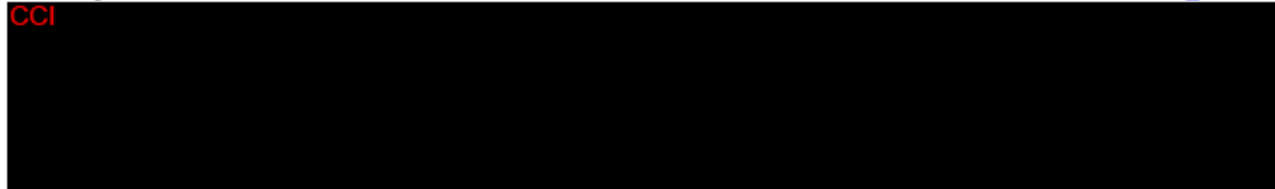


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**PROTOCOL TITLE:**

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-arm Study to Assess the Efficacy, Safety, and Tolerability of AVP-786 (Deudextromethorphan Hydrobromide [d6-DM]/Quinidine sulfate [Q]) for the Treatment of Negative Symptoms of Schizophrenia**

**Protocol:** 18-AVP-786-207 Amendment 3

**EudraCT No.:** 2021-001352-33

**IND:** 124525

**Sponsor:** Otsuka Pharmaceutical Development  
& Commercialization, Inc.

**Date:** 31 March 2022

**Drug:** AVP-786 (deudextromethorphan  
hydrobromide [d6-DM]/quinidine sulfate [Q])

**Version:** 4.0  
**Supersedes Version:** 3.0

**Immediately Reportable Event**

Syneos Health

Fax: CCI

Email: CCI

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

2440 Research Blvd

Rockville, MD 20850, United States

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## PROTOCOL AGREEMENT

### Protocol Title:

A multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of negative symptoms of schizophrenia

### Protocol Number: 18-AVP-786-207 – Amendment 3

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The signatures of the principal investigator and representative of the sponsor below constitute their approval of this protocol and further provide the necessary assurances that:

1. This study will be conducted according to Good Clinical Practice (GCP) and to all stipulations, as specified in both clinical and administrative sections of the protocol including the Declaration of Helsinki.
2. The conduct and results of this study will be kept confidential, and the electronic case report forms (eCRFs) and other pertinent data will become the property of OPDC Pharmaceuticals.
3. The protocol contains all necessary information required to conduct the study, as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC/EC).
4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (CFR) (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by OPDC or its representatives, the United States (US) Food and Drug Administration (FDA), or other regulatory agencies if applicable.

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

Principal Investigator Name: \_\_\_\_\_

\_\_\_\_\_  
OPDC Representative Signature

\_\_\_\_\_  
Date

OPDC Representative: PPD

Senior Director, Global Clinical Development

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## SYNOPSIS

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| <b>Name of Sponsor/Company:</b><br>Otsuka Pharmaceutical Development & Commercialization, Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     |
| <b>Name of Investigational Product:</b><br>AVP-786                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |
| <b>Name of Active Ingredient:</b><br>Deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                     |
| <b>Title of Study:</b><br>A multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of negative symptoms of schizophrenia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     |
| <b>Study center(s):</b> Approximately 60 centers in North America and Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                     |
| <b>Studied period (years):</b><br>Estimated date first patient enrolled: 1Q 2019<br>Estimated date last patient completed: 4Q 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Phase of development:</b><br>2/3 |
| <b>Objectives:</b><br>The primary objective of the study is to evaluate the efficacy, safety, and tolerability of AVP-786, as compared with placebo, for the treatment of negative symptoms of schizophrenia. The secondary objective is to evaluate the effects of AVP-786, as compared with placebo, on global assessments of severity and improvement of negative symptoms of schizophrenia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                     |
| <b>Methodology:</b><br>This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 for treatment of negative symptoms of schizophrenia.<br>The study consists of an up to 4-week Screening period, a 15-week double-blind treatment period, and a 30-day follow-up period. After Screening, eligible patients will be randomized to receive either AVP-786 or matching placebo capsules.<br>Patients randomized to AVP-786 will begin a one-week titration period in which they will receive a dose of d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) every morning and a dose of placebo every evening for the first 3 days, followed by AVP-786-28/4.9 twice daily (BID) for the next 4 days. Following this one-week titration period, patients will then receive d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) administered orally BID for the remaining 14 weeks of the double-blind treatment period.<br>An interim analysis of efficacy data is planned during the course of the trial, and will be performed by an independent Data Monitoring Committee (DMC). CCI<br><div style="background-color: black; height: 20px; width: 100%;"></div> |                                     |

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**Assessments and Visits:**

Patients will attend clinic visits at Screening, Visit 1 (Day 1), and at Weeks 3, 6, 9, 12, and 15, or Early termination (ET). A phone call will occur at Weeks 1, 4, 7, 10, 13, and 30 days after the Week 15 or ET visit. Study procedures will be performed at each visit as outlined in [Table 2](#).

**Number of patients (planned):**

Up to 370 patients will be enrolled.

**Diagnosis and main criteria for inclusion:****Inclusion Criteria:**

1. Patients 18 to 60 years of age, inclusive, at time of informed consent
2. Patients who meet the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM-V) diagnostic criteria for schizophrenia confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I) Version 7.0.2 with onset at least 1 year before Screening, and there have been no inpatient psychiatric hospitalization or acute exacerbations in the past 12 weeks prior to Screening. Patients who have been hospitalized within the last 12 weeks before Screening for social reasons will be allowed upon consultation with the Medical Monitor, but currently hospitalized patients will be excluded.
3. Patients are required to have been in a stable living situation for at least 4 weeks before Screening.
4. Patients should be treated with a second-generation atypical antipsychotic drug (SGA) including long-acting injectable (LAI) treatments, other than clozapine, within the dose range recommended according to the local Prescribing Information for at least 4 weeks prior to Screening and expected to remain stable throughout the study. Patients 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 24 weeks, in the judgment of the Investigator.
6. Patients must have the following scores at Screening and Visit 1:
  - a.  $\leq 4$  on the Positive and Negative Syndrome Scale (PANSS) items P1: delusions; P3: hallucinations; P6: suspiciousness/persecution; and P7: hostility; and
  - b.  $\geq 4$  (moderate) on any 2, or  $\geq 5$  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. Patients of childbearing potential who are sexually active must use an effective method of birth control for at least 1 month prior to the Baseline, during participation in the study, and for at least 30 days after the last dose of study drug. The following should be taken into consideration:
  - Patients of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: 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

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abstinence (eg, 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.

- Patients who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 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.
  - Patients who are lactating, pregnant, or plan to become pregnant are excluded.
8. Concomitant use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine, sertraline, citalopram), the norepinephrine and dopamine reuptake inhibitor bupropion, and serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone) are allowed as long as the dose has been stable for 4 weeks prior to Visit 1, remains stable throughout the study (including paroxetine, a cytochrome P450 [CYP] 2D6 substrate), within the dose range recommended according to the local Prescribing Information.
  9. Concomitant use of hypnotics at bedtime (eg, zolpidem at a dose of 5 to 10 mg or equivalent given the dose range recommended according to the local Prescribing Information) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 4 weeks prior to Visit 1 and expected to remain stable during the study.
  10. [Inclusion Criterion #10 was removed in Protocol Amendment 1].
  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 (eg, 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).
  14. Patients must meet an additional predetermined blinded eligibility criterion.

#### **Exclusion Criteria:**

Patients will not be enrolled in the study if they meet any of the following criteria:

1. Patients with current major depressive disorder (MDD) and/or a Calgary Depression Scale for Schizophrenia (CDSS) score  $\geq 6$  at Screening or Visit 1.
2. Patients with a diagnosis of schizoaffective disorder or bipolar disorder.
3. Patients with a history of clozapine use within 12 weeks prior to Visit 1 or expected use during the study.

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4. [Exclusion Criterion #4 was removed in Protocol Amendment 3.]
5. Patients who score a  $> 3$  on the sum of the first eight items of the Simpson-Angus Scale (SAS) during Screening or Visit 1.
6. Patients treated with any typical antipsychotic (eg, haloperidol, thiorazine, etc.) within 12 weeks prior to Visit 1 or expected use during the study.
7. Patients using anticholinergic medications within 4 weeks prior to Visit 1 for treatment of adverse reaction associated with antipsychotic medications.
8. Patients using levodopa within 4 weeks prior to Visit 1 or expected use during the study.
9. Patients with undetectable levels of SGA at Screening. Patients with subtherapeutic levels of SGA at Screening will be reviewed by the Medical Monitor for eligibility.
10. Benzodiazepine use within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 1 with the exception of lorazepam if used for short-term or 'as needed' treatment of behavioral disturbances (agitation, anxiety, or restlessness) in doses up to 4 mg per day and not exceeding 3 days in a 7-day period.
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 12 weeks prior to Visit 1.
15. Patients who have ever received d6-DM co-administered with Q or were enrolled in any prior clinical study with AVP-786.

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16. Patients with myasthenia gravis (a contraindication for Q).
17. Patients treated with monoamine oxidase inhibitors (MAOIs) within 2 weeks prior to Visit 1 or expected use during the study and up to 2 weeks post study drug discontinuation.
18. Patients who have been taking prohibited concomitant medications (as specified in the protocol) 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 (protocol includes guidance for retesting).
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 of Screening or Visit 1, **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 of Screening or Visit 1, **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 of Screening or Visit 1, **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, repetitive transcranial magnetic stimulation or deep brain stimulation in the past year prior to Screening.
26. Women who are lactating, pregnant, or plan to become pregnant.
27. Patient has previously received any other investigational drug (either approved or unapproved) or has participated in other interventional (drug or device) clinical study within 4 weeks of Visit 1.  
  
Patient is found to be a “Virtually Certain” match in the Clinical Trial Subject Database (CTSdatabase; US patients only) with a patient who has participated in another interventional drug or device study within 4 weeks of Visit 1.

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**Investigational product, dosage and mode of administration:**

AVP-786 is provided as an immediate release, blue, opaque, printed hard gelatin capsule (size 3) containing the active ingredients d6-DM and Q. The inactive ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate.

Active capsules will contain AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) or AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg).

Matching AVP-786 placebo contains only the inactive ingredients.

Patients randomized to AVP-786 will begin a one-week titration period in which they will receive a dose of AVP-786-28/4.9 every morning and a dose of placebo every evening for the first 3 days, followed by AVP-786 -28/4.9 BID for the next 4 days. Following this one-week titration period, patients will then receive AVP-786-42.63/4.9 administered orally BID for the remaining 14 weeks of the treatment period.

**Duration of treatment:**

15 weeks

**Reference therapy, dosage and mode of administration:**

Matching placebo, consisting of identical-looking hard gelatin capsule containing excipients only (croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate), dosed BID (1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart).

**Criteria for evaluation:****Primary Outcome Measure**

- PANSS Marder negative factors score

**Secondary Outcome Measures**

- Negative Symptom Assessment-16 (NSA-16) Global Negative Symptom Score
- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C)

**Other Outcome Measures**

- PANSS positive subscale
- Calgary Depression Scale for Schizophrenia (CDSS)

**Pharmacokinetics (PK):**

Plasma concentrations of d6-DM, Q, and metabolites of d6-DM will be measured from samples collected post-dose on Day 22 (Week 3), pre- and post-dose on Day 64 (Week 9), and pre-dose on Day 106 (Week 15).

**Safety:**

Standard safety will be assessed by reported AEs, serious AEs (SAEs), physical and neurological examinations, vital signs, weight, pregnancy tests, clinical laboratory assessments, and resting 12-lead electrocardiograms (ECGs). In addition, the following scales will be used to assess safety:

- Columbia Suicide Severity Rating Scale (C-SSRS)

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- Abnormal Involuntary Movements Scale (AIMS)
- Barnes Akathisia Scale (BAS)
- Simpson Angus Scale for Extrapyrimal Symptoms (SAS)

#### Statistical methods:

##### Efficacy Analyses

All efficacy analyses will be based on the modified intent-to-treat (mITT) population, defined as all patients with at least one post-Baseline PANSS measurement.

The primary efficacy endpoint is the change from Baseline to Week 15 in the PANSS Marder negative factors score. For the primary estimand, hypothetical strategy will be followed for intercurrent events such as initiation of any prohibited medications. Treatment comparison will be performed by using a likelihood-based linear mixed-effects model for repeated measures (MMRM) on observed data. The model will include fixed effects for treatment, trial center, visit, treatment-by-visit interaction, and Baseline-by-visit interaction. An unstructured covariance model will be used. CCI

Secondary endpoints include change from Baseline to Week 15 for the following outcomes measures:

- The NSA-16 Global Negative Symptom Score
- PGI-S
- PGI-C

Other outcome measures include:

- PANSS positive subscale
- CDSS

##### PK Analyses

Plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be summarized descriptively.

