-week Parallel Group Population: This population comprised patients in the 12-week parallel group population who received at least one dose of study medication.

[300] Per-protocol 12-week Parallel Group Population: This population comprised patients in the mITT 12-week parallel group population who were also in the PP population defined in Section 1.7.2.1.

1.7.3 Efficacy Analysis

[301] All statistical testing was 2-sided and performed at the 0.05 level. Quantitative displays were summarized using descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum).

1.7.3.1 Primary Efficacy Analysis (SPCD, Mixed-Model Repeated Measures)

[302] The primary efficacy endpoint (change from baseline in NSA-16 total score) was analyzed using a SPCD weighted test statistic with the treatment effects in each stage estimated by a likelihood-based mixed-model repeated measures (MMRM) analysis on the

observed data (Chen et al. Contemp Clin Trials. 2011;32(4):592-604). This analysis included patients in the mITT population (Stage 1 mITT population and the placebo non-responder Stage 2 mITT subset). The MMRM analysis included terms for treatment, visit, treatment-by-visit interaction, baseline NSA-16 value, and baseline-by-visit interaction. Unstructured covariance was used. Treatment effect and standard error were obtained directly from the model output.

[303] Separate MMRMs were run to generate the least square (LS) mean difference between treatment groups at Week 6 for Stage 1 and Week 12 (Week 6 to 12) for Stage 2, to generate a combined weighted test statistic, Z_{MMRM}. A prespecified weight of w=0.6 was used for Stage 1, and the weight of 1-w=0.4 was used for Stage 2. The weighted test statistic was then used to generate a 2-sided p-value for the hypothesis test.

1.7.3.2 Sensitivity Analyses for the Primary Efficacy Endpoint

[304] The following sensitivity analyses were performed on the primary endpoint in order to show the robustness of the data when analyzed using different statistical analyses, imputation methods, or patient populations:

- SPCD with ordinary least squares (OLS) analysis of covariance (ANCOVA) using the mITT population and last observation carried forward (LOCF) for missing values.
- Seemingly unrelated regression (SUR) method (Tamura and Huang, Clin Trials. 2007;4(4):309-17) that accounted for the fact that random error from the 2 stages of the study may have been correlated for patients with data in both stages. This analysis was performed on the mITT population and LOCF was used for imputation of missing values.
- SPCD with MMRM on the PP population.

1.7.3.3 Secondary Efficacy Endpoints Analyses

[305] The secondary endpoints listed in Section 1.7.1.1 were analyzed using the methods described below. In addition, some efficacy analyses were performed on NSA-16 total scores (the primary efficacy measure).

1.7.3.3.1 Secondary Efficacy Endpoint Analyses by MMRM SPCD OLS ANCOVA SPCD

[306] The change from baseline for all quantitative secondary endpoints which were measured at baseline, Week 6 and 12 (except the CGI-C and the PGI-C) were analyzed using the SPCD OLS ANCOVA method on the mITT population and LOCF within a study stage was used for missing values at Week 6 or Week 12. The ANCOVA model included treatment as a factor and baseline value as a covariate. In addition, the secondary endpoints derived from the NSA-16, PANSS and CDSS (which were assessed at baseline, Week 3, 6, 9 and 12) were analyzed using the MMRM SPCD method.

[307] For the CGI-C and the PGI-C, an ANCOVA model with treatment as a factor and baseline NSA-16 total score as a covariate was used.

1.7.3.3.2 PANSS Response Analysis

[308] The number and percent of patients in the mITT population who had a favorable treatment response, i.e., ≥ 20 % reduction in the PANSS total score, at Week 6 and Week 12, were summarized by stage and treatment group. LOCF was used for patients' missing data. Overall Stage 1 and 2 treatment differences were tested via SPCD 1 degree of freedom score test assuming Stage 2 and 1 treatment effect ratio $\rho = 1$ (Ivanova et al. Stat Med. 2011;30(23):2793-2803). In addition, the treatment effect was tested at each visit by Chi-square test or Fisher's Exact .

[309] For the binary response variable of treatment response, a generalized estimating equation (GEE) model analysis on the observed data was performed. The generalized estimating equation model included terms of treatment, visit, treatment-by-visit

interaction, baseline value, and baseline-by-visit interaction. P-value, odds ratio (OR), and its 95% confidence interval (CI) were provided for each visit.

1.7.3.3.3 12-Week Parallel Group Analysis

[310] To evaluate the treatment effect under 12 weeks of exposure to the same treatment, a repeated measures analysis of the NSA-16 total score using observed data from all scheduled visits was performed on the mITT 12-Week Parallel Group Population and PP 12-Week Parallel Group Population. This analysis compared treatment groups over time using a linear mixed effects model. The model included fixed effects for treatment, visit, treatment-by-visit interaction, baseline NSA-16 total score, and baseline-by-visit interaction. Unstructured covariance was used as first preference, as in the primary.

[311] This analysis was performed on the NSA-16 total score in addition to all other secondary endpoints for the mITT 12-Week population. The model for CGI-C and PGI-C contained treatment, visit, and treatment-by-visit interaction.

1.7.3.3.4 Analyses Using the PP Population

[312] In addition to the primary efficacy end point NSA-16 analysis on the PP population (sensitivity analysis), the following secondary efficacy end points were also analyzed using the PP population: PANSS total score, PANSS Negative Subscale, PANSS Marder Negative Factors, MCCB composite score and CGI-C. Both SPCD and 12-week parallel group comparison analyses were performed.

1.7.3.4 Supplementary Analyses

1.7.3.4.1 12-Week Parallel Group ANCOVA

[313] For all efficacy variables, separate by-visit ANCOVA models was performed on the mITT 12-Week Parallel Group population. Missing values were imputed by LOCF (regardless of stage). The ANCOVA model included treatment as a factor, and baseline value as a covariate. For the CGI-C and the PGI-C, the model did not contain baseline value. For the CGI-C, the model for Week 12 assessed the difference relative to baseline.

1.7.3.4.2 CGI-C and PGI-C Proportional Odds Ratio

[314] For the CGI-C and PGI-C, odds ratios were obtained through a proportional odds regression model at each visit and represented the odds of a favorable response with d6-DM/Q compared to placebo. Odds ratios > 1 indicated an increased likelihood of a favorable response in patients taking d6-DM/Q. This analysis was performed the mITT population and on the 12-Week Parallel Group population.

1.7.3.4.3 Smoking Cessation Analysis

[315] Descriptive summaries of the number and percentage of patients in each tobacco use category (never, current, and former) were presented. Among those who were former tobacco users, descriptive statistics of the rate of use (defined as the number of units per day) were calculated. Among those who were current users at baseline or begin smoking post-baseline, the rate and change from baseline of the rate at each visit were calculated and summarized descriptively. All analyses were summarized by treatment group and performed on the mITT (Stage 1) and mITT 12-Week Parallel Group populations.

1.7.3.4.4 SPCD Analysis by Subgroup

[316] The primary endpoint was analyzed using the subgroups defined by each category below on the mITT population, using the OLS ANCOVA methodology.

- Age group (< 45, ≥ 45)
- Gender (male, female)
- Baseline MCCB composite score (< 30, ≥ 30)
- Baseline concomitant benzodiazepine/SSRI/SSNI medication use
- Onset of schizophrenia (< 20 years, ≥ 20 years) and residual schizophrenia (< 4 years, ≥ 4 years)

1.7.3.4.5 Treatment Effect by Baseline Concomitant Medication

[317] Analyses of the primary endpoint (NSA-16 total score) were performed for the subgroup of patients using concomitant psychotropic medications (antidepressants, antipsychotics) considered to be CYP2D6 major substrates (aripiprazole, risperidone,

duloxetine, fluoxetine, fluvoxamine, mirtazapine, paroxetine, and venlafaxine) and the subgroup with concomitant psychotropic medications that were considered not to be CYP2D6 major substrates. The ANCOVA analyses (LOCF) were conducted using the mITT (Stage 1) and mITT 12-Week Parallel Group Population.

[318] In addition, concomitant use of beta blockers that are CYP2D6 substrates was analyzed for TEAEs, such as cardiovascular-related AEs, falls, etc. The analysis was conducted for the subgroup of patients who were taking concomitant beta blockers that are considered to be major substrates of CYP2D6 and for patients taking beta blockers that are not major substrates of CYP2D6.

1.7.3.4.6 NSA-16 Band-Pass Filter Analysis

[319] Band-pass filtering is a statistical methodology that filters out data from trial sites generating non-plausible high or low levels of placebo response, thus yielding a more accurate effect size and greater separation of active drug (when efficacious) from placebo (Targum et al. Eur Neuropsychopharmacol. 2014;24(8):1188-1195). The NSA-16 total score change from baseline (on observed data) was analyzed using one band-pass filter (> 0 or < -7). Mean NSA-16 change from baseline scores for each site were calculated and the sites that had scores exceeding the boundaries of the band-pass filter threshold were considered non-informative and were excluded from the analysis. After applying the band-filter, NSA-16 total score change from baseline were analyzed using SPCD methodology (mITT) and on the 12-week parallel group population.

1.7.4 Pharmacokinetics and Pharmacodynamics Analysis

[320] Plasma concentrations of d6-DM, d3-DX, d3-3-MM and Q obtained from blood samples collected at baseline (Day 1), Visit 4 (Week 6) and Visit 7 (Week 12/ET) were summarized descriptively overall and by CYP2D6 metabolizer group. PK parameter (C_{max} and AUC) estimation was performed for d6-DM, d3-DX and Q. Predicted PK parameters were also summarized descriptively overall and by metabolizer group.

[321] Correlations between the estimated PK parameters of d6-DM, d3-DX and Q and the change from baseline in the NSA-16 were provided.

[322] Blood draws to assess concentrations of SGAs were performed at screening, Week 6, and Week 12, and results from the plasma concentrations were summarized descriptively.

1.7.5 Safety Analysis

[323] Unless otherwise specified, safety analyses that include summaries of number and percent (e.g., AEs) were displayed using the following treatment groups:

- Placebo/Placebo: patients receiving Placebo/Placebo during the study. Note that patients randomized to Placebo/d6-DM/Q but dropped out in Stage 1 were not included in this population. Instead, these were summarized under the 'All Placebo' treatment group.
- d6-DM/Q/d6-DM/Q: patients receiving d6-DM/Q for the entire duration of the study.
- Placebo/d6-DM/Q: patients who switched from placebo to d6-DM/Q. This group was further divided into data that occurred while on placebo and data that occurred while on d6-DM/Q.
- All Placebo: This included data from the stages when patients received placebo.
- All d6-DM/Q: This included data from the stages when patients received d6-DM/Q.

[324] For quantitative summaries (e.g., ECGs, labs), the All Placebo and All d6-DM/Q groups were not included.

1.7.5.1 Adverse Events

[325] AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Tabular summaries of TEAEs, AEs leading to discontinuation, treatment-related AEs, and SAEs were summarized by system organ class (SOC) and

preferred term (PT). Patients who took only d6-DM/Q or only placebo and had multiple AEs within the same SOC or PT were only counted once within a level of MedDRA. If patients switched from placebo to d6-DM/Q and had the same AE start in both study stages, it was counted under both placebo and d6-DM/Q.

1.7.5.2 Clinical Laboratory Assessments

[326] Hematology, chemistry, and urinalysis assessments were summarized descriptively using change from baseline and percent change from baseline, by visit and by stage. Out-of-range values were assessed through shift tables. Each value was assessed as low, normal, or high based on the normal ranges provided by the central lab. Frequencies of each combination of shifts were provided by treatment group.

[327] Shift tables were created by stage and also for the safety 12-week parallel group population (Placebo/Placebo and d6-DM/Q/d6-DM/Q). In both stages, patients taking d6-DM/Q were compared to those taking placebo. The Stage 1 shift table included all patients in the safety population, while the Stage 2 shift table included only re-randomized patients. Baseline in all shift tables was the last assessment prior to first dose in each stage.

[328] The number and percent of patients meeting PCS criteria any time post-baseline were summarized by treatment group.

[329] Over the course of the study, there may have been some lab tests performed that were not mentioned in the protocol. These tests were not to be summarized but were to be included in the listings and flagged as non-protocol tests.

1.7.5.3 Electrocardiogram

[330] The quantitative parameters of HR, PR interval, QRS duration, QT interval (uncorrected), and QTcF were reported by a central reader. Change from baseline and percent change from baseline were calculated for each parameter and summarized by treatment group. In addition, since ECGs were recorded pre-dose and post-dose at

baseline, Week 6, and Week 12, change from pre-dose to post-dose was summarized at these visits.

[331] The number and percentage of patients meeting the PCS criteria were summarized by treatment group. Summaries were given for any time post-baseline and by visit. For QTcF, males and females were assessed separately. Patients were included in all categories for which they qualified.

[332] ECG overall interpretations were summarized by the number and percentage that were normal or abnormal. Cardiologist interpretations (i.e., central ECG) were used for these summaries. All interpretations and corresponding details were listed by-patient.

1.7.5.4 Vital Signs

[333] The parameters summarized from when patients were in supine/semi-recumbent positions included SBP, DBP, and HR. These measurements were recorded twice, so the mean of the 2 measurements was taken and used for all summaries mentioned below. Weight was also summarized. These parameters were summarized through change from baseline and percentage change from baseline in similar fashion as the ECG parameters.

[334] Vital signs were also assessed through PCS criteria. Patients were counted if they met the established criteria at any time post-baseline. All vital sign parameters were included in by-patient listings.

1.7.5.5 Physical and Neurological Exams

[335] Physical and neurological exams were scheduled for assessment at screening only and were presented in by-patient listings.

1.7.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)

[336] The scoring for the C-SSRS was analyzed using the following indicators:

- Ideation severity: each of the 5 questions regarding type of ideation (yes/no)
- Intensity of most severe ideation: a sum of the 5 intensity items

- Suicidal behavior types: each of the 4 suicidal behavior types (yes/no)
- Suicidal behavior: suicidal behavior question
- Actual lethality: actual lethality question (0-5 scale) on most lethal attempt
- Potential lethality: potential lethality question (0-2 scale) on most lethal attempt

[337] The individual questions listed above that had yes/no responses were summarized by treatment group and visit. Intensity of most or severe ideation was summarized, descriptive by treatment group and visit. Items that contain an ordinal response were summarized through descriptive statistics, number, and percentage. All C-SSRS data, including individual text descriptions (included as part of some questions), were included in by-patient listings.

1.7.5.7 Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

[338] The individual items, as well as the total score of the SAS were summarized. Descriptive statistics were provided by treatment group and visit for males and females separately, as well as both sexes overall. For each item, a shift table of the number and percent of patients in each score (0 to 4) from baseline to Week 6 and baseline to Week 12 was summarized overall and for males and females separately.

1.7.5.8 Barnes Akathisia Scale (BAS)

[339] The objective assessment, subjective awareness, subjective distress, and global clinical assessment, as well as the total score for the BAS were summarized. Descriptive statistics were provided by treatment group and visit for males and females separately, as well as both sexes overall. Shift tables of the number and percent of patients of the total score and the global clinical assessment were presented for baseline to Week 6 and baseline to Week 12, for males and females separately as well as both sexes overall.

1.7.5.9 Abnormal Involuntary Movements Scale (AIMS)

[340] The scores on each subscale of the AIMS were summarized using descriptive statistics by treatment group and by visit for males and females separately, as well as both sexes overall. Shift tables of the number and percent of patients of the total

score and the global clinical assessment were presented for baseline to Week 6 and baseline to Week 12, for males and females separately as well as both sexes overall.

1.7.6 Determination of Sample Size

[341] Sample size calculations were performed assuming a bivariate normal distribution for the primary endpoint, based on published studies such as Kane et al. (Arch Gen Psychiatry. 1988;45(9):789-796) and Buchanan et al. (Schizophr Bull. 2015;41(4):900-908). Both Stage 1 and 2 treatment differences were assumed to be -2.5, and the standard deviation in drug and placebo groups was assumed to be equal to 5 (effect size of -0.5). It was further assumed that 82% of patients would complete Stage 1, 70% of these patients assigned to placebo would be placebo non-responders, and 91% of these would complete Stage 2. A sample size of 120 patients randomized in 1:2 ratio (active:placebo) in Stage 1 would have an approximate 80% power for this SPCD study with 2-sided type I error α=0.05. If the effect sizes in both stages were assumed to be -0.425, the power would be approximately 70%.

1.7.7 Statistical/Analytical Issues

1.7.7.1 Adjustments for Covariates

[342] The planned and actual covariates and methods used in analyses did not differ in this study.

1.7.7.2 Handling of Dropouts or Missing Data

[343] Missing data were handled differently depending on the parameter and analysis. Note that analyses done on 'observed cases' (such as MMRM analyses) did not follow any imputation rules below. See below for considerations:

- Missing baseline values were not imputed in any situation.
- For SPCD and by-stage and visit efficacy analyses (excluding observed cases analyses), missing data were imputed by LOCF within a study stage. No imputation was done for patients without data in Stage 2.

- A LOCF approach was also used for efficacy analyses on the mITT 12-week parallel group population, meaning the last non-missing post-baseline observation was carried forward to each visit.

1.7.7.3 Interim Analyses and Data Monitoring

[344] No data monitoring safety board was appointed for this study and no interim analyses were planned or carried out.

1.7.7.4 Multicenter Studies

[345] The data collected in this study were analyzed as a whole.

1.7.7.5 Multiple Comparisons/Multiplicity

[346] No adjustments were made for testing multiple secondary outcome measures. Since it was possible that some significant results could have occurred by chance alone, undue consideration was not given to isolated significant differences; rather, interpretations were made based on patterns of significant differences and their consistency with the primary endpoint analysis.

1.7.7.6 Use of an "Efficacy Subset" of Patients

[347] A post-hoc analysis was performed excluding all patients who had more than one rater from both the placebo and d6-DM/Q treatment groups to assess the impact of the use of a single-rater vs. multiple raters assessing the same endpoints throughout the study. Results of this analysis are presented in Section 3.4.1.4.1.

1.7.7.7 Examination of Subgroups

[348] Factors used for subgroup analysis of efficacy are described in Section 1.7.3.4.4. The categories included age, gender, baseline MCCB composite score, baseline concomitant benzodiazepine /SSRI/SSNI medication use, and onset of schizophrenia.

1.8 Changes in the Conduct of the Study or Planned Analyses

[349] 12-Week Parallel Group ANCOVA was specified for all efficacy endpoints in Section 1.7.3.4.1 but was only performed for NSA-16 related efficacy endpoints. This is

because similar 12-Week Parallel Group MMRM was performed as specified in Section 1.7.3.3.3 and MMRM is the preferred method.

[350] After database lock, one investigator (Site 117, Principal Investigator) communicated that there were some data entry errors identified at the site that were not corrected prior to database lock. These discrepancies were reviewed and it was concluded that the changes had no effect on the efficacy results or the overall integrity of the data, and there were no safety concerns, thus the database was not unlocked and relocked. A deviation report was filed in the trial master file per the SOP.

2 STUDY PATIENTS

2.1 Disposition of Patients

[351] Overall patient disposition is summarized in Table 4 and patient disposition for the mITT population is depicted in FIG. 3. Of the 286 patients screened, 145 patients were enrolled and randomized in Stage 1. Of the 145 patients randomized, 48 patients were randomized to d6-DM/Q and 97 patients to placebo in Stage 1; one patient was randomized to placebo but did not receive study drug. For all randomized patients, a total of 123 patients completed Stage 1 (d6-DM/Q: 43 patients; placebo: 80 patients) and the remaining 21 patients discontinued during Stage 1. For the mITT population, of the 47 patients received d6-DM/Q in Stage 1, 42 patients entered Stage 2 and continued to receive d6-DM/Q, while 80 patients received placebo in Stage 1, 66 entered Stage 2 and were re-randomized (d6-DM/Q: 32 patients; placebo: 34 patients). At the end of Stage 1, 64 patients were non-responders (< 20% reduction in PANSS total score) and 3 patients were responders (≥ 20% reduction in PANSS total score) in the placebo group, and 42 were non-responders and 5 were responders in the d6-DM/Q group.

[352] Overall, for all randomized patients, 118 patients completed the study (d6-DM/Q in Stages 1 and 2: 42 patients; placebo in Stages 1 and 2: 37 patients; placebo in Stage 1 and d6-DM/Q in Stage 2: 39 patients). Of the 27 patients (18.6%) who discontinued the study, 10 were due to an AE, 8 were withdrawal by patient, 4 were lost to

follow up, 3 were withdrawn due non-compliance with study drug, 1 was withdrawn due to physician decision, and 1 was withdrawn due to other reason(s) not listed. Reasons for discontinuation were similar across treatment groups.

Table 4. Overall Patient Disposition - All Patients

	Placebo/ Placebo N = 49	d6-DM/Q/ d6-DM/Q N = 48	Placebo/ d6-DM/Q N = 48	All d6-DM/Q N = 96	All Patients N = 286
Patients screened, n (%)	--	--	--	--	286
Screen failures	--	--	--	--	141 (49.3)
Inclusion/exclusion criteria unmet	--	--	--	--	115 (40.2)
Lost to follow-up	--	--	--	--	120 (42.0)
Withdrew consent	--	--	--	--	128 (44.8)
Other	--	--	--	--	5 (1.7)
Patients randomized[1]	42 (85.7)	48 (100.0)	42 (87.5)	90 (93.8)	132 (91.0)
Randomized but did not receive study drug, n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Completed study, n (%)	37 (75.5)	42 (87.5)	39 (81.3)	81 (84.4)	118 (81.4)
Patients who discontinued from study, n (%)	12 (24.5)	6 (12.5)	9 (18.8)	15 (15.6)	27 (18.6)
Adverse event	5 (10.2)	2 (4.2)	3 (6.3)	5 (5.2)	10 (6.9)
Lost to follow-up	3 (6.1)	0 (0.0)	1 (2.1)	1 (1.0)	4 (2.8)
Physician decision	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by patient	1 (2.0)	3 (6.3)	4 (8.3)	7 (7.3)	8 (5.5)
Noncompliance with study drug	1 (2.0)	1 (2.1)	1 (2.1)	2 (2.1)	3 (2.1)
Other	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)

Denominators for screen failures and reasons for screen failures are the number of patients screened.
Denominators for all other categories are the number of patients randomized (N = 145). -- = not applicable.
[1] A total of 13 patients with randomization error were excluded.

3 EFFICACY EVALUATION

3.1 Data Sets Analyzed

[353] Analysis populations are summarized by treatment groups in Table 5. Of the 145 patients randomized at the beginning of the study, 132 were included in the ITT population, 144 were included in the safety population, and 110 were included in the PP population. Of the randomized patients, 127 patients met the criteria for mITT population and were included in the Stage 1 mITT population. A total of 108 patients were included in

the Stage 2 ITT population, and Stage 2 mITT population. The disposition of patients included in the mITT population is provided in FIG. 3.

[354] For all data sets analyzed in this study, the patient criteria for each population are described in Section 1.7.2.

Table 5. Summary of Analysis Populations and Stage 2 Subsets - All Randomized Patients

Population Subset	Stage 1			Stage 2		
	Overall	d6-DM/Q	Placebo	Overall	d6-DM/Q	Placebo
mITT	127	47	80	108	76	32
Stage 2 mITT subsets						
Placebo non-responders	--	--	--	63	33	30
Placebo responders	--	--	--	3	1	2
Placebo non-responders + responders	--	--	--	66	34	32
PP	110	37	73	94	65	29
ITT	132	48	84	108	76	32
Safety	144	48	96	--	--	--
12-week parallel group		48	42			
mITT 12-week parallel group	87	47	40	--	--	--
Safety 12-week parallel group	89	48	41			
PP 12-week parallel group	74	37	37	--	--	--

Analyses on the 12-week parallel group and safety populations do not consider study stage, so it is not necessary to define Stage 2 Ns.
ITT = intent-to-treat; mITT = modified intent-to-treat; PP = per-protocol; -- = not applicable.

3.2 Demographic and Other Baseline Characteristics

3.2.1 Demographics

[355] Baseline and demographic characteristics of the Stage 1 mITT population are summarized in Table 6. The mean (SD) age at enrollment was 45.5 (11.19) years. There were 88 male patients (69.3%) and 39 female patients (30.7%) in the mITT population. The majority of the patients included in the mITT population were Black (69 patients [54.3%]) or White (48 patients, [37.8%]). Baseline and demographic characteristics were similar across treatment groups. The demographic and baseline

characteristics of the mITT 12-week parallel group and safety populations were comparable to the mITT population found in Table 6 across treatment groups.

Table 6. Demographics and Baseline Characteristics - mITT Population

Characteristics, n	d6-DM/Q (N = 47)	Placebo (N = 80)	All Patients (N = 127)
Gender, n (%)			
Female	17 (36.2)	22 (27.5)	39 (30.7)
Male	30 (63.8)	58 (72.5)	88 (69.3)
Race, n (%)			
Black or African American	25 (53.2)	44 (55.0)	69 (54.3)
White	18 (38.3)	30 (37.5)	48 (37.8)
Asian	4 (8.5)	4 (5.0)	8 (6.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (2.5)	2 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.5)	9 (11.3)	13 (10.2)
Not Hispanic or Latino	43 (91.5)	71 (88.8)	114 (89.8)
Age, years			
Mean (SD)	46.5 (12.17)	44.9 (10.60)	45.5 (11.19)
Median	51.0	47.0	48.0
Min, Max	18, 60	18, 60	18, 60
Age group, n (%)			
< 55 years	31 (66.0)	66 (82.5)	97 (76.4)
≥ 55 years	16 (34.0)	14 (17.5)	30 (23.6)
Height, cm			
Mean (SD)	173.2 (8.95)	173.3 (8.99)	173.2 (8.94)
Median	173.4	174.5	174.0
Min, Max	156, 191	152, 191	152, 191
Weight, kg			
Mean (SD)	98.5 (24.21)	96.7 (22.65)	97.4 (23.16)
Median	95.9	95.7	95.8
Min, Max	53, 192	55, 182	53, 192
BMI, kg/m^2			
Mean (SD)	32.9 (7.75)	32.3 (7.30)	32.5 (7.45)
Median	31.6	31.8	31.8
Min, Max	17, 57	19, 56	17, 57

For each categorical parameter, the denominator for the percent was the number of patients who had that parameter assessed.
BMI = body mass index; mITT = modified intent-to-treat; SD = standard deviation.

3.2.2 Medical History

[356] Because of the population being investigated in this study, the most commonly reported SOC and PT for medical history were psychiatric disorders (144 patients [100.0%]) and schizophrenia, residual type (144 patients [100.0%]), respectively. The next most frequently reported PTs in patient medical history was hypertension (35 patients [36.5%] placebo group and 12 patients [25.0%] in d6-DM/Q group).

3.2.3 Prior and Concomitant Medications

[357] Prior medications are presented by anatomical therapeutic subgroup and preferred base name for the safety population in Table 67. Concomitant medications are presented by anatomical therapeutic subgroup and preferred base name for the safety population in Table 68. Tables 17 to 94 are included in Appendix 1.

[358] Baseline concomitant use of SGAs was summarized for the safety population in Table 17. The most frequently used SGA at baseline by patients in the placebo and d6-DM/Q treatment group were aripiprazole (16.7% placebo, 31.3% d6-DM/Q), olanzapine (27.1% placebo, 25.0% d6-DM/Q), and risperidone (26.0% placebo, 20.8% d6-DM/Q).

3.2.4 Other Baseline Characteristics

[359] Baseline values at Stage 1 for the efficacy measures in the mITT population are summarized and presented in Table 7. Baseline values were comparable between the 2 treatment groups.

[360] Stage 2 baseline efficacy assessments for placebo non-responders and placebo responders in the mITT study population are presented in Table 19 and Table 20, respectively.

Table 7. Stage 1 Baseline Efficacy Assessments - mITT Population

Measure, Mean (SD)	Placebo (N = 80)	d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Total Score	60.4 (7.71)	61.0 (7.53)	60.6 (7.62)
NSA-16 Factor Domain: Communication	12.6 (2.71)	12.5 (2.54)	12.6 (2.64)
NSA-16 Factor Domain: Emotion/Affect	12.2 (1.81)	12.6 (2.11)	12.3 (1.93)
NSA-16 Factor Domain: Social Involvement	12.2 (2.20)	12.2 (2.02)	12.2 (2.13)
NSA-16 Factor Domain: Motivation	16.7 (2.33)	16.5 (2.37)	16.6 (2.33)
NSA-16 Factor Domain: Retardation	6.7 (1.61)	7.2 (1.54)	6.9 (1.59)
NSA-4 Total Score	17.3 (2.36)	17.4 (2.44)	17.3 (2.38)
NSA-16 Item 1: Prolonged Time to Respond	3.1 (1.13)	3.1 (1.22)	3.1 (1.15)
NSA-16 Item 2: Restricted Speech Quantity	3.8 (1.12)	3.5 (1.10)	3.7 (1.12)
NSA-16 Item 3: Impoverished Speech Content	3.7 (0.91)	3.6 (0.80)	3.6 (0.87)
NSA-16 Item 4: Inarticulate Speech	2.0 (1.07)	2.3 (1.16)	2.1 (1.11)
NSA-16 Item 5: Emotion: Reduced Range	4.2 (0.81)	4.4 (0.92)	4.3 (0.85)
NSA-16 Item 6: Affect: Reduce Modulation Intensity	4.2 (0.74)	4.2 (0.89)	4.2 (0.80)
NSA-16 Item 7: Affect: Reduced Display on Demand	3.8 (0.93)	4.0 (0.92)	3.9 (0.94)
NSA-16 Item 8: Reduced Social Drive	4.7 (0.75)	4.9 (0.55)	4.8 (0.68)
NSA-16 Item 9: Poor Rapport with Interviewer	3.4 (1.02)	3.3 (0.93)	3.3 (0.99)
NSA-16 Item 10: Sexual Interest	4.2 (1.52)	4.0 (1.54)	4.1 (1.52)
NSA-16 Item 11: Poor Grooming and Hygiene	2.6 (1.20)	2.5 (1.08)	2.6 (1.15)
NSA-16 Item 12: Reduced Sense of Purpose	4.7 (0.92)	4.5 (1.02)	4.6 (0.96)
NSA-16 Item 13: Reduced Interests	4.5 (0.84)	4.8 (0.84)	4.6 (0.84)
NSA-16 Item 14: Reduced Daily Activity	4.8 (0.57)	4.7 (0.74)	4.8 (0.64)
NSA-16 Item 15: Reduced Expressive Gestures	3.9 (1.09)	4.1 (1.13)	4.0 (1.11)
NSA-16 Item 16: Slowed Movements	2.8 (0.96)	3.0 (0.78)	2.9 (0.91)
NSA-16: Global Negative Symptoms Rating	4.6 (0.61)	4.6 (0.64)	4.6 (0.62)
NSA-16: Global Level of Functioning	4.6 (0.63)	4.7 (0.73)	4.6 (0.66)
PANSS Total Score	68.7 (7.99)	67.4 (8.26)	68.2 (8.08)
PANSS Total Score Reduction ≥ 20% n, (%)[1]			
Yes	3 (3.8)	5 (10.6)	8 (6.3)

Measure, Mean (SD)	Placebo (N = 80)	d6-DM/Q (N = 47)	All Patients (N = 127)
No	77 (96.3)	42 (89.4)	119 (93.7)
PANSS Negative Subscale	25.2 (3.64)	24.6 (3.51)	25.0 (3.59)
PANSS Positive Subscale	13.4 (2.81)	13.6 (3.65)	13.5 (3.13)
PANSS General Psychopathology Subscale	30.1 (5.05)	29.1 (4.66)	29.7 (4.91)
PANSS Prosocial Factors	18.4 (2.92)	18.3 (3.24)	18.4 (3.03)
PANSS Marder Negative Factors	24.2 (3.81)	24.1 (4.24)	24.2 (3.96)
PANSS Excitement Component	6.3 (2.10)	6.2 (1.57)	6.3 (1.92)
CGI-S	3.9 (0.74)	3.7 (0.74)	3.9 (0.74)
CDSS Total Score	0.9 (1.31)	1.1 (1.34)	0.9 (1.32)

CDSS = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression of Severity of Illness; mITT = modified intent-to treat; NSA-16 = 16-Item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation

1 The data presented is the frequency (%) of patients who had (yes/no) a reduction of ≥ 20% from baseline at Week 6 in PANSS Total score.

Source: Table 18

3.3 Measurements of Treatment Compliance

[361] Study drug compliance is summarized and presented for the safety population in Table 8. The majority of patients in each treatment group took between 80% and 120% of their scheduled doses and were considered compliant.

Table 8. Treatment Compliance – Safety Population

	d6-DM/Q/ d6-DM/Q (N = 48)	Placebo/ Placebo (N = 56)	Placebo/d6-DM/Q (N = 40)	
			Placebo	d6-DM/Q
Compliance (%), n	48	52	40	39
Mean (SD)	82.17 (13.628)	75.37 (21.206)	85.97 (11.013)	85.97 (9.424)
Median (min, max)	87.75 (12.5, 89.6)	86.20 (6.3, 92.2)	87.50 (43.8, 99.0)	86.50 (64.6, 132.3)
Compliance Ratio, n (%)	48	52	40	39
< 80%	10 (20.8)	17 (32.7)	4 (10.0)	6 (15.4)
80-120%	38 (79.2)	35 (67.3)	36 (90.0)	32 (82.1)
> 120%	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)

SD = standard deviation.

3.4 Efficacy Results and Tabulations of Individual Patient Data

3.4.1 Analysis of Efficacy

3.4.1.1 Primary Efficacy Endpoint (16-Item Negative Symptom Assessment [NSA-16] Total Score)

3.4.1.1.1 Primary Analysis

[362] The primary efficacy analysis was the SPCD analysis of the change from baseline in the NSA-16 total score for d6-DM/Q versus placebo. A numerically higher improvement was observed with d6-DM/Q compared to placebo in the change from baseline in the NSA-16 total score with the SPCD analysis using the mITT population (SPCD weighted Z-statistic = -1.79, p = 0.073, Table 9). In Stage 1 (which mimicked a parallel-group design), the mean (SD) change from baseline in NSA-16 total scores was -5.0 (5.64) with d6-DM/Q and -3.4 (5.54) with placebo, resulting in a LS mean treatment difference of -1.79 (95% CI -3.86, 0.29; p = 0.091). In Stage 2 which includes only placebo non-responders randomized to d6-DM/Q or placebo, the mean (SD) change from baseline in NSA-16 total scores was -3.7 (6.41) with d6-DM/Q and -2.4 (5.88) with placebo resulting in a LS mean treatment difference of -1.28 (95% CI -4.39, 1.83; p = 0.413; FIG. 4).

Table 9. NSA-16 Total Score: Change from Baseline SPCD MMRM (Observed Data) - mITT Population

Stage Parameter/Result	d6-DM/Q	Placebo
Stage 1		
Baseline, n	47	80
Mean (SD)	61.0 (7.53)	60.4 (7.71)
Visit 4 (Week 6), n	47	70
Mean change (SD)	-5.0 (5.64)	-3.4 (5.54)
Treatment difference vs. placebo (95% CI)[1]	-1.79 (-3.86, 0.29)	
p-value	0.091	
Stage 2 (Stage 1 placebo non-responders)		
Baseline, n	33	30
Mean[2] (SD)	57.6 (9.09)	57.6 (9.39)
Visit 7 (Week 12), n	32	29
Mean change (SD)	-3.7 (6.41)	-2.4 (5.88)
Treatment difference vs. placebo (95% CI)[1]	-1.28 (-4.39, 1.83)	
p-value	0.413	
MMRM weighted z-statistic, overall p-value[3]	-1.79, p = 0.073	

Possible NSA-16 total score ranged from 16 to 96; a higher score indicated a worse condition.
CI = confidence interval; NSA-16 = Negative Symptom Assessment Scale; mITT = modified intent-to-treat; MMRM = mixed model repeat measures; SD = standard deviation; SPCD = sequential parallel comparison design.
[1] The MMRM had a fixed effect of treatment, visit, treatment-by-visit interaction, baseline NSA-16, and baseline NSA-16-by-visit. Unstructured covariance matrix was used.
[2] Stage 2 baseline was the last non-missing assessment prior to Stage 2 re-randomization (re-randomization visit).
[3] An SPCD weighted z-statistic was used with a Stage 1 weight of 0.6 and a Stage 2 weight of 0.4. Treatment differences in each stage were estimated by the MMRM.

3.4.1.1.2 Sensitivity Analysis

[363] Sensitivity analyses on the primary endpoint using different statistical analyses methods (SUR method [LOCF] and SPCD with OLS ANCOVA [LOCF]) and different analysis population (PP population) corroborated the findings of the primary analysis; moreover, statistically significant treatment differences between d6-DM/Q and placebo, in favor of d6-DM/Q, were observed with both the SUR method (p = 0.048, Table

23) and SPCD OLS ANCOVA (p = 0.042, Table 24) but not using the PP population (Table 25). A summary of the results is provided in Table 10.

Table 10. Summary of Primary and Sensitivity Analysis of the NSA-16 Total Score

	Stage 1					Stage 2					SPCD Analysis	
Analyses (NSA-16 Total Score)	N (d6-DM/Q: Placebo)	Change from Baseline, Mean (SD)		Treatment Difference, LS Mean (CI)	p-value	N (d6-DM/Q: Placebo)	Change from Baseline, Mean (SD)		Treatment Difference, LS Mean (CI)	p-value	Z-Statistic	P-value
		d6-DM/Q	Placebo				d6-DM/Q	Placebo				
Primary Analysis												
MMRM, mITT	47:80	-5.0 (5.64)	-3.4 (5.54)	-1.79 (-3.86, 0.29)	0.091	33:30	-2.4 (5.88)	-3.7 (6.41)	-1.28 (-4.39, 1.83)	0.413	-1.79	0.073
Sensitivity Analyses												
SUR Analysis, LOCF	47:80	-5.0 (5.64)	-3.0 (5.78)	-2.05 (1.05)[1]		33:30	-3.6 (6.34)	-2.2 (5.89)	-1.26 (1.52)[1]		-1.98	0.048[1]
OLS ANCOVA, LOCF	47:80	-5.0 (5.64)	-3.0 (5.78)	-2.05 (-4.13, 0.04)	0.054	33:30	-3.6 (6.34)	-2.2 (5.89)	-1.40 (-4.46, 1.65)	0.362	-2.04	0.042
MMRM, Per-protocol	37:73	-4.8 (5.77)	-3.5 (5.76)	-1.57 (-3.94, 0.80)	0.191	29:27	-4.5 (5.96)	-3.0 (5.81)	-1.43 (-4.63, 1.76)	0.372	-1.58	0.114

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least square; mITT = modified intent-to-treat; MMRM = mixed model repeated measure; NSA-16 = 16-Item Negative Symptom Assessment; OLS = ordinary least squares; SD = standard deviation; SPCD = sequential parallel comparison design; SUR = seemingly unrelated regression.

Note: SPCD weighted Z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

[1] The data displayed is: SUR estimated difference versus placebo (standard error) and p-value from SUR.

Source: Tables 23-25

3.4.1.1.3 12-Week Analyses

[364] Analysis of the change in NSA-16 total scores for the patient cohort who were randomized and remained (or early withdraw) in the same treatment assignment in both stages, mimicking a traditional 12-week parallel comparison design instead of 2-stage SPCD, showed no difference between d6-DM/Q and placebo treatment. The mean (SD) change from baseline in NSA-16 total score was -6.6 (7.81) for the d6-DM/Q/d6-DM/Q group and -7.0 (7.71) for the placebo/placebo group of the mITT 12-week parallel group. population.

[365] Similar results were observed when analyzed with ANCOVA (LOCF) using the mITT 12-week parallel group population or with MMRM (observed data) using the PP 12 week parallel group population.

3.4.1.1.4 Subgroup Analysis

[366] The primary endpoint was analyzed using the subgroups defined by each category below on the mITT population, using the OLS ANCOVA SPCD methodology.

- Age group (< 45; ≥ 45)
- Gender (male; female)
- Baseline MCCB composite score (< 30; ≥ 30)
- Baseline concomitant benzodiazepine (Table 69), SNRI (Table 70), or SSRI medication use (Table 71)
- Onset of schizophrenia (< 20 years; ≥ 20 years) and residual schizophrenia (< 4 years; ≥ 4 years)

[367] No meaningful differential treatment effects between d6-DM/Q and placebo were observed for the subgroup analysis by age, gender, baseline MCCB composite score, baseline concomitant medication use, or onset of schizophrenia and residual schizophrenia.

3.4.1.1.5 Band-Pass Filter Analysis

[368] The primary endpoint was analyzed using one band-pass filter which excluded from the analysis, sites with mean NSA-16 change from baseline scores for placebo that exceeded the boundary (> 0 or <-7). Results of this analysis showed a statistically significant treatment difference in favor of d6-DM/Q with the SPCD ANCOVA analysis (SPCD weighted OLS Z-statistic = -2.25, p = 0.025, Table 26).

[369] Results for similar analysis performed for the mITT 12-week parallel group population are presented in Table 27.

3.4.1.2 Secondary Endpoints

3.4.1.2.1 Positive and Negative Syndrome Scale (PANSS)

[370] Analysis of the PANSS included the total score of all the 30-items and various subscales derived from these 30 items which include: negative subscale (N1 – N7), positive subscale (P1 – P7), general psychopathology subscale (G1 – G16), prosocial factors (G16, N2, N4, N7, P3, and P6), Marder negative factors (N1, N2, N3, N4, N6, G7, and G16), and excitement component (P4, P7, G4, G8, and G14). A summary of the results for the PANSS total score and subscales is included in Table 11.

Table 11. Summary of PANSS Results (SPCD, MMRM; mITT Population)

	Stage 1 d6-DM/Q N = 47, Placebo = 80				Stage 2 d6-DM/Q N = 33, Placebo N = 30				SPCD Analysis	
PANSS	Change from Baseline, Mean (SD)		Treatment Difference, LS Mean (CI)	p-value	Change from Baseline, Mean (SD)		Treatment Difference, LS Mean (CI)	p-value	Z-Statistic	P-value
	d6-DM/Q	Placebo			d6-DM/Q	Placebo				
Total score	-4.7 (6.98)	-2.5 (6.50)	-2.36 (-4.77, 0.06)	0.055	-4.0 (7.71)	-1.4 (7.64)	-2.53 (-6.51, 1.45)	0.209	-2.25	0.025
Negative subscale	-2.2 (3.33)	-1.5 (3.81)	-0.86 (-2.17, 0.45)	0.198	-2.3 (3.12)	-1.0 (2.69)	-1.43 (-2.88, 0.03)	0.054	-2.20	0.027
Marder negative factors	-2.1 (3.34)	-1.6 (3.48)	-0.63 (-1.89, 0.62)	0.320	-2.5 (4.27)	-0.8 (2.80)	-1.93 (-3.62, -0.24)	0.026	-2.26	0.024
Prosocial factors	-2.0 (2.18)	-1.1 (2.53)	-0.89 (-1.75, -0.03)	0.042	-1.4 (2.35)	-0.7 (2.02)	-0.89 (-2.00, 0.22)	0.115	-2.60	0.009
Positive subscale	-0.8 (2.63)	-0.3 (2.57)	-0.42 (-1.36, 0.52)	0.376	-0.3 (2.47)	-0.4 (1.99)	0.28 (-0.90, 1.45)	0.640	-0.39	0.700
General psychopathology	-1.7 (4.04)	-0.7 (3.21)	-1.14 (-2.40, 0.13)	0.077	-1.3 (5.10)	0.0 (5.14)	-1.40 (-3.99, 1.19)	0.284	-1.93	0.054
Excitement component	-0.4 (1.64)	-0.2 (1.57)	-0.34 (-0.83, 0.16)	0.177	-0.1 (1.77)	0.0 (2.04)	0.30 (-0.61, 1.21)	0.512	-0.35	0.723

CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measure; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SPCD = sequential parallel comparison design.
Note: SPCD weighted Z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment difference in each stage was estimated by the MMRM.

Source: Tables 28-34

3.4.1.2.1.1 PANSS Total Score

[371] The PANSS total score ranges from 30 to 210 with higher scores indicating greater severity of symptoms. A statistically significant difference between d6-DM/Q and placebo, in favor of d6-DM/Q, was observed in the PANSS total score with the primary SPCD MMRM analysis (SPCD weighted Z-statistic = -2.25, p = 0.025, Table 28). In Stage 1, the mean (SD) change from baseline in the PANSS total score was -4.7 (6.98) with d6-DM/Q and -2.5 (6.50) with placebo, resulting in a LS mean treatment difference of -2.36 (95% CI -4.77, 0.06; p = 0.055). In Stage 2 which includes only placebo non-responders randomized to d6-DM/Q or placebo, the mean (SD) change from baseline in the PANSS total score was -4.0 (7.71) with d6-DM/Q and -1.4 (7.64) with placebo resulting in a LS mean treatment difference of -2.53 (95% CI -6.51, 1.45; p = 0.209; FIG. 5). Similar results were observed with the OLS ANCOVA SPCD (p = 0.024, Table 36) using the mITT population and with the SPCD MMRM analysis (p = 0.022, Table 38) using the PP population.

[372] Analysis of change from baseline in the PANSS total score are summarized in Table 76 for the mITT 12-week parallel group population and in Table 39 for the PP 12-week parallel group population.

3.4.1.2.1.2 PANSS Negative Subscale

[373] The negative subscale comprises 7 items of the PANSS and the score ranges from 7 to 49, with higher scores indicative of greater severity of the negative symptoms. A statistically significant difference between d6-DM/Q and placebo, in favor of d6-DM/Q, was observed in the PANSS negative subscale with the primary SPCD MMRM analysis (SPCD weighted Z-statistic = -2.20, p = 0.027, Table 30) in the mITT population (FIG. 6) and in the PP population (p = 0.019, Table 40). Similar results were observed with the ANCOVA SPCD analysis in the mITT population (p = 0.019, Table 41).

[374] Analysis of change from baseline in the PANSS negative subscale score are summarized in Table 42 for the mITT 12-week parallel group population and in Table 43 for the PP 12-week parallel group population.

3.4.1.2.1.3 PANSS Marder Negative Factors

[375] The PANSS Marder negative factors comprise 7 items of the PANSS and the score ranges from 7 to 49, with higher scores indicative of greater severity of the negative symptoms of schizophrenia. A statistically significant difference between d6-DM/Q and placebo, in favor of d6-DM/Q, was observed in the PANSS Marder negative factors with the primary SPCD MMRM analysis (SPCD weighted Z-statistic = -2.26, p = 0.024, Table 32) in the mITT population (FIG. 7) and in the PP population (p = 0.019, Table 44). Similar results were observed with the SPCD ANCOVA analysis in the mITT population (p = 0.019, Table 45).

[376] Analysis of change from baseline in the PANSS Marder negative subscale score are summarized in Table 46 for the mITT 12-week parallel group population and in Table 47 for the PP 12-week parallel group population.

3.4.1.2.1.4 PANSS Prosocial Factors

[377] The PANSS prosocial factors comprises 6 items of the PANSS and the score ranges from 6 to 42, with higher scores indicative of greater severity of the specific negative symptoms. A statistically significant difference between d6-DM/Q and placebo, in favor of d6-DM/Q, was observed in the PANSS prosocial factors with the primary SPCD MMRM analysis (SPCD weighted Z-statistic = -2.60, p = 0.009, Table 34) in the mITT population (FIG. 8). Similar results were observed with the SPCD ANCOVA analysis in the mITT population (p = 0.007, Table 48).

[378] Analysis of change from baseline in the PANSS prosocial factors score are summarized in Table 49 for the mITT 12-week parallel group population.

3.4.1.2.1.5 PANSS Positive Subscale

[379] The positive subscale comprises 7 items of the PANSS and the score ranges from 7 to 49, with higher scores indicative of greater severity of the positive symptoms of schizophrenia. No significant difference in the PANSS positive subscale score was observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD MMRM analysis (Table 29), SPCD ANCOVA analysis (Table 50), or the 12-week analysis using the mITT 12-week parallel group population (Table 51).

3.4.1.2.1.6 PANSS General Psychopathology Subscale

[380] The general psychopathology subscale comprises 16 items of the PANSS and the score ranges from 16 to 112, with higher scores indicative of greater severity of symptoms of schizophrenia. A numerically higher improvement was observed with d6-DM/Q compared to placebo in the change from baseline in the PANSS general psychopathology subscale score with the SPCD analysis using the mITT population (SPCD weighted Z-statistic = -1.93, p = 0.054). In Stage 1, the mean (SD) change from baseline score was -1.7(4.04) with d6-DM/Q and -0.7 (3.21) with placebo, resulting in a LS mean treatment difference of -1.14 (95% CI -2.40, 0.13; p = 0.077). In Stage 2, the mean (SD) change from baseline was -1.3 (5.10) with d6-DM/Q and 0.0 (5.14) with placebo resulting in a LS mean treatment difference of -1.40 (95% CI -3.99, 1.19; p = 0.284) (Table 31). Analysis using SPCD ANCOVA (Table 37) and using the mITT 12-week parallel group population (Table 35) showed a similar trend with statistically significant difference, in favor of d6-DM/Q seen in the 12-week analysis using the mITT 12-week parallel group population (p = 0.028).

3.4.1.2.1.7 PANSS Excitement Component

[381] The excitement component comprises 5 items of the PANSS and the score ranges from 5 to 35, with higher scores indicative of greater severity of symptoms. No significant difference in the PANSS excitement component was observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD MMRM analysis,

SPCD ANCOVA analysis, or the 12-week analysis using the mITT 12-week parallel group population.

3.4.1.2.1.8 PANSS Responder Analysis

[382] Treatment effect was evaluated by analyzing the proportion of patients with a 20% reduction from baseline in the PANSS total score with SPCD analysis using the mITT population and with GEE analysis using the mITT 12-week parallel group population. No statistically significant differences between d6-DM/Q and placebo were observed in these analyses.

[383] Posthoc analysis were also performed using the same threshold (20% reduction from baseline) for the PANSS Marder Negative factors and the PANSS negative subscale (data not shown).

[384] The proportion of patients with 20% reduction from baseline in PANSS Marder Negative factors was statistically significantly higher in the d6-DM/Q group compared to placebo in both stages (Stage 1: 21.3% vs 16.3%; Stage 2: 27.3% vs 3.3%; SPCD p = 0.012).

[385] The proportion of patients with 20% reduction from baseline in PANSS negative subscale was higher in the d6-DM/Q group compared to placebo in both stages (Stage 1: 23.4% vs 13.8%; Stage 2: 21.2% vs 10%; SPCD p = 0.054).

3.4.1.2.2 NSA-16: Global Negative Symptoms, Global Level of Functioning, 5-Factor Domains, and NSA-4

3.4.1.2.2.1 Global Negative Symptoms Rating

[386] The global negative symptoms rating in the NSA-16 is a single score based on the overall impression of severity of negative symptoms on a 1 to 7 scale, where higher scores indicate greater severity. A statistically significant difference between d6-DM/Q and placebo, in favor of d6-DM/Q, was observed in the NSA-16 global negative symptoms rating with the primary SPCD MMRM analysis in the mITT population (SPCD weighted Z-statistic = -2.23, p = 0.026, Table 52). In Stage 1, the mean (SD) change from baseline in

the NSA-16 global negative symptoms rating was -0.4 (0.68) with d6-DM/Q and -0.2 (0.65) with placebo, resulting in a LS mean treatment difference of -0.17 (95% CI -0.40, 0.07; p = 0.167). In Stage 2 which includes only placebo non-responders randomized to d6-DM/Q or placebo, the mean (SD) change from baseline in the NSA-16 global negative symptoms rating was -0.5 (0.76) with d6-DM/Q and -0.1 (0.52) with placebo resulting in a LS mean treatment difference of -0.29 (95% CI -0.61, 0.03; p = 0.079; FIG. 9). Similar results were observed with the SPCD OLS ANCOVA (p = 0.016, Table 53).

[387] Analysis of change from baseline in the NSA-16 global negative symptoms rating using the mITT 12-week parallel group population are summarized in Table 54 (MMRM analysis) and Table 55 (ANCOVA).

3.4.1.2.2.2 Global Level of Functioning

[388] The global level of functioning is a single score on a scale of 1 to 7 that provides the overall assessment of the patient's level of functioning, with higher scores indicative of severe impairment in functioning. No significant difference in the NSA-16 global level of functioning score was observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD MMRM analysis, SPCD ANCOVA analysis, or the 12-week analysis using the mITT 12-week parallel group population.

3.4.1.2.2.3 NSA-4 Total Score

[389] The NSA-4 total score comprises items 2, 5, 8, and 13 of the NSA-16 which allow clinicians to rapidly determine the severity of negative symptoms of schizophrenia. These items focus on the following behaviors: restricted speech quantity (2), reduced range of emotion (5), reduced social drive (8) and reduced interest (13). No significant difference in the NSA-4 total score was observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population, or the 12-week analysis using the mITT 12-week parallel group population.

3.4.1.2.2.4 NSA-16 Factor Domains

[390] The items in the NSA-16 are grouped to describe negative symptoms using a 5-factor model, which includes the following domains: communication (items 1, 2, 3, and 4), emotion/affect (items 5, 6, and 7), social involvement (items 8, 9, and 10), motivation (items 11, 12, 13, and 14), and retardation (items 15 and 16). No significant differences between d6-DM/Q and placebo were observed in any of the 5-factor domains of the NSA-16 with the SPCD analysis using mITT population or the 12-week analysis using the mITT 12-week parallel group population.

[391] Results by domain were determined as follows:

- Communication: SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population; 12-week analysis using the mITT 12-week parallel group population
- Emotion/affect: SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population; 12-week analysis using the mITT 12-week parallel group population
- Social involvement: SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population; 12-week analysis using the mITT 12-week parallel group population
- Motivation: SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population; 12-week analysis using the mITT 12-week parallel group population
- Retardation: SPCD MMRM analysis, SPCD ANCOVA analysis with the mITT population; 12-week analysis using the mITT 12-week parallel group population

3.4.1.2.3 Patient Global Impression of Change (PGI-C)

[392] The PGI-C was used to evaluate patient's impression of treatment response relative to baseline at Week 6 (Stage 1) and relative to Visit 4 (end of Stage 1) at Week 12 (Stage 2), with 1=Very much improved to 7=Very much worse. A summary of the categorical responses by stage for the mITT population was determined. No statistically significant differences in PGI-C scores were observed between the d6-DM/Q and placebo

group with SPCD ANCOVA analysis on observed data (SPCD p = 0.170). In Stage 1, 27.7% of patients treated with d6-DM/Q vs. 24% on placebo rated their change in symptoms as “much improved” or “very much improved.” In Stage 2, 34.4% of patients treated with d6-DM/Q vs. 13.3% on placebo reported that their symptoms at Week 12 were “much improved” or “very much improved” (FIG. 10, SPCD p = 0.170). Analysis of PGI-C using proportional odds regression by stage are summarized for the mITT population.

[393] The 12-week analysis using the mITT 12-week parallel group population for the PGI-C scores is presented in Table 21 and for the proportional odds regression by stage in Table 22. The proportion of patients with ‘much improved’ or ‘very much improved’ rating at Week 12 relative to baseline was 33.3% (14/42) for the d6-DM/Q/d6-DM/Q group and 18.8% (6/32) for the placebo/placebo group (p = 0.158 by proportional odds regression) in the mITT 12-week parallel group population.

3.4.1.2.4 Clinical Global Impression of Change (CGI-S)

[394] The CGI-S score ranges from 1 to 7 with higher score indicative of greater severity of illness. The mean (SD) CGI-S scores at baseline were 3.7 (0.74) and 3.9 (0.74) for d6-DM/Q and placebo groups, respectively, in the mITT population. No significant difference in the CGI-S scores between d6-DM/Q and placebo was observed with the SPCD ANCOVA analysis or the 12-week analysis using the mITT 12-week parallel group population.

3.4.1.2.5 Clinical Global Impression of Change (CGI-C)

[395] The CGI-C was used to evaluate the global impression of change in mental illness relative to baseline at Week 6 (Stage 1) and relative to Visit 4 (end of Stage 1) at Week 12 (Stage 2), with 1=Very much improved to 7=Very much worse. A summary of the categorical responses by stage was determined for the mITT population. No statistically significant differences were observed between the d6-DM/Q and placebo group with SPCD ANCOVA analysis on observed data or proportional odds regression by stage for the mITT population. In Stage 1, 48.9% (23/47) of patients in the d6-DM/Q group and 35.9% (28/78)

of patients in the placebo group had 'minimally improved', 'much improved' or 'very much improved' rating on the CGI-C and in Stage 2, 43.7% (14/32) of patients in the d6-DM/Q group and 36.7% (11/30) of patients in the placebo had 'much improved' or 'very much improved' rating on the CGI-C (SPCD p = 0.057).

[396] Results of the analysis on the mITT 12-week parallel group population and PP 12-week parallel group population were similar, with no statistically significant differences between groups in CGI-C scores, however, statistically significant differences between groups were observed in the SPCD ANCOVA using the PP population (SPCD p = 0.044.

3.4.1.2.6 Calgary Depression Scale for Schizophrenia (CDSS)

[397] The CDSS score ranges from 0 to 27 with higher scores indicative of severe symptoms of depression. In this study, only patients with a score of < 6 were to be included. Overall, the patients enrolled in the study had low scores on the CDSS at baseline; the mean (SD) score was 1.1 (1.34) for patients randomized to d6-DM/Q and 0.9 (1.31) for patients randomized to placebo in Stage 1. No significant difference in CDSS score was observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD MMRM analysis (Table 56), SPCD ANCOVA analysis (Table 57), or the 12-week analysis using the mITT 12-week parallel group population (Table 58). The mean (SD) change from baseline in CDSS score at Week 12 was -0.2 (1.27) for the d6-DM/Q/d6-DM/Q group and -0.4 (0.99) for the placebo/placebo group in the mITT 12-week parallel group population (Table 58).

3.4.1.2.7 MATRICS Consensus Cognitive Battery (MCCB)

[398] The MCCB composite score ranges from 0 to 70 with higher scores indicative of less severe cognition symptoms. A numerically favorable improvement was observed with d6-DM/Q compared to placebo in the change from baseline in the MCCB composite score with the SPCD ANCOVA analysis using the mITT population (SPCD weighted OLS Z-statistic = 1.78, p = 0.074, Table 63). In Stage 1, the mean (SD) change

from baseline in the MCCB composite score was 1.2 (5.11) with d6-DM/Q and 1.6 (4.55) with placebo, resulting in a LS mean treatment difference of -0.12 (95% CI -1.88, 1.64; p = 0.893). In Stage 2, the mean (SD) change from baseline in the MCCB composite score was 1.6 (3.71) with d6-DM/Q and -1.6 (4.06) with placebo resulting in a LS mean treatment difference of 3.21(95% CI 1.11, 5.30; p = 0.003). Similar analyses using the PP population showed statistically significant difference in favor of d6-DM/Q (p = 0.046, Table 64).

[399] Results of the SPCD ANCOVA analysis of change from baseline in the MCCB composite score using the mITT 12-week parallel group population are presented in Table 65 and with the PP 12-week parallel group population in Table 66. No statistically significant differences between d6-DM/Q and placebo treatment were observed in these analyses.

3.4.1.2.8 Effort Expenditure for Reward Task (EEfRT)

[400] EEfRT scores were analyzed for the following 8 variables:

- Baseline Press Rate, subjects were first prompted to press the key for the hard task with their non-dominant pinky finger as fast as they can for 21 seconds. Value was coded as average presses per second.
- Choice RT 1st 50, average reaction time (in milliseconds) for making a choice during the first 50 trials. Only trials in which subjects made a choice.
- Completed, Proportion of completed tasks (Easy or Hard) during the first 50 trials.
- 12% Prob. -Prop. Hi Effort Opts -1st 50, Proportion of hard task choices made for the low (12%) probability condition during the first 50 trials of the task.
- 50% Prob. -Prop. Hi Effort Opts -1st 50, Proportion of hard task choices made for the medium (50%) probability condition during the first 50 trials of the task.
- 88% Prob. -Prop. Hi Effort Opts -1st 50, Proportion of hard task choices made for the high (88%) probability condition during the first 50 trials of the task.

- All -Proportion High Effort Opts -1st 50, Overall proportion of hard task choices made for the first 50 trials of the task.
- Diff-Proportion High Effort Opts -1st 50, Difference between proportion of hard task choices made for the high probability condition during the first 50 trials of the task.

[401] No significant differences were observed between the d6-DM/Q treated patients and the placebo treated patients by the SPCD ANCOVA analysis, or the 12-week analysis using the mITT 12-week parallel group population.

3.4.1.2.9 Smoking Cessation

[402] The change from baseline in number of cigarettes smoked per day for current smokers and for the mITT 12-week parallel group population were assessed, and there were no meaningful differences between the d6-DM/Q and placebo treated patients, in smoking cessation.

3.4.1.3 Exploratory Biomarkers

[403] Whole blood samples were collected at any visit when blood was already being drawn for exploratory biomarker analyses. The results of the biomarker analysis are presented in a separate report when available.

3.4.1.4 Posthoc Analyses

3.4.1.4.1 Assessments Performed by a Single-rater Throughout the Study

[404] Rater variance and drift from prescribed anchor points has long contributed to inconsistencies in reliable ratings despite training efforts. Approximately one third of patients in the study had more than one rater assessing the primary and secondary endpoints during the course of the study. A post-hoc analysis was performed excluding all patients who had more than one rater from both the placebo and d6-DM/Q treatment groups to assess impact of the use of a single-rater assessing the same endpoints throughout the study. These findings are summarized in Table 12.

