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 Intermittent Explosive Disorder (IED)

Protocol:	17-AVP-786-206	**IND:** 133049
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 20 October 2017
Drug:	AVP-786 (deudextromethorphan hydrobromide [d6-DM]/ quinidine sulfate [Q])	**Version:** 1.2

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT	Serotonin
AE	Adverse event
BID	Twice daily
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
CRO	Contract research organization
CTSdatabase	Clinical Trial Subject Database
[redacted]	
d6-DM	Deudextromethorphan hydrobromide (or free base form)
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
eCOA	Electronic clinical outcome assessments
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	US Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IED	Intermittent Explosive Disorder
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAOI	Monoamine oxidase inhibitor
mCGI-C	Modified Clinical Global Impression of Change for IED
mCGI-S	Modified Clinical Global Impression of Severity for IED
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mITT	Modified intent-to-treat
mPGI-C	Modified Patient Global Impression of Change for IED
mPGI-S	Modified Patient Global Impression of Severity for IED
MMRM	Mixed effects model repeated measures
NMDA	*N*-methyl-D-aspartate
OAS-M	Overt Aggression Scale – Modified for Outpatient Use
OTC	Over-the-counter
PET	Positron emission tomography
PHQ-9	Patient Health Questionnaire-9
PP	Per-protocol
Q	Quinidine sulfate or quinidine
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SDS	Sheehan Disability Scale
SF-12	Short-Form 12-Item Health Survey
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
STAXI-2	State-Trait Anger Expression Inventory-2
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
UDS	Urine drug screen
US	United States

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 Intermittent Explosive Disorder (IED)

Protocol Number: 17-AVP-786-206

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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 (IRB).
4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (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 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: [redacted]

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 Intermittent Explosive Disorder (IED)

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 IED.

Study Population

Number of Patients: Approximately 150 patients will be randomized at approximately 20 centers in the United States.

Condition/Disease: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for IED.

Key Inclusion Criteria: Diagnosis of current IED according to the DSM-5 criteria, as solicited by the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT). Patients must have at least 3 IED days (at least 1 IED episode each day, as recorded by the patient using the [redacted]) per week for the 2 consecutive weeks directly preceding baseline with 70% compliance during that time frame, as assessed by the investigator. Patients must have a score ≥ 12 on the Life History of Aggression scale at screening, a score ≥ 6 on the Overt Aggression Scale – Modified (OAS-M) Total Irritability at screening and baseline, and a score ≥ 4 on the modified Clinical Global Impression of Severity for IED (mCGI-S) at screening and baseline.

Key Exclusion Criteria: Patients with a diagnosis of major depressive disorder within 6 months of screening, patients with significant symptoms of a depressive disorder or with a Patient Health Questionnaire-9 (PHQ-9) score ≥ 10 at screening, and patients who meet only the DSM-5 A2 criterion for IED will be excluded. Patients with a lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, antisocial personality disorder, neurocognitive disorder, or mental retardation (DSM-5 criteria) will be excluded; patients with recurrent IED episodes that are better explained by another mental disorder or attributable to another medical condition (e.g., head trauma, Alzheimer's disease) or to the physiological effect of a substance (e.g., a drug of abuse, a medication) will be excluded (DSM-5 criteria).

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 parallel design study with 2 treatment groups (AVP-786 and placebo).

Duration: Randomized patients will participate in the study for approximately 17 weeks, with a screening period up to 4 weeks and a 12-week double-blind treatment period. All patients will receive a safety follow-up telephone contact 7 days after the last dose of study drug.

Study Treatment: The investigational product is AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) capsules. Dosing will start with d6-DM 28 mg/Q 4.9 mg (AVP-

786-28/4.9) that will be 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 AVP-786 will be used as the control.

Randomization: Eligible patients will be randomized on Day 1 to receive AVP-786 or placebo (1:1 ratio stratified by study site) for 12 weeks.

Dose Regimen: Patients randomized to receive AVP-786 will be titrated up to a dose of AVP-786-42.63/4.9 BID by Day 15. On Day 1 after all predose assessments have been completed, the first dose of study drug will be ingested in the clinic, in the presence of study site personnel. Beginning on Day 1, patients randomized to AVP-786 will ingest a dose of AVP-786-28/4.9 and a dose of placebo for 7 days. Beginning on Day 8, patients will ingest a dose of AVP-786-28/4.9 capsules BID for 7 days, and beginning on Day 15, patients will ingest a dose of AVP-786-42.63/4.9 BID for the remaining 10 weeks of treatment. If the patient cannot tolerate AVP-786-42.63/4.9 BID, a one-time down titration to AVP-786-28/4.9 BID will be allowed between Days 16 and 43; these patients will remain at the AVP-786-28/4.9 BID dose for the remainder of the study.