##### Safety Analyses

Safety analyses will be based on safety population defined as all patients who are randomized and take at least one dose of study drug. It will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAEs). Summary statistics of absolute values and percentage change from Baseline for blood pressure (diastolic and systolic), heart rate, respiratory rate, and ECG parameters will be provided. All values outside a predefined normal range will be highlighted in the individual patient data listings. Laboratory parameters will be summarized via descriptive statistics and via shifts in results with respect to normal ranges between Baseline and end of treatment as increased, decreased, or no change. The C-SSRS, SAS, BAS and AIMS will be summarized via descriptive statistics and via shift tables of the number and percent of patients in each score from Baseline to end of treatment.

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#### Sample Size Calculation

The power calculation was performed assuming a normal distribution for the primary efficacy endpoint PANSS Marder factor score. The treatment effect size observed from a completed Phase 2 study (15-AVP-786-202, Sponsor data on file) was 0.40 for the 12-week single rater data. For this study, it is assumed that 80% or more patients will have a single rater for their primary efficacy assessments throughout the study and a dropout rate of 20%, similar to the Phase 2 study, which in combination, will yield a treatment effect size (AVP-786 vs. placebo) of 0.40. The planned total sample size of up to 370 patients in a 1:1 ratio will ensure no less than 85% power with 2-sided type 1 error  $\alpha = 0.05$ .

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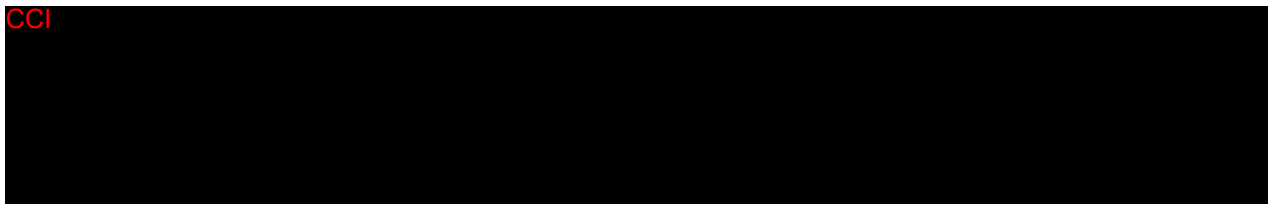
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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

| Abbreviation | Definition                                                         |
|--------------|--------------------------------------------------------------------|
| AE           | adverse event                                                      |
| AIMS         | Abnormal Involuntary Movements Scale                               |
| ALT/SGPT     | alanine aminotransferase/serum glutamic-pyruvic transaminase       |
| AST/SGOT     | aspartate aminotransferase/serum glutamic-oxaloacetic transaminase |
| AVP-786      | deudextromethorphan hydrobromide and quinidine sulfate combination |
| BAS          | Barnes Akathisia Scale                                             |
| BID          | twice-daily                                                        |
| BP           | blood pressure                                                     |
| CDSS         | Calgary Depression Scale for Schizophrenia                         |
| CFR          | Code of Federal Regulations                                        |
| CNS          | central nervous system                                             |
| C-SSRS       | Columbia Suicide Severity Rating Scale                             |
| CTSdatabase  | Clinical Trial Subject Database                                    |
| CYP2D6       | cytochrome P450 isoenzyme 2D6                                      |
| d6-DM        | deuterated (d6)-dextromethorphan (hydrobromide)                    |
| DM           | dextromethorphan (hydrobromide)                                    |
| DMC          | Data Monitoring Committee                                          |
| DSM-V        | Diagnostic and Statistical Manual of Mental Disorders, 5th Edition |
| ECG          | Electrocardiogram                                                  |
| eCRF         | electronic case report form                                        |
| EP           | European Pharmacopoeia                                             |
| EPS          | extrapyramidal symptoms                                            |
| ET           | early termination                                                  |
| FDA          | US Food and Drug Administration                                    |
| GCP          | Good Clinical Practice                                             |
| HbA1c        | glycosylated hemoglobin                                            |
| HBsAg        | hepatitis B surface antigen                                        |

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| Abbreviation | Definition                                                          |
|--------------|---------------------------------------------------------------------|
| HCvAb        | hepatitis C virus antibody                                          |
| HIV          | human immunodeficiency virus                                        |
| HR           | heart rate                                                          |
| ICF          | informed consent form                                               |
| ICH          | International Council for Harmonisation                             |
| IEC/EC       | Independent Ethics Committee                                        |
| IRB          | Institutional Review Board                                          |
| ITT          | intent-to-treat                                                     |
| IWRS         | interactive web response system                                     |
| LAI          | long-acting injectable                                              |
| MAOI         | monoamine oxidase inhibitor                                         |
| MAR          | missing at random                                                   |
| MedDRA       | Medical Dictionary for Regulatory Activities                        |
| M.I.N.I.     | Mini International Neuropsychiatric Interview                       |
| mITT         | Modified Intent-to-Treat                                            |
| MMRM         | mixed-effects model for repeated measures                           |
| <b>CCI</b>   |                                                                     |
| NSA-16       | 16-Item Negative Symptom Assessment                                 |
| OPDC         | Otsuka Pharmaceutical Development & Commercialization, Inc.         |
| PANSS        | Positive and Negative Syndrome Scale                                |
| PGI-C        | Patient Global Impression of Change                                 |
| PGI-S        | Patient Global Impression of Severity                               |
| PK           | pharmacokinetic(s)                                                  |
| Q            | quinidine (sulfate)                                                 |
| QRS          | Q-R-S complex from an ECG tracing                                   |
| QT           | QT interval from an ECG tracing                                     |
| QTc          | QT interval corrected for heart rate                                |
| QTcF         | QT interval corrected for heart rate using the Fridericia's formula |
| SAE          | serious adverse event                                               |
| SAP          | statistical analysis plan                                           |

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| Abbreviation | Definition                                      |
|--------------|-------------------------------------------------|
| SAS          | Simpson Angus Scale for Extrapyramidal Symptoms |
| SGA          | second generation antipsychotic                 |
| SNRI         | serotonin-norepinephrine reuptake inhibitor     |
| SOC          | system organ class                              |
| SSRI         | selective serotonin reuptake inhibitor          |
| TEAE         | treatment-emergent adverse event                |
| T3           | Triiodothyronine                                |
| TSH          | thyroid stimulating hormone                     |
| US           | United States                                   |
| USP          | United States Pharmacopeia                      |

## 1. INTRODUCTION

### 1.1. Schizophrenia Background

Schizophrenia is a severe mental disorder with a prevalence of approximately 1% of the world's population and is a leading cause of disability.<sup>1,2</sup> Antipsychotics are the mainstay of pharmacological management of schizophrenia. These agents are effective in treating positive symptoms, but they have limited to no efficacy in improving the negative symptoms of schizophrenia.<sup>3,4,5</sup> There is currently no Food and Drug Administration (FDA) approved medication for the treatment of negative symptoms of schizophrenia.

Negative symptoms of schizophrenia are characterized by blunted affect, alogia, anhedonia, apathy, and amotivation. Primary negative symptoms affect between 20% and 40% of individuals with schizophrenia.<sup>6</sup> Nearly 60% of stable outpatients with schizophrenia have at least one negative symptom, with a recent study finding that 41% of those with schizophrenia have two or more negative symptoms.<sup>7</sup> Negative symptoms impact the course of schizophrenia and account for much of patients' long-term morbidity.<sup>8-10</sup> Patients with more prominent negative symptoms of schizophrenia have consistently shown worse functional outcomes.<sup>11-15</sup> Negative symptoms are also associated with greater reductions in quality of life than positive symptoms<sup>16-19</sup> and with greater family/caregiver burdens.<sup>20</sup> As such, negative symptoms of schizophrenia represent a critical component of illness management and are a clinically important target for pharmacologic treatment.<sup>21-24</sup>

Individuals with schizophrenia often have severe expressive deficits in both verbal and non-verbal communication. This impairment in communication skill is considered a core feature of negative symptoms and causes severe functional deficits that results in impaired adaptive prosocial behaviors, social isolation, and withdrawal.<sup>25,26</sup> A recent study found that communication skills play a critical role in employment status among those with schizophrenia, with higher rates of employment among those with better symptomatic remission and communication skills.<sup>26</sup> Furthermore, patients suffering from expressive deficit negative symptoms of schizophrenia may turn away from social interactions and become increasingly withdrawn or isolated, further adding to the severity of their illness. Therefore, treatments that decrease the severity of these expressive and communication deficits have the potential to fundamentally improve patients' functional ability and quality of life.

Detection and monitoring of negative symptoms of schizophrenia is challenging, as symptoms are typically less clinically obvious and disruptive than positive symptoms and current rating scales have inherent limitations (eg, highly detailed, require rater training, often are not used in clinical practice). 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, eg, 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 patient's functional impairment.<sup>22,27,28</sup> Furthermore, a 2009 ISCTM consensus statement expressed preference for the PANSS negative factors that have emerged from factor analysis (eg, the PANSS Marder negative factors) over the original PANSS negative subscale, as the original subscale includes N5, difficulty with abstract thinking and N7,

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stereotyped thinking, which are felt to be outside the accepted domains of negative symptoms of schizophrenia.<sup>21</sup>

## **1.2. Rationale for Investigating AVP-786 in Patients with Negative Symptoms of Schizophrenia**

Despite drug development efforts over the past decade, a critical need remains for a safe and effective pharmacologic intervention for treating negative symptoms of schizophrenia, as no treatment has been approved for this serious condition.<sup>29,30</sup> An available treatment for negative symptoms of schizophrenia could profoundly improve patients' mental health, quality of life, caregiver burden, and reduce healthcare costs.

AVP-786 (d6-DM/Q) is a drug combination product containing deuterated (d6)-dextromethorphan (DM) hydrobromide and quinidine sulfate (Q), and is currently being developed for the treatment of certain neurological and psychiatric disorders, including the negative symptoms of schizophrenia.

In a completed Phase 2 study (15-AVP-786-202), patients treated with AVP-786 at a dose of 34/4.9 mg twice daily (BID) demonstrated greater improvements in negative symptoms of schizophrenia versus patients on placebo. AVP-786 was safe and well tolerated in Study 15-AVP-786-202, consistent with studies throughout the clinical development program of AVP-786.

## **1.3. Rationale for AVP-786 Dose and Duration of Treatment**

Patients randomized to AVP-786 will be titrated from an initial dose of AVP-786 of d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) once to twice daily during the first week of the randomized treatment period; patients will then receive d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) administered orally BID for the remainder of the randomized treatment period.

In a completed Phase 2 study (15-AVP-786-202), patients treated with AVP-786 at a dose of 34/4.9 mg BID demonstrated improvements in negative symptoms of schizophrenia versus patients on placebo. AVP-786 was safe and well tolerated in Study 15-AVP-786-202. A higher dose of AVP-786 (42.63/4.9 mg) is being explored in this study. The AVP-786-42.63/4.9 BID dose is associated with d6-DM exposures within the range of exposures shown to be generally well tolerated in Phase 1 and Phase 2 studies of AVP-786, and within the range where receptor binding is sufficient to test the effectiveness hypothesis. This higher dose of AVP-786 42.63/4.9 mg BID is currently being studied across multiple indications, without new safety signals emerging across the AVP-786 clinical development programs to date.

The 15-week treatment duration ensures exposure to the targeted dose of AVP-786 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.<sup>21</sup>

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## **2. TRIAL OBJECTIVES AND PURPOSE**

### **2.1. Primary Objective**

The primary objective of the study is to evaluate the efficacy, safety, and tolerability of AVP-786, as compared with placebo, for the treatment of negative symptoms of schizophrenia.

### **2.2. Secondary Objective**

The secondary objective of the study is to evaluate the effects of AVP-786, as compared with placebo, on global assessments of severity and improvement of negative symptoms of schizophrenia.

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### 3. INVESTIGATIONAL PLAN

#### 3.1. Overall Study Design

This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 in patients with negative symptoms of schizophrenia. The study consists of up to a 4-week Screening period, a 15-week double-blind treatment period, and a 30-day follow-up period. Up to 370 patients will be enrolled at approximately 60 study centers in North America and Europe. [Figure 1](#) illustrates the overall design of the study and [Figure 2](#) illustrates the overall design and visit schedule.

##### ***Screening Period (Day -28 to Day -1)***

The Screening period will be 28 days (4 weeks) and will begin 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***

Patients will be randomized in a 1:1 ratio to receive either AVP-786 or matching placebo capsules. Patients randomized to AVP-786 will begin a one-week titration period in which they will receive a dose of d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) every morning and a dose of placebo every evening for the first 3 days, followed by AVP-786-28/4.9 BID for the next 4 days. Following this one-week titration period, patients will then receive d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) administered orally BID for the remainder of the double-blind treatment period.

##### ***Follow-Up Period***

The 30-day follow-up period will begin following the last visit (Visit 6 [Week 15] or Early Termination [ET]). The patient will be contacted by phone at Week 19 to collect adverse event (AE) and concomitant medication information for the 30 days following the last dose of study medication. In addition to the 30-day follow-up visit, patients who terminate the study early will receive a safety follow-up phone call 7 days after the last dose of study medication.