Table 12. A Summary of NSA-16 and PANSS Score Results Among Patients with a Single-Rater Throughout Study

Outcome Measure	Stage 1: Change from Baseline to Week 6 (d6-DM/Q N = 32; Placebo N = 55)			Stage 2: Change from Week 6 to Week 12 (d6-DM/Q N=23; Placebo N=20)			SPCD
	LS Mean Treatment Difference (95% CI)	Standard Effect Size	p-value	LS Mean Treatment Difference (95% CI)	Standard Effect Size	p-value	P-value
NSA-16 Total Score	-3.49 (-5.82 to -1.15)	-0.69	0.004	-1.51 (-4.71 to 1.70)	-0.30	0.347	0.004
NSA-16 Global Negative Symptoms	-0.30 (-0.59 to -0.02)	-0.45	0.039	-0.30 (-0.70 to 0.10)	-0.48	0.138	0.010
NSA-16 Communication Domain	-1.16 (-2.05 to -0.27)	-0.58	0.011	-1.19 (-2.13 to -0.24)	-0.79	0.015	<0.001
PANSS Total	-3.57 (-6.58 to -0.56)	-0.52	0.021	-3.82 (-9.13 to 1.49)	-0.50	0.153	0.008
PANSS Negative Subscale	-1.36 (-3.05 to 0.34)	-0.36	0.115	-1.90 (-3.54 to -0.26)	-0.75	0.024	0.009
PANSS Marder Factor	-1.44 (-3.07 to 0.19)	-0.40	0.083	-2.15 (-4.19 to -0.12)	-0.63	0.038	0.007
PANSS General Psychopathology	-1.58 (-3.06 to -0.09)	-0.46	0.038	-1.85 (-5.54 to 1.85)	-0.33	0.317	0.049
PANSS Prosocial Factors	-1.28 (-2.37 to -0.19)	-0.53	0.021	-0.87 (-2.25 to 0.51)	-0.42	0.208	0.009

MMRM = mixed-model repeated measures; NSA-16 = Negative Symptom Assessment scale; PANSS = Positive and Negative Syndrome Scale; SPCD = sequential parallel comparison design; LS Mean = least square mean

Standard Effect Size was estimated by LS Mean Difference/Pooled Standard Deviation.

Note: Negative value indicates improvement. Stage 1 and 2 treatment effects were analyzed by MMRM on observed data with fixed effect of treatment, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. An unstructured covariance matrix was used. SPCD weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

[405] Despite the smaller patient cohorts, the positive treatment effects on negative symptoms were enhanced across many endpoints of the NSA-16 and the PANSS. Statistically significant treatment benefit was observed in the SPCD Combined Stage 1 and Stage 2 NSA-16 Total score ($p = 0.004$), the NSA-16 Global Negative Symptoms score ($p = 0.010$), and the NSA-16 Communication Domain ($p < 0.001$).

[406] Single-rater analysis of the SPCD Combined Stage 1 and Stage 2 Total score ($p = 0.008$), Negative subscale ($p = 0.009$), PANSS Marder Negative factors ($p = 0.007$), General Psychopathology score ($p = 0.049$), and Prosocial Factors score ($p = 0.009$) also consistently demonstrated augmentation of positive treatment effects seen in the primary data analysis.

3.4.1.4.2 Assessments on Communication and Expression

[407] Individuals with schizophrenia often have severe expressive deficits in both verbal and non-verbal communication. This impairment in communicative abilities causes severe functional deficits that results in impaired adaptive prosocial behaviors, social isolation and withdrawal. Post-hoc analysis was conducted for specific factors of the PANSS, as well as the NSA-16 and MCCB that measure communicative and expressive domains. The instruments used in the study capture both verbal and non-verbal communication (Axelrod et al. J Psychiatr Res. 1993;27(3):253-8) used by the participant.

[408] In patients treated with d6-DM/Q there is a strong trend toward improvement in the subdomains that focus on communication and interaction. It is believed that this overall pattern of change reflects an improvement in the patients' ability to interact and engage with others, impairment of which is one of the hallmarks of negative symptoms of schizophrenia and a key reason for long-term withdrawal from society of these patients. Support for improvement in these communicative domains was also evident in the Attention/Vigilance subdomain of the MCCB and in the NSA-16 Communication Factors Domain. These results are presented in Table 13.

Table 13. Communication and Expression Factor Analysis

Outcome Measure	Stage 1: Change from Baseline to Week 6 (d6-DM/Q N=47; Placebo N=80)			Stage 2: Change from Week 6 to Week 12 (d6-DM/Q N=33; Placebo N=30)			SPCD
	LS Mean Treatment Difference (95% CI)	Standard Effect Size	p-value	LS Mean Treatment Difference (95% CI)	Standard Effect Size	p-value	p-value
NSA-16 Communication Factor Domain	-0.46 (-1.22, 0.29)	-0.22	0.228	-0.64 (-1.52, 0.23)	-0.38	0.147	0.064
PANSS Prosocial factors	-0.89 (-1.75, -0.03)	-0.38	0.042*	-0.89 (-2.00, 0.22)	-0.41	0.115	0.009*
PANSS Expressive deficits domain	-0.42 (-1.36, 0.52)	-0.16	0.381	-1.27 (-2.34, -0.19)	-0.58	0.022*	0.034*
PANSS N3 Poor Rapport	-0.17 (-0.48, 0.15)	-0.18	0.299	-0.20 (-0.63, 0.24)	-0.23	0.373	0.169
PANSS N4 Passive/ Apathetic Social Withdrawal	-0.15 (-0.46, 0.16)	-0.18	0.351	-0.60 (-0.99, -0.21)	-0.73	0.003*	0.007*
PANSS N6 Lack of Spontaneity	0.04 (-0.29, 0.37)	0.04	0.813	-0.35 (-0.71, 0.02)	-0.47	0.060	0.346
PANSS G7 Motor Retardation	0.04 -0.24, 0.32)	0.05	0.777	-0.40 (-0.80, -0.00)	-0.43	0.048*	0.243
PANSS G11 Poor Attention	-0.10 (-0.30, 0.10)	-0.17	0.328	-0.20 (-0.58, 0.19)	-0.25	0.313	0.159
MCCB: Attention/Vigilance	0.65 (-1.87, 3.18)	0.09	0.611	3.35 (0.02, 6.68)	0.53	0.049*	0.088

CI = confidence interval; MCCB = MATRICS Consensus Cognitive Battery; MMRM = mixed-model repeated measures; NSA-16 = Negative Symptom Assessment scale; PANSS = Positive and Negative Syndrome Scale; SPCD = sequential parallel comparison design; LS Mean = least square mean

Standard Effect Size was estimated by LS Mean Difference/Pooled Standard Deviation.

Note: Negative value indicates improvement (except MCCB). Stage 1 and 2 treatment effects were analyzed by MMRM on observed data with fixed effect of treatment, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. An unstructured covariance matrix was used. SPCD weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

3.4.2 Tabulation of Individual Response Data

[409] By-patient listings of response data and other relevant study information were determined for the following:

- Randomization scheme
- Discontinued patients
- Protocol deviations
- Excluded patients from analysis
- Demographic and baseline characteristics data
- Concomitant medication
- Compliance/drug concentration
- By-patient efficacy response

3.4.3 Drug Dose, Drug Concentration, and Relationship to Response

3.4.3.1 Drug Dose

[410] The dose for patients randomized or re-randomized to d6-DM/Q was based on a fixed-titration scheme of d6-DM/Q-24/4.9 QD for 1 week, d6-DM/Q-24/4.9 BID for 1 week, and d6-DM/Q-34/4.9 BID for 4 or 10 weeks. The duration of d6-DM/Q exposure in the safety population is presented in Table 14.

Table 14. Duration of Exposure – Safety Population

	Placebo/Placebo (N = 56)	d6-DM/Q/d6-DM/Q (N = 48)	Placebo/d6-DM/Q (N = 40)		All d6-DM/Q (N = 88)
			Placebo	d6-DM/Q	
Duration of exposure, days					
Mean (SD)	61.41 (34.786)	75.94 (24.059)	43.18 (2.406)	41.83 (4.113)	60.43 (24.741)
Median (min, max)	84.0 (1, 89)	75.0 (1, 88)	42.0 (40, 51)	43.0 (20, 47)	45.0 (1, 88)
Number of patient-days	3439	3645	1727	1673	5318
Number of patient-years	9.42	9.98	4.73	4.58	14.56

Number of patient-years equals the sum of all patient exposure duration in days divided by 365.25.
SD = standard deviation.

3.4.3.2 Drug Concentrations and PK Parameter Estimates: d6-DM/Q

[411] Plasma concentrations were measured for d6-DM, d3-DX, and Q at baseline (Day 1), Visit 4 (Week 6) and Visit 7 (Week 12) and summarized by metabolizer subgroup and all metabolizer types. Mean concentrations of d6-DM for all patients were 49.7 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 4 [Week 6]), 53.2 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 7 [Week 12]), and 54.0 ng/mL (placebo/d6-DM/Q group at Visit 7 [Week 12]). Mean concentrations of d3-DX for all patients were 101.2 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 4 [Week 6]), 111.6 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 7 [Week 12]), and 124.5 ng/mL (placebo/d6-DM/Q group at Visit 7 [Week 12]). Mean concentrations of d3-3-MM for all patients were 20.5 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 4 [Week 6]), 19.4 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 7 [Week 12]), and 23.4 ng/mL (placebo/d6-DM/Q group at Visit 7 [Week 12]). Mean values for d6-DM, d3-DX and d3-3-MM varied by metabolizer type. Mean concentrations of Q for all patients were 17.9 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 4 [Week 6]), 20.1 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 7 [Week 12]), and 21.2 ng/mL (placebo/d6-DM/Q group at Visit 7 [Week 12]).

[412] C_{max} and AUC for d6-DM, d3-DX, and Q were estimated at Visit 4 (Week 6) and Visit 7 (Week 12) for all patients randomized to receive d6-DM/Q and are summarized for all metabolizer types and by metabolizer subgroups in Table 15.

3.4.3.3 d6-DM/Q PK Parameter Relationship to Response

[413] The association between the NSA-16 total score change from baseline and the C_{max} and AUC for d6-DM, d3-DX, or Q, respectively, was summarized at Visit 4 (Week 6; C_{max}, Table 77, Table 80, and Table 83; AUC, Table 86, Table 89, and Table 92) and Visit 7 (Week 12; $C_{max,}$ Table 78, Table 81, and Table 84; AUC, Table 87, Table 90, and Table 93) for the mITT population. The Pearson correlation coefficient values generally indicated poor correlation between the NSA-16 total score change from baseline and the C_{max} and AUC values for all 3 analytes. These analyses were repeated for the 12-week

mITT population subset with similar results (C_{max}, Table 79, Table 82, and Table 85; AUC, Table 88, Table 91, and Table 94).

Table 15. Summary of PK Parameters Estimated from Measured Drug Concentrations of Study Drug and Metabolites - Safety Population

	Metabolizer Subgroup				
	Poor	Intermediate	Extensive	Ultra-Rapid	All
Visit 4 (Week 6) (d6-DM/Q/d6-DM/Q) N = 48					
d6-DM					
C_{max} (ng/mL), n	1	22	19	1	43
Mean (SD)	28.7 (na)	63.9 (44.15)	38.2 (27.99)	58.6 (na)	51.6 (38.53)
Median (min, max)	28.7 (29, 29)	48.1 (17, 192)	32.2 (8, 130)	58.6 (59, 59)	40.0 (8, 192)
AUC (h×ng/mL), n	1	22	19	1	43
Mean (SD)	204.6 (na)	573.2 (418.66)	333.3 (255.24)	468.0 (na)	456.2 (362.05)
Median (min, max)	204.6 (205, 205)	401.7 (139, 1793)	271.9 (73, 1183)	468.0 (468, 468)	355.4 (73, 1793)
d3-DX					
C_{max} (ng/mL), n	1	22	19	1	43
Mean (SD)	87.2 (na)	111.5 (38.83)	144.6 (56.42)	193.1 (na)	127.4 (50.25)
Median (min, max)	87.2 (87, 87)	101.2 (56, 195)	134.9 (72, 332)	193.1 (193, 193)	121.6 (56, 332)
AUC (h×ng/mL), n	1	22	19	1	43
Mean (SD)	887.2 (na)	1044.8 (340.96)	1235.3 (389.01)	1774.7 (na)	1142.3 (378.08)
Median (min, max)	887.2 (887, 887)	991.6 (506, 1847)	1119.6 (729, 2091)	1774.7 (1775, 1775)	1083.8 (506, 2091)
Q					
C_{max} (ng/mL), n	1	22	19	1	43
Mean (SD)	9.3 (na)	20.8 (9.22)	19.0 (6.27)	33.7 (na)	20.0 (8.21)
Median (min, max)	9.3 (9, 9)	18.2 (10, 43)	17.6 (10, 32)	33.7 (34, 34)	17.7 (9, 43)
AUC (h×ng/mL), n	1	22	19	1	43
Mean (SD)	74.6 (na)	164.4 (72.16)	152.0 (48.60)	261.2 (na)	159.1 (63.81)
Median (min, max)	74.6 (75, 75)	139.9 (80, 325)	143.2 (83, 258)	261.2 (261, 261)	142.1 (75, 325)
Visit 7 (Week 12) (d6-DM/Q/d6-DM/Q) N = 48					
d6-DM					
C_{max} (ng/mL), n	0	20	19	1	40
Mean (SD)	na	67.0 (46.98)	38.7 (26.74)	62.1 (na)	53.4 (40.09)
Median (min, max)	na	45.9 (16, 194)	34.1 (8, 124)	62.1 (62, 62)	42.3 (8, 194)

	Metabolizer Subgroup				
	Poor	Intermediate	Extensive	Ultra-Rapid	All
AUC (h×ng/mL), n	0	20	19	1	40
Mean (SD)	na	601.9 (442.90)	336.7 (244.01)	498.8 (na)	473.4 (375.01)
Median (min, max)	na	375.7 (132, 1810)	288.9 (70, 1127)	498.8 (499, 499)	369.4 (70, 1810)
d3-DX					
C_{max} (ng/mL), n	0	20	19	1	40
Mean (SD)	na	106.3 (33.76)	144.9 (56.98)	190.3 (na)	126.8 (50.32)
Median (min, max)	na	100.6 (57, 187)	133.9 (76, 337)	190.3 (190, 190)	123.0 (57, 337)
AUC (h×ng/mL), n	0	20	19	1	40
Mean (SD)	na	1015.0 (312.22)	1243.6 (394.70)	1783.3 (na)	1142.8 (378.46)
Median (min, max)	na	1000.2 (511, 1833)	1123.4 (740, 2115)	1783.3 (1783, 1783)	1087.1 (511, 2115)
Q					
C_{max} (ng/mL), n	0	20	19	1	40
Mean (SD)	na	20.9 (10.25)	19.4 (6.39)	35.3 (na)	20.6 (8.73)
Median (min, max)	na	17.7 (10, 45)	19.4 (10, 33)	35.3 (35, 35)	18.8 (10, 45)
AUC (h×ng/mL), n	0	20	19	1	40
Mean (SD)	na	166.3 (80.69)	155.2 (50.01)	274.8 (na)	163.7 (68.42)
Median (min, max)	na	141.5 (81, 347)	149.0 (82, 262)	274.8 (275, 275)	146.5 (81, 347)
Visit 7 (Week 12) (placebo/d6-DM/Q) N = 40					
d6-DM					
C_{max} (ng/mL), n	1	13	19	0	33
Mean (SD)	47.9 (na)	56.2 (29.94)	47.2 (26.57)	Na	50.8 (27.44)
Median (min, max)	47.9 (48, 48)	56.1 (15, 106)	44.2 (7, 121)	Na	47.7 (7, 121)
AUC (h×ng/mL), n	1	13	19	0	33
Mean (SD)	427.4 (na)	492.1 (271.83)	404.3 (239.02)	Na	439.6 (248.41)
Median (min, max)	427.4 (427, 427)	492.9 (124, 945)	368.0 (53, 1081)	Na	413.0 (53, 1081)
d3-DX					
C_{max} (ng/mL), n	1	13	19	0	33
Mean (SD)	65.1 (na)	108.0 (24.89)	142.5 (56.08)	Na	126.6 (49.10)
Median (min, max)	65.1 (65, 65)	105.2 (76, 168)	130.9 (80, 318)	Na	116.4 (65, 318)
AUC (h×ng/mL), n	1	13	19	0	33
Mean (SD)	651.2 (na)	1014.1 (202.39)	1323.8 (623.07)	Na	1181.4 (515.68)

	Metabolizer Subgroup				
	Poor	Intermediate	Extensive	Ultra-Rapid	All
Median (min, max) Q	651.2 (651, 651)	940.4 (745, 1367)	1131.7 (750, 3622)	Na	1085.8 (651, 3622)
C_{max}, n (ng/mL)	1	13	19	0	33
Mean (SD)	23.1 (na)	19.7 (4.28)	21.7 (9.93)	Na	21.0 (7.96)
Median (min, max)	23.1 (23, 23)	19.5 (11, 27)	20.3 (10, 45)	Na	20.3 (10, 45)
AUC, n (h×ng/mL)	1	13	19	0	33
Mean (SD)	185.1 (na)	153.8 (31.55)	168.9 (74.91)	Na	163.5 (60.00)
Median (min, max)	185.1 (185, 185)	155.5 (90, 208)	157.9 (84, 336)	Na	157.9 (84, 336)

Patients who were not assigned a metabolizer group are excluded from this table. Visit 7 (Week 12) includes early termination visits.

AUC = area under the curve; Cmax = maximum concentration; d6-DM = deudextromethorphan hydrobromide; d3-DX = deuterated (d3) dextrorphan; Q = quinidine sulfate; SD = standard deviation.

3.4.4 Drug Concentration: Second-Generation Antipsychotics (SGA)

[414] Per the study entry criteria, patients were on at least 1 SGA at baseline. Plasma concentrations were analyzed for the following SGAs, aripiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Results are summarized by metabolizer subgroups for patients who were randomized to receive d6-DM/Q in Stage 1 and 2 (d6-DM/Q/d6-DM/Q), placebo in Stage 1 and 2 (d6-DM/Q/d6-DM/Q) or d6-DM/Q in Stage 2 only (placebo/d6-DM/Q) and. The number of patients taking each SGA at baseline were as follows: aripiprazole 32 patients, lurasidone 6 patients, olanzapine 36 patients, paliperidone 18 patients, quetiapine 23 patients, risperidone 31 patients, and ziprasidone 3 patients.

3.4.5 Drug-Drug and Drug-Disease Interactions

[415] Analyses of the primary endpoint (NSA-16 total score) were performed for the subset of patients in the mITT population with baseline concomitant use of benzodiazepines (Table 69), SNRIs (Table 70), or SRRIs (Table 71) to determine whether the concomitant drugs being taken at baseline affected patient NSA-16 total scores. Similar analyses were performed for subgroup with concomitant psychotropic medications (antidepressants, antipsychotics) considered as CYP2D6 major substrates (Tables 72 and 74) and subgroup with concomitant psychotropic medications not considered as CYP2D6 major substrates (Tables 73 and 75). The number of patients in each subgroup were too few to make a meaningful interpretation of the analysis.

[416] Analyses of the primary endpoint was also performed on the subgroup of patients with a composite score of < 30 (Table 59) versus patients with ≥ 30 (Table 60) on the MCCB at baseline to assess the effect of cognition level on the patient NSA-16 total scores. Although there were no statistically significant differences between placebo and d6-DM/Q in either subgroup, numerically higher improvement in NSA-16 total scores were observed in the subgroup with MCCB score of ≥ 30 at baseline. The standard effect size was -0.477 (Stage 1) and -0.527 (Stage 2) for the subgroup with MCCB score of ≥ 30 at

baseline and was -0.226 (Stage 1) and 0.059 (Stage 2) for the subgroup with MCCB score of ≤ 30 at baseline.

3.4.6 By-Patient Displays

[417] By-patient display data were not reported in this study because group mean data represent the principal analyses.

3.4.7 Efficacy

- A numerically higher improvement was observed with d6-DM/Q compared to placebo in the primary efficacy endpoint, change from baseline in the NSA-16 total score, with the SPCD analysis (SPCD weighted Z-statistic = -1.79, p = 0.073). The LS mean treatment difference between d6-DM/Q and placebo was -1.79 (95% CI -3.86, 0.29) in Stage 1 and -1.28 (95% CI -4.39, 1.83) in Stage 2. Significant treatment effects were seen in the sensitivity analysis of the primary endpoint with both the SUR method (p = 0.048) and SPCD OLS ANCOVA LOCF Data (p = 0.042) method of analyses.
- Statistically significant differences in favor of d6-DM/Q versus placebo were observed in the SPCD analysis of PANSS total score (p = 0.025), PANSS negative subscale (p = 0.027), PANSS Marder negative factors (p = 0.024), and PANSS prosocial factors (p = 0.009). No statistically significant differences were observed between the 2 groups in the positive subscale (p = 0.700), excitement component, (p = 0.723), and general psychopathology subscale (p = 0. 054) of the PANSS.
- Statistically significant differences (p = 0.026) in favor of d6-DM/Q versus placebo were also observed in the SPCD analysis of the NSA-16 global negative symptoms rating. The LS mean treatment difference between d6-DM/Q and placebo was -0.17 (95% CI -0.40, 0.07) in Stage 1 and -0.29 (95% CI -0.61, 0.03) in Stage 2.

- In Stage 1, 27.7% of patients treated with d6-DM/Q vs. 24% on placebo rated their change in symptoms as “much improved” or “very much improved” on the PGI-C scale. In Stage 2, 34.4% of patients treated with d6-DM/Q vs. 13.3% on placebo reported that their symptoms at Week 12 were “much improved” or “very much improved” (SPCD p = 0.170). In the 12-week parallel group mITT population, the proportion of patients with ‘much improved’ or ‘very much improved’ rating at Week 12 relative to baseline was 33.3% (14/42) for the d6-DM/Q/d6-DM/Q group and 18.8% (6/32) for the placebo/placebo group (p=0.158 by proportional odds regression).
- No statistically significant differences were observed between the d6-DM/Q and placebo group with SPCD analysis of other secondary endpoints including CGI-S, CGI-C, CDSS total score, MCCB composite score, and NSA-4 total score, however numerically higher improvements in favor of d6-DM/Q were observed for the CGI-C score and the MCCB composite score.
- Mean concentrations of d6-DM for all patients were 49.7 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 4 [Week 6]), 53.2 ng/mL (d6-DM/Q/d6-DM/Q group at Visit 7 [Week 12]), and 54.0 ng/mL (placebo/d6-DM/Q group at Visit 7 [Week 12]). Concentrations of d6-DM, d3-DX and d3-3MM varied with metabolizer type. PK parameters were estimated for d6-DM, d3-DX and Q. In a PK/Pharmacodynamic (PD) analysis using these estimated PK parameters, Pearson correlation coefficient values generally indicated poor correlation with the NSA-16 total score change from baseline.

4 SAFETY EVALUATION

4.1 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.1.1 Vital Signs

[418] Vital sign actual values, the change from baseline, and percent change from baseline were determined. No trends suggesting an impact of d6-DM/Q on measured vital sign values were observed.

[419] A summary of potentially clinically significant (PCS) vital sign abnormalities was determined. There were no meaningful differences in the incidence of PCS vital sign abnormalities between treatment groups.

4.1.2 Physical and Neurological Exam

[420] A full physical and neurological examination was scheduled for all patients at the screening visit only. Clinically significant abnormalities in physical examination were reported for 3 patients and recorded in the medical history of the patient.

4.1.3 Electrocardiogram

[421] Summaries of ECG parameters and the change from baseline and percent change from baseline in these parameters were determined by treatment group. Additionally, changes in ECG parameters from pre-dose to post-dose at Day 1 and Week 6 were determined. Overall, the changes from baseline in ECG parameters were small with no trends suggesting an impact of d6-DM/Q on ECG results.

[422] None of the patients had a QTcF change from baseline of ≥ 60 msec, and no patient had a PR interval of > 200 msec in either the all placebo group or all d6-DM/Q group. Overall, 2 females (1 in the all d6-DM/Q and 1 in the all placebo group) met the PCS criteria for ECG abnormality in QTcF interval with postbaseline values in the > 460 to ≤ 485 msec range and 3 males (1 in the all d6-DM/Q and 2 in the all placebo group) met the PCS criteria for ECG abnormality in QTcF interval, with postbaseline values in the > 450 to ≤ 480 msec range.

[423] Two patients reported AEs in the cardiac disorders SOC; 1 patient (120-003) in the all d6-DM/Q group reported tachycardia and 1 patient (119-004) in the all placebo group reported atrial fibrillation.

4.1.4 Other Safety Observations

4.1.4.1 Columbia Suicide Severity Rating Scale (C-SSRS)

[424] Summaries of C-SSRS ideation severity by visit and C-SSRS suicidal behavior type by visit were determined. The intensity of most severe ideation by was determined. Additionally, actual and potential lethality on most lethal attempts by visit was determined. Overall, no clinically meaningful signals related to suicidal ideation, severity, and lethality were observed with either placebo or d6-DM/Q treatment.

4.1.4.2 Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

[425] A summary of the total scores and individual item scores on the SAS is provided by gender and for males and females combined in Table 61. In addition, shift tables of individual items on the SAS are presented for the safety population, and by the female and male subgroups, in Table 62.

[426] Overall, there were no signals or trends indicating that treatment with d6-DM/Q played a role in worsening of extrapyramidal symptoms in patients with such symptoms at baseline.

4.1.4.3 Barnes Akathisia Scale (BAS)

[427] A summary of the total scores and individual item scores on the BAS was determined by gender and for males and females combined. In addition, shift tables of the global clinical assessment and individual items on the BAS for the safety population were determined and by the female and male subgroups.

[428] Overall, there were no signals or trends indicating that treatment with d6-DM/Q played a role in worsening of restlessness symptoms in patients with such symptoms at baseline.

4.1.4.4 Abnormal Involuntary Movements Scale (AIMS)

[429] A summary of the total scores and subscale scores on the AIMS was determined by gender and for males and females combined. In addition, shift tables of individual items on the AIMS were determined for the safety population and by the female and male subgroups.

[430] Overall, there were no signals or trends indicating that treatment with d6-DM/Q played a role in worsening of dyskinesia symptoms in patients with such symptoms at baseline. There were no AEs of dyskinesia reported in patients treated with d6-DM/Q. One patient in the all placebo group reported dyskinesia as an AE in Stage 2. The AE was deemed to be mild and possibly related to the study drug, by the investigator.

4.2 Safety

- No deaths were reported during this study.
- Overall, 30 (34.1%) patients in the all d6-DM/Q treatment group and 39 (40.6%) patients in the all placebo treatment group reported ≥ 1 TEAE. The TEAEs were mild to moderate in severity.
- The most frequently (> 2 patient) reported TEAEs in either the all d6-DM/Q group or the all placebo group, respectively, were dry mouth (4.5% vs. 1.0%), diarrhea (2.3% vs. 3.1%), dizziness (3.4% vs. 3.1%), headache (2.3% vs. 5.2%), somnolence (1.1% vs. 3.1%) and nasopharyngitis (3.4% vs. 4.2%).
- Treatment-related TEAEs were reported by 13.6% and 18.8% for the all d6-DM/Q and the all placebo treatment group, respectively. Treatment-related TEAEs reported in ≥ 2 patients in the all d6-DM/Q included dry mouth (2.3%) and headache (2.3%), and in the all placebo group, these included headache (3.1%), dizziness (2.1%), somnolence (3.1%), diarrhea (2.1%), and sedation (2.1%).
- SAEs were reported by 2 patients in the all placebo group and none in the all d6-DM/Q group. The 2 SAEs were exacerbation of schizophrenia and urinary

tract infection. Study drug was discontinued in the patient who experienced the SAE of exacerbation of schizophrenia upon their hospitalization and was not resumed. Study drug was interrupted for one day in the patient who experienced the SAE of urinary tract infection. This patient completed the study. Neither of the SAEs were considered related to the study drug.

- Overall, 10 patients discontinued the study due to TEAEs; 2 patients in the all d6-DM/Q group and 8 patients in the all placebo group. TEAEs that led to study discontinuation in the all d6-DM/Q group were vision blurred and rash, and, in the all placebo group, were eye pain, rash, atrial fibrillation, dizziness, headache, schizophrenia, and erectile dysfunction.
- None of the patients had a QTcF change from baseline of ≥ 60 msec, and no patient had a PR interval of > 200 msec in either the all placebo group or all d6-DM/Q group.
- Patients had low scores on the SAS (extrapyramidal symptoms), BAS (restlessness) and AIMS (dyskinesia) at baseline and there were no AEs events or trends indicating that treatment with d6-DM/Q played a role in worsening of such symptoms during the course of the study.

5 RESULTS

[431] In this study conducted in patients with negative symptoms of schizophrenia, consistent efficacy signals for d6-DM/Q were observed across multiple, well-validated, and reliable instruments that have historically been accepted for evaluating negative symptoms of schizophrenia. Although the primary endpoint, change in the NSA-16 Total Score did not reach statistical significance, there was a trend for improvement ($p = 0.073$). Patients treated with d6-DM/Q experienced a significantly greater improvement from baseline compared to placebo in the combined (Stage 1 and Stage 2) SPCD mITT analyses for several efficacy rating scales specifically assessing negative symptoms. These included the NSA-16 Global Negative Symptoms score ($p = 0.026$), the PANSS Marder Negative

Factors (p = 0.024), and PANSS Negative Factors score (p = 0.027). There were significant improvements in favor of d6-DM/Q over placebo treatment in the PANSS Expressive Deficit Domain (p = 0.034) and the PANSS Experiential Deficit Domain (p = 0.022), the PANSS Prosocial Factors Score (p = 0.009), and a trend towards positive effect on the PANSS General Psychopathology Subscale Score (p = 0.054). Improvement in the PANSS total was driven by improvement in negative symptoms and in the General Psychopathology Subscale. Patients had low baseline PANSS positive scores and demonstrated little change during the study, hence the findings were not pseudo-specific.

[432] The standardized effect size (absolute value) by stage ranged from 0.30 to 0.75 for NSA-16 Total score, PANSS Total score, PANSS Marder, and PANSS Negative (data on file), suggesting that even when one of the results was not statistically significant, meaningful treatment effects were observed when compared to other approved neuroscience compounds.

[433] To determine the impact of rater variability on efficacy end points, a post-hoc analysis of patients who were consistently rated by the same rater throughout the study was performed for the NSA-16 and the PANSS. Results of this post-hoc analysis were highly significant and enhanced on several outcome measures including the NSA-16 Total Score (p = 0.004), the NSA-16 Global Negative Symptoms score (p = 0.010), and the PANSS Marder negative factors (p = 0.007) and negative Factor Scores (p = 0.009). This analysis included a total of 87 patients in the mITT population.

[434] In a consensus statement, Schooler and colleagues (Schooler et al. Schizophr Res. 2015;162(1-3):169-174) suggest that a meaningful therapeutic benefit on negative symptoms of schizophrenia would be “a significant improvement, greater than or equal to 20% of the total score, on a valid and reliable measure assessing negative symptoms”. In this study (Example 1), analyses of the PANSS Negative subscale and the

PANSS Marder negative factors scores were performed using this threshold of a 20% or more improvement.

[435] A significantly greater percentage of d6-DM/Q treated patients compared to placebo demonstrated a 20% or greater improvement from baseline on the PANSS Marder Negative Factors score (Stage 1: 21.3% vs 16.3%; Stage 2: 27.3% vs 3.3%; p = 0.012). The proportion of patients with 20% reduction from baseline in PANSS Negative subscale was also higher in the d6-DM/Q group compared to placebo in both stages (Stage 1: 23.4% vs 13.8%; Stage 2: 21.2% vs 10%; SPCD p = 0.054).

[436] Using a patient-reported outcome measure, the PGI-C, the proportion of patients with 'much improved' or 'very much improved' rating on the PGI-C at the end of Stage 1 was 27.7% for patients treated with d6-DM/Q and 24% for patients treated with placebo and in Stage 2 (Week 12 relative to baseline). In Stage 2, there was more than a 2-fold higher percentage of patients given d6-DM/Q than placebo (34.4% vs 13.3%) that rated their symptoms as "very much" or "much" improved from baseline to end of study. In the 12-week parallel group mITT population, the proportion of patients with 'much improved' or 'very much improved' rating at Week 12 relative to baseline was 33.3% (14/42) for the d6-DM/Q/d6-DM/Q group and 18.8% (6/32) for the placebo/placebo group (p = 0.158 by proportional odds regression). In this population of stable patients who were in a residual state of their illness and on a stable dose of an atypical antipsychotics (~3 months), the PGI-C could be used in a reliable manner in support of clinically meaningful information.

[437] The clinician's view of the patient's global severity of negative symptoms was assessed through the NSA-16 Global negative symptoms severity score, while the overall level of illness was assessed with the CGI-S and CGI-C. A statistically significant benefit was observed on the NSA-16 Global negative symptoms severity score (SPCD; p = 0.026). Although no statistically significant differences between d6-DM/Q and placebo were observed with the CGI-C and CGI-S measures, the results indicated a trend for benefit of d6-DM/Q over placebo. The different anchor points and type of illness assessed in the

NSA-16 Global Negative symptoms score vs. the CGI-C/S may explain the stronger, statistically significant results seen with the NSA-16 Global Negative symptoms score. The NSA-16 Global is very specific for negative symptoms in comparison to a normal healthy young adult, whereas the CGI-C/S use the patient themselves or other patients with schizophrenia as the anchor point and are specific to overall illness and not to negative symptoms. Modified versions of the CGI-C/S which assess the severity and change in target symptomatology may provide more meaningful information and could be considered in future studies.

[438] There was also a trend towards improvement in cognition as assessed by the MCCB Composite Score and the Attention/Vigilance domain of the MCCB with significant benefits that were seen in Stage 2 of the study. Ability to demonstrate improvements in cognition has been another difficult hurdle for the field and here it appears there may be a potential towards a cognitive benefit that merits exploration in additional studies.

[439] In this study (Example 1), there was a signal of efficacy demonstrated on aspects of verbal and non-verbal communication in specific factors of the PANSS in patients treated with d6-DM/Q vs placebo. These were also evident in the Attention/Vigilance subdomain of the MCCB and in the NSA-16 Communication Factors Domain.

[440] Patients had low baseline symptoms of depression (evaluated with the Calgary Depression Scale for Schizophrenia) and extrapyramidal symptoms and did not experience significant changes in these symptoms throughout the study, supporting the specificity of the study findings for negative symptoms. In general, d6-DM/Q was safe and well-tolerated in this study (Example 1) with a safety profile consistent with other clinical trials of the same compound. The most frequently (> 2 patients) reported TEAEs in either the all d6-DM/Q group or the all placebo group, respectively, were dry mouth (4.5% vs. 1.0%), diarrhea (2.3% vs. 3.1%), dizziness (3.4% vs. 3.1%), headache (2.3% vs. 5.2%),

somnolence (1.1% vs. 3.1%) and nasopharyngitis (3.4% vs. 4.2%). No deaths were reported in the study and no serious AEs occurred in the all d6-DM/Q group.

[441] Taken together, the results from this study (Example 1) demonstrate a consistent, positive signal of efficacy across a wide range of reliable and validated measures indicating that adjunctive treatment with d6-DM/Q could provide a safe, effective, and clinically meaningful therapeutic option for stable schizophrenia patients exhibiting negative symptoms. The safety profile of d6-DM/Q was favorable and supportive of further development for this indication.

Example 2

Exemplary parameters for a multicenter, randomized, double-blind, placebo-controlled, parallel-arm studies to assess the efficacy, safety, and tolerability of d6-DM/Q (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of negative symptoms of schizophrenia

[442] In the study from Example 1, patients treated with d6-DM/Q at a dose of 34/4.9 mg twice daily (BID) demonstrated improvements in negative symptoms of schizophrenia compared to patients on placebo. d6-DM/Q was safe and well-tolerated in that study.

[443] To evaluate the efficacy, safety, and tolerability of a higher dose of d6-DM/Q (42.63/4.9 mg), patients randomized to d6-DM/Q are titrated from an initial dose of d6-DM/Q of d6-DM 28 mg/Q 4.9 mg (d6-DM/Q-28/4.9) once to twice daily during the first week of the randomized treatment period; patients then receive d6-DM 42.63 mg/Q 4.9 mg (d6-DM/Q-42.63/4.9) administered orally BID for the remainder of the randomized treatment period.

[444] The d6-DM/Q-42.63/4.9 BID dose is associated with d6-DM exposures within the range shown to be generally well tolerated in Phase 1 and Phase 2 studies of d6-DM/Q, and within the range where receptor binding is sufficient to test the effectiveness hypothesis. This higher dose of d6-DM/Q 42.63/4.9 mg BID is studied across multiple

indications, without new safety signals emerging across the d6-DM/Q clinical development programs to date.

[445] The 12-week treatment duration ensures exposure to the targeted optimal dose of d6-DM/Q for an adequate period of time to observe a treatment response and to assess duration of response. The consensus group comprising the National Institute of Mental Health (NIMH), FDA, academic, and industry representatives, have identified a minimum 12-week duration of treatment as appropriate for designing studies of negative symptoms of schizophrenia (Laughren and Levin, Schizophr Bull. 2006;32(2):220-222).

1 INVESTIGATIONAL PLAN

1.1 Overall Study Design

[446] This is a possible design for multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of d6-DM/Q in patients with negative symptoms of schizophrenia. The study includes up to a 4-week Screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. Up to 370 patients are enrolled

Screening Period (Day -28 to Day -1)

[447] The Screening period is 28 days (4 weeks) and begins when consent has been obtained. An extension of up to 14 additional days (42-day maximum total) can be requested from the Medical Monitor, if needed, to meet eligibility requirements.

Double-Blind Treatment Period

[448] Patients are randomized in a 1:1 ratio to receive either d6-DM/Q or matching placebo capsules during. Patients randomized to d6-DM/Q begin a one-week titration period in which they receive a dose of d6-DM 28 mg/Q 4.9 mg (d6-DM/Q-28/4.9) every morning (qam) and a dose of placebo every evening (qpm) for the first 3 days, followed by d6-DM/Q-28/4.9 BID for the next 4 days. Following this one-week titration period, patients receive d6-DM 42.63 mg/Q 4.9 mg (d6-DM/Q-42.63/4.9) administered orally BID for the remaining 11 weeks of the double-blind treatment period.

Follow-Up Period

[449] The 30-day follow-up period begins following the last visit (Visit 5 [Week 12] or Early Termination [ET]). The patient is contacted by phone at Week 16 to collect adverse event (AE) and concomitant medication information for the 30 days following the last dose of study medication.

Assessments and Visits:

[450] Patients attend clinic visits at Screening, Visit 1 (Day 1 (Baseline)), and at Weeks 3, 6, 9, and 12, or at ET. A phone call occurs at Week 1, Week 4, Week 7, Week 10, and 30 days after the Week 12 or ET Visit.

[451] Study procedures are performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 16). The primary efficacy measure is the PANSS Marder negative factors score. Secondary efficacy measures include: NSA-16 Global Negative Symptom Score, Patient Global Impression of Severity (PGI-S), and Patient Global Impression of Change (PGI-C). Other outcome measures include: PANSS positive subscale and Calgary Depression Scale for Schizophrenia (CDSS). The NSA-16 is conducted at all visits where the NSA-16 Global is assessed, however the NSA-16 is not an efficacy measure in the study.

[452] Pharmacokinetic (PK) measurements of plasma concentrations of d6-DM, Q, and certain metabolites are measured from samples collected at Visits 2, 4, and 6 (or ET).

[453] The safety and tolerability of d6-DM/Q is assessed by reported AEs, physical examination, vital signs, clinical laboratory measures, 12-lead electrocardiograms (ECG), and the following scales: Columbia Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movements Scale (AIMS), Barnes Akathisia Scale (BAS), and the Simpson Angus Scale for Extrapyramidal Symptoms (SAS).

1.2 Number of Patients

[454] Up to 370 patients are enrolled.

1.3 Treatment Assignment

[455] Treatment (12-week, double-blind, treatment period; d6-DM/Q or placebo) is randomly assigned (1:1 ratio) based on a randomization scheme provided by the Sponsor.

1.4 Study Assessments and Procedures

[456] A description of the study assessments and procedures is provided in Section 8.

Table 16. Schedule of Evaluation and Visits

Procedure	Visit:	Screening		Baseline		Study Treatment Period								Post Exit Phone[2]
	Study Day:	Day -28 to -1		Day 1	Day 8	Day 22	Day 29	Day 43	Day 50	Day 64	Day 71	Day 85	Day 115	
	End of Study Week:	Week -4 to -1		Week 0	Week 1	Week 3	Week 4	Week 6	Week 7	Week 9	Week 10	Week 12	Week 16	
Informed Consent Form signed		X												
CTSdatabase Entry		X										X		
Medical History/Psychiatric History		X												
M.I.N.I. Exam		X												
Review Inclusion and Exclusion Criteria		X		X										
Document Patient's Informant Information		X												
NSA-16 and NSA Global				X		X		X		X		X		
PANSS		X		X		X		X		X		X		
PGI-S				X		X		X		X		X		
PGI-C				X		X		X		X		X		
Enrollment (Visit 1)/ Randomization (Visit 2)				X										
AiCure (Patient Training)														
Physical and Neurological Examinations		X										X		

Table 16. Schedule of Evaluation and Visits (Continued)

			Baseline		Study Treatment Period								
Procedure	**Visit:**	**Screening**		**Visit 1[1]**	**Phone[2]**	**Visit 2[1]**	**Phone[2]**	**Visit 3[1]**	**Phone[2]**	**Visit45[1]**	**Phone[2]**	**Visit 5[1] /ET**	**Post Exit Phone[2]**
	Study Day:	**Day -28 to -1**		**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**	**Day 50**	**Day 64**	**Day 71**	**Day 85**	**Day 115**
	End of Study Week:	**Week -4 to -1**		**Week 0**	**Week 1**	**Week 3**	**Week 4**	**Week 6**	**Week 7**	**Week 9**	**Week 10**	**Week 12**	**Week 16**
Resting 12-lead ECG[3]		X		X		X		X		X		X	
Chemistry, Hematology, and Urinalysis[4]		X		X				X				X	
Pregnancy Test[5]		X		X		X		X		X		X	
Urine Drug Screen		X											
Hepatitis B and C; HIV antibody		X											
Lab -CYP2D6[6]				X									
Pharmacokinetic sampling[7]				X				X				X	
Plasma Antipsychotic Levels		X		X				X				X	
Review of Adverse Events				X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X		X	X	X	X	X	X	X	X	X	X
Record Vital Signs/Weight[8]		X		X		X		X		X		X	
CDSS		X		X				X				X	
Extrapyramidal Symptoms Assessment Scales (AIMS, BAS, SAS)		X[9]		X				X				X	

Table 16. Schedule of Evaluation and Visits (Continued)

			Baseline			Study Treatment Period								
Procedure	Visit:	Screening			Visit 1[1]	Phone[2]	Visit23[1]	Phone[2]	Visit 3[1]	Phone[2]	Visit 4[1]	Phone[2]	Visit 5[1] /ET	Post Exit Phone[2]
	Study Day:	Day -28 to -1			Day 1	Day 8	Day 22	Day 29	Day 43	Day 50	Day 64	Day 71	Day 85	Day 115
	End of Study Week:	Week -4 to -1			Week 0	Week 1	Week 3	Week 4	Week 6	Week 7	Week 9	Week 10	Week 12	Week 16
C-SSRS		X			X		X		X		X		X	
Dispense Study Drug					X		X		X		X			
Dose in Clinic (first dose of the day)					X		X		X		X		X	
Review Returned Unused Study Drug					X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	

[1] Visit 1 has a ±3 day window; Visits 2-5 have a ± 6 day window.
[2] Telephone calls have a +3 day window.
[3] Triplicate ECGs at Screening only. Electrocardiogram is performed pre-dose and 1-2 hours (±15 minutes) post-dose at Visit 1 and Visit 2; ECGs at all other visits are performed pre-dose only (Visits 3, 4, and 5).
[4] Fasting glucose and lipids are measured at Screening, Visits 1, 3, and Visit 5/ ET visit for patients who withdraw prior to study completion. HbA1c is measured at Screening and Visit 5 / ET. Thyroid function tests are measured at Screening only.
[5] Urinary (beta-hCG) test is performed for all females of childbearing potential (serum beta-hCG at Screening only).
[6] Blood samples for CYP2D6 genotyping are taken at Visit 1.
[7] Plasma concentrations of d6-DM, its metabolites (d3-DX and d3-3-MM), and Q are measured from samples collected post-dose on Day 1 (Week 0), pre- and post-dose on Day 43 (Week 6), and pre-dose on Day 85 (Week 12).
[8] BP and HR measurements are performed (in duplicate) at all clinic visits. Orthostatic BP and HR is measured at the Screening visit only; all other BP and HR measurements are taken while the patient is sitting/semi-recumbent. Respiratory rate and body temperature are measured at Screening, Day 1 (Visit 1), and Day 85 (Visit 5)/ET. Weight and height are measured at Screening, Day 1 (Visit 1), and Day 85 (Visit 5).
[9] Only the SAS is measured at Screening (AIMS and BAS not measured at Screening).
[10]Patient is asked if they have taken their medications as directed during telephone calls at Days 8, 29, 50, and 71.

2 SELECTION AND WITHDRAWAL OF PATIENTS

[457] Eligible patients are adult outpatients, between 18 and 60 years of age, who are diagnosed with schizophrenia, show evidence of negative symptoms of schizophrenia, are clinically stable, and meet all the inclusion criteria and none of the exclusion criteria noted in the following sections.

[458] The initial diagnostic assessment is performed by the Investigator to assess if the patients meet the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), using the Mini International Neuropsychiatric Interview (M.I.N.I.) Version 6.0.0 or 7.0.2 (Appendix 11A or 11B, respectively).

2.1 Patient Inclusion Criteria

1. Males and females 18 to 60 years of age, inclusive, at time of informed consent.
2. Patients who meet DSM-V diagnostic criteria for schizophrenia confirmed by the M.I.N.I Version 7.0.2, with onset at least 1 year before Screening and have been clinically stable for at least 6 months (no psychiatric hospital admissions or acute exacerbations). Patients who have been hospitalized within the last 6 months before Screening for social reasons are allowed upon consultation with the Medical Monitor, but currently hospitalized patients are excluded.
3. Patients are required to have been in a stable living situation for at least 30 days before Screening.
4. Patients should be treated with a second-generation atypical antipsychotic drug (SGA) other than clozapine in any approved dosage form for at least 3 months prior to Screening and be on a stable dose for at least 30 days prior to Screening; patients must remain clinically stable (in the opinion of the Principal Investigator) through Visit 1 and may not be treated with more than one SGA with the exception of low dose quetiapine (up to 50 mg at night) for insomnia.

5. Negative symptoms that have been present for at least 6 months, in the judgment of the Investigator.
6. Patients must have a score of:
   a. ≤ 4 on PANSS items P1: delusions; P3: hallucinations; P6: suspiciousness/persecution; and P7: hostility; and
   b. ≥ 4 (moderate) on any 2, or ≥ 5 on any 1, of the following items of the PANSS: N1: blunted affect; N2: emotional withdrawal; N4: passive/apathetic social withdrawal; or N6: lack of spontaneity/flow of conversation.
7. Women of childbearing potential who are sexually active must use an effective method of birth control during the course of the trial, and for at least 30 days after the last dose of study drug. To minimize the risk of failure of one method of birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, or condom with spermicide or sponge with spermicide. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception. Women who are sterile (i.e., had an oophorectomy and/or hysterectomy), postmenopausal (12 consecutive months with no menses without an alternative medical cause), or practice true abstinence (when this method is in line with the preferred and usual lifestyle of the patient) are exempt from this requirement.
8. Concomitant use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, citalopram) and serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone) are allowed as long as the dose has been stable for 3 months (90 days) prior to Screening, remains stable throughout the study, and the dose used is within the guidance from the U.S. label for that drug. Paroxetine,

a cytochrome P450 (CYP) 2D6 substrate, is allowed provided the dose does not exceed 10 mg/day.

9. Concomitant use of hypnotics at bedtime (e.g., zolpidem at a dose of 5 to 10 mg or equivalent) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 1 month (30 days) prior to Visit 1 and remains stable throughout the study.
10. Patients on lorazepam up to a total dose of 2 mg per day for treatment of insomnia, anxiety, restlessness, or agitation. Patients should be on a stable dose for at least 1 month (30 days) prior to Visit 1 and the dose should remain stable for the duration of the study.
11. Willing to sign and receive a copy of the patient informed consent form (ICF) after the nature and risks of study participation have been fully explained.
12. Sufficient comprehension and cooperation to enable compliance with all procedures and assessments.
13. Patients must have a reliable informant (e.g., case manager, social worker, family member). In the opinion of the Investigator, the informant should spend an adequate amount of time with the patient to be able to address behaviors, activities and symptoms. The Investigator (or designee) should address this relationship in their initial assessment of the patient (or during the Screening period).

2.2 Patient Exclusion Criteria

[459] Patients are not enrolled in the study if they meet any of the following criteria:

1. Patients with current major depressive disorder (MDD) and/or a CDSS score ≥ 6 at the Screening Visit.
2. Patients with a diagnosis of schizoaffective disorder or bipolar disorder.
3. Patients with a history of clozapine use within 3 months (90 days) prior to Visit 1. Clozapine is not allowed during the study.

4. Patients with pseudo-parkinsonism secondary to their ongoing antipsychotic medication based on Investigator judgment.
5. Patients who score a >3 on the sum of the first eight items of the Simpson-Angus Scale (SAS) during Screening.
6. Patients treated with any typical antipsychotic (e.g. haloperidol, thorazine, etc.) within 3 months (90 days) prior to Visit 1 or during the study duration.
7. Patients using anticholinergic medications within 1 month (30 days) prior to Visit 1 for treatment of AEs associated with antipsychotic medications.
8. Patients on levodopa.
9. Patients with undetectable levels of SGA at Screening. Patients with subtherapeutic levels of SGA at Screening are reviewed by the Medical Monitor for eligibility.
10. Patients on any benzodiazepine other than lorazepam as described in Inclusion Criteria number 10. Benzodiazepines other than lorazepam are not allowed in the study.
11. Patients with any of the following cardiovascular history or findings at Screening or Visit 1:
    a. History or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation or torsades de pointes.
    b. QTc using the Fridericia's formula (QTcF) at Screening > 450 msec for males and > 470 msec for females based on central review at the Screening Visit, unless due to ventricular pacing.
    c. Any family history of congenital QT interval prolongation syndrome.
    d. History or presence of clinically significant syncope, orthostatic hypotension or postural tachycardia.
12. Patients with current clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal

disorders, such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, or chronic hepatitis B or C. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the patient to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation.

13. Patients with known hypersensitivity to DM, d6-DM, Q, opiate drugs (codeine, etc.), or any other ingredient of the study medication.
14. Patients who have received DM co-administered with Q within 3 months (90 days) prior to Visit 1.
15. Patients who have ever received d6-DM co-administered with Q or were enrolled in the study from Example 1.
16. Patients with myasthenia gravis (a contraindication for Q).
17. Patients treated with monoamine oxidase inhibitors (MAOIs) within 2 weeks prior to Visit 1. MAOIs are prohibited throughout the study until 2 weeks post study drug discontinuation.
18. Patients who have been taking prohibited concomitant medications within 2 weeks or 5 half-lives, whichever is longer, prior to Visit 1.
19. Patients who use recreational or medicinal marijuana as evidenced by a positive urine drug screen for cannabis at Screening.
20. Patients who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without specific plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months,

OR

Patients who answer “Yes” on the C-SSRS Suicidal Ideation Item 5 (active suicidal ideation with specific plan and intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months **OR**

Patients who answer “Yes” on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR**

Patients who, in the opinion of the Investigator, present a serious risk of suicide or homicide.

21. Patients with clinically significant laboratory abnormalities (hematology, chemistry, and urinalysis) or with safety values of potential clinical concern or with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN) at the Screening Visit.
22. Unwilling or unable, in the opinion of the Investigator, to comply with study instructions.
23. Patients with a history of substance and/or alcohol abuse within 6 months prior to Screening. All tobacco and nicotine products are allowed.
24. Patients who test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.
25. Patients who have received electroconvulsive treatment (ECT), repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation (DBS) in the past year prior to Screening.
26. Women who are lactating, pregnant, or plan to become pregnant.
27. Patients who are found to be a “Virtually Certain” match in the Clinical Trial Subject Database (CTSdatabase) with a patient who has participated in another interventional drug or device study within 30 days prior to Visit 1.

2.3 Optional Patient Inclusion and Exclusion Criteria

[460] In inclusion criterion 1 above, the 6 month period with no hospitalizations can be reduced to a 4 month period.

[461] Inclusion criterion 6(a) above can be replaced with the following inclusion criterion: patients must have a score of ≤ 4 on PANSS items P1: delusions; P3: hallucinations; and P7: hostility.

[462] The following additional inclusion criterion can be applied: patients must have a PANSS Marder negative factors score of ≥ 20 at Screening and Visit 1 AND < 4 points absolute difference between the 2 visits. PANSS Marder negative factors: N1: blunted affect; N2: emotional withdrawal; N3: poor rapport; N4: passive/apathetic social withdrawal; N6: lack of spontaneity/flow of conversation; G7: motor retardation; G16: active social avoidance.

[463] Inclusion criteria 9 and 10 above can be replaced with the following inclusion criterion: concomitant use of hypnotics at bedtime (e.g., eszopiclone, solpidem, zaleplon, trazodone [up to 100 mg/day]) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 1 month (30 days) prior to baseline and remains stable throughout the study. Patients on lorazepam for anxiety, restlessness, or agitation prior to study entry should remain on the same treatment regimen for the duration of the study. All other benzodiazepines are disallowed, except for lorazepam use for short term or prn treatment of insomnia and behavioral disturbances. The duration of dosing should not exceed 3 days in a 7-day period.

[464] Exclusion criterion 12 above can be replaced with the following exclusion criterion: patients with concurrent clinically significant or unstable systemic diseases that could confound the interpretation of safety results of the study (e.g., malignancy [except skin basal-cell carcinoma or untreated prostate cancer], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease), cognitive and

other neurodegenerative disorders. Some cases might be evaluated individually with the Investigator and medical monitor.

[465] The following additional exclusion criterion can be applied: patients who are currently participating in, or who had participated in other interventional (drug or device) clinical study within 30 days prior to baseline.

2.4 Patient Informant

[466] It is recognized that due to their illness, patients with negative symptoms often have difficulty engaging in relationships with others. However, for the accuracy of data, it is critical that an informant be familiar enough with the patient in order to be able to report on their behaviors, activities and symptoms, as well as any changes in these. The informant should spend a sufficient amount of time with the patient each week to be able to accurately report on these items. While there are no specific requirements, Investigators are asked to document the relationship between the informant and the patient (i.e., family member, social worker, or case manager) and to specify the length of the relationship. This documentation is reviewed by the Medical Monitor and the informant relationship is taken into account in the eligibility process for the study.

2.5 Patient Withdrawal Criteria

[467] Patients and caregivers are advised verbally and in the written ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. The Investigator or Sponsor may discontinue a patient from the study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, decline in patient's comprehension or cognitive function that affects their ability to continue in the study, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient/caregiver. Regardless of the circumstance, every effort should be made to document patient outcome. The Investigator should inquire about the reason for

withdrawal, request the patient/caregiver return all unused study drug, and follow-up with the patient/caregiver regarding any unresolved adverse events.

[468] In addition, patients who present with a QTc interval (QTcF) > 500 msec (unless due to ventricular pacing) or a QTcF interval change from the pre-dose Baseline ECG of > 60 msec at any time after randomization, are withdrawn from the study. The QTcF values are assessed for clinical significance and recorded.

3 TREATMENT OF PATIENTS

3.1 Description of Study Drug

[469] d6-DM/Q is provided as an immediate release, blue, opaque, printed hard gelatin capsule (size 3) containing the active ingredient d6-DM and Q. The inactive ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate. Each capsule of study drug contains one of the following:

- **d6-DM/Q-28/4.9:** 28 mg of d6-DM and 4.9 mg of Q
- **d6-DM/Q-42.63/4.9:** 42.63 mg of d6-DM and 4.9 mg of Q
- **Matching Placebo:** identical in appearance to d6-DM/Q capsules; containing inactive ingredients only

[470] Drug supplies are provided to the study sites in blinded (double-blind), individual, prelabeled blister cards.

[471] Study drug is prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Council on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

3.2 Administration of Study Drug

[472] The administration of study drug is as follows.

Double-Blind, Randomized, Treatment Period:

[473] Patients are randomized in a 1:1 ratio, stratified by placebo-responder status and center, to receive either d6-DM/Q or matching placebo capsules administered orally.

[474] Patients randomized to d6-DM/Q have the following fixed-titration schedule:

d6-DM/Q-28/4.9 qam for the first 3 days, d6-DM/Q-28/4.9 BID for the following 4 days, and then d6-DM/Q-42.63/4.9 BID beginning on the eighth day through the remaining 11 weeks.

[475] Administration of study drug during the double-blind treatment period is as follows:

d6-DM/Q Group:

- **Day 1-Day 3:** d6-DM/Q-28/4.9 capsule every morning; a dose of matching placebo every evening
- **Day 4-Day 7:** d6-DM/Q-28/4.9 capsule, BID
- **Day 8-Day 85:** d6-DM/Q-42.63/4.9 capsule, BID

Placebo Group:

- **Day 22-Day 106:** Matching d6-DM/Q placebo capsule, BID

[476] Packaging of the study drug is described in Section 4.2.

3.3 Concomitant Medications

[477] Patients may not take any of the prohibited medications listed in Section 3.3.2 during the study or 2 weeks or 5 half-lives (whichever is longer) prior to the start of dosing on Day 1. At each visit, patients are queried as to whether they had taken any concomitant medications and, if so, the Investigator records the medications taken and the reasons for their use.

[478] d6-DM/Q contains quinidine sulfate (Q), which is a P-glycoprotein inhibitor. Concomitant administration of Q at higher doses used for cardiac indications, with digoxin, a P-glycoprotein substrate, results in plasma or serum digoxin concentrations that may be as much as doubled; digoxin concentrations should be closely monitored in patients taking digoxin concomitantly and the dose reduced, as necessary.

[479] In cases of prodrugs whose actions are mediated by cytochrome P450 isoenzyme 2D6 (CYP2D6-produced metabolites) for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively, it may not be possible to achieve the desired clinical benefits

in the presence of d6-DM/Q due to Q-mediated inhibition of CYP2D6. An alternative treatment should be considered.

3.3.1 Allowed Concomitant Medications, Use of Benzodiazepines and Hypnotics

[480] Allowed concomitant medications should be evaluated by the Investigator and discussed with the Medical Monitor as necessary to determine if there is any concern for use during the study.

[481] Concomitant use of hypnotics at bedtime (e.g., zolpidem at a dose of 5 to 10 mg or equivalent) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 1 month prior to Visit 1 and remains stable throughout the study. Patients on lorazepam up to a total dose of 2 mg per day for treatment of insomnia, anxiety, restlessness, or agitation should be on a stable dose for 1 month (30 days) prior to Visit 1 and remain on the same treatment regimen for the duration of the study.

[482] All other benzodiazepines are disallowed except for lorazepam use for short term or “as needed” treatment of anxiety, insomnia, and/or behavioral disturbances. The dose should not exceed 2 mg per day for 3 days in a 7-day period and no more than 45 total days of such therapy is allowed during the study.

[483] Benzodiazepines and non-benzodiazepine sleep aids must not be administered within 8 hours prior to any scheduled efficacy or safety scale assessments, including extrapyramidal symptoms (EPS) scales. Investigators are encouraged to delay scale administration until a full 8 hours have elapsed since the last benzodiazepine or sleep aid dose, if at all possible, including at Screening and Baseline assessments. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine or sleep aid documented, including a notation of the drug name, dose, and time of administration on the electronic case report forms (eCRF).

[484] Concomitant use of antidepressants, such as SSRIs (e.g., fluoxetine, sertraline, citalopram) and SNRIs (e.g., venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone), are allowed as long as the dose has been stable for 3 months (90 days) prior to Screening, remains stable throughout the study, and the dose used is within the guidance from the U.S. label for that drug. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day.

3.3.2 Prohibited Medications

[485] Prohibited concomitant medications include medications that could potentially alter plasma levels of Q and/or d6-DM, or medications related to Q. A list of examples of prohibited medications is provided in Table 3 above.

[486] Patients may not take any of the prohibited medications listed in Table 3 during the study or within 2 weeks or 5 half-lives, whichever is longer, of study drug dosing (Day 1). Monoamine oxidase inhibitors (MAOIs) are prohibited throughout the study. Patients taking an MAOI should allow at least 14 days before taking the first dose of study drug and at least 14 days after the last dose of study drug before starting an MAOI.

[487] Use of levodopa is not allowed in the study. Recreational and/or medicinal marijuana use is not allowed during the study.

3.4 Treatment Compliance

[488] Each patient is instructed to return any unused study drug and empty drug blister cards during each study visit during treatment. Site staff conduct a capsule count and record the compliance on the Drug Accountability log as well as enter the information in the eCRF.

[489] Study drug compliance is assessed after a capsule count and patient interview; compliance is defined as ingesting at least 80% of the scheduled dose of study drug (compliance range: 80 to 120%).

[490] An additional exploratory tool (AiCure) is used to help ensure patient compliance; however, the primary method of measuring compliance is a capsule count conducted by the site staff.

3.5 Randomization and Blinding

[491] Upon entry into the study (after the ICF is signed at Screening), each patient is assigned a 9-digit patient number. The first 6 digits consist of the country code - center number; the last 3 digits are assigned sequentially by the interactive web response system (IWRS) starting with 001. This 9-digit number is the main identifier for each patient.

[492] Patients are randomized to receive either d6-DM/Q capsules or matching placebo capsules (double-blind manner) in a 1:1 ratio. The randomization scheme is devised by Sponsor or designee and managed within an IWRS. Each patient has a 50% chance of receiving d6-DM/Q.

4 STUDY DRUG MATERIALS AND MANAGEMENT

4.1 Study Drug

[493] d6-DM/Q is provided as an immediate release, blue, opaque, printed hard gelatin capsule (size 3) containing the active ingredients d6-DM (28 mg or 42.63 mg) and Q (4.9 mg). The composition of the d6-DM/Q and matching placebo capsules is described in Section 3.1.

4.2 Study Drug Packaging and Labeling

Packaging

[494] Each study drug kit is an individually labeled blister card pre-packaged for 3 weeks of treatment plus an additional week of supply. Inside the blister card there are four panels, each consisting of 2 rows of blister strips, one row for the morning dose (as indicated AM) and one row for the evening dose (as indicated PM) for 1 week of supply.

