Table of Contents

PROTOCOL TITLE:

A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI)

Protocol:	17-AVP-786-205 Amendment 5	**IND:**132395
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 23 March 2020
Drug:	AVP-786 (deudextromethorphan hydrobromide [d6-DM]/ quinidine sulfate [Q])	**Version:** 6.0

Medical Monitor: PPD , MD, PPD
Phone: PPD
Avanir Pharmaceuticals, Inc.
30 Enterprise, Suite 200
Aliso Viejo, California 92656

Study Manager: PPD
Phone: PPD
Avanir Pharmaceuticals, Inc.
30 Enterprise, Suite 200
Aliso Viejo, California 92656

AVANIR PHARMACEUTICALS, INC.

30 Enterprise, Suite 200
Aliso Viejo, California 92656
Phone: (949) 389-6700 Fax: (949) 643-6800
24-hour Emergency Phone Number: +1-434-951-4082

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AOC	Alteration of consciousness
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
CK	Creatine kinase
CRO	Contract research organization
CT	Computed tomography
CYP2D6	Cytochrome P450 isoenzyme 2D6
d6-DM	Deudextromethorphan hydrobromide (or free base form)
DoD	Department of Defense
DM	Dextromethorphan hydrobromide or dextromethorphan
DMP	Data management plan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCOA	Electronic clinical outcome assessments
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
eCRF	Electronic case report form
EDC	Electronic data capture
EP	European Pharmacopeia
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat

Abbreviation	Definition
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LOC	Loss of consciousness
MAOI	Monoamine oxidase inhibitor
MAR	Missing at random
mCGI-C	Modified Clinical Global Impression of Change
mCGI-S	Modified Clinical Global Impression of Severity
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent-to-treat
MMRM	Mixed effects model repeated measures
MNAR	Missing not at random
MRI	Magnetic Resonance Imaging
NF	National Formulary
NMDA	*N*-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory Clinician
NPI-C-3	Composite of the Clinical Impression severity scores on the NPI-C Aggression, Agitation, and Irritability/Lability subscales
OTC	Over-the-counter
PBEF	Pregnancy and Breastfeeding Exposure Form
PD	Pharmacodynamic(s)
PEF	Protocol Eligibility Form
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic(s)
PP	Per-protocol
PR	The P-R interval from an ECG tracing
PTA	Post-traumatic amnesia
Q	Quinidine sulfate or quinidine
QRS	The 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
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class

Abbreviation	Definition
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
T3	Triiodothyronine
T4	Thyroxine
TBI	Traumatic brain injury
TEAE	Treatment-emergent adverse event
TMS	Transcranial magnetic stimulation
TSH	Thyroid-stimulating hormone
US	United States
USP	United States Pharmacopoeia
VA	Veterans Administration
WBC	White blood cell
WHO	World Health Organization

PROTOCOL AGREEMENT

Protocol Title:

A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI).

Protocol Number: 17-AVP-786-205-Amendment 5

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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 Avanir 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/Ethics Committee (IRB/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 Avanir 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: _____

_____ _____

Avanir Representative Signature Date

Avanir Representative: PPD MD

STUDY SYNOPSIS

Title: A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI).

Study Objectives

The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with TBI.

Study Population

Number of Patients: Approximately 150 patients will be enrolled at approximately 40 centers in the US.

Condition/Disease: Treatment of neurobehavioral disinhibition including aggression, agitation, and irritability that persists following non-penetrating brain injury.

Key Inclusion Criteria: Patients with TBI that is classified as mild, moderate, or severe in intensity, as determined by the modified Veterans Administration/Department of Defense (VA/DoD) criteria[1] will be enrolled. The neurobehavioral disinhibition symptoms must present after the trauma or after recovery of consciousness, must persist past the acute post-injury period, and cannot be accounted for by a preexisting neurobehavioral disorder diagnosis, substance use disorder, or other medical disorder. Patients must have a score of ≥ 4 (moderately ill) on the modified Clinical Global Impression of Severity (mCGI-S) scale at Screening and Baseline visits, and a score of ≥ 4 on the Agitation/Aggression or Irritability/Lability subscales of the Neuropsychiatric Inventory (NPI) scale at Screening and Baseline visits (derived from the NPI-Clinician [NPI- C] rating scale at both visits), confirming symptom severity. Each eligible patient must have a reliable informant/caregiver who interacts with the patient at least 2 hours per day for at least 3 days a week and is able and willing to comply with study procedures and attend all in-clinic study visits. In the event that the informant/caregiver cannot meet the specified time requirements of 2 hours per day for at least 3 days a week, the Investigator must discuss this potential patient with the Medical Monitor. Informant/Caregivers must sign an informed consent form (ICF) for this study.

Key Exclusion Criteria: Patients with a history of a neurodevelopmental disorder (including attention-deficit/hyperactivity disorder), intermittent explosive disorder, or post-traumatic stress disorder, presenting before the TBI will be excluded from participating in the study. Patients with a history of an anxiety or depressive disorder that preceded the TBI are allowed providing that, in the opinion of the Investigator, the symptoms of disinhibition (e.g., agitation, aggression, and/or irritability) are not better accounted for by a comorbid psychiatric disorder. Patients with a history of or current clinical symptoms of schizophrenia, schizoaffective disorder, bipolar disorder, or progressive dementia are also excluded.

A complete list of inclusion/exclusion criteria is presented in Section 4 of the protocol.

Study Design

Structure: This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study.

Duration: Patients will be enrolled in the study for approximately 17 weeks, with an approximate 4-week screening period, a 12-week treatment period and a 1-week follow-up period (phone call).

Study Treatment: The investigational product is AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]), which is titrated over a 2-week period to d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) twice daily (BID).

Control: Placebo capsules appearing identical to study medication will be used as control.

Randomization: Eligible patients will be randomized into the study to receive AVP-786 or placebo and stratified by study site.

Dose Regimen: Eligible patients will be randomly assigned at the Baseline visit to receive AVP-786 or matching placebo capsules. Patients will have at least a 50% chance of receiving AVP-786 during the study.

Study medication will be administered orally BID (1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart) throughout the 12-week treatment period.

For patients randomized to receive AVP-786, their dosage regimen will begin with d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) and placebo once a day for the first 7 days followed by AVP-786-28/4.9 BID for the next 7 days. Patients will then receive AVP-786-42.63/4.9 BID for the remaining duration of the 12-week treatment period.

Assessments and Visits

Patients will attend clinic visits at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85). A phone call will be made at Visit 2 (Day 8). A safety follow-up phone call will be made 7 days after the last clinic visit for all patients who complete the study (Day 92) or 7 days after last dose of study medication for patients who terminate early. Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1).

Response Measures

Efficacy

Primary measure:

- A composite of the Clinical Impression severity scores on the Neuropsychiatric Inventory-Clinician (NPI-C) rating subscales of Aggression, Agitation, and Irritability/Lability, hereafter referred to as NPI-C-3.

Secondary measures:

- modified Clinical Global Impression of Change (mCGI-C)
- NPI-C subscales (Aggression, Agitation, Irritability/Lability, and Disinhibition)
- modified Clinical Global Impression of Severity (mCGI-S)

- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C)

Pharmacokinetics

Blood samples will be collected at Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85) for determination of plasma concentrations of d6-DM, d6-DM metabolites (d3-DX and d3-3-MM), and Q and for estimations of pharmacokinetic parameters.

Safety and Tolerability

Safety and tolerability of AVP-786 will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), and the Sheehan Suicidality Tracking Scale (S-STS).

Pregnancy tests will be conducted for patients of childbearing potential.

General Statistical Methods and Types of Analyses

Analysis Populations

Three analysis populations will be used; modified intent-to-treat (mITT), per-protocol (PP) and safety. The mITT population includes all patients who take at least one dose of study medication and have at least one post-treatment efficacy assessment and will be used for all analyses of efficacy. Patients in the mITT population will be included in the treatment group to which they were randomized regardless of treatment received. The PP population includes all patients who have no significant protocol deviation that may impact efficacy evaluation. Patients in the PP will be included in the treatment group based on the actual treatment received. The safety population includes all patients who receive study treatment and will be used for all analyses of safety. Patients will be included in the treatment group based on the actual treatment received.

Efficacy Analyses

The primary efficacy endpoint of the study is the change from Baseline to Week 12 in the NPI-C-3 composite score. The treatment effect will be estimated by using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data under missing at random (MAR) assumption. An unstructured covariance model will be used. The model will include fixed effects for treatment, visit, study site, treatment-by-visit interaction, baseline-by-visit interaction, and baseline value. Analyses with missing values imputed by multiple imputation (MI) may be performed as sensitivity analyses under missing not at random (MNAR) assumptions.

Safety Analyses

Safety measures will be summarized by treatment groups.

Sample Size Calculation

Sample size calculations are performed assuming a normal distribution for the primary efficacy endpoint of change from baseline in NPI-C-3 composite score.

It is assumed that the treatment difference is -2.50 and the standard deviation in drug and placebo groups is assumed to be equal to 5.0, producing an effect size of -0.50. The total cumulative dropout rate is assumed to be 30%.

A sample size of 150 patients will have an approximate 74% power to reject the null hypothesis in the comparison of AVP-786 versus placebo with 2-sided type I error α=0.05.

Table 1: Schedule of Evaluations and Visits

Procedure	**Visit:**	**Screening[1]**	**Visit 1 Baseline[1]**	**Visit 2 Phone Call[1]**	**Visit 3[1]**	**Visit 4[1]**	**Visit 5[1]**	**Visit 6/Early Termination[1,2,3]**	**Follow-up Phone Call[1]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 22**	**Day 43**	**Day 64**	**Day 85**	**Day 92**
	End of Study Week:	**Week -4 to -1**		**Week 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 13**
Sign informed consent forms		X							
Medical history (including TBI severity classification)		X							
Review of eligibility		X[4]	X						
Randomization			X						
Physical and neurological examination		X						X	
Risk assessment of falls		X							
Vital signs, height, and weight		X	X[5]		X	X	X	X[5]	
Electrocardiogram		X[6]	X[7]		X[7]	X[7]	X[7]	X[7]	
Adverse events		X	X	X	X	X	X	X	X
Prior and concomitant medication use assessments		X	X[8]	X	X[8]	X[8]	X[8]	X[8]	X
NPI-C subscales: Agitation, Aggression, Irritability/Lability, and Disinhibition[9]		X	X		X	X	X	X	
mCGI-S		X	X			X		X	
mCGI-C						X		X	
S-STS		X	X		X	X	X	X	
PHQ-9		X							

Table 1 Schedule of Evaluations and Visits (Continued)

Procedure	**Visit:**	**Screening[1]**	**Visit 1 Baseline[1]**	**Visit 2 Phone Call[1]**	**Visit 3[1]**	**Visit 4[1]**	**Visit 5[1]**	**Visit 6/Early Termination[1,2,3]**	**Follow-up Phone Call[1]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 22**	**Day 43**	**Day 64**	**Day 85**	**Day 92**
	End of Study Week:	**Week -4 to -1**		**Week 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 13**
PGI-S			X			X		X	
PGI-C						X		X	
Administer morning dose of study medication in clinic			X		X	X	X	X	
Chemistry, hematology, and urinalysis		X[10]				X		X[10]	
Pregnancy test[11]		X	X		X	X	X	X	
Blood sample for pharmacokinetic analysis						X[12]	X[13]	X[12]	
Blood sample for CYP2D6			X						
Urine sample for drug screening/toxicology		X			X		X	X	
Dispense study medication blister card and diary card			X		X	X	X		
Collect study medication blister card and review diary card[14]					X	X	X	X	

CYP2D6 = cytochrome P450 isoenzyme 2D6; mCGI-C = modified Clinical Global Impression of Change (assessment of change in aggression, agitation, and irritability symptoms); mCGI-S = modified Clinical Global Impression of Severity (assessment of severity of aggression, agitation, and irritability symptoms); NPI-C = Neuropsychiatric Inventory Clinician; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire; S-STS = Sheehan Suicidality Tracking Scale; TBI = Traumatic Brain Injury

Note: Whenever possible, for consistency of ratings, the same rater should rate a patient (and the informant/caregiver) at each of the patient's visits for all 3 of the following scales: the NPI-C, the mCGI-S, and the mCGI-C. The mCGI-S and mCGI-C must be administered after the NPI-C subscales. If it is not possible to have the same rater for the NPI-C and the mCGI subscales (mCGI-S and mCGI-C); it is critical that 1 rater assesses both of the mCGI subscales for a patient. In

addition, if the NPI-C rater differs from the mCGI rater, prior to making the mCGI assessment, the mCGI rater must review the NPI-C results, discuss the results with the NPI-C rater, and review any additional pertinent information.