##### **Assessments and Visits:**

Patients will attend clinic visits at Screening, Visit 1 (Day 1), and at Weeks 3, 6, 9, 12, and 15, or at ET. A phone call will occur at Week 1, Week 4, Week 7, Week 10, Week 13, and 30 days after the Week 15 or ET Visit.

Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits ([Table 2](#)). 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 measures include the PANSS positive subscale and Calgary Depression Scale for Schizophrenia (CDSS). The NSA-16 will be conducted at all visits where the NSA-16 Global is assessed, however the NSA-16 is not an efficacy measure in the study.

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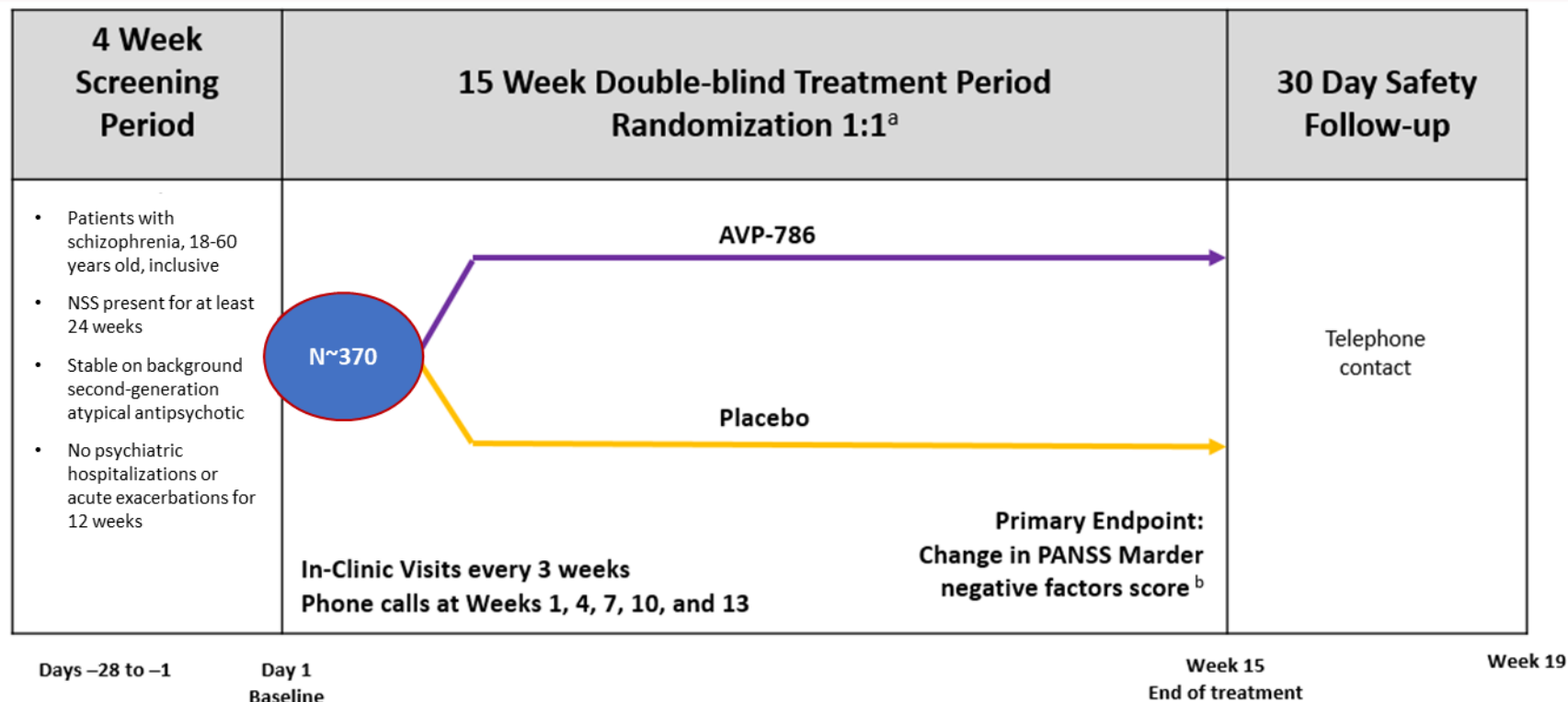
Pharmacokinetic (PK) measurements of plasma concentrations of d6-DM, Q, and certain metabolites will be measured from samples collected at Visits 2, 4, and 6 (or ET).

The safety and tolerability of AVP-786 will be 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 Extrapyrimal Symptoms (SAS).

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**Figure 1: Overall Design of Study 18-AVP-786-207**



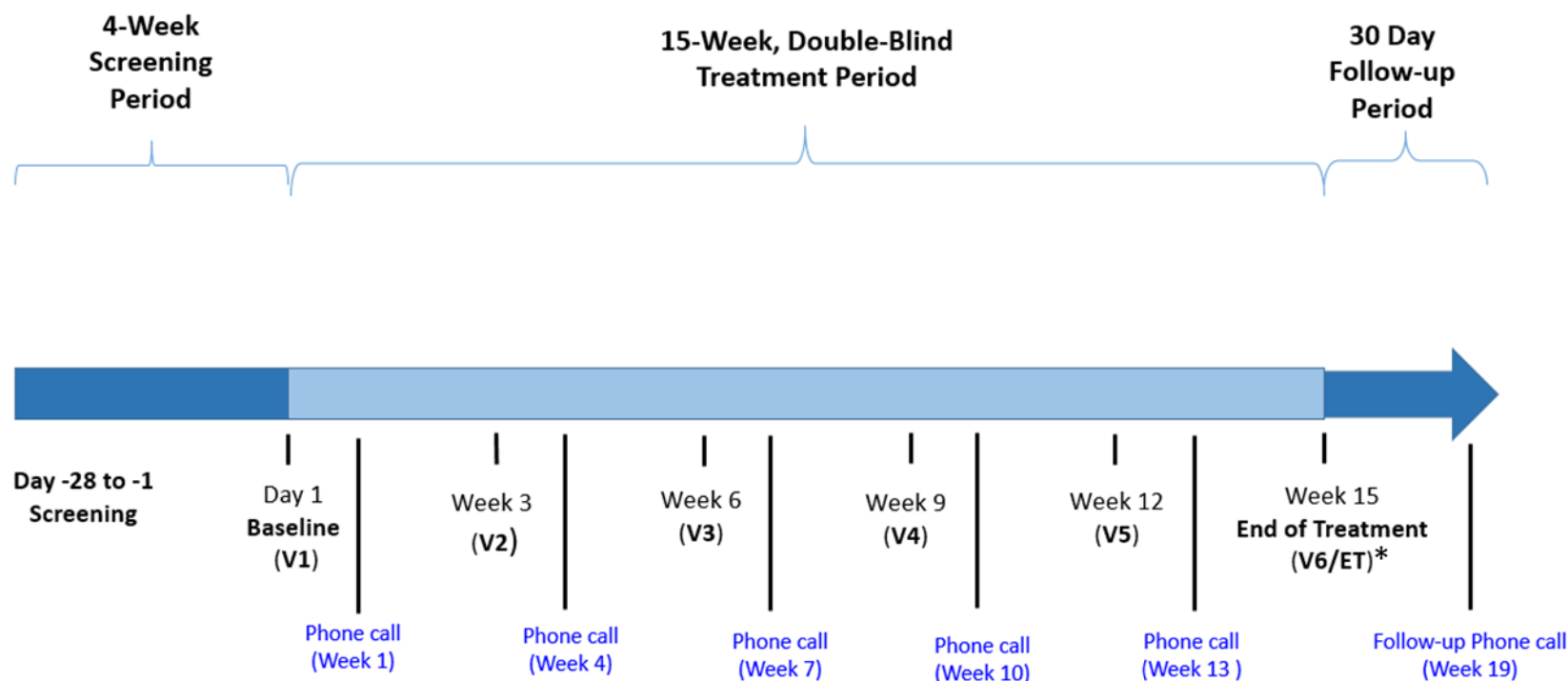
<sup>a</sup>AVP-786-28/4.9 once-daily for the first 3 days of the titration period; AVP-786-28/4.9 BID for the following 4 days and then AVP-786-42.63/4.9 BID starting on Day 8 for the remaining duration of the study

<sup>b</sup>PANSS Marder Negative Factors: N1. Blunted affect N2. Emotional withdrawal N3. Poor rapport N4. Passive/apathetic social withdrawal N6. Lack of spontaneity G7. Motor retardation G16. Active social avoidance

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**Figure 2: Overall Design and Visit Schedule for Study 18-AVP-786-207**



**Note:** All patients will take study medication twice a day (BID), one capsule in the morning and one in the evening; patients randomized to AVP-786 will have a fixed titration schedule of: AVP-786-28/4.9 once-daily for the first 3 days of the titration period; AVP-786-28/4.9 BID for the following 4 days, and then AVP-786-42.63/4.9 BID starting on Day 8 for the remaining duration of the study.

\* Patients who withdraw prior to study completion will be asked to return to the clinic to complete the evaluation specified at Visit 6 (ET) and will receive a safety follow-up phone call 7 days after the last dose of study medication (in addition to the 30-day safety follow-up phone call).

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### **3.2. Number of Patients**

Up to 370 patients will be enrolled at approximately 60 centers in North America and Europe.

### **3.3. Treatment Assignment**

Treatment during the 15-week, double-blind, treatment period (AVP-786 or placebo) will be randomly assigned (1:1 ratio) based on a randomization scheme provided by the Sponsor.

### **3.4. Study Assessments and Procedures**

A description of the study assessments and procedures is provided in [Section 10.1](#).

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## 4. SELECTION AND WITHDRAWAL OF PATIENTS

Eligible patients for this study will be 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.

The initial diagnostic assessment will be 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 7.0.2.

### 4.1. Patient Inclusion Criteria

1. Patients 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 there have been no inpatient psychiatric hospitalization or acute exacerbations in the past 12 weeks prior to Screening. Patients who have been hospitalized within the last 12 weeks before Screening for social reasons will be allowed upon consultation with the Medical Monitor, but currently hospitalized patients will be excluded.
3. Patients are required to have been in a stable living situation for at least 4 weeks before Screening
4. Patients should be treated with second-generation atypical antipsychotic drug (SGA), including long-acting injectable (LAI) treatments, other than clozapine, within the dose range recommended according to the local Prescribing Information for at least 4 weeks prior to Screening and expected to remain stable throughout the study. Patients 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 24 weeks, in the judgment of the Investigator.
6. Patients must have the following scores at Screening and Visit 1:
  - a.  $\leq 4$  on PANSS items P1: delusions; P3: hallucinations; P6: suspiciousness/persecution; and P7: hostility; and
  - b.  $\geq 4$  (moderate) on any 2, or  $\geq 5$  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. Patients of childbearing potential who are sexually active must use an effective method of birth control for at least 1 month prior to the Baseline, during participation in the study, and for at least 30 days after the last dose of study drug. The following should be taken into consideration:

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- Patients of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: 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 (eg, 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.
  - Patients who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 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.
  - Patients who are lactating, pregnant, or plan to become pregnant are excluded.
8. Concomitant use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine, sertraline, citalopram), the norepinephrine and dopamine reuptake inhibitor bupropion, and serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone) are allowed as long as the dose has been stable for 4 weeks prior to Visit 1, remains stable throughout the study (including paroxetine, a cytochrome P450 [CYP] 2D6 substrate), within the dose range recommended according to the local Prescribing Information.
  9. Concomitant use of hypnotics at bedtime (eg, zolpidem at a dose of 5 to 10 mg or equivalent given the dose range recommended according to the local Prescribing Information) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 4 weeks prior to Visit 1 and expected to remain stable during the study.
  10. [Inclusion Criterion #10 was removed in Protocol Amendment 1.]
  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 (eg, 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).
  14. Patients must meet an additional predetermined blinded eligibility criterion.

## 4.2. Patient Exclusion Criteria

Patients will not be enrolled in the study if they meet any of the following criteria:

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1. Patients with current major depressive disorder (MDD) and/or a CDSS score  $\geq 6$  at Screening or Visit 1.
2. Patients with a diagnosis of schizoaffective disorder or bipolar disorder.
3. Patients with a history of clozapine use within 12 weeks prior to Visit 1 or expected use during the study.
4. [Exclusion Criterion #4 was removed in Protocol Amendment 3.]
5. Patients who score a  $> 3$  on the sum of the first eight items of the Simpson-Angus Scale (SAS) during Screening or Visit 1.
6. Patients treated with any typical antipsychotic (eg, haloperidol, thorazine, etc.) within 12 weeks prior to Visit 1 or expected use during the study.
7. Patients using anticholinergic medications within 4 weeks prior to Visit 1 for treatment of adverse reaction associated with antipsychotic medications.
8. Patients using levodopa within 4 weeks prior to Visit 1 or expected use during the study.
9. Patients with undetectable levels of SGA at Screening. Patients with subtherapeutic levels of SGA at Screening will be reviewed by the Medical Monitor for eligibility.
10. Benzodiazepine use within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 1 with the exception of lorazepam if used for short-term or 'as needed' treatment of behavioral disturbances (agitation, anxiety, or restlessness) in doses up to 4 mg per day and not exceeding 3 days in a 7-day period.
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

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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 12 weeks prior to Visit 1.
15. Patients who have ever received d6-DM co-administered with Q or were enrolled in any prior clinical study with AVP-786.
16. Patients with myasthenia gravis (a contraindication for Q).
17. Patients treated with monoamine oxidase inhibitors (MAOIs) within 2 weeks prior to Visit 1 or expected use during the study and up to 2 weeks post study drug discontinuation.
18. Patients who have been taking prohibited concomitant medications (as specified in the protocol) 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 (protocol includes guidance for retesting).
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 of Screening or Visit 1, **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 of Screening or Visit 1, **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 of Screening or Visit 1, **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.