4.3 Study Drug Storage

[495] Clinical supplies must be stored in compliance with label requirements in a secure place and kept at room temperature; 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

4.4 Study Drug Administration

[496] Each patient receives study drug according to their medicine identification number (randomization number) assigned by the IWRS randomization scheme. Designated staff at each study site dispense the study drug blister cards. Study drug is self-administered, except on the applicable study visit days when patients take their morning dose of study drug in the clinic in the presence of study site personnel, regardless of the time of day.

[497] Each patient is instructed to ingest 1 capsule of study drug orally with water BID, approximately every 12 (± 4) hours (morning and evening) (2 capsules daily). For each patient, the time each dose of study drug is ingested should remain consistent throughout double-blind treatment. Study drug doses are recorded in the AiCure medication adherence monitoring platform.

[498] All study drug is supplied and administered in a double-blind manner.

5 ASSESSMENT OF EFFICACY

[499] Efficacy assessments include the PANSS Marder negative factors score as the primary assessment and NSA Global Negative Symptom Score, Patient Global Impression – Severity (PGI-S), and Patient Global Impression – Change (PGI-C) as secondary endpoints. Other outcome measures include the PANSS positive subscale and the Calgary Depression Scale for Schizophrenia (CDSS). These scales are described in the following sections.

5.1 Positive and Negative Syndrome Scale (PANSS) Marder Negative Factors Score

[500] The PANSS (Appendix 2) is a validated clinical scale that has been extensively used as a reliable and valid measure of the negative and positive symptoms of schizophrenia (Daniel, Schizophr Res. 2013;150(2-3):343-5). The scale comprises 30 disparate items that collectively assess the positive and negative syndromes in schizophrenia, including their relationship to one another and to global psychopathology. Each is scored for “1” (absent) to “7” (extremely severe).

[501] The established psychometric properties of the PANSS allow for the assessment of positive, negative, and general psychopathology as part of a categorical or dimensional perspective of schizophrenia (Kay et al. Schizophr Bull. 1987;13(2):261-276; Kumari et al. J Addict Res Ther. 2017;8(3)). Thus, different combinations of items are generally analyzed as factor structures to score specific aspects of the negative syndrome of schizophrenia.

[502] The concept of a five-factor solution for the PANSS has been successfully used in clinical trials, and identifies five factors or dimensions of schizophrenia: 1) negative symptoms; 2) positive symptoms; 3) disorganized thought; 4) uncontrolled hostility/excitement; and 5) anxiety/depression (Lindenmayer et al. Psychopathology. 1995;28(1):22-31; Marder et al. J Clin Psychiatry. 1997;58(12):538-546). Marder investigated the five-factor solution in two controlled trials and found that risperidone produced significantly greater improvements than haloperidol on all five dimensions, with a particularly potent effect of risperidone vs. haloperidol on Factor 1 (negative symptoms). Factor 1, i.e., the PANSS Marder negative factors has several aspects of improved content validity versus the negative subscale, meeting more consistently with the domains identified in the 2006 NIMH-MATRICS Consensus Statement (Kirkpatrick et al. Schizophr Bull. 2006;32(2):214-219).

PANNS Marder Negative Factors Score

[503] The PANSS Marder negative factors score is a reliable and validated measure of the negative symptoms of schizophrenia, and is comprised of the following 7 items of the 30-item PANSS:

Marder Negative Factors:

1. N1: Blunted affect
2. N2: Emotional withdrawal
3. N3: Poor rapport
4. N4: Passive/apathetic social withdrawal
5. N6: Lack of spontaneity and flow of conversation
6. G7: Motor retardation
7. G16: Active social avoidance

[504] Each of the PANSS Marder negative factors correlates with one of the five main domains of negative symptoms (Kirkpatrick et al. Schizophr Bull. 2006;32(2):214-219). PANSS item N1: blunted affect, correlates with Blunted affect; N6: lack of spontaneity and conversation flow, correlates with Alogia; and N4: passive/apathetic social withdrawal; G16: active social avoidance; and N3: poor rapport, are factors that correlate with Asociality. PANSS item N2: emotional withdrawal, correlates with Anhedonia; and G7: motor retardation, correlates with both Anhedonia and Avolition (Daniel, Schizophr Res. 2013;150(2-3):343-5).

[505] Two of the items in the PANSS Marder negative factors score (N4 and G16) are based solely on information obtained from an informant. Patients need to identify a reliable informant (e.g., case manager, social worker, family member) who spends sufficient time with them to be able to provide information to PANSS raters.

[506] The PANSS positive subscale (P1 - P7) is also assessed for changes in psychotic symptoms, and includes P1: delusions; P2: conceptual disorganization; P3:

hallucinatory behavior; P4: excitement; P5: grandiosity; P6: suspicious/persecution; and P7: hostility.

[507] The PANSS evaluation is performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), and Visit 5/ET Visit (Day 85).

5.2 Negative Symptom Assessment-16 (NSA-16) Global Negative Symptom Score

[508] The NSA-16 (Appendix 3A or 3B) is considered a valid and reliable measure of the presence, severity, and range of negative symptoms associated with schizophrenia; it has high inter-rater and test-retest- reliability across languages and cultures (Daniel, Schizophr Res. 2013;150(2-3):343-345; Axelrod et al. J Psychiatr Res. 1993;27(3):253-258). The NSA-16 uses a 5-factor model to describe negative symptoms: 1) Communication, 2) Emotion/affect, 3) Social involvement, 4) Motivation, and 5) Retardation. These factors, assessed through a structured interview, are comprehensive and well-defined to help standardize assessment. As a truncated version of the 25- item NSA, the NSA-16 still captures the multidimensionality of negative symptoms but can be completed in approximately 15 to 20 minutes. The “normal” reference population against which the subject is to be compared is a healthy young person in their twenties.

[509] NSA Global negative symptom score rates the overall severity of negative symptoms when defined as the absence or reduction of behaviors normally present in a healthy young person. Ratings should not depend on any specific item or items from the NSA or any other similar instrument. Instead, it should measure the rater’s gestalt of the interview and is assessed following completion of the NSA-16 interview (Alphs et al. Int J Methods Psychiatr Res. 2011;20(2):e31-37).

[510] The NSA-16 and NSA Global Negative Symptom Score evaluations are performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), and Visit 5/ET Visit (Day 85).

5.3 Patient Global Impression – Severity (PGI-S)

[511] The PGI-S (Appendix 4) is a 7-point (1–7), patient-rated scale used to assess the severity of the patient's schizophrenia as follows: 1) normal, not at all ill; 2) borderline ill; 3) mildly ill; 4) moderately ill; 5) markedly ill; 6) severely ill; 7) extremely ill.

[512] The PGI-S evaluation is performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), and Visit 5/ET (Day 85), and is focused on the negative symptoms of schizophrenia.

5.4 Patient Global Impression – Change (PGI-C)

[513] The PGI-C (Appendix 5A or 5B) is a 7-point (1–7), patient-rated scale used to assess treatment response with respect to the patient's schizophrenia as follows: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

[514] The PGI-C evaluation is performed at Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), and Visit 5/ET Visit (Day 856), and is focused on the negative symptoms of schizophrenia.

5.5 Calgary Depression Scale for Schizophrenia (CDSS)

[515] The CDSS (Appendix 6) is a 9-item scale derived from the Hamilton Depression Scale (Ham-D) that is designed to assess depression specifically in patients with schizophrenia (Addington et al. Schizophr Res. 1996;19(2-3):205-212). Unlike the Ham-D, the CDSS does not contain depressive symptoms that overlap with negative symptoms of schizophrenia, such as anhedonia and social withdrawal. The CDSS has shown excellent psychometric properties. Each item on the scale is scored as 0, Absent; 1, Mild; 2, Moderate; or 3, Severe. The CDSS score is obtained by adding each of the item scores. A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

[516] The CDSS evaluation is performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 3 (Day 43), and Visit 5/ET Visit (Day 85).

6 ASSESSMENT OF PHARMACOKINETICS

[517] Plasma concentrations of d6-DM, its metabolites (d3-DX and d3-3-MM), and Q are measured from samples collected post-dose on Day 1 (Week 0), pre- and post-dose on Day 43 (Week 6), and pre-dose on Day 85 (Week 12). These samples are collected per instructions provided by the sponsor.

[518] The date and time of each sample collection and the date and time of the last dose of study drug prior to the sample collection are recorded on the eCRF.

[519] Blood samples are separated by centrifugation and then frozen at -20°C until assayed at the analytical unit. Procedures for the collection, storage, and shipping of samples for analysis are provided to the study sites by the sponsor at the time of study initiation.

[520] Plasma concentrations of d6-DM, d3-DX, d3-3-MM, and Q are summarized descriptively and may be used in future population PK analyses.

7 ASSESSMENT OF SAFETY

7.1 Adverse Events

[521] An AE is any untoward medical occurrence or unintended change (including physical, psychiatric [e.g., depression], or behavioral) from the time the ICF is signed, including intercurrent illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

[522] Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of “runny nose”).

[523] An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome, even if toxic effects were not observed.

[524] AEs are graded on a 3-point scale and reported in detail as indicated on the eCRF:

Mild: easily tolerated, causing minimal discomfort and not interfering with normal everyday activities

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

[525] The relationship of each AE to study medication should be determined by the Investigator using the following explanations:

Not related: the event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Unlikely related: the event is most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; and does not follow a known response pattern to the study medication

Possibly related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Related: the event follows a reasonable temporal sequence from the time of drug administration; and follows a known response pattern to the study medication; and cannot be reasonably explained by other factors such as the subject's clinical

state, therapeutic interventions, or concomitant medications administered to the subject

7.2 Serious Adverse Events

[526] A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience (one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
- Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
- Inpatient hospitalization or prolongation of hospitalization
- Congenital anomaly/birth defect

[527] Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the listed outcomes.

[528] Pregnancy is not considered to be an AE or an SAE, unless a complication occurs that meets the requirements for an AE or SAE, but must be reported on a pregnancy report form. Females who are pregnant or likely to become pregnant are excluded from this study. In the event a patient becomes pregnant during the study, study medication must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. Any pregnant patient must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery,

spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., mother and fetus) must be followed-up through delivery with regard to outcome.

[529] A pregnancy report form must also be completed in the event that a female partner of a male patient becomes pregnant within 30 days after the last dose of study drug or study completion, whichever is greater.

[530] The term “severe” is a measure of intensity; thus, a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe, but may not be clinically serious.

7.3 Reporting Adverse Events

[531] Patients are queried regarding AEs at all visits post Screening. The Investigator assesses and records all reported AEs. Any AE newly reported after a patient has received the last dose of study drug and up until the End-of-Study visit is followed until resolution (patient’s health has returned to his/her Baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

[532] A death occurring during the study, or which comes to the attention of the Investigator within 30 days after stopping study drug, whether considered treatment-related or not, must be reported to the Sponsor.

[533] For all SAEs, including an abnormal laboratory test value assessed as clinically significant, the Investigator should consult with the sponsor’s Medical Monitor or designated representative as needed and report any SAE by fax/email form as detailed below no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to study drug, action taken regarding test drug, treatment required, and outcome to date.

7.4 Physical and Neurological Examinations

[534] Physical and neurological examinations are performed at Screening (Day -28 to Day -1), and at the final clinic visit (Visit 5 [Week 12]). The physical examination includes assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination includes assessments of mental status, cranial nerves, motor system, reflexes, coordination, gait and station, and sensory system. The physical and neurological examinations should be performed by the same person each time, whenever possible.

[535] Physical and neurological examination abnormalities determined by the Investigator to be clinically significant at Screening should be recorded as medical history. Any clinically significant changes in physical and neurological examination findings from the Screening examination should be recorded as AEs.

7.5 Vital Sign Measurements

[536] Blood pressure (BP) and heart rate (HR) measurements are performed (in duplicate) at all clinic visits. Orthostatic BP and HR is measured at the Screening visit only, and is described below; all other BP and HR measurements are taken while the patient is sitting/semi-recumbent.

[537] Orthostatic BP and HR at Screening Visit: supine BP and HR is measured after the patient has rested for at least 5 minutes in the supine position; BP and HR measurements are taken twice in the same position and recorded. Following the measurement of supine BP and HR, the patient stands still for up to 3 minutes and a single measurement of standing BP and HR is recorded (within 3 minutes of standing).

[538] Respiratory rate (breaths/minute) and body temperature (°F) are assessed at Screening, Day 1 (prior to dosing), and at the final clinic visit (Visit 5 [Week 12]).

[539] Weight and height are recorded at Screening, Day 1 (Visit 1), and Day 85 (Visit 5).

7.6 Electrocardiogram (ECG)

[540] A resting 12-lead ECG is performed at Screening and each clinic visit (Visits 1, 2, 3, 4, 5, and 6); the Screening ECG is performed in triplicate (1 minute apart). ECGs are performed pre-dose and 1-2 hours (±15 minutes) post-dose at Visit 1 and Visit 2; ECGs at all other visits are performed pre-dose only (Visits 3, 4, and 5).

[541] The ECG equipment is provided to the study center by the central reader. The ECG assessment is recorded at the study center and includes general findings, including heart rate (beats/minute), QRS complex and PR and QTc intervals. Results are provided by the central reader to the Investigators within 72 hours. Any ECG abnormality present at Screening is recorded as medical history. Any changes from the ECG status at Screening that are deemed to be clinically significant by the Investigator should be captured as AEs.

[542] Any clinically significant abnormal ECG should be discussed with the Medical Monitor and, if necessary, the ECG should be repeated within approximately 1 week. In addition, any patient who presents with a QTcF interval > 500 msec (unless due to ventricular pacing) or a QTcF interval increase from the pre-dose Baseline ECG (Day 22/Week 3) > 60 msec at any time after randomization, is withdrawn from the study.

7.7 Safety Scales

[543] The AIMS, BAS, SAS, and C-SSRS scales are assessed for purposes of safety, and are briefly described in the following sections.

7.7.1 Abnormal Involuntary Movement Scale (AIMS)

[544] The AIMS (Appendix 7A or 7B) is composed of 12 items and used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness are rated using a 5-point scale (0=none to 4=severe). Two items related to dental status are scored using “yes” or “no” responses.

[545] The AIMS evaluation is performed at Visit 1 (Day 1), Visit 3 (Day 43), and Visit 5/ET Visit (Day 85).

7.7.2 Barnes Akathisia Scale (BAS)

[546] The BAS (Appendix 8) consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity.

[547] The BAS is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0-3 and are summed yielding a total score ranging from 0 to 9. The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0-4.

[548] The BAS evaluation is performed at Visit 1 (Day 1), Visit 3 (Day 43), and Visit 5/ET Visit (Day 85).

7.7.3 Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

[549] The SAS (Appendix 9A or 9B) is composed of 10 items and is used to assess pseudoparkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Signs assessed include gait, arm-dropping, shoulder-shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, glabella tap, tremor, and salivation.

[550] The SAS evaluation is performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 3 (Day 43), and Visit 5/ET Visit (Day 85).

7.7.4 Columbia Suicide Severity Rating Scale (C-SSRS)

[551] The C-SSRS (Appendix 10) is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

[552] Suicidality is monitored during the study using the “Baseline/Screening” and “Since Last Visit” versions of the C-SSRS scale. The “Baseline/Screening” version, which assesses the lifetime experience of the patient with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the study, is completed for all patients at Screening to determine eligibility. Any patient with active suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgement of the Investigator presents a serious risk of suicide should be excluded from the study (see Section 2.2, Exclusion Criteria). The “Since Last Visit” C-SSRS form is also completed at visits after Screening.

[553] The C-SSRS evaluation is performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), and Visit 5/ET Visit (Day 85).

8 SCHEDULE OF EVALUATIONS AND PROCEDURES

[554] A schedule of evaluations and procedures is provided in Table 16.

Description of Study Procedures

[555] At each study visit, a member of the study staff is required to enter information into the IWRS database regarding patient data and pre-defined study assessment results. Further instructions are provided in the IRT Site Manual.

[556] The pre- and post-dose procedures listed below are generally listed in the order in which they should be performed, within a reasonable amount of flexibility. The NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C assessments are all done pre-dose and should be completed as early as possible during the study procedures for the applicable visits. Any pre-dose ECGs and pre-dose blood draws should only be conducted after the above scales have been completed at each visit. The CTSdatabase check for dual enrollment at Screening should be performed as one of the first post-consent procedures, so that sites are aware of potential dual enrollment before more complex tasks are performed.

Screening Visit (Days -28 to -1)

[557] The following procedures are performed at Screening within 28 days prior to Day 1.

1. The Investigator or delegated site staff provide the patients with informed consent documents and explain the rationale for the study, providing ample time for patients to ask questions. Patients must provide written informed consent before any study-related procedures are performed.
2. Authorization form completed and patient information is entered into the CTSdatabase.
3. A qualified and certified rater administers the PANSS.
4. Psychiatric history is recorded and M.I.N.I. exam is conducted.
5. An adequately trained and certified rater administers the CDSS to assess for symptoms of depression.
6. The Investigator (or qualified designee) who is adequately trained completes the “Baseline/Screening” C-SSRS form to exclude patients with a significant risk of suicidal behavior.
7. Medical history, including patient demographics, and any concomitant medications use (including over-the-counter [OTC] medications, vitamins, and supplements) are reviewed and recorded.
8. Inclusion and exclusion criteria (eligibility form) are reviewed.
9. Detailed information on the patient’s relationship with their informant is collected and documented.
10. Vital signs are measured in duplicate and recorded (orthostatic BP and HR at Screening only [See Section 7.5], respiratory rate, and body temperature); weight and height are also recorded.
11. Physical and neurological examinations are conducted.

12. An adequately trained and experienced clinician administers the SAS to assess for EPS.
13. Resting 12-lead ECGs are performed in triplicate (1 minute apart).
14. Blood and urine specimens are collected for clinical laboratory assessments (chemistry, including fasting glucose, lipids, TSH, and HbA1c; hematology; and urinalysis).
15. Blood specimen is collected for assessment of plasma antipsychotic levels.
16. A serum pregnancy test is performed on all females of childbearing potential.
17. A blood specimen is collected for hepatitis B and C (HBsAg and HCAb) and HIV antibody screening.
18. Urine specimen is collected for drug screening.
19. Review assessments to verify that patients are eligible to continue study participation.

[558] Following Screening procedures for assessment of inclusion and exclusion criteria, a protocol eligibility form is submitted to the Medical Monitor for approval. Patients deemed eligible by the Investigator and the Medical Monitor return for Visit 1 (Day 1). Patients having ECG findings or laboratory test results outside of the reference normal range that the Investigator considers as clinically significant, and that may place the patient at a higher risk for study participation, are discontinued (not randomized).

Visit 1 (Baseline, Randomization; Day 1/Week 0 ±3-day window)

[559] Patients are randomized (1:1 ratio) to receive either d6-DM/Q or matching placebo capsules for 12 weeks during the double-blind treatment period. The first dose of study drug for the double-blind treatment period is administered in the clinic on Day 1.

[560] Randomization occurs after all Visit 2 pre-dose procedures have been completed; this visit should occur within a 3-day window. The following procedures are performed at Visit 1 (Day 1 ±3-day window):

Pre-dose:

1. A qualified and certified rater administers the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. An adequately trained and certified rater administers the CDSS to assess for symptoms of depression.
3. The Investigator (or qualified designee) who is adequately trained completes the "Since Last Visit" C-SSRS form.
4. Vital signs are measured and recorded (sitting/semi-recumbent BP and HR [in duplicate]).
5. Resting 12-lead ECG is performed (pre-dose, after the above scales have been administered).
6. Patient is queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
7. Blood and/or urine specimens are collected for safety laboratory assessments (chemistry [including fasting glucose and lipids], hematology, urinalysis)—all blood draws should be done after the above scales have been administered.
8. Blood specimen is collected for assessment of plasma antipsychotic levels.
9. Urine pregnancy test is performed on all females of childbearing potential.
10. An adequately trained and experienced clinician administers the AIMS, SAS, and BAS to assess for EPS.
11. A review of all unused study drug is performed by site staff. Sufficient study drug is dispensed for BID dosing through the following visit.

[561] Patients are randomized once it is determined that they satisfy all of the inclusion and none of the exclusion criteria (on the basis of the Screening and Visit 1 assessments described above), and are assigned a study drug kit number via IWRS.

Study Drug Dosing:

[562] The first dose of study medication is administered from the AM strip of the study drug blister card at the clinic regardless of the time of day.

Post-dose:

1. Blood specimen is collected for PK assessment of plasma d6-DM, Q, and d6-DM metabolites (between 1 and 3 hours post-dose).
2. Resting 12-lead ECG is performed between 1 and 2 hours post-dose (±15 minutes).

Patient Instructions

[563] Patients are instructed to take the study drug BID (1 capsule from the blister pack labeled AM in the morning and 1 capsule from the blister pack labeled PM in the evening; approximately every 12 hours) until the next visit. Patients are also instructed to bring any unused study drug at each study visit.

[564] Patients are reminded to use AiCure to monitor study drug compliance outside of the clinic.

[565] The Investigator and/or study coordinator gives patients detailed instructions regarding study procedures. They are also instructed to consult with the study site prior to taking any non-study medications. These requirements are reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

[566] The Investigator queries patients at the end of each visit to be certain they understand what is required of them.

12-Week, Double-Blind Treatment Period

8.1.3.1 Safety Telephone Contact (Day 8/Week 1 ±3-day window)

[567] Patients receive a telephone call to assess AEs and query regarding concomitant medications at Week 1 (Day 8 ±3 days). Patients are also asked if they have taken their study drug as directed.

Visit 2 (Day 22/Week 3 ±6-day window)

[568] The following procedures are performed on the morning of Day 22 (±6-day window):

Pre-Dose:

1. A qualified and certified rater administers the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Resting 12-lead ECG is performed (pre-dose, after the above scales have been administered).

Study Drug Dosing:

[569] Study drug is administered from the AM strip of the newly dispensed blister pack at the clinic after the completion of the above procedures.

Post-dose:

1. Patient is queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
2. The Investigator (or qualified designee) who is adequately trained completes the "Since Last Visit" C-SSRS form.
3. Vital signs are measured in duplicate and recorded (sitting/semi-recumbent BP and HR).
4. Urine pregnancy test is performed on all females of childbearing potential.
5. A review of all unused study drug is performed by site staff. Sufficient study drug is dispensed for BID dosing through the following visit.
6. Resting 12-lead ECG is performed 1 to 2 hours post-dose (±15 minutes).

Patient Instructions

[570] Patients are instructed to take the study drug BID (1 capsule from the blister pack labeled AM in the morning and 1 capsule from the blister pack labeled PM in the

evening; approximately every 12 hours) until the next visit. Patients are also instructed to bring any unused study drug at each study visit.

[571] Patients are reminded to use AiCure to monitor study drug compliance outside of the clinic.

[572] The Investigator and/or study coordinator gives patients detailed instructions regarding study procedures. They are also instructed to consult with the study site prior to taking any non-study medications. These requirements are reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

[573] The Investigator queries patients at the end of each visit to be certain they understand what is required of them.

Safety Telephone Contact (Day 29/Week 4 ±3-day window)

[574] Patients receive a telephone call to assess AEs and query regarding concomitant medications at Week 4 (Day 29 ±3 days). Patients are also asked if they have taken their study drug as directed.

Visit 3 (Day 43/Week 6 ±6-day window)

[575] The following procedures are performed on the morning of Day 64 (±6-day window):

Pre-dose:

1. A qualified and certified rater administers the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Resting 12-lead ECG is performed (pre-dose, after the above scales have been administered).
3. Blood specimen is collected for PK assessment of plasma d6-DM, Q, and metabolites (pre-dose, after the above scales have been administered).

Study Drug Dosing:

[576] Study drug is administered from the AM strip of the newly dispensed blister pack at the clinic, regardless of the time of day.

Post-dose:

1. Patient is queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
2. An adequately trained and experienced clinician administers the AIMS, SAS, and BAS to assess for EPS.
3. An adequately trained and certified rater administers the CDSS to assess for symptoms of depression.
4. The Investigator (or qualified designee) who is adequately trained completes the "Since Last Visit" C-SSRS form.
5. Urine pregnancy test is performed on all females of childbearing potential.
6. Blood and/or urine specimens are collected for safety laboratory assessments (chemistry [including fasting glucose and lipids], hematology, urinalysis).
7. Blood specimen is collected for assessment of plasma antipsychotic levels.
8. Blood specimen is collected for PK assessment of plasma d6-DM, Q, and metabolites (between 1 and 3 hours post-dose).
9. A review of all unused study drug is performed by site staff. Sufficient study drug is dispensed for BID dosing through the following visit.

Patient Instructions

[577] Patients are instructed to take the study drug BID (1 capsule from the blister pack labeled AM in the morning and 1 capsule from the blister pack labeled PM in the evening; approximately every 12 hours) until the next visit. Patients are also instructed to bring any unused study drug at each study visit.

[578] Patients are reminded to use AiCure to monitor study drug compliance outside of the clinic.

[579] The Investigator and/or study coordinator gives patients detailed instructions regarding study procedures. They are also instructed to consult with the study site prior to taking any non-study medications. These requirements are reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

[580] The Investigator queries patients at the end of each visit to be certain they understand what is required of them.

Safety Telephone Contact (Day 50/Week 7 ±3-day window)

[581] Patients receive a telephone call to assess AEs and query regarding concomitant medications at Week 7 (Day 50 ±3 days). Patients are also asked if they are taking their study drug as directed.

Visit 4 (Day 64/Week 9 ±6-day window)

[582] The following procedures are performed on the morning of Day 85 (±6-day window).

Pre-dose:

1. A qualified and certified rater administers the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Resting 12-lead ECG is performed (pre-dose, after the above scales have been administered).

Study Drug Dosing:

[583] Study drug is administered from the AM strip of the newly dispensed blister pack at the clinic, regardless of the time of day.

Post-dose:

1. Vital signs are measured in duplicate and recorded (sitting/semi-recumbent BP and HR).
2. Patient is queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).

3. The Investigator (or qualified designee) who is adequately trained completes the "Since Last Visit" C-SSRS form.
4. Urine pregnancy test is performed on all females of childbearing potential.
5. A review of all unused study drug is performed by site staff. Sufficient study drug is dispensed for BID dosing through the following visit.

Patient Instructions

[584] Patients are instructed to take the study drug BID (1 capsule from the blister pack labeled AM in the morning and 1 capsule from the blister pack labeled PM in the evening; approximately every 12 hours) until the final visit (Visit 6; Day 106). Patients are also instructed to bring any unused study drug at each study visit.

[585] Patients are reminded to use AiCure to monitor study drug compliance outside of the clinic.

[586] The Investigator and/or study coordinator gives patients detailed instructions regarding study procedures. They are also instructed to consult with the study site prior to taking any non-study medications. These requirements are reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

[587] The Investigator queries patients at the end of each visit to be certain they understand what is required of them.

Safety Telephone Contact (Day 71/Week 10 ±3-day window)

[588] Patients receive a telephone call to assess AEs and query regarding concomitant medications at Week 10 (Day 71 ±3 days). Patients are also asked if they have taken their study drug as directed.

Visit 5 (Day 85/Week 12 ±6-day window)/Early-Termination Visit

[589] The following procedures are performed on Day 85 (±6-day window) or for the ET Visit for those patients who withdraw prior to Week 12:

Pre-dose:

- A qualified and certified rater administers the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
- Resting 12-lead ECG is performed (pre-dose, after the above scales have been administered).
- Blood specimen is collected for PK assessment of plasma d6-DM, Q, and metabolites (pre-dose, after the above scales have been administered).

Study Drug Dosing:

[590] Last dose of study drug is administered from the AM strip of the study drug blister card brought in by the patient, regardless of the time of day, for those patients who complete double-blind treatment (not those who prematurely discontinue).

Post-dose:

- Vital signs are measured in duplicate and recorded (sitting/semi-recumbent BP and HR, respiratory rate, and body temperature); weight and height are also recorded.
- Physical and neurological examinations are conducted.
- Patient is queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
- An adequately trained and experienced clinician administers the AIMS, SAS, and BAS to assess for EPS.
- An adequately trained and certified rater administers the CDSS to assess for symptoms of depression.
- The Investigator (or qualified designee) who is adequately trained completes the “Since Last Visit” C-SSRS form.

- Blood and/or urine specimens are collected for safety laboratory assessments (chemistry [including fasting glucose, lipids, and HbA1c], hematology, urinalysis).
- Blood specimen is collected for assessment of plasma antipsychotic levels.
- Urine pregnancy test is performed on all females of childbearing potential.
- Patients return all unused study medication; a review of all unused study drug is performed by site staff.

[591] At the last patient contact, site staff access CTSdatabase, enter the patient Study ID and the nature of the last contact (i.e., completer or ET).

Procedures for Early Termination:

[592] All patients undergo a complete evaluation at Visit 5/ET. In addition, Visit 5/ET evaluations are completed for any patient withdrawn at any time after randomization into the trial; evaluations should be completed within 48 hours of the last dose of study drug, whenever possible. Attempts should be made to complete all evaluations, particularly efficacy assessments, for the Visit 5/ET visit prior to the administration of any new psychotropic medications. However, if the patient receives a new rescue medication for worsening schizophrenia symptoms prior to the V5/ET procedures, no efficacy assessments should be performed.

[593] For patients who discontinue treatment, study drug is not administered in the clinic on that day and, therefore, there is no specific time frame for the 12-lead ECG and the blood/urine specimen collection (clinical laboratory tests or pharmacokinetics).

Safety Follow-up Telephone Contact (Week 16/Day 115 ±3-day window)

[594] Patients are contacted by phone at Week 16 (Day 115 ±3 days) and asked if they have experienced any AEs or changes to their medications since their final visit. Patients who experience AEs may need to return to the clinic for an unscheduled visit for safety assessments.

[595] Any AE previously reported and not yet resolved at the time of this phone contact, is followed-up until resolution (patient's health has returned to his/her Baseline

status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

[596] Any newly reported AE after receiving and up to 30 days after the last dose of study drug is followed up until resolution (patient's health has returned to his/her Baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

9 STATISTICS

[597] An overview of the planned statistical methods for this study are provided below. The full statistical methods are provided in the statistical analysis plan (SAP) prior to the unblinding of the study.

9.1 Analysis Populations

[598] Analysis populations for this study are defined as follows:

[599] **Safety Population:** all patients who are randomized and take at least one dose of study drug. All safety analyses are based on the safety population.

[600] **Modified Intent-to-Treat (mITT):** all patients in the Safety Population with both Baseline and at least one post Baseline PANSS measurement. All efficacy analyses are based on mITT population.

9.2 Demographics and Baseline Characteristics

[601] Demographics and Baseline characteristics are summarized by treatment group using descriptive statistics.

9.3 Efficacy Analysis

9.3.1 Study Endpoints

9.3.1.1 Primary Efficacy Endpoint

[602] The primary efficacy endpoint is the change from Baseline to Visit 5 (Week 12) in the PANSS Marder negative factors score.

9.3.1.2 Secondary Efficacy Endpoints

[603] Secondary efficacy endpoints include change from Baseline to Visit 5 (Week 12) for the following outcomes measures (PGI-C raw score measures change):

- NSA-16 Global Negative Symptom Score
- PGI-S
- PGI-C

9.3.1.3 Other Outcome Measures

[604] Other outcome measures include change from Baseline to Visit 5 (Week 12) for the following measures:

- PANSS positive subscale
- Calgary Depression Scale for Schizophrenia (CDSS)

9.3.2 Primary Efficacy Analysis

[605] The primary efficacy endpoint is the change in PANSS Marder negative factors score from Baseline to Week 12. The primary efficacy endpoint is analyzed using the likelihood-based linear mixed effects model repeated measures (MMRM) on observed data. The model includes fixed effects for treatment, trial center, visit, treatment-by-visit interaction, and Baseline-by-visit interaction. An unstructured covariance model is used. Small trial centers are pooled according to region and practice for the analysis before database unblinding.

[606] The purpose of this study is to assess the expected drug effect in a future population that results from patients initiating d6-DM/Q vs Placebo. The estimand of primary interest is defined as follows:

- Population: mITT
- Variable: change in PANSS Marder negative factors score from Baseline to Week 12.
- Intercurrent event(s): The “treatment policy” strategy is followed, whereby the value for the variable of interest is used regardless of adherence to randomized treatment

and/or initiation of prohibited medications.

- Population-level summary: The between-treatment difference in the mean changes from Baseline to Week 12 in the PANSS Marder negative factors score.

[607] All data collected during the study are used in the statistical analysis. For the primary efficacy analysis, the treatment effect is estimated using the MMRM method described above. Under the missing at random (MAR) assumption, MMRM provides an unbiased estimate of treatment effect for the treatment period. Analyses with missing values imputed by multiple imputation (MI) under missing not at random (MNAR), and other methods are performed as sensitivity analyses.

9.3.3 Secondary Efficacy and Other Outcome Measures Analysis

[608] Secondary efficacy endpoints and Other outcome measures are analyzed in a similar manner as the primary efficacy analysis when appropriate. Further details and analysis methods are described in the SAP.

9.4 Pharmacokinetic Analysis

[609] Plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q are summarized descriptively.

9.5 Safety Analysis

[610] Safety analyses are based on safety population defined as all patients who are randomized and take at least one dose of study drug. It consists of data summaries for biological parameters and AEs. Safety analyses are tabulated by treatment.

9.5.1 Adverse Events

[611] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing 1 or more AEs are summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAEs).

9.5.2 Vital Signs and Electrocardiograms

[612] Summary statistics of absolute values and percentage change from

Baseline (Visit 1; Day 1/Week 0) for BP (diastolic and systolic), heart rate, respiratory rate, weight, and ECG parameters are provided. All values outside a predefined normal range are highlighted in the individual patient data listings.

9.5.3 Clinical Laboratory Measures

[613] Laboratory parameters are summarized via descriptive statistics and via shifts in results with respect to normal ranges between Visit 1 (Week 0) and end-of-treatment as increased, decreased, or no change.

9.5.4 Safety Scales

[614] The C-SSRS, SAS, BAS, and AIMS are summarized via descriptive statistics and via shift tables of the number and percent of patients in each score from Baseline (Visit 1; Day 1/Week 0) to post-Baseline visits and end of treatment.

APPENDIX 1

Table 17
Baseline Second-Generation Antipsychotic (SGA) Use

Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Stage 1 Placebo** **(N=96)**	**Stage 1 d6-DM/Q** **(N=48)**
Number of Patients taking Baseline SGAs	96 (100.0)	48 (100.0)
PSYCHOLEPTICS	96 (100.0)	48 (100.0)
Aripiprazole	16 (16.7)	15 (31.3)
Lithium	1 (1.0)	0 (0.0)
Lurasidone	2 (2.1)	1 (2.1)
Lurasidone Hydrochloride	2 (2.1)	3 (6.3)
Olanzapine	26 (27.1)	12 (25.0)
Paliperidone	3 (3.1)	3 (6.3)
Paliperidone Palmitate	11 (11.5)	2 (4.2)
Quetiapine	2 (2.1)	2 (4.2)
Quetiapine Fumarate	14 (14.6)	7 (14.6)
Risperidone	25 (26.0)	10 (20.8)
Ziprasidone	2 (2.1)	1 (2.1)

Note: Baseline concomitant medications are defined as medications with a start date on or before the first dose date of randomized study medication, and an end date on or after the first dose date (or the medication is ongoing) of randomized study medication. Medications are coded using WHO Drug Dictionary Version September 2015
Treatment allocation based on Stage 1 randomization.

Table 18
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Total Score			
N	80	47	127
Mean (SD)	60.4 (7.71)	61.0 (7.53)	60.6 (7.62)
Median	60.0	60.0	60.0
Min, Max	43, 85	45, 79	43, 85
NSA-16 Factor Domain: Communication			
N	80	47	127
Mean (SD)	12.6 (2.71)	12.5 (2.54)	12.6 (2.64)
Median	13.0	12.0	13.0
Min, Max	6, 21	8, 21	6, 21
NSA-16 Factor Domain: Emotion/Affect			
N	80	47	127
Mean (SD)	12.2 (1.81)	12.6 (2.11)	12.3 (1.93)
Median	12.0	13.0	12.0
Min, Max	8, 17	8, 17	8, 17
NSA-16 Factor Domain: Social Involvement			
N	80	47	127
Mean (SD)	12.2 (2.20)	12.2 (2.02)	12.2 (2.13)
Median	12.0	12.0	12.0
Min, Max	8, 17	9, 16	8, 17

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	**Stage 1 Placebo (N = 80)**	**Stage 1 d6-DM/Q (N = 47)**	**All Patients (N = 127)**
NSA-16 Total Score			
N	80	47	127
Mean (SD)	60.4 (7.71)	61.0 (7.53)	60.6 (7.62)
Median	60.0	60.0	60.0
Min, Max	43, 85	45, 79	43, 85
NSA-16 Factor Domain: Communication			
N	80	47	127
Mean (SD)	12.6 (2.71)	12.5 (2.54)	12.6 (2.64)
Median	13.0	12.0	13.0
Min, Max	6, 21	8, 21	6, 21
NSA-16 Factor Domain: Emotion/Affect			
N	80	47	127
Mean (SD)	12.2 (1.81)	12.6 (2.11)	12.3 (1.93)
Median	12.0	13.0	12.0
Min, Max	8, 17	8, 17	8, 17
NSA-16 Factor Domain: Social Involvement			
N	80	47	127
Mean (SD)	12.2 (2.20)	12.2 (2.02)	12.2 (2.13)
Median	12.0	12.0	12.0
Min, Max	8, 17	9, 16	8, 17

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Factor Domain: Motivation			
N	80	47	127
Mean (SD)	16.7 (2.33)	16.5 (2.37)	16.6 (2.33)
Median	17.0	17.0	17.0
Min, Max	9, 22	11, 22	9, 22
NSA-16 Factor Domain: Retardation			
N	80	47	127
Mean (SD)	6.7 (1.61)	7.2 (1.54)	6.9 (1.59)
Median	7.0	7.0	7.0
Min, Max	2, 10	4, 10	2, 10
NSA-4 Total Score			
N	80	47	127
Mean (SD)	17.3 (2.36)	17.4 (2.44)	17.3 (2.38)
Median	17.0	17.0	17.0
Min, Max	12, 24	13, 22	12, 24

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Item 1: Prolonged Time to Respond			
N	80	47	127
Mean (SD)	3.1 (1.13)	3.1 (1.22)	3.1 (1.15)
Median	3.0	3.0	3.0
Min, Max	1, 6	1, 6	1, 6
NSA-16 Item 2: Restricted Speech Quantity			
N	80	47	127
Mean (SD)	3.8 (1.12)	3.5 (1.10)	3.7 (1.12)
Median	4.0	3.0	4.0
Min, Max	1, 6	1, 5	1, 6
NSA-16 Item 3: Impoverished Speech Content			
N	80	47	127
Mean (SD)	3.7 (0.91)	3.6 (0.80)	3.6 (0.87)
Median	4.0	4.0	4.0
Min, Max	1, 5	1, 5	1, 5
NSA-16 Item 4: Inarticulate Speech			
N	80	47	127
Mean (SD)	2.0 (1.07)	2.3 (1.16)	2.1 (1.11)
Median	2.0	2.0	2.0
Min, Max	1, 5	1, 5	1, 5

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Item 5: Emotion:Reduced Range			
N	80	47	127
Mean (SD)	4.2 (0.81)	4.4 (0.92)	4.3 (0.85)
Median	4.0	4.0	4.0
Min, Max	3, 6	3, 6	3, 6
NSA-16 Item 6: Affect:Reduce Modulation Intensity			
N	80	47	127
Mean (SD)	4.2 (0.74)	4.2 (0.89)	4.2 (0.80)
Median	4.0	4.0	4.0
Min, Max	3, 6	3, 6	3, 6
NSA-16 Item 7: Affect:Reduced Display on Demand			
N	80	47	127
Mean (SD)	3.8 (0.93)	4.0 (0.92)	3.9 (0.94)
Median	4.0	4.0	4.0
Min, Max	1, 5	2, 6	1, 6
NSA-16 Item 8: Reduced Social Drive			
N	80	47	127
Mean (SD)	4.7 (0.75)	4.9 (0.55)	4.8 (0.68)
Median	5.0	5.0	5.0
Min, Max	1, 6	3, 6	1, 6

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Item 9: Poor Rapport With Interviewer			
N	80	47	127
Mean (SD)	3.4 (1.02)	3.3 (0.93)	3.3 (0.99)
Median	3.0	3.0	3.0
Min, Max	1, 5	1, 5	1, 5
NSA-16 Item 10: Sexual Interest			
N	80	47	127
Mean (SD)	4.2 (1.52)	4.0 (1.54)	4.1 (1.52)
Median	4.0	4.0	4.0
Min, Max	1, 6	1, 6	1, 6
NSA-16 Item 11: Poor Grooming and Hygiene			
N	80	47	127
Mean (SD)	2.6 (1.20)	2.5 (1.08)	2.6 (1.15)
Median	2.0	2.0	2.0
Min, Max	1, 5	1, 5	1, 5
NSA-16 Item 12: Reduced Sense of Purpose			
N	80	47	127
Mean (SD)	4.7 (0.92)	4.5 (1.02)	4.6 (0.96)
Median	5.0	5.0	5.0
Min, Max	2, 6	2, 6	2, 6

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
NSA-16 Item 13: Reduced Interests			
N	80	47	127
Mean (SD)	4.5 (0.84)	4.8 (0.84)	4.6 (0.84)
Median	5.0	5.0	5.0
Min, Max	2, 6	2, 6	2, 6
NSA-16 Item 14: Reduced Daily Activity			
N	80	47	127
Mean (SD)	4.8 (0.57)	4.7 (0.74)	4.8 (0.64)
Median	5.0	5.0	5.0
Min, Max	3, 6	2, 6	2, 6
NSA-16 Item 15: Reduced Expressive Gestures			
N	80	47	127
Mean (SD)	3.9 (1.09)	4.1 (1.13)	4.0 (1.11)
Median	4.0	4.0	4.0
Min, Max	1, 6	2, 6	1, 6
NSA-16 Item 16: Slowed Movements			
N	80	47	127
Mean (SD)	2.8 (0.96)	3.0 (0.78)	2.9 (0.91)
Median	3.0	3.0	3.0
Min, Max	1, 5	2, 5	1, 5

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	**Stage 1 Placebo (N = 80)**	**Stage 1 d6-DM/Q (N = 47)**	**All Patients (N = 127)**
NSA-16: Global Negative Symptoms Rating			
N	80	47	127
Mean (SD)	4.6 (0.61)	4.6 (0.64)	4.6 (0.62)
Median	5.0	5.0	5.0
Min, Max	3, 6	3, 6	3, 6
NSA-16: Global Level of Functioning			
N	80	46	126
Mean (SD)	4.6 (0.63)	4.7 (0.73)	4.6 (0.66)
Median	5.0	5.0	5.0
Min, Max	3, 6	3, 6	3, 6
PANSS Total Score			
N	80	47	127
Mean (SD)	68.7 (7.99)	67.4 (8.26)	68.2 (8.08)
Median	69.0	68.0	69.0
Min, Max	51, 93	47, 83	47, 93
PANSS Total Score Reduction >=20%	80	47	127
Yes	3 (3.8)	5 (10.6)	8 (6.3)
No	77 (96.3)	42 (89.4)	119 (93.7)

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	**Stage 1 Placebo (N = 80)**	**Stage 1 d6-DM/Q (N = 47)**	**All Patients (N = 127)**
PANSS Negative Subscale			
N	80	47	127
Mean (SD)	25.2 (3.64)	24.6 (3.51)	25.0 (3.59)
Median	26.0	24.0	25.0
Min, Max	18, 36	19, 35	18, 36
PANSS Positive Subscale			
N	80	47	127
Mean (SD)	13.4 (2.81)	13.6 (3.65)	13.5 (3.13)
Median	13.0	13.0	13.0
Min, Max	7, 22	7, 23	7, 23
PANSS General Psychopathology Subscale			
N	80	47	127
Mean (SD)	30.1 (5.05)	29.1 (4.66)	29.7 (4.91)
Median	29.0	30.0	30.0
Min, Max	18, 45	18, 38	18, 45
PANSS Prosocial Factors			
N	80	47	127
Mean (SD)	18.4 (2.92)	18.3 (3.24)	18.4 (3.03)
Median	19.0	18.0	19.0
Min, Max	11, 28	10, 28	10, 28

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
PANSS Marder Negative Factors			
N	80	47	127
Mean (SD)	24.2 (3.81)	24.1 (4.24)	24.2 (3.96)
Median	24.0	23.0	24.0
Min, Max	17, 35	17, 37	17, 37
PANSS Excitement Component			
N	80	47	127
Mean (SD)	6.3 (2.10)	6.2 (1.57)	6.3 (1.92)
Median	6.0	6.0	6.0
Min, Max	5, 17	5, 12	5, 17
CGI-S			
N	80	47	127
Mean (SD)	3.9 (0.74)	3.7 (0.74)	3.9 (0.74)
Median	4.0	4.0	4.0
Min, Max	2, 6	1, 5	1, 6
CGI-S Group	78	46	124
Percent Change =< 65%	78 (100.0)	46 (100.0)	124 (100.0)
Percent Change > 65%	0 (0.0)	0 (0.0)	0 (0.0)
CDSS Total Score			
N	80	47	127
Mean (SD)	0.9 (1.31)	1.1 (1.34)	0.9 (1.32)
Median	0.0	1.0	0.0
Min, Max	0, 5	0, 5	0, 5

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
MCCB Composite Score			
N	80	47	127
Mean (SD)	28.8 (13.09)	32.5 (11.37)	30.2 (12.56)
Median	28.5	35.0	30.0
Min, Max	4, 56	9, 53	4, 56
MCCB Speed of Processing			
N	80	47	127
Mean (SD)	35.0 (11.37)	35.3 (10.88)	35.1 (11.15)
Median	35.5	37.0	36.0
Min, Max	12, 58	12, 61	12, 61
MCCB Attention/Vigilance			
N	80	47	127
Mean (SD)	37.4 (13.28)	40.6 (13.18)	38.6 (13.28)
Median	39.0	38.0	39.0
Min, Max	11, 70	15, 69	11, 70
MCCB Working Memory			
N	80	47	127
Mean (SD)	35.7 (12.05)	40.6 (11.94)	37.5 (12.19)
Median	37.0	41.0	38.0
Min, Max	4, 60	17, 69	4, 69

Table 18 (continued)
Stage 1 Baseline Efficacy Assessments
Stage 1 mITT Population (N = 127)

Assessment Statistics	Stage 1 Placebo (N = 80)	Stage 1 d6-DM/Q (N = 47)	All Patients (N = 127)
MCCB Verbal Learning			
N	80	47	127
Mean (SD)	36.1 (8.14)	38.9 (8.84)	37.1 (8.48)
Median	35.0	38.0	36.0
Min, Max	21, 65	25, 73	21, 73
MCCB Visual Learning			
N	80	47	127
Mean (SD)	34.5 (11.18)	37.1 (12.90)	35.5 (11.87)
Median	32.0	35.0	34.0
Min, Max	13, 62	17, 67	13, 67
MCCB Reasoning and Problem Solving			
N	80	47	127
Mean (SD)	43.9 (9.61)	43.5 (9.25)	43.8 (9.44)
Median	43.0	42.0	42.0
Min, Max	24, 63	28, 65	24, 65
MCCB Social Cognition			
N	80	47	127
Mean (SD)	36.5 (13.29)	39.6 (11.04)	37.6 (12.55)
Median	36.0	40.0	38.0
Min, Max	11, 68	17, 64	11, 68

Table 19
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Total Score			
N	30	33	63
Mean (SD)	57.6 (9.39)	57.6 (9.09)	57.6 (9.16)
Median	57.0	57.0	57.0
Min, Max	43, 86	43, 76	43, 86
NSA-16 Factor Domain: Communication			
N	30	33	63
Mean (SD)	12.0 (2.98)	11.8 (3.12)	11.9 (3.03)
Median	12.0	12.0	12.0
Min, Max	7, 21	4, 19	4, 21
NSA-16 Factor Domain: Emotion/Affect			
N	30	33	63
Mean (SD)	11.7 (1.84)	11.7 (2.09)	11.7 (1.96)
Median	11.0	11.0	11.0
Min, Max	8, 16	8, 16	8, 16
NSA-16 Factor Domain: Social Involvement			
N	30	33	63
Mean (SD)	12.1 (2.12)	12.0 (2.56)	12.0 (2.34)
Median	12.0	13.0	12.0
Min, Max	8, 17	5, 16	5, 17

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Factor Domain: Motivation			
N	30	33	63
Mean (SD)	15.8 (2.61)	15.8 (2.39)	15.8 (2.48)
Median	16.0	16.0	16.0
Min, Max	11, 23	9, 19	9, 23
NSA-16 Factor Domain: Retardation			
N	30	33	63
Mean (SD)	6.0 (2.00)	6.3 (2.05)	6.2 (2.02)
Median	6.0	6.0	6.0
Min, Max	2, 9	3, 11	2, 11
NSA-4 Total Score			
N	30	33	63
Mean (SD)	16.5 (2.64)	16.4 (2.84)	16.4 (2.72)
Median	16.0	17.0	16.0
Min, Max	12, 24	8, 21	8, 24

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Item 1: Prolonged Time to Respond			
N	30	33	63
Mean (SD)	3.1 (1.21)	2.5 (1.12)	2.8 (1.20)
Median	3.0	2.0	3.0
Min, Max	1, 6	1, 6	1, 6
NSA-16 Item 2: Restricted Speech Quantity			
N	30	33	63
Mean (SD)	3.4 (1.28)	3.8 (1.25)	3.6 (1.27)
Median	3.0	4.0	3.0
Min, Max	1, 6	1, 6	1, 6
NSA-16 Item 3: Impoverished Speech Content			
N	30	33	63
Mean (SD)	3.7 (0.80)	3.4 (0.90)	3.5 (0.86)
Median	4.0	3.0	4.0
Min, Max	2, 5	1, 5	1, 5
NSA-16 Item 4: Inarticulate Speech			
N	30	33	63
Mean (SD)	1.9 (1.01)	2.2 (1.18)	2.0 (1.10)
Median	2.0	2.0	2.0
Min, Max	1, 4	1, 4	1, 4

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Item 5: Emotion:Reduced Range			
N	30	33	63
Mean (SD)	4.1 (0.74)	4.1 (0.89)	4.1 (0.82)
Median	4.0	4.0	4.0
Min, Max	3, 6	2, 6	2, 6
NSA-16 Item 6: Affect:Reduce Modulation Intensity			
N	30	33	63
Mean (SD)	4.1 (0.69)	4.0 (0.90)	4.0 (0.80)
Median	4.0	4.0	4.0
Min, Max	3, 5	2, 6	2, 6
NSA-16 Item 7: Affect:Reduced Display on Demand			
N	30	33	63
Mean (SD)	3.5 (0.94)	3.5 (1.15)	3.5 (1.04)
Median	4.0	4.0	4.0
Min, Max	2, 5	1, 6	1, 6
NSA-16 Item 8: Reduced Social Drive			
N	30	33	63
Mean (SD)	4.6 (0.67)	4.2 (1.20)	4.4 (0.99)
Median	5.0	5.0	5.0
Min, Max	3, 6	1, 5	1, 6

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Item 9: Poor Rapport With Interviewer			
N	30	33	63
Mean (SD)	3.3 (1.09)	3.5 (1.25)	3.4 (1.17)
Median	3.5	4.0	4.0
Min, Max	1, 5	1, 5	1, 5
NSA-16 Item 10: Sexual Interest			
N	30	33	63
Mean (SD)	4.1 (1.28)	4.3 (1.67)	4.2 (1.49)
Median	4.0	4.0	4.0
Min, Max	2, 6	1, 6	1, 6
NSA-16 Item 11: Poor Grooming and Hygiene			
N	30	33	63
Mean (SD)	2.2 (1.34)	2.3 (1.08)	2.3 (1.20)
Median	2.0	2.0	2.0
Min, Max	1, 5	1, 4	1, 5
NSA-16 Item 12: Reduced Sense of Purpose			
N	30	33	63
Mean (SD)	4.4 (1.10)	4.5 (0.97)	4.5 (1.03)
Median	5.0	5.0	5.0
Min, Max	2, 6	3, 6	2, 6

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16 Item 13: Reduced Interests			
N	30	33	63
Mean (SD)	4.4 (0.81)	4.3 (1.01)	4.3 (0.92)
Median	4.0	5.0	5.0
Min, Max	3, 6	1, 5	1, 6
NSA-16 Item 14: Reduced Daily Activity			
N	30	33	63
Mean (SD)	4.8 (0.46)	4.6 (0.78)	4.7 (0.65)
Median	5.0	5.0	5.0
Min, Max	4, 6	2, 6	2, 6
NSA-16 Item 15: Reduced Expressive Gestures			
N	30	33	63
Mean (SD)	3.5 (1.25)	3.8 (1.48)	3.7 (1.38)
Median	4.0	4.0	4.0
Min, Max	1, 5	1, 6	1, 6
NSA-16 Item 16: Slowed Movements			
N	30	33	63
Mean (SD)	2.5 (1.07)	2.5 (1.18)	2.5 (1.12)
Median	3.0	2.0	3.0
Min, Max	1, 4	1, 5	1, 5

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
NSA-16: Global Negative Symptoms Rating			
N	30	33	63
Mean (SD)	4.3 (0.71)	4.4 (0.75)	4.4 (0.73)
Median	4.0	4.0	4.0
Min, Max	3, 6	3, 6	3, 6
NSA-16: Global Level of Functioning			
N	29	33	62
Mean (SD)	4.5 (0.74)	4.4 (0.70)	4.4 (0.72)
Median	4.0	4.0	4.0
Min, Max	3, 6	3, 6	3, 6
PANSS Total Score			
N	30	33	63
Mean (SD)	67.1 (9.00)	65.6 (8.07)	66.3 (8.49)
Median	66.5	64.0	66.0
Min, Max	51, 87	53, 80	51, 87
PANSS Total Score Reduction >=20%	30	33	63
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	30 (100.0)	33 (100.0)	63 (100.0)

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
PANSS Negative Subscale			
N	30	33	63
Mean (SD)	24.4 (4.55)	23.6 (4.53)	24.0 (4.52)
Median	25.0	23.0	24.0
Min, Max	16, 35	13, 32	13, 35
PANSS Positive Subscale			
N	30	33	63
Mean (SD)	13.1 (3.64)	13.3 (3.39)	13.2 (3.48)
Median	13.0	13.0	13.0
Min, Max	8, 23	7, 22	7, 23
PANSS General Psychopathology Subscale			
N	30	33	63
Mean (SD)	29.7 (5.40)	28.7 (4.84)	29.2 (5.10)
Median	29.0	28.0	29.0
Min, Max	20, 43	20, 39	20, 43
PANSS Prosocial Factors			
N	30	33	63
Mean (SD)	17.7 (3.27)	17.0 (3.30)	17.3 (3.28)
Median	18.0	17.0	18.0
Min, Max	12, 26	11, 24	11, 26

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
PANSS Marder Negative Factors			
N	30	33	63
Mean (SD)	23.0 (4.62)	22.3 (5.45)	22.6 (5.05)
Median	24.0	21.0	22.0
Min, Max	13, 34	8, 38	8, 38
PANSS Excitement Component			
N	30	33	63
Mean (SD)	5.8 (1.27)	6.7 (2.59)	6.3 (2.10)
Median	5.5	6.0	6.0
Min, Max	5, 11	5, 14	5, 14
CGI-S			
N	30	31	61
Mean (SD)	3.8 (0.79)	3.7 (0.69)	3.8 (0.74)
Median	4.0	4.0	4.0
Min, Max	3, 6	2, 5	2, 6
CGI-S Group	30	31	61
Percent Change =< 65%	30 (100.0)	31 (100.0)	61 (100.0)
Percent Change > 65%	0 (0.0)	0 (0.0)	0 (0.0)
CDSS Total Score			
N	30	33	63
Mean (SD)	1.0 (1.56)	0.8 (1.54)	0.9 (1.54)
Median	0.0	0.0	0.0
Min, Max	0, 6	0, 7	0, 7

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
MCCB Composite Score			
N	27	30	57
Mean (SD)	31.7 (14.99)	28.9 (10.69)	30.2 (12.87)
Median	32.0	31.0	32.0
Min, Max	7, 56	8, 50	7, 56
MCCB Speed of Processing			
N	30	32	62
Mean (SD)	36.7 (12.76)	35.2 (11.68)	35.9 (12.14)
Median	34.5	35.5	35.5
Min, Max	7, 58	13, 58	7, 58
MCCB Attention/Vigilance			
N	29	31	60
Mean (SD)	40.4 (13.00)	36.2 (12.98)	38.3 (13.05)
Median	40.0	36.0	36.5
Min, Max	17, 68	14, 67	14, 68
MCCB Working Memory			
N	30	32	62
Mean (SD)	38.8 (12.21)	36.0 (9.96)	37.4 (11.11)
Median	40.0	39.0	39.5
Min, Max	15, 60	15, 53	15, 60

Table 19 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Non-Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 30)	Placebo/d6-DM/Q (N = 33)	All Stage 1 Placebo Non-Responder (N = 63)
MCCB Verbal Learning			
N	30	32	62
Mean (SD)	36.3 (7.35)	34.8 (6.77)	35.6 (7.04)
Median	36.0	33.0	34.0
Min, Max	22, 55	25, 56	22, 56
MCCB Visual Learning			
N	29	31	60
Mean (SD)	37.3 (13.46)	39.9 (9.69)	38.7 (11.64)
Median	36.0	40.0	36.5
Min, Max	16, 61	21, 57	16, 61
MCCB Reasoning and Problem Solving			
N	30	32	62
Mean (SD)	43.4 (9.76)	42.8 (8.45)	43.1 (9.04)
Median	41.0	42.0	41.0
Min, Max	26, 68	29, 57	26, 68
MCCB Social Cognition			
N	29	32	61
Mean (SD)	38.0 (14.80)	34.5 (12.91)	36.2 (13.84)
Median	36.0	33.5	36.0
Min, Max	14, 73	10, 62	10, 73

Table 20
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Total Score			
N	2	1	3
Mean (SD)	48.0 (4.24)	46.0 (na)	47.3 (3.21)
Median	48.0	46.0	46.0
Min, Max	45, 51	46, 46	45, 51
NSA-16 Factor Domain: Communication			
N	2	1	3
Mean (SD)	10.0 (0.00)	9.0 (na)	9.7 (0.58)
Median	10.0	9.0	10.0
Min, Max	10, 10	9, 9	9, 10
NSA-16 Factor Domain: Emotion/Affect			
N	2	1	3
Mean (SD)	9.5 (0.71)	9.0 (na)	9.3 (0.58)
Median	9.5	9.0	9.0
Min, Max	9, 10	9, 9	9, 10
NSA-16 Factor Domain: Social Involvement			
N	2	1	3
Mean (SD)	7.5 (2.12)	13.0 (na)	9.3 (3.51)
Median	7.5	13.0	9.0
Min, Max	6, 9	13, 13	6, 13

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Factor Domain: Motivation			
N	2	1	3
Mean (SD)	15.5 (0.71)	12.0 (na)	14.3 (2.08)
Median	15.5	12.0	15.0
Min, Max	15, 16	12, 12	12, 16
NSA-16 Factor Domain: Retardation			
N	2	1	3
Mean (SD)	5.5 (0.71)	3.0 (na)	4.7 (1.53)
Median	5.5	3.0	5.0
Min, Max	5, 6	3, 3	3, 6
NSA-4 Total Score			
N	2	1	3
Mean (SD)	15.0 (1.41)	13.0 (na)	14.3 (1.53)
Median	15.0	13.0	14.0
Min, Max	14, 16	13, 13	13, 16

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Item 1: Prolonged Time to Respond			
N	2	1	3
Mean (SD)	2.0 (0.00)	2.0 (na)	2.0 (0.00)
Median	2.0	2.0	2.0
Min, Max	2, 2	2, 2	2, 2
NSA-16 Item 2: Restricted Speech Quantity			
N	2	1	3
Mean (SD)	3.0 (0.00)	3.0 (na)	3.0 (0.00)
Median	3.0	3.0	3.0
Min, Max	3, 3	3, 3	3, 3
NSA-16 Item 3: Impoverished Speech Content			
N	2	1	3
Mean (SD)	3.0 (0.00)	3.0 (na)	3.0 (0.00)
Median	3.0	3.0	3.0
Min, Max	3, 3	3, 3	3, 3
NSA-16 Item 4: Inarticulate Speech			
N	2	1	3
Mean (SD)	2.0 (0.00)	1.0 (na)	1.7 (0.58)
Median	2.0	1.0	2.0
Min, Max	2, 2	1, 1	1, 2

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Item 5: Emotion:Reduced Range			
N	2	1	3
Mean (SD)	3.5 (0.71)	3.0 (na)	3.3 (0.58)
Median	3.5	3.0	3.0
Min, Max	3, 4	3, 3	3, 4
NSA-16 Item 6: Affect:Reduce Modulation Intensity			
N	2	1	3
Mean (SD)	3.5 (0.71)	3.0 (na)	3.3 (0.58)
Median	3.5	3.0	3.0
Min, Max	3, 4	3, 3	3, 4
NSA-16 Item 7: Affect:Reduced Display on Demand			
N	2	1	3
Mean (SD)	2.5 (0.71)	3.0 (na)	2.7 (0.58)
Median	2.5	3.0	3.0
Min, Max	2, 3	3, 3	2, 3
NSA-16 Item 8: Reduced Social Drive			
N	2	1	3
Mean (SD)	4.0 (0.00)	4.0 (na)	4.0 (0.00)
Median	4.0	4.0	4.0
Min, Max	4, 4	4, 4	4, 4

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Item 9: Poor Rapport With Interviewer			
N	2	1	3
Mean (SD)	2.0 (1.41)	3.0 (na)	2.3 (1.15)
Median	2.0	3.0	3.0
Min, Max	1, 3	3, 3	1, 3
NSA-16 Item 10: Sexual Interest			
N	2	1	3
Mean (SD)	1.5 (0.71)	6.0 (na)	3.0 (2.65)
Median	1.5	6.0	2.0
Min, Max	1, 2	6, 6	1, 6
NSA-16 Item 11: Poor Grooming and Hygiene			
N	2	1	3
Mean (SD)	1.5 (0.71)	1.0 (na)	1.3 (0.58)
Median	1.5	1.0	1.0
Min, Max	1, 2	1, 1	1, 2
NSA-16 Item 12: Reduced Sense of Purpose			
N	2	1	3
Mean (SD)	5.0 (0.00)	4.0 (na)	4.7 (0.58)
Median	5.0	4.0	5.0
Min, Max	5, 5	4, 4	4, 5

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16 Item 13: Reduced Interests			
N	2	1	3
Mean (SD)	4.5 (0.71)	3.0 (na)	4.0 (1.00)
Median	4.5	3.0	4.0
Min, Max	4, 5	3, 3	3, 5
NSA-16 Item 14: Reduced Daily Activity			
N	2	1	3
Mean (SD)	4.5 (0.71)	4.0 (na)	4.3 (0.58)
Median	4.5	4.0	4.0
Min, Max	4, 5	4, 4	4, 5
NSA-16 Item 15: Reduced Expressive Gestures			
N	2	1	3
Mean (SD)	3.5 (0.71)	2.0 (na)	3.0 (1.00)
Median	3.5	2.0	3.0
Min, Max	3, 4	2, 2	2, 4
NSA-16 Item 16: Slowed Movements			
N	2	1	3
Mean (SD)	2.0 (0.00)	1.0 (na)	1.7 (0.58)
Median	2.0	1.0	2.0
Min, Max	2, 2	1, 1	1, 2

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
NSA-16: Global Negative Symptoms Rating			
N	2	1	3
Mean (SD)	3.5 (0.71)	3.0 (na)	3.3 (0.58)
Median	3.5	3.0	3.0
Min, Max	3, 4	3, 3	3, 4
NSA-16: Global Level of Functioning			
N	2	1	3
Mean (SD)	3.5 (0.71)	3.0 (na)	3.3 (0.58)
Median	3.5	3.0	3.0
Min, Max	3, 4	3, 3	3, 4
PANSS Total Score			
N	2	1	3
Mean (SD)	51.5 (0.71)	51.0 (na)	51.3 (0.58)
Median	51.5	51.0	51.0
Min, Max	51, 52	51, 51	51, 52
PANSS Total Score Reduction >=20%	2	1	3
Yes	2 (100.0)	1 (100.0)	3 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
PANSS Negative Subscale			
N	2	1	3
Mean (SD)	18.5 (2.12)	20.0 (na)	19.0 (1.73)
Median	18.5	20.0	20.0
Min, Max	17, 20	20, 20	17, 20
PANSS Positive Subscale			
N	2	1	3
Mean (SD)	10.0 (0.00)	7.0 (na)	9.0 (1.73)
Median	10.0	7.0	10.0
Min, Max	10, 10	7, 7	7, 10
PANSS General Psychopathology Subscale			
N	2	1	3
Mean (SD)	23.0 (1.41)	24.0 (na)	23.3 (1.15)
Median	23.0	24.0	24.0
Min, Max	22, 24	24, 24	22, 24
PANSS Prosocial Factors			
N	2	1	3
Mean (SD)	13.5 (0.71)	12.0 (na)	13.0 (1.00)
Median	13.5	12.0	13.0
Min, Max	13, 14	12, 12	12, 14

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
PANSS Marder Negative Factors			
N	2	1	3
Mean (SD)	19.0 (2.83)	19.0 (na)	19.0 (2.00)
Median	19.0	19.0	19.0
Min, Max	17, 21	19, 19	17, 21
PANSS Excitement Component			
N	2	1	3
Mean (SD)	6.0 (1.41)	5.0 (na)	5.7 (1.15)
Median	6.0	5.0	5.0
Min, Max	5, 7	5, 5	5, 7
CGI-S			
N	2	1	3
Mean (SD)	3.0 (0.00)	3.0 (na)	3.0 (0.00)
Median	3.0	3.0	3.0
Min, Max	3, 3	3, 3	3, 3
CGI-S Group	2	1	3
Percent Change =< 65%	2 (100.0)	1 (100.0)	3 (100.0)
Percent Change > 65%	0 (0.0)	0 (0.0)	0 (0.0)
CDSS Total Score			
N	2	1	3
Mean (SD)	0.5 (0.71)	0.0 (na)	0.3 (0.58)
Median	0.5	0.0	0.0
Min, Max	0, 1	0, 0	0, 1

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
MCCB Composite Score			
N	2	1	3
Mean (SD)	35.0 (11.31)	41.0 (na)	37.0 (8.72)
Median	35.0	41.0	41.0
Min, Max	27, 43	41, 41	27, 43
MCCB Speed of Processing			
N	2	1	3
Mean (SD)	32.0 (4.24)	47.0 (na)	37.0 (9.17)
Median	32.0	47.0	35.0
Min, Max	29, 35	47, 47	29, 47
MCCB Attention/Vigilance			
N	2	1	3
Mean (SD)	45.5 (13.44)	39.0 (na)	43.3 (10.21)
Median	45.5	39.0	39.0
Min, Max	36, 55	39, 39	36, 55
MCCB Working Memory			
N	2	1	3
Mean (SD)	45.5 (6.36)	50.0 (na)	47.0 (5.20)
Median	45.5	50.0	50.0
Min, Max	41, 50	50, 50	41, 50

Table 20 (continued)
Stage 2 Baseline Efficacy Assessments - Stage 1 Placebo Responders
Stage 2 mITT Population (N = 108)

Assessment Statistics	Placebo/Placebo (N = 2)	Placebo/d6-DM/Q (N = 1)	All Stage 1 Placebo Responder (N = 3)
MCCB Verbal Learning			
N	2	1	3
Mean (SD)	35.5 (3.54)	46.0 (na)	39.0 (6.56)
Median	35.5	46.0	38.0
Min, Max	33, 38	46, 46	33, 46
MCCB Visual Learning			
N	2	1	3
Mean (SD)	38.5 (0.71)	50.0 (na)	42.3 (6.66)
Median	38.5	50.0	39.0
Min, Max	38, 39	50, 50	38, 50
MCCB Reasoning and Problem Solving			
N	2	1	3
Mean (SD)	46.0 (5.66)	46.0 (na)	46.0 (4.00)
Median	46.0	46.0	46.0
Min, Max	42, 50	46, 46	42, 50
MCCB Social Cognition			
N	2	1	3
Mean (SD)	44.5 (17.68)	35.0 (na)	41.3 (13.65)
Median	44.5	35.0	35.0
Min, Max	32, 57	35, 35	32, 57

Table 21
PGIC Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Week 6 Change from Baseline: N, Mean (SD)	37, 3.2 (0.89)	47, 3.1 (0.94)
Week 12 Change from Baseline: N, Mean (SD)	32, 3.2 (0.88)	42, 2.9 (0.95)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.106, -0.35 (-0.77, 0.08)

Note: PGIC Score ranges from 1 to 7, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 22
PGIC Score: Proportional Odds Regression by Stage, Observed Data
mITT 12-Week Parallel Group Population (N = 87)

Visit	Result/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Stage 1, Week 6 (Relative to Baseline)	N	37	47
Stage 1, Week 6 (Relative to Baseline)	1 = Very much improved, n (%)	2 (5.4)	2 (4.3)
Stage 1, Week 6 (Relative to Baseline)	2 = Much improved, n (%)	5 (13.5)	11 (23.4)
Stage 1, Week 6 (Relative to Baseline)	3 = Minimally improved, n (%)	13 (35.1)	15 (31.9)
Stage 1, Week 6 (Relative to Baseline)	4 = No change, n (%)	17 (45.9)	18 (38.3)
Stage 1, Week 6 (Relative to Baseline)	5 = Minimally worse, n (%)	0 (0.0)	1 (2.1)
Stage 1, Week 6 (Relative to Baseline)	6 = Much worse, n (%)	0 (0.0)	0 (0.0)
Stage 1, Week 6 (Relative to Baseline)	7 = Very much worse, n (%)	0 (0.0)	0 (0.0)
Stage 1, Week 6 (Relative to Baseline)	Odds ratio (d6-DM/Q to Placebo) (95% CI), p-value		1.29 (0.58, 2.86), 0.530
Stage 2, Week 12 (Relative to Stage 1 Baseline)	N	32	42
Stage 2, Week 12 (Relative to Stage 1 Baseline)	1 = Very much improved, n (%)	2 (6.3)	4 (9.5)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	2 = Much improved, n (%)	4 (12.5)	10 (23.8)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	3 = Minimally improved, n (%)	13 (40.6)	16 (38.1)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	4 = No change, n (%)	13 (40.6)	12 (28.6)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	5 = Minimally worse, n (%)	0 (0.0)	0 (0.0)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	6 = Much worse, n (%)	0 (0.0)	0 (0.0)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	7 = Very much worse, n (%)	0 (0.0)	0 (0.0)
Stage 2, Week 12 (Relative to Stage 1 Baseline)	Odds ratio (d6-DM/Q to Placebo) (95% CI), p-value		1.85 (0.79, 4.36), 0.158

p-values are calculated using proportional odds regression analysis.