1. Study visits after Baseline have a ± 3-day window, except Visit 2 and the Follow-up Phone Call, which have a +3-day window. The Screening period may be extended after discussion with and approval by the Medical Monitor.
2. Early termination visit for patients who withdraw prior to study completion.
3. A safety Follow-up Phone Call should be made to the patient or informant/caregiver 7 (+3) days after last dose of study medication.
4. For each patient, a protocol eligibility form will be completed.
5. Weight should be measured at the Baseline visit (Day 1) and Visit 6 (Day 85); height is only measured at Baseline.
6. Electrocardiogram should be performed in triplicate at the Screening visit.
7. Electrocardiogram to be performed pre-dose and post-dose at the Baseline visit (Day 1) and Visit 4 (Day 43). To be performed post-dose at Visit 3 (Day 22), Visit 5 (Day 64), and Visit 6 (Day 85).
8. On the days of study visits (i.e., Baseline [Day 1], Visit 3 [Day 22], Visit 4 [Day 43], Visit 5 [Day 64], and Visit 6 [Day 85]), patients are instructed to refrain from the use of benzodiazepine medications, medicinal/recreational marijuana, and alcohol for 12 hours prior to the visit and until all study assessments have been completed.
9. For eligibility, the responses to the Agitation/Aggression and Irritability/Lability subscales of the NPI will be derived directly from the NPI-C at Screening and Baseline.
10. Thyroid function tests (thyroid-stimulation hormone [TSH] and, if TSH is abnormal, reflex triiodothyronine [T3], reflex total thyroxine [T4], and reflex free T4) and glycosylated hemoglobin (HbA1c) test should be performed at the Screening visit and Visit 6 (Day 85).
11. Serum pregnancy test to be performed for patients of childbearing potential at the Screening visit. Urine pregnancy tests to be performed for patients of childbearing potential at all other visits prior to dosing; if positive, the patient must be discontinued from the study.
12. Blood sample for pharmacokinetic analysis should be collected 1 to 3 hours after administering the morning dose.
13. Blood sample for pharmacokinetic analysis should be collected before administering the morning dose.
14. The study medication blister card and diary card should be collected and reviewed at each visit for compliance.

1. BACKGROUND AND CLINICAL RATIONALE

Traumatic Brain Injury (TBI) is a disruption of brain function resulting from an external physical force.[2] It is a common medical condition with serious and long term sequelae that impact patients' ability to function. In the United States (US), there are 204 TBI-related emergency room (ER) visits, 33 TBI-related hospitalizations, and 6 TBI-related deaths every hour. In 2010, there were more than 2.5 million ER visits, 280,000 hospitalizations, and 50,000 deaths related to non-military TBI - either TBI alone, or TBI in combination with other injuries.[3] Of the patients brought to an ER for TBI, 87% were treated and released from the ER, 11% were admitted to hospitals, and 2% died. The Department of Defense (DoD) reported that from 2000 through 2011, 4% of the 6 million workforce in the Army, Air Force, Navy, and Marine Corps were diagnosed with TBI.[2] The incidence of TBI is eight times that of breast cancer, and 30 times that of human immunodeficiency virus (HIV).[4]

The most common TBI is caused by impact and acceleration-deceleration forces, like the injuries that occur in high-speed motor vehicle crashes. Both the traumatic impact and noncontact acceleration-deceleration affect the frontal, temporal, and parietal lobes of the brain, which are particularly susceptible to damage from the adjacent bony structures.[5] The neurological insult may induce marked behavioral changes: damage to the orbitofrontal cortex, left anteromedial frontal lobe and anterior cingulate can impair the normal inhibitory modulation of impulsivity and aggression, while damage to the temporal lobes can contribute to non-purposeful outbursts of excessive anger.[4] Such behavioral disorders, common after TBI, contribute to subsequent deficits in function.[6,7] The most troublesome behavioral symptoms are aggression, agitation, and irritability; patients and their families find these disruptive behaviors harder to accommodate than the physical sequelae of the traumatic brain injury.[8] Aggressive behavior occurs in 40-70% of TBI cases, and is severely destructive to patients and their caregivers.[4,9,5] In patients who sustained multiple traumas, significant aggression was three times more prevalent in those with head trauma than in those where the head was not injured. (33.7% vs. 11.5%).[10] In a study of 732 subjects with TBI and 120 non-TBI general trauma victims, self-reports of bad temper, irritability, and anxiety were equally common in both cohorts 1 month after trauma (TBI 18%, 40%, 35%; non-TBI 18%, 39%, 34%, respectively), but one year later were significantly more frequent in those with TBI (TBI 24%, 35%, 30%; non-TBI 11%, 17%, 14%).[11]

The consequences of TBI extend to patients' caregivers. When interviewed 6, 12, and 24 months post-injury, caregivers reported that patients showed increasingly severe temper outbursts, with moderate or severe aggressiveness noted in 31% of the cases at the 24-month follow-up. Over this 24-month period, the caregivers reported increases in their own use of medications and intoxicants, and decreases in their employment and financial status.[12]

Aggressive behavior after TBI can be persistent. Baguley et al.[13] found that following discharge from an Australian inpatient brain injury rehabilitation unit, 25% of the patients continued to display aggressive behaviors, which were persistent over the 5 years of the study. During this period the proportion of aggressive patients, their aggression levels, and the type of aggression did not change. Brooks et al.[14] followed 42 patients with TBI and interviewed their family members over a period of 5 years. One year after the injury, 67% reported that patients showed

persistent irritability, 64% bad temper, and 57% rapid mood changes. Persistent irritability was seen in 64%, bad temper in 64%, and rapid mood changes in 57% of these patients, 5 years after the injury.

The diminished ability to regulate or inhibit impulsive behaviors increases the risk of violent acts that may lead to further TBIs. Thus, reducing post-TBI neurobehavioral disinhibition is an important therapeutic goal to reduce subsequent violence and diminish the risk of further injuries.[4]

Despite a clear and urgent need for effective treatments to reduce the neurobehavioral disinhibited behaviors after TBI, including aggression, agitation, and irritability, effective pharmaceutical treatments are lacking, and no drug or medical device for patients suffering from TBI has been approved by the US FDA.

1.1. Rationale for Studying AVP-786 in Patients with TBI

Neuroimaging and postmortem studies show that the neuropathological changes of TBI continue to evolve while neurobehavioral symptoms emerge in the weeks and months after the injury.[15,16] The neural trauma from TBI triggers a secondary cascade of processes marked by glutamatergic excitotoxicity, calcium overload, spreading cortical depression, oxidative stress, neuroinflammation, and vascular dysfunction. These can persist for years as chronic progressive neuroinflammatory, neurodegenerative disease, with marked disruption of axonal function, tissue degeneration, and functional loss.[17,18] During this post-acute period, many of the characteristic behavioral dysfunctions, cognitive deficits, and psychiatric disorders associated with TBI emerge.[19–21] The cognitive and behavioral outcomes follow a highly variable course, reflecting the important influence of pre-trauma constitutional variables and the subsequent brain milieu.[22] AVP-786 may ameliorate the neuropathological changes in chronic TBI through its neuroprotective effects as an *N*-methyl-D-aspartate (NMDA) antagonist and sigma-1 agonist, reducing reactive astrocytosis and the microglial inflammatory response.[23]

AVP-786 actions as a serotonin reuptake inhibitor may contribute to its efficacy in treating neurobehavioral disinhibition in TBI. TBI impacts levels of serotonin in the brain, and a decrease in serotonin level has been documented up to 60 days following TBI.[24] Case reports and small, uncontrolled case series have reported that selective serotonin reuptake inhibitors (SSRI) and buspirone, a 5-HT1A agonist, were effective in reducing aggression, agitation, and irritability in patients with TBI.[25,6] Controlled studies and case reports have found that SSRI improved symptoms of depressed mood that emerged in patients after traumatic brain injuries.[26–30] These case reports and studies suggest that increasing serotonergic activity in the brain could reduce symptoms in patients with chronic TBI.

1.2. Rationale for the Dose

The planned dose of AVP-786 for this study is d6-DM 42.63 mg/Q 4.9 mg, hereafter referred to as AVP-786-42.63/4.9. 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.

1.3. Rationale for the Treatment Duration

This will be a double-blind, placebo-controlled study of 12-weeks of treatment. Dosing of patients with AVP-786 continuously for 12 weeks facilitates detection of treatment response and provides further assessment of its sustained efficacy and safety in treating patients with TBI.

The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo, for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI).

2. STUDY OBJECTIVES

The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo, for the treatment of neurobehavioral disinhibition including aggression, agitation, and irritability in patients with traumatic brain injury (TBI).

3. STUDY DESIGN

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study. Approximately 150 patients with TBI neurobehavioral disinhibition including aggression, agitation, and irritability following non-penetrating brain injury will be enrolled at approximately 40 centers in the US. Patients will be enrolled in the study for approximately 17 weeks; with an approximate 4-week screening period, a 12-week treatment period, and a 1-week follow-up period (phone call). The screening period may be extended after discussion with and approval by the Medical Monitor. A safety follow-up phone call will be made 7 days after the last clinic visit for all patients who complete the study (Day 92) or 7 days after last dose of study medication for patients who terminate early.

The investigational product (IP) is AVP-786 (d6-DM/Q), which is titrated over a 2-week period to d6-DM 42.63 mg/Q 4.9 mg BID. Placebo capsules appearing identical to study medication will be used as control. Eligible patients will be randomized into the study to receive AVP-786 or placebo. Patients will have at least a 50% chance of receiving AVP-786 during the study. Study medication will be administered orally BID (1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart) throughout the treatment period. The morning dose of study medication will be administered at the site during scheduled visits.

For patients randomized to receive AVP-786, their dosage regimen will begin with d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) and placebo once a day for the first 7 days followed by AVP-786-28/4.9 BID for the next 7 days. Patients will then receive AVP-786-42.63/4.9 BID for the remaining duration of the 12-week treatment period.

Patients will attend clinic visits at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85). A phone call will be performed at Visit 2 (Day 8). Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1). The primary efficacy measure of the study is a composite of the Clinical Impression severity scores on the NPI-C Aggression, Agitation, and Irritability/Lability subscales (NPI-C-3). Secondary efficacy measures include: modified Clinical Global Impression of Change (mCGI-C), NPI-C subscales (Aggression, Agitation, Irritability/Lability, and Disinhibition), modified Clinical Global Impression of Severity (mCGI-S), Patient Global Impression of Severity (PGI-S), and the Patient Global Impression of Change (PGI-C).

Pharmacokinetic assessment of d6-DM, Q, and metabolites will be performed on samples collected at Visits 4, 5, and 6 (Days 22, 64, and 85). The safety and tolerability of AVP-786 will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), and the Sheehan Suicidality Tracking Scale (S-STS). Pregnancy tests will be conducted for patients of childbearing potential.