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25. Patients who have received electroconvulsive treatment, repetitive transcranial magnetic stimulation or deep brain stimulation in the past year prior to Screening.
26. Women who are lactating, pregnant, or plan to become pregnant.
27. Patient has previously received any other investigational drug (either approved or unapproved) or has participated in other interventional (drug or device) clinical study within 4 weeks of Visit 1.

Patient is found to be a “Virtually Certain” match in the Clinical Trial Subject Database (CTSdatabase; US patients only) with a patient who has participated in another interventional drug or device study within 4 weeks of Visit 1.

### **4.3. Patient Informant Requirements**

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. The informant may provide an assessment about the patient, as requested, to the investigator or study personnel remotely (either by telephone or video conference communication). While there are no specific requirements, Investigators will be asked to document the relationship between the informant and the patient (ie, family member, social worker, or case manager) and to specify the length of said relationship. This documentation will be reviewed by the Medical Monitor and the informant relationship will be taken into account in the eligibility process for the study.

### **4.4. CTSdatabase and Subject Database Authorization**

Clinical trial registries, such as CTSdatabase, seek to reduce duplicate enrollment by identifying duplicates before randomization. For patients in the US, at the time of providing the Informed Consent for the study, the Investigator or designee will explain the Institutional Review Board (IRB)-approved Subject Database Authorization to the patient and witness the signature.

During Screening, site staff who have received training and login information access to [www.ctsdatabase.com](http://www.ctsdatabase.com) will enter the patient study ID and authorized patient identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days, or (3) the subject matches with a subject who has pre-screened at another site.

At the last patient contact, site staff will access CTSdatabase, enter the patient Study ID and nature of the last contact (ie, Completer or ET).

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#### **4.5. Patient Withdrawal Criteria**

Patients and caregivers will be 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.

In addition, patients who present with a persistent 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, will be withdrawn from the study only after consultation with the Medical Monitor. The QTcF values will be assessed for clinical significance and recorded.

Patients who withdraw prior to study completion will be asked to return to the clinic to complete the evaluation specified at Visit 6 (ET) and will receive a safety follow-up phone call 7 days after last dose of study medication (in addition to the 30-day safety follow-up phone call).

If the patient withdraws from the study, and consent is withdrawn by the caregiver/patient's representative for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Patients who withdraw from the study will not be replaced.

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## 5. TREATMENT OF PATIENTS

### 5.1. Description of Study Drug

AVP-786 is provided as an immediate release, blue, opaque, printed hard gelatin capsule (size 3) containing the active ingredients d6-DM and Q. The inactive ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate. Each capsule of study drug will contain one of the following:

- **AVP-786-28/4.9:** 28 mg of d6-DM and 4.9 mg of Q (US Pharmacopeia [USP]; European Pharmacopoeia [EP])
- **AVP-786-42.63/4.9:** 42.63 mg of d6-DM and 4.9 mg of Q (USP; EP)
- **Matching Placebo:** identical in appearance to AVP-786 capsules; containing inactive ingredients only

Drug supplies will be provided to the study sites in blinded (double-blind), individual, prelabeled blister cards.

Study drug will be 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.

### 5.2. Administration of Study Drug

The administration of study drug during the randomized treatment period is as follows.

#### ***Double-Blind, Randomized, Treatment Period:***

Patients will be randomized in a 1:1 ratio to receive either AVP-786 or matching placebo capsules administered orally.

Patients randomized to AVP-786 will have the following fixed-titration schedule during the double-blind treatment period: AVP-786-28/4.9 every morning for the first 3 days, AVP-786-28/4.9 BID for the following 4 days, and then AVP-786-42.63/4.9 BID starting on Day 8 for the remaining 14 weeks of the double-blind treatment period.

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

#### **AVP-786 Group:**

- **Day 1-Day 3:** AVP-786-28/4.9 capsule every morning; a dose of matching placebo every evening
- **Day 4-Day 7:** AVP-786-28/4.9 capsule, BID
- **Day 8-Day 106:** AVP-786-42.63/4.9 capsule, BID

#### **Placebo Group:**

- **Day 1-Day 106:** Matching AVP-786 placebo capsule, BID

Packaging of the study drug is described in [Section 6.2](#).

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### 5.3. Concomitant Medications

Patients may not take any of the prohibited medications listed in [Section 5.3.2](#) 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 will be queried as to whether they had taken any concomitant medications and, if so, the Investigator will record the medications taken and the reasons for their use.

AVP-786 contains quinidine which is a P-glycoprotein inhibitor. Concomitant administration of quinidine 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.

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 AVP-786 due to quinidine-mediated inhibition of CYP2D6. An alternative treatment should be considered.

Due to differences in the commercial availability of allowed concomitant medications in the specific country, please contact a Medical Monitor to discuss any alternative medications not noted below.

#### 5.3.1. Allowed Concomitant Medications, Use of Hypnotics

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.

Concomitant use of hypnotics at bedtime (eg, zolpidem at a dose of 5 to 10 mg or equivalent given the dose range recommended according to the local Prescribing Information) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 4 weeks prior to Visit 1 and remains stable during the study (Inclusion Criterion 9).

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 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 sleep aid documented, including a notation of the drug name, dose, and time of administration on the electronic case report forms (eCRF).

Concomitant use of antidepressants such as SSRIs (eg, fluoxetine, sertraline, citalopram), the norepinephrine and dopamine reuptake inhibitor bupropion, and SNRIs (eg, venlafaxine, desvenlafaxine, duloxetine, vortoxetine, vilazodone) are allowed as long as the dose has been stable for 4 weeks prior to Visit 1, remains stable during the study (including paroxetine, a cytochrome P450 [CYP] 2D6 substrate), within the dose range recommended according to the local Prescribing Information.

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Lorazepam is allowed for short term use or ‘as needed’ in doses up to 4 mg per day and not to exceed 3 days in a 7-day period as a rescue medication for treatment of behavioral disturbances (agitation, restlessness, or anxiety)

- Patients using lorazepam prior to study entry should remain on the same treatment regimen for the duration of the study
- Lorazepam may not be used within 12 hours prior to an assessment visit
- Reassessment and discussion with Medical Monitor is required if needed beyond 1 week.

### 5.3.2. Prohibited Medications

Restrictions for concomitant medications (see [Appendix 1](#)) should be followed between the initial Screening visit and Visit 6 (Week 15/ET). Prohibited concomitant medications include medications that could potentially alter plasma levels of Q and/or d6-DM, or medications related to Q. Strong inducers of CYP3A4, but not moderate or weak inducers, are prohibited during the study. A list of examples of prohibited medications is provided in [Appendix 1](#).

Patients may not take any of the prohibited medications listed in [Appendix 1](#) 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.

Use of levodopa is not allowed 4 weeks prior to Visit 1 and during the study. Recreational and/or medicinal cannabis use is not allowed during the study ([Section 9.1.5.3](#) for screening strategy). Benzodiazepine use is not allowed during the study, except lorazepam for treatment of behavioral disturbances ([Section 5.3.1](#)).

### 5.4. Treatment Compliance

Each patient will be instructed to return any unused study drug and empty drug blister cards during each post-Baseline study visit. Site staff will conduct a capsule count and record the compliance on the Drug Accountability log as well as enter the information in the eCRF.

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

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

### 5.5. Randomization and Blinding

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

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Eligible patients will be randomized to receive AVP-786 capsules or matching placebo capsules in a 1:1 ratio, stratified by trial center, at Baseline (pre-dose) in a double-blind manner according to a randomization scheme devised by the Sponsor or designee and managed within an IWRS. Each patient will have a 50% chance of receiving AVP-786 during double-blind treatment.

The study drug dosing schedule is provided in [Section 5.2](#).

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## 6. STUDY DRUG MATERIALS AND MANAGEMENT

### 6.1. Study Drug

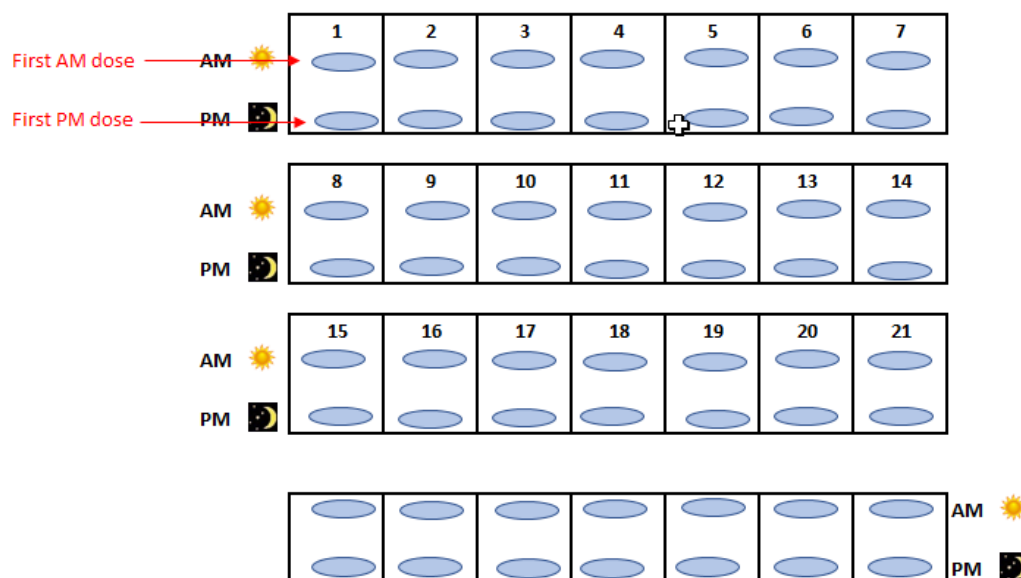
AVP-786 will be provided as an immediate release, blue, opaque, printed hard gelatin capsule (size 3) containing the active ingredient d6-DM (28 mg or 42.63 mg) and Q (4.9 mg) (USP; EP). The composition of the AVP-786 and matching placebo capsules is described in [Section 5.1](#).

### 6.2. Study Drug Packaging and Labeling

#### Packaging

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. The morning and evening doses of each day are marked with a numeric treatment day, with Day 1 the first day of dosing followed by Day 2 and all the way to Day 21. The fourth panel is the extra drug supply and does not have the treatment dosing day. In total, each blister card contains 56 capsules. See [Figure 3](#).

**Figure 3: Sample Configuration of Investigational Product Blister Card**



#### Labeling

Labels will include the protocol number, product name, medicine identification number (randomization number), an investigational drug warning, dosing instructions, storage conditions, “keep out of reach of children” statement, and company name. The blister card label will consist of 2 panels or booklet label, with 1 detachable panel that will be removed and affixed

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to the study drug Dispensing Log page at the time of dispensing. The study drug labels will comply with all applicable federal and local regulations.

### **6.3. Study Drug Storage**

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).

### **6.4. Study Drug Administration**

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

Each patient will be instructed to ingest 1 capsule of study drug orally with water BID, approximately every 12 ( $\pm$  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 will be recorded in the AiCure medication adherence monitoring platform.

All study drug will be supplied and administered in a double-blind manner throughout the 15-week treatment period.

### **6.5. Study Drug Accountability**

#### **6.5.1. Receipt of Drug Supplies**

The Investigator or designee is responsible for maintaining an inventory of each shipment of study drug supplies received and comparing it with the accompanying packing list. The Investigator or designee will verify the content of the shipment to the information on the packing list and register the shipment receipt in IWRS. Study drug supplies are for use only in this study and should not be used for any other purpose. All blister card identification numbers will be recorded and tracked at the study site using the Drug Accountability Log.

#### **6.5.2. Record of Dispensing**

Accurate recording of all study drug dispensed to patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: patient number to whom the drug was dispensed, date(s), and quantity of study drug dispensed to the patient. Additionally, the detachable panel of the 2-panel label or booklet label on each blister card will be removed and affixed to the study medication Dispensing Log page at the time of dispensing.

### **6.6. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug supplies must be inventoried on the Drug Accountability Log. All used and unused study drug supplies will be returned to the Sponsor or

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designee. If any study drug is lost or damaged, it should be indicated on the Drug Accountability Log and in IWRS.