Table 23
NSA-16 Total Score: Change from Baseline SPCD SUR, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	N	80	47
Stage 1	Baseline: Mean (SD)	60.4 (7.71)	61.0 (7.53)
Stage 1	Week 6: Mean (SD)	57.4 (9.21)	55.9 (8.75)
Stage 1	Change from Baseline Mean (SD)	-3.0 (5.78)	-5.0 (5.64)
Stage 1	Standard Effect Size		-0.365
Stage 1	SUR Estimated Difference versus Placebo (SE)		-2.05 (1.05)
Stage 2 (Stage 1 Placebo Non-responders)	N	30	33
Stage 2 (Stage 1 Placebo Non-responders)	Baseline: Mean (SD)	57.6 (9.39)	57.6 (9.09)
Stage 2 (Stage 1 Placebo Non-responders)	Week 6: Mean (SD)	55.4 (11.28)	54.0 (8.63)
Stage 2 (Stage 1 Placebo Non-responders)	Change from Baseline Mean (SD)	-2.2 (5.89)	-3.6 (6.34)
Stage 2 (Stage 1 Placebo Non-responders)	Standard Effect Size		-0.230
Stage 2 (Stage 1 Placebo Non-responders)	SUR Estimated Difference versus Placebo (SE)		-1.26 (1.52)
	SUR z-statistic, overall p-value		-1.98, 0.0481

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
SPCD SUR z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 24
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 60.4 (7.71)	47, 61.0 (7.53)
	Week 6: N, Mean (SD)	80, 57.4 (9.21)	47, 55.9 (8.75)
	Change from Baseline: N, Mean (SD)	80, -3.0 (5.78)	47, -5.0 (5.64)
	Standard Effect Size		-0.365
	% Change from Baseline: N, Mean (SD)	80, -4.8 (9.47)	47, -8.2 (9.36)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.05 (-4.13, 0.04)
	p-value [1]		0.054
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 57.6 (9.39)	33, 57.6 (9.09)
	Week 12: N, Mean (SD)	30, 55.4 (11.28)	33, 54.0 (8.63)
	Change from Baseline [2]: N, Mean (SD)	30, -2.2 (5.89)	33, -3.6 (6.34)
	Standard Effect Size		-0.230
	% Change from Baseline [2]: N, Mean (SD)	30, -4.0 (9.81)	33, -5.6 (10.70)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.40 (-4.46, 1.65)
	p-value [1]		0.362
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.04, 0.042

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 25
NSA-16 Total Score: Change from Baseline SPCD MMRM, Observed Data
Per Protocol Population (N = 110)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	73, 60.9 (7.57)	37, 60.4 (7.83)
	Week 3 Change from Baseline: N, Mean (SD)	72, -3.0 (6.53)	37, -1.8 (5.60)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		1.19 (-1.29, 3.67)
	p-value [1]		0.342
	Week 6 Change from Baseline: N, Mean (SD)	63, -3.5 (5.76)	37, -4.8 (5.77)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.57 (-3.94, 0.80)
	p-value [1]		0.191
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	27, 57.4 (9.85)	29, 59.0 (8.67)
	Week 9 Change from Baseline [2]: N, Mean (SD)	27, -0.4 (5.42)	29, -4.2 (5.98)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.65 (-6.73, -0.56)
	p-value [1]		0.021
	Week 12 Change from Baseline [2]: N, Mean (SD)	26, -3.0 (5.81)	29, -4.5 (5.96)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.43 (-4.63, 1.76)
	p-value [1]		0.372
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-1.58, 0.114

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline NSA-16, and baseline NSA-16-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 26
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Band-Pass Filter #1

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	14, 60.9 (7.59)	19, 63.9 (7.61)
	Week 6: N, Mean (SD)	14, 61.8 (10.64)	19, 59.5 (7.36)
	Change from Baseline: N, Mean (SD)	14, 0.9 (6.87)	19, -4.5 (5.12)
	Standard Effect Size		-0.900
	% Change from Baseline: N, Mean (SD)	14, 1.3 (11.61)	19, -6.7 (8.28)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-4.97 (-9.33, -0.60)
	p-value [1]		0.027
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	1, 72.0 ( )	11, 59.8 (10.94)
	Week 12: N, Mean (SD)	1, 74.0 ( )	11, 55.0 (9.55)
	Change from Baseline [2]: N, Mean (SD)	1, 2.0 ( )	11, -4.8 (7.83)
	Standard Effect Size		
	% Change from Baseline [2]: N, Mean (SD)	1, 2.8 ( )	11, -7.2 (11.64)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-11.39 (-28.92, 6.14)
	p-value [1]		0.176
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.25, 0.025

Note: Band-pass filter: Any site with mean placebo NSA-16 total score changes from baseline in Stage 1 (Baseline to Week 6) more than 0 or less than -7 is excluded.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.
Note: Band-pass filter: Any site with mean placebo NSA-16 total score changes from baseline in Stage 1 (Baseline to Week 6) more than 0 or less than -7 is excluded.

Table 27
NSA-16 Total Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group Population (N = 87)
Subgroup: Band-Pass Filter #1

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	2, 70.5 (2.12)	19, 63.9 (7.61)
Week 3 Change from Baseline: N, Mean (SD)	2, -4.5 (3.54)	18, -2.1 (5.98)
Week 6 Change from Baseline: N, Mean (SD)	1, 0.0 (NA)	19, -4.5 (5.12)
Week 9 Change from Baseline: N, Mean (SD)	1, 7.0 (NA)	18, -7.2 (8.43)
Week 12 Change from Baseline: N, Mean (SD)	1, 2.0 (NA)	18, -3.3 (7.85)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.329, -8.38 (-26.02, 9.27)

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Note: Band-pass filter: Any site with mean placebo NSA-16 total score changes from baseline in Stage 1 (Baseline to Week 6) more than 0 or less than -7 is excluded.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 28
PANSS Total Score: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 68.7 (7.99)	47, 67.4 (8.26)
	Week 3 Change from Baseline: N, Mean (SD)	79, -2.4 (6.97)	45, -3.2 (6.84)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.08 (-3.55, 1.39)
	p-value [1]		0.389
	Week 6 Change from Baseline: N, Mean (SD)	70, -2.5 (6.50)	47, -4.7 (6.98)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.36 (-4.77, 0.06)
	p-value [1]		0.055
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 67.1 (9.00)	33, 65.6 (8.07)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.2 (5.60)	33, -2.5 (8.26)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.04 (-6.54, 0.45)
	p-value [1]		0.087
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -1.4 (7.64)	32, -4.0 (7.71)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.53 (-6.51, 1.45)
	p-value [1]		0.209
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.25, 0.025

Note: PANSS Total Score ranges from 30 to 210, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Total Score and baseline PANSS Total Score-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 29
PANSS Positive Subscale: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 13.4 (2.81)	47, 13.6 (3.65)
	Week 3 Change from Baseline: N, Mean (SD)	79, -0.3 (2.53)	45, -0.6 (1.83)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.25 (-1.08, 0.58)
	p-value [1]		0.553
	Week 6 Change from Baseline: N, Mean (SD)	70, -0.3 (2.57)	47, -0.8 (2.63)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.42 (-1.36, 0.52)
	p-value [1]		0.376
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 13.1 (3.64)	33, 13.3 (3.39)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.3 (1.80)	33, 0.2 (2.97)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.10 (-1.30, 1.10)
	p-value [1]		0.864
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -0.4 (1.99)	32, -0.3 (2.47)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.28 (-0.90, 1.45)
	p-value [1]		0.640
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-0.39, 0.700

Note: PANSS Positive Subscale ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Positive Subscale and baseline PANSS Positive Subscale-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 30
PANSS Negative Subscale: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 25.2 (3.64)	47, 24.6 (3.51)
	Week 3 Change from Baseline: N, Mean (SD)	79, -1.5 (3.52)	45, -1.6 (2.78)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.13 (-1.31, 1.06)
	p-value [1]		0.830
	Week 6 Change from Baseline: N, Mean (SD)	70, -1.5 (3.81)	47, -2.2 (3.33)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.86 (-2.17, 0.45)
	p-value [1]		0.198
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 24.4 (4.55)	33, 23.6 (4.53)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, -0.4 (2.30)	33, -1.7 (3.61)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.42 (-2.94, 0.09)
	p-value [1]		0.066
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -1.0 (2.69)	32, -2.3 (3.12)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.43 (-2.88, 0.03)
	p-value [1]		0.054
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.20, 0.027

Note: PANSS Negative Subscale ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Negative Subscale and baseline PANSS Negative Subscale-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).

[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 31
PANSS General Psychopathology Subscale: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 30.1 (5.05)	47, 29.1 (4.66)
	Week 3 Change from Baseline: N, Mean (SD)	79, -0.6 (3.85)	45, -1.0 (4.35)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.81 (-2.19, 0.57)
	p-value [1]		0.250
	Week 6 Change from Baseline: N, Mean (SD)	70, -0.7 (3.21)	47, -1.7 (4.04)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.14 (-2.40, 0.13)
	p-value [1]		0.077
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 29.7 (5.40)	33, 28.7 (4.84)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.3 (3.57)	33, -0.9 (4.44)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.49 (-3.45, 0.46)
	p-value [1]		0.132
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, 0.0 (5.14)	32, -1.3 (5.10)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.40 (-3.99, 1.19)
	p-value [1]		0.284
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-1.93, 0.054

Note: PANSS General Psychopathology Subscale ranges from 16 to 112, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS General Psychopathology Subscale and baseline PANSS General Psychopathology Subscale-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 32
PANSS Marder Negative Factors: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 24.2 (3.81)	47, 24.1 (4.24)
	Week 3 Change from Baseline: N, Mean (SD)	79, -1.5 (3.28)	45, -1.1 (3.29)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.30 (-0.87, 1.46)
	p-value [1]		0.616
	Week 6 Change from Baseline: N, Mean (SD)	70, -1.6 (3.48)	47, -2.1 (3.34)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.63 (-1.89, 0.62)
	p-value [1]		0.320
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 23.0 (4.62)	33, 22.3 (5.45)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, -0.2 (2.55)	33, -1.8 (4.33)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.81 (-3.51, -0.11)
	p-value [1]		0.038
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -0.8 (2.80)	32, -2.5 (4.27)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.93 (-3.62, -0.24)
	p-value [1]		0.026
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.26, 0.024

Note: PANSS Marder Negative Factors ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Marder Negative Factors and baseline PANSS Marder Negative Factors-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 33
PANSS Excitement Component: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 6.3 (2.10)	47, 6.2 (1.57)
	Week 3 Change from Baseline: N, Mean (SD)	79, -0.1 (1.51)	45, -0.4 (1.63)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.39 (-0.88, 0.10)
	p-value [1]		0.114
	Week 6 Change from Baseline: N, Mean (SD)	70, -0.2 (1.57)	47, -0.4 (1.64)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.34 (-0.83, 0.16)
	p-value [1]		0.177
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 5.8 (1.27)	33, 6.7 (2.59)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.1 (1.52)	33, -0.4 (1.60)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.11 (-0.78, 0.56)
	p-value [1]		0.739
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, 0.0 (2.04)	32, -0.1 (1.77)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.30 (-0.61, 1.21)
	p-value [1]		0.512
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-0.35, 0.723

Note: PANSS Excitement Component ranges from 5 to 35, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Excitement Component and baseline PANSS Excitement Component-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 34
PANSS Prosocial Factors: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 18.4 (2.92)	47, 18.3 (3.24)
	Week 3 Change from Baseline: N, Mean (SD)	79, -1.0 (2.31)	45, -1.4 (2.26)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.44 (-1.27, 0.38)
	p-value [1]		0.288
	Week 6 Change from Baseline: N, Mean (SD)	70, -1.1 (2.53)	47, -2.0 (2.18)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.89 (-1.75, -0.03)
	p-value [1]		0.042
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 17.7 (3.27)	33, 17.0 (3.30)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.2 (1.90)	33, -0.5 (3.05)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.80 (-2.07, 0.46)
	p-value [1]		0.209
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -0.7 (2.02)	32, -1.4 (2.35)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.89 (-2.00, 0.22)
	p-value [1]		0.115
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.60, 0.009

Note: PANSS Prosocial Factors ranges from 6 to 42, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Prosocial Factors and baseline PANSS Prosocial Factors-by-visit interaction An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).

[3] SPCD Weighted Z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 35
PANSS General Psychopathology Subscale: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 30.5 (5.03)	47, 29.1 (4.66)
Week 3 Change from Baseline: N, Mean (SD)	40, -0.9 (3.90)	45, -1.0 (4.35)
Week 6 Change from Baseline: N, Mean (SD)	35, -0.8 (3.46)	47, -1.7 (4.04)
Week 9 Change from Baseline: N, Mean (SD)	32, -0.6 (4.48)	42, -2.5 (4.56)
Week 12 Change from Baseline: N, Mean (SD)	31, -0.6 (5.97)	42, -2.8 (4.51)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.028, -2.53 (-4.77, -0.28)

Note: PANSS General Psychopathology Subscale Score ranges from 16 to 112, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 36
PANSS Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 68.7 (7.99)	47, 67.4 (8.26)
	Week 6: N, Mean (SD)	80, 66.1 (9.11)	47, 62.7 (9.30)
	Change from Baseline: N, Mean (SD)	80, -2.6 (6.36)	47, -4.7 (6.98)
	Standard Effect Size		-0.331
	% Change from Baseline: N, Mean (SD)	80, -3.6 (9.24)	47, -6.8 (10.68)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.42 (-4.77, -0.07)
	p-value [1]		0.043
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 67.1 (9.00)	33, 65.6 (8.07)
	Week 12: N, Mean (SD)	30, 65.9 (10.84)	33, 62.3 (9.75)
	Change from Baseline [2]: N, Mean (SD)	30, -1.2 (7.60)	33, -3.3 (8.67)
	Standard Effect Size		-0.253
	% Change from Baseline [2]: N, Mean (SD)	30, -1.6 (10.96)	33, -4.6 (12.86)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.43 (-6.49, 1.62)
	p-value [1]		0.235
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.25, 0.024

Note: PANSS Total Score ranges from 30 to 210, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 37
PANSS General Psychopathology Subscale: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 30.1 (5.05)	47, 29.1 (4.66)
	Week 6: N, Mean (SD)	80, 29.2 (5.18)	47, 27.4 (4.89)
	Change from Baseline: N, Mean (SD)	80, -0.9 (3.22)	47, -1.7 (4.04)
	Standard Effect Size		-0.252
	% Change from Baseline: N, Mean (SD)	80, -2.4 (10.88)	47, -5.2 (13.95)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.11 (-2.34, 0.13)
	p-value [1]		0.078
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 29.7 (5.40)	33, 28.7 (4.84)
	Week 12: N, Mean (SD)	30, 29.8 (5.96)	33, 27.8 (6.32)
	Change from Baseline [2]: N, Mean (SD)	30, 0.1 (5.07)	33, -0.9 (5.53)
	Standard Effect Size		-0.196
	% Change from Baseline [2]: N, Mean (SD)	30, 1.4 (18.50)	33, -2.6 (18.42)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.35 (-3.93, 1.24)
	p-value [1]		0.302
	SPCD Weighted OLS z-statistic, overall p-value [3]		-1.88, 0.060

Note: PANSS General Psychopathology Subscale ranges from 16 to 112, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 38
PANSS Total Score: Change from Baseline SPCD MMRM, Observed Data
Per Protocol Population (N = 110)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	73, 68.8 (7.88)	37, 68.1 (8.72)
	Week 3 Change from Baseline: N, Mean (SD)	72, -2.7 (6.98)	37, -2.7 (6.33)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.17 (-2.82, 2.48)
	p-value [1]		0.898
	Week 6 Change from Baseline: N, Mean (SD)	63, -2.9 (5.99)	37, -4.9 (6.68)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.06 (-4.57, 0.45)
	p-value [1]		0.106
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	27, 66.4 (8.85)	29, 65.8 (8.03)
	Week 9 Change from Baseline [2]: N, Mean (SD)	27, -0.6 (5.23)	29, -4.0 (6.38)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.61 (-6.55, -0.67)
	p-value [1]		0.017
	Week 12 Change from Baseline [2]: N, Mean (SD)	26, -2.3 (7.35)	29, -4.9 (7.05)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.92 (-6.57, 0.73)
	p-value [1]		0.115
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.29, 0.022

Note: PANSS Total Score ranges from 30 to 210, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Total Score and baseline PANSS Total Score-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 39
PANSS Total Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
Per Protocol 12-Week Parallel Group (N = 74)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	37, 69.4 (8.50)	37, 68.1 (8.72)
Week 3 Change from Baseline: N, Mean (SD)	37, -2.8 (7.50)	37, -2.7 (6.33)
Week 6 Change from Baseline: N, Mean (SD)	32, -3.8 (5.37)	37, -4.9 (6.68)
Week 9 Change from Baseline: N, Mean (SD)	29, -4.6 (6.73)	35, -6.7 (6.94)
Week 12 Change from Baseline: N, Mean (SD)	28, -5.9 (7.88)	35, -6.9 (8.17)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.614, -0.98 (-4.86, 2.89)

Note: PANSS Total Score ranges from 30 to 210, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 40
PANSS Negative Subscale: Change from Baseline SPCD MMRM, Observed Data
Per Protocol Population (N = 110)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	73, 25.5 (3.68)	37, 24.9 (3.63)
	Week 3 Change from Baseline: N, Mean (SD)	72, -1.6 (3.60)	37, -1.3 (2.64)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.28 (-1.03, 1.59)
	p-value [1]		0.675
	Week 6 Change from Baseline: N, Mean (SD)	63, -1.7 (3.60)	37, -2.2 (3.11)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.75 (-2.12, 0.62)
	p-value [1]		0.280
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	27, 24.2 (4.74)	29, 24.1 (4.09)
	Week 9 Change from Baseline [2]: N, Mean (SD)	27, -0.5 (2.31)	29, -2.2 (2.80)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.77 (-3.15, -0.38)
	p-value [1]		0.014
	Week 12 Change from Baseline [2]: N, Mean (SD)	26, -1.1 (2.78)	29, -2.7 (2.83)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.65 (-3.14, -0.15)
	p-value [1]		0.031
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.17, 0.030

Note: PANSS Negative Subscale ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Negative Subscale and baseline PANSS Negative Subscale-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 41
PANSS Negative Subscale: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 25.2 (3.64)	47, 24.6 (3.51)
	Week 6: N, Mean (SD)	80, 23.8 (4.30)	47, 22.4 (4.64)
	Change from Baseline: N, Mean (SD)	80, -1.4 (3.65)	47, -2.2 (3.33)
	Standard Effect Size		-0.217
	% Change from Baseline: N, Mean (SD)	80, -5.1 (14.33)	47, -8.9 (13.81)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.90 (-2.16, 0.36)
	p-value [1]		0.159
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 24.4 (4.55)	33, 23.6 (4.53)
	Week 12: N, Mean (SD)	30, 23.4 (4.94)	33, 21.3 (4.49)
	Change from Baseline [2]: N, Mean (SD)	30, -1.0 (2.65)	33, -2.3 (3.08)
	Standard Effect Size		-0.452
	% Change from Baseline [2]: N, Mean (SD)	30, -3.9 (10.14)	33, -8.9 (14.10)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.43 (-2.86, -0.01)
	p-value [1]		0.049
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.34, 0.019

Note: PANSS Negative Subscale ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 42
PANSS Negative Subscale: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 25.9 (3.93)	47, 24.6 (3.51)
Week 3 Change from Baseline: N, Mean (SD)	40, -1.7 (3.61)	45, -1.6 (2.78)
Week 6 Change from Baseline: N, Mean (SD)	35, -2.0 (3.20)	47, -2.2 (3.33)
Week 9 Change from Baseline: N, Mean (SD)	32, -2.6 (4.16)	42, -3.6 (3.63)
Week 12 Change from Baseline: N, Mean (SD)	31, -3.1 (4.35)	42, -3.5 (3.74)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.566, -0.52 (-2.31, 1.27)

Note: PANSS Negative Subscale Score ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 43
PANSS Negative Subscale: Change from Baseline Parallel Group MMRM Analysis, Observed Data
Per Protocol 12-Week Parallel Group (N = 74)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	37, 26.1 (4.03)	37, 24.9 (3.63)
Week 3 Change from Baseline: N, Mean (SD)	37, -1.8 (3.67)	37, -1.3 (2.64)
Week 6 Change from Baseline: N, Mean (SD)	32, -2.3 (3.13)	37, -2.2 (3.11)
Week 9 Change from Baseline: N, Mean (SD)	29, -3.0 (4.04)	35, -3.2 (3.62)
Week 12 Change from Baseline: N, Mean (SD)	28, -3.6 (4.25)	35, -3.2 (3.65)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.872, 0.16 (-1.76, 2.07)

Note: PANSS Negative Subscale Score ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 44
PANSS Marder Negative Factors: Change from Baseline SPCD MMRM, Observed Data
Per Protocol Population (N = 110)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	73, 24.5 (3.85)	37, 24.2 (4.27)
	Week 3 Change from Baseline: N, Mean (SD)	72, -1.6 (3.29)	37, -0.9 (3.47)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.59 (-0.71, 1.89)
	p-value [1]		0.371
	Week 6 Change from Baseline: N, Mean (SD)	63, -1.6 (3.09)	37, -2.1 (3.31)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.51 (-1.79, 0.77)
	p-value [1]		0.433
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	27, 22.8 (4.82)	29, 22.9 (5.02)
	Week 9 Change from Baseline [2]: N, Mean (SD)	27, -0.2 (2.54)	29, -2.4 (3.47)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.21 (-3.83, -0.60)
	p-value [1]		0.008
	Week 12 Change from Baseline [2]: N, Mean (SD)	26, -0.7 (2.92)	29, -3.0 (3.90)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.31 (-4.08, -0.53)
	p-value [1]		0.012
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.34, 0.019

Note: PANSS Marder Negative Factors ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline PANSS Marder Negative Factors and baseline PANSS Marder Negative Factors-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 45
PANSS Marder Negative Factors: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 24.2 (3.81)	47, 24.1 (4.24)
	Week 6: N, Mean (SD)	80, 22.7 (4.77)	47, 21.9 (5.07)
	Change from Baseline: N, Mean (SD)	80, -1.5 (3.33)	47, -2.1 (3.34)
	Standard Effect Size		-0.187
	% Change from Baseline: N, Mean (SD)	80, -6.1 (14.26)	47, -8.8 (15.30)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.64 (-1.85, 0.57)
	p-value [1]		0.296
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 23.0 (4.62)	33, 22.3 (5.45)
	Week 12: N, Mean (SD)	30, 22.2 (4.67)	33, 19.8 (4.96)
	Change from Baseline [2]: N, Mean (SD)	30, -0.8 (2.75)	33, -2.5 (4.20)
	Standard Effect Size		-0.479
	% Change from Baseline [2]: N, Mean (SD)	30, -2.6 (11.93)	33, -8.4 (24.53)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.93 (-3.59, -0.28)
	p-value [1]		0.023
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.34, 0.019

Note: PANSS Marder Negative Factors ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 46
PANSS Marder Negative Factors: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 24.9 (3.93)	47, 24.1 (4.24)
Week 3 Change from Baseline: N, Mean (SD)	40, -1.7 (3.34)	45, -1.1 (3.29)
Week 6 Change from Baseline: N, Mean (SD)	35, -2.0 (2.53)	47, -2.1 (3.34)
Week 9 Change from Baseline: N, Mean (SD)	32, -2.4 (3.65)	42, -3.4 (3.66)
Week 12 Change from Baseline: N, Mean (SD)	31, -3.0 (3.72)	42, -3.4 (4.29)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.520, -0.59 (-2.39, 1.22)

Note: PANSS Marder Negative Factors Score ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 47
PANSS Marder Negative Factors: Change from Baseline Parallel Group MMRM Analysis, Observed Data
Per Protocol 12-Week Parallel Group (N = 74)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	37, 25.0 (4.08)	37, 24.2 (4.27)
Week 3 Change from Baseline: N, Mean (SD)	37, -1.8 (3.44)	37, -0.9 (3.47)
Week 6 Change from Baseline: N, Mean (SD)	32, -2.2 (2.50)	37, -2.1 (3.31)
Week 9 Change from Baseline: N, Mean (SD)	29, -2.7 (3.63)	35, -3.1 (3.75)
Week 12 Change from Baseline: N, Mean (SD)	28, -3.2 (3.85)	35, -3.1 (4.45)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.846, -0.20 (-2.19, 1.80)

Note: PANSS Marder Negative Factors Score ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 48
PANSS Prosocial Factors: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 18.4 (2.92)	47, 18.3 (3.24)
	Week 6: N, Mean (SD)	80, 17.4 (3.30)	47, 16.3 (3.55)
	Change from Baseline: N, Mean (SD)	80, -1.0 (2.44)	47, -2.0 (2.18)
	Standard Effect Size		-0.392
	% Change from Baseline: N, Mean (SD)	80, -5.1 (14.18)	47, -10.7 (12.27)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.94 (-1.78, -0.11)
	p-value [1]		0.027
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 17.7 (3.27)	33, 17.0 (3.30)
	Week 12: N, Mean (SD)	30, 17.2 (3.81)	33, 15.8 (3.00)
	Change from Baseline [2]: N, Mean (SD)	30, -0.5 (2.16)	33, -1.2 (2.57)
	Standard Effect Size		-0.311
	% Change from Baseline [2]: N, Mean (SD)	30, -2.8 (11.81)	33, -5.9 (16.78)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.91 (-2.07, 0.25)
	p-value [1]		0.124
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.70, 0.007

Note: PANSS Prosocial Factors ranges from 6 to 42, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 49
PANSS Prosocial Factors: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 18.7 (2.66)	47, 18.3 (3.24)
Week 3 Change from Baseline: N, Mean (SD)	40, -0.9 (2.03)	45, -1.4 (2.26)
Week 6 Change from Baseline: N, Mean (SD)	35, -1.3 (2.09)	47, -2.0 (2.18)
Week 9 Change from Baseline: N, Mean (SD)	32, -1.2 (2.88)	42, -2.4 (2.58)
Week 12 Change from Baseline: N, Mean (SD)	31, -2.0 (3.16)	42, -2.5 (2.66)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.405, -0.54 (-1.84, 0.75)

Note: PANSS Prosocial Factors Score ranges from 6 to 42, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 50
PANSS Positive Subscale: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 13.4 (2.81)	47, 13.6 (3.65)
	Week 6: N, Mean (SD)	80, 13.1 (3.67)	47, 12.8 (3.43)
	Change from Baseline: N, Mean (SD)	80, -0.3 (2.57)	47, -0.8 (2.63)
	Standard Effect Size		-0.201
	% Change from Baseline: N, Mean (SD)	80, -1.7 (19.66)	47, -3.9 (18.73)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.47 (-1.40, 0.45)
	p-value [1]		0.313
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 13.1 (3.64)	33, 13.3 (3.39)
	Week 12: N, Mean (SD)	30, 12.8 (3.88)	33, 13.2 (3.63)
	Change from Baseline [2]: N, Mean (SD)	30, -0.3 (2.06)	33, -0.1 (2.93)
	Standard Effect Size		0.107
	% Change from Baseline [2]: N, Mean (SD)	30, -2.1 (14.27)	33, 1.3 (23.34)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.31 (-0.94, 1.56)
	p-value [1]		0.620
	SPCD Weighted OLS z-statistic, overall p-value [3]		-0.42, 0.672

Note: PANSS Positive Subscale ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 51
PANSS Positive Subscale: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 12.9 (2.42)	47, 13.6 (3.65)
Week 3 Change from Baseline: N, Mean (SD)	40, -0.2 (2.75)	45, -0.6 (1.83)
Week 6 Change from Baseline: N, Mean (SD)	35, -0.2 (3.06)	47, -0.8 (2.63)
Week 9 Change from Baseline: N, Mean (SD)	32, 0.2 (2.87)	42, -1.2 (2.66)
Week 12 Change from Baseline: N, Mean (SD)	31, -0.6 (3.04)	42, -1.1 (2.69)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.791, -0.17 (-1.42, 1.09)

Note: PANSS Positive Subscale Score ranges from 7 to 49, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 52
NSA-16 Global Negative Symptoms Rating: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 4.6 (0.61)	47, 4.6 (0.64)
	Week 3 Change from Baseline: N, Mean (SD)	79, -0.2 (0.65)	45, -0.2 (0.52)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.02 (-0.19, 0.24)
	p-value [1]		0.840
	Week 6 Change from Baseline: N, Mean (SD)	70, -0.2 (0.65)	47, -0.4 (0.68)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.17 (-0.40, 0.07)
	p-value [1]		0.167
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 4.3 (0.71)	33, 4.4 (0.75)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, -0.0 (0.49)	33, -0.2 (0.55)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.17 (-0.43, 0.09)
	p-value [1]		0.206
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -0.1 (0.52)	32, -0.5 (0.76)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.29 (-0.61, 0.03)
	p-value [1]		0.079
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		-2.23, 0.026

Note: NSA-16 Global Negative Symptoms Rating ranges from 1 to 7, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline NSA-16 Global Negative Symptoms Rating, and baseline NSA-16 Global Negative Symptoms Rating-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 53
NSA-16 Global Negative Symptoms Rating: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 4.6 (0.61)	47, 4.6 (0.64)
	Week 6: N, Mean (SD)	80, 4.4 (0.73)	47, 4.2 (0.81)
	Change from Baseline: N, Mean (SD)	80, -0.2 (0.64)	47, -0.4 (0.68)
	Standard Effect Size		-0.310
	% Change from Baseline: N, Mean (SD)	80, -3.7 (14.75)	47, -8.4 (14.46)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.18 (-0.41, 0.05)
	p-value [1]		0.122
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 4.3 (0.71)	33, 4.4 (0.75)
	Week 12: N, Mean (SD)	30, 4.2 (0.89)	33, 4.0 (0.73)
	Change from Baseline [2]: N, Mean (SD)	30, -0.1 (0.51)	33, -0.5 (0.75)
	Standard Effect Size		-0.495
	% Change from Baseline [2]: N, Mean (SD)	30, -3.1 (12.81)	33, -9.2 (14.28)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.30 (-0.61, 0.02)
	p-value [1]		0.064
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.42, 0.016

Note: NSA-16 Global Negative Symptoms Rating ranges from 1 to 7, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 54
NSA-16 Global Negative Symptoms Rating: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 4.6 (0.59)	47, 4.6 (0.64)
Week 3 Change from Baseline: N, Mean (SD)	40, -0.2 (0.64)	45, -0.2 (0.52)
Week 6 Change from Baseline: N, Mean (SD)	35, -0.3 (0.52)	47, -0.4 (0.68)
Week 9 Change from Baseline: N, Mean (SD)	32, -0.3 (0.60)	42, -0.5 (0.59)
Week 12 Change from Baseline: N, Mean (SD)	31, -0.5 (0.68)	42, -0.6 (0.62)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.250, -0.17 (-0.47, 0.12)

Note: NSA-16 Global Negative Symptoms Rating Score ranges from 1 to 7, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 55
NSA-16 Global Negative Symptoms Rating: Change from Baseline Parallel Group ANCOVA by Visit, LOCF Data
mITT 12-Week Parallel Group Population (N = 87)

Visit	Result/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline	N, Mean (SD)	40, 4.6 (0.59)	47, 4.6 (0.64)
Week 3	N, Mean (SD)	40, 4.4 (0.81)	45, 4.5 (0.66)
Week 3	Change from Baseline: N, Mean (SD)	40, -0.2 (0.64)	45, -0.2 (0.52)
Week 3	Standard Effect Size		0.034
Week 3	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.810, 0.03 (-0.22, 0.27)
Week 6	N, Mean (SD)	40, 4.3 (0.69)	47, 4.2 (0.81)
Week 6	Change from Baseline: N, Mean (SD)	40, -0.3 (0.49)	47, -0.4 (0.68)
Week 6	Standard Effect Size		-0.256
Week 6	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.272, -0.14 (-0.39, 0.11)
Week 9	N, Mean (SD)	40, 4.3 (0.79)	47, 4.1 (0.76)
Week 9	Change from Baseline: N, Mean (SD)	40, -0.3 (0.55)	47, -0.5 (0.58)
Week 9	Standard Effect Size		-0.450
Week 9	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.046, -0.25 (-0.49, -0.00)
Week 12	N, Mean (SD)	40, 4.2 (0.85)	47, 4.0 (0.91)
Week 12	Change from Baseline: N, Mean (SD)	40, -0.4 (0.63)	47, -0.6 (0.61)
Week 12	Standard Effect Size		-0.356
Week 12	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.103, -0.22 (-0.49, 0.05)

Note: NSA-16 Global Negative Symptoms Rating Score ranges from 1 to 7, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
Missing values were imputed by LOCF and visit windows were used to classify unscheduled or ET visits.
LS mean difference and p-values were from ANCOVA with treatment as fixed effect and Stage 1 Baseline value as a covariate.
Patients within each treatment group received the same treatment throughout their participation in the study.

Table 56
CDSS Score: Change from Baseline SPCD MMRM, Observed Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 0.9 (1.31)	47, 1.1 (1.34)
	Week 3 Change from Baseline: N, Mean (SD)	79, 0.2 (1.11)	45, 0.0 (1.24)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.15 (-0.56, 0.26)
	p-value [1]		0.474
	Week 6 Change from Baseline: N, Mean (SD)	70, -0.1 (1.02)	47, -0.2 (1.34)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.07 (-0.48, 0.35)
	p-value [1]		0.747
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 1.0 (1.56)	33, 0.8 (1.54)
	Week 9 Change from Baseline [2]: N, Mean (SD)	30, 0.1 (1.32)	33, 0.1 (0.91)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.04 (-0.57, 0.48)
	p-value [1]		0.870
	Week 12 Change from Baseline [2]: N, Mean (SD)	29, -0.4 (1.24)	32, -0.0 (1.66)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.34 (-0.29, 0.96)
	p-value [1]		0.285
	SPCD Week 6 and 12 MMRM Weighted z-statistic, overall p-value [3]		0.53, 0.595

Note: CDSS Score ranges from 0 to 27, with higher scores indicating greater clinical severity of symptoms.
[1] MMRM with fixed effect of treatment, visit, treatment-by-visit interaction, baseline CDSS Score and baseline CDSS Score-by-visit interaction. An unstructured covariance matrix was used.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4. Treatment differences in each stage were estimated by the MMRM.

Table 57
CDSS Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 0.9 (1.31)	47, 1.1 (1.34)
	Week 6: N, Mean (SD)	80, 0.8 (1.52)	47, 0.9 (1.49)
	Change from Baseline: N, Mean (SD)	80, -0.0 (1.03)	47, -0.2 (1.34)
	Standard Effect Size		-0.126
	% Change from Baseline: N, Mean (SD)	34, -28.6 (68.86)	25, -19.3 (127.81)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.10 (-0.50, 0.31)
	p-value [1]		0.640
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	30, 1.0 (1.56)	33, 0.8 (1.54)
	Week 12: N, Mean (SD)	30, 0.6 (1.13)	33, 0.9 (1.69)
	Change from Baseline [2]: N, Mean (SD)	30, -0.3 (1.24)	33, 0.0 (1.67)
	Standard Effect Size		0.246
	% Change from Baseline [2]: N, Mean (SD)	13, -41.0 (65.48)	12, -68.1 (50.48)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.30 (-0.33, 0.94)
	p-value [1]		0.343
	SPCD Weighted OLS z-statistic, overall p-value [3]		0.36, 0.722

Note: CDSS Score ranges from 0 to 27, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 58
CDSS Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 0.9 (1.44)	47, 1.1 (1.34)
Week 3 Change from Baseline: N, Mean (SD)	40, 0.2 (1.29)	45, 0.0 (1.24)
Week 6 Change from Baseline: N, Mean (SD)	35, -0.1 (1.26)	47, -0.2 (1.34)
Week 9 Change from Baseline: N, Mean (SD)	32, 0.0 (0.88)	42, 0.0 (1.68)
Week 12 Change from Baseline: N, Mean (SD)	31, -0.4 (0.99)	42, -0.2 (1.27)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.368, 0.19 (-0.23, 0.61)

Note: CDSS Score ranges from 0 to 27, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 59
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Baseline MCCB Composite < 30

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	42, 61.8 (8.48)	19, 60.8 (7.38)
	Week 6: N, Mean (SD)	42, 58.3 (9.62)	19, 56.1 (8.50)
	Change from Baseline: N, Mean (SD)	42, -3.5 (5.28)	19, -4.7 (5.46)
	Standard Effect Size		-0.226
	% Change from Baseline: N, Mean (SD)	42, -5.6 (8.65)	19, -7.7 (9.53)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.28 (-4.24, 1.69)
	p-value [1]		0.393
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	15, 60.4 (11.37)	20, 56.3 (7.75)
	Week 12: N, Mean (SD)	15, 58.4 (13.25)	20, 54.6 (8.71)
	Change from Baseline [2]: N, Mean (SD)	15, -2.0 (4.84)	20, -1.8 (3.68)
	Standard Effect Size		0.059
	% Change from Baseline [2]: N, Mean (SD)	15, -3.8 (8.37)	20, -3.2 (6.64)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		0.50 (-2.52, 3.52)
	p-value [1]		0.737
	SPCD Weighted OLS z-statistic, overall p-value [3]		-0.53, 0.598

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 60
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Baseline MCCB Composite ≥ 30

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	38, 58.8 (6.49)	28, 61.1 (7.76)
	Week 6: N, Mean (SD)	38, 56.4 (8.75)	28, 55.8 (9.07)
	Change from Baseline: N, Mean (SD)	38, -2.4 (6.30)	28, -5.3 (5.85)
	Standard Effect Size		-0.477
	% Change from Baseline: N, Mean (SD)	38, -4.0 (10.35)	28, -8.6 (9.40)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.73 (-5.82, 0.37)
	p-value [1]		0.083
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	15, 54.7 (6.02)	13, 59.6 (10.85)
	Week 12: N, Mean (SD)	15, 52.4 (8.28)	13, 53.2 (8.80)
	Change from Baseline [2]: N, Mean (SD)	15, -2.3 (6.96)	13, -6.4 (8.47)
	Standard Effect Size		-0.527
	% Change from Baseline [2]: N, Mean (SD)	15, -4.1 (11.36)	13, -9.5 (14.46)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-2.06 (-7.74, 3.62)
	p-value [1]		0.463
	SPCD Weighted OLS z-statistic, overall p-value [3]		-1.71, 0.088

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).

[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 61
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Total Score

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.04 (0.130)	0.00 (0.0, 0.8)	36	0.05 (0.159)	0.00 (0.0, 0.8)	20	0.01 (0.031)	0.00 (0.0, 0.1)
Week 6	51	0.03 (0.132)	0.00 (0.0, 0.9)	33	0.05 (0.162)	0.00 (0.0, 0.9)	18	0.00 (0.000)	0.00 (0.0, 0.0)
Week 12	39	0.03 (0.132)	0.00 (0.0, 0.8)	26	0.04 (0.160)	0.00 (0.0, 0.8)	13	0.00 (0.000)	0.00 (0.0, 0.0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.05 (0.092)	0.00 (0.0, 0.4)	30	0.05 (0.107)	0.00 (0.0, 0.4)	18	0.04 (0.062)	0.00 (0.0, 0.2)
Week 6	47	0.05 (0.093)	0.00 (0.0, 0.5)	30	0.04 (0.073)	0.00 (0.0, 0.2)	17	0.05 (0.123)	0.00 (0.0, 0.5)
Week 12	42	0.04 (0.062)	0.00 (0.0, 0.2)	28	0.03 (0.061)	0.00 (0.0, 0.2)	14	0.04 (0.065)	0.00 (0.0, 0.2)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.08 (0.137)	0.00 (0.0, 0.5)	33	0.09 (0.147)	0.00 (0.0, 0.5)	7	0.01 (0.038)	0.00 (0.0, 0.1)
Week 6	40	0.07 (0.120)	0.00 (0.0, 0.4)	33	0.07 (0.115)	0.00 (0.0, 0.4)	7	0.07 (0.150)	0.00 (0.0, 0.4)
d6-DM/Q									
Week 6 (BL) [2]	39	0.07 (0.120)	0.00 (0.0, 0.4)	32	0.07 (0.115)	0.00 (0.0, 0.4)	7	0.07 (0.150)	0.00 (0.0, 0.4)
Week 12	39	0.08 (0.188)	0.00 (0.0, 1.0)	32	0.09 (0.205)	0.00 (0.0, 1.0)	7	0.01 (0.038)	0.00 (0.0, 0.1)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Gait

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.1 (0.43)	0.0 (0, 2)	36	0.2 (0.51)	0.0 (0, 2)	20	0.1 (0.22)	0.0 (0, 1)
Week 6	51	0.1 (0.36)	0.0 (0, 2)	33	0.2 (0.44)	0.0 (0, 2)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.35)	0.0 (0, 2)	26	0.1 (0.43)	0.0 (0, 2)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.2 (0.39)	0.0 (0, 1)	30	0.2 (0.38)	0.0 (0, 1)	18	0.2 (0.43)	0.0 (0, 1)
Week 6	47	0.2 (0.43)	0.0 (0, 1)	30	0.2 (0.41)	0.0 (0, 1)	17	0.3 (0.47)	0.0 (0, 1)
Week 12	42	0.2 (0.40)	0.0 (0, 1)	28	0.1 (0.36)	0.0 (0, 1)	14	0.3 (0.47)	0.0 (0, 1)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.3 (0.51)	0.0 (0, 2)	33	0.3 (0.53)	0.0 (0, 2)	7	0.1 (0.38)	0.0 (0, 1)
Week 6	40	0.3 (0.49)	0.0 (0, 2)	33	0.3 (0.52)	0.0 (0, 2)	7	0.1 (0.38)	0.0 (0, 1)
d6-DM/Q									
Week 6 (BL) [2]	39	0.3 (0.50)	0.0 (0, 2)	32	0.3 (0.52)	0.0 (0, 2)	7	0.1 (0.38)	0.0 (0, 1)
Week 12	39	0.2 (0.43)	0.0 (0, 1)	32	0.3 (0.44)	0.0 (0, 1)	7	0.1 (0.38)	0.0 (0, 1)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Arm Dropping

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.13)	0.0 (0, 1)	36	0.0 (0.17)	0.0 (0, 1)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.14)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.16)	0.0 (0, 1)	26	0.0 (0.20)	0.0 (0, 1)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.14)	0.0 (0, 1)	30	0.0 (0.00)	0.0 (0, 0)	18	0.1 (0.24)	0.0 (0, 1)
Week 6	47	0.0 (0.00)	0.0 (0, 0)	30	0.0 (0.00)	0.0 (0, 0)	17	0.0 (0.00)	0.0 (0, 0)
Week 12	42	0.0 (0.00)	0.0 (0, 0)	28	0.0 (0.00)	0.0 (0, 0)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.22)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.0 (0.16)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.0 (0.16)	0.0 (0, 1)	32	0.0 (0.18)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.22)	0.0 (0, 1)	32	0.1 (0.25)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Shoulder Shaking

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.27)	0.0 (0, 2)	36	0.1 (0.33)	0.0 (0, 2)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.20)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.32)	0.0 (0, 2)	26	0.1 (0.39)	0.0 (0, 2)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.20)	0.0 (0, 1)	30	0.1 (0.25)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 6	47	0.0 (0.20)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	17	0.1 (0.24)	0.0 (0, 1)
Week 12	42	0.0 (0.15)	0.0 (0, 1)	28	0.0 (0.19)	0.0 (0, 1)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.22)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.1 (0.27)	0.0 (0, 1)	33	0.1 (0.29)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.1 (0.27)	0.0 (0, 1)	32	0.1 (0.30)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.22)	0.0 (0, 1)	32	0.1 (0.25)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Elbow Rigidity

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.13)	0.0 (0, 1)	36	0.0 (0.17)	0.0 (0, 1)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.28)	0.0 (0, 2)	33	0.1 (0.35)	0.0 (0, 2)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.16)	0.0 (0, 1)	26	0.0 (0.20)	0.0 (0, 1)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.14)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 6	47	0.0 (0.15)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	17	0.0 (0.00)	0.0 (0, 0)
Week 12	42	0.0 (0.00)	0.0 (0, 0)	28	0.0 (0.00)	0.0 (0, 0)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.0 (0.16)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.0 (0.16)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.0 (0.16)	0.0 (0, 1)	32	0.0 (0.18)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.27)	0.0 (0, 1)	32	0.1 (0.30)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Wrist Rigid/Fixation of Position

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.27)	0.0 (0, 2)	36	0.1 (0.33)	0.0 (0, 2)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.28)	0.0 (0, 2)	33	0.1 (0.35)	0.0 (0, 2)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.00)	0.0 (0, 0)	26	0.0 (0.00)	0.0 (0, 0)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.14)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 6	47	0.0 (0.20)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	17	0.1 (0.24)	0.0 (0, 1)
Week 12	42	0.0 (0.00)	0.0 (0, 0)	28	0.0 (0.00)	0.0 (0, 0)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.0 (0.00)	0.0 (0, 0)	33	0.0 (0.00)	0.0 (0, 0)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.0 (0.00)	0.0 (0, 0)	33	0.0 (0.00)	0.0 (0, 0)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.0 (0.00)	0.0 (0, 0)	32	0.0 (0.00)	0.0 (0, 0)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.27)	0.0 (0, 1)	32	0.1 (0.30)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Leg Pendulousness

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.27)	0.0 (0, 2)	36	0.1 (0.33)	0.0 (0, 2)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.00)	0.0 (0, 0)	33	0.0 (0.00)	0.0 (0, 0)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.00)	0.0 (0, 0)	26	0.0 (0.00)	0.0 (0, 0)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.14)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 6	47	0.0 (0.15)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	17	0.0 (0.00)	0.0 (0, 0)
Week 12	42	0.1 (0.34)	0.0 (0, 2)	28	0.0 (0.19)	0.0 (0, 1)	14	0.1 (0.53)	0.0 (0, 2)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.35)	0.0 (0, 2)	33	0.1 (0.38)	0.0 (0, 2)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.1 (0.22)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.1 (0.22)	0.0 (0, 1)	32	0.1 (0.25)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.35)	0.0 (0, 2)	32	0.1 (0.39)	0.0 (0, 2)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Head Rotation

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.27)	0.0 (0, 2)	36	0.1 (0.33)	0.0 (0, 2)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.14)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.48)	0.0 (0, 3)	26	0.1 (0.59)	0.0 (0, 3)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.14)	0.0 (0, 1)	30	0.0 (0.00)	0.0 (0, 0)	18	0.1 (0.24)	0.0 (0, 1)
Week 6	47	0.0 (0.15)	0.0 (0, 1)	30	0.0 (0.00)	0.0 (0, 0)	17	0.1 (0.24)	0.0 (0, 1)
Week 12	42	0.0 (0.00)	0.0 (0, 0)	28	0.0 (0.00)	0.0 (0, 0)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.33)	0.0 (0, 1)	33	0.2 (0.36)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.1 (0.22)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.0 (0.16)	0.0 (0, 1)	32	0.0 (0.18)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.27)	0.0 (0, 1)	32	0.1 (0.30)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Glabella Tap

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.13)	0.0 (0, 1)	36	0.0 (0.17)	0.0 (0, 1)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.14)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.00)	0.0 (0, 0)	26	0.0 (0.00)	0.0 (0, 0)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.20)	0.0 (0, 1)	30	0.0 (0.18)	0.0 (0, 1)	18	0.1 (0.24)	0.0 (0, 1)
Week 6	47	0.0 (0.15)	0.0 (0, 1)	30	0.0 (0.00)	0.0 (0, 0)	17	0.1 (0.24)	0.0 (0, 1)
Week 12	42	0.0 (0.22)	0.0 (0, 1)	28	0.1 (0.26)	0.0 (0, 1)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.22)	0.0 (0, 1)	33	0.1 (0.24)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.1 (0.65)	0.0 (0, 4)	33	0.0 (0.17)	0.0 (0, 1)	7	0.6 (1.51)	0.0 (0, 4)
d6-DM/Q									
Week 6 (BL) [2]	39	0.1 (0.64)	0.0 (0, 4)	32	0.0 (0.00)	0.0 (0, 0)	7	0.6 (1.51)	0.0 (0, 4)
Week 12	39	0.0 (0.16)	0.0 (0, 1)	32	0.0 (0.18)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Tremor

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.13)	0.0 (0, 1)	36	0.0 (0.17)	0.0 (0, 1)	20	0.0 (0.00)	0.0 (0, 0)
Week 6	51	0.0 (0.14)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.16)	0.0 (0, 1)	26	0.0 (0.20)	0.0 (0, 1)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.1 (0.33)	0.0 (0, 1)	30	0.2 (0.38)	0.0 (0, 1)	18	0.1 (0.24)	0.0 (0, 1)
Week 6	47	0.1 (0.25)	0.0 (0, 1)	30	0.1 (0.31)	0.0 (0, 1)	17	0.0 (0.00)	0.0 (0, 0)
Week 12	42	0.0 (0.15)	0.0 (0, 1)	28	0.0 (0.19)	0.0 (0, 1)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.0 (0.16)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.1 (0.30)	0.0 (0, 1)	33	0.1 (0.33)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.1 (0.31)	0.0 (0, 1)	32	0.1 (0.34)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.22)	0.0 (0, 1)	32	0.1 (0.25)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 61 (continued)
Summary of Simpson-Angus Scale (SAS) by Gender and Visit
Safety Population (N = 144)
Item: Salivation

Treatment	Males and Females			Males Only			Females Only		
Visit	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
Placebo/Placebo (N = 56)									
Baseline [1]	56	0.0 (0.13)	0.0 (0, 1)	36	0.0 (0.00)	0.0 (0, 0)	20	0.1 (0.22)	0.0 (0, 1)
Week 6	51	0.0 (0.00)	0.0 (0, 0)	33	0.0 (0.00)	0.0 (0, 0)	18	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.0 (0.00)	0.0 (0, 0)	26	0.0 (0.00)	0.0 (0, 0)	13	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q/d6-DM/Q (N = 48)									
Baseline [1]	48	0.0 (0.00)	0.0 (0, 0)	30	0.0 (0.00)	0.0 (0, 0)	18	0.0 (0.00)	0.0 (0, 0)
Week 6	47	0.0 (0.00)	0.0 (0, 0)	30	0.0 (0.00)	0.0 (0, 0)	17	0.0 (0.00)	0.0 (0, 0)
Week 12	42	0.0 (0.00)	0.0 (0, 0)	28	0.0 (0.00)	0.0 (0, 0)	14	0.0 (0.00)	0.0 (0, 0)
Placebo/d6-DM/Q (N = 40)									
Placebo									
Baseline [1]	40	0.1 (0.44)	0.0 (0, 2)	33	0.1 (0.48)	0.0 (0, 2)	7	0.0 (0.00)	0.0 (0, 0)
Week 6	40	0.0 (0.16)	0.0 (0, 1)	33	0.0 (0.17)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
d6-DM/Q									
Week 6 (BL) [2]	39	0.0 (0.16)	0.0 (0, 1)	32	0.0 (0.18)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)
Week 12	39	0.1 (0.27)	0.0 (0, 1)	32	0.1 (0.30)	0.0 (0, 1)	7	0.0 (0.00)	0.0 (0, 0)

Note: SAS total score ranges from 0 to 40, with higher scores indicating greater severity of extrapyramidal symptoms. Individual item scores range from 0 to 4.
Visit windows are used to classify unscheduled or early termination visits.
[1] Baseline for Placebo/Placebo and d6-DM/Q/d6-DM/Q is defined as the last non-missing assessment prior to randomization.
[2] Baseline for Stage 2 is the Week 6 assessment for the Placebo/d6-DM/Q group.