Patients randomized to receive placebo will ingest placebo BID for 12 weeks.

Patients requiring a dose-adjustment between Days 16 and 43 will return to the study site for an unscheduled visit to perform safety assessments.

The patient should ingest study drug orally BID with water, 1 capsule in the morning and 1 capsule in the evening approximately 12 (± 4) hours apart. The time of dosing should be consistent throughout the study and must be recorded on the study drug diary.

Assessments and Visits

Patients will attend clinic visits at screening, baseline (Day 1), and Days 15 (Week 2), 29 (Week 4), 43 (Week 6), 57 (Week 8), 71 (Week 10), and 85 (Week 12). On Day 8 (Week 1), a safety telephone contact will be performed to assess adverse events (AEs) and query regarding concomitant medications. A safety follow-up telephone contact, to assess AEs, will be performed 7 days after the last dose of study drug.

During screening and double-blind treatment, patients will record information regarding their IED episodes using the [redacted].

Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1).

Response Measures

Primary Efficacy Measure: OAS-M - Total Aggression

Secondary Efficacy Measures:

- OAS-M - Total Irritability
- OAS-M - individual items for Aggression and Irritability
- [redacted] – IED days, IED episodes, IED severity, and patient's distress

- IED days - investigator assessment
- OAS-M - number of discrete IED episodes
- Modified Clinical Global Impression of Severity for IED (mCGI-S)
- Modified Clinical Global Impression of Change for IED (mCGI-C)
- Modified Patient Global Impression of Severity for IED (mPGI-S)
- Modified Patient Global Impression of Change for IED (mPGI-C)
- Sheehan Disability Scale (SDS)
- Short-Form 12-Item Health Survey (SF-12)
- State-Trait Anger Expression Inventory-2 (STAXI-2)

Safety and Tolerability

Safety and tolerability of AVP-786 will be assessed by reported AEs, physical and neurological examinations, vital signs including orthostatic measurements, clinical laboratory assessments (chemistry, hematology and urinalysis), resting 12-lead electrocardiograms (ECGs), concomitant medications, and the Sheehan-Suicidality Tracking Scale (S-STS). Pregnancy tests will be conducted for females of childbearing potential only.

Pharmacokinetics [redacted]

Plasma concentrations of d6-DM, Q, and certain metabolites will be measured; [redacted]

General Statistical Methods and Types of Analyses

Analysis Populations

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

mITT – The mITT population will include all patients who ingest at least 1 dose of study medication and have at least 1 postbaseline primary efficacy assessment; this population will be used for all efficacy analyses. Patients in the mITT population will be included in the treatment group to which they were randomized regardless of the treatment received.

PP – The PP population will include all patients with no significant protocol deviation that may impact the efficacy evaluations. Patients in the PP population will be included in the treatment group based on the actual treatment received.

Safety – The safety population part of the safety analyses will include all patients who ingest study medication. Patients in the safety population will be included in the treatment group based on the actual treatment received and all the safety measures will be analyzed and summarized by treatment group.

Efficacy Analysis

The primary efficacy endpoint of the study is the change from baseline to Week 12 in the OAS-M Total Aggression score. The treatment effect will be analyzed using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data. The model will include fixed effects for treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, and baseline value. The OAS-M Total Aggression scores are highly skewed and, in general, not normally-distributed; a log-transformation will be applied first before using the MMRM. The analysis on the original scale will be the sensitivity analysis. Detailed analyses will be specified in the statistical analysis plan prior to unblinding the study.

The secondary efficacy endpoints will be the change from baseline to Week 12, and will be analyzed in a similar manner to the primary endpoint or as appropriate.

Sample Size Calculation

Sample size calculation was performed based on the results of a 12-week study of fluoxetine vs. placebo in patients with IED.[1] The observed OAS-M aggression score effect size was approximate 0.45 taking into account a 45% discontinuation rate. For the current study, the planned sample size of 150 patients (75 per group) will have approximately 80% power to detect a treatment effect size of 0.45 in the comparison of AVP-786 vs. placebo with a 2-sided type I error α=0.05. If the effect size is assumed to be 0.50, the power is approximately 85%.