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## 7. ASSESSMENT OF EFFICACY

Efficacy assessments will 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 Calgary Depression Scale for Schizophrenia (CDSS). These scales are described in the following sections.

### 7.1. Positive and Negative Syndrome Scale (PANSS) Marder Negative Factors Score

The PANSS is a validated clinical scale that has been extensively used as a reliable and valid measure of the negative and positive symptom of schizophrenia.<sup>31</sup> 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 item is scored for “1” (absent) to “7” (extremely severe).

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.<sup>32, 33</sup> Thus, different combinations of items are generally analyzed as factor structures to score specific aspects of the negative syndrome of schizophrenia.

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.<sup>34,35</sup> Marder investigated the five-factor solution in two pivotal controlled trials and found that risperidone produced significantly greater improvements than haloperidol on all five dimensions, with a particularly potent effect of risperidone versus 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-MATRICES Consensus Statement.<sup>36</sup>

#### *PANNS Marder Negative Factors Score*

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

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– G16: Active social avoidance

Each of the PANSS Marder negative factors correlates with one of the five main domains of negative symptoms.<sup>36</sup> PANSS item N1: blunted affect, correlates with Blunted affect; N6: lack of spontaneity and conversation flow, correlates with Alogia; N4: passive/apathetic social withdrawal; G16: active social avoidance; and N3: poor rapport are factors that correlate with Asociality. Item N2: emotional withdrawal, correlates with Anhedonia; and G7: motor retardation, correlates with both Anhedonia and Avolition.<sup>31</sup>

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

The PANSS positive subscale (P1 - P7) will also be 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.

The PANSS evaluation will be performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), Visit 5 (Day 85), and Visit 6/ET Visit (Day 106).

## **7.2. Negative Symptom Assessment-16 (NSA-16) Global Negative Symptom Score**

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 inter-rater and test-retest-reliability across languages and cultures.<sup>31,37</sup> 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 patient is to be compared is a healthy young person in their twenties.

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.<sup>38</sup>

The NSA-16 and NSA Global Negative Symptom Score evaluations will be performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), Visit 5 (Day 85), and Visit 6/ET Visit (Day 106).

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### **7.3. Patient Global Impression – Severity (PGI-S)**

The PGI-S is a 7-point (1–7), patient-rated scale used to assess the severity of the patients' illness with respect to their 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.

The PGI-S evaluation will be performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), Visit 5 (Day 85), and Visit 6/ET Visit (Day 106), and will be focused on the negative symptoms of schizophrenia.

### **7.4. Patient Global Impression – Change (PGI-C)**

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

The PGI-C evaluation will be performed at Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), Visit 5 (Day 85), and Visit 6/ET Visit (Day 106), and will be focused on the negative symptoms of schizophrenia.

### **7.5. Calgary Depression Scale for Schizophrenia (CDSS)**

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.<sup>39</sup> 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.

The CDSS evaluation will be performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 4 (Day 64), and Visit 6/ET Visit (Day 106).

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## **8. ASSESSMENT OF PHARMACOKINETICS**

Plasma concentrations of d6-DM, its metabolites (d3-DX and d3-3-MM), and Q will be measured from samples collected post-dose on Day 22 (Week 3), pre- and post-dose on Day 64 (Week 9), and pre-dose on Day 106 (Week 15). These samples will be collected per instructions provided by the sponsor.

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 will be recorded on the eCRF.

Blood samples will be 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 will be provided to the study sites by the sponsor at the time of study initiation.

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

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## 9. ASSESSMENT OF SAFETY

### 9.1. Safety Parameters

#### 9.1.1. Adverse Events and Serious Adverse Events

##### 9.1.1.1. Adverse Events

An AE is any untoward medical occurrence or unintended change (including physical, psychiatric [eg, 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 (eg, onset of menstruation occurring at a physiologically appropriate time).

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

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.

AEs will be graded on a 3-point scale and reported in detail as indicated on the eCRF:

|                  |                                                                                                  |
|------------------|--------------------------------------------------------------------------------------------------|
| <u>Mild:</u>     | easily tolerated, causing minimal discomfort and not interfering with normal everyday activities |
| <u>Moderate:</u> | sufficiently discomforting to interfere with normal everyday activities                          |
| <u>Severe:</u>   | incapacitating and/or preventing normal everyday activities                                      |

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

|                          |                                                                                                                                                                                                                                                  |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>Not related:</u>      | the event is clearly related to other factors such as the patient’s clinical state, therapeutic interventions, or concomitant medications administered to the patient                                                                            |
| <u>Unlikely related:</u> | the event is most likely produced by other factors such as the patient’s clinical state, therapeutic interventions, or concomitant medications administered to the patient; and does not follow a known response pattern to the study medication |
| <u>Possibly related:</u> | 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                                |

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patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

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 patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

#### 9.1.1.2. Serious Adverse Events

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 patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, ie, 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

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 patient or require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Pregnancy is not considered to be an AE or an SAE, but all reported pregnancies occurring during the study will be reported on the Pregnancy and Breastfeeding Exposure Form. The site should follow-up each trimester with the patient/partner until the final outcome is known (ie, normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). Should a complication occur that meets the requirements for an AE or SAE, it must be reported within 24 hours of awareness. Patients 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 awareness. Any pregnant patient must be followed until the outcome of her pregnancy is known. The pregnancy (ie, mother and fetus) must be followed-up through delivery with regard to outcome.

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

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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.

#### 9.1.1.3. Reporting Adverse Events

Patients will be queried regarding AEs at all visits post Screening. The Investigator will assess and record 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 will be 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).

The Sponsor may request additional information on certain events, such as falls. Event to Monitor data collection forms and completion guidelines will be provided for the Investigator to complete for such events. These forms should be submitted to the Sponsor as specified on the form.

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.

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. The narrative section of the form may be used to detail any treatment information.

These details must be recorded on the SAE report form that is provided. The SAE report form should be transmitted by FAX or e-mail to:

**SAE and Events to Monitor reporting by FAX or email correspondence:**

FAX: PPD

Email: PPD

Such preliminary reports will be followed by detailed descriptions later, which may include copies of hospital case reports/discharge summaries, autopsy reports, and other related documents when requested.

The IRB/IEC/EC will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

#### 9.1.2. Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1), and at the final clinic visit (Visit 6 [Week 15]). The physical examination will include assessments of

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head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination will include 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.

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.

### **9.1.3. Vital Sign Measurements**

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed at all clinic visits. Supine BP and HR will be measured after the patient has rested for at least 5 minutes in the supine position. Each measurement will be taken twice in the same position with approximately 1 minute between readings and recorded. Following the measurement of supine BP and HR, the patient will stand and a single measurement of standing BP and HR will be recorded within 1 to 3 minutes of standing.

Respiratory rate (breaths/minute) and body temperature (°F/°C) will be assessed at Screening, Day 1 (prior to dosing), and at the final clinic visit (Visit 6 [Week 15]).

Weight and height will be recorded at Screening, Day 1 (Visit 1), and Day 106 (Visit 6).

### **9.1.4. Electrocardiogram (ECG)**

A resting 12-lead ECG will be performed at Screening and each clinic visit (Visits 1, 2, 3, 4, 5, and 6); the Screening ECG will be performed in triplicate (1 minute apart). ECGs will be performed pre-dose and 1-2 hours ( $\pm 15$  minutes) post-dose at Visit 1, Visit 2, and Visit 3; ECGs at all other visits will be performed pre-dose only (Visits 4, 5, and 6).

The ECG equipment will be provided to the study center by the central reader. The ECG assessment will be recorded at the study center and will include general findings, including heart rate (beats/minute), QRS complex and PR and QTc intervals. Results will be provided by the central reader to the Investigators within 72 hours. Any ECG abnormality present at Screening will be 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.

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  $> 60$  msec at any time after randomization, will be withdrawn from the study.

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## 9.1.5. Laboratory Assessments

### 9.1.5.1. Clinical Laboratory

Clinical laboratory tests will be analyzed by a central laboratory that will provide laboratory kits and instructions to the study sites at the time of study initiation. Specimens will be appropriately processed by the central laboratory and laboratory reports will be made available to the investigator in a timely manner to ensure appropriate clinical review. The laboratory test battery will include both Screening and routine laboratory tests. The following clinical laboratory assessments will be performed at the specified visits.

#### Clinical Laboratory Tests

The following clinical laboratory tests (chemistry, hematology, and urinalysis) will be performed at Screening, Visit 1 (Day 1), Visit 2 (Day 22), Visit 4 (Day 64), and Visit 6/ET Visit (Day 106):

- **Chemistry panel** - 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, alanine aminotransferase/serum glutamic pyruvic transaminase, creatine kinase, gamma-glutamyl transferase, triglycerides, total protein, and total cholesterol; additionally, glycosylated hemoglobin (HbA1c) will be measured at Screening and Visit 6 (Day 106) or ET only
- **Hematology panel** - 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, blood, leucocyte esterase, nitrates, and microscopic appearance

The following clinical laboratory tests will be performed at Screening only:

- **Thyroid function tests** – Thyroid function will be measured by thyroid stimulating hormone (TSH) at Screening. If the TSH results are abnormal, reflex triiodothyronine (T3) and thyroxine (reflex free T4 and total T4) tests will be performed. If the thyroid function tests results are judged clinically significant by the investigator, the patient will be excluded from further study participation.

Any patient with clinically significant abnormal laboratory test results may be required by the Medical Monitor or Principal Investigator to have a repeat test 1 week later or earlier, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry.

### 9.1.5.2. Genotyping

A blood sample will be collected at Visit 1 for CYP2D6 genotyping, which will be used to classify patients as either poor, intermediate, extensive, or ultra-rapid metabolizers of d6-DM.

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#### **9.1.5.3. Drug Screen**

Urine specimens will be tested for selected drugs of abuse at Screening only. The drug screens will include, but are not limited to, the following:

- amphetamines
- barbiturates
- benzodiazepines
- cocaine
- cannabis
- opiates

Patients with a positive urine drug screen may be excluded after discussion with the Medical Monitor. Patients who have a positive drug screen for cannabis at Screening may retest for confirmation within the screening period after discussion with and permission from the Medical Monitor.

#### **9.1.5.4. Other Screening Measures**

Screens for hepatitis B and C (HBsAg, and HCVAb), and HIV antibody will be performed at Screening only; patients who test positive for HBsAg, HCV, or HIV antibody, will be excluded from the study.

Plasma levels of antipsychotics will be determined at Screening; and Weeks 3, 9, and 15.

#### **9.1.5.5. Pregnancy Testing**

Serum pregnancy tests will be performed for females of childbearing potential at Screening; urine pregnancy tests will be performed for females of childbearing potential at all other study visits. Patients with a positive pregnancy test must be discontinued from the study.

Patients who are of childbearing potential and are sexually active must use an effective method of birth control for at least 1 month prior to the Baseline, during participation in the study, and for at least 30 days after the last dose of study drug. The following requirements must be met:

- Patients of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: 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 (eg, 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.
- Patients who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 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.

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- Patients who are lactating, pregnant, or plan to become pregnant are excluded.

#### **9.1.6. Safety Scales**

The AIMS, BAS, SAS, and C-SSRS will be assessed for purposes of safety, and are briefly described in the following sections.

##### **9.1.6.1. Abnormal Involuntary Movement Scale (AIMS)**

The AIMS 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.

The AIMS evaluation will be performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 4 (Day 64), and Visit 6/ET Visit (Day 106).

##### **9.1.6.2. Barnes Akathisia Scale (BAS)**

The BAS 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 will be performed at Visit 1 (Day 1), Visit 2 (Day 22), Visit 4 (Day 64), and Visit 6/ET Visit (Day 106).

##### **9.1.6.3. Simpson Angus Scale for Extrapyrimal Symptoms (SAS)**

The SAS is composed of 10 items and is used to assess pseudo-parkinsonism. 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.

The SAS evaluation will be performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 4 (Day 64), and Visit 6/ET Visit (Day 106).

##### **9.1.6.4. Columbia Suicide Severity Rating Scale (C-SSRS)**

The C-SSRS 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.

Suicidality will be 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

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suicide events or ideation within a specified time period prior to entry into the study, will be 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 4.2](#), Exclusion Criteria). The “Since Last Visit” C-SSRS form will also be completed at visits after Screening.

The C-SSRS evaluation will be performed at Screening (Day -28 to -1), Visit 1 (Day 1), Visit 2 (Day 22), Visit 3 (Day 43), Visit 4 (Day 64), Visit 5 (Day 85), and Visit 6/ET Visit (Day 106).

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## **10. SCHEDULE OF EVALUATIONS AND PROCEDURES**

A schedule of evaluations and procedures is provided in [Table 2](#).