Table 62
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Gait

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	75 (82.4)	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	78 (85.7)
Stage 1	Stage 1 Placebo (N = 96)	1	2 (2.2)	8 (8.8)	1 (1.1)	0 (0.0)	0 (0.0)	11 (12.1)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	35 (74.5)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	36 (76.6)
	Stage 1 d6-DM/Q (N = 48)	1	3 (6.4)	8 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (23.4)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	37 (94.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	37 (94.9)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	28 (71.8)	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	30 (76.9)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	2 (5.1)	7 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (23.1)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Arm Dropping

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	87 (95.6)	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	89 (97.8)
Stage 1	Stage 1 Placebo (N = 96)	1	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	46 (97.9)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	47 (100.0)
	Stage 1 d6-DM/Q (N = 48)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (97.4)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	36 (92.3)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	37 (94.9)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Shoulder Shaking

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	85 (93.4)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	86 (94.5)
Stage 1	Stage 1 Placebo (N = 96)	1	3 (3.3)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	5 (5.5)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	44 (93.6)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	45 (95.7)
	Stage 1 d6-DM/Q (N = 48)	1	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (97.4)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	35 (89.7)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	37 (94.9)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Elbow Rigidity

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	88 (96.7)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	89 (97.8)
Stage 1	Stage 1 Placebo (N = 96)	1	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	46 (97.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	46 (97.9)
	Stage 1 d6-DM/Q (N = 48)	1	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (97.4)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	35 (89.7)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	36 (92.3)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.7)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Wrist Rigid/Fixation of Position

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	90 (98.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	90 (98.9)
Stage 1	Stage 1 Placebo (N = 96)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	45 (95.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	45 (95.7)
	Stage 1 d6-DM/Q (N = 48)	1	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	39 (100.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	36 (92.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (92.3)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.7)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Leg Pendulousness

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	88 (96.7)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	89 (97.8)
Stage 1	Stage 1 Placebo (N = 96)	1	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	46 (97.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	46 (97.9)
	Stage 1 d6-DM/Q (N = 48)	1	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	39 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	39 (100.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	36 (92.3)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	37 (94.9)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Head Rotation

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	84 (92.3)	4 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	88 (96.7)
Stage 1	Stage 1 Placebo (N = 96)	1	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.3)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	45 (95.7)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	46 (97.9)
	Stage 1 d6-DM/Q (N = 48)	1	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (97.4)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	36 (92.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (92.3)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	2 (5.1)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.7)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Glabella Tap

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	87 (95.6)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	88 (96.7)
Stage 1	Stage 1 Placebo (N = 96)	1	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
	Stage 1 d6-DM/Q (N = 48)	0	44 (93.6)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	46 (97.9)
	Stage 1 d6-DM/Q (N = 48)	1	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	38 (97.4)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	39 (100.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	37 (94.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	38 (97.4)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Tremor

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	85 (93.4)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	86 (94.5)
Stage 1	Stage 1 Placebo (N = 96)	1	4 (4.4)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.5)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	40 (85.1)	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	44 (93.6)
	Stage 1 d6-DM/Q (N = 48)	1	1 (2.1)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.4)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	37 (94.9)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	38 (97.4)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	34 (87.2)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	37 (94.9)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 62 (continued)
Shift Table of SAS from Baseline to End of Stage
Safety Population (N = 144)
Item: Salivation

Stage	Treatment	End of Stage	Baseline 0	1	2	3	4	Total
Stage 1	Stage 1 Placebo (N = 96)	0	88 (96.7)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	90 (98.9)
Stage 1	Stage 1 Placebo (N = 96)	1	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)
Stage 1	Stage 1 Placebo (N = 96)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 1	Stage 1 Placebo (N = 96)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	0	47 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	47 (100.0)
	Stage 1 d6-DM/Q (N = 48)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 d6-DM/Q (N = 48)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	0	39 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	39 (100.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2	Stage 1 Placebo Re-randomized to Placebo (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	0	35 (89.7)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	36 (92.3)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	1	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.7)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Stage 1 Placebo Re-randomized to d6-DM/Q (N = 40)	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are based on the number of patients in each treatment with a baseline and post-baseline value within a stage.
Stage 1 compares the Stage 1 Baseline to the last post-baseline visit in Stage 1, including Week 6.
Stage 1 re-randomized compares Stage 2 Baseline to the last assessment, whenever it occurred.

Table 63
MCCB Composite Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	80, 28.8 (13.09)	47, 32.5 (11.37)
	Week 6: N, Mean (SD)	75, 30.1 (12.44)	46, 33.6 (12.73)
	Change from Baseline: N, Mean (SD)	75, 1.6 (4.55)	46, 1.2 (5.11)
	Standard Effect Size		-0.083
	% Change from Baseline: N, Mean (SD)	75, 15.7 (50.64)	46, 4.7 (17.95)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.12 (-1.88, 1.64)
	p-value [1]		0.893
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	27, 31.7 (14.99)	30, 28.9 (10.69)
	Week 12: N, Mean (SD)	27, 30.0 (15.60)	30, 30.5 (10.99)
	Change from Baseline [2]: N, Mean (SD)	27, -1.6 (4.06)	30, 1.6 (3.71)
	Standard Effect Size		0.833
	% Change from Baseline [2]: N, Mean (SD)	27, -7.9 (23.15)	30, 6.6 (15.50)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		3.21 (1.11, 5.30)
	p-value [1]		0.003
	SPCD Weighted OLS z-statistic, overall p-value [3]		1.78, 0.074

Note: MCCB Composite Score with higher scores indicating less clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 64
MCCB Composite Score: Change from Baseline SPCD ANCOVA, LOCF Data
Per Protocol Population (N = 110)

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	73, 28.4 (13.06)	37, 32.6 (10.94)
	Week 6: N, Mean (SD)	69, 29.6 (12.14)	36, 33.6 (11.66)
	Change from Baseline: N, Mean (SD)	69, 1.7 (4.51)	36, 1.1 (4.76)
	Standard Effect Size		-0.112
	% Change from Baseline: N, Mean (SD)	69, 16.8 (52.49)	36, 5.2 (17.35)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.04 (-1.87, 1.80)
	p-value [1]		0.967
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	24, 31.6 (14.75)	28, 28.4 (10.88)
	Week 12: N, Mean (SD)	24, 29.8 (15.29)	28, 30.3 (11.34)
	Change from Baseline [2]: N, Mean (SD)	24, -1.8 (4.23)	28, 1.9 (3.70)
	Standard Effect Size		0.923
	% Change from Baseline [2]: N, Mean (SD)	24, -8.6 (24.33)	28, 7.5 (15.69)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		3.62 (1.37, 5.87)
	p-value [1]		0.002
	SPCD Weighted OLS z-statistic, overall p-value [3]		2.00, 0.046

Note: MCCB Composite Score ranges from 1 to 70, with higher scores indicating less clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 65
MCCB Composite Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 30.8 (14.26)	47, 32.5 (11.37)
Week 6 Change from Baseline: N, Mean (SD)	36, 0.6 (4.03)	46, 1.2 (5.11)
Week 12 Change from Baseline: N, Mean (SD)	31, -1.2 (4.59)	42, -0.0 (6.22)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.498, 0.91 (-1.76, 3.59)

Note: MCCB Composite Score ranges from 1 to 70, with higher scores indicating less clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 66
MCCB Composite Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
Per Protocol 12-Week Parallel Group (N = 74)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	37, 30.5 (14.20)	37, 32.6 (10.94)
Week 6 Change from Baseline: N, Mean (SD)	33, 0.8 (4.04)	36, 1.1 (4.76)
Week 12 Change from Baseline: N, Mean (SD)	28, -1.1 (4.51)	35, 0.1 (6.48)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.524, 0.93 (-1.97, 3.84)

Note: MCCB Composite Score ranges from 1 to 70, with higher scores indicating less clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 67
Prior Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Stage 1 Placebo (N=96)**	**Stage 1 d6-DM/Q (N=48)**
Overall	12 (12.5)	7 (14.6)
ANALGESICS	1 (1.0)	2 (4.2)
Lenoltec With Codeine No 1	0 (0.0)	1 (2.1)
Oxycocet	1 (1.0)	0 (0.0)
Paracetamol	0 (0.0)	1 (2.1)
ANTI-PARKINSON DRUGS	0 (0.0)	1 (2.1)
Benzatropine Mesilate	0 (0.0)	1 (2.1)
ANTIANEMIC PREPARATIONS	1 (1.0)	0 (0.0)
Mecobalamin	1 (1.0)	0 (0.0)
ANTIBACTERIALS FOR SYSTEMIC USE	1 (1.0)	0 (0.0)
Cefadroxil	1 (1.0)	0 (0.0)
ANTIEMETICS AND ANTINAUSEANTS	0 (0.0)	1 (2.1)
Ondansetron	0 (0.0)	1 (2.1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1 (1.0)	0 (0.0)
Ibuprofen	1 (1.0)	0 (0.0)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1 (1.0)	0 (0.0)
Seretide	1 (1.0)	0 (0.0)
DRUGS USED IN DIABETES	1 (1.0)	0 (0.0)

Note: Prior medications are defined as medications with a stop date prior to the first dose date of randomized study medication. Medications are coded using WHO Drug Dictionary Version September 2015
Treatment allocation based on Stage 1 randomization.

Table 67 (continued)
Prior Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Stage 1 Placebo** **(N=96)**	**Stage 1 d6-DM/Q** **(N=48)**
DRUGS USED IN DIABETES (cont'd)		
Metformin	1 (1.0)	0 (0.0)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (1.0)	0 (0.0)
Methionine	1 (1.0)	0 (0.0)
PSYCHOANALEPTICS	1 (1.0)	1 (2.1)
Fluoxetine	0 (0.0)	1 (2.1)
Trazodone	1 (1.0)	0 (0.0)
PSYCHOLEPTICS	7 (7.3)	5 (10.4)
Aripiprazole	0 (0.0)	2 (4.2)
Diphenhydramine	0 (0.0)	1 (2.1)
Diphenhydramine Hydrochloride	0 (0.0)	1 (2.1)
Hydroxyzine	0 (0.0)	1 (2.1)
Lithium Carbonate	1 (1.0)	0 (0.0)
Olanzapine	0 (0.0)	1 (2.1)
Paliperidone Palmitate	1 (1.0)	0 (0.0)
Quetiapine Fumarate	1 (1.0)	0 (0.0)
Risperidone	4 (4.2)	0 (0.0)
VITAMINS	1 (1.0)	0 (0.0)
Inositol	1 (1.0)	0 (0.0)

Note: Prior medications are defined as medications with a stop date prior to the first dose date of randomized study medication. Medications are coded using WHO Drug Dictionary Version September 2015
Treatment allocation based on Stage 1 randomization.

Table 68
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
Overall	56 (100.0)	48 (100.0)	40 (100.0)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	13 (23.2)	7 (14.6)	7 (17.5)
Benazepril	1 (1.8)	1 (2.1)	0 (0.0)
Enalapril	2 (3.6)	1 (2.1)	0 (0.0)
Lisinopril	6 (10.7)	3 (6.3)	3 (7.5)
Losartan	1 (1.8)	1 (2.1)	0 (0.0)
Quinapril	0 (0.0)	1 (2.1)	0 (0.0)
Quinapril Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
Ramipril	1 (1.8)	0 (0.0)	0 (0.0)
Valsartan	0 (0.0)	0 (0.0)	1 (2.5)
Zestoretic	2 (3.6)	0 (0.0)	2 (5.0)
ANABOLIC AGENTS FOR SYSTEMIC USE	0 (0.0)	0 (0.0)	1 (2.5)
Prasterone	0 (0.0)	0 (0.0)	1 (2.5)
ANALGESICS	8 (14.3)	6 (12.5)	5 (12.5)
Gabapentin	4 (7.1)	0 (0.0)	0 (0.0)
Medinite	0 (0.0)	0 (0.0)	1 (2.5)
Panadeine Co	1 (1.8)	0 (0.0)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
ANALGESICS (cont'd)			
Paracetamol	5 (8.9)	1 (2.1)	3 (7.5)
Safapryn	0 (0.0)	1 (2.1)	0 (0.0)
Singlet	0 (0.0)	1 (2.1)	1 (2.5)
Topiramate	0 (0.0)	1 (2.1)	0 (0.0)
Tramadol	0 (0.0)	1 (2.1)	0 (0.0)
Vicks Formula 44m	0 (0.0)	0 (0.0)	1 (2.5)
Vicodin	0 (0.0)	1 (2.1)	0 (0.0)
ANESTHETICS	1 (1.8)	0 (0.0)	0 (0.0)
Anaesthetics, Local	1 (1.8)	0 (0.0)	0 (0.0)
ANTI-PARKINSON DRUGS	1 (1.8)	1 (2.1)	0 (0.0)
Benzatropine Mesilate	1 (1.8)	1 (2.1)	0 (0.0)
ANTIANEMIC PREPARATIONS	3 (5.4)	2 (4.2)	2 (5.0)
Cyanocobalamin	0 (0.0)	1 (2.1)	1 (2.5)
Ferrous Sulfate	2 (3.6)	1 (2.1)	0 (0.0)
Folic Acid	1 (1.8)	0 (0.0)	0 (0.0)
Iron	0 (0.0)	0 (0.0)	1 (2.5)
ANTIBACTERIALS FOR SYSTEMIC USE	4 (7.1)	1 (2.1)	2 (5.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
ANTIBACTERIALS FOR SYSTEMIC USE (cont'd)			
Amoxicillin	2 (3.6)	1 (2.1)	0 (0.0)
Azithromycin	1 (1.8)	0 (0.0)	0 (0.0)
Bactrim	1 (1.8)	0 (0.0)	0 (0.0)
Cefalexin	0 (0.0)	0 (0.0)	1 (2.5)
Metronidazole	0 (0.0)	0 (0.0)	1 (2.5)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0 (0.0)	0 (0.0)	1 (2.5)
Loperamide Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
ANTIEMETICS AND ANTINAUSEANTS	0 (0.0)	1 (2.1)	0 (0.0)
Ondansetron	0 (0.0)	1 (2.1)	0 (0.0)
ANTIEPILEPTICS	3 (5.4)	2 (4.2)	2 (5.0)
Valproate Semisodium	3 (5.4)	2 (4.2)	2 (5.0)
ANTIFUNGALS FOR DERMATOLOGICAL USE	0 (0.0)	1 (2.1)	0 (0.0)
Nystatin	0 (0.0)	1 (2.1)	0 (0.0)
ANTIGOUT PREPARATIONS	0 (0.0)	0 (0.0)	1 (2.5)
Allopurinol	0 (0.0)	0 (0.0)	1 (2.5)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (1.8)	3 (6.3)	4 (10.0)
Cetirizine Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
ANTIHISTAMINES FOR SYSTEMIC USE (cont'd)			
Diphenhydramine	0 (0.0)	1 (2.1)	1 (2.5)
Loratadine	1 (1.8)	1 (2.1)	2 (5.0)
Meclozine	0 (0.0)	1 (2.1)	0 (0.0)
ANTIHYPERTENSIVES	0 (0.0)	1 (2.1)	0 (0.0)
Clonidine	0 (0.0)	1 (2.1)	0 (0.0)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	5 (8.9)	8 (16.7)	8 (20.0)
Advil Pm	0 (0.0)	1 (2.1)	0 (0.0)
Ibuprofen	3 (5.4)	5 (10.4)	5 (12.5)
Naproxen	2 (3.6)	3 (6.3)	3 (7.5)
Naproxen Sodium	0 (0.0)	1 (2.1)	0 (0.0)
ANTIMYCOTICS FOR SYSTEMIC USE	1 (1.8)	0 (0.0)	0 (0.0)
Antibiotics	1 (1.8)	0 (0.0)	0 (0.0)
ANTITHROMBOTIC AGENTS	6 (10.7)	3 (6.3)	1 (2.5)
Acetylsalicylic Acid	6 (10.7)	3 (6.3)	1 (2.5)
BETA BLOCKING AGENTS	4 (7.1)	1 (2.1)	3 (7.5)
Atenolol	0 (0.0)	1 (2.1)	0 (0.0)
Metoprolol	3 (5.4)	0 (0.0)	1 (2.5)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
BETA BLOCKING AGENTS (cont'd)			
Metoprolol Tartrate	1 (1.8)	0 (0.0)	0 (0.0)
Propranolol	0 (0.0)	0 (0.0)	2 (5.0)
CALCIUM CHANNEL BLOCKERS	9 (16.1)	4 (8.3)	7 (17.5)
Amlodipine	4 (7.1)	3 (6.3)	5 (12.5)
Amlodipine Besilate	5 (8.9)	1 (2.1)	1 (2.5)
Nifedipine	0 (0.0)	0 (0.0)	1 (2.5)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (1.8)	0 (0.0)	1 (2.5)
Hydrocortisone	1 (1.8)	0 (0.0)	0 (0.0)
Triamcinolone Acetonide	0 (0.0)	0 (0.0)	1 (2.5)
COUGH AND COLD PREPARATIONS	1 (1.8)	0 (0.0)	1 (2.5)
Dextromethorphan Hydrobromide	0 (0.0)	0 (0.0)	1 (2.5)
Tussin Dm	1 (1.8)	0 (0.0)	0 (0.0)
DIURETICS	4 (7.1)	7 (14.6)	3 (7.5)
Chlortalidone	0 (0.0)	0 (0.0)	1 (2.5)
Furosemide	1 (1.8)	0 (0.0)	0 (0.0)
Hydrochlorothiazide	3 (5.4)	7 (14.6)	2 (5.0)
DRUGS FOR ACID RELATED DISORDERS	5 (8.9)	7 (14.6)	3 (7.5)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
DRUGS FOR ACID RELATED DISORDERS (cont'd)			
Calcium Carbonate	0 (0.0)	0 (0.0)	1 (2.5)
Novalucol Novum	0 (0.0)	0 (0.0)	1 (2.5)
Omeprazole	4 (7.1)	5 (10.4)	1 (2.5)
Ranitidine	1 (1.8)	2 (4.2)	0 (0.0)
DRUGS FOR CONSTIPATION	5 (8.9)	1 (2.1)	4 (10.0)
Bisacodyl	0 (0.0)	0 (0.0)	1 (2.5)
Docusate	0 (0.0)	0 (0.0)	1 (2.5)
Docusate Sodium	4 (7.1)	0 (0.0)	0 (0.0)
Macrogol	0 (0.0)	0 (0.0)	1 (2.5)
Magnesium Hydroxide	0 (0.0)	1 (2.1)	0 (0.0)
Psyllium Hydrophilic Mucilloid	0 (0.0)	0 (0.0)	1 (2.5)
Senokot-S	1 (1.8)	0 (0.0)	0 (0.0)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	5 (8.9)	3 (6.3)	2 (5.0)
Budesonide W/Formoterol Fumarate	1 (1.8)	0 (0.0)	2 (5.0)
Combivent	0 (0.0)	2 (4.2)	0 (0.0)
Montelukast	1 (1.8)	0 (0.0)	0 (0.0)
Montelukast Sodium	1 (1.8)	1 (2.1)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (cont'd)			
Salbutamol	3 (5.4)	1 (2.1)	1 (2.5)
Salbutamol Sulfate	0 (0.0)	0 (0.0)	1 (2.5)
Seretide	1 (1.8)	0 (0.0)	0 (0.0)
Tiotropium Bromide	0 (0.0)	1 (2.1)	0 (0.0)
DRUGS FOR TREATMENT OF BONE DISEASES	0 (0.0)	0 (0.0)	1 (2.5)
Alendronate Sodium	0 (0.0)	0 (0.0)	1 (2.5)
DRUGS USED IN DIABETES	10 (17.9)	12 (25.0)	9 (22.5)
Glibenclamide	1 (1.8)	0 (0.0)	0 (0.0)
Glimepiride	1 (1.8)	1 (2.1)	0 (0.0)
Glipizide	0 (0.0)	0 (0.0)	4 (10.0)
Insulin Glargine	1 (1.8)	1 (2.1)	1 (2.5)
Linagliptin	1 (1.8)	0 (0.0)	0 (0.0)
Metformin	10 (17.9)	10 (20.8)	8 (20.0)
Metformin Hydrochloride	0 (0.0)	2 (4.2)	0 (0.0)
Sitagliptin	0 (0.0)	1 (2.1)	0 (0.0)
EMOLLIENTS AND PROTECTIVES	1 (1.8)	0 (0.0)	1 (2.5)
Emollients And Protectives	1 (1.8)	0 (0.0)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
EMOLLIENTS AND PROTECTIVES (cont'd)			
Magnesium Stearate	0 (0.0)	0 (0.0)	1 (2.5)
LIPID MODIFYING AGENTS	16 (28.6)	12 (25.0)	12 (30.0)
Atorvastatin	4 (7.1)	0 (0.0)	4 (10.0)
Atorvastatin Calcium	1 (1.8)	0 (0.0)	0 (0.0)
Colecalciferol W/Fish Oil	1 (1.8)	0 (0.0)	0 (0.0)
Fenofibrate	2 (3.6)	0 (0.0)	0 (0.0)
Fish Oil	0 (0.0)	2 (4.2)	2 (5.0)
Gemfibrozil	0 (0.0)	1 (2.1)	1 (2.5)
Inegy	0 (0.0)	1 (2.1)	0 (0.0)
Lovastatin	1 (1.8)	0 (0.0)	0 (0.0)
Pravastatin	1 (1.8)	1 (2.1)	2 (5.0)
Rosuvastatin	1 (1.8)	1 (2.1)	0 (0.0)
Simvastatin	9 (16.1)	6 (12.5)	4 (10.0)
MINERAL SUPPLEMENTS	3 (5.4)	0 (0.0)	2 (5.0)
Calcium	1 (1.8)	0 (0.0)	1 (2.5)
Calcium Carbonate	1 (1.8)	0 (0.0)	0 (0.0)
Magnesium	0 (0.0)	0 (0.0)	1 (2.5)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
MINERAL SUPPLEMENTS (cont'd)			
Potassium	0 (0.0)	0 (0.0)	1 (2.5)
Potassium Chloride	2 (3.6)	0 (0.0)	0 (0.0)
MUSCLE RELAXANTS	0 (0.0)	1 (2.1)	0 (0.0)
Baclofen	0 (0.0)	1 (2.1)	0 (0.0)
NASAL PREPARATIONS	1 (1.8)	0 (0.0)	3 (7.5)
Fluticasone	0 (0.0)	0 (0.0)	2 (5.0)
Mometasone Furoate	1 (1.8)	0 (0.0)	0 (0.0)
Oxymetazoline Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
Phenylephrine Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
Sodium Chloride	0 (0.0)	0 (0.0)	1 (2.5)
OPHTHALMOLOGICALS	0 (0.0)	0 (0.0)	2 (5.0)
Bimatoprost	0 (0.0)	0 (0.0)	1 (2.5)
Dorzolamide W/Timolol	0 (0.0)	0 (0.0)	1 (2.5)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	0 (0.0)	0 (0.0)	1 (2.5)
Probiotics Nos	0 (0.0)	0 (0.0)	1 (2.5)
OTHER NERVOUS SYSTEM DRUGS	1 (1.8)	1 (2.1)	1 (2.5)
Bupropion Hydrochloride	1 (1.8)	1 (2.1)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
OTHER NERVOUS SYSTEM DRUGS (cont'd)			
Naltrexone	0 (0.0)	0 (0.0)	1 (2.5)
PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	1 (1.8)	0 (0.0)	0 (0.0)
Desmopressin	1 (1.8)	0 (0.0)	0 (0.0)
PSYCHOANALEPTICS	21 (37.5)	12 (25.0)	9 (22.5)
Bupropion	1 (1.8)	1 (2.1)	0 (0.0)
Bupropion Hydrochloride	1 (1.8)	0 (0.0)	0 (0.0)
Citalopram Hydrobromide	1 (1.8)	0 (0.0)	1 (2.5)
Escitalopram	0 (0.0)	0 (0.0)	1 (2.5)
Escitalopram Oxalate	2 (3.6)	1 (2.1)	1 (2.5)
Fluoxetine	1 (1.8)	2 (4.2)	0 (0.0)
Fluoxetine Hydrochloride	1 (1.8)	1 (2.1)	2 (5.0)
Fluvoxamine	1 (1.8)	0 (0.0)	0 (0.0)
Memantine	1 (1.8)	0 (0.0)	0 (0.0)
Mirtazapine	1 (1.8)	2 (4.2)	0 (0.0)
Paroxetine	2 (3.6)	0 (0.0)	0 (0.0)
Paroxetine Hydrochloride	1 (1.8)	0 (0.0)	0 (0.0)
Sertraline	2 (3.6)	1 (2.1)	2 (5.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
PSYCHOANALEPTICS (cont'd)			
Sertraline Hydrochloride	3 (5.4)	2 (4.2)	2 (5.0)
Trazodone	7 (12.5)	2 (4.2)	0 (0.0)
Trazodone Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
Venlafaxine	2 (3.6)	1 (2.1)	0 (0.0)
PSYCHOLEPTICS	56 (100.0)	48 (100.0)	40 (100.0)
Aripiprazole	11 (19.6)	16 (33.3)	5 (12.5)
Buspirone	1 (1.8)	0 (0.0)	0 (0.0)
Buspirone Hydrochloride	0 (0.0)	0 (0.0)	2 (5.0)
Clonazepam	0 (0.0)	1 (2.1)	0 (0.0)
Diphenhydramine	0 (0.0)	2 (4.2)	0 (0.0)
Hydroxyzine	2 (3.6)	0 (0.0)	1 (2.5)
Lithium	1 (1.8)	0 (0.0)	0 (0.0)
Lorazepam	3 (5.4)	0 (0.0)	3 (7.5)
Lurasidone	2 (3.6)	1 (2.1)	0 (0.0)
Lurasidone Hydrochloride	1 (1.8)	3 (6.3)	2 (5.0)
Olanzapine	13 (23.2)	12 (25.0)	13 (32.5)
Paliperidone	3 (5.4)	3 (6.3)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) **Preferred Term, n (%)**	**Placebo/Placebo (N=56)**	**d6-DM/Q/d6-DM/Q (N=48)**	**Placebo/d6-DM/Q (N=40)**
PSYCHOLEPTICS (cont'd)			
Paliperidone Palmitate	7 (12.5)	2 (4.2)	4 (10.0)
Quetiapine	1 (1.8)	2 (4.2)	1 (2.5)
Quetiapine Fumarate	9 (16.1)	7 (14.6)	5 (12.5)
Risperidone	13 (23.2)	10 (20.8)	12 (30.0)
Ziprasidone	1 (1.8)	1 (2.1)	1 (2.5)
Zolpidem	3 (5.4)	1 (2.1)	1 (2.5)
Zolpidem Tartrate	1 (1.8)	1 (2.1)	1 (2.5)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (1.8)	0 (0.0)	0 (0.0)
Anovlar	1 (1.8)	0 (0.0)	0 (0.0)
THYROID THERAPY	6 (10.7)	4 (8.3)	3 (7.5)
Levothyroxine	4 (7.1)	2 (4.2)	3 (7.5)
Levothyroxine Sodium	2 (3.6)	2 (4.2)	0 (0.0)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	0 (0.0)	0 (0.0)	1 (2.5)
Berberis Vulgaris	0 (0.0)	0 (0.0)	1 (2.5)
Linum Usitatissimum Seed Oil	0 (0.0)	0 (0.0)	1 (2.5)
UROLOGICALS	3 (5.4)	0 (0.0)	1 (2.5)
Mirabegron	1 (1.8)	0 (0.0)	0 (0.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 68 (continued)
Concomitant Medications
Safety Population (N = 144)

Anatomical Therapeutic Subgroup (ATC Level 2), n (%) Preferred Term, n (%)	Placebo/Placebo (N=56)	d6-DM/Q/d6-DM/Q (N=48)	Placebo/d6-DM/Q (N=40)
UROLOGICALS (cont'd)			
Oxybutynin Hydrochloride	0 (0.0)	0 (0.0)	1 (2.5)
Tamsulosin	3 (5.4)	0 (0.0)	0 (0.0)
VITAMINS	7 (12.5)	8 (16.7)	8 (20.0)
Ascorbic Acid	0 (0.0)	0 (0.0)	1 (2.5)
Cod-Liver Oil	0 (0.0)	1 (2.1)	0 (0.0)
Colecalciferol	3 (5.4)	2 (4.2)	2 (5.0)
Ergocalciferol	0 (0.0)	1 (2.1)	0 (0.0)
Herbal Nos W/Vitamins Nos	0 (0.0)	0 (0.0)	1 (2.5)
Minerals Nos W/Vitamins Nos	0 (0.0)	0 (0.0)	1 (2.5)
Multivitamins, Plain	4 (7.1)	5 (10.4)	4 (10.0)
Thiamine Hydrochloride	1 (1.8)	0 (0.0)	0 (0.0)
Vitamin B Complex	0 (0.0)	1 (2.1)	1 (2.5)
Vitamin D Nos	1 (1.8)	0 (0.0)	2 (5.0)

Note: Concomitant medications are defined as medications with a start date on or before the last dose date of randomized study medication, and a stop date on or after the first dose date of randomized study medication. Concomitant medications are coded using WHO Drug Dictionary Version September 2015.

Table 69
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Baseline Conmeds Benzodiazepine Use

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	10, 62.8 (5.96)	3, 64.7 (6.03)
	Week 6: N, Mean (SD)	10, 59.3 (6.53)	3, 56.7 (8.62)
	Change from Baseline: N, Mean (SD)	10, -3.5 (6.10)	3, -8.0 (6.08)
	Standard Effect Size		-0.738
	% Change from Baseline: N, Mean (SD)	10, -5.3 (9.22)	3, -12.4 (9.54)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.86 (-12.79, 5.06)
	p-value [1]		0.358
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	4, 59.5 (5.51)	3, 54.3 (3.06)
	Week 12: N, Mean (SD)	4, 57.5 (5.97)	3, 46.3 (1.53)
	Change from Baseline [2]: N, Mean (SD)	4, -2.0 (5.66)	3, -8.0 (2.65)
	Standard Effect Size		-1.279
	% Change from Baseline [2]: N, Mean (SD)	4, -3.1 (8.84)	3, -14.6 (4.10)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-8.54 (-20.07, 2.98)
	p-value [1]		0.109
	SPCD Weighted OLS z-statistic, overall p-value [3]		-1.96, 0.050

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 70
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Baseline Conmeds SNRI Use

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	2, 67.0 (1.41)	1, 54.0 ( )
	Week 6: N, Mean (SD)	2, 63.0 (2.83)	1, 51.0 ( )
	Change from Baseline: N, Mean (SD)	2, -4.0 (4.24)	1, -3.0 ( )
	Standard Effect Size		
	% Change from Baseline: N, Mean (SD)	2, -5.9 (6.21)	1, -5.6 ( )
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-38.00 ()
	p-value [1]		
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	2, 63.0 (2.83)	
	Week 12: N, Mean (SD)	2, 55.0 (0.00)	
	Change from Baseline [2]: N, Mean (SD)	2, -8.0 (2.83)	
	Standard Effect Size		
	% Change from Baseline [2]: N, Mean (SD)	2, -12.6 (3.92)	
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		
	p-value [1]		

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 71
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Baseline Conmeds SSRI Use

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	22, 61.7 (8.51)	7, 63.4 (8.98)
	Week 6: N, Mean (SD)	22, 58.7 (11.24)	7, 60.3 (9.14)
	Change from Baseline: N, Mean (SD)	22, -3.0 (5.99)	7, -3.1 (4.06)
	Standard Effect Size		-0.025
	% Change from Baseline: N, Mean (SD)	22, -5.1 (9.97)	7, -4.9 (6.08)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-0.27 (-5.36, 4.82)
	p-value [1]		0.914
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	10, 58.1 (11.61)	8, 60.6 (12.58)
	Week 12: N, Mean (SD)	10, 57.3 (11.86)	8, 55.9 (11.80)
	Change from Baseline [2]: N, Mean (SD)	10, -0.8 (4.37)	8, -4.8 (6.98)
	Standard Effect Size		-0.698
	% Change from Baseline [2]: N, Mean (SD)	10, -1.4 (7.32)	8, -7.3 (10.16)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.63 (-9.35, 2.10)
	p-value [1]		0.197
	SPCD Weighted OLS z-statistic, overall p-value [3]		-0.88, 0.379

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 72
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Patients Who Took Baseline Concomitant Psychotropic Medications with Major CYP2D6 Substrate = Yes

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	36, 61.8 (8.11)	25, 59.8 (7.27)
	Week 6: N, Mean (SD)	36, 58.6 (9.78)	25, 55.0 (8.45)
	Change from Baseline: N, Mean (SD)	36, -3.2 (4.63)	25, -4.8 (4.40)
	Standard Effect Size		-0.356
	% Change from Baseline: N, Mean (SD)	36, -5.4 (7.50)	25, -8.2 (7.41)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.54 (-3.94, 0.86)
	p-value [1]		0.203
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	16, 59.8 (10.23)	12, 59.7 (10.00)
	Week 12: N, Mean (SD)	16, 55.7 (11.86)	12, 56.7 (9.94)
	Change from Baseline [2]: N, Mean (SD)	16, -4.1 (6.74)	12, -3.0 (5.97)
	Standard Effect Size		0.175
	% Change from Baseline [2]: N, Mean (SD)	16, -6.9 (10.87)	12, -4.8 (8.67)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		1.11 (-3.98, 6.20)
	p-value [1]		0.657
	SPCD Weighted OLS z-statistic, overall p-value [3]		-0.39, 0.693

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 73
NSA-16 Total Score: Change from Baseline SPCD ANCOVA, LOCF Data
mITT Population (N = 127)
Subgroup: Patients Who Took Baseline Concomitant Psychotropic Medications with Major CYP2D6 Substrate = No

Stage	Visit Statistics	Placebo	d6-DM/Q
Stage 1	Baseline: N, Mean (SD)	44, 59.2 (7.25)	22, 62.2 (7.78)
	Week 6: N, Mean (SD)	44, 56.5 (8.72)	22, 57.0 (9.16)
	Change from Baseline: N, Mean (SD)	44, -2.7 (6.62)	22, -5.3 (6.89)
	Standard Effect Size		-0.379
	% Change from Baseline: N, Mean (SD)	44, -4.4 (10.88)	22, -8.3 (11.38)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-1.96 (-5.47, 1.55)
	p-value [1]		0.269
Stage 2 (Stage 1 Placebo Non-responders)	Baseline [2]: N, Mean (SD)	14, 55.0 (7.91)	21, 56.4 (8.55)
	Week 12: N, Mean (SD)	14, 55.1 (11.01)	21, 52.5 (7.64)
	Change from Baseline [2]: N, Mean (SD)	14, 0.1 (3.85)	21, -3.9 (6.67)
	Standard Effect Size		-0.694
	% Change from Baseline [2]: N, Mean (SD)	14, -0.6 (7.45)	21, -6.1 (11.87)
	Treatment Difference vs. Placebo: LS Mean Difference, 95% CI [1]		-3.78 (-7.81, 0.24)
	p-value [1]		0.064
	SPCD Weighted OLS z-statistic, overall p-value [3]		-2.04, 0.041

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
[1] Change from Baseline was analyzed at each stage by ANCOVA with treatment as fixed effect and baseline value as covariate. Missing values were imputed by LOCF within each stage.
[2] Stage 2 Baseline is the last non-missing assessment prior to re-randomization into Stage 2 (re-randomization visit).
[3] SPCD Weighted OLS z-statistic was calculated using Stage 1 weight = 0.6 and Stage 2 weight = 0.4.

Table 74
NSA-16 Total Score: Change from Baseline Parallel Group ANCOVA by Visit, LOCF Data
mITT 12-Week Parallel Group Population (N = 87)
Subgroup: Patients Who Took Baseline Concomitant Psychotropic Medications with Major CYP2D6 Substrate = Yes

Visit	Result/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline	N, Mean (SD)	23, 62.2 (8.38)	25, 59.8 (7.27)
Week 3	N, Mean (SD)	23, 58.3 (8.36)	24, 57.7 (8.38)
Week 3	Change from Baseline: N, Mean (SD)	23, -3.9 (4.78)	24, -2.6 (5.07)
Week 3	Standard Effect Size		0.270
Week 3	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.446, 1.11 (-1.80, 4.01)
Week 6	N, Mean (SD)	23, 58.5 (9.71)	25, 55.0 (8.45)
Week 6	Change from Baseline: N, Mean (SD)	23, -3.7 (4.03)	25, -4.8 (4.40)
Week 6	Standard Effect Size		-0.281
Week 6	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.372, -1.12 (-3.64, 1.39)
Week 9	N, Mean (SD)	23, 57.6 (11.04)	25, 55.0 (9.82)
Week 9	Change from Baseline: N, Mean (SD)	23, -4.6 (6.77)	25, -4.9 (5.08)
Week 9	Standard Effect Size		-0.053
Week 9	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.960, -0.09 (-3.60, 3.42)
Week 12	N, Mean (SD)	23, 55.1 (11.21)	25, 53.1 (9.76)
Week 12	Change from Baseline: N, Mean (SD)	23, -7.0 (7.46)	25, -6.7 (7.10)
Week 12	Standard Effect Size		0.044
Week 12	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.911, 0.24 (-4.08, 4.57)

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
Missing values were imputed by LOCF and visit windows were used to classify unscheduled or ET visits.
LS mean difference and p-values were from ANCOVA with treatment as fixed effect and Stage 1 Baseline value as a covariate.
Patients within each treatment group received the same treatment throughout their participation in the study.

Table 75
NSA-16 Total Score: Change from Baseline Parallel Group ANCOVA by Visit, LOCF Data
mITT 12-Week Parallel Group Population (N = 87)
Subgroup: Patients Who Took Baseline Concomitant Psychotropic Medications with Major CYP2D6 Substrate = No

Visit	Result/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline	N, Mean (SD)	17, 59.5 (7.12)	22, 62.2 (7.78)
Week 3	N, Mean (SD)	17, 56.8 (10.02)	21, 59.3 (8.20)
Week 3	Change from Baseline: N, Mean (SD)	17, -2.8 (9.56)	21, -2.5 (6.58)
Week 3	Standard Effect Size		0.030
Week 3	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.684, 1.05 (-4.13, 6.23)
Week 6	N, Mean (SD)	17, 55.6 (8.41)	22, 57.0 (9.16)
Week 6	Change from Baseline: N, Mean (SD)	17, -3.9 (5.58)	22, -5.3 (6.89)
Week 6	Standard Effect Size		-0.209
Week 6	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.672, -0.89 (-5.10, 3.32)
Week 9	N, Mean (SD)	17, 56.1 (11.52)	22, 53.2 (11.24)
Week 9	Change from Baseline: N, Mean (SD)	17, -3.4 (7.86)	22, -9.0 (8.57)
Week 9	Standard Effect Size		-0.681
Week 9	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.044, -5.74 (-11.32, -0.16)
Week 12	N, Mean (SD)	17, 55.6 (10.88)	22, 56.9 (11.93)
Week 12	Change from Baseline: N, Mean (SD)	17, -3.9 (7.37)	22, -5.4 (8.57)
Week 12	Standard Effect Size		-0.183
Week 12	Treatment Difference versus Placebo: p-value, LS Mean Difference (95% CI)		0.522, -1.73 (-7.16, 3.70)

Note: NSA-16 Total Score ranges from 16 to 96, with higher scores indicating greater clinical severity of symptoms.
Standard Effect Size is defined as (mean change in d6-DM/Q – mean change in Placebo) / Change from Baseline Pooled SD.
Missing values were imputed by LOCF and visit windows were used to classify unscheduled or ET visits.
LS mean difference and p-values were from ANCOVA with treatment as fixed effect and Stage 1 Baseline value as a covariate.
Patients within each treatment group received the same treatment throughout their participation in the study.

Table 76
PANSS Total Score: Change from Baseline Parallel Group MMRM Analysis, Observed Data
mITT 12-Week Parallel Group (N = 87)

Visit/Statistics	Placebo/Placebo	d6-DM/Q/d6-DM/Q
Baseline: N, Mean (SD)	40, 69.4 (8.18)	47, 67.4 (8.26)
Week 3 Change from Baseline: N, Mean (SD)	40, -2.8 (7.56)	45, -3.2 (6.84)
Week 6 Change from Baseline: N, Mean (SD)	35, -3.0 (6.27)	47, -4.7 (6.98)
Week 9 Change from Baseline: N, Mean (SD)	32, -3.0 (8.43)	42, -7.3 (6.91)
Week 12 Change from Baseline: N, Mean (SD)	31, -4.3 (9.82)	42, -7.4 (7.66)
Week 12 Treatment Difference vs. Placebo: p-value, LS Mean Difference (95% CI)		0.141, -2.90 (-6.78, 0.98)

Note: PANSS Total Score ranges from 30 to 210, with higher scores indicating greater clinical severity of symptoms.
Patients within each treatment group received the same treatment throughout their participation in the study.
Repeated measures model includes fixed effect for treatment, visit, treatment-by-visit interaction, baseline value, and baseline value-by-visit interaction. An unstructured covariance matrix was used.

Table 77
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) Cmax in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 6						
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)
d6-DM Cmax at Week 6						
d6-DM/Q (N = 47)	43	51.6 (38.53)	40.0 (8, 192)			
Pearson correlation coefficient, p-value [1])						-0.132, 0.4001

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 78
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) Cmax in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 12						
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)
d6-DM Cmax at Week 12						
d6-DM/Q (N = 33)	31	48.9 (28.34)	44.3 (7, 121)			
Pearson correlation coefficient, p-value [1])						-0.249, 0.1774

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 79
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) Cmax at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
d6-DM Cmax at Week 12							
d6-DM/Q (N = 47)	40	53.4 (40.09)	42.3 (8, 194)				
Pearson correlation coefficient, p-value [1])							0.140, 0.3887

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 80
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) Cmax in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 6							
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)	
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)	
d3-DX Cmax at Week 6							
d6-DM/Q (N = 47)	43	127.4 (50.25)	121.6 (56, 332)				
Pearson correlation coefficient, p-value [1])							-0.158, 0.3124

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 81
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) Cmax in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)	
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)	
d3-DX Cmax at Week 12							
d6-DM/Q (N = 33)	31	127.1 (50.06)	116.4 (65, 318)				
Pearson correlation coefficient, p-value [1])							-0.026, 0.8876

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 82
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) Cmax at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
d3-DX Cmax at Week 12							
d6-DM/Q (N = 47)	40	126.8 (50.32)	123.0 (57, 337)				
Pearson correlation coefficient, p-value [1])							-0.036, 0.8243

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 83
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) Cmax in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 6							
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)	
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)	
Quinidine Cmax at Week 6							
d6-DM/Q (N = 47)	43	20.0 (8.21)	17.7 (9, 43)				
Pearson correlation coefficient, p-value [1])							-0.231, 0.1367

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 84
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) Cmax in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)	
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)	
Quinidine Cmax at Week 12							
d6-DM/Q (N = 33)	31	21.4 (9.05)	19.5 (10, 45)				
Pearson correlation coefficient, p-value [1])							0.013, 0.9436

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 85
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) Cmax at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
Quinidine Cmax at Week 12							
d6-DM/Q (N = 47)	40	20.6 (8.73)	18.8 (10, 45)				
Pearson correlation coefficient, p-value [1])							0.147, 0.3667

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 86
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) AUC in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 6						
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)
d6-DM AUC at Week 6						
d6-DM/Q (N = 47)	43	456.2 (362.05)	355.4 (73, 1793)			
Pearson correlation coefficient, p-value [1])						-0.131, 0.4008

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 87
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) AUC in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 12						
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)
d6-DM AUC at Week 12						
d6-DM/Q (N = 33)	31	422.8 (255.94)	374.8 (53, 1081)			
Pearson correlation coefficient, p-value [1])						-0.239, 0.1955

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 88
Association between NSA-16 Total Score Change from Baseline (LOCF) and Deuterated (d6)-dextromethorphan (d6-DM) AUC at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
d6-DM AUC at Week 12							
d6-DM/Q (N = 47)	40	473.4 (375.01)	369.4 (70, 1810)				
Pearson correlation coefficient, p-value [1])							0.129, 0.4269

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 89
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) AUC in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 6							
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)	
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)	
d3-DX AUC at Week 6							
d6-DM/Q (N = 47)	43	1142.3 (378.08)	1083.8 (506, 2091)				
Pearson correlation coefficient, p-value [1])							-0.207, 0.1834

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 90
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) AUC in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 12						
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)
d3-DX AUC at Week 12						
d6-DM/Q (N = 33)	31	1173.1 (537.52)	1072.1 (620, 3622)			
Pearson correlation coefficient, p-value [1])						-0.126, 0.4993

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 91
Association between NSA-16 Total Score Change from Baseline (LOCF) and d3-dextrorphan (d3-DX) AUC at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
d3-DX AUC at Week 12							
d6-DM/Q (N = 47)	40	1142.8 (378.46)	1087.1 (511, 2115)				
Pearson correlation coefficient, p-value [1])							-0.141, 0.3847

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 92
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) AUC in Stage 1
mITT Population (N = 127)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 6						
d6-DM/Q (N = 47)	47	55.9 (8.75)	55.0 (37, 72)	47	-5.0 (5.64)	-5.0 (-17, 10)
Placebo (N = 80)	80	57.4 (9.21)	57.0 (43, 86)	80	-3.0 (5.78)	-2.5 (-15, 10)
Quinidine AUC at Week 6						
d6-DM/Q (N = 47)	43	159.1 (63.81)	142.1 (75, 325)			
Pearson correlation coefficient, p-value [1])						-0.224, 0.1490

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 93
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) AUC in Stage 2
Stage 1 Placebo Non-Responders (N = 77)

Treatment	Actual			Change from Baseline		
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)
NSA-16 Total Score at Week 12						
d6-DM/Q (N = 33)	33	54.0 (8.63)	55.0 (42, 75)	33	-3.6 (6.34)	-2.0 (-19, 11)
Placebo (N = 31)	30	55.4 (11.28)	55.0 (37, 81)	30	-2.2 (5.89)	-1.0 (-23, 7)
Quinidine AUC at Week 12						
d6-DM/Q (N = 33)	31	167.1 (69.68)	155.5 (84, 342)			
Pearson correlation coefficient, p-value [1])						0.017, 0.9291

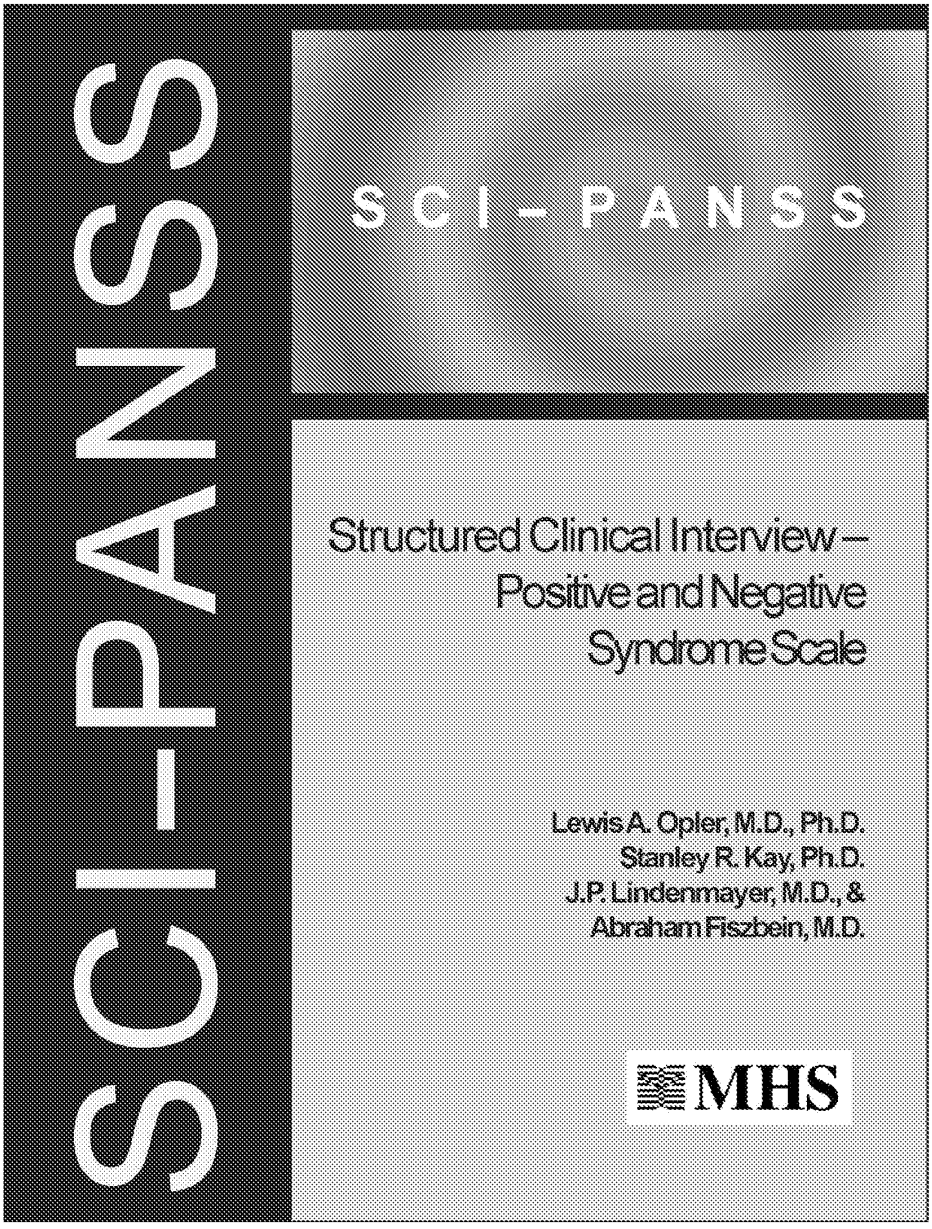
Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

Table 94
Association between NSA-16 Total Score Change from Baseline (LOCF) and Quinidine (Q) AUC at Week 12
mITT 12-Week Parallel Group (N = 87)

Treatment	Actual			Change from Baseline			
	N	Mean (SD)	Median (Min, Max)	N	Mean (SD)	Median (Min, Max)	
NSA-16 Total Score at Week 12							
d6-DM/Q (N = 47)	47	54.9 (10.87)	53.0 (31, 76)	47	-6.1 (7.77)	-5.0 (-23, 10)	
Placebo (N = 40)	40	55.4 (10.93)	55.0 (37, 81)	40	-5.7 (7.50)	-4.5 (-24, 9)	
Quinidine AUC at Week 12							
d6-DM/Q (N = 47)	40	163.7 (68.42)	146.5 (81, 347)				
Pearson correlation coefficient, p-value [1])							0.151, 0.3511

Note: Missing values for the NSA-16 were imputed by LOCF within each stage.
[1] Test of whether the correlation between change in NSA-16 total score and the PK parameter is significantly different from 0.

APPENDIX 2. Positive and Negative Syndrome Scale (PANSS)



Structured Clinical Interview for the Positive and Negative Syndrome Scale

SCI-PANSS

L. A. Opler, M.D., Ph.D. S. R. Kay, Ph.D. J. P. Lindenmayer, M.D. A. Fiszbein, M.D.

Data on "Lack of Spontaneity and Flow of Conversation" (N6), "Poor Rapport" (N3), and "Conceptual Disorganization" (P2)

Hi, I'm ... We're going to be spending the next 30 to 40 minutes talking about you and your reasons for being here. Maybe you can start out by telling me something about yourself and your background?

(Instruction to interviewer: Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on "Anxiety" (G2)

1. Have you been feeling worried or nervous in the past week?

   _____

   IF YES, skip to question 3. IF NO, continue.

2. Would you say that you're usually calm and relaxed?

   _____

   IF YES, skip to question 8. IF NO, continue.

3. What's been making you feel nervous (worried, not calm, not relaxed)?

   _____

4. Just how nervous (worried, etc.) have you been feeling?

   _____

5. Have you been shaking at times, or has your heart been racing?

   _____

6. Do you get into a state of panic?

   _____

7. Has your sleep, eating, or participation in activities been affected?

Data on "Delusions (General)" (P1) and "Unusual Thought Content" (G9)

8. Have things been going well for you?

9. Has anything been bothering you lately?

10. Can you tell me something about your thoughts on life and its purpose?

11. Do you follow a particular philosophy (any special rules, teachings, or religious doctrine)?

---

12. Some people tell me they believe in the Devil; what do you think?

IF NO (i.e., he/she doesn't believe in the Devil), skip to question 14.

IF YES (i.e., he/she does believe), continue.

13. Can you tell me more about this?

---

14. Can you read other people's minds?

IF NO, skip to question 16. IF YES, continue.

15. How does that work?

---

16. Can others read your mind?

IF NO, skip to question 19. IF YES, continue.

17. How can they do that?

---

18. Is there any reason that someone would want to read your mind?

---

19. Who controls your thoughts?

Data on "Suspiciousness/Persecution" (P6) and "Poor Impulse Control" (G14)

20. How do you spend your time these days?

---

21. Do you prefer to be alone?

---

22. Do you join in activities with others?

_____

IF YES, skip to question 25. IF NO, continue.

23. Why not? ... Are you afraid of people, or do you dislike them?

_____

IF NO, skip to question 26. IF YES, continue.

24. Can you explain?

_____

Skip to question 26.

25. Tell me about it.

_____

26. Do you have many friends?

_____

IF YES, skip to question 30. IF NO, continue.

27. Just a few?

_____

IF YES, skip to question 29. IF NO, continue

28. Any? …
Why?_____

Skip to question 32.

29. Why just a few friends?

_____

30. Close friends?

_____

IF YES, skip to question 32. IF NO, continue.

31. Why not?

_____

32. Do you feel that you can trust most people?

_____

IF YES, skip to question 34. IF NO, continue.

33. Why not?

_____

34. Are there some people in particular who you don't trust?

_____

IF NO to question 34 and YES to question 32, skip to question 41.

IF NO to question 34 and NO to question 32, skip to question 36.

IF YES to question 34, continue.

35. Can you tell me who they are?

_____

36. Why don't you trust people (or name specific person)?

_____

IF "DON'T KNOW" OR "DON'T WANT TO SAY," continue. Otherwise, skip to question 41.

37. Do you have a good reason not to trust ...?

_____

_____

38. Is there something that .... did to you?

_____

39. Perhaps something that ... might do to you now?

_____

IF NO, skip to question 41. IF YES, continue.

40. Can you explain to me?

_____

41. Do you get along well with others?

_____

IF YES, skip to question 43. IF NO, continue.

42. What's the problem?

_____

43. Do you have a quick temper?

_____

44. Do you get into fights?

_____

IF NO, skip to question 48. IF YES, continue.

45. How do these fights start?

_____

46. Tell me about these fights.

_____

47. How often does this happen?

_____

48. Do you sometimes lose control of yourself?

_____

IF NO, skip to question 50. IF YES, continue.

49. What happens when you lose control of yourself?

_____

50. Do you like most people?

_____

IF YES, skip to question 52. IF NO, continue.

51. Why not?

_____

52. Are there perhaps some people who don't like you?

_____

IF NO, skip to question 54. IF YES, continue.

53. For what reason?

_____

54. Do others talk about you behind your back?

_____

IF NO, skip to question 57. IF YES, continue.

55. What do they say about you?

_____

56. Why?_____

_____

57. Does anyone ever spy on you or plot against you?

_____

58. Do you sometimes feel in danger?

_____

IF NO, skip to question 64. IF YES, continue.

59. Would you say that your life is in danger?

_____

60. Is someone thinking of harming you or even perhaps thinking of killing you?

61. Have you gone to the police for help?

62. Do you sometimes take matters into your own hands or take action against those who might harm you?

IF NO, skip to question 64. IF YES, continue.

63. What have you done?

Data on "Hallucinatory Behavior" (P3) and associated delusions

64. Do you once in a while have strange or unusual experiences?

65. Sometimes people tell me that they can hear noises or voices inside their head that others can't hear. What about you?

IF YES, skip to question 68. IF NO, continue.

66. Do you sometimes receive personal communications from the radio or TV?

IF YES, skip to question 68. IF NO, continue.

67. From God or the Devil?:

IF NO, skip to question 83. IF YES, continue.

68. What do you hear?

69. Are these as clear and loud as my voice?

70. How often do you hear these voices, noises, messages, etc.?

_____

71. Does this happen at a particular time of day or all the time?

_____

IF HEARING NOISES ONLY, skip to question 80. IF HEARING VOICES, continue.

72. Can you recognize whose voices these are?

_____

73. What do the voices say?

_____

74. Are the voices good or bad?

_____

75. Pleasant or unpleasant?

_____

76. Do the voices interrupt your thinking or your activities?

_____

77. Do they sometimes give you orders or instructions?

_____

IF NO, skip to question 80. IF YES, continue.

78. For example?

_____

79. Do you usually obey these orders (instructions)?

_____

80. What do you make of these voices (or noises); where do they really come from?

_____

81. Why do you have these experiences?_____

82. Are these normal

experiences?_____

83. Do ordinary things sometimes look strange or distorted to

you?_____

84. Do you sometimes have "visions" or see things that others can't see?

_____

IF NO, skip to question 88. IF YES, continue.

85. For example?

_____

86. Do these visions seem very real or life-like?

_____

87. How often do you have these experiences?

_____

88. Do you sometimes smell things that are unusual or that others don't smell?

_____

IF NO, skip to question 90. IF YES, continue.

89. Please explain.

_____

90. Do you get any strange or unusual sensations from your body?

_____

IF NO, skip to question 92. IF YES, continue.

91. Tell me about this.

_____

Data on "Somatic Concern" (G1)

92. How have you been feeling in terms of your

health?_____

IF OTHER THAN "GOOD," skip to question 94. IF "GOOD," continue.

93. Do you consider yourself to be in top health?

_____

IF YES, skip to question 95. IF NO, continue.

94. What has been troubling you?

_____

95. Do you have any medical illness or disease?

_____

96. Has any part of your body been troubling you?

_____

IF YES, skip to question 98. IF NO, continue.

97. How is your head? Your heart? Stomach? The rest of your body?

_____

98. Could you explain?_____

99. Has your head or body changed in shape or size?

_____

IF NO, skip to question 102. IF YES, continue.

100. Please explain.

_____

101. What is causing these changes?

_____

Data on "Depression" (G6)

102. How has your mood been in the past week: mostly good, mostly bad?

_____

IF "MOSTLY BAD," skip to question 104. IF "MOSTLY GOOD," continue.

103. Have there been times in the past week when you were feeling sad or unhappy?

_____

IF NO, skip to question 114. IF YES, continue.

104. Is there something in particular that is making you sad?

_____

105. How often do you feel sad?

_____

106. Just how sad have you been feeling?

_____

107. Have you been crying lately?

_____

108. Has your mood in any way affected your sleep?

_____

109. Has it affected your appetite?

_____

110. Do you participate less in activities on account of your mood?

_____

111. Have you had any thoughts of harming yourself?

_____

IF NO, skip to question 114. IF YES, continue.

112. Any thoughts about ending your life?_____

IF NO, skip to question 114. IF YES, continue.

113. Have you attempted suicide?

_____

Data on "Guilt Feelings" (G3) and "Grandiosity" (P5)

114. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same?

_____

IF "BETTER," skip to question 117.

IF "ABOUT THE SAME," skip to question 118.

IF "WORSE," continue.

115. Worse in what ways?

_____

116. Just how do you feel about yourself?

_____

Skip to question 120.

117. Better in what ways?

_____

Skip to question 120.

118. Are you special in some ways?

_____

IF NO, skip to question 120. IF YES, continue.

119. In what ways?

_____

120. Would you consider yourself gifted?

_____

121. Do you have talents or abilities that most people don't have?

_____

IF NO, skip to question 123. IF YES, continue.

122. Please explain.

_____

123. Do you have any special powers?

_____

IF NO, skip to question 126. IF YES, continue.

124. What are these?

_____

125. Where do these powers come from?

_____

126. Do you have extrasensory perception (ESP), or can you read other people's minds?_____

127. Are you very wealthy?

_____

IF NO, skip to question 129. IF YES, continue.

128. Explain please.

_____

129. Can you be considered to be very bright?

_____

IF NO, skip to question 131. IF YES, continue.

130. Why would you say so?

_____

131. Would you describe yourself as famous?_____

132. Would some people recognize you from TV, radio, or the newspaper?

_____

IF NO, skip to question 134. IF YES, continue.

133. Can you tell me about it?

_____

134. Are you a religious person?

_____

IF NO, skip to question 140. IF YES, continue.

135. Are you close to God?

_____

IF NO, skip to question 140. IF YES, continue.

136. Did God assign you some special role or purpose?

_____

137. Can you be one of God's messengers or angels?

_____

IF NO, skip to question 139. IF YES, continue.

138. What special powers do you have as God's messenger (angel)?

_____

139. Do you perhaps consider yourself to be God?

_____

140. Do you have some special mission in life?

_____

IF NO, skip to question 143. IF YES, continue.

141. What is your mission?

_____

142. Who assigned you to that mission?

_____

143. Did you ever do something wrong — something you feel bad or guilty about?

_____

IF NO, skip to question 149. IF YES, continue.

144. Just how much does that bother you now?

_____

145. Do you feel that you deserve punishment for that?

_____

IF NO, skip to question 149. IF YES, continue.

146. What kind of punishment would you deserve?

_____

147. Have you at times thought of punishing yourself?_____

IF NO, skip to question 149. IF YES, continue.

148. Have you ever acted on those thoughts of punishing yourself?

_____

Data on "Disorientation" (G10)

149. Can you tell me today's date (i.e., the day, month, and year)?

_____

IF YES, skip to question 151. IF NO, continue.

150. Can you tell me what day of the week it is?

_____

151. What is the name of the place that you are in now?_____

IF NOT HOSPITALIZED, skip to question 154. IF HOSPITALIZED, continue.

152. What ward are you on?_____

153. What is the address of where you're now staying?

_____

IF ABLE TO TELL, skip to question 155. IF NOT ABLE TO TELL, continue.

154. Can you tell me your home address?

_____

IF NOT HOSPITALIZED, skip to question 156. IF HOSPITALIZED, continue.

155. If someone had to reach you by phone, what number would that person call?

---

156. If someone had to reach you at home, what number would that person call?

---

157. What is the name of the doctor who is treating you?

IF NOT HOSPITALIZED, skip to question 159. IF HOSPITALIZED, continue.

158. Can you tell me who else is on the staff and what they do?

---

159. Do you know who is currently the president (prime minister, etc.)?

---

160. Who is our governor (premier, etc.)?

---

161. Who is the mayor (town supervisor, etc.) of this city (town, etc.)?

Data on "Difficulty in Abstract Thinking" (N5)

I'm going to now say a pair of words, and I'd like you to tell me in what important way they're alike. Let's start, for example, with the words "apple" and "banana." How are they alike — what do they have in common? **IF THE RESPONSE IS THAT "THEY'RE BOTH FRUIT", THEN SAY:** Good. Now what about ...? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

IF AN ANSWER IS GIVEN THAT IS CONCRETE, TANGENTIAL, OR IDIOSYNCRATIC (E.G., "THEY BOTH HAVE SKINS," "YOU CAN EAT THEM," "THEY'RE SMALL," OR "MONKEYS LIKE THEM"), THEN SAY: OK, but they're both fruit. Now how about ... and ... : how are these alike? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

APPENDIX A

Items for Similarities in the evaluation of "Difficulty in Abstract Thinking"

1.	How are a ball and an orange alike?	*Note on Appendix A:* Similarities are generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with
2.	Apple and banana ?	
3.	Pencil and pen?	
4.	Nickel and dime?	