Each eligible patient must have a reliable informant/caregiver; it is critical for the accuracy of the data that an informant or caregiver is familiar with the patient and is able to report on the patient's behaviors, activities and symptoms, as well as any changes in behaviors. An informant/caregiver should spend a sufficient amount of time with the patient each week (at least 2 hours per day for at least 3 days a week) to be able to accurately report on these behaviors. In the event that the informant/caregiver cannot meet the specified time requirements of at least

2 hours per day for at least 3 days a week, the Investigator must discuss this potential patient with the Medical Monitor.

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Patients in the study must have TBI, an injury to the brain produced by external physical force, after a non-penetrating head trauma. Six months or more must elapse between the injury and Screening.
2. The TBI meets the VA/DoD classification[1] for mild, moderate, or severe TBI:
    a. Mild TBI: Any of the following:
        i. Glasgow Coma Scale (GCS) score of 13-15,
        ii. Loss of consciousness (LOC) for 0-30 minutes,
        iii. Alteration of consciousness (AOC) for up to 24 hours,
        iv. Post-traumatic amnesia (PTA) for 0-1 day.
    b. Moderate TBI: Any of the following:
        i. GCS score of 9-12,
        ii. LOC for > 30 minutes and < 24 hours,
        iii. AOC for > 24 hours; severity based on other criteria,
        iv. PTA for > 1 and < 7 days
    c. Severe TBI: Any of the following:
        i. GCS score of < 9,
        ii. LOC for > 24 hours,
        iii. AOC for > 24 hours; severity based on other criteria,
        iv. PTA for > 7 days

    The AOC must immediately follow the head trauma.
3. The TBI history must be confirmed by evidence from medical records, clinician report, or detailed history provided by the patient, family member, or other competent reporter (as determined by the Investigator).
4. Patients must have had no further head trauma in the 6 months prior to Screening.
5. The patient should have a history of aggression, agitation, or irritability, which:
    a. Was not present before the injury,
    b. Presented after the injury or after recovery of consciousness,
    c. Persisted past the acute post-injury period,
    d. Are not explained by a preexisting diagnosis, substance use disorder or other medical disorder.
6. At the time of screening, the behavioral disinhibition symptoms of aggression, agitation, or irritability:

a. Recur at least weekly,
b. Are severe enough to interfere with daily routine,
c. Cause distress to the patient and the informant/caregiver,
d. Are severe enough to treat with medication, in the opinion of the treating physician.

7. Patient must have a score of ≥ 4 (moderately ill) on the mCGI-S scale at Screening and Baseline visits, and a score of ≥ 4 on the NPI Agitation/Aggression or Irritability/Lability subscales at the Screening and Baseline visits (derived from the NPI-C), confirming symptom severity.
8. The patient must be male or female, 18-75 years old at the time of informed consent.
9. The patient/informant/caregiver must have sufficient comprehension and cooperation to enable compliance with all procedures and assessments.
10. 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 medication. The following requirements must be met:

    - Patients who are 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception.
    - Patients who are sterile (i.e., 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 not eligible for participation in the study.

11. Concomitant use of nondrug therapies such as acupuncture, physical therapy, occupational therapy, speech therapy, vision therapy, vestibular therapy, cognitive behavioral therapy, other psychotherapies are allowed during the study. Such therapies should be stable for at least 3 months prior to screening and remain stable during the study. Such therapies should not be initiated after screening.
12. Concomitant use of hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 100 mg/day]) for the nighttime treatment of insomnia is allowed provided the dose has been stable for at least 1 month prior to Baseline and remains stable throughout the study.
13. Concomitant use of benzodiazepines is allowed provided the dose has been stable for at least 3 months prior to Screening and remains stable throughout the study.

14. Concomitant use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, citalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, desvenlafaxine, duloxetine) is allowed provided the dose has been stable for 3 months prior to Screening and remains stable throughout the study. Concomitant use of the SSRI paroxetine should be approached with caution. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day in elderly patients (i.e., ≥65 years of age) and for patients below 65 years of age the dosing is within the Package Insert guidance for this medication.
15. Concomitant use of prazosin, amantadine, methylphenidate, and atypical antipsychotic medication is allowed provided the dose is stable for at least 3 months prior to Screening and remains stable throughout the study.
16. Concomitant use of herbal supplements is allowed (with the exception of St. John's wort) provided the dose has been stable for at least 3 months prior to Screening and remains stable throughout the study.
17. Use of recreational and/or medicinal marijuana are allowed, provided the pattern and amount of use have been stable for at least 3 months prior to Screening and remain stable during the study. Marijuana use should not be initiated after Screening.
18. Use of all tobacco and nicotine products is permitted.
19. An eligible patient must have a reliable (able to comment accurately on the neuropsychiatric symptoms of the patient) informant/caregiver who interacts with the patient at least 2 hours per day for at least 3 days a week; is able and willing to comply with study procedures and attends all in-clinic study visits. In the event that the informant/caregiver cannot meet the specified time requirements of at least 2 hours per day for at least 3 days a week, the Investigator must discuss this potential patient with the Medical Monitor.
20. The patient and informant/caregiver must be willing to sign the informed consent form (ICF). Patients who are not capable of signing the ICF may be enrolled if they are able to provide assent and have an authorized representative who agrees to their participation and signs the ICF (as determined by local regulations) after the nature and risks of study participation have been fully explained.

4.2. Exclusion Criteria

1. Patients with progressive dementia, any progressive neurological disorders (e.g., multiple sclerosis, amyotrophic lateral sclerosis), or progressive deterioration in function.
2. Patients who have had any penetrating head trauma.
3. Patients with pseudobulbar affect (PBA).
4. Patients with significant symptoms of a depressive disorder, or a score > 14 on the Patient Health Questionnaire-9 (PHQ-9) at the Screening visit.
5. Patients with a history of a neurodevelopmental disorder (including attention-deficit/hyperactivity disorder), intermittent explosive disorder, or post-traumatic

stress disorder presenting before the TBI are excluded. Patients with a history of an anxiety or depressive disorder that preceded the TBI are allowed providing that, in the opinion of the Investigator, the symptoms of disinhibition (e.g., agitation, aggression, and/or irritability) are not better accounted for by a comorbid psychiatric disorder.

6. Patients with a history of or current clinical symptoms of schizophrenia, schizoaffective disorder, bipolar disorder, antisocial personality disorder, or borderline personality disorder as defined in the DSM-5.
7. Patients with any seizures during the 6 months prior to Screening. If patient is on antiepileptic medication, the dose should be stable for at least 3 months prior to Screening and should remain stable throughout the study.
8. Patients with myasthenia gravis (a contraindication for quinidine).
9. Patients with any personal history of complete heart block, QTc prolongation, or *torsades de pointes*.
10. Patients with Screening or Baseline QTcF of > 450 msec for males and > 470 msec for females, unless due to ventricular pacing (Screening ECG will be based on central review. Baseline ECG will be based on the machine read and Investigator's evaluation. If the Baseline ECG QTcF result from the machine read is exclusionary, do not dose the patient and contact the Medical Monitor).
11. Patients with premature ventricular contractions (PVCs) as evaluated by a central reader and deemed clinically significant by the Investigator.
12. Patients with any family history of congenital QT interval prolongation syndrome.
13. Patients with known hypersensitivity to DM, Q, opiate drugs (codeine, etc.), or any other ingredient of the study medication.
14. Patients with history of hypersensitivity to benzodiazepines (e.g., lorazepam).
15. Patients who currently are receiving DM/d6-DM co-administered with Q.
16. Patients who have been taking disallowed concomitant medications within 2 weeks or 5 half-lives, whichever is longer, prior to Baseline.
17. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (e.g., malignancy [except skin basal-cell carcinoma], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease). Certain other non-metastatic cancers may be allowed. Each case will be evaluated individually with the Medical Monitor.
18. Patients with history of postural syncope or any history of unexplained syncope (evaluated on a case by case basis) within 12 months of Baseline.
19. Patients determined to have a high imminent risk of falls during the study based on clinical evaluation by the Investigator.

20. Patients with a history of substance and/or alcohol or cannabis use disorder (as defined by DSM-5 criteria [Appendix 1]) within 6 months prior to Screening.
21. Patients planning on initiating recreational or medicinal marijuana use during the study.
22. Patients with evidence of serious risk of suicide at Screening or Baseline based on the S-STS, i.e., a score of 3 or 4 on any one question from 2 through 6 or question 11, or a score of 2 or higher on any one question of 1a, 7 through 10, or question 12, or patients who, in the opinion of the Investigator, present a serious risk of suicide.
23. Patients with an imminent risk of violence that could, in the opinion of the Investigator, put others at a significant risk of sustaining injury.
24. Patients who have received electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) within 1 month of Screening are excluded. ECT and TMS are not allowed during the study.
25. Patients of childbearing potential with a positive pregnancy test at Screening or Baseline or those who are breastfeeding or planning to become pregnant during the study.
26. Patients who are currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days prior to Baseline.
27. Patients residing in nursing homes are excluded (Note: patients in assisted living are allowed in the study).
28. Patients who, in the opinion of the Investigator, Medical Monitor, or sponsor, should not participate in the study.

4.3. Patient Withdrawal from the Study

Patients and informants/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/informant/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/informant/caregiver return all unused investigational product (IP), and follow-up with the patient/informant/caregiver regarding any unresolved adverse events.

In addition, patients who present at any time after Baseline visit (Day 1) with a persistent QTc interval (QTcF) > 500 msec (unless due to ventricular pacing) or a persistent QTcF interval change from the pre-dose Baseline ECG of > 60 msec, that is confirmed by the central ECG reader, will be withdrawn from the study after consultation with a 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 Visit 6 (Day 85) assessments and will receive a safety follow-up phone call 7 days after last dose of study medication.

If the patient withdraws from the study, and consent is withdrawn by the informant/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.

5. STUDY TREATMENTS

5.1. Treatments Administered

5.1.1. Description of Study Medications

Clinical study medication will be provided as hard, printed, opaque, blue, gelatin capsules (size 3). Each capsule of the study medication contains one of the following:

- 28 mg of d6-DM and 4.9 mg of Q (US Pharmacopoeia [USP], European Pharmacopeia [EP]): AVP-786-28/4.9
- 42.63 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-42.63/4.9
- Placebo

Drug supplies will be provided to the site in double-blind, individual, pre-labeled blister cards.

All medication used in this study 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.

5.1.2. Composition of AVP-786

The qualitative compositions of the two AVP-786 investigational products, in mg, and placebo are listed in Table 2.