Table 1: Schedule of Evaluations and Visits (17-AVP-786-206)

Procedure	Visit:	Screening[1]	Baseline	Phone Call[1,2]	Visit 2[1]	Visit 3[1]	Visit 4[1]	Visit 5[1]	Visit 6[1]	Visit 7/ET[1,3,4]
	Study Day:	Day -28 to -1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85
	End of Study Week:	Week -4 to -1		Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Sign informed consent form		X								
CTSdatabase		X								X
Medical history		X								
Review of eligibility[5]		X	X							
Randomization			X							
[redacted]		X								
[redacted]			X							
[redacted]										X
Life History of Aggression		X								
SCID-5-CT		X								
[redacted]										
PHQ-9		X								
Physical & neurological examination		X								X
Vital signs and weight		X	X[6]		X	X	X	X	X	X[6]
Electrocardiogram		X[7]	X[8]		X[8]		X[8]			X[8]

Procedure	Visit:	Screening[1]	Baseline	Phone Call[1,2]	Visit 2[1]	Visit 3[1]	Visit 4[1]	Visit 5[1]	Visit 6[1]	Visit 7/ET[1,3,4]
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**
	End of Study Week:	**Week -4 to -1**		**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Clinical laboratory tests		X[9]						X		X[9]
Pregnancy test[10]		X	X		X	X	X	X	X	X
Urine drug screen		X	X			X		X		X
Pharmacokinetic blood sample								X[11]		X[11]
Adverse events			X	X	X	X	X	X	X	X
Prior and concomitant medications, and nondrug therapies		X	X	X	X	X	X	X	X	X
S-STS		X	X		X	X	X	X	X	X
OAS-M		X	X		X	X	X	X	X	X
Review of [redacted] IED days - investigator assessment			X		X	X	X	X	X	X
mCGI-S		X	X				X			X
mCGI-C							X			X
mPGI-S			X				X			X
mPGI-C							X			X
SDS			X				X			X
SF-12			X				X			X
STAXI-2			X				X			X

Procedure	Visit:	Screening[1]	Baseline	Phone Call[1,2]	Visit 2[1]	Visit 3[1]	Visit 4[1]	Visit 5[1]	Visit 6[1]	Visit 7/ET[1,3,4]
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**
	End of Study Week:	**Week -4 to -1**		**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Collect/review returned study drug and study drug diary					X	X	X	X	X	X
Dispense study drug & study drug diary			X		X	X	X	X	X	
Study drug dosed in the clinic			X		X	X	X	X	X	X

Abbreviations: CTSdatabase = Clinical Trial Subject Database; [redacted]; ET = early termination; IED = Intermittent Explosive Disorder; mCGI-C = Modified Clinical Global Impression of Change for IED; mCGI-S = Modified Clinical Global Impression of Severity for IED; mPGI-C = Modified Patient Global Impression of Change for IED; mPGI-S = Modified Patient Global Impression of Severity for IED; OAS-M = Overt Aggression Scale – Modified; PHQ-9 = Patient Health Questionnaire-9; SCID-5-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version; SDS = Sheehan Disability Scale; SF-12 = Short-Form 12-Item Health Survey; S-STS = Sheehan Suicidality Tracking Scale; STAXI-2 = State-Trait Anger Expression Inventory-2.

Note: Whenever possible, each patient should have the rating scales administered by the same raters throughout the study, for consistency of ratings.

1. Study visits will have a ± 2-day window except the screening period, telephone call on Day 8 (Week 1), and the safety follow-up telephone contact, which will have a + 2-day window.
2. On Day 8 (Week 1), patients who experience adverse events may need to return to the clinic for an unscheduled visit for safety assessments.
3. Early termination visit will be performed for patients who discontinue double-blind treatment.
4. All patients will receive a safety follow-up phone call to assess adverse events 7 days after the last dose of study drug.
5. For each patient, a protocol eligibility form will be completed.
6. Weight should be measured only at baseline and Day 85 (Week 12) or early termination.
7. Electrocardiogram should be performed in triplicate at screening.
8. Electrocardiogram will be performed predose and between 2 and 3 hours (± 15 minutes) postdose on Days 1 and 43, and between 2 and 3 hours (± 15 minutes) postdose on Days 15 and 85.
9. Includes non-fasting chemistry, hematology, and urinalysis tests. Thyroid-stimulation hormone (TSH) will be performed at screening only. If TSH is abnormal, reflex triiodothyronine (T3) and thyroxine (T4) will be performed. Glycosylated hemoglobin (HbA1c) test should be performed at screening and Day 85 (Week 12) (within 3 hours postdose) or early termination.
10. Pregnancy test to be performed for females of child bearing potential only at all visits. Patients will be discontinued if the urine pregnancy test is positive.
11. Blood sample for pharmacokinetic analysis will be collected predose and between 2 and 4 hours postdose on Day 57 (Week 8) and Day 85 (Week 12).