5. Table and chair?
6. Tiger and elephant?
7. Hat and shirt?
8. Bus and train?

---

9. Arm and leg?
10. Rose and tulip?
11. Uncle and cousin?
12. The sun and the moon?

---

13. Painting and poem?
14. Hilltop and valley?
15. Air and water?
16. Peace and prosperity?

successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Similarities responses:

_____

You've probably heard the expression, "Carrying a chip on the shoulder." What does that really mean? There's a very old saying, "Don't judge a book by its cover." What is the deeper meaning of this proverb? *(Select two other proverbs from the list in Appendix B at varying levels of difficulty.)*

APPENDIX B

Items for assessing PROVERB INTERPRETATION in the evaluation of "Difficulty in Abstract Thinking"

Circle the Similarities Used

What does the saying mean:

1. "Plain as the nose on your face"
2. "Carrying a chip on your shoulder"
3. "Two heads are better than one"
4. "Too many cooks spoil the broth"

---

5. "Don't judge a book by its cover"
6. "One man's food is another man's poison"
7. "All that glitters is not gold"
8. "Don't cross the bridge until you come to it"

---

9. "What's good for the goose is good for the gander"
10. "The grass always looks greener on the other side"
11. "Don't keep all your eggs in one basket"
12. "One swallow does not make a summer"

---

13. "A stitch in time saves nine"
14. "A rolling stone gathers no moss"
15. "The acorn never falls far from the tree"
16. "People who live in glass houses should not throw stones at others"

Note on Appendix B: Proverb interpretation is generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Proverb responses:

Data on "Lack of Judgment and Insight" (G12)

162. How long have you been in the hospital (clinic, etc.)?

---

163. Why did you come to the hospital (clinic, etc.)?

---

164. Did you need to be in a hospital (clinic, etc.)?

IF YES, skip to question 167. IF NO, continue.

165. Did you have a problem that needed treatment?

_____

IF NO, skip to question 169. IF YES, continue.

166. Would you say that you had a psychiatric or mental problem?

_____

IF NO, skip to question 169. IFYES, continue.

167. Why?....would you say that you had a psychiatric or mental problem?

_____

IF NO, skip to question 169. IF YES, continue.

168. Can you tell me about it and what it consisted of?

_____

169. In your own opinion, do you need to be taking medicine?

_____

IF YES, skip to question 171.

IF NO and unmedicated, skip to question 172.

IF NO and medicated, continue.

170. Why then are you taking medicines?

_____

Skip to question 172.

171. Why?... Does the medicine help you in any way?

_____

172. Do you at this time have any psychiatric or mental problems?

_____

IF YES, skip to question 174. IF NO, continue.

173. For what reason are you at the hospital (clinic, etc.)?

_____

Skip to question 175.

174. Please explain

_____

175. Just how serious are these problems?

_____

IF UNHOSPITALIZED, skip to question 178.

IF HOSPITALIZED, continue.

176. Are you ready yet for discharge from the hospital?

_____

177. Do you think you'll be taking medicine for your problems after discharge?

_____

178. What are your future plans?

_____

179. What about your longer-range goals?

_____

Well, that's about all I have to ask of you now. Are there any questions that you might like to ask of me? Thank you for your cooperation.



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APPENDIX 3A. Negative Symptom Assessment-16 scale (NSA-16)

Negative Symptom Assessment-16 (NSA-16) Instruction Manual

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RULES FOR RATING THE NSA

Working Definition Of Negative Symptoms

Negative symptoms represent the reduction or absence of behaviors normally present in a healthy person. These include, but are not limited to, behaviors related to personal, social and affective behavior. Specifically, negative symptoms of schizophrenia are considered to include reduction in emotional expression and perception, reduction in the fluency and productivity of thought and speech, reduced desire for social involvement and reduced social interaction with others and a loss or lack of goal-directed behavior. These symptoms contribute to substantial reductions in the functioning of schizophrenic patients as compared to others in their society.

Purpose

The purpose of the Negative Symptom Assessment (NSA) is to permit the reliable rating of behaviors commonly associated with the concept of negative symptoms in schizophrenia. It should be emphasized that this scale rates behavior and not psychopathology. Thus, scores on this scale do not necessarily imply psychopathology or etiology. For instance, subjects could achieve high ratings on some items because of depression, medication regimen, institutionalization, uncooperativeness, deficit syndrome or, even personality style. Raters using this scale should not correct ratings because, in their judgment, the etiology is something other than that sought in the particular study where it is currently used.

Sources Of Information

The source of information for the NSA is a semi-structured, clinical interview. This information should be applied with good clinical judgment in making a final rating.

The rater may be, and is encouraged to be, aware of information from sources outside of the interview. If the subject's report is at variance with outside reports (of nurses, family, etc.), these discrepancies should be clarified. Similarly, if the patient provides contradictory information, or other information from the interview is at variance with the subject's stated performance in a particular area, the rater should use his/her best clinical judgment in assigning a severity score for this behavior.

Reference Population

The 'normal' reference population against which the subject is to be compared is a young person in their twenties. It is not (1) the same person at another point in time; (2) a healthy person of similar age, living under similar circumstances; nor (3) another hospitalized person.

Use Of Anchors (Item Descriptors)

The anchors that are provided for this scale should be used as guides and should be used insofar as they apply to the persons being rated. No set of anchors could possibly describe or be applicable to all persons. If the subject being rated is in special circumstances that make it difficult to use the anchors provided, the rater should make a best effort to extrapolate the anchors provided to the subject's situation.

In general, severity scores on the NSA can be interpreted as follows:

1. The behavior being assessed is not reduce or absent as compared to a healthy young human
2. The behavior being assessed is minimally reduced, significance is questionable
3. The behavior being assessed is mildly reduced, it might only be noted as reduced by a trained rater, but he/she notes a definite reduction

4. The behavior being assessed is moderately reduced, it reduction should be obvious to an untrained rater

5. The behavior being rated is markedly reduced, this behavior is easily observable and definitely interferes with the subject's functioning

6. The behavior being assessed is severely reduced or entirely absent, it is glaring and markedly interferes with functioning

If the behavior cannot be rated despite heroic efforts by the rater to get adequate information, make a best guess. The rater's best guess is likely to be better than that of someone not involved with the person.

Use Of The Semi-Structured Interview

The semi-structured interview should be used as a stimulus to help remind the rater of which questions must be asked. Some subjects may require that the question be asked in a different way than that provided. Most subjects will require that more detailed questions be asked to gather adequate information regarding the frequency and severity of reduction for behavior being assessed.

The interview can probably be accomplished in 20-30 minutes for most patients and is most efficiently done in conjunction with the BPRS interview.

Time Frame

The time frame during which items are to be rated should be defined by the particular study, however, for certain items (e.g., #1,#2, and #3) only behaviors noted during the interview are to be rated. For those items where a longer interval is required, the time frame is frequently defined as the previous 7 days. Information from earlier time points may be useful for the rater and subject to gain perspective, but only reduction in behaviors noted during the interview or during the specified time frame are to be rated.

Rating The Global Score

This item rates overall severity of negative symptoms when defined as the absence or reduction of behaviors normally present in a healthy, young person. Ratings should not depend on any specific item or items from the NSA or any other similar instrument. Instead, it should measure the rater's gestalt of the interview and often is ratable within a few minutes of initiating the interview.

Raters

Raters should be trained in the use of the NSA before they begin a clinical study. To achieve high inter-rater reliability for several raters, it is probably best to use exactly the same stimulus (like a videotape or a common interview). Although raters should be trained mental health professional persons, previous experience has demonstrated that they need not have advanced degrees to rate this scale reliably.

Negative Symptom Assessment-16 (NSA-16) Rating Scale—Short Form

1. **Prolonged time to respond**
   1) no abnormal pauses before speaking
   2) minimal evidence of inappropriate pauses, may be extreme of normal
   3) occasional long pauses before answering questions
   4) pauses occur frequently (20-40% of responses)
   5) pauses occur most of the time (40-80% of responses
   6) pauses occur with almost every response (80-100% of responses)
   9) not ratable

2. **Restricted speech quantity**
   1) normal speech quantity
   2) minimal reduction in quantity, may be extreme of normal
   3) speech quantity is reduced, but more obtained with minimal prodding
   4) flow of speech is maintained only by regularly prodding
   5) responses usually limited to a few words, and/or detail is only obtained by prodding or bribing
   6) responses usually nonverbal or limited to 1 or 2 words, despite efforts to elicit more
   9) not ratable

3. **Impoverished speech content**
   1) normal speech content
   2) minimal reduction in content, may be extreme of normal
   3) ideas are sometimes vague
   4) many ideas vague; some ideas remain vague, even after attempts to clarify
   5) most ideas remain vague, even after attempts to clarify
   6) no ideas can be clarified beyond vague impressions
   9) not ratable

4. **Inarticulate speech**
   1) speech clear, not mumbled
   2) minimal garbled speech, may be extreme of normal
   3) a few words are slurred, but can be understood in context
   4) the subject must occasionally be asked to repeat mumbled words
   5) many words are difficult to understand; the subject must frequently be asked to repeat but, on repeating, can usually be understood
   6) little language can be understood even after repeating
   9) not ratable

5. **Emotion: Reduced range (specify time frame for this assessment)**
   1) normal range of emotion
   2) minimal reduction in range, may be extreme of normal
   3) range seems restricted relative to a normal person, but during the specified time period subject convincingly reports at least 4 emotions
   4) subject convincingly identifies 2 or 3 emotional experiences
   5) subject can convincingly identify only 1 emotional experience
   6) subject reports little or no emotional range
   9) not ratable

6. **Affect: Reduced modulation of intensity**
   1) normal modulation of affect
   2) minimal reduction of modulation, may be extreme of normal
   3) affective intensity is muted relative to normal, but some spontaneous change in affective intensity appropriate to the content of conversation is observed

4) affective responses are clearly blunted, but by asking more pointed questions, appropriate changes in affective intensity can be elicited
5) intensity of affect is modulated only slightly, even after prodding
6) affective responses are never modulated, even after prodding
9) not ratable

7. **Affect: Reduced display on demand**
1) subject convincingly displays all requested affective expressions
2) subject convincingly displays 5 of the 6 requested affective expressions
3) subject displays any 4 of the 6 requested affective expressions
4) subject displays any 2 or 3 of the 6 requested affective expressions
5) subject displays any 1 of the 6 requested affective expressions
6) subject is unable to display any requested affective expression
9) not ratable

8. **Reduced social drive**
1) normal social drive
2) minimal reduction in social drive, may be extreme of normal
3) desire for social interactions seems somewhat reduced
4) obvious reduction in desire to initiate social contacts, but a number of social contacts are initiated each week
5) marked reduction in desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
6) no desire to initiate any social interactions
9) not ratable

9. **Poor rapport with interviewer**
1) normal rapport
2) minimal reduction in rapport, may be extreme of normal
3) interviewer sometimes has to carry the conversation because the subject's interest seems reduced
4) interchanges are generally dull and uninspiring; interviewer must often lead the conversation because subject is detached
5) interviewer must prod to engage the subject in the interview
6) prodding does not result in engagement with the interviewer
9) not ratable

10. **Sexual interest**
1) desires to engage in some form of sexual activity once a day or more
2) desires to engage in some form of sexual activity 3-6 times a week
3) desires to engage in some form of sexual activity once or twice a week
4) desires to engage in some form of sexual activity 1-3 times a month
5) desires to engage in some form of sexual activity several times a year
6) no sexual interest is reported
9) not ratable

11. **Poor grooming and hygiene**
1) normal grooming and hygiene
2) minimally reduced grooming and hygiene, may be extreme of normal
3) clean but untidy, or clothes are mismatched
4) clothes are unkempt or unbuttoned (looks as if subject just got out of bed)
5) clothes are dirty or stained, or subject has an odor
6) clothes are badly soiled and/or subject has a foul odor
9) not ratable

12. **Reduced sense of purpose**
1) normal sense of purpose
2) minimal reduction in purpose, may be extreme of normal
3) life goals somewhat vague, but current activities suggest purpose

4) subject has difficulty coming up with life goals, but activities are directed toward limited goal or goals
5) goals are very limited or have to be suggested, and activities are not focused toward achieving any of them
6) no identifiable life goals
9) not ratable

13. **Reduced interest**
1) normal interests
2) minimal reduction in interests, may be extreme of normal
3) range of interests and/or commitment to them seems diminished
4) range of interests is clearly diminished and subject is not particularly committed to interests held
5) only 1 or 2 interests reported, and these pursued superficially
6) little or nothing stimulates interest
9) not ratable

14. **Reduced daily activity**
1) normal daily activity
2) minimal reduction in activity, may be extreme of normal
3) employed, attends school or volunteers, but is underachieving; few hobbies
4) not involved in the activities expected of a normal young person (may be unemployed, or minimally employed for education, but he may be involved in mental health program one or more days a week)
5) most of day spent doing things that require minimal mental or physical exertion (watches TV, smokes, drinks coffee, walks to store, but he may be involved in a mental health program one or more days a week)
6) most of day is spent sitting in a chair or lying in bed; has little or no regard for what goes on in immediate environment
9) not ratable

15. **Reduced expressive gestures**
1) normal expressive gestures
2) minimal reduction in gestures, may be extreme of normal
3) hand and head gestures normally seen during conversation are reduced
4) hand or head gestures are infrequent; gestures may be limited to periods when the subject is discussing topics of special interest to him
5) gestures infrequent even during discussion of highly emotional topics
6) gestures are never observed
9) not ratable

16. **Slowed movements**
1) normal speed of movements
2) minimal reduction in speed of movements, may be extreme of normal
3) voluntary movements are slightly retarded or slowed
4) movements are generally sluggish
5) most movements are retarded and made with effort
6) all movements are made with extreme effort; subject must be assisted from chair
9) not ratable

GLOBAL NEGATIVE SYMPTOMS RATING

1	No evidence of this symptom
2	Minimal evidence of this symptom
3	Mild evidence of this symptom
4	Moderate evidence of this symptom, apparent to the casual observer
5	Marked evidence of this symptom, readily apparent to casual observer
6	Severe, not only obvious but has marked impact on functioning
7	Extremely severe symptom, it is incapacitating for subject

Negative Symptom Assessment-16 (NSA-16)—Long Form

1. **Prolonged time to respond.** After asking the subject a question, he/she pauses for inappropriately long periods before answering. Rate severity of the frequency of these pauses.

    1. No abnormal pauses before speaking
    2. Minimal evidence of inappropriate pauses, may be extreme of normal
    3. Occasionally pauses long enough before answering the question to cause you to wonder whether he/she heard it
    4. Pauses occur frequently (20-40% of responses)
    5. Pauses occur most of the time (40-80% of responses)
    6. Pauses occur with almost every response (80-100% of responses)
    9. Not ratable (use only when all efforts to rate this item have failed)

2. **Restricted speech quantity.** This item assesses the amount of speech the subject provides in the course of the interview. Ratings on this item suggest that the subject gives brief answers to questions and/or provides elaborating details only after the interviewer prods him.

    1. Normal speech quantity
    2. Minimal reduction in quantity, may be extreme of normal
    3. Speech seems reduced, but more can be obtained with minimal prodding
    4. Speech is maintained only by regularly prodding the subject
    5. Responses are usually limited to a few words and/or details are only obtained by prodding or bribing
    6. Responses are usually non-verbal or limited to 1 or 2 word answers (despite one's best efforts to get the subject to elaborate)
    9. Not ratable (use only when all efforts to rate this item have failed)

3. **Impoverished speech content.** The subject may talk a lot or a little but the information conveyed is very limited. If this symptom is pronounced, you will feel you have little more information at the end of the conversation than at the beginning. For subjects who give minimal responses, rate item based on what the interviewer knows after asking probing questions.

    1. Normal speech content
    2. Minimal reduction in content, may be extreme of normal
    3. Ideas are sometimes vague
    4. Ideas are vague and/or some ideas remain vague even after the interviewer asks for clarification
    5. Ideas remain vague even after the interviewer asks for clarification
    6. No ideas can be clarified beyond vague
    9. Not ratable (use only when all efforts to rate this item have failed)

4. **Inarticulate speech.** The subject's speech cannot be understood because enunciation is poor. Do not rate psychotic sub-vocalizations if the rest of the subject's speech is normal and these utterances are not addressed to the interviewer. For subjects with a strong dialect, rate on the basis of the subject's ability to articulate and not on their competence with the language.

    1. Clear speech, not mumbled
    2. Minimal garbled speech, may be extreme of normal
    3. A few words slurred, but can be understood in context
    4. The subject must occasionally be asked to repeat mumbled words
    5. Many words are difficult to understand; the subject must frequently be asked to repeat, but on repeating can usually be understood
    6. Little language can be understood even after repeating
    9. Not ratable (use only when all efforts to rate this item have failed)

5. **Emotion: Reduced range.** Emotion is the feeling content of a person's inner life. This item assesses the range of emotion experienced by the subject during the last week (or other specified time period). Base ratings on the subject's answers to queries of whether he/she has felt happy, sad, etc. during the last week, as well as any reports of having these emotions later in the interview. A full range of emotions would include, but not be limited to happiness, sadness, pride, fear, surprise, and anger. This item should be distinguished from the capacity to display affect, which is rated elsewhere. (If you sense that a subject's emotional life is autistic and not contextually validated, rate his/her emotional range according to your interpretations of his/her experience.)

    1. Normal range of emotion
    2. Minimal reduction in range, may be extreme of normal
    3. Range seems restricted relative to a normal person, but during the specified time frame subject convincingly reports at least 4 emotions.
    4. Subject convincingly identifies 2 or 3 emotional experiences
    5. Subject convincingly identifies only 1 emotional experience
    6. Subject reports little or no emotional range
    9. Not ratable (use only when all efforts to rate this item have failed)

6. **Affect: Reduced modulation of intensity.** This item assesses the subject's modulations of intensity of affect shown during the interview while discussing matters that would be expected to elicit significantly different affective intensities in a normal person

    1. Normal modulations of affect
    2. Minimal reduction of modulation, may be extreme of normal
    3. Affective intensity is muted relative to normal, but some spontaneous change in affective intensity appropriate to the content of conversation is observed
    4. Affective responses are clearly blunted; but by asking more pointed questions, appropriate changes in affective intensity can be elicited
    5. Intensity of affect is modulated only slightly, even after prodding
    6. Affective responses are never modulated, even after prodding
    9. Not ratable (use only when all efforts to rate this item have failed)

7. **Affect: Reduced display on demand.** Affect is the outward expression of a person's feelings. This items assesses the subject's ability to display a range of affect as expressed by changes in his/her facial expression and gestures when asked by the interviewer to show how his/her face appears when he/she feels happy, sad, proud, scared, surprised, and angry. (Although capable, some subjects are reticent about making facial expressions on demand. The interviewer may encourage the subject until convinced that he/she is unable, or unwilling to assume the expression. Do not accept correct affective expressions that are half-hearted and unconvincing, and do not accept descriptions of affective expressions.)

    1. Subject convincingly displays all requested affective expressions
    2. Subject convincingly displays 5 of 6 requested affective expressions
    3. Subject displays any 4 of 6 requested affective expressions
    4. Subject displays any 2 or 3 of 6 requested affective expressions
    5. Subject displays any 1 of 6 requested affective expressions
    6. Subject is unable to display any of the affective expressions
    9. Not ratable (use only when all efforts to rate this item have failed)

8. **Reduced social drive.** This item assesses how much the subject desires to initiate social interactions. Desire may be measured in part by the number of actual or attempted social contacts with others. To rate severity probes the type of social interactions, **and** their frequency. Remember the reference range is a normal 20 year old. Many subjects may be rated 2 to 3.

    1. Normal social drive
    2. Minimal reduction in social drive, may be extreme of normal
    3. Desire for social interactions seems somewhat reduced
    4. Obvious reduction in desire to initiate social contacts, but a number of contacts are initiated each week
    5. Marked reduction in the subject's desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
    6. No desire to initiate any social interactions
    9. Not ratable (use only when all efforts to rate this item have failed)

9. **Poor rapport with interviewer.** This item assesses the interviewer's subjective sense that he/she and the subject are actively engaged in communication with one another. Evaluate both verbal and nonverbal aspects of communication. Do no rate hostility as lack of rapport.

    1. Normal rapport
    2. Minimal reduction in rapport, may be extreme of normal
    3. Interviewer sometimes has to carry the conversation because the subject's interest seems reduced
    4. Interchanges are generally dull and uninspiring; interviewer must often lead the conversation because subject is detached
    5. Interviewer must prod to engage the subject in the interview
    6. Prodding does not result in engagement with the interviewer
    9. Not ratable (use only when all efforts to rate this item have failed)

10. **Sexual interest.** This item assesses how much the subject retains interest in sexual activity. Do not exclusively rate actual performance though in many instances performance might indicate desire and non-performance the absence of it. Take the subject's marital and environmental situations into account when rating this item. (Because of his/her illness, he/she may be unable to find a suitable sex partner; if hospitalized, he/she may be discouraged from having sex.) Sexual interest can be expressed by any sexual activity or interest including, but not limited to: intercourse, foreplay, masturbation, fantasy, flirtations, etc. If the subject claims to be interested in sex but his/her performance is not consistent with his/her claim, the rater should ask him/her to account for this discrepancy.

    1. Desires to engage in some form of sexual activity once a day or more
    2. Desires to engage in some form of sexual activity 3-6 times a week
    3. Desires to engage in some form sexual activity once or twice a week
    4. Desires to engage in some form of sexual activity 1-3 time a month
    5. Desires to engage in some form of sexual activity several times a year
    6. No sexual interest is reported
    9. Not ratable (use only when all efforts to rate this item have failed)

11. **Poor grooming and hygiene.** The subject presents with poorly groomed hair, disheveled clothing, etc. Do not rate grooming as poor if it is simply done in what a middle-class observer might consider poor taste (e.g.; wild hairdo or excessive facial makeup).

    1. Normal grooming and hygiene
    2. Minimal reduction of grooming and hygiene, may be extreme of normal
    3. Clean but untidy, or clothes are mismatched
    4. Clothes are unkempt and unbuttoned (looks as if subject just got out of bed)
    5. Clothes are dirty or stained, or has an odor
    6. Clothes are badly soiled and/or subject has a foul odor
    9. Not ratable (use only when all efforts to rate this item have failed)

12. **Reduced sense of purpose.** This item assesses whether the subject posits integrated goals for his/her life. If the subject already has what seems to be a satisfactory and well-integrated life, it is not necessary that he/she be planning a change to be judged as having a good sense of purpose.

    1. Normal sense of purpose
    2. Minimal reduction in purpose, may be extreme of normal
    3. Life goals somewhat vague, but current activities suggest purpose
    4. Subject has difficulty coming up with life goals, but activities are directed toward limited goal or goals
    5. Goals are very limited or have to be suggested, and activities are not focused toward achieving any of them
    6. No identifiable life goals
    9. Not ratable (use only when all efforts to rate this item have failed)

13. **Reduced hobbies and interest.** This item assesses the range and intensity of the subject's interests.

    1. Normal interests
    2. Minimal reduction in interests, may be extreme of normal
    3. Range of interests and/or commitment to them seems diminished
    4. Range of interests is clearly diminished and is not particularly committed to interests held
    5. Only 1 or 2 interests reported, and these pursued superficially
    6. No identifiable goals
    9. Not ratable (use only when all efforts to rate this item have failed)

14. **Reduced daily activity.** This item assesses the level of the subject's daily activity and his/her failure to take advantage of the opportunities his/her environment offers. Get a complete

account of what the subject does from the time he/she gets up until he goes to bed. Compare his/her activities with those of a young person who is not mentally ill. If the subject participates as an outpatient in a mental health program, determine the level of his/her participation, i.e. whether he/she is actively involved, or just passes time there. If the subject is hospitalized rate his/her daily activity as you would for a young person who is not hospitalized and without regard for the limitations that the hospital routine may place on him/her.

1. Normal daily activity
2. Minimal reduction in activity, may be extreme of normal
3. Employed, attends school or volunteers, but is underachieving; few hobbies
4. Not involved in the activities expected of a normal young person (may be unemployed, or minimally employed for education, but may be involved in a mental health program one or more days a week)
5. Most of day spent doing activities, things that require minimal mental or physical exertion (watches TV, smokes, drinks coffee, walks to store, but may be involved in a mental health program one or more days a week)
6. Most of day is spent sitting in a chair or lying in bed; has little or no regard for what goes on in immediate environment
9. Not ratable (use only when all efforts to rate this item have failed)

15. **Reduced expressive gestures.** Gestures and body movements that normally facilitate communication during speech are less than normal, or are not observed at all. Do not rate involuntary movement disorders.

    1. Normal expressive gestures
    2. Minimal reduction in gestures, may be extreme of normal
    3. Hand and head gestures normally seen during conversation are reduced
    4. Hand or head gestures are infrequent; gestures may be limited to periods when the subject is discussing topics of special interest
    5. Gestures infrequent even during discussion of highly emotional topics
    6. Gestures are never observed
    9. Not ratable (use only when all efforts to rate this item have failed)

16. **Slowed movements.** This item assesses how much the subject's voluntary movements are slowed. At a minimum one should rate movements as gait and those of rising from a chair. Rate these movements in comparison to a normal young person

    1. Normal speed of movements
    2. Minimal reduction in speed of movements, may be extreme of normal
    3. Voluntary movements are slightly retarded or slowed
    4. Movements are generally sluggish
    5. Most movements are retarded and made with effort
    6. All movements are made with extreme effort; subject must be assisted from chair
    9. Not ratable (use only when all efforts to rate this item have failed)

GLOBAL NEGATIVE SYMPTOMS RATING. Rate this item on the basis of overall impression of negative symptoms in the subject, not on the basis of a single item or total score.

1. No evidence of negative symptoms
2. Minimal evidence of negative symptoms
3. Mild evidence of negative symptoms
4. Moderate evidence of negative symptoms apparent to the casual observer
5. Marked evidence of negative symptoms readily apparent to the casual observer
6. Severe evidence of negative symptoms marked and obvious impact on functioning
7. Extremely severe negative symptoms (incapacitating)

Negative Symptom Assessment Global Rating

Definition Of Negative Symptoms

Negative symptoms represent the reduction or absence of behaviors normally present in a healthy person. These include, but are not limited to, behaviors related to personal, social and affective behaviors. Specifically, negative symptoms of schizophrenia are considered to include reduction in emotional expression and perception, reduction in the fluency and productivity of thought and speech, reduced desire for social involvement and reduced social interaction with others and a loss or lack of goal-directed behavior. These symptoms contribute substantially to reductions in functioning for schizophrenic patients as compared to others in their society.

Global Negative Symptoms Rating--Severity

This score represents your overall assessment of the subject's negative symptoms. The rating should not be an average of any particular behavior, but a gestalt of everything seen in the interview. When rating impairment, only impairment that you judge is due to negative symptoms should be rated. The referent is a normal healthy young adult.

1) No impairment (No question of negative symptoms has been raised in the rater's mind.)
2) Minimal negative symptoms (A trained observer is uncertain if clinically meaningful negative symptoms are present. If present, they have little or no adverse impact on the subject's life.)
3) Mild negative symptoms (Close observation suggests that negative symptoms are present, but they might be missed in casual conversation or by an untrained observer. The subject is able to overcome most problems related to these deficits.)
4) Moderate negative symptoms (Negative symptoms are obviously present and they have adverse impact on some areas of the subject's life.)
5) Marked negative symptoms (Negative symptoms are obviously present by all who meet this person. Many aspects of the subject's life are adversely impacted by these symptoms.)
6) Severe negative symptoms (Negative symptoms are very prominent and the subject's life is severely disrupted because of them.)
7) Extremely severe negative symptoms (Negative symptoms are extremely prominent and the subject's life is completely disrupted because of them. These symptoms are amongst the most prominent that the rater has observed, or, if the rater has limited experienced, among the most severe that the rater can imagine.)

Global Level Of Functioning

This score represents your overall assessment of the subject's level of functioning. The rating should not be an average of any particular area, but a gestalt of everything known about the subject's level of functioning in all areas of his/her life. The referent is a normal healthy young adult.

1) No impairment (No question of impairment in functioning has been raised in the rater's mind.)
2) Minimal impairment (A trained observer is uncertain if there is impairment in functioning, and, if present, this impairment has little or no adverse impact on the subject's life.)
3) Mild impairment (Close observation suggests that the subject experiences some impairment in functioning, but this impairment might be missed in casual interactions or by an untrained observer. The subject is able to achieve most of his/her life goals.)
4) Moderate impairment (Impairment in functioning is obvious to any trained observer. Some life goals are not attained.)
5) Marked impairment (Impairment in functioning is obviously present by all who meet this person. Many aspects of the subject's life are adversely affected.)
6) Severe impairment (Impairment in functioning is extremely prominent and the subject's life is severely disrupted because of it.)
7) Extremely severe impairment (Impairment in functioning is extremely prominent and the subject's life is completely disrupted because of it. Functioning is at amongst the lowest levels that the rater has observed, or, if inexperienced, at the lowest level that the rater can imagine.)

SEMI-STRUCTURED INTERVIEW FOR RATING THE NSA-16

Emotion

1. How have you been doing in the past 7 days?

2. Have you felt anxious, nervous or worried during the past week? What has that been like for you? How bad was it? What makes you feel this way? Do you feel anxious about participating in this interview?

3. Have you felt sad or depressed during the past week? What has that been like for you? How bad was it? What makes you feel this way?

4. Have there been times during the past week when you felt happy? What made you feel this way? What is it like when you feel happy? (Repeat these questions for proud, scared, surprised and angry. If after the completion of this section, few emotions are identified, suggest a situation that might have caused emotion [getting lost, a near car accident, an award, a quarrel, a party], but do **not** suggest the emotion that might have been experienced.)

5. During the last week, were there times when you felt numb or empty inside?

Affect

6. Could you show me what it looks like on your face when you feel happy? (Repeat question for sad, proud, scared, surprised and angry.)

Daily Activity

7. Are you employed now? What do you do? Do you work full time? Is your employer satisfied with the work you do?

8. Starting with the time you get up, could you tell me how you have spent a typical day during the past week?

General Interests

9. What do you enjoy doing? What else do you enjoy? Have you done these things in the past week?

10. Are you interested in what is going on in the world? Do you read the newspapers? Do you watch the news on TV? Can you tell me about some of the important news stories of the past week?

11. Do you like sports? What is you favorite sport? Which is your favorite team? Who are the top players in this sport? Have you played in any sport during the past week?

Social Interest

12. Do you live alone, or with someone else?

13. Do you like to be around other people? Do you spend much time with others? Do you have difficulty feeling close to them?

14. Who are your friends? How often do you seem them? Did you see them this past week? Have you called them on the phone? When you got together this past week, who decided what to do and where to go?

15. Is anyone concerned about your happiness and well-being?

Sexual Interest

16. Do you sometimes have sexual thoughts or desires? How frequently do you have them? How many times in the last week have you thought you would like to have sex?

17. When you do have sexual desires, how do you release the tension that comes with them? How many times in the past week have you experienced some form of sexual activity?

18. Are you more or less interested in sex than you used to be?

Sense of Purpose

19. What makes life worth living for you? What have you done in the past that has been important for you?

20. What goals or plans do you have for the future? What do you see yourself doing a year from now? Five years from now? How do you plan to achieve these goals?

Motor Retardation

21. Do you have any problems with your movements? Could you walk back and forth across the room, so I can see how you walk?

Psychometric Development of Negative Symptom Assessment-16 (NSA-16)

Goal

Development of a new scale that broadly and sensitively assesses negative symptoms of schizophrenia

Rationale

Scales existing at the time of scale development had one or more of the following problems

- Not comprehensive of general concept of schizophrenia
- Anchors not well defined
- Inadequate psychometric development
- Not sensitive to change
- Difficult to train raters

Principles

Rate behaviors without attribution of etiology (including other disease states, side effects of drug treatment, or age) that minimizes possibility for cultural bias

TABLE 1. Psychometric Development

Publication	NSA Version	Analysis	Factors Identified	Resulting Changes
Alphs, et al 1989	NSA-26	Principal Components Factor Analysis with varimax rotation	• Affect/Emotion (10) • External Involvement (5) • Retardation (3) • Personal Presentation (3) • Thinking (2) • Interpersonal interest (2) • Blocking (1)	• Redefined and clarified anchors • Added additional items to more adequately cover factors identified
Raskin, et al, 1993	NSA-30	Principal Components Factor Analysis with varimax rotation	• Difficulties in communicating (10) • Lack of Emotion/ Flattened Affect (7) • Social Inactivity (4) • Loss of Interest/Motivation (4) • Cognitive Difficulties (4) • Psychomotor Activity (1)	• Redefined and clarified anchors • Removed redundant or high variance items
Axelrod, et al, 1994	NSA-26	Confirmatory factor analysis	• Communication (6) • Emotion/Affect (4) • Social Involvement (4) • Motivation (4) • Gross Cognition (3) • Retardation (4)	• Redefined and clarified anchors • Removed redundant or high variance items within factors • Removed cognition items
Axelrod et al, 1994	NSA-16	Confirmatory factor analysis	• Communication (4) • Emotion/Affect (3) • Social Involvement (3)	• 5-factor model represents optimal structure of instrument and is

			• Motivation (4) • Retardation (2)	descriptively much better than null model

TABLE 2. Additional Psychometric Development

Publication	Psychometric Analysis	Findings
Alphs, et al, 1989	Validity and Reliability	• Construct validity established • Inter and Intra-rater reliability established
Axelrod, et al, 1994	Rater Trainability	• Raters can be trained to high reliability after 30-60-minute training session
Eckert, et al, 1996	Sensitivity to Change	• Effect size similar to SANS

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APPENDIX 3B. Negative Symptom Assessment-16 scale (NSA-16)

Negative Symptom Assessment-16 (NSA-16) Instruction Manual

Larry Alphs, MD, PhD

Version 3.0

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RULES FOR RATING THE NSA

Working Definition Of Negative Symptoms

Negative symptoms represent the reduction or absence of emotional expression and volitional behaviors normally present in a healthy person. These include, but are not limited to, behaviors related to personal, social and affective behavior. Specifically, negative symptoms of schizophrenia are considered to include reduction in emotional expression and perception, reduction in the fluency and productivity of thought and speech, reduced desire for social involvement and reduced social interaction with others, a loss or lack of goal-directed behavior, and a diminished sense of purpose. These symptoms contribute to substantial reductions in the functioning of individuals with schizophrenia as compared to others in their society.

A. Purpose

The Negative Symptom Assessment (NSA) aims to permit the reliable rating of behaviors commonly associated with the concept of negative symptoms in schizophrenia. It should be emphasized that this scale rates behavior and not psychopathological conditions. Thus, scores on this scale do not necessarily have psychopathological or etiological implications. For instance, subjects could achieve high ratings on some items because of depression, medication regimen, institutionalization, uncooperativeness, deficit syndrome, motor symptoms or even personality style. Raters using this scale should not correct ratings because, in their judgment, the etiology is something other than that sought in the particular study where it is currently used.

B. Sources of Information

The source of information for the NSA is a semi-structured, clinical interview. This information should be applied with good clinical judgment in making a final rating.

The rater may be, and is encouraged to be, aware of information from sources outside of the interview. If the subject's report is at variance with outside reports (of nurses, family, etc.), these discrepancies should be clarified. Similarly, if the patient provides contradictory information, or other information from the interview is at variance with the subject's stated performance in a particular area, the rater should use his/her best clinical judgment in assigning a severity score for this behavior. Note that the same sources of information should be used throughout the study to decrease variability in scores over time due to changes in data sources.

C. Reference Population

The 'normal' reference population against which the subject is to be compared is a young person in their twenties without schizophrenia. It is not (1) the same person at another point in time; (2) a healthy person of similar age, living under similar circumstances; nor (3) another hospitalized person.

D. Use of Anchors (Item Descriptors)

The anchors that are provided for this scale should be used as guides and should be used insofar as they apply to the persons being rated. No set of anchors could possibly describe or be applicable to all persons. If the subject being rated is in special circumstances that make it difficult to use the anchors provided, the rater should make a best effort to extrapolate the anchors provided to the subject's situation.

In general, severity scores on the NSA can be interpreted as follows:

1. The behavior being assessed is not reduced or absent as compared to a healthy young person
2. The behavior being assessed is minimally reduced, significance is questionable
3. The behavior being assessed is mildly reduced, it might only be noted as reduced by a trained rater, but he/she notes a definite reduction
4. The behavior being assessed is moderately reduced, it reduction should be obvious to an untrained rater
5. The behavior being rated is markedly reduced, this behavior is easily observable and definitely interferes with the subject's functioning
6. The behavior being assessed is severely reduced or entirely absent, it is glaring and markedly interferes with functioning

If the behavior cannot be rated despite heroic efforts by the rater to get adequate information, make a best guess. The rater's best guess is likely to be better than that of someone not involved with the person.

E. Use of The Semi-Structured Interview

The semi-structured interview should be used as a stimulus to help remind the rater of which questions must be asked. Some subjects may require that the question be asked in a different way than that provided. Most subjects will require that more detailed questions be asked to gather adequate information regarding the frequency, severity, and impact on function of the reduction for behavior being assessed.

The interview can probably be accomplished in 20-30 minutes for most patients and can be efficiently done in conjunction with other symptoms interviews such as the Positive and Negative Symptom Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) interview.

F. Time Frame

The time frame during which items are to be rated should be defined by the particular study, however, for certain items (e.g., 1-4, 6-7, 9, 15-16) only behaviors noted during the interview are to be rated. For those items where a longer interval is required, the time frame is frequently defined as the past week. Information from earlier time points may be useful for the rater and subject to gain perspective, but only reduction in behaviors noted during the interview or during the specified time frame are to be rated.

G. Rating the Global Score

This item rates overall severity of negative symptoms when defined as the absence or reduction of behaviors normally present in a healthy, young person. Ratings should not depend on any specific item or items from the NSA or any other similar instrument. Instead, it should measure the rater's gestalt of the frequency, severity and functional impact of the negative symptoms during the interview and rating period. The global score often is ratable within a few minutes of initiating the interview.

H. Raters

Raters should be trained in the use of the NSA-16 before they begin a clinical study. To achieve high inter-rater reliability for several raters, it is probably best to use exactly the same stimulus (like a videotape or a common interview). Although raters should be trained mental health professional persons, previous experience has demonstrated that they need not have advanced degrees to rate this scale reliably.

Negative Symptom Assessment-16 (NSA-16) Rating Scale—Short Form

1. **Prolonged time to respond**
   - 1) no abnormal pauses before speaking
   - 2) minimal evidence of inappropriately long pauses; may be extreme of normal
   - 3) occasional long pauses before answering questions
   - 4) long pauses occur frequently (20-40% of responses)
   - 5) long pauses occur most of the time (40-80% of responses
   - 6) long pauses occur with almost every response (80-100% of responses)
   - 9) not ratable (use only when all efforts to rate have failed)

2. **Restricted speech quantity**
   - 1) normal speech quantity
   - 2) minimal reduction in quantity, may be extreme of normal
   - 3) speech quantity is reduced, but more obtained with minimal prodding
   - 4) flow of speech is maintained only by regularly prodding
   - 5) responses usually limited to a few words, and/or detail is only obtained by prodding or bribing
   - 6) responses usually nonverbal or limited to 1 or 2 words, despite efforts to elicit more
   - 9) not ratable (use only when all efforts to rate have failed)

3. **Impoverished speech content**
   - 1) normal speech content
   - 2) minimal reduction in content, may be extreme of normal
   - 3) ideas are sometimes vague
   - 4) many ideas vague; some ideas remain vague, even after attempts to clarify
   - 5) most ideas remain vague, even after attempts to clarify
   - 6) no ideas can be clarified beyond vague impressions
   - 9) not ratable (use only when all efforts to rate have failed)

4. **Inarticulate speech**
   - 1) speech clear, not mumbled
   - 2) minimal garbled speech, may be extreme of normal
   - 3) a few words are slurred, but can be understood in context
   - 4) the subject must occasionally be asked to repeat mumbled words
   - 5) many words are difficult to understand; the subject must frequently be asked to repeat but, on repeating, can usually be understood
   - 6) little language can be understood even after repeating
   - 9) not ratable (use only when all efforts to rate have failed)

5. **Emotion: Reduced range (specify time frame for this assessment)**
   - 1) normal range of emotion
   - 2) minimal reduction in range, may be extreme of normal
   - 3) range seems restricted relative to a normal person, but during the specified time period subject convincingly reports at least 4 emotions
   - 4) subject convincingly identifies 2 or 3 emotional experiences
   - 5) subject can convincingly identify only 1 emotional experience
   - 6) subject reports little or no emotional range
   - 9) not ratable (use only when all efforts to rate have failed)

6. **Affect: Reduced modulation of intensity**
   - 1) normal modulation of affect
   - 2) minimal reduction of modulation, may be extreme of normal

3) affective intensity is muted relative to normal, but some spontaneous change in affective intensity appropriate to the content of conversation is observed
4) affective responses are clearly blunted, but by asking more pointed questions, appropriate changes in affective intensity can be elicited
5) intensity of affect is modulated only slightly, even after prodding
6) affective responses are never modulated, even after prodding
9) not ratable (use only when all efforts to rate have failed)

7. **Affect: Reduced display on demand**
1) subject convincingly displays all requested affective expressions
2) subject convincingly displays 5 of the 6 requested affective expressions
3) subject displays any 4 of the 6 requested affective expressions
4) subject displays any 2 or 3 of the 6 requested affective expressions
5) subject displays any 1 of the 6 requested affective expressions
6) subject is unable to display any requested affective expression
9) not ratable (use only when all efforts to rate have failed)

8. **Reduced social drive**
1) normal social drive
2) minimal reduction in social drive, may be extreme of normal
3) desire for social interactions seems somewhat reduced
4) obvious reduction in desire to initiate social contacts, but a number of social contacts are initiated each week
5) marked reduction in desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
6) no desire to initiate any social interactions
9) not ratable (use only when all efforts to rate have failed)

9. **Poor rapport with interviewer**
1) normal rapport
2) minimal reduction in rapport, may be extreme of normal
3) interviewer sometimes has to carry the conversation because the subject's interest seems reduced
4) interchanges are generally dull and uninspiring; interviewer must often lead the conversation because subject is detached
5) interviewer must prod to engage the subject in the interview
6) prodding does not result in engagement with the interviewer
9) not ratable (use only when all efforts to rate have failed)

10. **Interest in emotional and physical intimacy**
1) desires to engage in some form of emotional and/or physical intimate activity once a day or more
2) desires to engage in some form of emotional and/or physical intimate activity 3-6 times a week
3) desires to engage in some form emotional and/or physical intimate activity once or twice a week
4) desires to engage in some form of emotional and/or physical intimate activity 1-3 time a month
5) desires to engage in some form of emotional and/or physical intimate activity several times a year
6) no emotional and/or physical intimate interest is reported
9) not ratable (use only when all efforts to rate this item have failed)

11. **Poor grooming and hygiene**
1) normal grooming and hygiene
2) minimally reduced grooming and hygiene, may be extreme of normal
3) clean but untidy, or clothes are mismatched
4) clothes are unkempt or unbuttoned (looks as if subject just got out of bed)
5) clothes are dirty or stained, or subject has an odor

6) clothes are badly soiled and/or subject has a foul odor
9) not ratable (use only when all efforts to rate have failed)

12. **Reduced sense of purpose**
1) normal sense of purpose
2) minimal reduction in purpose, may be extreme of normal
3) life goals somewhat vague, but current activities suggest purpose
4) subject has difficulty coming up with life goals, but activities are directed toward limited goal or goals
5) goals are very limited or have to be suggested, and activities are not focused toward achieving any of them
6) no identifiable life goals
9) not ratable (use only when all efforts to rate have failed)

13. **Reduced interest**
1) normal interests
2) minimal reduction in interests, may be extreme of normal
3) range of interests and/or commitment to them seems diminished
4) range of interests is clearly diminished and subject is not particularly committed to interests held
5) only 1 or 2 interests reported, and these pursued superficially
6) little or nothing stimulates interest
9) not ratable (use only when all efforts to rate have failed)

14. **Reduced daily activity**
1) normal daily activity
2) minimal reduction in activity, may be extreme of normal
3) employed, attends school or volunteers, but is underachieving; few hobbies
4) not involved in the activities expected of a normal young person (may be unemployed, or minimally employed for education, but he may be involved in mental health program one or more days a week)
5) most of day spent doing things that require minimal mental or physical exertion (watches TV, smokes, drinks coffee, walks to store, but he may be involved in a mental health program one or more days a week)
6) most of day is spent sitting in a chair or lying in bed; has little or no regard for what goes on in immediate environment
9) not ratable (use only when all efforts to rate have failed)

15. **Reduced expressive gestures**
1) normal expressive gestures
2) minimal reduction in gestures, may be extreme of normal
3) hand and head gestures normally seen during conversation are reduced
4) hand or head gestures are infrequent; gestures may be limited to periods when the subject is discussing topics of special interest to him
5) gestures infrequent even during discussion of highly emotional topics
6) gestures are never observed
9) not ratable (use only when all efforts to rate have failed)

16. **Slowed movements**
1) normal speed of movements
2) minimal reduction in speed of movements, may be extreme of normal
3) voluntary movements are slightly retarded or slowed
4) movements are generally sluggish
5) most movements are retarded and made with effort
6) all movements are made with extreme effort; subject must be assisted from chair
9) not ratable (use only when all efforts to rate have failed)

GLOBAL NEGATIVE SYMPTOMS RATING

1	No evidence of this symptom
2	Minimal evidence of this symptom
3	Mild evidence of this symptom
4	Moderate evidence of this symptom, apparent to the casual observer
5	Marked evidence of this symptom, readily apparent to casual observer
6	Severe, not only obvious but has marked impact on functioning
7	Extremely severe symptom, it is incapacitating for subject

Negative Symptom Assessment-16 (NSA-16)—Long Form

1. **Prolonged time to respond.** After asking the subject a question, he/she pauses for inappropriately long periods before answering. Rate severity of the frequency of these pauses.

    1. No abnormal pauses before speaking
    2. Minimal evidence of inappropriate pauses, may be extreme of normal
    3. Occasionally pauses long enough before answering the question to cause you to wonder whether he/she heard it
    4. Long pauses occur frequently (20-40% of responses)
    5. Long pauses occur most of the time (40-80% of responses)
    6. Long pauses occur with almost every response (80-100% of responses)
    9. Not ratable (use only when all efforts to rate this item have failed)

2. **Restricted speech quantity.** This item assesses the amount of speech the subject provides in the course of the interview. Ratings on this item suggest that the subject gives brief answers to questions and/or provides elaborating details only after the interviewer prods him.

    1. Normal speech quantity
    2. Minimal reduction in quantity, may be extreme of normal
    3. Speech seems reduced, but more can be obtained with minimal prodding
    4. Speech is maintained only by regularly prodding the subject
    5. Responses are usually limited to a few words and/or details are only obtained by prodding or bribing
    6. Responses are usually non-verbal or limited to 1 or 2 word answers (despite one's best efforts to get the subject to elaborate)
    9. Not ratable (use only when all efforts to rate this item have failed)

3. **Impoverished speech content.** The subject may talk a lot or a little but the information conveyed is very limited. If this symptom is pronounced, you will feel you have little more information at the end of the conversation than at the beginning. For subjects who give minimal responses, rate item based on what the interviewer knows after asking probing questions.

    1. Normal speech content
    2. Minimal reduction in content, may be extreme of normal
    3. Ideas are sometimes vague
    4. Ideas are vague and/or some ideas remain vague even after the interviewer asks for clarification
    5. Ideas remain vague even after the interviewer asks for clarification
    6. No ideas can be clarified beyond vague
    9. Not ratable (use only when all efforts to rate this item have failed)

4. **Inarticulate speech.** The subject's speech cannot be understood because enunciation is poor. Do not rate psychotic sub-vocalizations if the rest of the subject's speech is normal and these utterances are not addressed to the interviewer. For subjects with a strong dialect, rate on the basis of the subject's ability to articulate and not on their competence with the language.

    1. Clear speech, not mumbled
    2. Minimal garbled speech, may be extreme of normal
    3. A few words slurred, but can be understood in context
    4. The subject must occasionally be asked to repeat mumbled words
    5. Many words are difficult to understand; the subject must frequently be asked to repeat, but on repeating can usually be understood
    6. Little language can be understood even after repeating
    9. Not ratable (use only when all efforts to rate this item have failed)

5. **Emotion: Reduced range.** Emotion is the feeling content of a person's inner life. This item assesses the range of emotion experienced by the subject during the last week (or other specified time period). Base ratings on the subject's answers to queries of whether he/she has felt happy, sad, etc. during the last week, as well as any reports of having these emotions later in the interview. A full range of emotions would include, but not be limited to happiness, sadness, pride, fear, surprise, and anger. This item should be distinguished from the capacity to display affect, which is rated elsewhere. (If you sense that a subject's emotional life is autistic and not contextually validated, rate his/her emotional range according to your interpretations of his/her experience.)

    1. Normal range of emotion
    2. Minimal reduction in range, may be extreme of normal
    3. Range seems restricted relative to a normal person, but during the specified time frame subject convincingly reports at least 4 emotions.
    4. Subject convincingly identifies 2 or 3 emotional experiences
    5. Subject convincingly identifies only 1 emotional experience
    6. Subject reports little or no emotional range
    9. Not ratable (use only when all efforts to rate this item have failed)

6. **Affect: Reduced modulation of intensity.** This item assesses the subject's modulations of intensity of affect shown during the interview while discussing matters that would be expected to elicit significantly different affective intensities in a normal person

    1. Normal modulations of affect
    2. Minimal reduction of modulation, may be extreme of normal
    3. Affective intensity is muted relative to normal, but some spontaneous change in affective intensity appropriate to the content of conversation is observed
    4. Affective responses are clearly blunted; but by asking more pointed questions, appropriate changes in affective intensity can be elicited
    5. Intensity of affect is modulated only slightly, even after prodding
    6. Affective responses are never modulated, even after prodding
    9. Not ratable (use only when all efforts to rate this item have failed)

7. **Affect: Reduced display on demand.** Affect is the outward expression of a person's feelings. This items assesses the subject's ability to display a range of affect as expressed by changes in his/her facial expression and gestures when asked by the interviewer to show how his/her face appears when he/she feels happy, sad, proud, scared, surprised, and angry. (Although capable, some subjects are reticent about making facial expressions on demand. The interviewer may encourage the subject until convinced that he/she is unable, or unwilling to assume the expression. Do not accept correct affective expressions that are half-hearted and unconvincing, and do not accept descriptions of affective expressions.)

    1. Subject convincingly displays all requested affective expressions
    2. Subject convincingly displays 5 of 6 requested affective expressions
    3. Subject displays any 4 of 6 requested affective expressions
    4. Subject displays any 2 or 3 of 6 requested affective expressions
    5. Subject displays any 1 of 6 requested affective expressions
    6. Subject is unable to display any of the affective expressions
    9. Not ratable (use only when all efforts to rate this item have failed)

8. **Reduced social drive.** This item assesses how much the subject desires to initiate social interactions. Desire may be measured in part by the number of actual or attempted social contacts with others. To rate severity probes the type of social interactions, **and** their frequency. Remember the reference range is a normal 20 year old. Many subjects may be rated 2 to 3.

    1. Normal social drive
    2. Minimal reduction in social drive, may be extreme of normal
    3. Desire for social interactions seems somewhat reduced
    4. Obvious reduction in desire to initiate social contacts, but a number of contacts are initiated each week
    5. Marked reduction in the subject's desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
    6. No desire to initiate any social interactions
    9. Not ratable (use only when all efforts to rate this item have failed)

9. **Poor rapport with interviewer.** This item assesses the interviewer's subjective sense that he/she and the subject are actively engaged in communication with one another. Evaluate both verbal and nonverbal aspects of communication. Do no rate hostility as lack of rapport.

    1. Normal rapport
    2. Minimal reduction in rapport, may be extreme of normal
    3. Interviewer sometimes has to carry the conversation because the subject's interest seems reduced
    4. Interchanges are generally dull and uninspiring; interviewer must often lead the conversation because subject is detached
    5. Interviewer must prod to engage the subject in the interview
    6. Prodding does not result in engagement with the interviewer
    9. Not ratable (use only when all efforts to rate this item have failed)

10. **Interest in emotional and physical intimacy.** This item assesses how much the subject retains interest in emotional and/or physical intimate activities. Do not exclusively rate actual performance even though in many instances performance might indicate desire and non-performance the absence of it. Take the subject's marital and environmental situations into account when rating this item. (Because of his/her illness, he/she may be unable to find a suitable partner; if hospitalized, he/she may be discouraged from being intimate with others.) Emotional and physical intimacy interest can be expressed by a wide variety of activities. If the subject claims to be interested in emotional and physical intimacy interest but his/her performance is not consistent with his/her claim, the rater should ask him/her to account for this discrepancy.

    1. Desires to engage in some form of emotional and/or physical intimate activity once a day or more
    2. Desires to engage in some form of emotional and/or physical intimate activity 3-6 times a week
    3. Desires to engage in some form emotional and/or physical intimate activity once or twice a week
    4. Desires to engage in some form of emotional and/or physical intimate activity 1-3 time a month
    5. Desires to engage in some form of emotional and/or physical intimate activity several times a year
    6. No emotional and/or physical intimate interest is reported
    9. Not ratable (use only when all efforts to rate this item have failed)

11. **Poor grooming and hygiene.** The subject presents with poorly groomed hair, disheveled clothing, etc. Do not rate grooming as poor if it is simply done in what a middle-class observer might consider poor taste (e.g.; wild hairdo or excessive facial makeup).

    1. Normal grooming and hygiene
    2. Minimal reduction of grooming and hygiene, may be extreme of normal
    3. Clean but untidy, or clothes are mismatched
    4. Clothes are unkempt and unbuttoned (looks as if subject just got out of bed)
    5. Clothes are dirty or stained, or has an odor
    6. Clothes are badly soiled and/or subject has a foul odor
    9. Not ratable (use only when all efforts to rate this item have failed)

12. **Reduced sense of purpose.** This item assesses whether the subject posits integrated goals for his/her life. If the subject already has what seems to be a satisfactory and well-integrated life, it is not necessary that he/she be planning a change to be judged as having a good sense of purpose.

    1. Normal sense of purpose
    2. Minimal reduction in purpose, may be extreme of normal
    3. Life goals somewhat vague, but current activities suggest purpose
    4. Subject has difficulty coming up with life goals, but activities are directed toward limited goal or goals
    5. Goals are very limited or have to be suggested, and activities are not focused toward achieving any of them
    6. No identifiable life goals
    9. Not ratable (use only when all efforts to rate this item have failed)

13. **Reduced hobbies and interest.** This item assesses the range and intensity of the subject's interests.

    1. Normal interests
    2. Minimal reduction in interests, may be extreme of normal
    3. Range of interests and/or commitment to them seems diminished

4. Range of interests is clearly diminished and is not particularly committed to interests held
5. Only 1 or 2 interests reported, and these pursued superficially
6. No identifiable goals
9. Not ratable (use only when all efforts to rate this item have failed)

14. **Reduced daily activity.** This item assesses the level of the subject's daily activity and his/her failure to take advantage of the opportunities his/her environment offers. Get a complete account of what the subject does from the time he/she gets up until he goes to bed. Compare his/her activities with those of a young person who is not mentally ill. If the subject participates as an outpatient in a mental health program, determine the level of his/her participation, i.e. whether he/she is actively involved, or just passes time there. If the subject is hospitalized rate his/her daily activity as you would for a young person who is not hospitalized and without regard for the limitations that the hospital routine may place on him/her.

    1. Normal daily activity
    2. Minimal reduction in activity, may be extreme of normal
    3. Employed, attends school or volunteers, but is underachieving; few hobbies
    4. Not involved in the activities expected of a normal young person (may be unemployed, or minimally employed for education, but may be involved in a mental health program one or more days a week)
    5. Most of day spent doing activities, things that require minimal mental or physical exertion (watches TV, smokes, drinks coffee, walks to store, but may be involved in a mental health program one or more days a week)
    6. Most of day is spent sitting in a chair or lying in bed; has little or no regard for what goes on in immediate environment
    9. Not ratable (use only when all efforts to rate this item have failed)

15. **Reduced expressive gestures.** Gestures and body movements that normally facilitate communication during speech are less than normal, or are not observed at all. Do not rate involuntary movement disorders.

    1. Normal expressive gestures
    2. Minimal reduction in gestures, may be extreme of normal
    3. Hand and head gestures normally seen during conversation are reduced
    4. Hand or head gestures are infrequent; gestures may be limited to periods when the subject is discussing topics of special interest
    5. Gestures infrequent even during discussion of highly emotional topics
    6. Gestures are never observed
    9. Not ratable (use only when all efforts to rate this item have failed)

16. **Slowed movements.** This item assesses how much the subject's voluntary movements are slowed. At a minimum one should rate movements as gait and those of rising from a chair. Rate these movements in comparison to a normal young person

    1. Normal speed of movements
    2. Minimal reduction in speed of movements, may be extreme of normal
    3. Voluntary movements are slightly retarded or slowed
    4. Movements are generally sluggish
    5. Most movements are retarded and made with effort
    6. All movements are made with extreme effort; subject must be assisted from chair
    9. Not ratable (use only when all efforts to rate this item have failed)

GLOBAL NEGATIVE SYMPTOMS RATING. Rate this item on the basis of overall impression of negative symptoms in the subject, not on the basis of a single item or total score.

1. No evidence of negative symptoms
2. Minimal evidence of negative symptoms
3. Mild evidence of negative symptoms
4. Moderate evidence of negative symptoms apparent to the casual observer
5. Marked evidence of negative symptoms readily apparent to the casual observer
6. Severe evidence of negative symptoms marked and obvious impact on functioning
7. Extremely severe negative symptoms (incapacitating)

Negative Symptom Assessment Global Rating

Definition of Negative Symptoms

Negative symptoms represent the reduction or absence of emotional expression and volitional behaviors normally present in a healthy person. These include, but are not limited to, behaviors related to personal, social and affective behavior. Specifically, negative symptoms of schizophrenia are considered to include reduction in emotional expression and perception, reduction in the fluency and productivity of thought and speech, reduced desire for social involvement and reduced social interaction with others, and a loss or lack of goal-directed behavior and a diminished sense of purpose. These symptoms contribute to substantial reductions in the functioning of individuals with schizophrenia as compared to others in their society.

Global Negative Symptoms Rating--Severity

This score represents your overall assessment of the subject's negative symptoms. The rating should not be an average of any particular behavior, but a gestalt of everything seen in the interview. When rating impairment, only impairment that you judge is due to negative symptoms should be rated. The referent is a normal healthy young adult.

1) No impairment (No question of negative symptoms has been raised in the rater's mind.)
2) Minimal negative symptoms (A trained observer is uncertain if clinically meaningful negative symptoms are present. If present, they have little or no adverse impact on the subject's life.)
3) Mild negative symptoms (Close observation suggests that negative symptoms are present, but they might be missed in casual conversation or by an untrained observer. The subject is able to overcome most problems related to these deficits.)
4) Moderate negative symptoms (Negative symptoms are obviously present and they have adverse impact on some areas of the subject's life.)
5) Marked negative symptoms (Negative symptoms are obviously present by all who meet this person. Many aspects of the subject's life are adversely impacted by these symptoms.)
6) Severe negative symptoms (Negative symptoms are very prominent and the subject's life is severely disrupted because of them.)
7) Extremely severe negative symptoms (Negative symptoms are extremely prominent and the subject's life is completely disrupted because of them. These symptoms are amongst the most prominent that the rater has observed, or, if the rater has limited experienced, among the most severe that the rater can imagine.)

Global Level of Functioning

This score represents your overall assessment of the subject's level of functioning. The rating should not be an average of any particular area, but a gestalt of everything known about the subject's level of functioning in all areas of his/her life. The referent is a normal healthy young adult.

1) No impairment (No question of impairment in functioning has been raised in the rater's mind.)
2) Minimal impairment (A trained observer is uncertain if there is impairment in functioning, and, if present, this impairment has little or no adverse impact on the subject's life.)
3) Mild impairment (Close observation suggests that the subject experiences some impairment in functioning, but this impairment might be missed in casual interactions or by an untrained observer. The subject is able to achieve most of his/her life goals.)
4) Moderate impairment (Impairment in functioning is obvious to any trained observer. Some life goals are not attained.)
5) Marked impairment (Impairment in functioning is obviously present by all who meet this person. Many aspects of the subject's life are adversely affected.)
6) Severe impairment (Impairment in functioning is extremely prominent and the subject's life is severely disrupted because of it.)
7) Extremely severe impairment (Impairment in functioning is extremely prominent and the subject's life is completely disrupted because of it. Functioning is at amongst the lowest levels that the rater has observed, or, if inexperienced, at the lowest level that the rater can imagine.)

SEMI-STRUCTURED INTERVIEW FOR RATING THE NSA-16

Emotion

For each emotion endorsed ask: How frequently did this occur? How intense was it? Did it affect your ability to do things you wanted to do?

1. How have you been feeling in the past week?

2. Have you felt anxious, nervous or worried during the past week? If so: What was that like for you? What were you worried or nervous about this past week? Do you feel anxious about participating in this interview?

3. Have you felt sad or depressed during the past week? What has that been like for you? How bad was it? What were you sad about?

4. Have there been times during the past week when you felt happy? What made you feel this way? What is it like when you feel happy? (Repeat these questions for proud, scared, surprised and angry. If after the completion of this section, few emotions are identified, suggest a situation that might have caused emotion [getting lost, a near car accident, an award, a quarrel, a party], but do **not** suggest the emotion that might have been experienced.)

Affect

5. Now I am going to ask you to demonstrate some emotions. This may work best if you pretend that you are an actor in a movie. I am going to ask you to show me how different feelings would look your face. Could you show me what it looks like on your face when you feel happy? (Repeat question for sad, proud, scared, surprised and angry.)

Daily Activity

6. Are you employed now? What do you do? Do you work full time? If not, how many hours per week? Is your employer satisfied with the work that you do? Do you go to school? If so, how many hours per week. What types of grades do you receive?
Are you responsible for cooking, cleaning or other housework where you live? What are your responsibilities? Have you been able to perform this work as expected?
Do you attend a day program, vocational rehabilitation or a sheltered workshop? If so, how many hours per week do you attend? Do attend as required?

7. Starting with the time you get up, could you tell me how you have spent a typical day during the past week? What do you do next? (Follow up on ambiguous statements. For example, if the patient says, "I eat breakfast," ask what he or she eats and who makes it. If the patient says, "I take my medication", you may want to ask if she takes it herself or if someone reminds her.