Table 2 Composition of Investigational Product and Placebo

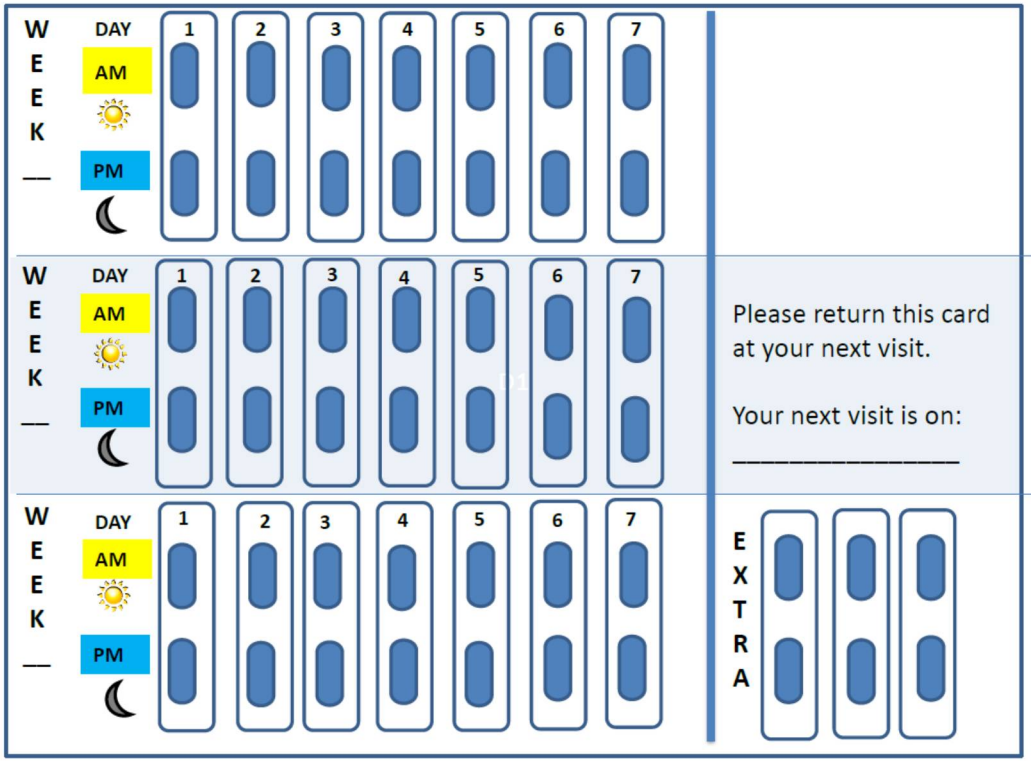
Ingredient	AVP-786-28/4.9*	AVP-786 42.63/4.9*	Placebo
Deudextromethorphan Hydrobromide Monohydrate, in mg	29.41	44.77	0
Equivalent to Deudextromethorphan Hydrobromide (d6-DM)*, in mg	28.00*	42.63*	0
Equivalent to Deudextromethorphan, in mg	21.67	33.00	0
Quinidine sulfate USP, EP, in mg	4.9	4.9	0
Croscarmellose sodium NF	√	√	√
Microcrystalline cellulose NF	√	√	√
Colloidal silicone dioxide NF	√	√	√
Magnesium stearate NF	√	√	√

EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary
* Used to express strength of clinical trial material.
√ Used to express presence of ingredient in AVP-786 or placebo capsule.

5.1.3. Packaging

The Investigators will be supplied with pre-labeled, individually pre-packaged sealed blister cards. Each panel of the blister card (1 week of study medication) consists of 2 rows of blister strips, one row for the morning dose and one row for the evening dose (Figure 1). Each blister card will contain 3 panels, providing sufficient study medication for 3 weeks of treatment, and an extra 3 days of supply is also provided (total of 48 capsules).

Figure 1 Sample Configuration of Investigational Product Blister Card



5.1.4. Labeling

All labels will contain the protocol number, product name, medicine identification number, an investigational drug warning, and dosage instructions to take 1 capsule in the morning and 1 capsule in the evening, storage conditions, patient number, visit number, date dispensed, keep out of reach of children statement, and company name. The blister card label will consist of 2 panels, with 1 detachable panel that will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the card label to record patient number, the visit week, and dispensing date. All investigational product labels comply with all applicable federal and local regulations.

5.1.5. Storage of Clinical Supplies

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-86°F).

5.1.6. Study Medication Administration

All patients will receive study medication according to the medicine identification numbers assigned by an interactive web response system (IWRS) randomization scheme. Designated staff at each site will dispense the study medication. Study medications should be administered to the patient by the informant/caregiver, family member, or be self-administered, except on the applicable clinic visit days when patients will take their dose of study medication at the clinic in the presence of site personnel, regardless of the time of day. Patient and informant/caregiver will be instructed that the patient should take the study medication orally with water approximately every 12 hours ± 4 hours (morning and evening). The time the patient takes each dose of medication should be recorded in the diary card. Patients' missed doses will be noted in the electronic case report form (eCRF).

All study medication will be supplied and administered in a double-blind manner throughout the entire duration of the study.

5.2. Accountability of Study Supplies

5.2.1. Receipt of Supplies

The Investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The Investigator will verify the accuracy of the information on the form, sign and date it, and return the form to the sponsor or its representative. All IP supplied is for use only in this study and should not be used for any other purpose. All blister card material identification numbers will also be recorded and tracked at the site using the Drug Accountability Log.

5.2.2. Record of Dispensing

Accurate recording of all IP dispensing for individual patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: (i) patient number to whom the drug was dispensed; (ii) the date(s) and quantity of the drug dispensed to the patient.

Additionally, the detachable panel of the two-panel label on each blister card will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the blister card label to record patient number, the visit week and dispensing date.

5.2.3. Unused Supplies

At the end of the study, all unused investigational supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or its representative, along with a completed and signed Drug Accountability Report/Material Shipping Form. If any study medication is lost or damaged, it should be indicated on the form.

5.3. Methods of Assigning Patients to Treatment Groups

5.3.1. Randomization

Upon entry into the study (after ICF is signed at screening), all patients will be assigned a 6-digit patient number. The first 3 digits consist of the center number. The last 3 digits will be assigned sequentially starting with 001. This 6-digit number is the main identifier for patients. Eligible patients will be randomized to receive AVP-786 capsules or matching placebo capsules on Baseline (Day 1) in a double-blind manner according to a randomization scheme devised by Avanir or its representative and managed within an IWRS. Patients will be stratified by study site.

Patients will have at least a 50% chance of receiving AVP-786 during the study.

For patients randomized to receive AVP-786, their dosage regimen will begin with d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) once a day in the morning and placebo in the evening for the first 7 days followed by AVP-786-28/4.9 BID for the next 7 days. Patients will then receive AVP-786-42.63/4.9 BID for the remaining duration of the study.

5.3.2. Blinding/Masking

If in the Investigator's judgment, it becomes medically necessary to identify which treatment a patient has received, the blind can be broken by the Investigator. If identification of the study treatment is required for emergency therapeutic measures, the Investigator or designee can immediately obtain the current treatment assignment electronically through the IWRS. In any situation requiring un-blinding, ideally the Investigator should contact the study Medical Monitor to discuss the unmasking of a patient. If this is not possible, the study Medical Monitor should be notified as soon as possible.

5.4. Patient Compliance

Patients/informants/caregivers will be provided with diary cards and will be instructed to record daily the number of capsules taken and the time of administration. Diary cards and blister cards will be collected and reviewed for compliance at each study visit (i.e., Visits 3 to 6 [Days 22, 43, 64, and 85]) or at the time of early study discontinuation. Patients/informants/caregivers will be instructed to bring diary cards and study medication blister cards to the clinic at each study visit. Following compliance review, the diary cards will be returned to the patient and collected for review at the next visit. For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses (compliance range 80% to 120%).

5.5. Concomitant Medications and Nondrug Therapies

Patients may not take any of the disallowed medications listed in Appendix 2 during the study or within the prior 2 weeks or 5 half-lives, whichever is longer, prior to the start of dosing on Day 1. At each visit, patients/informants/caregivers will be queried as to whether or not the patient has taken any concomitant medications and, if so, the Investigator will record the medications taken and the reasons for their use. The patient/informant/caregiver will be instructed to record concomitant use of rescue medication (lorazepam) in the diary card.

On the days of the Study Visits (i.e., Baseline [Day 1], Visit 3 [Day 22], Visit 4 [Day 43], Visit 5 [Day 64], and Visit 6 [Day 85]), patients will be instructed to refrain from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

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 serum digoxin levels that may be as much as doubled. Plasma 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 the 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. Alternative treatment should be considered.

5.5.1. Allowed Concomitant Medications and Nondrug Therapies

Concomitant use of antidepressants such as SSRI (e.g., fluoxetine, sertraline, citalopram) and SNRIs (e.g., venlafaxine, desvenlafaxine, duloxetine) is allowed, provided the dose is stable for 3 months prior to Screening and remains stable throughout the study. Concomitant use of the SSRI paroxetine should be approached with caution. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day in elderly patients (i.e., ≥65 years of age) and for patients below 65 years of age the dosing should be within the Package Insert guidance for this medication.

Concomitant use of hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 100 mg/day]) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 1 month prior to Baseline and remains stable throughout the study.

Concomitant use of benzodiazepines is allowed, provided the dose has been stable for at least 3 months prior to Screening and remains stable throughout the study. On the days of the Study Visits (i.e., Baseline [Day 1], Visit 3 [Day 22], Visit 4 [Day 43], Visit 5 [Day 64], and Visit 6 [Day 85]) patients are instructed to refrain from using benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed. See Section 5.5.2 for lorazepam as rescue medication.

Concomitant use of prazosin, amantadine, methylphenidate, and doses of atypical antipsychotic medication for control of aggression, agitation, and irritability behaviors is allowed, provided the dose is stable for at least 3 months prior to Screening and remains stable throughout the study.

Patients concomitantly taking SSRIs, SNRIs, triptans, or other drugs that may increase serotonin should be monitored for serotonin syndrome, which includes altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Concomitant use of herbal supplements is allowed (with the exception of St. John's wort) provided the dose has been stable for at least 3 months prior to Screening and remains stable throughout the study.

Nondrug therapies such as acupuncture, physical therapy, occupational therapy, speech therapy, vision therapy, vestibular therapy, cognitive behavioral therapy, and other psychotherapies are allowed in the study. Such therapies should be stable for at least 3 months prior to screening and remain stable during the study. Such therapies should not be initiated after Screening.

Use of recreational and/or medicinal marijuana is allowed during the study provided the pattern and amount of use remain stable during the study. On the days of the Study Visits (i.e., Baseline [Day 1], Visit 3 [Day 22], Visit 4 [Day 43], Visit 5 [Day 64], and Visit 6 [Day 85]), patients will be instructed to refrain from using or consuming any recreational and/or medicinal marijuana for 12 hours prior to the visit and until the study assessments have been completed. Patients with cannabis use disorder per DSM-5 within 6 months of Screening are excluded.

Use of alcohol is permitted. On the days of the Study Visits (Baseline [Day 1], Visit 3 [Day 22], Visit 4 [Day 43], Visit 5 [Day 64], and Visit 6 [Day 85]), patients will be instructed to refrain from consuming alcohol for 12 hours prior to the visit and until the study assessments have been completed.

Use of all tobacco and nicotine products is permitted.

5.5.2. Rescue Medication

Patients will be allowed to receive oral lorazepam as rescue medication for the short-term treatment of TBI symptoms if deemed necessary by the Investigator. Lorazepam will be administered in a dose up to 1.5 mg/day and not to exceed 3 days in a 7-day period in the study. The patient/informant/caregiver must record concomitant use of lorazepam in the diary and must be reminded of the potential increase in the risk of falling by benzodiazepines.

5.5.3. Prohibited Concomitant Medications and Nondrug Therapies

A list of examples of prohibited medications is provided in Appendix 2.

CCI [redacted]

6. STUDY ASSESSMENTS AND PROCEDURES

Whenever possible, for consistency of ratings, the same rater should rate a patient (and the informant/caregiver) at each of the patient's visits for all 3 of the following scales: the NPI-C, the mCGI-S, and the mCGI-C. The mCGI-S and mCGI-C must be administered after the NPI-C subscales. If it is not possible to have the same rater for the NPI-C and mCGI subscales (mCGI-S and mCGI-C); it is critical that 1 rater assesses both of the mCGI subscales for a patient. In addition, if the NPI-C rater differs from the mCGI rater, prior to making the mCGI assessment, the mCGI rater must review the NPI-C results, discuss the results with the NPI-C rater, and review any additional pertinent information.