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**Table 2: Schedule of Evaluations and Visits**

|                                                       |                          |                  | Study Treatment Period |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
|-------------------------------------------------------|--------------------------|------------------|------------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|-------------------------------------------|---------------------------------|
| Procedure                                             | Visit:                   | Screening        | Visit 1                | Phone <sup>2</sup> | Visit 2 <sup>1</sup> | Phone <sup>2</sup> | Visit 3 <sup>1</sup> | Phone <sup>2</sup> | Visit 4 <sup>1</sup> | Phone <sup>2</sup> | Visit 5 <sup>1</sup> | Phone <sup>2</sup> | Visit 6 <sup>1</sup><br>/ET <sup>11</sup> | Post Exit<br>Phone <sup>2</sup> |
|                                                       | Study Day:               | Day -28<br>to -1 | Day 1                  | Day 8              | Day 22               | Day 29             | Day 43               | Day 50             | Day 64               | Day 71             | Day 85               | Day 92             | Day 106                                   | Day 136                         |
|                                                       | End of<br>Study<br>Week: | Week -4<br>to -1 | Week 0                 | Week 1             | Week 3               | Week 4             | Week 6               | Week 7             | Week 9               | Week 10            | Week 12              | Week 13            | Week 15                                   | Week 19                         |
| Obtain Informed Consent                               |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| CTSDatabase Entry*                                    |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    | X                                         |                                 |
| Medical<br>History/Psychiatric History                |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| M.I.N.I. Exam                                         |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| Review Inclusion and<br>Exclusion Criteria            |                          | X                | X                      |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| Document Patient's<br>Informant Information           |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| NSA-16 and NSA Global                                 |                          |                  | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                         |                                 |
| PANSS                                                 |                          | X                | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                         |                                 |
| PGI-S                                                 |                          |                  | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                         |                                 |
| PGI-C                                                 |                          |                  |                        |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                         |                                 |
| Enrollment/Randomization                              |                          |                  | X                      |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| AiCure (Patient Training)                             |                          |                  | X                      |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                           |                                 |
| Physical and Neurological<br>Examinations             |                          | X                |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    | X                                         |                                 |
| Resting 12-lead ECG <sup>3</sup>                      |                          | X                | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                         |                                 |
| Chemistry, Hematology,<br>and Urinalysis <sup>4</sup> |                          | X                | X                      |                    | X                    |                    |                      |                    | X                    |                    |                      |                    | X                                         |                                 |

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**Table 2: Schedule of Evaluations and Visits (Continued)**

|                                                            |                    |                | Study Treatment Period |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                        |                              |
|------------------------------------------------------------|--------------------|----------------|------------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------------------------|------------------------------|
| Procedure                                                  | Visit:             | Screening      | Visit 1                | Phone <sup>2</sup> | Visit 2 <sup>1</sup> | Phone <sup>2</sup> | Visit 3 <sup>1</sup> | Phone <sup>2</sup> | Visit 4 <sup>1</sup> | Phone <sup>2</sup> | Visit 5 <sup>1</sup> | Phone <sup>2</sup> | Visit 6 <sup>1</sup> /ET <sup>11</sup> | Post Exit Phone <sup>2</sup> |
|                                                            | 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 92             | Day 106                                | Day 136                      |
|                                                            | 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 13            | Week 15                                | Week 19                      |
| Pregnancy Test <sup>5</sup>                                |                    | X              | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                      |                              |
| Urine Drug Screen                                          |                    | X              |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                        |                              |
| Hepatitis B, C; HIV antibody                               |                    | X              |                        |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                        |                              |
| Lab -CYP2D6 <sup>6</sup>                                   |                    |                | X                      |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                        |                              |
| Pharmacokinetic sampling <sup>7</sup>                      |                    |                |                        |                    | X                    |                    |                      |                    | X                    |                    |                      |                    | X                                      |                              |
| Plasma Antipsychotic Levels                                |                    | X              |                        |                    | X                    |                    |                      |                    | X                    |                    |                      |                    | X                                      |                              |
| Review of Adverse Events                                   |                    |                | X                      | X                  | X                    | X                  | X                    | X                  | X                    | X                  | X                    | X                  | X                                      | X                            |
| Review Concomitant Medications                             |                    | X              | X                      | X                  | X                    | X                  | X                    | X                  | X                    | X                  | X                    | X                  | X                                      | X                            |
| Record Vital Signs/Weight <sup>8</sup>                     |                    | X              | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                      |                              |
| CDSS                                                       |                    | X              | X                      |                    | X                    |                    |                      |                    | X                    |                    |                      |                    | X                                      |                              |
| Extrapyramidal Symptoms Assessment Scales (AIMS, BAS, SAS) |                    | X <sup>9</sup> | X                      |                    | X                    |                    |                      |                    | X                    |                    |                      |                    | X                                      |                              |
| C-SSRS                                                     |                    | X              | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                      |                              |
| Dispense Study Drug                                        |                    |                | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    |                                        |                              |

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**Table 2: Schedule of Evaluations and Visits (Continued)**

|                                        |                    |               | Study Treatment Period |                    |                      |                    |                      |                    |                      |                    |                      |                    |                                        |                              |
|----------------------------------------|--------------------|---------------|------------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|----------------------------------------|------------------------------|
| Procedure                              | Visit:             | Screening     | Visit 1                | Phone <sup>2</sup> | Visit 2 <sup>1</sup> | Phone <sup>2</sup> | Visit 3 <sup>1</sup> | Phone <sup>2</sup> | Visit 4 <sup>1</sup> | Phone <sup>2</sup> | Visit 5 <sup>1</sup> | Phone <sup>2</sup> | Visit 6 <sup>1</sup> /ET <sup>11</sup> | Post Exit Phone <sup>2</sup> |
|                                        | 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 92             | Day 106                                | Day 136                      |
|                                        | 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 13            | Week 15                                | Week 19                      |
| Dose in Clinic (first dose of the day) |                    |               | X                      |                    | X                    |                    | X                    |                    | X                    |                    | X                    |                    | X                                      |                              |
| Review Returned Unused Study Drug      |                    |               |                        | X <sup>10</sup>    | X                    | X <sup>10</sup>    | X                    | X <sup>10</sup>    | X                    | X <sup>10</sup>    | X                    | X <sup>10</sup>    | X                                      |                              |

\*US patients/sites only

<sup>1</sup> Visit 2 has a  $\pm 3$  day window; Visits 3-6 have a  $\pm 6$  day window.

<sup>2</sup> Telephone calls will have a +3 day window.

<sup>3</sup> Triplicate ECGs at Screening only. Electrocardiogram will be performed pre-dose and 1-2 hours ( $\pm 15$  minutes) post-dose at Visit 1, Visit 2, and Visit 3; ECGs at all other visits will be performed pre-dose only (Visits 4, 5, and 6).

<sup>4</sup> Fasting glucose and lipids will be measured at Screening, Visits 2, 4 and Visit 6/ ET visit for patients who withdraw prior to study completion. HbA1c will be measured at Screening and Visit 6 / ET. Thyroid function tests will be measured at Screening only.

<sup>5</sup> Urinary (beta-hCG) test will be performed for all females of childbearing potential (serum beta-hCG at Screening only).

<sup>6</sup> Blood samples for CYP2D6 genotyping will be taken at Visit 1.

<sup>7</sup> Plasma concentrations of d6-DM, its metabolites (d3-DX and d3-3-MM), and Q will be measured from samples collected post-dose on Day 22 (Week 3), pre- and post-dose on Day 64 (Week 9), and pre-dose on Day 106 (Week 15). Samples collected after efficacy assessments are completed.

<sup>8</sup> Orthostatic BP and HR measurements will be performed (in duplicate) at all clinic visits (See [Section 9.1.3](#)). Respiratory rate and body temperature will be measured at Screening, Day 1 (Visit 1), and Day 106 (Visit 6)/ET. Weight and height will be measured at Screening, Day 1 (Visit 1), and Day 106 (Visit 6).

<sup>9</sup> Only the SAS will be measured at Screening (AIMS and BAS not measured at Screening).

<sup>10</sup> Patient will be asked if they have taken their medications as directed during telephone calls at Days 8, 29, 50, 71, and 92.

<sup>11</sup> Patients who withdraw prior to study completion (ET) will be asked to return to the clinic to complete the Visit 6 assessments, and will receive a follow-up phone call 7 days after the last dose of study medication (for adverse events and concomitant medications information). These patients will also receive the safety follow-up phone call 30 days after the last dose of study medication.

## 10.1. Description of Study Procedures

At each study visit, a member of the study staff will be required to enter information into the IWRS database regarding patient data and pre-defined study assessment results. Further instructions will be provided in the Interactive Response Technology Site Manual.

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 will all be 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. For US patients, 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 (see [Section 4.4](#)).

### 10.1.1. Screening Visit (Days -28 to -1)

The following procedures will be performed at Screening within 28 days prior to Day 1.

1. The Investigator or delegated site staff will provide the patients with informed consent documents and will 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. For US patients, authorization form completed and patient information will be entered into the CTSdatabase.
3. A qualified and certified rater will administer the PANSS.
4. Psychiatric history will be recorded and M.I.N.I. exam will be conducted.
5. An adequately trained and certified rater will administer the CDSS to assess for symptoms of depression.
6. The Investigator (or qualified designee) who is adequately trained will complete 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) will be reviewed and recorded.
8. Inclusion and exclusion criteria (eligibility form) will be reviewed.
9. Detailed information on the patient’s relationship with their informant will be collected and documented.
10. Vital signs will be measured and recorded (orthostatic BP and HR [in duplicate] [See [Section 9.1.3](#)], respiratory rate, and body temperature); weight and height will also be recorded. If any vital sign measurements are potentially exclusionary, repeat the vital sign measurements to confirm the reproducibly prior to excluding a patient for safety reasons.

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11. Physical and neurological examinations will be conducted.
12. An adequately trained and experienced clinician will administer the SAS to assess for EPS.
13. Resting 12-lead ECGs will be performed in triplicate (1 minute apart).
14. Blood and urine specimens will be collected for clinical laboratory assessments (chemistry, including fasting glucose, lipids, TSH, and HbA1c; hematology; and urinalysis). If clinical laboratory assessments are potentially exclusionary, the patient can be retested after discussion with and permission from the medical monitor to confirm reproducibility.
15. Blood specimen will be collected for assessment of plasma antipsychotic levels.
16. A serum pregnancy test will be performed on all females of childbearing potential.
17. Urine specimen will be collected for drug screening. If the drug screen is positive for cannabis use, the patient can be retested within 7 days of the Screening visit after discussion with and permission from the Medical Monitor.
18. Blood specimen will be collected for hepatitis B and C (HBsAg and HCAb) and HIV antibody screening.
19. Review assessments to verify that patients are eligible to continue study participation.

Following Screening procedures for assessment of inclusion and exclusion criteria, a protocol eligibility form will be submitted to the Medical Monitor for approval. Patients deemed eligible by the investigator and the Medical Monitor will 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, will be discontinued (not randomized).

#### **10.1.2. Double-Blind Study Treatment Period**

##### **10.1.2.1. Visit 1 (Randomization; Day 1 [Baseline])**

In the morning of Visit 1 (Day 1), the following procedures and assessments will be completed.

##### Pre-dose:

1. A qualified and certified rater will administer the NSA-16, NSA-16 Global, PANSS, and PGI-S.
2. Resting 12-lead ECG will be performed (pre-dose, after the above scales have been administered).
3. Review inclusion/exclusion criteria; eligibility will be reconfirmed prior to enrollment at this visit.
4. An adequately trained and certified rater will administer the CDSS to assess for symptoms of depression.

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5. The Investigator (or qualified designee) who is adequately trained will complete the “Since Last Visit” C-SSRS form.
6. An adequately trained and experienced clinician will administer the AIMS, SAS, and BAS to assess for EPS.
7. Vital signs will be measured and recorded (orthostatic BP and HR [in duplicate], respiratory rate, and body temperature); weight and height will also be recorded.
8. Patient will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
9. Blood and/or urine specimens will be collected for safety laboratory assessments (chemistry, hematology, urinalysis)—all blood draws should be done after the above scales have been administered.
10. Blood sample will be collected for CYP2D6 genotyping.
11. Urine pregnancy test will be performed on all females of childbearing potential.
12. Train patient on use of AiCure compliance monitoring platform.

Patients will be 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 will be assigned a study drug kit number via IWRS.

#### Study Drug Dosing:

The first dose of study drug will be administered from the AM strip of the study drug blister card at the clinic, regardless of the time of day. Sufficient study drug will be dispensed for a 3-week treatment period (until study drug is dispensed at next visit).

#### Post-dose:

1. Resting 12-lead ECG will be performed 1 to 2 hours post-dose ( $\pm 15$  minutes).
2. Patient will be queried regarding any post-dose AEs

#### **Patient Instructions**

Patients will be 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 (Week 3). Patients will also be instructed to bring any unused study drug at each study visit.

Patients will be reminded to use AiCure to monitor study drug compliance outside of the clinic.

The Investigator and/or study coordinator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

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The Investigator will query patients at the end of each visit to be certain they understand what is required of them.

#### **10.1.2.2. Safety Telephone Contact (Day 8/Week 1 +3-day window)**

Patients will receive a telephone call to assess AEs and query regarding concomitant medications at Week 1 (Day 8). Patients will also be asked if they have taken their study drug as directed.