1. BACKGROUND AND CLINICAL RATIONALE

1.1. Intermittent Explosive Disorder

[redacted]

[redacted]

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 IED.

3. STUDY DESIGN

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study. Approximately 150 patients with IED will be randomized to 1 of 2 groups [redacted] ratio stratified by study site) (n=75 per group) at approximately 20 centers in the US. Randomized patients will participate in the study for approximately 17 weeks, with a screening period of up to 4 weeks and a 12-week double-blind treatment period. All patients will receive a safety follow-up telephone call to assess adverse events (AEs), 7 days after the last dose of study drug.

Patients will participate in a screening period of up to 4 weeks, during which time they will record information regarding their IED episodes, using the [redacted] that will be completed each evening before bedtime. During screening, the [redacted] will be used to determine whether patients are experiencing an adequate and stable number of IED days to qualify for randomization. To qualify, patients must have at least 3 IED days (at least 1 IED episode each day) per week for 2 consecutive weeks directly preceding baseline with 70% [redacted] compliance during this time frame, as assessed by the investigator.

To reduce duplicate patient enrollment (e.g., enrollment in more than one study contemporaneously or in close succession), this study will survey the Clinical Trial Subject Database (CTSdatabase), a clinical trial registry, for a potential patient match before randomization. Patients who match in the database with a patient who has participated in another clinical trial within the last 30 days will be excluded.

AVP-786 will be titrated over a 2-week period to d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) BID. Placebo capsules appearing identical to AVP-786 study medication will be used as the control. Eligible patients will be randomized to receive AVP-786 or placebo on Day 1. Patients will have at least a [redacted] chance of receiving AVP-786 during double-blind treatment. Study drug will be administered orally with water BID, 1 capsule in the morning and 1 capsule in the evening approximately 12 (± 4) hours apart throughout double-blind treatment period. The first dose of study drug will be administered in the study center on Day 1; morning dose of study drug will be administered in the study center at each remaining double-blind visit.

Patients randomized to AVP-786 will a dose of AVP-786 d6-DM 28 mg/Q 4.9 mg (AVP-786-28/4.9) and a dose of placebo for the first 7 days followed by AVP-786-28/4.9 BID for the next 7 days. Beginning on Day 15, patients will receive AVP-786-42.63/4.9 BID for the remaining 10 weeks of treatment. If the patient cannot tolerate AVP-786-42.63/4.9 BID, a one-time down titration to AVP-786-28/4.9 BID will be allowed between Days 16 and 43; these patients will remain at the AVP-786-28/4.9 BID dose for the remainder of the study.

Patients randomized to receive placebo will ingest placebo BID for 12 weeks.

Patients requiring a dose-adjustment between Days 16 and 43 will return to the study site for an unscheduled visit to perform safety assessments.

Patients will attend clinic visits at screening, baseline (Day 1), and Days 15 (Week 2), 29 (Week 4), 43 (Week 6), 57 (Week 8), 71 (Week 10), and 85 (Week 12). On Day 8 (Week 1), a safety telephone call will be performed to assess AEs and query regarding concomitant medications; patients who experience AEs may need to return to the clinic for an unscheduled

visit for safety assessments. During double-blind treatment, patients will continue to complete the [redacted] each evening before bedtime.

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 the OAS-M Total Aggression score. Secondary efficacy measures include: OAS-M Total Irritability, OAS-M individual items for Aggression and Irritability, [redacted] - IED days, IED episodes, IED severity, and patient's distress, IED days – investigator assessment, OAS-M for the number of discrete IED episodes, mCGI-S, modified Clinical Global Impression of Change for IED (mCGI-C), modified Patient Global Impression of Severity for IED (mPGI-S), modified Patient Global Impression of Change for IED (mPGI-C), Sheehan Disability Scale (SDS), Short-Form 12-Item Health Survey (SF-12), and the State-Trait Anger Expression Inventory-2 (STAXI-2).