6.1. Screening

6.1.1. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a multiple-choice self-report inventory that is used in this study for the evaluation of depression symptoms. The PHQ-9 is specific to depression, scoring each of the 9 DSM-4 related criteria. In addition to making criteria-based diagnoses of depressive disorders, the PHQ-9 is also a reliable and valid measure of depression severity.[32] PHQ-9 has been studied in TBI,[33] supporting the screening criteria (total score ≤ 14) used in this study.

The PHQ-9 will be assessed at Screening (Day -28 to Day -1).

6.2. Efficacy

6.2.1. Neuropsychiatric Inventory- Clinician Rating Scale (NPI-C)

The NPI-C is a clinical instrument that has been validated in a variety of neuropsychiatric diseases and has been used for evaluating psychopathology in TBI.[34,35] The NPI-C is a retrospective informant/caregiver interview covering 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavioral disorders, and appetite/eating disorders. Neuropsychiatric manifestations within a domain are collectively rated by the informant/caregiver in terms of both frequency (1 to 4) and severity (1 to 3), yielding a composite symptom domain score (frequency x severity). In this study, scores for the NPI Aggression/Agitation and Irritability/Lability subscales will be derived from the NPI-C at the Screening and Baseline visits, to determine if the patient's behavior meets a clinically relevant threshold (score of ≥ 4 on any of the three subscales) for entry into the study.

The theoretical framework of the NPI-C was based on the NPI which has been extensively validated. In addition to an expansion (more questions and more domains), the NPI-C is structured such that every question in each domain is evaluated through informant/caregiver and patient interview and all of this information then leads to a clinical interpretation of the severity of the behavior by a clinician. Fourteen neuropsychiatric symptom domains are covered: delusions, hallucinations, agitation, aggression, dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor disturbance, sleep disorders,

appetite and eating disorders, and aberrant vocalizations. The scripted NPI-C interview for each domain opens with a screening question, followed by questions about each domain-specific behaviors. Individual neuropsychiatric manifestations within a domain are each rated by the informant/caregiver for frequency (1 to 4), severity (0 to 3) and informant/caregiver distress (0 to 5). The frequency of these behaviors is elicited from the patient, which the clinician integrates into a (0 to 3) clinical severity rating that is based on all the available information. The frequency, severity, and informant/caregiver distress ratings have defined anchor points to enhance the reliability of responses. The NPI-C allows for use of each domain independently as stand-alone based on the objectives of the research question. Ratings on the clinician score of the Agitation, Aggression, and Irritability/Lability domains of the NPI-C will be combined into a composite score that serves as the primary efficacy endpoint of the study.

Psychometric properties of the NPI-C were demonstrated in a study by de Medeiros et al, 2010[36] in 8 different countries and were also confirmed in another study in a Brazilian community by Stella et al, 2013,[37] in patients with dementia. These studies showed strong inter-rater reliability and moderate to strong convergent validity for the clinician ratings of the NPI-C domains that included apathy, agitation, hallucination, delusion, aberrant vocalization, and depression.[36,37] In addition, the NPI-C demonstrates strong internal consistency with high correlations (Cronbach's alpha values) for items within each domain between themselves and with the total of that domain (Avanir data on file).

In this study, only the following subscales will be administered: Agitation, Aggression, Irritability/Lability, and Disinhibition. The NPI-C subscales will be administered to the patient and informant/caregiver at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85). The recall period for the behaviors in each domain will be 3 weeks, for all visits. The NPI-C subscales should be administered by the same rater at each visit.

For the purpose of assessing Inclusion Criterion #7, the NPI Agitation/Aggression and the Irritability/Lability subscale scores will be derived from the NPI-C at Screening and Baseline. The derivation will be done by the electronic device used for collection of clinical outcomes assessment data (Section 7.2).

6.2.2. Clinical Global Impression (CGI) Scales

The CGI was developed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication.[38] The Early Clinical Drug Evaluation Unit (ECDEU) version of the CGI is the most widely used format of this validated tool, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information.[39] The CGI scales are quick to administer, provided that the clinician knows the patient well.

Reliability and validity of CGI have been tested in multiple studies, including patients with dementia, schizophrenia, and affective disorders.[40,41] Overall, CGI showed high correlation (r: ~90%) with other assessment instruments, and it has also shown positive significant relationships and concurrent validity with other clinician's rating. In addition, the scale has good sensitivity to change over time.

In patients with TBI who present with marked impairments in motor function, cognition, or other areas, global assessments may not be sensitive to specific changes in their target neuropsychiatric symptoms of aggression, agitation, and irritability. The CGI scales are modified in this study, and the clinician is explicitly instructed to rate the severity (mCGI-S) or change (mCGI-C) of the patient's aggression, agitation, and irritability symptoms, to ensure that the global ratings specifically evaluate the target symptoms. At each visit, the NPI-C is administered before the mCGI-C and mCGI-S scales are rated, to ensure the mCGI-C and mCGI-S scale ratings reflect a thorough assessment of the patient's neurobehavioral symptoms.

The mCGI-S and mCGI-C must be administered after the NPI-C. Whenever possible, each of the raters should be the same rater for a patient (and the informant/caregiver) for each scale at each of the patient's visits. If it is not possible to have the same rater for the NPI-C and the mCGI subscales (mCGI-S and mCGI-C); it is critical that 1 rater assesses both of the mCGI subscales for a patient. In addition, if the NPI-C rater differs from the mCGI rater, prior to making the mCGI assessment, the mCGI rater must review the NPI-C results, discuss the results with the NPI-C rater, and review any additional pertinent information.

6.2.2.1. Modified Clinical Global Impression of Severity (mCGI-S)

The mCGI-S is a 7-point (1-7) modified version of the CGI-S scale,[39] and requires that the clinician rate the severity of the patient's neurobehavioral disinhibition including aggression, agitation, and irritability, at the time of assessment relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating as 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, among the most extremely ill patients.

The mCGI-S will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 4 (Day 43), and Visit 6 (Day 85). The mCGI-S must be completed at each of these visits after the NPI-C is completed.

6.2.2.2. Modified Clinical Global Impression of Change (mCGI-C)

The mCGI-C is a 7-point modified version of the CGI-C scale,[39] that requires the clinician to rate their general impression of the change in patient's neurobehavioral disinhibition including aggression, agitation, and irritability at the time of assessment, relative to the clinician's past experience with the patient's neurobehavioral disinhibition at admission. Considering total clinical experience, a patient is assessed for change of mental illness as: 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse.

The mCGI-C will be assessed at Visit 4 (Day 43) and Visit 6 (Day 85) for the clinician's general impression of the change in the patient's overall clinical status. At Visit 4 (Day 43), change from the Baseline visit (Day 1) will be assessed. At Visit 6 (Day 85), change from Visit 4 (Day 43) and change from the Baseline visit (Day 1) will also be assessed.

The mCGI-C must be completed at each of these visits after the NPI-C interview is completed.

6.2.3. Patient Global Impression of Severity (PGI-S)

The PGI-S is a single-question scale that will specifically assess the severity of symptoms of neurobehavioral disinhibition including aggression, agitation, and irritability, on a 7-point scale, as: 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. The PGI-S will be completed by the patient at Baseline (Day 1), Visit 4 (Day 43), and Visit 6 (Day 85).

6.2.4. Patient Global Impression of Change (PGI-C)

The PGI-C is a 7-point (1-7) scale used to assess treatment response and is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.[39]

The PGI-C will be assessed and rated by the patient at Visit 4 (Day 43) and Visit 6 (Day 85) and will focus on the patient's neurobehavioral disinhibition symptoms including aggression, agitation, and irritability.

6.3. Pharmacokinetic/Pharmacodynamic Analyses

At Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85), patients will have blood samples collected per instructions provided by the sponsor for analysis of plasma levels of d6-DM, d6-DM metabolites, and Q and estimations of pharmacokinetic parameters. The time when the patient was administered the dose of study medication and the time of the blood draw will be recorded on the eCRF. At Visit 4 (Day 43) and Visit 6 (Day 85) the blood samples should be obtained at 1 to 3 hours following study medication administration. At Visit 5 (Day 64) the blood sample should be obtained just prior to study medication administration. Plasma samples will be separated by centrifugation and then frozen at -20°C until assayed at the analytical unit.

6.4. Safety

6.4.1. Adverse Events

6.4.1.1. Definitions

An adverse event (AE) is any untoward medical occurrence or unintended change (physical, psychological, or behavioral) from the time the ICF is signed, including inter-current illness, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including any clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold or 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:

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

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

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

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

Unlikely related: 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

Possibly related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; but could have been produced by other factors such as the 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

6.4.1.2. Serious Adverse Events

A Serious Adverse Event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. 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, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
3. Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
4. In-patient hospitalization or prolongation of hospitalization

5. 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.

The terms "cancer" and "overdose" are not always considered to be SAEs, but if a patient experiences cancer or overdose, they are still reportable as AEs.

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 (PBEF). The site should follow-up each trimester with the patient/partner until the final outcome is known (i.e., 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.

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

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.

6.4.1.3. Reporting Adverse Events

Patients/informants/caregivers will be queried regarding AEs at each clinic visit after the Screening visit and during the Visit 2 (Day 8) phone call. The Investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication and up until 30 days after receiving the last dose of study medication will be followed. Patients/informants/caregivers will receive a phone call 7 days after the last clinic visit (Visit 6) to query on any adverse events experienced since the last visit. Patients who terminate early, will receive the phone call 7 days after the last dose of study medication.

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 the treatment whether considered treatment-related or not, must be reported to the sponsor.

For all SAEs, the Investigator should consult with Avanir's Medical Monitor or designated representative as needed and report any SAE via the Serious Adverse Event Reporting (SAER) Form by fax/email form (as detailed below) no later than 24 hours after becoming aware of the

event. The SAE must be assessed for the following details: seriousness criteria of the event, SAE start date, SAE stop date, severity, relationship to study medication, action taken regarding the study medication, and outcome to date. The narrative section of the form may be used to detail any treatment information.

SAE and Events to Monitor reporting by FAX or e-mail correspondence:
FAX: CCI [redacted] or CCI [redacted]
E-mail: CCI [redacted]

SAE hotline (24-hour/7 days a week)
Phone: CCI [redacted] or CCI [redacted]

Preliminary (initial) reports will be followed by detailed descriptions, which may include copies of hospital records/discharge summaries, autopsy reports, death certificates and other related documents as requested.

The Institutional Review Board/Ethics Committee (IRB/EC) will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

6.4.1.4. Procedures to be Followed in the Event of Abnormal Test Values

Any patients with clinically significant abnormal laboratory test results may be required by the Medical Monitor 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.

6.4.2. Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1) and Visit 6 (Day 85). The physical examination will include assessments of 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.

6.4.3. Vital Signs

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed at all clinic visits. Supine BP and HR will be measured after a 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 in between readings and recorded. After 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 (ºF) will be assessed at all clinic visits. Weight will be recorded at Baseline (Day 1) and Visit 6 (Day 85). Height will be recorded at Baseline (Day 1).

6.4.4. Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at the specified visits.

At the Screening visit (Day -28 to Day -1) and Visit 6 (Day 85) only:

- Thyroid function tests (thyroid stimulation hormone [TSH] and, if TSH is abnormal, reflex triiodothyronine [T3], reflex free thyroxine [T4], and reflex total T4)
- Glycosylated hemoglobin (HbA1c) test

At the Screening visit (Day -28 to Day -1), Visit 4 (Day 43), and Visit 6 (Day 85):

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen [BUN], serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], aspartate aminotransferase/serum glutamic-oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic-pyruvic transaminase [ALT/SGPT], creatine kinase [CK], gamma-glutamyl transferase [GGT], triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] 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)

At the Screening visit (Day -28 to Day -1), Visit 3 (Day 22), Visit 5 (Day 64), and Visit 6 (Day 85) only:

- Urine toxicology screening for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and marijuana metabolites.