#### **10.1.2.3. Visit 2 (Day 22/Week 3 ±3-day window)**

The following procedures will be performed at Visit 2 (Day 22 ±3-day window):

##### Pre-dose:

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

##### Study Drug Dosing:

Study drug will be administered from the AM strip of the newly dispensed blister pack at the clinic, regardless of the time of day.

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Post-dose:

1. Blood specimen will be 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 will be performed between 1 and 2 hours post-dose ( $\pm 15$  minutes).

**Patient Instructions**

Patients will be 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 (Visit 3). Patients will also be instructed to bring any unused study drug at each study visit.

Patients will be reminded to use AiCure to monitor study drug compliance outside of the clinic.

The Investigator and/or study coordinator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

The Investigator will query patients at the end of each visit to be certain they understand what is required of them.

**10.1.2.4. Safety Telephone Contact (Day 29/Week 4 +3-day window)**

Patients will receive a telephone call to assess AEs and query regarding concomitant medications at Week 4 (Day 29 +3 days). Patients will also be asked if they have taken their study drug as directed.

**10.1.2.5. Visit 3 (Day 43/Week 6  $\pm 6$ -day window)**

The following procedures will be performed on the morning of Day 43 ( $\pm 6$ -day window), all pre-dose, unless indicated otherwise:

Pre-dose:

1. A qualified and certified rater will administer the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Patient will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
3. Urine pregnancy test will be performed on all females of childbearing potential.
4. Resting 12-lead ECG will be performed (pre-dose, after the above scales have been administered).

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#### Study Drug Dosing:

Study drug will be administered from the AM strip of the newly dispensed blister pack at the clinic after the completion of the above procedures.

#### Post-dose:

1. The Investigator (or qualified designee) who is adequately trained will complete the “Since Last Visit” C-SSRS form.
2. Vital signs will be measured in duplicate and recorded (orthostatic BP and HR).
3. A review of all unused study drug will be performed by site staff. Sufficient study drug will be dispensed for BID dosing through the following visit.
4. Resting 12-lead ECG will be performed 1 to 2 hours post-dose ( $\pm 15$  minutes).

#### **Patient Instructions**

Patients will be 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 (Week 9). Patients will also be instructed to bring any unused study drug at each study visit.

Patients will be reminded to use AiCure to monitor study drug compliance outside of the clinic.

The Investigator and/or study coordinator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any nonstudy medications. These requirements will be reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

The Investigator will query patients at the end of each visit to be certain they understand what is required of them.

#### **10.1.2.6. Safety Telephone Contact (Day 50/Week 7 +3-day window)**

Patients will receive a telephone call to assess AEs and query regarding concomitant medications at Week 7 (Day 50 +3 days). Patients will also be asked if they have taken their study drug as directed.

#### **10.1.2.7. Visit 4 (Day 64/Week 9 $\pm 6$ -day window)**

The following procedures will be performed on the morning of Day 64 ( $\pm 6$ -day window):

#### Pre-dose:

1. A qualified and certified rater will administer the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Patient will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
3. Urine pregnancy test will be performed on all females of childbearing potential.

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4. Resting 12-lead ECG will be performed (pre-dose after the above scales have been administered).
5. Blood specimen will be collected for PK assessment of plasma d6-DM, Q, and metabolites (pre-dose, after the above scales have been administered).

Study Drug Dosing:

Study drug will be administered from the AM strip of the newly dispensed blister pack at the clinic, regardless of the time of day.

Post-dose:

1. An adequately trained and experienced clinician will administer the AIMS, SAS, and BAS to assess for EPS.
2. An adequately trained and certified rater will administer the CDSS to assess for symptoms of depression.
3. The Investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
4. Vital signs will be measured in duplicate and recorded (orthostatic BP and HR).
5. Blood and/or urine specimens will be collected for safety laboratory assessments (chemistry [including fasting glucose and lipids], hematology, urinalysis).
6. Blood specimen will be collected for assessment of plasma antipsychotic levels.
7. Blood specimen will be collected for PK assessment of plasma d6-DM, Q, and metabolites (between 1 and 3 hours post-dose).
8. A review of all unused study drug will be performed by site staff. Sufficient study drug will be dispensed for BID dosing through the following visit.

**Patient Instructions**

Patients will be 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 (Week 12). Patients will also be instructed to bring any unused study drug at each study visit.

Patients will be reminded to use AiCure to monitor study drug compliance outside of the clinic.

The Investigator and/or study coordinator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

The Investigator will query patients at the end of each visit to be certain they understand what is required of them.

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#### **10.1.2.8. Safety Telephone Contact (Day 71/Week 10 +3-day window)**

Patients will receive a telephone call to assess AEs and query regarding concomitant medications at Week 10 (Day 71 +3 days). Patients will also be asked if they are taking their study drug as directed.

#### **10.1.2.9. Visit 5 (Day 85/Week 12 ±6-day window)**

The following procedures will be performed on the morning of Day 85(±6-day window):

##### Pre-dose:

1. A qualified and certified rater will administer the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Patient will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
3. Urine pregnancy test will be performed on all females of childbearing potential.
4. Resting 12-lead ECG will be performed (pre-dose, after the above scales have been administered).

##### Study Drug Dosing:

Study drug will be 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 will be measured in duplicate and recorded (orthostatic BP and HR).
2. The Investigator (or qualified designee) who is adequately trained will complete the “Since Last Visit” C-SSRS form.
3. A review of all unused study drug will be performed by site staff. Sufficient study drug will be dispensed for BID dosing through the following visit.

#### **Patient Instructions**

Patients will be 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 will also be instructed to bring any unused study drug at each study visit.

Patients will be reminded to use AiCure to monitor study drug compliance outside of the clinic.

The Investigator and/or study coordinator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions may also be provided to the patient in addition to the informed consent per Investigator discretion.

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The Investigator will query patients at the end of each visit to be certain they understand what is required of them.

#### **10.1.2.10. Safety Telephone Contact (Day 92/Week 13 +3-day window)**

Patients will receive a telephone call to assess AEs and query regarding concomitant medications at Week 13 (Day 92 +3 days). Patients will also be asked if they have taken their study drug as directed.

#### **10.1.2.11. Visit 6 (Day 106/Week 15 ±6-day window)/Early-Termination Visit**

The following procedures will be performed on Day 106 (±6-day window) or for the ET Visit for those patients who withdraw prior to Week 15:

##### Pre-dose:

1. A qualified and certified rater will administer the NSA-16, NSA-16 Global, PANSS, PGI-S, and PGI-C.
2. Patient will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
3. Urine pregnancy test will be performed on all females of childbearing potential.
4. Resting 12-lead ECG will be performed (pre-dose, after the above scales have been administered).
5. Blood specimen will be collected for PK assessment of plasma d6-DM, Q, and metabolites (pre-dose, after the above scales have been administered).

##### Study Drug Dosing:

Last dose of study drug will be 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:

1. Vital signs will be measured in duplicate and recorded (orthostatic BP and HR, respiratory rate, and body temperature); weight and height will also be recorded.
2. Physical and neurological examinations will be conducted.
3. An adequately trained and experienced clinician will administer the AIMS, SAS, and BAS to assess for EPS.
4. An adequately trained and certified rater will administer the CDSS to assess for symptoms of depression.
5. The Investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
6. Blood and/or urine specimens will be collected for safety laboratory assessments (chemistry [including fasting glucose, lipids, and HbA1c], hematology, urinalysis).

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7. Blood specimen will be collected for assessment of plasma antipsychotic levels.
8. Patients will return all unused study medication; a review of all unused study drug will be performed by site staff.

For US patients, at the last patient contact, site staff will access CTSdatabase, enter the patient Study ID and the nature of the last contact (ie, completer or ET).

#### **Procedures for Early Termination:**

All patients will undergo a complete evaluation at Visit 6/ET. In addition, Visit 6/ET evaluations are to be 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 6/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 Visit 6/ET procedures, no efficacy assessments should be performed. Patients who terminate the study early should be contacted by phone 7 days after the last dose of study medication and asked if they have experienced any AEs or changes to their medications since their final visit. In addition, these patients should also receive the safety follow-up phone call 30 days after the last dose of study medication (See [Section 10.1.3](#)).

For patients who discontinue treatment, study drug will not be 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).

#### **10.1.3. Safety Follow-up Telephone Contact (Week 19/Day 136 +3-day window) or Early Termination**

Patients will be contacted by phone at Week 19 (Day 136 +3 days) (or 30 days after the last dose of study medication) 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.

Any AE previously reported and not yet resolved at the time of this phone contact, will be 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).

Any newly reported AE after receiving and up to 30 days after the last dose of study drug will be 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).

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## 11. STATISTICS

An overview of the planned statistical methods for this study are provided below. The full statistical methods will be provided in the statistical analysis plan (SAP) prior to the unblinding of the study.

### 11.1. Analysis Populations

Analysis populations for this study are defined as follows:

**Safety Population:** all patients who are randomized and take at least one dose of study drug. All safety analyses will be based on the safety population.

**Modified Intent-to-Treat (mITT):** all patients who are randomized with at least one post-Baseline PANSS measurement. All efficacy analyses will be based on mITT population.

### 11.2. Demographics and Baseline Characteristics

Demographics and Baseline characteristics will be summarized by treatment group using descriptive statistics.

### 11.3. Efficacy Analysis

#### 11.3.1. Study Endpoints

##### 11.3.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline to Week 15 in the PANSS Marder negative factors score.

##### 11.3.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include change from Baseline to Week 15 for the following outcomes measures:

- NSA-16 Global Negative Symptom Score
- PGI-S
- PGI-C

##### 11.3.1.3. Other Outcome Measures

Other outcome measures include change from Baseline to Visit 6 (Week 15) for the following measures:

- PANSS positive subscale
- Calgary Depression Scale for Schizophrenia (CDSS)

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### 11.3.2. Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 15 in PANSS Marder negative factors score. The primary efficacy endpoint will be analyzed using the likelihood-based linear mixed-effects model for repeated measures (MMRM) on observed data. The model will include fixed effects for treatment, trial center, visit, treatment-by-visit interaction, and Baseline-by-visit interaction. An unstructured covariance model will be used. Small study centers will be pooled according to region and practice for the analysis before database unblinding.

The purpose of this study is to assess the expected drug effect in a future population that results from patients initiating AVP-786 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 15.
- Intercurrent event(s): The “hypothetical strategy” as specified in the International Conference on Harmonization (ICH) E9 (R1) will be the primary estimand to define the treatment effect of AVP-786 versus placebo on the primary efficacy endpoint. In the hypothetical strategy, a scenario is envisaged in which the intercurrent event would not occur: the value to reflect that the scientific question of interest will fit the defined hypothetical scenario.

The hypothetical estimand is justifiable to evaluate the pharmacological effect had no withdrawals occurred or no rescue medication provided. Patients who withdraw from a symptomatic investigational medical treatment could have either lost their treatment effect, had the patient not taken any other symptomatic medication after withdrawal, or could have masked their treatment effect had the patient taken another symptomatic medication after withdrawal. This means that any observations taken after the patient stopped study medication will most likely not contribute relevant information about the pharmacological effect of AVP-786.

- Population-level summary: The between-treatment difference in the mean changes from Baseline to Week 15 in the PANSS Marder negative factors score.

All data collected during the study will be used in the statistical analysis. For the primary efficacy analysis, the treatment effect will be 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. CCI [REDACTED]

### 11.3.3. Secondary Efficacy and Other Outcome Measures Analysis

Secondary efficacy endpoints and other outcome measures will be analyzed in a similar manner as the primary efficacy analysis when appropriate. Further details will be provided in the SAP.

#### **11.4. Pharmacokinetic Analysis**

Plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be summarized descriptively.

#### **11.5. Safety Analysis**

Safety analyses will be based on safety population defined as all patients who are randomized and take at least one dose of study drug. It will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment.

##### **11.5.1. Adverse Events**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAEs).

##### **11.5.2. Vital Signs and Electrocardiograms**

Summary statistics of absolute values and percentage change from Baseline for BP (diastolic and systolic), heart rate, respiratory rate, weight, and ECG parameters will be provided. All values outside a predefined normal range will be highlighted in the individual patient data listings.

##### **11.5.3. Clinical Laboratory Measures**

Laboratory parameters will be summarized via descriptive statistics and via shifts in results with respect to normal ranges between Baseline and end-of-treatment as increased, decreased, or no change.