General Interests

8. What do you enjoy doing? What else do you enjoy? Do you have any hobbies? Do you enjoy TV? Do you spend time using the internet?, movies, music or games? Have you done these things in the past week?

9. Are you interested in what is going on in the world? Do you read the newspapers or check the news on line? Do you watch the news on TV? Can you tell me about some of the important news stories of the past week?

10. Do you like sports? What is your favorite sport? Which is your favorite team? Do you watch or listen to them often? Do you know their record? Are their top players you keep up with? Have you played in any sport during the past week?

Social Interest

11. Do you live alone, or with someone else?

12. Are there people you feel close to? Are there people you would like to be close to? Can you share very personal information about yourself with anyone? How often have you spent time with others during the last week? What sort of activities did you share? Do you contact them by phone, email or text messaging? Do you wish you could spend more time around other people?

13. Have you spent time physically present with friends or speaking to them on the phone or by email or texting this week? How often? If so, how often did you initiate these contacts? Who are your friends? Has anyone invited you to do anything this week? Did you accept? Have you asked anyone to go anywhere with you this week?

14. Is anyone concerned about your happiness and well-being?

Interest in Emotional and Physical Intimacy

15. Do you sometimes have strong feelings or desires to seek emotional and physical intimacy with others? ? How frequently do you think about this? How many times in the last week have you thought you would like to be close or intimate with someone? Is there any one in your life with whom you are or would like to be emotionally or physically intimate?

16. If we say that emotional and physical intimacy includes activities like, watching intimate material on the internet or tv, or touching yourself or someone else,, how many times in the past week have you done any of these things?

17. Are you more or less interested in emotional or physical intimacy than you used to be?

Sense of Purpose

18. What sort of things give you satisfaction or make life worth living for you? Do you have goals for your life that you would like to accomplish? What do you see yourself doing a year from now? Five years from now?

19. How do you plan to achieve these goals? How often have you thought of these your goals during the last week? In the past week, what steps have you taken to achieve your goals?

Motor Retardation

20. Do you have any problems with your movements? Do your movements seem slowed? Have others commented on your movements? Could you walk back and forth across the room, so I can see how you walk?

Psychometric Development of Negative Symptom Assessment-16 (NSA-16)

Goal

Development of a new scale that broadly and sensitively assesses negative symptoms of schizophrenia

Rationale

Scales existing at the time of scale development had one or more of the following problems

- Not comprehensive of general concept of schizophrenia
- Anchors not well defined
- Inadequate psychometric development
- Not sensitive to change
- Difficult to train raters

Principles

Rate behaviors without attribution of etiology (including other disease states, side effects of drug treatment, or age) that minimizes possibility for cultural bias

TABLE 1. Psychometric Development

Publication	NSA Version	Analysis	Factors Identified	Resulting Changes
Alphs, et al 1989	NSA-26	Principal Components Factor Analysis with varimax rotation	• Affect/Emotion (10) • External Involvement (5) • Retardation (3) • Personal Presentation (3) • Thinking (2) • Interpersonal interest (2) • Blocking (1)	• Redefined and clarified anchors • Added additional items to more adequately cover factors identified
Raskin, et al, 1993	NSA-30	Principal Components Factor Analysis with varimax rotation	• Difficulties in communicating (10) • Lack of Emotion/ Flattened Affect (7) • Social Inactivity (4) • Loss of Interest/Motivation (4) • Cognitive Difficulties (4) • Psychomotor Activity (1)	• Redefined and clarified anchors • Removed redundant or high variance items
Axelrod, et al, 1994	NSA-26	Confirmatory factor analysis	• Communication (6) • Emotion/Affect (4) • Social Involvement (4) • Motivation (4) • Gross Cognition (3) • Retardation (4)	• Redefined and clarified anchors • Removed redundant or high variance items within factors • Removed cognition items

Axelrod et al, 1994	NSA-16	Confirmatory factor analysis	• Communication (4) • Emotion/Affect (3) • Social Involvement (3) • Motivation (4) • Retardation (2)	• 5-factor model represents optimal structure of instrument and is descriptively much better than null model

TABLE 2. Additional Psychometric Development

Publication	Psychometric Analysis	Findings
Alphs, et al, 1989	Validity and Reliability	• Construct validity established • Inter and Intra-rater reliability established
Axelrod, et al, 1994	Rater Trainability	• Raters can be trained to high reliability after 30-60-minute training session
Eckert, et al, 1996	Sensitivity to Change	• Effect size similar to SANS

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APPENDIX 4. Patient Global Impression – Severity (PGI-S)

PATIENT GLOBAL IMPRESSION SEVERITY (PGI-S)

Severity of Schizophrenia Symptoms:

Please choose the response below that best describes the current severity of your

schizophrenia symptoms.

- ☐ 1 = Normal, not at all ill
- ☐ 2 = Borderline ill
- ☐ 3 = Mildly ill
- ☐ 4 = Moderately ill
- ☐ 5 = Markedly ill
- ☐ 6 = Severely ill
- ☐ 7 = Extremely ill

APPENDIX 5A. Patient Global Impression of Change (PGI-C)

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85)

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Rate the total impression of change with respect to your symptoms of schizophrenia from the time of admission to the study to the present?

☐ 1 = Very much improved

☐ 2 = Much improved

☐ 3 = Minimally improved

☐ 4 = No change

☐ 5 = Minimally worse

☐ 6 = Much worse

☐ 7 = Very much worse

Reference: Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare.

APPENDIX 5B. Patient Global Impression of Change (PGI-C)

Patient Global Impression of Change (PGI-C)

Comparison to Baseline

Please choose the response below that best describes the overall change in your schizophrenia symptoms since you started taking the study medication.

- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No Change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

APPENDIX 6. Calgary Depression Scale for Schizophrenia (CDSS)

The Calgary Depression Scale for Schizophrenia

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last one week unless stipulated. **N.B.** The last item, #9, is based on observations of the entire interview.

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

0. Absent	
1. Mild	Expresses some sadness or discouragement on questioning.
2. Moderate	Distinct depressed mood persisting up to half the time over last 1 week: present daily.
3. Severe	Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

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

0. Absent	
1. Mild	Has at times felt hopeless over the last one week but still has some degree of hope for the future.
2. Moderate	Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
3. Severe	Persisting and distressing sense of hopelessness.

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

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

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

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

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

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

6. MORNING DEPRESSION: When you have felt depressed over the last one week have you noticed the depression being worse at any particular time of day?

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

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

0. Absent	No early wakening.
1. Mild	Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. Moderate	Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. Severe	Daily wakes 1 hour or more before normal time

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

0. Absent	
1. Mild	Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. Moderate	Deliberately considered suicide with a plan, but made no attempt.
3. Severe	Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

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

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

APPENDIX 7A. Abnormal Involuntary Movement Scale (AIMS)

Abnormal Involuntary Movement Scale (AIMS) - Overview

- The AIMS records the occurrence of tardive dyskinesia (TD) in patients receiving neuroleptic medications.
- The AIMS test is used to detect TD and to follow the severity of a patient's TD over time.

Clinical Utility

The AIMS is a 12 item anchored scale that is clinician administered and scored

- Items 1-10 are rated on a 5 point anchored scale.
  - Items 1-4 assess orofacial movements.
  - Items 5-7 deal with extremity and truncal dyskinesia.
  - Items 8-10 deal with global severity as judged by the examiner, and the patient's awareness of the movements and the distress associated with them.
- Items 11-12 are yes-no questions concerning problems with teeth and/or dentures, because such problems can lead to a mistaken diagnosis of dyskinesia.

Examination Procedure

The indirect observation and the AIMS examination procedure are on the following two pages.

Scoring[1]

1. A total score of items 1-7 (Categories I, II, III) can be calculated. These represent observed movements.
2. Item 8 can be used as an overall severity index.
3. Items 9 (incapacitation) and 10 (awareness) provide additional information that may be useful in clinical decision making.
4. Items 11 (dental status) and 12 (dentured) provide information that may be useful in determining lip, jaw and tongue movements.

Psychometric Properties

The AIMS is a global rating method. The AIMS requires the raters to compare the observed movements to the average movement disturbance seen in persons with TD. Such relative judgments may vary among raters with different backgrounds and experience.

1. Rush M.A., Handbook of Psychiatric Measures, American Psychiatric Association, 2000, 168-168.

AIMS Examination Procedure

Either before or after completing the AIMS on the following page, observe the patient unobtrusively at rest (e.g., in the waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

Questions

1. Ask the patient whether there is anything in his or her mouth (such as gum or candy) and, if so, to remove it.
2. Ask about the current condition of the patient's teeth. Ask if he or she wears dentures. Ask whether teeth or dentures bother the patient now.
3. Ask whether the patient notices any movements in his or her mouth, face, hands, or feet. If yes, ask the patient to describe them and to indicate to what extent they currently bother the patient or interfere with activities.
4. Have the patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at the entire body for movements while the patient is in this position.)
5. Ask the patient to sit with hands hanging unsupported -- if male, between his legs, if female and wearing a dress, hanging over her knees. (Observe hands and other body areas).
6. Ask the patient to open his or her mouth. (Observe the tongue at rest within the mouth.) Do this twice.
7. Ask the patient to protrude his or her tongue. (Observe abnormalities of tongue movement.) Do this twice.
8. Ask the patient to tap his or her thumb with each finger as rapidly as possible for 10 to 15 seconds, first with right hand, then with left hand. (Observe facial and leg movements.)
9. Flex and extend the patient's left and right arms, one at a time.
10. Ask the patient to stand up. (Observe the patient in profile. Observe all body areas again, hips included.)
11. Ask the patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth.)
12. Have the patient walk a few paces, turn, and walk back to the chair. (Observe hands and gait.) Do this twice.

Abnormal Involuntary Movement Scale (AIMS)

Patient Name _____ Date of Visit _____

Code: 0 = None 1 = Minimal 2 = Mild 3 = Moderate 4 = Severe

Movement Ratings:
- Rate highest severity observed in category I, II, III.
- Rate movements that occur upon activation one point less than those observed spontaneously.
- Circle movements as well as code number that applies.

		xxxx	xxxx	xxxx	xxxx
		xxx	xxx	xxx	xxx
I FACIAL & ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. **Lips and Perioral Area** e.g. puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. **Jaw** Biting, clenching, chewing, mouth opening , lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth, NOT in ability to sustain movement. Darting in and out of mouth	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
II EXTREMITY MOVEMENTS	5. **Upper (arms, wrists, hands, fingers)** Include: choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
III TRUNK MOVEMENTS	7. **Neck, shoulders and hips** Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
IV GLOBAL JUDGEMENT	8. **Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. **Incapacitation due to abnormal movements**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. **Patient's awareness of abnormal movements. Rate only patient's report:** No Awareness = 0 Aware, no distress = 1 Aware, mild distress = 2 Aware, moderate distress = 3 Aware, severe distress = 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
V DENTAL STATUS	11. **Current problems with teeth and/or dentures**	YES NO	YES NO	YES NO	YES NO
	12. **Are dentures usually worn**	YES NO	YES NO	YES NO	YES NO
	13. **Edentia?**	YES NO	YES NO	YES NO	YES NO
	14. **Do movements disappear with sleep?**	YES NO	YES NO	YES NO	YES NO

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APPENDIX 7B. Abnormal Involuntary Movement Scale (AIMS)

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)							
Movement Ratings: rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.		**Code:** **0** = None **1** = Minimal, may be extreme normal **2** = Mild **3** = Moderate **4** = Severe					
			(Circle One)				
FACIAL AND ORAL MOVEMENTS	1. **MUSCLES OF FACIAL EXPRESSION** e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing		**0**	**1**	**2**	**3**	**4**
	2. **LIPS AND PERIORAL AREA** e.g. puckering, pouting, smacking		**0**	**1**	**2**	**3**	**4**
	3. **JAW** e.g. biting, clenching, chewing, mouth opening, lateral movement		**0**	**1**	**2**	**3**	**4**
	4. **TONGUE** Rate only increase in movement both in and out of mouth, NOT inability to sustain movement		**0**	**1**	**2**	**3**	**4**
EXTREMITY MOVEMENTS	5. **UPPER (ARMS, WRISTS, HANDS, FINGERS)** include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), or athetoid movements (i.e. slow, irregular, complex, serpentine). Do NOT include tremor (i.e. repetitive, regular, rhythmic movements).		**0**	**1**	**2**	**3**	**4**
	6. **LOWER (LEGS, KNEES, ANKLES, TOES)** e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.		**0**	**1**	**2**	**3**	**4**
TRUNK MOVEMENTS	7. **NECK, SHOULDERS, HIPS** e.g. rocking, twisting, squirming, pelvic gyrations		**0**	**1**	**2**	**3**	**4**
GLOBAL JUDGMENTS	8. Severity of abnormal movements		None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4				
	9. Incapacitation due to abnormal movements		None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4				
	10. Patient's awareness of abnormal movements. Rate only patient's report.		No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4				
DENTAL STATUS	11. Current problems with teeth and/or dentures?		No 0 Yes 1				
	12. Does patient usually wear dentures?		No 0 Yes 1				

APPENDIX 8. Barnes Akathisia Scale (BAS)

II. Rating scale for drug-induced akathisia (Barnes Akathisia Rating Scale)

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress
1 Mild

2 Moderate
3 Severe

Global clinical assessment of akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable.* Non-specific inner tension and fidgety movements

2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: A rating scale for drug-induced akathisia. T.R.E. Barnes, *British Journal of Psychiatry* (1989), **154**, 672-676.

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APPENDIX 9A. Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

SIMPSON-ANGUS SCALE (SAS)

1. GAIT: The subject is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:	
0 = Normal	☐
1 = Diminution in swing while the patient is walking	☐
2 = Marked diminution in swing with obvious rigidity in the arm	☐
3 = Stiff gait with arms held rigidly before the abdomen	☐
4 = Stopped shuffling gait with propulsion and retropulsion	☐

2. ARM DROPPING: The subject and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the subject with extreme Parkinson's syndrome, the arms fall very slowly:	
0 = Normal, free fall with loud slap and rebound	☐
1 = Fall slowed slightly with less audible contact and little rebound	☐
2 = Fall slowed, no rebound	☐
3 = Marked slowing, no slap at all	☐
4 = Arms fall as though against resistance; as though through glue	☐

3. SHOULDER SHAKING: The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the subject's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen joint	☐

4. ELBOW RIGIDITY: The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.):	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen joint	☐

5. **WRIST RIGIDITY or Fixation of position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulner and radial deviation:	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen joint	☐

6. **LEG PENDULOUSNESS:** The subject sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:	
0 = The legs swing freely	☐
1 = Slight diminution in the swing of the legs	☐
2 = Moderate resistance to swing	☐
3 = Marked resistance and damping of swing	☐
4 = Complete absence of swing	☐

7. HEAD ROTATION: The subject sits or stands and is told that the examiner will move his head from side to side, that it will not hurt, and that he should try to relax. Clasp the subject's head between the two hands with the fingers on the back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to this movement:	
0 = Loose, no resistance	☐
1 = Slight resistance to movement	☐
2 = Resistance is apparent and the time of rotation is shortened	☐
3 = Resistance is obvious and rotation is slowed	☐
4 = Head appears stiff and rotation is difficult to carry out	☐

8. GLABELLA TAP: Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times the subject blinks in succession is noted:	
0 = 0 - 5 blinks	☐
1 = 6 – 10 blinks	☐
2 = 11 – 15 blinks	☐
3 = 16 – 20 blinks	☐
4 = 21 and more blinks	☐

9. TREMOR: Subject is observed walking into examining room and is then reexamined for this item:	
0 = Normal	☐
1 = Mild finger tremor, obvious to sight and touch	☐
2 = Tremor of hand or arm occurring spasmodically	☐
3 = Persistent tremor of one or more limbs	☐
4 = Whole body tremor	☐

10. SALIVATION: Subject is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:	
0 = Normal	☐
1 = Excess salivation to the extent that pooling takes place if the mouth is open and the tongue is raised.	☐
2 = When excess salivation is present and might occasionally result in difficulty in speaking	☐
3 = Speaking with difficulty because of excessive salivation	☐
4 = Frank drooling	☐

APPENDIX 9B. Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE (SAS)

Circle the appropriate score for each item:

1 GAIT

The patient is examined as he walks into the examining room; his gait, the swing of arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:

0 Normal

1 Mild diminution in swing while the patient is walking

2 Obvious diminution in swing suggesting shoulder rigidity

3 Stiff gait with little or no arm swing noticeable

4 Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion

2 ARM DROPPING

The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

0 Normal, free fall with loud slap and rebound

1 Fall slowed slightly with less audible contact and little rebound

2 Fall slowed, no rebound

3 Marked slowing, no slap at all

4 Arms fall as though against resistance; as though through glue

3 SHOULDER SHAKING

The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen joint

4 ELBOW RIGIDITY

The elbow joints are separately bent at right angles and are passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen joint

5 WRIST RIGIDITY OR FIXATION OF POSITION

The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen joint

6 HEAD ROTATION

The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt, and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patient's head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.

0 Loose, no resistance

1 Slight resistance to movement although the time to rotate may be normal

2 Resistance is apparent and time of rotation is slowed

3 Resistance is obvious and rotation is slowed

4 Head appears stiff and rotation is difficult to carry out

7 GLABELLA TAP

Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

0 0 – 5 blinks

1 6 – 10 blinks

2 11 – 15 blinks

3 16 – 20 blinks

4 21 and more blinks

8 TREMOR
Patient is observed walking into examining room and is then reexamined for this item:

0 Normal

1 Mild finger tremor, obvious to sight and touch

2 Tremor of hand or arm occurring spasmodically

3 Persistent tremor of one or more limbs

4 Whole body tremor

9 SALIVATION
Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0 Normal

1 Excess salivation so that pooling takes place if the mouth is open and the tongue raised

2 Excess salivation is present and might occasionally result in difficulty in speaking

3 Speaking with difficulty because of excess salivation

4 Frank drooling

10 AKATHISIA
Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient can help make the assessment.

0 No restlessness reported or observed

1 Mild restlessness observed

2 Moderate restlessness observed

3 Restlessness is frequently observed

4 Restlessness persistently observed

APPENDIX 10. Columbia Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below	**Lifetime: Time He/She Felt**	**Past 6 Months**

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

INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation*** Past 6 Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 24 Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

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

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

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).	*Enter Code* _____

4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 11A. Mini International Neuropsychiatric Interview (M.I.N.I)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW FOR **SCHIZOPHRENIA** AND **PSYCHOTIC DISORDERS** STUDIES

English Version 6.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 6.0 for Psychotic Disorders (October 10, 2010) (10/10/10)

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

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	❒			
		Past	❒			
		Recurrent	❒			
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	❒	296.20-296.26 Single	F32.x	❒
		Past	❒	296.20-296.26 Single	F32.x	❒
		Recurrent	❒	296.30-296.36 Recurrent	F33.x	❒
B	SUICIDALITY	Current (Past Month) ❒ Low ❒ Moderate ❒ High	❒			
C	MANIC EPISODE	Current	❒			
		Past	❒			
	HYPOMANIC EPISODE	Current	❒			
		Past	❒	❒ Not Explored		
	BIPOLAR I DISORDER	Current	❒	296.0x-296.6x	F30.x- F31.9	❒
		Past	❒	296.0x-296.6x	F30.x- F31.9	❒
	BIPOLAR II DISORDER	Current	❒	296.89	F31.8	❒
		Past	❒	296.89	F31.8	❒
	BIPOLAR DISORDER NOS	Current	❒	296.80	F31.9	❒
		Past	❒	296.80	F31.9	❒
D	PANIC DISORDER	Current (Past Month)	❒	300.01/300.21	F40.01-F41.0	❒
		Lifetime	❒	300.01/300.21	F40.01-F41.0	❒
E	AGORAPHOBIA	Current	❒	300.22	F40.00	❒
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	❒	300.23	F40.1	❒
		Non-Generalized	❒	300.23	F40.1	❒
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	❒	300.3	F42.8	❒
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	❒	309.81	F43.1	❒
I	ALCOHOL DEPENDENCE	Past 12 Months	❒	303.9	F10.2x	❒
	ALCOHOL ABUSE	Past 12 Months	❒	305.00	F10.1	❒
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.2X-F19.2X	❒
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.1-F19.1	❒
K	PSYCHOTIC DISORDERS	Lifetime	❒	295.10-295.90/297.1/	F20.xx-F29	❒
		Current	❒	297.3/293.81/293.82/ 293.89/298.8/298.9		❒
	SCHIZOPHRENIA	Current	❒	295.10-295.60	F20.xx	❒
		Lifetime	❒	295.10-295.60	F20.xx	❒
	SCHIZOAFFECTIVE DISORDER	Current	❒	295.70	F25.x	❒
		Lifetime	❒	295.70	F25.x	❒
	SCHIZOPHRENIFORM DISORDER	Current	❒	295.40	F20.8	❒
		Lifetime	❒	295.40	F20.8	❒
	BRIEF PSYCHOTIC DISORDER	Current	❒	298.8	F23.80-F23.81	❒
		Lifetime	❒	298.8	F23.80-F23.81	❒

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M.I.N.I. 6.0 for Psychotic Disorders (October 10, 2010)

	DELUSIONAL DISORDER	Lifetime	❒	297.1	F22.0	❒
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current	❒	293.xx	F06.0-F06.2	❒
		Lifetime	❒	293.xx	F06.0-F06.2	❒
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current	❒	291.5-292.12	none	❒
		Lifetime	❒	291.5-292.12	none	❒
	PSYCHOTIC DISORDER NOS	Current	❒	298.9	F29	❒
		Lifetime	❒	298.9 296.24	F29	❒
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.24/296.04-296.94	F32.3/F33.3	❒
		Lifetime	❒	296.24/296.04-296.94	F31.3/F31.2/F31.5	❒
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.24/296.34	F33.X3	❒
		Past	❒	296.24/296.34	F33.X3	❒
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.04-296.64	F31.X2/F31.X5	❒
		Past	❒	296.04-296.64	F31.X2/F31.X5	❒
	MOOD DISORDER NOS	Lifetime	❒	296.90	F39	❒
L	ANOREXIA NERVOSA	Current (Past 3 Months)	❒	307.1	F50.0	❒
M	BULIMIA NERVOSA	Current (Past 3 Months)	❒	307.51	F50.2	❒
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	❒	307.1	F50.0	❒
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	❒	300.02	F41.1	❒
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		❒ No	❒ Yes	❒ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	❒	301.7	F60.2	❒

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

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GENERAL INSTRUCTIONS

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

INTERVIEW:

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

GENERAL FORMAT:

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

CONVENTIONS:

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

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

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

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

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question G6).

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

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.
The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

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

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

A1	a	Were you ever depressed or down, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	For the past two weeks, were you depressed or down, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
			➡	
		IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **A1b** AND **A2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

Over that two week period, when you felt depressed or uninterested:

		Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ±3.5 kg, for a 160 lb/70 kg. person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes Past Episode ❒ No ❒ Yes	NO	YES	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF **YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? NO YES

M.I.N.I. 6.0 for Psychotic Disorders (October 10, 2010)

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ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED YES FOR THAT TIME FRAME?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO	**YES**
MAJOR DEPRESSIVE EPISODE	
CURRENT	❒
PAST	❒
RECURRENT	❒

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

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B. SUICIDALITY

				Points
	In the past month did you:			
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident either actively or passively (e.g. by not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Think about hurting or injuring yourself or have mental images of harming yourself, with at least some intent or awareness that you might die as a result?	NO	YES	4
B5	Think about suicide (killing yourself)?	NO	YES	6
	IF NO TO B5, SKIP TO B7. OTHERWISE ASK:			

Frequency		Intensity	
Occasionally	❒	Mild	❒
Often	❒	Moderate	❒
Very often	❒	Severe	❒

B6	Have difficulty restraining yourself from acting on these impulses?	NO	YES	8
B7	Have a suicide method in mind (e.g. how)?	NO	YES	8
B8	Have a suicide plan in mind (e.g. when or where)?	NO	YES	8
B9	Intend to act on thoughts of killing yourself?	NO	YES	8
B10	Intend to die as a result of a suicidal act?	NO	YES	8
B11	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO B11, SKIP TO B12.	NO	YES	9
B11a	Take active steps to prepare to kill yourself, but you did not start the suicide attempt?	NO	YES	
B11b	Start a suicide attempt, but then **you stopped yourself** before harming yourself (aborted attempt)?	NO	YES	
B11c	Start a suicide attempt, but then **someone or something stopped you** before harming yourself (interrupted attempt)?	NO	YES	
B12	Injure yourself on purpose without intending to kill yourself?	NO	YES	4
B13	Attempt suicide (to kill yourself)?	NO	YES	10
	A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die.			

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IF NO, SKIP TO B14:

Hope to be rescued / survive ❒
Expected / intended to die ❒

In your lifetime:

B14 Did you ever make a suicide attempt (try to kill yourself)? NO YES 4

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result or if intent can be inferred, e.g. if it is clearly not an accident or the individual thinks the act could be lethal, even though denying intent." (C-CASA definition). Posner K et al. Am J Psychiatry 164:7, July 2007.

IS AT LEAST **1** OF THE ABOVE (EXCEPT B1) CODED **YES**?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B14) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO	YES

SUICIDALITY CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

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C. MANIC AND HYPOMANIC EPISODES

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

Do you have any family history of manic depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER .

IF YES, PLEASE SPECIFY WHO:_____

C1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money. IF NO, CODE NO TO **C1b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
C2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **C2b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling persistently irritable?	NO	YES
			➡	
		IS **C1a** OR **C2a** CODED **YES**?	NO	YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes Past Episode ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES

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		Current Episode		Past Episode	
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES
C3	SUMMARY: WHEN RATING CURRENT EPISODE: IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES? WHEN RATING PAST EPISODE: IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES? CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD. RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.	NO	YES	NO	YES
C4	What is the longest time these symptoms lasted? a) 3 days or less b) 4 to 6 days c) 7 days or more		❒ ❒ ❒		❒ ❒ ❒
C5	Were you hospitalized for these problems? IF YES, CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO C7.	NO	YES	NO	YES
C6	Did these symptoms cause significant problems at home, at work, socially in your relationships with others, at school or in some other important way?	NO	YES	NO	YES

ARE **C3** SUMMARY AND **C5** AND **C6** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4c** AND **C6** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	❒
PAST	❒

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IS **C3** SUMMARY **CODED YES** AND ARE **C5** AND **C6** CODED **NO** AND IS EITHER **C4B** OR **C4C** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4B** AND **C6** CODED **YES** AND IS **C5** CODED **NO?**

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO.**

IF **YES** TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED.**

HYPOMANIC EPISODE

CURRENT ❒ **NO**
❒ **YES**

PAST ❒ **NO**
❒ **YES**
❒ **NOT EXPLORED**

ARE **C3** SUMMARY AND **C4a** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE, THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO.**

IF **YES** TO PAST MANIC EPISODE OR YES TO PAST HYPOMANIC EPISODE, THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ❒ **NO**
❒ **YES**

PAST ❒ **NO**
❒ **YES**
❒ **NOT EXPLORED**

C7 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting just 4 to 6 days (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

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D. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**? IF YES TO D5, SKIP TO D7.	NO	YES *PANIC DISORDER LIFETIME*
D6		IF **D5** = **NO,** ARE ANY D4 ANSWERS CODED **YES**? THEN SKIP TO **E1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*

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D7	In the past month, did you have such attacks repeatedly (2 or more), and did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES *PANIC DISORDER CURRENT*

E. AGORAPHOBIA

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about?	NO	YES

IF **E1** = **NO**, CIRCLE **NO** IN **E2**.

E2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO	YES *AGORAPHOBIA CURRENT*

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

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F. SOCIAL PHOBIA (Social Anxiety Disorder)

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

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
F2	Is this social fear excessive or unreasonable and does it almost always make you anxious?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them or suffer through them most of the time?	➡ NO	YES
F4	Do these social fears disrupt your normal work, school or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE:

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

NO	YES

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

DO NOT COPY

G. OBSESSIVE-COMPULSIVE DISORDER

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

G1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **G4**
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **G4**
G3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES obsessions
G4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES compulsions
	IS **G3** OR **G4** CODED **YES**?	➡ NO YES
G5	At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
G6	In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

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H. POSTTRAUMATIC STRESS DISORDER

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

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
H3	During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event?	➡ NO	YES
H4	**In the past month:**		
a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	ARE **3** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES
H5	**In the past month:**		
a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	ARE **2** OR MORE **H5** ANSWERS CODED **YES**?	➡ NO	YES
H6	During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?		

NO	YES
	POSTTRAUMATIC STRESS DISORDER CURRENT

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I. ALCOHOL DEPENDENCE / ABUSE

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

		➡ NO	YES
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?		

I2 **In the past 12 months**:

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

ARE **3** OR MORE **I2** ANSWERS CODED **YES**?

NO	YES*
	ALCOHOL DEPENDENCE **CURRENT**

* IF YES, SKIP I3 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

I3 **In the past 12 months:**

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

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ARE **1** OR MORE **I3** ANSWERS CODED **YES**?

NO	YES
	ALCOHOL ABUSE **CURRENT**

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J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

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

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

			➡ NO	YES
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?		

CIRCLE EACH DRUG TAKEN:

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

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

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

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "Peace Pill", "Tranq", "Hog"), or ketamine ("Special K").

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

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

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

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

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? IF **YES** TO EITHER, CODE **YES**.	NO	YES
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or recovering from the drug, or thinking about the drug?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO	YES

Proof

g If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it? NO YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

* IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO **YES** *

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **YES**

SUBSTANCE ABUSE
CURRENT

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K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES - Part 1

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

ALL OF THE PATIENT'S RESPONSES TO THE QUESTIONS SHOULD BE CODED IN COLUMN A. USE THE CLINICIAN JUDGMENT COLUMN (COLUMN B) ONLY IF THE CLINICIAN KNOWS FROM OTHER OUTSIDE EVIDENCE (FOR EXAMPLE, FAMILY INPUT) THAT THE SYMPTOM IS PRESENT BUT IS BEING DENIED BY THE PATIENT.

Now I am going to ask you about unusual experiences that some people have.

			COLUMN A Patient Response			COLUMN B Clinician Judgment (if necessary)	
					BIZARRE		BIZARRE
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you?	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things? **NOTE**: ASK FOR EXAMPLES, TO RULE OUT ACTUAL STALKING.	NO	YES	YES →**K6**	YES	YES →**K6**
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →**K6**	YES →**K6**	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN**:** ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →**K6**	YES	YES →**K6**
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspaper, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →**K6**	YES	YES →**K6**

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					BIZARRE		BIZARRE
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? **INTERVIEWER:** ASK FOR EXAMPLES. CODE **YES** ONLY IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS (FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION OR OTHERS NOT EXPLORED IN **K1** TO **K4**).	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do they currently consider your beliefs strange?	NO	YES	YES	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:	NO	YES		YES	
		IF **YES:** Did you hear a voice commenting on your thoughts or behavior, or did you hear two or more voices talking to each other?	NO		YES		YES
	b	IF **YES**: Have you heard these things in the past month? SCORE AS "YES BIZARRE" IF PATIENT HEARD A VOICE COMMENTING ON THEIR THOUGHTS OR BEHAVIOR OR HEARD TWO OR MORE VOICES TALKING TO EACH OTHER.	NO	YES	YES →**K8b**	YES	YES →**K8b**
K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES		YES	
	b	IF **YES**: Have you seen these things in the past month?	NO	YES		YES	

CLINICIAN'S JUDGMENT

K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, FOR EXAMPLE, SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL- DIRECTED ACTIVITIES (AVOLITION) PROMINENT DURING THE INTERVIEW?	NO	YES
K11	a	IS THERE AT LEAST ONE "**YES**" FROM **K1** TO **K10b**?	NO	YES

DO NOT COPY

K11 b

ARE THE ONLY SYMPTOMS PRESENT THOSE IDENTIFIED BY THE CLINICIAN FROM **K1** TO **K7** (COLUMN B) AND FROM **K8b** OR **K9b** OR **K10b**?

IF **YES**, SPECIFY IF THE LAST EPISODE IS CURRENT (AT LEAST ONE "b" QUESTION IS CODED "**YES**" FROM **K1b** TO **K10b**) AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **K1a** TO **K10b**) AND PASS TO THE NEXT DIAGNOSTIC MODULE.

IF **NO**, CONTINUE.

WARNING: IF AT LEAST ONE "b" QUESTION IS CODED **YES**, CODE **K11c** AND **K11d**.
IF ALL "b" QUESTIONS ARE CODED NO, CODE ONLY **K11d**.

NO **YES**

PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED*

Current ❒
Lifetime ❒

***Provisional diagnosis due to insufficient information available at this time.**

K11c

FROM **K1b** TO **K6b**: ARE ONE OR MORE "b" ITEMS CODED "**YES BIZARRE**"?

OR

ARE TWO OR MORE "b" ITEMS FROM **K1b TO K10b** CODED "**YES**" BUT NOT "**YES BIZARRE**"?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO
Then Criterion "A" of Schizophrenia is not currently met

YES
Then Criterion "A" of Schizophrenia is currently met

K11d FROM **K1a** TO **K6a**: ARE ONE OR MORE "a" ITEMS CODED "**YES BIZARRE**"

OR

ARE TWO OR MORE "a" ITEMS CODED FROM **K1a** TO **K7a** "**YES**" BUT NOT "**YES BIZARRE**"?

(CHECK THAT AT LEAST 2 ITEMS OCCURRED DURING THE SAME 1 MONTH PERIOD.)

NO
Then Criterion "A" of Schizophrenia is not met Lifetime

OR IS **K11c** CODED "**YES**"

YES
Then Criterion "A" of Schizophrenia is met Lifetime

Just before these symptoms began:

K12 a Were you taking any drugs or medicines? ❒ No ❒ Yes ❒ Uncertain

b Did you have any medical illness? ❒ No ❒ Yes ❒ Uncertain

c IN THE CLINICIAN'S JUDGMENT:
ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS. ❒ No ❒ Yes ❒ Uncertain

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K12d **SUMMARY**: HAS AN ORGANIC CAUSE BEEN RULED OUT? ❒ No ❒ Yes ❒ Uncertain

IF **K12d = NO**: SCORE **K13 (a and b)** AND GO TO THE NEXT MODULE
IF **K12d = YES**: CODE **NO** IN **K13 (a and b)** AND GO TO **K14**
IF **K12d = UNCERTAIN**: CODE **UNCERTAIN** IN **K13 (a and b)** AND GO TO **K14**

K13a IS **K12d** CODED **NO** BECAUSE OF A GENERAL MEDICAL CONDITION?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE "b" QUESTION IS CODED **YES** FROM **K1b** TO **K10b**)
AND/OR LIFETIME ("a" OR "b") QUESTION IS CODED **YES** FROM **K1a** TO **K10b**.

IF YES TO **K13a** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS

NO	YES
PSYCHOTIC DISORDER **Due to a General Medical Condition**	
Current	❒
Lifetime	❒
Uncertain, code later	❒

K13 b IS **K12d** CODED **NO** BECAUSE OF A DRUG?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE QUESTION "b" IS CODED **YES** FROM **K1b** TO **K10b**)
AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **K1a** TO **K10b**).
IF YES TO **K13b** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS

NO	YES
Substance Induced ***PSYCHOTIC DISORDER***	
Current	❒
Lifetime	❒
Uncertain, code later	❒

K14 Did your ability to function at work, at school, socially and with your family return completely to how you were before these experiences (CLINICIAN: PROVIDE EXAMPLES OF EXISTING HALLUCINATIONS, DELUSIONS OR DISORGANIZED SPEECH OR BEHAVIOR)? NO YES

K15 a During or after a period when you had these beliefs or experiences, did you have difficulty working, or difficulty in your relationships with others, or in taking care of yourself? NO YES

b IF **YES**, how long did these difficulties last? _____
IF ≥6 MONTHS, GO TO **K16.**

c Have you been treated with medications or were you hospitalized because of these beliefs or experiences, or the difficulties caused by these problems? NO YES

d IF **YES**, what was the longest time you were treated with medication or were hospitalized for these problems? _____

K16 a THE PATIENT REPORTED DISABILITY (**K15a CODED YES**) OR WAS TREATED OR HOSPITALIZED FOR PSYCHOSIS (**K15c = YES**). NO YES

b CLINICIAN'S JUDGMENT: CONSIDERING YOUR EXPERIENCE, RATE THE PATIENT'S **LIFETIME** DISABILITY CAUSED BY THE PSYCHOSIS.

absent	❒	1
mild	❒	2
moderate	❒	3
severe	❒	4

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K17 How long was the longest period during which you had those beliefs or experiences? _____

WHAT WAS THE TOTAL DURATION OF THE PSYCHOSIS, TAKE INTO ACCOUNT THE ACTIVE PHASE (**K17**) AND THE ASSOCIATED DIFFICULTIES (**K15b**) AND PSYCHIATRIC TREATMENT (**K15d**) IN CHOOSING THE TIME FRAME.

1 ❒ ≥1 day to <1 month
2 ❒ ≥1 month to <6 months
3 ❒ ≥6 months
4 ❒ < 1 day

CHRONOLOGY

K18 a How old were you when you first began having these unusual beliefs or experiences? ☐ age

b Since the first onset how many distinct times did you have significant episodes of these unusual beliefs or experiences? ☐

PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES - PART 2

DIFFERENTIAL DIAGNOSIS BETWEEN PSYCHOTIC AND MOOD DISORDERS

CODE THE QUESTIONS **K19** TO **K23** ONLY IF THE PATIENT DESCRIBED AT LEAST 1 PSYCHOTIC SYMPTOM (**K11a = YES** AND **K11b = NO**), NOT EXPLAINED BY AN ORGANIC CAUSE (**K12d = YES** OR **UNCERTAIN**).

K19 a DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MAJOR DEPRESSIVE EPISODE (QUESTIONS **A3 SUMMARY** OR **A4b** CODED **YES**)? NO YES

b IF **YES**: IS **A1** (DEPRESSED MOOD) CODED **YES**? NO YES

c DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MANIC EPISODE (**MODULE C**)? NO YES

d IS **K19a** OR **K19c** CODED **YES**? NO YES

↓
STOP.
Skip to K24

NOTE: VERIFY THAT THE RESPONSES TO THE QUESTIONS **K20** TO **K23** REFER TO THE PSYCHOTIC, DEPRESSIVE (**A3 SUMMARY OR A4b**) AND MANIC EPISODES (**MODULE C**), ALREADY IDENTIFIED IN **K11c** AND **K11d, A3 SUMMARY OR A4b AND MODULE C**. IN CASE OF DISCREPANCIES, RE-EXPLORE THE SEQUENCE OF DISORDERS, TAKING INTO ACCOUNT IMPORTANT LIFE ANCHOR POINTS/MILESTONES AND CODE **K20** TO **K23** ACCORDINGLY.

K20 When you were having the beliefs and experiences you just described (GIVE EXAMPLES TO PATIENT), were you also feeling depressed/high/irritable at the same time? NO YES

↓
STOP.
Skip to K24

K21 Were the beliefs or experiences you just described (GIVE EXAMPLES TO PATIENT) restricted exclusively to times you were feeling depressed/high/irritable? NO YES

K22 Have you ever had a period of two weeks or more of having these beliefs or experiences when you were not feeling depressed/high/irritable? NO YES

↓
STOP.
Skip to K24

K23 a) Which lasted longer: these beliefs or experiences or the periods of feeling depressed/high/irritable?

1 ❒ mood
2 ❒ beliefs, experiences
3 ❒ same

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IF THE RESPONSE TO K23a) WAS 2, ASK K2

b) Did the beliefs or experiences you just described (GIVE EXAMPLES OF DELUSIONS OR HALLUCINATIONS TO PATIENT) occur for at least 2 weeks without your also feeling depressed/high/irritable? NO YES

c) Did the depressed/high/irritable feelings last more than 50% of the total time that you had these beliefs and experiences? (GIVE EXAMPLES TO PATIENT) NO YES

K24 AT THE END OF THE INTERVIEW, GO TO THE DIAGNOSTIC ALGORITHMS FOR PSYCHOTIC DISORDERS.

CONSULT ITEMS **K11a** AND**K11b**:

IF THE CRITERION "A" OF SCHIZOPHRENIA IS MET (**K11c** AND/OR **K11d** = **YES**) GO TO DIAGNOSTIC ALGORITHM **I**

IF THE CRITERION "A" OF SCHIZOPHRENIA IS NOT MET (**K11c** AND/OR **K11d** = **NO**) GO TO DIAGNOSTIC ALGORITHM **II**

FOR MOOD DISORDERS GO TO THE DIAGNOSTIC ALGORITHM **III**.

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L. ANOREXIA NERVOSA

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

L1	a	How tall are you?	❑ ft ❑❑ in. ❑❑❑ cm	
	b.	What was your lowest weight in the past 3 months?	❑❑❑ lb ❑❑❑ kg	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO	YES
		In the past 3 months:		
L2		In spite of this low weight, have you tried not to gain weight?	➡ NO	YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO	YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
L5		ARE 1 OR MORE ITEMS FROM **L4** CODED **YES**?	➡ NO	YES
L6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO	YES

FOR WOMEN: ARE **L5** AND **L6** CODED **YES**?

FOR MEN: IS **L5** CODED **YES**?

NO	YES
ANOREXIA NERVOSA **CURRENT**	

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M²

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	125	129	132	136	140
cm	180	183	185	188	191
kg	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m² for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

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M. BULIMIA NERVOSA

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

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
M3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to M8	YES
M7	Do these binges occur only when you are under (____lb/kg)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES
M8	IS **M5** CODED **YES** AND IS EITHER **M6** OR **M7** CODED **NO**?	**NO**	**YES**

BULIMIA NERVOSA
CURRENT

IS **M7** CODED **YES**?

NO	**YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

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N. GENERALIZED ANXIETY DISORDER

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

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a "worry wart") AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	➡ NO	YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES?**	➡ NO	YES
N4		Do these anxieties and worries disrupt your normal work, school or social functioning or cause you significant distress?		

NO	YES
GENERALIZED ANXIETY DISORDER **CURRENT**	

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

O2	**SUMMARY**: HAS AN ORGANIC CAUSE BEEN RULED OUT?	❒ No	❒ Yes	❒ Uncertain

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P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1	**Before you were 15 years old, did you:**			
a	repeatedly skip school or run away from home overnight?		NO	YES
b	repeatedly lie, cheat, "con" others, or steal?		NO	YES
c	start fights or bully, threaten, or intimidate others?		NO	YES
d	deliberately destroy things or start fires?		NO	YES
e	deliberately hurt animals or people?		NO	YES
f	force someone to have sex with you?		NO ➡	YES
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?		NO	YES
	DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.			
P2	**Since you were 15 years old, have you:**			
a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?		NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?		NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?		NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?		NO	YES
e	exposed others to danger without caring?		NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?		NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

THIS CONCLUDES THE INTERVIEW

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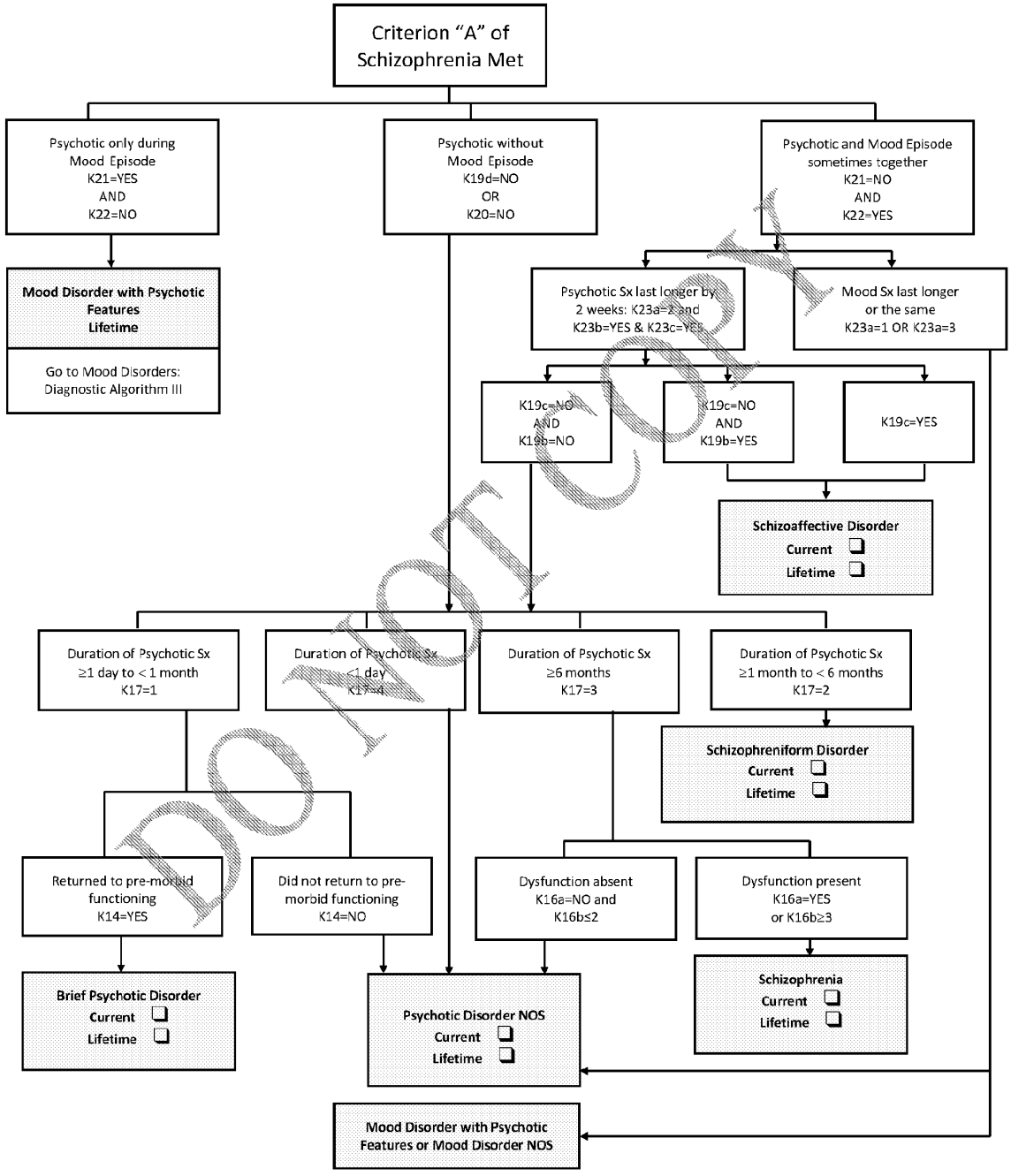
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PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM I

For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is not currently met, but is present lifetime, current and lifetime diagnoses may be different.

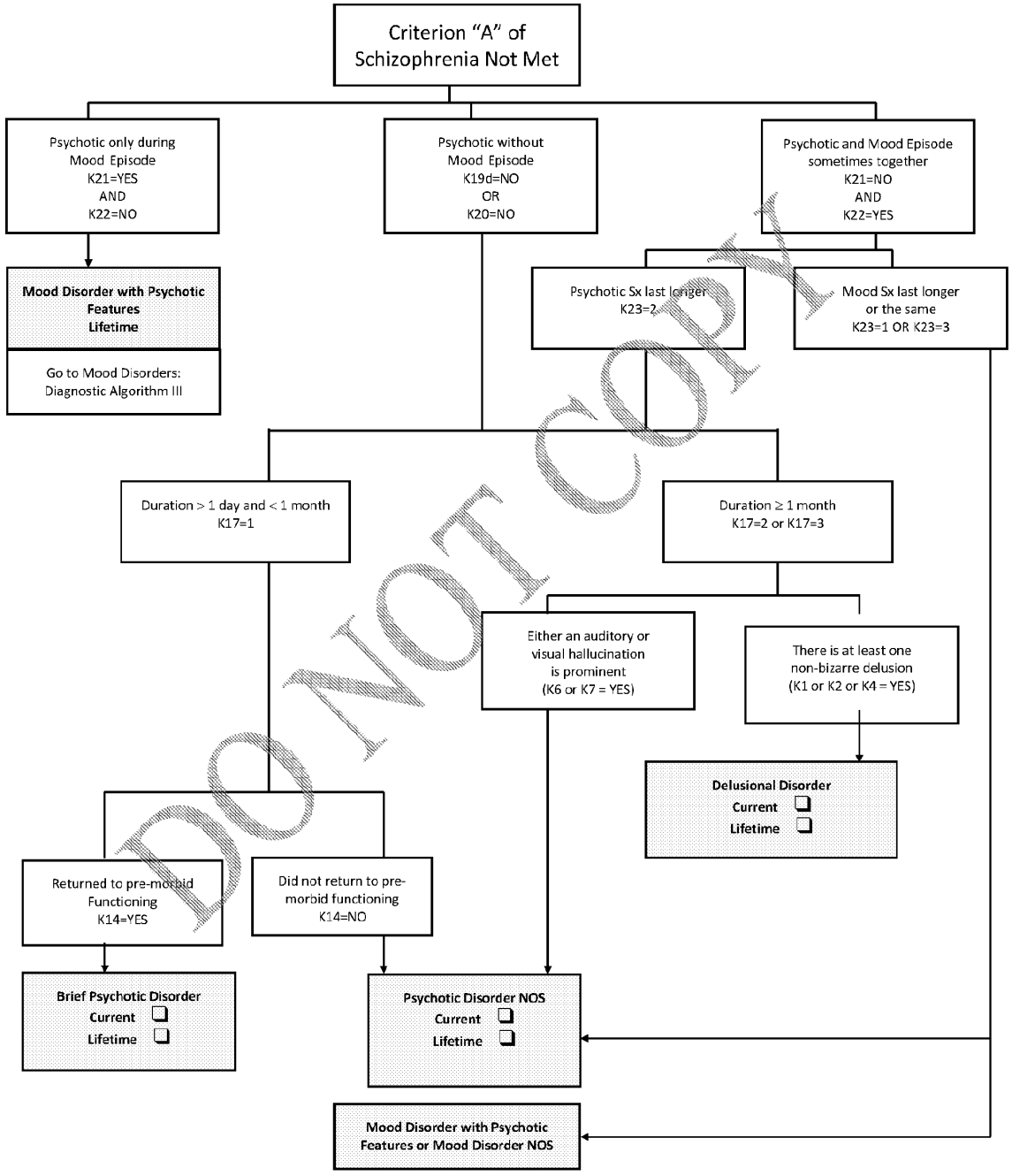


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PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM II

For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is present lifetime, current and lifetime diagnoses may be different.



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MOOD DISORDERS: DIAGNOSTIC ALGORITHM III

Consult Modules:
- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders

MODULE K:

1a	IS **K21** CODED YES?	NO	YES
1b	IS **K19d** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2 a	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e**	YES	YES
b	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a**	YES	YES

c Is a Major Depressive Episode coded YES (current or past)?
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)?
and
is "Hypomanic Symptoms" coded NO (current and past)?

Specify:
- If the depressive episode is **current** or **past** or both
- **With Psychotic Features** Current: If 1b or 2a (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) = YES

MAJOR DEPRESSIVE DISORDER

	current	past
MDD	❑	❑

With Psychotic Features

Current	❑
Past	❑

d Is a Manic Episode coded YES (current or past)?

Specify:
- If the Bipolar I Disorder is **current** or **past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES
  and MDE (current and past) = NO
- **With Psychotic Features** Current: If 1b or 2a (current) or 2b (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) or 2b (past) = YES
- If the **most recent episode** is manic, depressed, mixed or hypomanic or unspecified (all mutually exclusive)
- **Unspecified** if the Past Manic Episode is coded YES AND
  Current (C3 Summary AND C4a AND C6 AND O2) are coded YES

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Mixed	❑
Hypomanic	❑
Unspecified	❑

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e Is Major Depressive Episode coded YES (current or past)
and
Is Hypomanic Episode coded YES (current or past)
and
Is Manic Episode coded NO (current and past)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑

f Is MDE coded NO (current and past)
and
Is Manic Episode coded NO (current and past)
and
Is C4b coded YES for the appropriate time frame
and
Is C7b coded YES?

or

Is Manic Episode coded NO (current and past)
and
Is Hypomanic Episode coded NO (current and past)
and
Is C4a coded YES for the appropriate time frame
and
Is C7c coded YES?

Specify if the Bipolar Disorder NOS is **current** or **past** or both.

BIPOLAR DISORDER NOS

	current	past
Bipolar Disorder NOS	❑	❑

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M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI.
The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDE WITH CATATONIC FEATURES	Current (2 weeks)
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MINOR DEPRESSIVE DISORDER (DEPRESSIVE DISORDER NOS)	Current (2 weeks) Past Recurrent
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MOOD DISORDER	Current (2 weeks) Past
AY	DYSTHYMIA	Current
B	SUICIDALITY	Current (Past Month) ❒ Low ❒ Moderate ❒ High
C	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR DISORDER NOS	Current Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MANIC EPISODE	Current (2 weeks) Past

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	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current (2 weeks) Past
	MOOD DISORDER NOS	Lifetime
D	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
E	AGORAPHOBIA	Current
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month) Generalized Non-Generalized
FA	SPECIFIC PHOBIA	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
I	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months
IL	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Lifetime Lifetime
J	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months
JL	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Lifetime Lifetime
K	PSYCHOTIC DISORDERS	Lifetime Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Lifetime

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	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current Lifetime
	PSYCHOTIC DISORDER NOS	Current Lifetime
L	ANOREXIA NERVOSA	Current (Past 3 Months)
M	BULIMIA NERVOSA	Current (Past 3 Months)
	BULMIA NERVOSA, PURGING TYPE	Current
	BULMIA NERVOSA, NON-PURGING TYPE	Current
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	GAD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
O	SOMATIZATION DISORDER	Current Lifetime
P	HYPOCHONDRIASIS	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	PAIN DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Children /Adolescents)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	MIXED ANXIETY DEPRESSIVE DISORDER	Current
W	ADJUSTMENT DISORDERS	Current
X	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT	
Y	ANTISOCIAL PERSONALITY DISORDER	Lifetime

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APPENDIX 11B. Mini International Neuropsychiatric Interview (M.I.N.I)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW
FOR PSYCHOTIC DISORDERS STUDIES

English Version 7.0.2

For

DSM-5

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

M.I.N.I. 7.0.2 for Psychotic Disorders Studies (August 8, 2016) (8/8/16)

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

	MODULES	TIME FRAME	MEETS CRITERIA	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	F32.x	☐
		Past	☐	F32.x	☐
		Recurrent	☐	F33.x	☐
B	SUICIDALITY	Current (Past Month)	☐		☐
		Lifetime attempt	☐	☐ Low ☐ Moderate ☐ High	☐
	SUICIDE BEHAVIOR DISORDER	Current	☐	(In Past Year)	☐
		In early remission	☐	(1 - 2 Years Ago)	☐
C	MANIC EPISODE	Current	☐		
		Past	☐		
	HYPOMANIC EPISODE	Current	☐		
		Past	☐	☐ Not Explored	
	BIPOLAR I DISORDER	Current	☐	F31.0 - F31.76	☐
		Past	☐	F31.0 - F31.76	☐
	BIPOLAR II DISORDER	Current	☐	F31.81	☐
		Past	☐	F31.81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31.89	☐
		Past	☐	F31.89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41.0	☐
		Lifetime	☐	F40.0	☐
E	AGORAPHOBIA	Current	☐	F40.00	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10 - F10.21	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10 - F19.21	☐
K	ANY PSYCHOTIC DISORDER	Current	☐	F20.xx-F29	☐
		Lifetime	☐	F20.xx-F29	☐
	SCHIZOPHRENIA	Current	☐	F20.9	☐
		Lifetime	☐	F20.9	☐
	SCHIZOAFFECTIVE DISORDER	Current	☐	F25.0/F25.1	☐
		Lifetime	☐	F25.0/F25.1	☐
	SCHIZOPHRENIFORM DISORDER	Current	☐	F20.81	☐
		Lifetime	☐	F20.81	☐
	BRIEF PSYCHOTIC DISORDER	Current	☐	F23	☐
		Lifetime	☐	F23	☐
	DELUSIONAL DISORDER	Current	☐	F22.0	☐
		Lifetime	☐	F22.0	☐

	SUBSTANCE- / MEDICATION-INDUCED PSYCHOTIC DISORDER	Current	☐	F10.159-F19.959	☐
		Lifetime	☐	F10.159-F19.959	☐
	PSYCHOTIC DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current	☐	F06.0/F06.2	☐
		Lifetime	☐	F06.0/F06.2	☐
	OTHER SPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER				
	OR				
	UNSPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER	Current	☐	F28 / F29	☐
		Lifetime	☐	F28 / F29	☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F32.3/F33.3	☐
		Past	☐	F32.3/F33.3	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/F31.5/F31.64	☐
		Past	☐	F31.2/F31.5/F31.64	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

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

GENERAL FORMAT:

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

CONVENTIONS:

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

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

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

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

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

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

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:
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M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

A. MAJOR DEPRESSIVE EPISODE

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

A1	a	Were you ever depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF YES ASK:		
	b	For the past two weeks, were you depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF YES ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
			➡	
		IS **A1a** OR **A2a** CODED YES?	NO	YES

A3 IF **A1b** OR **A2b** = YES: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **A1b** AND **A2b** = NO: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE.

		Over that two-week period, when you felt depressed or uninterested:	Past 2 Weeks		Past Episode	
	a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
	b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
	c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
	d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
	e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
		IF YES, ASK FOR EXAMPLES. LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
	f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
	g	Did you repeatedly think about death (FEAR OF DYING DOES NOT COUNT HERE), or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
A4		Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

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A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED YES AND IS **A4** CODED YES FOR THAT TIME FRAME?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED YES, CODE YES FOR RECURRENT.

NO	YES
MAJOR DEPRESSIVE EPISODE	
CURRENT	☐
PAST	☐
RECURRENT	☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

B. SUICIDALITY

				Points
	In the past month did you:			
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO **B1**, SKIP TO **B2**. IF YES, ASK **B1a**:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose? IF NO TO **B1a**, SKIP TO **B2**. IF YES, ASK **B1b**:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Think (even momentarily) that you would be better off dead or wish you were dead or needed to be dead?	NO	YES	1
B3	Think (even momentarily) about harming or of hurting or of injuring yourself - with at least some intent or awareness that you might die as a result - or think about suicide (i.e. about killing yourself)? IF NO TO **B2 + B3**, SKIP TO **B4**. OTHERWISE ASK: Frequency / Intensity Occasionally ☐ Mild ☐ Often ☐ Moderate ☐ Very often ☐ Severe ☐	NO	YES	6
B4	Hear a voice or voices telling you to kill yourself or have a dream with any suicidal content? IF YES, mark either or both: ☐ was it a voice or voices? ☐ was it a dream?	NO	YES	4
B5	Have a suicide method in mind (i.e. how)?	NO	YES	8
B6	Have a suicide means in mind (i.e. with what)?	NO	YES	8
B7	Have any place in mind to attempt suicide (i.e. where)?	NO	YES	8
B8	Have any date/timeframe in mind to attempt suicide (i.e. when)?	NO	YES	8
B9	Think about any task you would like to complete before trying to kill yourself? (e.g. writing a suicide note)	NO	YES	8
B10	Intend to act on thoughts of killing yourself? IF YES, mark either or both: ☐ did you intend to act at the time? ☐ did you intend to act at some time in the future?	NO	YES	8
B11	Intend to die as a result of a suicidal act? IF YES, mark either or both: ☐ did you intend to die by suicide at the time? ☐ did you intend to die by suicide at some time in the future?	NO	YES	8
B12	Feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? IF YES, mark either or both: ☐ was this to kill yourself? ☐ was this to plan to kill yourself? IF YES, mark either or both: ☐ was this largely unprovoked? ☐ was this provoked? IN ASSESSING WHETHER THIS WAS LARGELY UNPROVOKED ASK: "5 minutes before this impulse, could you have predicted it would occur at that time?" IF NO TO **B12**, SKIP TO **B14**.	NO	YES	8

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

B13	Have difficulty resisting these impulses?	NO	YES	8
B14	Take any active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO **B14**, SKIP TO **B15**.	NO	YES	
B14a	Take active steps to prepare to kill yourself, but you **did not start** the suicide attempt?	NO	YES	9
B14b	Take active steps to prepare to kill yourself, but then **you stopped yourself just before** harming yourself ("aborted")?	NO	YES	10
B14c	Take active steps to prepare to kill yourself, but then **someone or something stopped you just before** harming yourself ("interrupted")?	NO	YES	11
B15	Injure yourself on purpose without intending to kill yourself? (B15 IS NOT COUNTED AS SUICIDAL BEHAVIOR)	NO	YES	0
B16	Attempt suicide (to kill yourself)? IF NO TO **B16**, SKIP TO **B17**.	NO	YES	
B16a	Start a suicide attempt (to kill yourself), but then **you decided to stop** and did not finish the attempt?	NO	YES	12
B16b	Start a suicide attempt (to kill yourself), but then **you were interrupted** and did not finish the attempt?	NO	YES	13
B16c	Went through with a suicide attempt (to kill yourself), **completely** as you meant to? A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die. IF NO TO **B16c**, SKIP TO **B17**:	NO	YES	14

Hope to be rescued / survive ☐
Expected / intended to die ☐

B17 **TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS:**
Usual time spent per day: _____ hours _____ minutes.
Least amount of time spent per day: _____ hours _____ minutes.
Most amount of time spent per day: _____ hours _____ minutes.