Any patients with clinically significant abnormal laboratory test results may be required by the Medical Monitor 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.

6.4.5. Pregnancy Tests

A serum pregnancy test is to be performed for patients of childbearing potential at the Screening visit (Day -28 to Day -1), and urine pregnancy tests will be performed for patients of childbearing potential at all other clinic visits prior to dosing of study medication. Patients with a positive pregnancy test should be discontinued from the study (refer to Section 6.4.1.2 for follow-up instructions).

All patients of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication. Patients of childbearing

potential are defined as any patient who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

6.4.6. Electrocardiograms

A resting 12-lead electrocardiogram (ECG) will be performed at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85). Triplicate ECGs will be performed at Screening. At Baseline (Day 1) and Visit 4 (Day 43) two ECGs will be performed; one prior to study medication dosing and one at 1 to 2 hours after dosing. At Visit 3 (Day 22), Visit 5 (Day 64), and Visit 6 (Day 85), post-dose ECGs will be collected.

ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute), QRS complex, and PR and QTc intervals (milliseconds). Results will be provided by the central reader to the Investigators within 24 hours. ECG data will be transferred automatically from the central reader into Avanir's database monthly. ECG abnormalities present at Screening will be recorded as medical history. Any changes from the ECG status at the Screening Visit 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, be repeated within a 1-week period.

6.4.7. Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors.[42] Each item of the S-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). The S-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. For the screening visit, the timeframe for the items on the scale will be 'in the past 6 months' and for all other visits it will be 'since last visit'. The S-STS is administered on paper for all visits.

The S-STS will be assessed at all clinic visits. Any change in the S-STS score indicating the presence of suicidality should be evaluated by the Investigator and reported to the Medical Monitor. The Investigator must provide necessary intervention to manage suicidal ideation or refer the patient to their primary physician.

6.5. Schedule of Evaluations and Procedures

A schedule of evaluations and procedures is provided in Table 1.

6.5.1. Description of Study Procedures

At each visit throughout the study, site staff will be required to enter information into the IWRS regarding patient data and pre-defined study assessment results. Further instructions will be provided in the IWRS Site Manual. Every attempt should be made to complete the specified procedures in the order provided. However, given the nature of the symptoms under study,

changes can be made to accommodate the well-being of patient and informant/caregiver, with the following exception: NPI-C must be performed prior to the mCGI-S and mCGI-C.

6.5.1.1. Screening Visit (Days -28 to -1)

The following procedures will be performed at Screening (approximately 28 days prior to Day 1). The screening period may be extended after discussion with, and approval by, the Medical Monitor. In the event that a patient is rescreened for enrollment, a new ICF must be signed, a new patient number assigned, and all screening procedures repeated.

1. The Investigator will provide the patients and informants/caregivers with informed consent and will explain the rationale for the study, providing ample time to ask questions.
2. Medical history, including patient demographics, any prior and concomitant medications (including over-the-counter [OTC], vitamins, and supplements), medicinal/recreational marijuana and alcohol use will be reviewed and recorded.
3. Review inclusion/exclusion criteria (eligibility form).
4. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
      (Note: the NPI Agitation/Aggression and Irritability/Lability subscale scores will be derived from the NPI-C for eligibility assessment)
    - mCGI-S
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.1)
    - PHQ-9
    - S-STS (paper worksheet)
    - Risk assessment for falls
5. Vital signs will be measured and recorded.
6. Physical and neurological examination will be performed.
7. A resting 12-lead ECG will be performed in triplicate.
8. A blood specimen will be collected for:
    - Safety laboratory assessments
    - A serum pregnancy test (for patients of childbearing potential only)
9. A urine specimen will be collected for drug screening/toxicology and safety laboratory assessments.

Following screening procedures for assessment of inclusion and exclusion criteria, the site will complete a Protocol Eligibility Form (PEF) and submit to the Medical Monitor for review and approval. Patients deemed eligible by the Principal Investigator and the Medical Monitor will be randomized into the study should they continue to qualify at the Baseline (Day 1) visit. Patients

who have ECG or laboratory test results outside of the reference normal range that the Investigator considers to be clinically significant and may put the patient at a higher risk for study participation, will not be enrolled.

Patient and Informant/Caregiver Instructions

Patients approved for the study will be instructed to return to the site for the Baseline (Day 1) visit. On the day of the Baseline visit (Day 1), patients will be instructed to refrain from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the Baseline (Day 1) study assessments have been completed.

6.5.1.2. Baseline Visit (Day 1)

The Baseline visit (Day 1) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. Inclusion/exclusion criteria will be reviewed.
2. Patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements), and the patient's use of benzodiazepines, medicinal/recreational marijuana, and alcohol during the 12 hour time window prior to the visit and through completion of the study visit procedures will be assessed.
3. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
      (Note: the NPI Agitation/Aggression and Irritability/Lability subscale scores will be derived from the NPI-C for eligibility assessment)
    - mCGI-S
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.1)
    - PGI-S
    - S-STS (paper worksheet)
4. Vital signs, height and weight will be measured and recorded.
5. A pre-dose resting 12-lead ECG will be performed.
6. A urine pregnancy test will be performed for patients of childbearing potential only.
7. A blood specimen will be collected for CYP2D6 genotyping.

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 baseline assessments described above) and will be assigned with a study medication kit number via IWRS.

Study Medication Dosing:

The first dose of study medication will be administered from the AM strip of blister card at the clinic regardless of the time of day.

After Dosing:

1. A resting 12-lead ECG will be performed between 1 and 2 hours after taking the morning dose of study medication.
2. The patient/informant/caregiver will be queried regarding AEs.
3. Patient diary card and study medication blister card for a 3-week treatment period will be dispensed.

Patient and Informant/Caregiver Instructions

Patients/informants/caregivers will be instructed to continue BID study medication administration to the patient (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the phone visit (i.e., Visit 2 [Day 8]).

The Investigator and/or study coordinator will give patients and informants/caregivers detailed instructions regarding study procedures including how to complete the patient's diary card. 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. Patients and informants/caregivers will also be instructed to bring to the clinic any unused study medication and patient's diary card at each study visit.

On the days of the Study Visits (i.e., Visits 3 to 6 [Day 22, Day 43, Day 64, and Day 85]), patients will be instructed to refrain from taking their morning dose of study medication and from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

Patients/informants/caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.5.1.3. Visit 2 (Day 8 + 3-day window) – phone call

The patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements).

Patient and Informant/Caregiver Instructions

Patients/informants/caregivers will be instructed to continue BID study medication administration to the patient (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next clinic visit (i.e., Visit 3 [Day 22]). On the day of the next study visit (i.e., Visit 3 [Day 22]), patients will be instructed to refrain from taking their morning dose of study medication and from using or

consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

Informants/caregivers/patients will be instructed to consult with the study site prior to the patient taking any non-study medications. They will also be instructed to bring to the clinic any unused study medication and patient's diary card at each study visit. Patients/informants/caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.5.1.4. Visit 3 (Day 22 ± 3-day window)

Visit 3 (Day 22) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. The patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements), and the patient's use of benzodiazepines, medicinal/recreational marijuana, and alcohol during the 12 hours prior to the visit and through completion of the study visit procedures will be assessed.
2. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
    - S-STS (paper worksheet)
3. Vital signs will be measured and recorded.
4. A urine specimen will be collected for:
    - Drug screening
    - A pregnancy test for patients of childbearing potential only
5. Returned study medication blister card will be reviewed for compliance.
6. Patient's diary card will be collected and reviewed for compliance.

Study Medication Dosing:

Patients will be assigned with a study medication kit number via IWRS.

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. A resting 12-lead ECG will be performed between 1 and 2 hours after taking the morning dose of study medication.
2. Patient diary card and study medication blister card for a 3-week treatment period will be dispensed.

Patient and Informant/Caregiver Instructions

Patients/informants/caregivers will be instructed to continue BID study medication administration to the patient (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next scheduled visit (i.e., Visit 4 [Day 43]). On the day of the next study visit (i.e., Visit 4 [Day 43]), patients will be instructed to refrain from taking their morning dose of study medication and from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

The Investigator and/or study coordinator will give patients and informants/caregivers detailed instructions regarding study procedures including how to complete the patient's diary card. 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. Patients/informants/caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Patients/informants/caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.5.1.5. Visit 4 (Day 43 ± 3-day window)

Visit 4 (Day 43) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. The patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements), and the patient's use of benzodiazepines, medicinal/recreational marijuana, and alcohol during the 12 hours prior to the visit and through completion of the study visit procedures will be assessed.
2. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
    - mCGI-S
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.1)
    - mCGI-C
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.2)
3. Vital signs will be measured and recorded.
4. A pre-dose resting 12-lead ECG will be performed.
5. A urine specimen will be collected for:
    - A pregnancy test for patients of childbearing potential only
    - Urinalysis
6. Returned study medication blister card will be reviewed for compliance.
7. Patient's diary card will be collected and reviewed for compliance.

Study Medication Dosing:

Patients will be assigned with a study medication kit number via IWRS.

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. The following assessments will be completed:
    - PGI-S
    - PGI-C
    - S-STS (paper worksheet)
2. A resting 12-lead ECG will be performed between 1 and 2 hours after taking the morning dose of study medication.
3. Blood specimens will be collected 1 to 3 hours after taking the morning dose of study medication for PK analysis and for safety laboratory assessments.
4. Patient diary card and study medication blister card will be dispensed for a 3-week treatment period.

Patient and Informant/Caregiver Instructions

Patients/informants/caregivers will be instructed to continue BID study medication administration to the patient (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next scheduled visit (i.e., Visit 5 [Day 64]). On the day of the next study visit (i.e., Visit 5 [Day 64]), patients will be instructed to refrain from taking their morning dose of study medication and from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

The Investigator and/or study coordinator will give patients and informants/caregivers detailed instructions regarding study procedures including how to complete the patient's diary card. 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. Patients/informants/caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Patients/informants/caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.5.1.6. Visit 5 (Day 64 ± 3-day window)

Visit 5 (Day 64) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. The patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements), and the patient's use of

benzodiazepines, medicinal/recreational marijuana, and alcohol during the 12 hours prior to the visit and through completion of the study visit procedures will be assessed.

2. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
    - S-STS (paper worksheet)
3. Vital signs will be measured and recorded.
4. A urine specimen will be collected for:
    - Drug screening
    - A pregnancy test for patients of childbearing potential only
5. A blood specimen will be collected before dosing for PK analysis.
6. Returned study medication blister card will be reviewed for compliance.
7. Patient's diary card will be collected and reviewed for compliance.

Study Medication Dosing:

Patients will be assigned with a study medication kit number via IWRS.

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. A resting 12-lead ECG will be performed between 1 and 2 hours after taking the morning dose of study medication.
2. Patient diary card and study medication blister card will be dispensed for a 3-week treatment period.

Patient and Informant/Caregiver Instructions

Patients/informants/caregivers will be instructed to continue BID study medication administration to the patient (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next scheduled visit (i.e., Visit 6 [Day 85]). On the day of the next study visit (i.e., Visit 6 [Day 85]), patients will be instructed to refrain from taking their morning dose of study medication and from using or consuming any recreational and/or medicinal marijuana, alcohol, or benzodiazepine medications for 12 hours prior to the visit and until the study assessments have been completed.

The Investigator and/or study coordinator will give patients and informants/caregivers detailed instructions regarding study procedures including how to complete the patient's diary card. 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. Patients/informants/caregivers will also be instructed to bring to the clinic any unused study medication at each study visit.