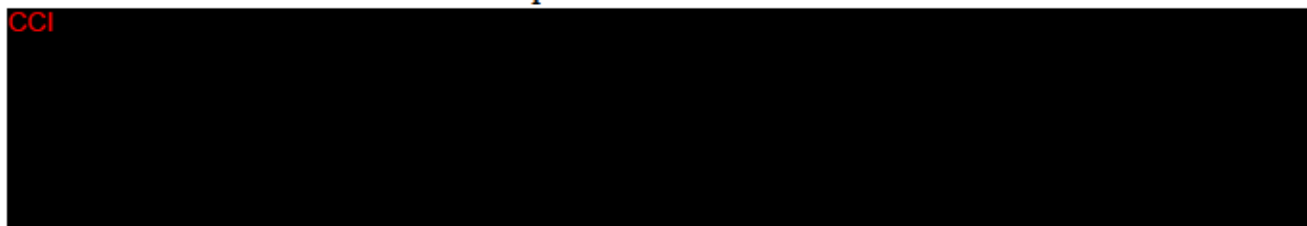
##### **11.5.4. Safety Scales**

The C-SSRS, SAS, BAS, and AIMS will be summarized via descriptive statistics and via shift tables of the number and percent of patients in each score from Baseline to post-Baseline visits and end of treatment.

#### **11.6. Data Monitoring Committee**

There is a Data Monitoring Committee (DMC) planned for this study (see below). The details of the DMC structure and its roles and responsibilities will be documented in a DMC Charter.

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## 11.8. Sample Size Calculation

Up to 370 patients are expected to be enrolled in this study.

Power calculation was performed assuming a normal distribution for the primary efficacy endpoint PANSS Marder factor score. The treatment effect size observed from a completed Phase 2 study (15-AVP-786-202, Sponsor data on file) was 0.40 for the 12-week single rater data. For this study, it is assumed that 80% or more patients will have single rater for their primary efficacy assessments throughout the study and a dropout rate is similar to the Phase 2 study at 20%, which in combination will yield a treatment effect size (AVP-786 vs. placebo) of 0.40. The planned total sample size of up to 370 patients in a 1:1 ratio will ensure no less than 85% power with 2-sided type 1 error  $\alpha = 0.05$ .

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## **12. QUALITY CONTROL AND QUALITY ASSURANCE**

### **12.1. Documentation**

For each process, evaluation, or test that generates study data but is not described in the protocol or eCRF, a written description of the data generation procedures shall be retained in the quality assurance section of the study files. In the case of routine clinical diagnostic procedures, only a copy of the relevant certification document is required.

### **12.2. Study Monitoring**

Throughout the study, the Study Monitor will make frequent contacts with the Investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the Study Monitor. The Study Monitor may periodically request review of the Investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The Study Monitor will verify that each patient has proper consent documentation from the patient and/or the patient's legally authorized representative for study procedures and for the release of medical records to the Sponsor, FDA, other regulatory authorities, and the IRB/IEC/EC. The Investigator or appointed delegate will receive the Study Monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

On completion of the study, the Study Monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

### **12.3. Direct Access to Source Data/Documents for Audits and Inspections**

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from the Sponsor or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

The inspector from the regulatory authority will be especially interested in the following items:

- Visits from the Sponsor's representatives
- IRB/IEC/EC approval(s)
- Study drug accountability
- Study protocol and amendments
- ICFs of the patients

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- Medical records supportive of eCRF data
- Reports to the IRB/IEC/EC and the Sponsor
- Record retention

The Sponsor will be available to help Investigators prepare for an inspection.

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## **13. ETHICS**

### **13.1. Ethical Conduct of the Study**

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and Council for International Organizations of Medical Science; and will be consistent with GCP, ICH Guidelines, and the United States (US) Food and Drug Administration (FDA) CFR (21 CFR Parts 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research, and the applicable regulatory requirements.

### **13.2. Institutional Review Board - Ethics Review**

All IRBs/IECs/ECs must meet the requirements as described in Part 56, Title 21 of the Code of Federal Regulations (CFR) and conform to local laws and customs where appropriate. Written IRB/IEC/EC approval for the protocol and the signed ICF must be obtained and transmitted to the Sponsor or its representative before the study can be initiated.

The protocol, the protocol amendments, and the sample ICF must be reviewed and approved by an IRB/IEC/EC of the participating study center in accordance with the CFR, the International Conference on Harmonisation (ICH), and Good Clinical Practice (GCP) before initiation of the study at their respective center. All protocol amendments and any changes to the ICF that occurred during the study must be approved by the Sponsor. and the IRB/IEC/EC.

The Investigator will ensure that this study is conducted in full conformance with local laws and according to National and State laws of the US (Investigator Responsibilities<sup>40</sup> and the World Medical Association Declaration of Helsinki). The Principal Investigator is responsible for informing the IRB/IEC/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC/EC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/IEC/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB/IEC/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC/EC according to local regulations and guidelines.

### **13.3. Written Informed Consent**

All participants in this study must provide written informed consent in accordance with the requirements specified in the 21 CFR (Parts 50, 56, 312) and/or the Declaration of Helsinki. Patients will be properly informed of the purpose of the study. The Investigators will provide patients with the ICF and explain the rationale for the study, providing ample time for patients to ask questions. Patients will be alerted to any anticipated AE that may be encountered with the study drug. A signed ICF will be obtained from all patients prior to patient entry into this study; patients will be provided with a copy of their signed ICF. The Investigators or designee will also

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explain the IRB/IEC/EC-approved Subject Database Authorization to the patient and witness the signature. All participants will also be informed that their medical records will be kept confidential except for review by the Sponsor or its representatives, the US FDA, or other regulatory agencies if applicable.

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## **14. DATA HANDLING AND RECORDKEEPING**

Data collected on the eCRFs will be entered into EDC system by trained site staff. Any queries arising from data entry will be checked with the Investigator and changes approved.

### **14.1. Source Data**

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs, which will be checked against source data during monitoring visits, must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

### **14.2. Retention of Records**

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records should be retained by the Investigator according to International Conference on Harmonization standards, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable by the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

### **14.3. Confidentiality of Study Documents and Patient Records**

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All investigational medicinal products, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject identification. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

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The Investigator should keep a separate log of patient's codes, names, and addresses. Documents not for submission to the Sponsor, for example, patients' signed ICFs, should be maintained by the Investigator in strict confidence.

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## **15. CRITERIA FOR STUDY TERMINATION**

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures to effect study termination will be arranged after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

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## **16. PUBLICATION POLICY**

It is anticipated that a report of this study will be published in the scientific literature by the Sponsor. The Investigator will not seek to arrange for publication of any of the information or results from the study in any scientific journal, or other publication or by way of lecture without the Sponsor's prior review and written consent.

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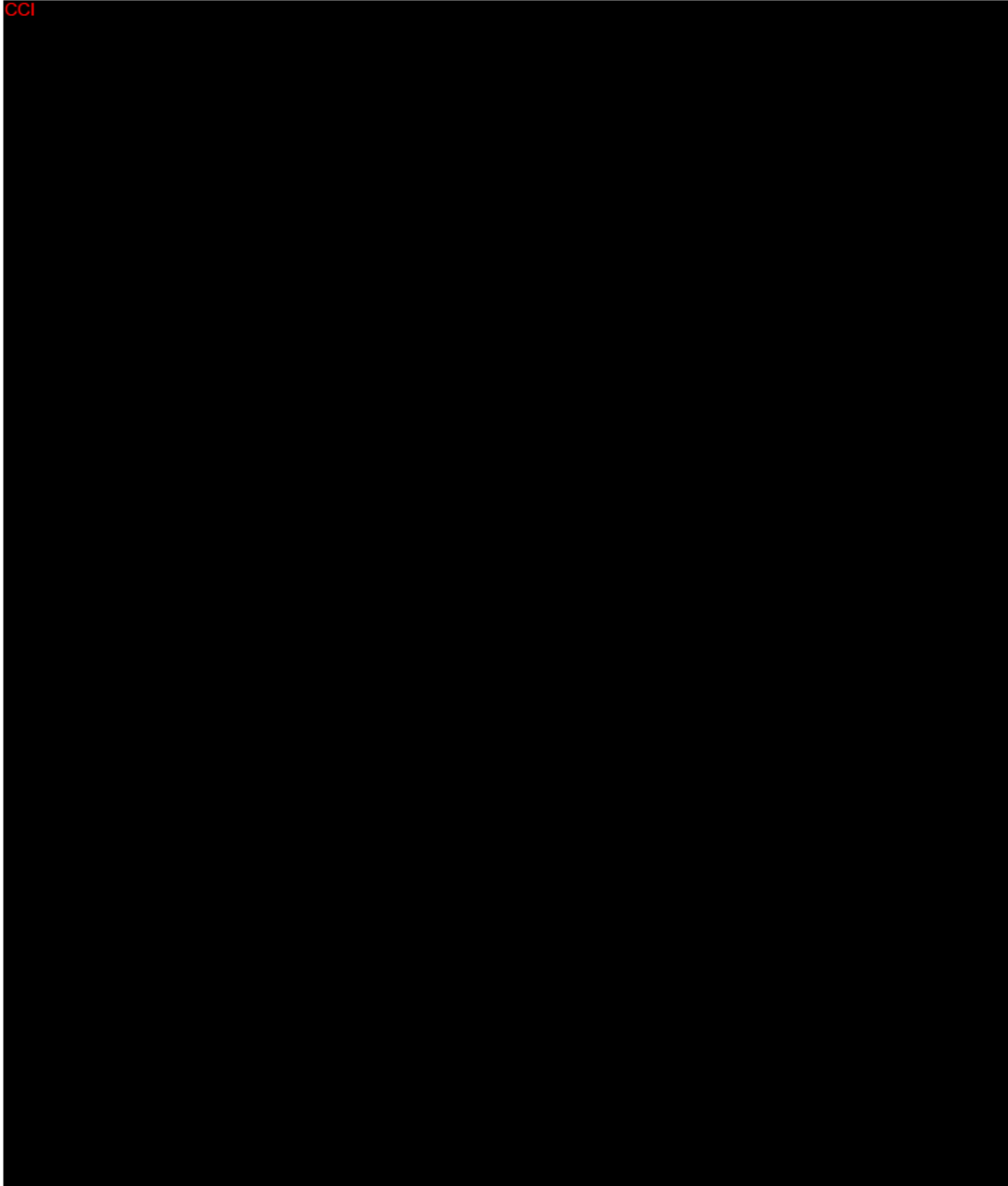
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## **18. SUMMARY OF CHANGES**

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## 19. APPENDICES

[Appendix 1 Prohibited Concomitant Medications](#)

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## APPENDIX 1. PROHIBITED CONCOMITANT MEDICATIONS

**Patients who are currently taking, or have taken any of the following drugs, within 2 weeks or 5 half-lives, whichever is longer, prior to the initiation of the study medication administration (unless otherwise noted), are to be excluded.**

**Typical antipsychotic medications are not allowed during the study or within 12 weeks prior to Visit 1.**

**Drugs that may increase Quinidine (Q) levels are not allowed (topical preparations are permitted unless applied under occlusive dressing or other technique that is intended to increase systemic absorption):**

- Amiodarone
- Antifungals (eg, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)
- Carbonic anhydrase inhibitors (strong inhibitors are prohibited; topiramate is allowed)
- Cimetidine
- Delavirdine
- Diltiazem
- Macrolide antibiotics (eg, erythromycin, azithromycin, clarithromycin, dirithromycin, roxithromycin)
- Mexiletine
- Nefazodone
- Protease inhibitors (eg, saquinavir, ritonavir, atazanavir, indinavir, **amprenavir**, **fosamprenavir**)
- Ranolazine
- Verapamil

**Drugs that are metabolized by CYP2D6 and may have increased plasma levels if co-administered with Q:**

- Dextromethorphan (DM, over-the-counter [OTC] and prescription)
- Tricyclic antidepressants (eg, imipramine, desipramine, amitriptyline, **amoxapine**, **clomipramine**, **doxepin**, nortriptyline, protriptyline)
- Atomoxetine
- Pimavanserin

**Drugs that are related to Q:**

- Mefloquine

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- **Quinidine**
- **Quinine**

**Drugs that may produce serotonin syndrome when co-administered with DM:**

- **MAOIs (may increase the risk of serotonin syndrome)**
  - Patients should allow at least 2 weeks after stopping study medication before starting an MAOI.

**Drugs that are strong CYP3A4 inducers that may decrease DM and Q plasma levels:**

- **Apalutamide**
- **Dexamethasone**
- **Enzalutamide**
- **Fosphenytoin**
- **Phenytoin**
- **Lumacaftor**
- **Mitotane**
- **Carbamazepine**
- **Cyproterone**
- **Pentobarbital**
- **Phenobarbital**
- **Primidone**
- **Rifampicin**
- **Rifamycin**
- **Rifaximin**
- **St. John's Wort**

**Other drugs:**

- **Clozapine is not allowed during the study or within 12 weeks prior to Visit 1**
- **Levodopa is not allowed within 4 weeks prior to Visit 1 and throughout the study**
- **Benzodiazepines are not allowed during the study, except for lorazepam use for short-term or 'as needed' treatment of behavioral disturbances (agitation, anxiety, or restlessness) in doses up to 4 mg per day and not exceeding 3 days in a 7-day period**



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| PPD              | Clinical Approval           | 31-Mar-2022<br>21:28:47                                          |
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| PPD              | Biostatistics Approval      | 31-Mar-2022<br>18:15:30                                          |







































