In your lifetime:

B18 Did you ever make a suicide attempt (try to kill yourself)? NO YES 4
If **YES**, how many times? _____
If **YES**, when was the last suicide attempt?
- Current: within the past 12 months ☐
- In early remission: between 12 and 24 months ago ☐
- In remission: more than 24 months ago ☐

"A suicide attempt is any self-injurious behavior, with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him-or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. For example, it is defined as a suicide attempt if it is clearly not an accident or if the individual thinks the act could be lethal, even though denying intent." (FDA Guidance for Industry Suicidal Ideation and Behavior Document 2012 and C-CASA definition). Posner K et al. Am J Psychiatry 2007; 164 (7): 1035-1043 & http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/

B19	How likely are you to try to kill yourself within the next 3 months on a scale of 0-100% _____% ANY LIKELIHOOD > 0% ON **B19** SHOULD BE CODED YES	NO	YES	13

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

IS AT LEAST **1** OF THE ABOVE (EXCEPT **B1**) CODED YES?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (**B1-B19**) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE CATEGORY AS INDICATED IN THE DIAGNOSTIC BOX:

INDICATE WHETHER THE SUICIDALITY IS CURRENT (PAST MONTH) OR A LIFETIME SUICIDE ATTEMPT OR BOTH BY MARKING THE APPROPRIATE BOXES OR BY LEAVING EITHER OR BOTH OF THEM UNMARKED.
CURRENT = ANY POSITIVE RESPONSE IN **B1a** THROUGH **B16c** (EXCEPT **B15**) OR ANY TIME SPENT IN **B17**.
LIFETIME ATTEMPT = **B18** CODED YES.
LIKELY IN THE NEAR FUTURE = **B19** CODED YES.

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO	YES

SUICIDALITY

1-8 points Low	☐
9-16 points Moderate	☐
≥ 17 points High	☐
CURRENT	☐
LIFETIME ATTEMPT	☐
LIKELY IN NEAR FUTURE	☐

IS **B18** CODED YES?

AND A YES RESPONSE TO

WAS THE SUICIDAL ACT STARTED WHEN THE SUBJECT WAS NOT IN A STATE OF CONFUSION OR DELIRIUM?

AND A YES RESPONSE TO

WAS THE SUICIDAL ACT DONE WITHOUT A POLITICAL OR RELIGIOUS PURPOSE?
IF YES, SPECIFY WHETHER THE DISORDER IS CURRENT, IN EARLY REMISSION OR IN REMISSION.

NO	YES

SUICIDAL BEHAVIOR DISORDER

Current	☐
In early remission	☐
In remission	☐

C. MANIC AND HYPOMANIC EPISODES

(➠ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' and so active or full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy or increased activity; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO **C1b**: IF YES ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO **C2b**: IF YES ASK:

b Are you currently feeling persistently irritable? NO YES ➠

IS **C1a** OR **C2a** CODED YES? NO YES

C3 IF **C1b** OR **C2b** = YES: EXPLORE THE **CURRENT** EPISODE FIRST AND THEN THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = NO: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE

WHEN EXPLORING THE CURRENT EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLORING THE PAST EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most irritable, did you:

	Current Episode		Past Episode	
a Feel that you could do things others couldn't do, or that you were an especially important person? IF YES, ASK FOR EXAMPLES.	NO	YES	NO	YES
THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

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		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless? This increase in activity may be with or without a purpose.	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RATING CURRENT EPISODE: NO YES NO YES

IF **C1b** IS NO, ARE 4 OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?
IF **C1b** IS YES, ARE 3 OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

WHEN RATING PAST EPISODE:
IF **C1a** IS NO, ARE 4 OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?
IF **C1a** IS YES, ARE 3 OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY 3 OF THE **C3** SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE **C3** SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS THIS DURATION FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 consecutive days or less	☐		☐	
b)	4, 5 or 6 consecutive days or more	☐		☐	
c)	7 consecutive days or more	☐		☐	

C5	Were you hospitalized for these problems?	NO	YES	NO	YES
C6	Did these symptoms cause significant problems at home, at work, socially, in your relationships, at school or in some other important way?	NO	YES	NO	YES
C7	Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are?	NO	YES	NO	YES

IF YES, CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO **C7**.

ARE **C3 SUMMARY** AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K8**) CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	YES
MANIC EPISODE	
CURRENT	☐
PAST	☐

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IS **C3** SUMMARY CODED YES AND ARE **C5** AND **C6** CODED NO AND **C7** CODED YES,
AND IS EITHER **C4b** OR **C4c** CODED YES?
AND
IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?
AND
ARE ALL PSYCHOTIC FEATURES IN **K1** THROUGH **K8** CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF YES TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO**.

IF YES TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED**.

HYPOMANIC EPISODE

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

ARE **C3** SUMMARY AND **C4a** CODED YES AND IS **C5** CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF YES TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE,
THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO**.

IF YES TO PAST MANIC EPISODE OR YES TO PAST HYPOMANIC EPISODE,
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED**.

HYPOMANIC SYMPTOMS

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

C8 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting 4 days or more (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

D. PANIC DISORDER

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

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, very frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➠ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➠ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➠ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make any significant change in your behavior because of the attacks (e.g., avoiding unfamiliar situations, or avoiding leaving your house or shopping alone, or doing things to avoid having a panic attack or visiting your doctor or the emergency room more frequently)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing or a smothering sensation?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or feel faint?	NO	YES
	i	Did you have hot flushes or chills?	NO	YES
	j	Did you have tingling or numbness in parts of your body?	NO	YES
	k	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	l	Did you fear that you were losing control or going crazy?	NO	YES
	m	Did you fear that you were dying?	NO	YES
D5		ARE BOTH **D3**, AND **4** OR MORE **D4** ANSWERS, CODED YES?	➠ NO	YES *PANIC DISORDER LIFETIME*
D6		In the past month did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES *PANIC DISORDER CURRENT*

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IS EITHER **D5** OR **D6** CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED YES?

SPECIFY IF THE EPISODE IS CURRENT AND / OR LIFETIME.

NO	YES
PANIC DISORDER	
LIFETIME	☐
CURRENT	☐

E. AGORAPHOBIA

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

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult if you had a panic attack or panic-like or embarrassing symptoms, like: being in a crowd, or standing in a line (queue), being in an open space or when crossing a bridge, being in an enclosed space, when you are alone away from home, or alone at home, or traveling in a bus, train or car or using public transportation?	➠ NO	YES
	ARE **2** OR MORE OF THE ABOVE SITUATIONS IN **E1** CODED YES?	➠ NO	YES
E2	Do these situations almost always bring on fear or anxiety?	➠ NO	YES
E3	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	➠ NO	YES
E4	Is this fear or anxiety excessive or out of proportion to the real danger in the situation?	➠ NO	YES
E5	Did this avoidance, fear or anxiety persist for at least 6 months?	➠ NO	YES
E6	Did these symptoms cause significant distress or problems at home, at work, socially, at school or in some other important way?	➠ NO	YES

IS **E6** CODED YES?

NO	YES
AGORAPHOBIA CURRENT	

F. SOCIAL ANXIETY DISORDER (Social Phobia)

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

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	⇻ NO	YES

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- PERFORMING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	⇻ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	⇻ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	⇻ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	⇻ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	⇻ NO	YES

IS **F6** CODED YES?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

NOTE TO CLINICIAN: PLEASE SPECIFY IF THE SUBJECT'S FEARS ARE RESTRICTED TO SPEAKING OR PERFORMING IN PUBLIC.

NO	YES
SOCIAL ANXIETY DISORDER *(Social Phobia)* ***CURRENT***	
RESTRICTED TO PERFORMANCE SAD ONLY ☐	

G. OBSESSIVE-COMPULSIVE DISORDER

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

G1a	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** religious obsessions.)	NO YES ↓ SKIP TO G3a
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO HOARDING, HAIR PULLING, SKIN PICKING, BODY DYSMORPHIC DISORDER, EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO G3a
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES obsessions
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES compulsions
	ARE (**G1a** AND **G1b** AND **G2**) OR (**G3a** AND **G3b**) CODED YES?	➠ NO YES
G4	In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day? AND IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES? (CHECK FOR ANY OBSESSIVE-COMPULSIVE SYMPTOMS STARTING WITHIN 3 WEEKS OF AN INFECTION) SPECIFY THE LEVEL OF INSIGHT AND IF THE EPISODE IS TIC-RELATED.	NO YES *O.C.D. CURRENT* **INSIGHT:** GOOD OR FAIR ☐ POOR ☐ ABSENT ☐ DELUSIONAL ☐ TIC-RELATED ☐

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H. POSTTRAUMATIC STRESS DISORDER

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

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury or sexual violence to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➠ NO	YES
H2	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	➠ NO	YES

H3	**In the past month:**			
	a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event?	NO	YES
	b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
		ARE **1** OR MORE **H3** ANSWERS CODED YES?	➠ NO	YES
H4	**In the past month:**			
	a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
	b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
	c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
	d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
	e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
	f	Did you feel detached or estranged from others?	NO	YES
	g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
		ARE **2** OR MORE **H4** ANSWERS CODED YES?	➠ NO	YES

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H5 **In the past month:**

a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
b	Were you more reckless or more self-destructive?	NO	YES
c	Were you more nervous or constantly on your guard?	NO	YES
d	Were you more easily startled?	NO	YES
e	Did you have more difficulty concentrating?	NO	YES
f	Did you have more difficulty sleeping?	NO	YES

ARE **2** OR MORE **H5** ANSWERS CODED YES? NO YES

H6 Did all these problems start after the traumatic event and last for more than one month? NO YES

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

SPECIFY IF THE CONDITION IS ASSOCIATED WITH DEPERSONALIZATION, DEREALIZATION OR WITH DELAYED EXPRESSION.

NO YES

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH
DEPERSONALIZATION ☐
DEREALIZATION ☐
DELAYED EXPRESSION ☐

I. ALCOHOL USE DISORDER

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

		➡ NO	YES
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3-hour period, - on 3 or more occasions?		

I2 **In the past 12 months:**

a	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
b	Did you repeatedly want to reduce or control your alcohol use? Did you try to cut down or control your alcohol use, but failed? IF YES TO EITHER, CODE YES.	NO	YES
c	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
d	Did you crave or have a strong desire or urge to use alcohol?	NO	YES
e	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated drinking?	NO	YES
f	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES
g	Were you intoxicated more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
h	Did you continue to use alcohol, even though it was clear that the alcohol had caused or worsened psychological or physical problems?	NO	YES
i	Did you reduce or give up important work, social or recreational activities because of your drinking?	NO	YES
j	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
k1	When you cut down on heavy or prolonged drinking did you have any of the following:	NO	YES

1. increased sweating or increased heart rate, ☐
2. hand tremor or "the shakes" ☐
3. trouble sleeping ☐
4. nausea or vomiting ☐
5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐
6. agitation ☐
7. anxiety ☐
8. seizures ☐

IF YES TO **2** OR MORE OF THE ABOVE 8, CODE **k1** AS YES.

k2	Did you drink alcohol to reduce or avoid withdrawal symptoms or to avoid being hung-over?	NO	YES

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I2k SUMMARY: IF YES TO I2k1 OR I2k2, CODE YES NO YES

ARE 2 OR MORE I2 ANSWERS FROM I2a THROUGH I2k SUMMARY CODED YES?
(I2k1 AND I2k2 TOGETHER COUNT AS ONE AMONG THESE CHOICES)

NO YES

ALCOHOL USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR ALCOHOL USE DISORDER:

MILD = 2-3 OF THE I2 SYMPTOMS
MODERATE = 4-5 OF THE I2 SYMPTOMS
SEVERE = 6 OR MORE OF THE I2 SYMPTOMS

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS.
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE.
(BOTH WITH THE EXCEPTION OF CRITERION d [CRAVING] ABOVE.)

IN A CONTROLLED ENVIRONMENT = WHERE ALCOHOL ACCESS IS RESTRICTED.

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

J. SUBSTANCE USE DISORDER (NON-ALCOHOL)

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

		Now I am going to show you / read to you a list of street drugs or medicines.		
J1	a	**In the past 12 months,** did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	➡ NO	YES

CIRCLE EACH DRUG TAKEN:

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

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

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

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Dissociative Drugs: PCP (Phencyclidine ,"Angel Dust", "Peace Pill", "Hog"), or ketamine ("Special K").

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

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

Sedatives, Hypnotics or Anxiolytics: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

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

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS? _____

FIRST EXPLORE THE CRITERIA BELOW FOR THE DRUG CLASS CAUSING THE BIGGEST PROBLEMS AND THE ONE MOST LIKELY TO MEET CRITERIA FOR SUBSTANCE USE DISORDER. IF SEVERAL DRUG CLASSES HAVE BEEN MISUSED, EXPLORE AS MANY OR AS FEW AS REQUIRED BY THE PROTOCOL.

J2		**Considering your use of (NAME OF DRUG / DRUG CLASS SELECTED), in the past 12 months:**		
	a	During the times when you used the drug, did you end up using more (NAME OF DRUG / DRUG CLASS SELECTED) than you planned when you started?	NO	YES
	b	Did you repeatedly want to reduce or control your (NAME OF DRUG / DRUG CLASS SELECTED) use? Did you try to cut down or control your (NAME OF DRUG / DRUG CLASS SELECTED) use, but failed? IF YES TO EITHER, CODE YES.	NO	YES
	c	On the days that you used more (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time obtaining (NAME OF DRUG / DRUG CLASS SELECTED), using it, or recovering from the its effects?	NO	YES
	d	Did you crave or have a strong desire or urge to use (NAME OF DRUG / DRUG CLASS SELECTED)?	NO	YES
	e	Did you spend less time meeting your responsibilities at work, at school, or at home, because of your repeated (NAME OF DRUG / DRUG CLASS SELECTED) use?	NO	YES
	f	If your (NAME OF DRUG / DRUG CLASS SELECTED) use caused problems with your family or other people, did you still keep on using it?	NO	YES
	g	Did you use the drug more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
	h	Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it was clear that the (NAME OF DRUG / DRUG CLASS SELECTED) had caused or worsened psychological or physical problems?	NO	YES

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i Did you reduce or give up important work, social or recreational activities because of your (NAME OF DRUG / DRUG CLASS SELECTED) use? NO YES

j Did you need to use (NAME OF DRUG / DRUG CLASS SELECTED) a lot more in order to get the same effect that you got when you first started using it or did you get much less effect with continued use of the same amount? NO YES
THIS CRITERION IS CODED **NO** IF THE MEDICATION IS PRESCRIBED AND USED UNDER APPROPRIATE MEDICAL SUPERVISION.

k1 When you cut down on heavy or prolonged use of the drug did you have any of the following withdrawal symptoms: NO YES
IF **YES** TO THE REQUIRED NUMBER OF WITHDRAWAL SYMPTOMS FOR EACH CLASS, CODE **J2k1** AS **YES**.
THIS CRITERION IS CODED **NO** IF THE MEDICATION IS PRESCRIBED AND USED UNDER APPROPRIATE MEDICAL SUPERVISION.

Sedatives, Hypnotics or Anxiolytics (2 or more withdrawal symptoms)
1. increased sweating or increased heart rate ☐
2. hand tremor or "the shakes" ☐
3. trouble sleeping ☐
4. nausea or vomiting ☐
5. hearing or seeing things other people could not see or hear or having sensations in your skin for no apparent reason ☐
6. agitation ☐
7. anxiety ☐
8. seizures ☐

Opiates (3 or more withdrawal symptoms)
1. feeling depressed ☐
2. nausea or vomiting ☐
3. muscle aches ☐
4. runny nose or teary eyes ☐
5. dilated pupils, goose bumps or hair standing on end or sweating ☐
6. diarrhea ☐
7. yawning ☐
8. hot flashes ☐
9. trouble sleeping ☐

Stimulants and Cocaine (2 or more withdrawal symptoms)
1. fatigue ☐
2. vivid or unpleasant dreams ☐
3. difficulty sleeping or sleeping too much ☐
4. increased appetite ☐
5. feeling or looking physically or mentally slowed down ☐

Cannabis (3 or more withdrawal symptoms)
1. irritability, anger or aggression ☐
2. nervousness or anxiety ☐
3. trouble sleeping ☐
4. appetite or weight loss ☐
5. restlessness ☐
6. feeling depressed ☐
7. significant discomfort from one of the following: "stomach pain", tremors or "shakes", sweating, hot flashes, chills, headaches. ☐

k2 Did you use (NAME OF DRUG / DRUG CLASS SELECTED) to reduce or avoid withdrawal symptoms? NO YES

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J2k SUMMARY: IF YES TO **J2k1** OR **J2k2**, CODE YES. NO YES

ARE **2** OR MORE **J2** ANSWERS FROM **J2a** THROUGH **J2k** SUMMARY CODED YES?
(**J2k1** AND **J2k2** TOGETHER COUNT AS ONE AMONG THESE CHOICES.)

NO **YES**

SUBSTANCE
(Drug or Drug Class Name)
USE DISORDER

PAST 12 MONTHS

SPECIFIERS FOR SUBSTANCE USE DISORDER:

MILD = **2-3** OF THE **J2** SYMPTOMS
MODERATE = **4-5** OF THE **J2** SYMPTOMS
SEVERE = **6** OR MORE OF THE **J2** SYMPTOMS

IN EARLY REMISSION = CRITERIA NOT MET FOR BETWEEN 3 & 12 MONTHS.
IN SUSTAINED REMISSION = CRITERIA NOT MET FOR 12 MONTHS OR MORE.
(BOTH WITH THE EXCEPTION OF **CRITERION d** [CRAVING] ABOVE.)

IN A CONTROLLED ENVIRONMENT = WHERE SUBSTANCE / DRUG ACCESS IS RESTRICTED.

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐

IN EARLY REMISSION ☐
IN SUSTAINED REMISSION ☐

IN A CONTROLLED ENVIRONMENT ☐

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K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. THE PURPOSE OF THIS MODULE IS TO ELICIT INFORMATION TO USE IN CONJUNCTION WITH ALGORITHMS I AND II TO IDENTIFY EACH PSYCHOTIC DISORDER. THIS MODULE NEEDS CLINICAL SKILL AND EXPERIENCE TO IMPLEMENT ACCURATELY.

Now I am going to ask you about unusual experiences that some people have.

K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CLINICIAN: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS **K1** TO **K4**. FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.	NO	YES
	b	IF YES: do they currently consider your beliefs strange or unusual?	NO	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES
	b	IF YES TO **K6a**: have you heard sounds / voices in the past month?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES

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K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES
	b	IF YES: have you seen these things in the past month?	NO	YES

CLINICIAN'S JUDGMENT

K8	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	a	DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?	NO	YES
K11	a	ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K7a**, CODED YES?		

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES?

AND

HOW LONG HAS THE MOOD EPISODE LASTED? _____
HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? .....
IF SUCH A MOOD EPISODE IS PRESENT, CODE YES TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE NO. NO YES

K11 b

ARE THE ONLY SYMPTOMS PRESENT THOSE IDENTIFIED BY THE CLINICIAN FROM **K1** TO **K10** AND NOT FULLY ENDORSED BY THE PATIENT?

IF **YES**, SPECIFY IF THE LAST EPISODE IS CURRENT (AT LEAST **1** "b" QUESTION IS CODED "**YES**" FROM **K1b** TO **K10b**) AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **K1a** TO **K10b**) AND PASS TO THE NEXT DIAGNOSTIC MODULE.

IF **NO**, CONTINUE.

WARNING: IF AT LEAST **1** « **b** » QUESTION IS CODED **YES**, CODE **K11c** AND **K11d**.
IF ALL « **b** » QUESTIONS ARE CODED **NO**, CODE ONLY **K11d**.

NO	YES

UNSPECIFIED* SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER

Current ☐
Lifetime ☐

***Provisional diagnosis due to insufficient information available at this time.**

K11 c ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K8b** CODED **YES**?
AND
ARE **2** OR MORE « **b** » QUESTIONS FROM **K1b TO K10b** CODED **YES**?
AND
DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS LAST FOR A SIGNIFICANT PORTION OF TIME DURING THE **PAST** MONTH (OR LESS IF SUCCESSFULLY TREATED)?

Then Criterion "A" of Schizophrenia

☐ **Is currently met**
☐ **Is not currently met**
☐ **Uncertain, code later**

K11 d ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K8a** CODED **YES**?
AND
ARE **2** OR MORE « **a** » QUESTIONS FROM **K1a TO K10a** CODED **YES**?
AND
AT ANY TIME IN THE PATIENT'S LIFETIME, DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS LAST FOR A SIGNIFICANT PORTION OF TIME DURING THE **SAME** 1-MONTH PERIOD (OR LESS IF SUCCESSFULLY TREATED)?
OR
IS **K11c** CODED **YES**?

Then Criterion "A" of Schizophrenia

☐ **Is met Lifetime**
☐ **Is not met Lifetime**
☐ **Uncertain, code later**

DISABILITY

K12	Did your ability to function at work, at school, with your family and in taking care of yourself and socially with others, return completely to how you were before these experiences (CLINICIAN: PROVIDE EXAMPLES OF EXISTING HALLUCINATIONS, DELUSIONS OR DISORGANIZED SPEECH OR BEHAVIOR)?	NO	YES
K13 a	During or after a period when you had these beliefs or experiences, did you have difficulty working, or difficulty in your relationships with others, or in taking care of yourself?	NO	YES
b	IF **YES**, how long did these difficulties last? IF **≥6 MONTHS**, GO TO **K14.**	_____	
c	Have you been treated with medications or were you hospitalized because of these beliefs or experiences, or the difficulties caused by these problems?	NO	YES
d	IF **YES**, what was the longest time you were treated with medication or were hospitalized for these problems?	_____	

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K14 a DID THE PATIENT REPORT DISABILITY (**K13a** CODED YES) OR WAS THE PATIENT TREATED OR HOSPITALIZED FOR PSYCHOSIS (**K13c** = YES)? NO YES

b CLINICIAN'S JUDGMENT: CONSIDERING YOUR EXPERIENCE, RATE THE PATIENT'S LIFETIME DISABILITY CAUSED BY THE PSYCHOSIS.

absent	☐	1
mild	☐	2
moderate	☐	3
severe	☐	4

K15 How long was the longest period during which you had those beliefs or experiences? _____

WHAT WAS THE TOTAL DURATION OF THE PSYCHOSIS? TAKE INTO ACCOUNT THE ACTIVE PHASE (**K15**) AND THE ASSOCIATED DIFFICULTIES (**K13b**) AND PSYCHIATRIC TREATMENT (**K13d**) IN CHOOSING THE TIME FRAME.

1 ☐ ≥1 day to <1 month
2 ☐ ≥1 month to <6 months
3 ☐ ≥6 months
4 ☐ < 1 day

RULE OUT "ORGANIC CAUSE" (DUE TO A MEDICAL ILLNESS OR TO EXPOSURE OR WITHDRAWAL FROM A MEDICINE/DRUG)

Just before these symptoms began:

K16 a Were you taking any drugs or medicines or in withdrawal from any of these? ☐ No ☐ Yes ☐ Uncertain

b Did you have any medical illness? ☐ No ☐ Yes ☐ Uncertain

c IF **K16a** OR **K16b** IF CODED YES, IN THE CLINICIAN'S JUDGMENT IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS. ☐ No ☐ Yes ☐ Uncertain

K16 d HAS AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT? ☐ No ☐ Yes ☐ Uncertain

IF **K16d** = NO: SCORE **K17** (**a** AND **b**) AND GO TO THE NEXT MODULE
IF **K16d** = YES: CODE NO IN **K17** (**a** AND **b**) AND GO TO **K18**
IF **K16d** = UNCERTAIN: CODE UNCERTAIN IN **K17** (**a** AND **b**) AND GO TO **K18**

K17 a IS **K16d** CODED NO BECAUSE OF ANOTHER MEDICAL CONDITION (INCLUDING DELIRIUM)?

IF RESPONSE TO **K17a** IS CODED YES, SPECIFY IF THE LAST EPISODE IS CURRENT OR LIFETIME OR BOTH:

CURRENT: (AT LEAST **1** « **b** » RESPONSE IS CODED YES FROM **K1b** THROUGH **K5b** = DELUSION, OR AT LEAST ONE « **b** » RESPONSE IS CODED YES FROM **K6b** OR **K7b** = HALLUCINATION)
AND
IS **K13a** CODED YES?

AND/OR

LIFETIME: (AT LEAST **1** « **a** » RESPONSE IS CODED YES FROM **K1a** THROUGH **K5a**, OR AT LEAST **1** « **a** » RESPONSE IS CODED YES FROM **K6a** OR **K7a**)
AND
IS **K13a** CODED YES?

IF YES TO **K17a** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS.

NO	YES

PSYCHOTIC DISORDER
Due to Another Medical Condition

Current	☐
Lifetime	☐
Uncertain, code later	☐

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K17 b IS **K16d** CODED NO, BECAUSE OF A DRUG/MEDICINE, OR WITHDRAWAL FROM A DRUG /MEDICINE, OR BECAUSE OF A DELIRIUM DIRECTLY INDUCED BY A DRUG/MEDICINE?

IF RESPONSE TO **K17b** IS CODED YES, SPECIFY IF THE LAST EPISODE IS CURRENT OR LIFETIME OR BOTH:

CURRENT: (AT LEAST **1** « **b** » RESPONSE IS CODED YES FROM **K1b** THROUGH **K5b** = DELUSION, OR AT LEAST ONE « **b** » RESPONSE IS CODED YES FROM **K6b** OR **K7b** = HALLUCINATION)
AND
IS **K13a** CODED YES?

AND/OR

LIFETIME: (AT LEAST **1** « **a** » RESPONSE IS CODED YES FROM **K1a** THROUGH **K5a**, OR AT LEAST **1** « **a** » RESPONSE IS CODED YES FROM **K6a** OR **K7a**)
AND
IS **K13a** CODED YES?

IF YES TO **K17b** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS.

NO	YES
Substance Induced ***PSYCHOTIC DISORDER***	
Current	☐
Lifetime	☐
Uncertain, code later	☐

CHRONOLOGY

K18 How old were you when you first began having these unusual beliefs or experiences? ☐ age

PART 2 - DIFFERENTIAL DIAGNOSIS BETWEEN A PSYCHOTIC DISORDER AND A MOOD DISORDER WITH PSYCHOTIC FEATURES

CODE THE QUESTIONS **K19** TO **K23** ONLY IF THE PATIENT DESCRIBED AT LEAST **1** PSYCHOTIC SYMPTOM (**K11a** = YES AND **K11b** = NO), NOT EXPLAINED BY AN ORGANIC CAUSE (**K16d** = YES OR UNCERTAIN).

K19 a DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MAJOR DEPRESSIVE EPISODE (IS THE DIAGNOSTIC BOX IN **A5** CODED YES)? NO YES

b IF YES: IS **A1a** OR **A1b** (DEPRESSED MOOD) CODED YES? NO YES

c DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MANIC EPISODE (MODULE **C**)? NO YES

d IS **K19a** OR **K19c** CODED YES? NO YES

↓

STOP.
Skip to K24

NOTE: VERIFY THAT THE RESPONSES TO THE QUESTIONS **K20** TO **K23** REFER TO THE PSYCHOTIC, DEPRESSIVE (MODULE **A**), AND MANIC EPISODES (MODULE **C**), ALREADY IDENTIFIED IN **K11c** AND **K11d.** IN CASE OF DISCREPANCIES, RE-EXPLORE THE SEQUENCE OF DISORDERS, TAKING INTO ACCOUNT IMPORTANT LIFE ANCHOR POINTS/MILESTONES AND CODE **K20** TO **K23** ACCORDINGLY.

K20 When you were having the beliefs and experiences you just described (GIVE EXAMPLES TO PATIENT), were you also feeling depressed/high/irritable at the same time? NO YES

↓

STOP.
Skip to K24

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K21 Were the beliefs or experiences you just described (GIVE EXAMPLES TO PATIENT) restricted exclusively to times you were feeling depressed/high/irritable? NO YES

K22 Have you ever had a period of two weeks or more of having these beliefs or experiences when you were not feeling depressed/high/irritable? NO YES
↓
STOP.
Skip to K24

K23 a Which lasted longer: these beliefs or experiences or the periods of feeling depressed/high/irritable?
1 ☐ mood
2 ☐ beliefs, experiences
3 ☐ same

IF THE RESPONSE TO **K23a** WAS **2**, ASK **K23b** AND **K23c**:

b Did the beliefs or experiences you just described (GIVE EXAMPLES OF DELUSIONS OR HALLUCINATIONS TO PATIENT) occur for at least 2 weeks without your also feeling depressed/high/irritable? NO YES

c Did the depressed/high/irritable feelings last more than 50% of the total time that you had these beliefs and experiences (GIVE EXAMPLES TO PATIENT)? = NO YES
THIS CALCULATION SHOULD EMBRACE THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PHASES OF THE ILLNESS.

K24 AT THE END OF THE INTERVIEW, GO TO THE DIAGNOSTIC ALGORITHMS FOR PSYCHOTIC DISORDERS.

CONSULT ITEMS **K11a** AND **K11b**:

CURRENT:

IF THE CRITERION "A" OF SCHIZOPHRENIA IS MET (**K11c** = YES) GO TO DIAGNOSTIC ALGORITHM I

IF THE CRITERION "A" OF SCHIZOPHRENIA IS NOT MET (**K11c** = NO) GO TO DIAGNOSTIC ALGORITHM II

FOR MOOD DISORDERS GO TO THE DIAGNOSTIC ALGORITHM III.

LIFETIME:

IF THE CRITERION "A" OF SCHIZOPHRENIA IS MET (**K11d** = YES) GO TO DIAGNOSTIC ALGORITHM I

IF THE CRITERION "A" OF SCHIZOPHRENIA IS NOT MET (**K11d** = NO) GO TO DIAGNOSTIC ALGORITHM II

FOR MOOD DISORDERS GO TO THE DIAGNOSTIC ALGORITHM III.

L. ANOREXIA NERVOSA

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

L1	a	How tall are you?	☐☐ ft ☐☐ in. ☐☐☐ cm
	b	What was your lowest weight in the past 3 months?	☐☐☐ lb ☐☐☐ kg
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW.)	⇛ NO YES

In the past 3 months:

L2		In spite of this low weight, have you tried not to gain weight or to restrict your food intake?	⇛ NO YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	⇛ NO YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO YES
	c	Have you thought that your current low body weight was normal or excessive?	NO YES
L5		ARE **1** OR MORE ITEMS FROM **L4** CODED YES?	⇛ NO YES

IS **L5** CODED YES?

NO **YES**

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A **BMI THRESHOLD** OF **17.0** KG/M²

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	79	82	84	87	90	93	96	99	102	106	109	112	115	119
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	36	37	38.5	39.5	41	42.5	43.5	45.5	46.5	48	49	51	52	54

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	122	125	129	133	136
cm	180	183	185	188	191
kg	55	57	58.5	60	62

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.0 kg/m² for the patient's height using the Center of Disease Control & Prevention BMI Calculator. This is the threshold guideline below which a person is deemed underweight by the DSM-5 for Anorexia Nervosa.

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M. BULIMIA NERVOSA

(➠ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN THE BULIMIA NERVOSA AND IN THE ANOREXIA NERVOSA BINGE EATING / PURGING TYPE DIAGNOSTIC BOXES. BUT IF ANOREXIA NERVOSA (IN MODULE L) IS CODED YES, CONTINUE WITH THE QUESTIONS TO BE ABLE TO PROPERLY CODE ANOREXIA NERVOSA RESTRICTING TYPE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➠ NO YES
M2	During these binges, did you feel that your eating was out of control?	➠ NO YES

In the past 3 months:

M3	Did you have eating binges as often as once a week?	➠ NO YES
M4	Did you do anything to compensate for, or to prevent a weight gain, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications? Did you do this as often as once a week?	➠ NO YES
M4a	Number of Episodes of Inappropriate Compensatory Behaviors per Week? _____	
	Number of Days of Inappropriate Compensatory Behaviors per Week? _____	
M5	Did your body weight or shape greatly influence how you felt about yourself?	➠ NO YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO YES ↓ Skip to M8
M7	Did these binges occur only when you were under (_____lb/kg)? CLINICIAN: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO YES
M8	IS **M5** CODED YES AND IS EITHER **M6** OR **M7** CODED NO?	NO YES ***BULIMIA NERVOSA*** **CURRENT**
	IS **M7** CODED YES?	NO YES ***ANOREXIA NERVOSA*** *Binge Eating/Purging Type* **CURRENT**

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DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?

AND

IS **M2** OR **M4** CODED NO?

NO YES

ANOREXIA NERVOSA
Restricting Type
CURRENT

SPECIFIERS OF EATING DISORDER:

MILD = **1-3** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
MODERATE = **4-7** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
SEVERE = **8-13** EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS
EXTREME = **14** OR MORE EPISODES OF INAPPROPRIATE COMPENSATORY BEHAVIORS

SPECIFY IF:

MILD ☐
MODERATE ☐
SEVERE ☐
EXTREME ☐

MB. BINGE EATING DISORDER

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

MB1	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	➠ YES
MB2	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR BULIMIA NERVOSA?	NO	➠ YES
MB3	IS **M2** CODED YES?	➠ NO	YES
MB4	IS **M3** CODED YES?	➠ NO	YES
MB5	IS **M4** CODED YES? IF M4 WAS BYPASSED IN MODULE M (BULIMIA NERVOSA), ASK M4 NOW TO CODE MB5	NO	➠ YES
	In the last 3 months during the binging did you:		
MB6a	Eat more rapidly than normal?	NO	YES
MB6b	Eat until you felt uncomfortably full?	NO	YES
MB6c	Eat large amounts of food when you were not hungry?	NO	YES
MB6d	Eat alone because you felt embarrassed about how much you were eating?	NO	YES
MB6e	Feel guilty, depressed or disgusted with yourself after binging?	NO	YES
	ARE **3** OR MORE **MB6** QUESTIONS CODED YES?	➠ NO	YES

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MB7 Does your binging distress you a lot? NO YES

MB8 Number of Binge Eating Episodes per Week? _____

Number of Binge Eating Days per Week? _____

IS **MB7** CODED YES?

NO YES

BINGE-EATING DISORDER

CURRENT

SPECIFIERS OF EATING DISORDER:

MILD = **1-3** EPISODES OF BINGE EATING PER WEEK
MODERATE = **4-7** EPISODES OF BINGE EATING PER WEEK
SEVERE = **8-13** EPISODES OF BINGE EATING PER WEEK
EXTREME = **14** OR MORE EPISODES OF BINGE EATING PER WEEK

SPECIFY IF:

- MILD ☐
- MODERATE ☐
- SEVERE ☐
- EXTREME ☐

N. GENERALIZED ANXIETY DISORDER

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

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a worrier or a "worry wart"?) AND GET EXAMPLES.	➠ NO	YES
	b	Are these anxieties and worries present most days?	➠ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➠ YES
N2		Do you find it difficult to control the worries?	➠ NO	YES
N3		FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE 3 OR MORE N3 ANSWERS CODED YES?	➠ NO	YES
N4		Do these anxieties and worries significantly disrupt your ability to work, to function socially or in your relationships or in other important areas of your life or cause you significant distress? AND IS "RULE OUT ORGANIC CAUSE (O2 SUMMARY)" CODED YES?	NO	YES *GENERALIZED ANXIETY DISORDER* CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER OR A MAJOR DEPRESSIVE EPISODE OR A MANIC OR A HYPOMANIC EPISODE ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines or in withdrawal from any of these?	☐ No	☐ Yes ☐ Uncertain
O1b	Did you have any medical illness?	☐ No	☐ Yes ☐ Uncertain
O2	IF O1a OR O1b IS CODED YES, IN THE CLINICIAN'S JUDGMENT, IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.	☐ No	☐ Yes ☐ Uncertain
O2 SUMMARY:	HAS AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT?	☐ No	☐ Yes ☐ Uncertain

IF O2 IS YES, THEN O2 SUMMARY IS NO. IF O2 IS NO, THEN O2 SUMMARY IS YES. OTHERWISE IT IS UNCERTAIN.

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P. ANTISOCIAL PERSONALITY DISORDER

(➠ MEANS: SKIP ALL THE **P2** QUESTIONS, GO TO THE DIAGNOSTIC BOX AND CIRCLE **NO**)

P1		**Before you were 15 years old, did you:**		
	a	repeatedly skip school or run away from home overnight or stayed out at night against your parent's rules?	NO	YES
	b	repeatedly lie, cheat, "con" others, or steal or break into someone's house or car?	NO	YES
	c	start fights or bully, threaten, or intimidate others?	NO	YES
	d	deliberately destroy things or start fires?	NO	YES
	e	deliberately hurt animals or people?	NO	YES
	f	force someone into sexual activity?	NO ➠	YES
		ARE **2** OR MORE **P1** ANSWERS CODED YES?	NO	YES

DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2		**Since you were 15 years old, have you:**		
	a	done things that are illegal or would be grounds to get arrested, even if you didn't get caught (for example destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
	b	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
	c	been impulsive and didn't care about planning ahead?	NO	YES
	d	been in physical fights repeatedly or assaulted others (including physical fights with your spouse or children)?	NO	YES
	e	exposed others or yourself to danger without caring?	NO	YES
	f	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
	g	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

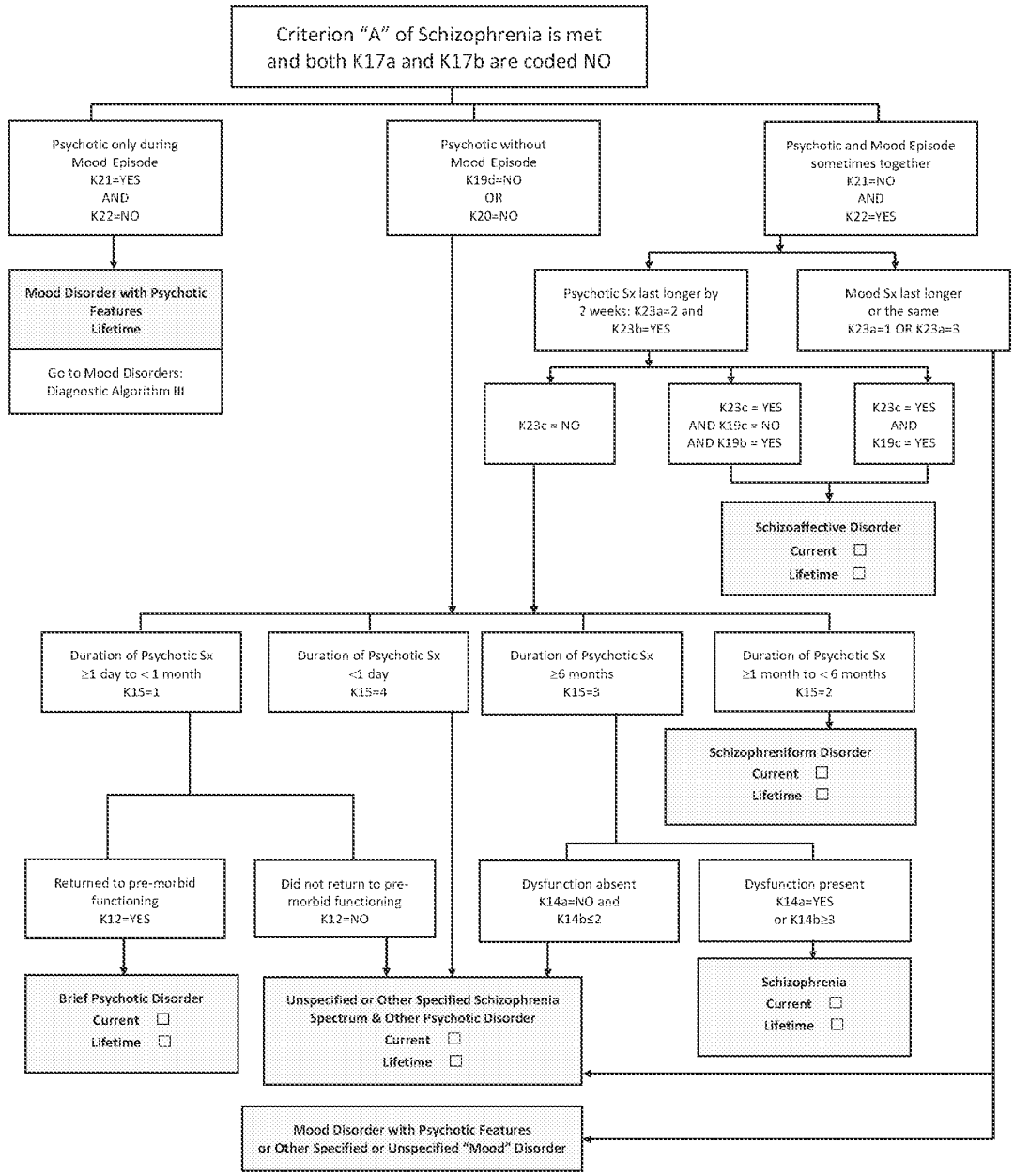
ARE **3** OR MORE **P2** QUESTIONS CODED YES?

NO	YES
ANTISOCIAL PERSONALITY DISORDER LIFETIME	

ADDITIONAL OPTIONAL INTERVIEW ASSESSMENTS ON PAGES 41 & 42

PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM I

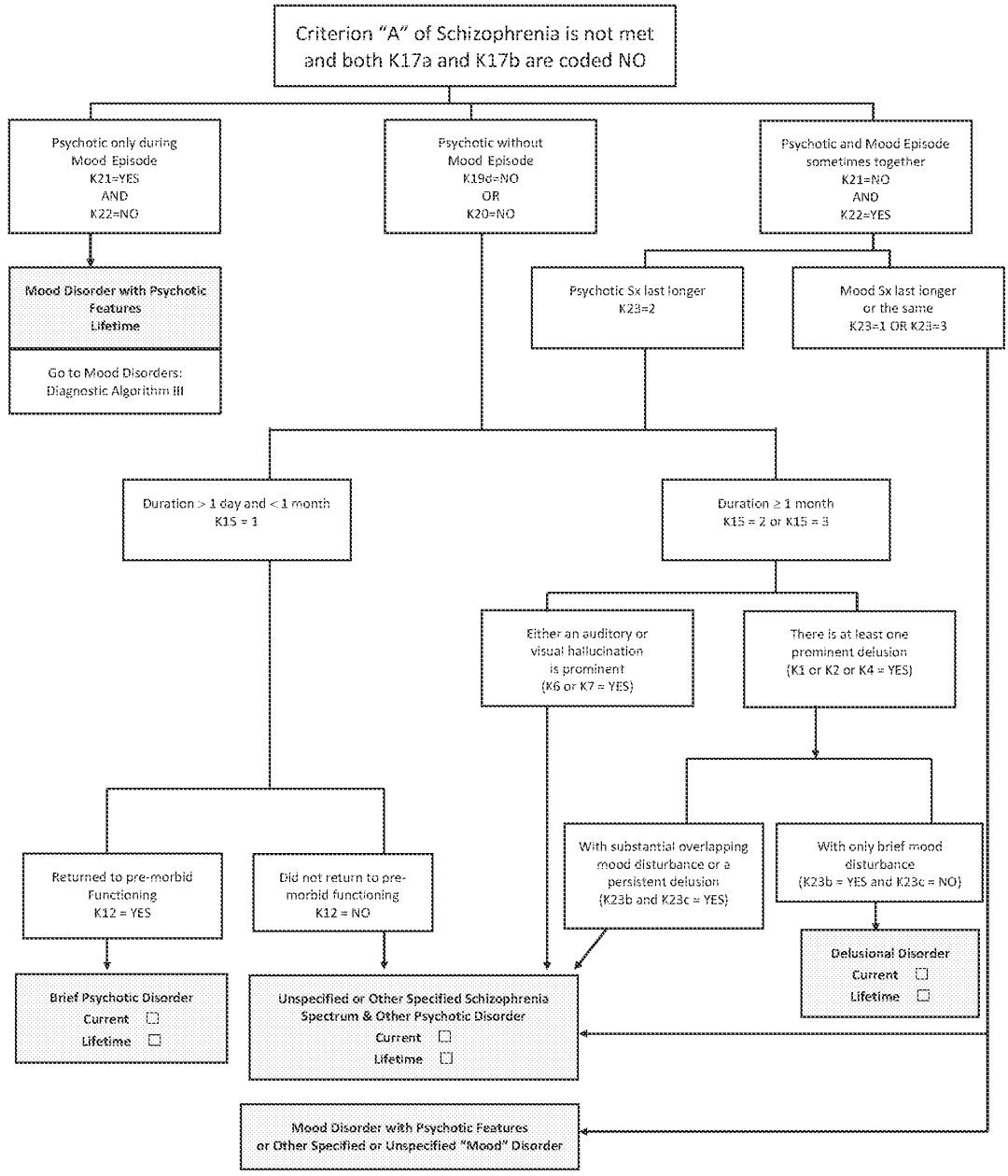
For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is not currently met, but is present lifetime, current and lifetime diagnoses may be different.



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PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM II

For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is present lifetime, current and lifetime diagnoses may be different.



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MOOD DISORDERS: DIAGNOSTIC ALGORITHM III

Consult Modules:
- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders

MODULES A and C: Current Past

1 a CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e** OR IN ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7** — YES YES

b CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a** OR IN ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7** — YES YES

c IS MAJOR DEPRESSIVE EPISODE CODED YES (CURRENT OR PAST)?
AND
IS MANIC EPISODE CODED NO (CURRENT AND PAST)?
AND
IS HYPOMANIC EPISODE CODED NO (CURRENT AND PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?
AND
ARE ALL THE PSYCHOTIC DISORDERS IN ALGORITHMS I & II (WITH THE EXCEPTION OF MOOD DISORDERS WITH PSYCHOTIC FEATURES) RULED OUT?

SPECIFY:

- IF THE DEPRESSIVE EPISODE IS **CURRENT** OR **PAST** OR BOTH
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1a** (CURRENT) = YES
  WITH PSYCHOTIC FEATURES, PAST: IF **1a** (PAST) = YES

MAJOR DEPRESSIVE DISORDER

	Current	Past
MDD	☐	☐

With Psychotic Features

Current	☐
Past	☐

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d IS MANIC EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?
AND
ARE ALL THE PSYCHOTIC DISORDERS IN ALGORITHMS I & II (WITH THE EXCEPTION OF MOOD DISORDERS WITH PSYCHOTIC FEATURES) RULED OUT?

SPECIFY:

- IF THE BIPOLAR I DISORDER IS **CURRENT** OR **PAST** OR BOTH
- WITH SINGLE MANIC EPISODE: IF MANIC EPISODE (CURRENT OR PAST) = **YES**
  AND MAJOR DEPRESSIVE EPISODE (CURRENT AND PAST) = **NO**
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1a** (CURRENT) OR **1b** (CURRENT) = **YES**
  WITH PSYCHOTIC FEATURES, PAST: IF **1a** (PAST) OR **1b** (PAST) = **YES**
- IF THE MOST RECENT EPISODE IS MANIC, DEPRESSED, OR HYPOMANIC (MUTUALLY EXCLUSIVE)
- IF THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES

  HYPO/MANIC WITH MIXED FEATURES = HYPO/MANIC + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**

  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR I DISORDER

	Current	Past
Bipolar I Disorder	☐	☐
Single Manic Episode	☐	☐

With Psychotic Features
Current ☐
Past ☐

Most Recent Episode
Manic ☐
Depressed ☐
Hypomanic ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

e IS MAJOR DEPRESSIVE EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS HYPOMANIC EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?
AND
ARE ALL THE PSYCHOTIC DISORDERS IN ALGORITHMS I & II (WITH THE EXCEPTION OF MOOD DISORDERS WITH PSYCHOTIC FEATURES) RULED OUT?

SPECIFY:

- IF THE BIPOLAR DISORDER IS **CURRENT** OR **PAST** OR BOTH
- IF THE MOST RECENT MOOD EPISODE IS HYPOMANIC OR DEPRESSED (MUTUALLY EXCLUSIVE)
- IF THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES

  HYPOMANIC WITH MIXED FEATURES = HYPOMANIC + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**

  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR II DISORDER

	Current	Past
Bipolar II Disorder	☐	☐

Most Recent Episode
Hypomanic ☐
Depressed ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

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f IS MAJOR DEPRESSIVE EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **C4b** CODED YES FOR THE APPROPRIATE TIME FRAME?
AND
IS **C8b** CODED YES?
AND
ARE ALL THE PSYCHOTIC DISORDERS IN ALGORITHMS I & II (WITH THE EXCEPTION OF MOOD DISORDERS WITH PSYCHOTIC FEATURES) RULED OUT?

OR

IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS HYPOMANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **C4a** CODED YES FOR THE APPROPRIATE TIME FRAME?
AND
IS **C8c** CODED YES?
AND
ARE ALL THE PSYCHOTIC DISORDERS IN ALGORITHMS I & II (WITH THE EXCEPTION OF MOOD DISORDERS WITH PSYCHOTIC FEATURES) RULED OUT?

SPECIFY IF THE OTHER SPECIFIED BIPOLAR AND RELATED DISORDER IS **CURRENT** OR **PAST** OR BOTH.

OTHER SPECIFIED BIPOLAR AND RELATED DISORDER

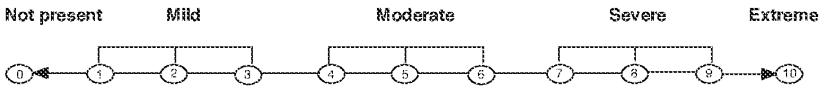
	Current	Past
Other Specified Bipolar and Related Disorder	☐	☐

OPTIONAL ASSESSMENT MEASURES TO TRACK CHANGES OVER TIME

A: CROSS CUTTING MEASURES

SEVERITY OF SYMPTOM

Use this scale to rate the severity of your symptom in the score column in the table below:



Assessment of Symptoms That Cut Across Disorders

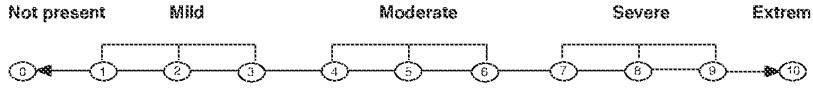
	Symptom Name	Score
1	Depression	
2	Anger	
3	Mania (feeling up or high or hyper or full of energy with racing thoughts)	
4	Anxiety	
5	Physical (somatic) symptoms	
6	Suicidal thoughts, impulses, plans, intent, (ANY thoughts of killing yourself), or ANY preparations to kill yourself or ANY attempt to kill yourself	
7	Hearing sounds or voices others can't hear or fearing someone can hear or read your thoughts or believing things others don't accept as true e.g. that people are spying on you or plotting against you or talking about you (Psychosis)	
8	Sleep problems	
9	Memory problems	
10	Repetitive or obsessive thoughts or compulsive behaviors	
11	Feeling things around you are strange, unreal, detached or unfamiliar, or feeling outside or detached from part or all of your body (Dissociation)	
12	Ability to function at work, at home, in your life, or in your relationships	
13	Overusing alcohol or drugs	

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B: DISABILITY / FUNCTIONAL IMPAIRMENT

SEVERITY OF DISABILITY / IMPAIRMENT

Use this scale to rate in the score column of the table below, how much your symptoms have disrupted your ability to function in the following areas of your life:



Assessment of Impairment of Functioning /Disability

	Domain Name	Score
1	Work or school work	
2	Social life or leisure activities (like hobbies or things you do for enjoyment)	
3	Family life and / or home responsibilities	
4	Ability to get along with people	
5	Personal and social relationships	
6	Ability to understand and to communicate with others	
7	Ability to take care of yourself (washing, showering, bathing, dressing properly, brushing teeth, laundry, combing / brushing hair, eating regularly)	
8	Made you disruptive or aggressive towards others	
9	Financially (ability to manage your money)	
10	Ability to get around physically	
11	Spiritual or religious life	
12	How much did your condition have an impact on other people in your family?	

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4. Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. European Psychiatry. 1998; 13:26-34.

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4 Executive Scientific committee for the MINI 6.0.0 for DSM-IV:
   Christer Allgulander, Stockholm, Sweden
   A. Carlo Altamura, Milano, Italy
   Cyril Hoschl, Praha, Czech Republic
   George Papadimitriou, Athens, Greece
   Hans Ågren, Göteborg, Sweden
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5. Mapi and the many academic translation teams internationally who collaborated in ensuring that quality translations became available in over 70 languages or language variants. Mapi (http://www.mapigroup.com) is now the official translation and linguistic validation service for all variants of the MINI.
6. Individual clinicians and patients who over the years made countless suggestions to help improve the accuracy and clinical value to the MINI: JM Giddens for her advice on the MINI 7 version of the Suicidality Disorders Module, Dr. Michael Van Ameringen for assistance with the ADHD module, and Dr Pauline Powers for her advice on the modules on Anorexia Nervosa and Bulimia.
7. Validation studies of the MINI were made possible, in part, by grants from SmithKlineBeecham and the European Commission.

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M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI. The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
	MDD WITH ANXIOUS DISTRESS	Current (2 weeks)
	MDD WITH MIXED FEATURES	Current (2 weeks)
	MDD WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDD WITH ATYPICAL FEATURES	Current (2 weeks)
	MDD WITH PSYCHOTIC FEATURES	Current (2 weeks)
	MDD WITH CATATONIA	Current (2 weeks)
	MDD WITH SEASONAL PATTERN	Current (2 weeks)
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past
	SUBSTANCE- / MEDICATION-INDUCED DEPRESSIVE DISORDER	Current (2 weeks) Past
	DEPRESSIVE DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current (2 weeks) Past
AY	PERSISITENT DEPRESSIVE DISORDER	Current
	OTHER SPECIFIED DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
B	SUICIDALITY	Current (Past Month) ☐ Lifetime attempt ☐ ☐ Low ☐ Moderate ☐ High
	SUICIDE BEHAVIOR DISORDER	Current ☐ (In Past Year) In early remission ☐ (1 - 2 Years Ago) In remission ☐ (> 2 Years Ago)
C	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past
	SUBSTANCE- / MEDICATION-INDUCED BIPOLAR DISORDER AND RELATED DISORDER	Current (2 weeks) Past

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	BIPOLAR DISORDER AND RELATED DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	OTHER SPECIFIED BIPOLAR DISORDER AND RELATED DISORDER	Current (2 weeks) Past
	UNSPECIFIED BIPOLAR AND RELATED DISORDER	Current (2 weeks) Past
D	PANIC DISORDER	Current (Past Month) Lifetime
E	AGORAPHOBIA	Current
F	SOCIAL ANXIETY DISORDER (Social Phobia) Performance only type ☐	Current (Past Month)
FA	SPECIFIC PHOBIA	Current
	SUBSTANCE- / MEDICATION-INDUCED ANXIETY DISORDER	Current
	ANXIETY DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	SUBSTANCE- / MEDICATION-INDUCED OBSESSIVE- COMPULSIVE DISORDER AND RELATED DISORDER	Current (2 weeks) Past
	OBSESSIVE-COMPULSIVE AND RELATED DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	HOARDING DISORDER	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
HAS	ACUTE STRESS DISORDER	Current (2 weeks)
I	ALCOHOL USE DISORDER	Past 12 Months
IL	ALCOHOL USE DISORDER	Lifetime
J	SUBSTANCE USE DISORDER	Past 12 Months
JL	SUBSTANCE USE DISORDER (Non-alcohol)	Lifetime
K	ANY PSYCHOTIC DISORDER	Current Lifetime
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER Bipolar type ☐ Depressive type ☐	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	SUBSTANCE- / MEDICATION-INDUCED PSYCHOTIC DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO ANOTHER MEDICAL CONDITION	Current Lifetime

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	OTHER SPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER	Current Lifetime
	UNSPECIFIED SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDER	Current Lifetime
L	ANOREXIA NERVOSA	Current (Past 3 Months)
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
M	BULIMIA NERVOSA	Current (Past 3 Months)
MB	BINGE-EATING DISORDER	Current (Past 3 Months)
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	SUBSTANCE- / MEDICATION-INDUCED GAD	Current
	GAD DUE TO ANOTHER MEDICAL CONDITION	Current
O	SOMATIC SYMPTOM DISORDER	Current
P	ILLNESS ANXIETY DISORDER	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	INTERMITTENT EXPLOSIVE DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Children /Adolescents)
	ADHD COMBINED PRESENTATION ☐	
	ADHD PREDOMINANTLY INATTENTIVE PRESENTATION ☐	
	ADHD PREDOMINANTLY HYPERACTIVE / IMPULSIVE PRESENTATION ☐	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED PRESENTATION ☐	
	ADHD PREDOMINANTLY INATTENTIVE PRESENTATION ☐	
	ADHD PREDOMINANTLY HYPERACTIVE / IMPULSIVE PRESENTATION ☐	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	ADJUSTMENT DISORDERS	Current
W	BORDERLINE PERSONALITY DISORDER	Current
X	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT	
Y	ANTISOCIAL PERSONALITY DISORDER	Lifetime

For Schizophrenia and psychotic disorder studies and for psychotic disorder subtyping in clinical settings, use the MINI for Psychotic Disorders instead of the standard MINI. For many clinical settings this level of psychotic disorder subtyping detail is not necessary and the standard MINI is sufficient.

For children and adolescents, use the MINI Kid or the MINI Kid Parent of the MIN Kid for Psychotic Disorders.

A computerized version of the MINI is available. For information on the availability and licensing of any version of the MINI, whether computerized or paper / pdf versions, contact David Sheehan MD MBA at davidvsheehan@gmail.com

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CLAIMS

1. A method of treating negative symptoms of schizophrenia in a patient having schizophrenia and as having clinically stable positive symptoms, comprising administering to the patient therapeutically effective amounts of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) and quinidine sulfate (Q).

2. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient d6-DM in a 27 mg to 54 mg dose twice daily and Q in a 4 mg to 7.5 mg dose twice daily.

3. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient d6-DM in a 30 mg to 45 mg dose twice daily and Q in a 4 mg to 6 mg dose twice daily.

4. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient d6-DM in a 34 mg to 42.63 mg dose twice daily and Q in a 4.9 mg dose twice daily.

5. A method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

6. A method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

7. A method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility.

8. The method of claim 7, wherein the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6).

9. The method of claim 7 or 8, wherein the patient has been assessed as having a total PANSS negative subscale score (N1 to N7) of greater than or equal to 18.

10. A method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility.

11. The method of claim 10, wherein the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6).

12. The method of claim 10 or 11, wherein the patient has been assessed as having a total PANSS Marder negative factors score of greater than or equal to 20.

13. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an atypical antipsychotic, wherein the patient has been treated with the atypical antipsychotic for at least 3 months prior to treatment with d6-DM and Q and the dose of the atypical antipsychotic has been stable for at least 1 month prior to treatment with d6-DM and Q.

14. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an antidepressant, wherein the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to treatment with d6-DM and Q.

15. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with a hypnotic, wherein the dose of the hypnotic has been stable for at least 1 month prior to treatment with d6-DM and Q.

16. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with lorazepam up to a total

dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation, wherein the dose of the lorazepam has been stable for at least 1 month prior to treatment with d6-DM and Q.

17. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs).

18. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with clozapine.

19. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

20. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with levodopa.

21. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a typical antipsychotic.

22. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an agent that:

(a) increases plasma levels of quinidine;

(b) is metabolized by CYP2D6;

(c) is related to quinidine;

(d) produces serotonin syndrome when co-administered with dextromethorphan;

(e) decreases plasma levels of dextromethorphan and quinidine;

(f) is clozapine; or

(g) is a typical antipsychotic.

23. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an anticholinergic medication.

24. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

25. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have myasthenia gravis.

26. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have schizoaffective disorder.

27. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have bipolar disorder.

28. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

29. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

30. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a concurrent clinically significant or unstable systemic disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

31. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a suicide risk.

32. The method of claim 31, wherein suicide risk is determined by one or more of the following:

(a) judgment of the prescribing doctor;

(b) the patient answers yes on the Columbia Suicide Severity Rating Scale (C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without a specific plan) and the patient's most recent episode meeting this C-SSRS Item 4 occurred within six months;

(c) the patient answers yes on the C-SSRS Suicidal Behavior Item 5 (active suicidal ideation with specific plan and intent) and the patient's most recent episode meeting this C-SSRS Item 5 occurred within six months; and

(d) the patient answers yes on any of the 5 on the C-SSRS Suicidal Behavior Items (active attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and the patient's most recent episode meeting any of these C-SSRS Items occurred within two years prior to treatment.

33. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a cardiovascular history of any one or more of:

(a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes;

(b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing;

(c) family history of congenital QT interval prolongation syndrome; and

(d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia.

34. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

35. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

36. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

37. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

38. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein

during the first week of treatment, the d6-DM is administered in a 24 mg dose once daily and the Q is administered in a 4.9 mg dose once daily;

during the second week of treatment, the d6-DM is administered in a 24 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and

during the remainder of the treatment, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

39. A method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein

during the first three days of treatment, the d6-DM is administered in a 28 mg dose once daily and the Q is administered in a 4.9 mg dose once daily;

during the next four days of treatment, the d6-DM is administered in a 28 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and

during the remainder of the treatment, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

40. The method of any one of claims 1 to 39, wherein the patient is further administered an atypical antipsychotic other than clozapine.

41. The method of any one of claims 1 to 40, wherein the patient is a male or female patient from 18 to 60 years of age.

42. The method of any one of claims 1 to 41, wherein the patient is a female of childbearing potential.

43. The method of claim 42, wherein the patient:

(a) has a negative urine pregnancy test;

(b) is not nursing or planning a pregnancy for the duration of treatment through 30 days after the last dose; and

(c) is abstinent or willing to use a method of birth control prior to treatment, and to continue with the same method until 28 days after the last dose.

44. The method of any one of claims 1 to 43, wherein the patient does not have hypersensitivity to dextromethorphan, quinidine, an opiate drug, d6-DM, Q, or any ingredient thereof.

45. The method of any one of claims 1 to 44, wherein the patient does not have allergy or hypersensitivity to one or more medications.

46. The method of any one of claims 1 to 45, wherein the patient does not have one or more clinically significant laboratory abnormalities, one or more safety values of clinical concern, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper limit of normal, as determined by the prescribing doctor.

47. The method of any one of claims 1 to 46, wherein the patient has been diagnosed as having schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia.

48. The method of claim 47, wherein the diagnosis based on the DSM criteria has been confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.).

49. The method of any one of claims 1 to 48, wherein the treatment results in an at least 20% decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

50. The method of any one of claims 1 to 49, wherein the treatment results in an at least 2 point decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

51. The method of any one of claims 1 to 3 or 5 to 50, wherein the d6-DM is administered in a dose of 34 mg to 42.63 mg twice daily and the Q is administered in a dose of 4.9 mg twice daily.

52. The method of claim 4 or 51, wherein the d6-DM is administered in a 34 mg dose twice daily.

53. The method of claim 4 or 51, wherein the d6-DM is administered in a 42.63 mg dose twice daily.

54. The method of any one of claims 1 to 53, further comprising treating prosocial factors by the administration of the d6-DM and the Q.