Patients/informants/caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.5.1.7. Visit 6 (Day 85 ± 3-day window) / Early Termination

Visit 6 (Day 85) should occur in the morning. Patients who withdraw prior to study completion are required to complete study procedures as listed in Visit 6 within 48 hours of the last dose of study medication. The following procedures will be performed.

Before Dosing:

1. The patient/informant/caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements), and the patient's use of benzodiazepines, medicinal/recreational marijuana, and alcohol during the 12 hours prior to the visit and through completion of the study visit procedures will be assessed.
2. The following assessments will be completed:
    - NPI-C Agitation, Aggression, Irritability/Lability, and Disinhibition subscales (conducted in accordance with Section 6.2.1)
    - mCGI-S
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.1)
    - mCGI-C
      (conducted after the NPI-C in accordance with the guidance in Section 6.2.2.2)
    - PGI-S
    - PGI-C
    - S-STS (paper worksheet)
3. Returned study medication blister card will be reviewed for compliance.
4. Patient's diary card will be collected and reviewed for compliance.
5. Vital signs and weight will be measured and recorded.
6. Physical and neurological examination will be performed.
7. A urine specimen will be collected for:
    - Urinalysis
    - Drug screening
    - A pregnancy test for patients of childbearing potential only
8. Early Termination only: For patients who withdraw prior to study completion, a 12-lead ECG should be collected prior to a blood specimen for safety laboratory assessments.

Study Medication Dosing (not applicable for Early Termination):

The last dose of study medication will be administered to the patient at the clinic from the blister card brought in by the patient/informant/caregiver.

After Dosing (not applicable for Early Termination):

1. A resting 12-lead ECG will be performed between 1 and 2 hours after taking the morning dose of study medication.
2. Blood specimens will be collected for PK analysis and for safety laboratory assessments between 1 and 3 hours after dosing.

Any previously reported and not yet resolved AE, and any newly reported AE at the time of this visit will be followed-up for up to 30 days after the last dose of study medication.

6.5.1.8. Safety Follow-up Phone Calls

Patients/informants/caregivers will receive a phone call 7 (+3) days after the last clinic visit (Visit 6 [Day 85]) to query on any adverse events experienced and concomitant medication changes since the last visit. Patients who terminate early will receive the phone call 7 (+3) days after the last dose of study medication.

7. DATA MANAGEMENT

7.1. Data Collection

The sponsor or designated representative (e.g., Contract Research Organization [CRO]) will perform the data management activities in accordance with the data management plan (DMP). The DMP will outline the systems and procedures to be used in the study.

Clinical study data will be reported (captured) by study site personnel on eCRFs. An eCRF must be completed for every patient enrolled in the study. The eCRF data will be entered by trained study-site personnel and then reviewed for completeness and accuracy and electronically signed by the Investigator or authorized designee. All study-site personnel must use a password-protected user account to enter, review, or correct study data. Electronic signature procedures shall comply with the Code of Federal Regulations (CFR) Title 21 Part 11. Passwords will be strictly confidential.

All eCRF data will be exported from the electronic data capture (EDC) system and transferred to the sponsor or representative. The sponsor or representative will also receive electronic transfers of non-eCRF data such as laboratory data from the central laboratory, ECG data from the central ECG reader, as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the sponsor or representative and documented in the DMP or vendor data transfer requirements document as appropriate.

The clinical monitoring staff will perform source data verification of the data recorded in the EDC system with source documents at the clinical study sites according to the data management plan and clinical monitoring plan. The data will be subjected to consistency and validation checks within the EDC system with supplemental data reviews performed outside of the EDC system.

Medical history and adverse events will be coded using a current version of Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications using a current version of the World Health Organization (WHO) Drug Dictionary. The sponsor or representative will perform a medical safety review of the coding.

Completed eCRF images with a date- and time-stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the Investigator's site and at the sponsor's site.

7.2. Electronic Clinical Outcomes Assessment Data

This study will use electronic clinical outcome assessments (eCOA) to capture questionnaire data and associated audio recordings during patient/informant/caregiver interviews. The data will be transmitted electronically to a centralized database at the eCOA vendor. Data may be reviewed by site staff via secure access.

Upon study completion, the eCOA data, audit trail, and trial and system documentation will be archived. The Investigator will receive questionnaire data for the site that must be kept with the study records as source data. Acknowledgement of receipt of the archival data is required.

eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with US FDA regulations for electronic records and electronic signatures (CFR Title 21 Part 11). The eCOA device data are available for view access only via secure access. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will routinely review data in a blinded manner only.

8. STATISTICAL METHODS

8.1. Analysis Populations

Three analysis populations will be used, modified intent-to-treat (mITT), per-protocol (PP), and safety.

- mITT: The mITT population includes all patients who take at least one dose of study medication and who have at least one post-baseline efficacy assessment. The mITT population will be used for all analyses of efficacy. Patients will be included in the treatment group to which they were randomized regardless of treatment received.
- PP: The per-protocol population (PP) includes all patients who have no significant protocol deviation that may impact efficacy evaluation. Patients in PP will be included in the treatment group based on the actual treatment received.
- Safety: The safety population includes all patients who receive study treatment. The safety population will be used for all analyses of safety. Patients will be included in the treatment group based on the actual treatment received.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group using descriptive statistics.

8.3. Efficacy Analysis

8.3.1. Study Endpoints

Primary efficacy endpoint:

The primary efficacy endpoint is the change from Baseline to Week 12 in the NPI-C-3 composite score.

Secondary efficacy endpoints:

The secondary efficacy endpoints are the change from Baseline to Week 12 in the following measures (raw score for mCGI-C and PGI-C):

- NPI-C subscales (Aggression, Agitation, Irritability/Lability, and Disinhibition)
- mCGI-C
- mCGI-S
- PGI-S
- PGI-C

8.3.2. Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 12 in the NPI-C-3 composite score.

For the primary efficacy endpoint, the null hypothesis is that there is no treatment effect and it will be tested against the alternative that there is a treatment effect. The treatment effect will be estimated by using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data under missing at random (MAR) assumption. The model will include fixed effects for treatment, visit, study site, treatment-by-visit interaction, baseline-by-visit interaction and baseline value. An unstructured covariance model will be used. Analyses with missing values imputed Multiple Imputation (MI) may be performed as sensitivity analyses under missing not at random (MNAR) assumptions.

8.3.3. Secondary Efficacy Analyses

Secondary efficacy endpoints include change from Baseline to Week 12 for the following efficacy measures: NPI-C subscales (Aggression, Agitation, Irritability/Lability, and Disinhibition), mCGI-C (raw score), mCGI-S, PGI-S, and PGI-C (raw score).

Treatment comparison tests using similar method as the primary efficacy analysis will be performed. Detailed analyses will be described in the Statistical Analysis Plan (SAP).

8.4. Pharmacokinetic/Pharmacodynamic Analysis

Plasma concentrations of d6-DM, Q, and metabolites will be measured and results will be summarized descriptively overall and by CYP2D6 metabolizer group. Plasma concentration results will be used to assess the pharmacokinetic (PK) properties of d6-DM and its metabolites. Additional PK and pharmacodynamic (PD) correlations may also be performed. Additional details will be described in the SAP.

8.5. CYP2D6 Genotype

Genotype information will be used to classify patients as poor metabolizers, intermediate metabolizers, extensive metabolizers, or ultra-rapid metabolizers of d6-DM.

8.6. Safety Analysis

Safety will be assessed by the following measurements: AEs, physical and neurological examination, vital signs, urine pregnancy test, clinical laboratory assessments, resting 12-lead ECG, and S-STS. All safety measures will be summarized by treatment group.

Safety analyses will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment.

8.6.1. 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, non-fatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAE). TEAEs are those AEs that occur after the first dose of study medication up until 30 days after last dose.

8.6.2. Vital Signs and Electrocardiograms

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

8.6.3. Clinical Laboratory Values

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

8.7. Data and Safety Monitoring Board

There will be no Data and Safety Monitoring Board (DSMB) in the study.

8.8. Interim Analysis

An interim analysis may be performed and will be pre-specified in the SAP.

8.9. Sample Size Calculations

Sample size calculations are performed assuming a normal distribution for the primary efficacy endpoint of change from baseline in NPI-C-3 composite score. It is assumed that the treatment difference is -2.50, and the standard deviation in drug and placebo groups is assumed to be equal to 5.0, producing an effect size of -0.50. The total cumulative drop-out rate is assumed to be 30%. A sample size of 150 patients will have an approximate 74% power to reject the null hypothesis in the comparison of AVP-786 versus placebo with 2-sided type I error α=0.05.

9. ADMINISTRATIVE PROCEDURES

9.1. Institutional Review Board/Ethics Committee Approval

Institutional Review Boards/Ethics Committees (IRBs/ECs) must meet the guidelines set out by the US FDA and conform to local laws and customs where appropriate. Written IRB/EC approval for the protocol and the signed ICF must be obtained and transmitted to Avanir Pharmaceuticals or representative before the study can be initiated. The IRB/EC must be informed of and approve all protocol amendments. The Investigator will ensure that this study is conducted in full conformance with local laws and according to National and State/Provincial laws, ICH E6 (r2) and the World Medical Association Declaration of Helsinki.

9.2. Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed consent will be obtained from the patient. The patient's informant/caregiver will also be asked to provide informed consent as they will be providing data on themselves and the patient, as well as, being responsible for ensuring compliance from the patient between study visits.

The patients and their informants/caregivers will be properly informed of the purpose of the study. The patients and the informant/caregiver will be alerted to any anticipated AE that may be encountered with the study medication. A signed ICF will be obtained from all patients and their informant/caregiver prior to patient entry into this study. Patients and informants/caregivers will be provided with a copy of their signed ICF.

9.3. Patient's Diary Card

The patient's diary card will be reviewed by clinical study personnel at all study treatment visits for confirmation of medication dosage and any rescue medication received. The study personnel are responsible for (i) ensuring that patients and/or informants/caregivers are properly collecting data and recording it into the diaries; and (ii) transcribing the diary recordings into the eCRF. The diary card will be collected at all study visits after baseline except the Visit 2 (Day 8) phone visit. The diaries will be reviewed and returned to the patient. The originals of all diaries will be maintained at the site as source documents.

9.4. Electronic Case Report Forms

For each patient enrolled who has given informed consent, an eCRF must be completed and electronically signed by the Investigator to certify that the data within each eCRF are complete and correct. This also applies to those patients who fail to complete the study. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome.

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The electronic data capture (EDC) vendor will provide user-specific access to the live (production) eCRF once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it

has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

The eCRFs will be reviewed by the study monitor at the study site. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors. All changes will be documented and approved by the Investigator.

All Investigators will be provided with copies of the eCRFs for their site on a compact disc read-only memory (CD-ROM) at the end of the study.

9.5. Quality Assurance

9.5.1. 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.

9.5.2. Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the Investigator. This will include telephone calls and in-clinic visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the in-clinic 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 the informant/caregiver for study procedures and for the release of medical records to the sponsor, US FDA, other regulatory authorities, and the IRB/EC. The Investigator or appointed delegate will receive the study monitor during these in-clinic 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.

9.6. Record Retention

To enable evaluations and/or audits from regulatory authorities or Avanir, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs 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 (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

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

9.7. Source Data

The documents that will form the source data for the clinical study (e.g., 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.

9.8. Data Handling

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.

9.9. Laboratory Procedures

Each individual site laboratory will collect hematology and chemistry blood samples and urine samples at Screening (Day -28 to Day -1), Visit 4 (Day 43), and Visit 6 (Day 85) for safety analysis. Urine samples will also be collected for toxicology screening at Screening (Day -28 to Day -1), Visit 3 (Day 22), Visit 5 (Day 43), and Visit 6 (Day 85). Blood samples will also be taken for CYP2D6 genotyping at Baseline (Day 1) and for PK analysis at Visit 4 (Day 43), Visit 5 (Day 64), and Visit 6 (Day 85).

Instructions for specimen evaluation and transport to a central laboratory will be provided at the time of study initiation. Further instructions on PK procedures including sampling timepoints will be provided by the sponsor at the time of study initiation.

9.10. Guidelines for Good Clinical Practice

Standards for GCP must be adhered to for all study-based procedures.

9.11. Conditions for Amending the Protocol

Protocol modification to ongoing studies which could potentially adversely affect the safety of patients or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of patients treated, or patient selection criteria must be made only after appropriate consultation between an appropriate representative of Avanir and the Investigator.

Protocol modifications must be prepared by a representative of Avanir or the Investigator and reviewed and approved by Avanir.

All protocol modifications must be reviewed and approved by the appropriate IRB/EC in accordance with local requirements, before the revised edition can be implemented. Modifications which eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB/EC.

9.12. Conditions for Terminating the Study

Both Avanir and the Principal Investigator reserve the right to terminate the study at the site 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, Avanir and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

9.13. Confidentiality of Study Documents and Patient Records

The Investigator must assure that the patient's anonymity will be maintained. On eCRFs or other documents submitted to Avanir, patients should not be identified by their names but by an identification code.

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

9.14. Reports

At the completion of the study, the Investigator shall provide the sponsor with an adequate report shortly after completion of the Investigator's participation in the study as described in CFR Title 21, Part 312.64.

9.15. Publications

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 Avanir's prior review and written consent.

9.16. Audits/Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from Avanir 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/EC approval(s)
- Study medication accountability

- Study protocol and amendments
- ICFs of the patient and informant/caregiver
- Medical records supportive of eCRF data
- Reports to the IRB/EC and the sponsor
- Record retention

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

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11. SUMMARY OF CHANGES

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12. APPENDICES

APPENDIX 1. DSM-5 DEFINITIONS FOR ALCOHOL AND CANNABIS USE DISORDER

Alcohol Use Disorder Criteria

	DSM–5 In the past year, have you:	
1	Had times when you ended up drinking more, or longer, than you intended?	The presence of at least 2 of these symptoms indicates an **Alcohol Use Disorder (AUD).** The severity of the AUD is defined as: **Mild:** The presence of 2 to 3 symptoms **Moderate:** The presence of 4 to 5 symptoms **Severe:** The presence of 6 or more symptoms
2	More than once wanted to cut down or stop drinking, or tried to, but couldn't?	
3	Spent a lot of time drinking? Or being sick or getting over other aftereffects?	
4	Wanted a drink so badly you couldn't think of anything else? ****This is new to DSM–5****	
5	Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?	
6	Continued to drink even though it was causing trouble with your family or friends?	
7	Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?	
8	More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	
9	Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	
10	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	
11	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	

CANNABIS USE DISORDER DSM-5, 305.20, 304.30

DSM-5 CATEGORY: SUBSTANCE-RELATED DISORDERS

Introduction

Delta-9-THC (Delta-9-TetraHydrocannabinol) is a psychoactive compound contained in the plant cannabis sativa, which is one the most widely abused illicit drugs in the United States. The buds, stems, seeds, and leaves of the cannabis plant all contain varying amounts of Delta-9-THC, (National Institute of Drug Abuse, 2014), with the highest concentrations typically in the bud. The typical methods of administration are inhalation of smoke or steam, or PO administration. All of the parts of the plant can be dried, and smoked in a pipe, hand-rolled cigarette (joint), or a hollowed out cigar (blunt). The plant matter is also exposed to steam, and the steam is inhaled in a method referred to as vaporizing. The plant matter can be taken PO, and is typically baked into brownies or chocolate chip cookies. Gummy candies that contain Delta-9 THC are also consumed. Resinous oil called Hashish, or more commonly, hash, can also be extracted and introduced into baked goods, or butter used in the production of baked goods.

Cannabis use produces reward and dependence, and withdrawal symptoms upon cessation of use. Its regular use can result in varying degrees of impairment. The designation of the drug is typically cannabis, although the active ingredient is Delta-9-THC (American Psychiatric Association, 2013).It's use is widely accepted by a subculture of users, who do not see the use as problematic, and will rationalize and justify use.

Cannabis has an affinity for CB1 (Cannabinoid Receptors Type 1) receptors, which are located in the central nervous system, specifically in the frontal cortices and the thalamus. The CB1 Binding produces the psychoactive effects of cannabis (Lazenka, 2014).

Symptoms of Cannabis Use Disorder

According to the DSM-5, (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) the criteria for Cannabis Use Disorder is as follows:

1. Use of cannabis for at least a one-year period, with the presence of at least two of the following symptoms, accompanied by significant impairment of functioning and distress:
2. Difficulty containing use of cannabis- the drug is used in larger amounts and over a longer period than intended.
3. Repeated failed efforts to discontinue or reduce the amount of cannabis that is used

4. An inordinate amount of time is occupied acquiring, using, or recovering from the effects of cannabis.
5. Cravings or desires to use cannabis. This can include intrusive thoughts and images, and dreams about cannabis, or olfactory perceptions of the smell of cannabis, due to preoccupation with cannabis.
6. Continued use of cannabis despite adverse consequences from its use, such as criminal charges, ultimatums of abandonment from spouse/partner/friends, and poor productivity.
7. Other important activities in life, such as work, school, hygiene, and responsibility to family and friends are superseded by the desire to use cannabis.
8. Cannabis is used in contexts that are potentially dangerous, such as operating a motor vehicle.
9. Use of cannabis continues despite awareness of physical or psychological problems attributed to use- e.g., anergia, amotivation, chronic cough.
10. Tolerance to Cannabis, as defined by progressively larger amounts of cannabis are needed to obtain the psychoactive effect experienced when use first commenced, or, noticeably reduced effect of use of the same amount of cannabis
11. Withdrawal, defined as the typical withdrawal syndrome associate with cannabis, or cannabis or a similar substance is used to prevent withdrawal symptoms.

The status of the disorder can be further qualified as follows:

- Early remission
- Sustained remission

An additional specifier for the status of the disorder is:

- In a Controlled Environment, e.g. a treatment facility or correctional facility where access to cannabis is limited.

The severity of the disorder is also noted, depending on the number of symptoms noted:

- Mild – Two or Three Symptoms
- Moderate- Four or five symptoms
- Severe- Six or more symptoms (American Psychiatric Association, 2013).

Risk Factors for Cannabis Use Disorder

Risk factors identified in the DSM-5 include: A family history of chemical dependence and a history of Conduct Disorder or Antisocial Personality Disorder are noted as risk factors. Other risk factors are described in the DSM-5 are low SES (Socio-Economic Status), history of tobacco smoking, unstable/abusive family, other family members who smoke cannabis, and poor academic performance.

(American Psychiatric Association, 2013). However, it could be speculated these factors are correlational rather than causal. The DSM-5 also notes that the local ease of access to cannabis is

a risk factor, (American Psychiatric Association, 2013) for individuals who are inclined to use cannabis. A drug-tolerant culture as a risk factor for use, as conformity to social norms has been established as a powerful influence on behavior.

Onset of Cannabis Use Disorder

The DSM-5 notes that most users begin in early adolescence or as young adults (American Psychiatric Association, 2013).

Differential Diagnosis in Cannabis Use Disorder

Depression can present with symptoms of anergia, amotivation, short-term memory deficits, and difficulty concentrating. In a young person, who fits the demographic of a cannabis user, parents or others may attribute the symptoms to cannabis use and denial, particularly if the adolescent cannot articulate their feelings. To rule out other disorders, in addition to meeting the diagnostic criteria listed above, diagnosis of use can be determined through enzyme immunoassay testing of a urine sample for cannabinoid metabolites. The presence of metabolites can indicate recent use, and if quantitative testing is done, the levels of metabolites can be measured, indicating the relative amount of cannabis recently used.

Comorbidity of Cannabis Use Disorder

There is a number of long-term health risks associated with Cannabis Use Disorder. Inhaling the smoke from burnt vegetation, whether it is tobacco leaves or cannabis, is harmful. Use of cannabis by smoking can result in long term, comorbid health problems involving:

- The Respiratory system- COPD (Chronic Obstructive Pulmonary Disease), chronic inflammation of the upper respiratory tract, bronchitis, and damage to cilia, which can increase frequency and severity of common upper respiratory infections such as rhinovirus and influenza.
- The Cardiovascular system- elevated heart rate and blood pressure, which can adversely affect individuals with pre-existing heart disease.
- The Reproductive system- multiple effects in both men and women, although the clinical impact is not well understood.
- Increased risk of cancers of the lungs, oral cavity, esophagus, and associated structures.

(California Society for Addiction Medicine, 2011)

Treatment of Cannabis Use Disorder

The DSM-5 does not specify treatment options for Cannabis Use Disorder (American Psychiatric Association, 2013). Cannabis Use Disorder is treatable by individual or group therapy following the REBT (Rational Emotive Behavior Therapy) model, (Albert Ellis Institute, 2014) as well as psycho-education, self –help groups, and lifestyle changes. REBT can assist the recovering user to recognize dysfunctional thought patterns and replace them with adaptive thinking and to recognize, tolerate and manage their emotions, rather than using cannabis for mood management. Psycho-education can challenge fallacious beliefs about cannabis, which can make use perceived

as benign, and provide concrete, didactic information about the nature of addiction in general. Self-help or 12-step groups are an important component of recovery to provide support and accountability, and to maintain motivation. They are also a means of changing associations, and developing healthier relationships.

It is widely accepted in the addiction treatment community that changing associations in a critical part of recovery. This refers to no longer associating with those that are actively using substances, and making connections with sober, responsible, goal oriented individuals who can model pro-social behavior, offer encouragement to remain abstinent, express social disapproval for use, and generally support the individual in their recovery, while holding them accountable for their actions.

Prognosis of Cannabis Use Disorder

For many, cannabis use will not exceed the mild form of the disorder, and they will use typically during their teens and early twenties. As an individual ages, expectations for their conduct, both internally and externally dictated, will change. By the late twenties, most young Americans have completed their education, and are embarking on a career, and family of procreation. This entails responsibilities, which will outweigh the reward from cannabis use, and their use will either be discontinued or be reduced to a sub-clinical level in terms of frequency and quantity, with negligible impact on their functioning.

For others, use of cannabis will remain heavy in terms of frequency and quantity, and the subcultural norms justifying and rationalizing use will be embraced. Long-term use of cannabis is associated with an amotivational syndrome. The effects of cannabis are subtle and insidious, unlike other illicit substances. Use of heroin, crack cocaine, or alcohol can rapidly cause life to become unmanageable. There tends to be a lack of obvious and dramatic effects from smoking cannabis, but rather a gradual slide into amotivation, indifference and apathy. Goals will not be met, and new goals will not be established, important day-to-day tasks will not be completed, and responsibilities will be gradually neglected. Overall, quality of life will be impaired, and the individual will not reach their potential.

If an individual embraces treatment, the prognosis is excellent. Some will recognize that their use of cannabis is preventing goal achievement, but are unable to stop on their own due to the intrinsic reward properties of cannabis. Many individuals are coerced into treatment by either the criminal justice system, or family members exerting pressure on them to meet age expected behavior. A major treatment challenge can be convincing someone that his or her use is problematic. The combination of cultural tolerance and acceptability of cannabis, misconceptions and fallacies fueled by abundant misinformation available on line, and among users, and the apathy and indifference inducing effects of the drug itself can make motivation to quit challenging.

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