Pharmacokinetic measurements of d6-DM, Q, and certain metabolites will be performed on blood samples collected on Days 57 and 85 (Weeks 8 and 12) or early termination. The safety and tolerability of AVP-786 will be assessed by reported AEs, physical and neurological examinations, vital signs including orthostatic measurements, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), and the Sheehan Suicidality Tracking Scale (S-STS). Pregnancy tests will be conducted at all visits only for females of childbearing potential.

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Males or females 18 to 65 years of age, inclusive, at the time of informed consent
2. Diagnosis of current IED according to the DSM-5 criteria, based on the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)
3. At least 3 IED days (at least 1 IED episode on each day) per week for the 2 consecutive weeks directly preceding baseline with 70% [redacted] compliance during that time frame, as assessed by the investigator
4. Life History of Aggression score ≥ 12 at screening
5. OAS-M Total Irritability score ≥ 6 at screening and baseline
6. Modified CGI-S score ≥ 4 at screening and baseline
7. Sufficient comprehension and cooperation to enable compliance with all procedures and assessments

[redacted]

4.2. Exclusion Criteria

1. Meeting only the DSM-5 A2 criterion for IED
2. Diagnosis of major depressive disorder within 6 months of screening, significant symptoms of a depressive disorder or a score ≥ 10 on the Patient Health Questionnaire-9 (PHQ-9) at screening
3. Evidence of serious risk of suicide or self-injury at screening or baseline based on the S-STS (i.e., score of 3 or 4 on any one question 2 through 6 or 11 or a score of 2 or higher on any one question 1a, 7 through 10, or 12) or who, in the opinion of the investigator, present a serious risk of suicide

4. Lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, antisocial personality disorder, neurocognitive disorder, or mental retardation (DSM-5 criteria). Patients with recurrent IED episodes that are better explained by another mental disorder or attributable to another medical condition (e.g., head trauma, Alzheimer's disease) or to the physiological effect of a substance (e.g., a drug of abuse, a medication) will be excluded (DSM-5 criteria).

[redacted]

4.3. Patient Withdrawal from the Study

Patients 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, AE, pregnancy, 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. The early termination visit should be completed. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Regardless of the circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire regarding the reason for withdrawal, and request that the patient return any unused study drug blister card, study drug diary, and the [redacted], and follow-up with the patient regarding any unresolved AEs.

In addition, any patient with a QTcF > 500 msec (unless due to ventricular pacing) or a QTcF interval increase from the predose baseline ECG (Day 1) > 60 msec at any time after

randomization, will be withdrawn from the study. The QTcF values will be assessed by the investigator for clinical significance and recorded.

Patients who prematurely discontinue will be asked to return to the clinic to complete the Day 85 (Week 12) assessments (study drug will not be administered in the clinic on that day for patients who prematurely discontinue). A safety follow-up telephone call will be performed 7 days after the last dose of study drug for all patients.

If the patient withdraws from the study, and consent is withdrawn by the 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 Medication

Study medication will be provided as printed [redacted], hard gelatin immediate-release capsules [redacted] Each capsule of study medication will contain 1 of the following:

- 28 mg of d6-DM and 4.9 mg of Q: AVP-786-28/4.9
- 42.63 mg of d6-DM and 4.9 mg of Q: AVP-786-42.63/4.9
- Placebo (identical in appearance to AVP-786)

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

Study medication 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 both strengths of AVP-786 and placebo are listed in Table 2.

Table 2: Composition of Investigational Product (17-AVP-786-206)

Ingredient (amount in mg)	AVP-786-28/4.9*	AVP-786-42.63/4.9*	AVP-786 Placebo
Deudextromethorphan hydrobromide monohydrate	29.41	44.77	
Equivalent to deudextromethorphan hydrobromide (d6-DM)*	28.00*	42.63*	
Equivalent to deudextromethorphan	21.67	33.00	
Quinidine sulfate USP, EP	4.9	4.9	
Croscarmellose sodium NF	X	X	X
Microcrystalline cellulose NF	X	X	X
Colloidal silicone dioxide NF	X	X	X
Magnesium stearate NF	X	X	X
[redacted] **hard gelatin capsules**	X	X	X

EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary
* Used to express strength of study medication

5.1.3. Packaging

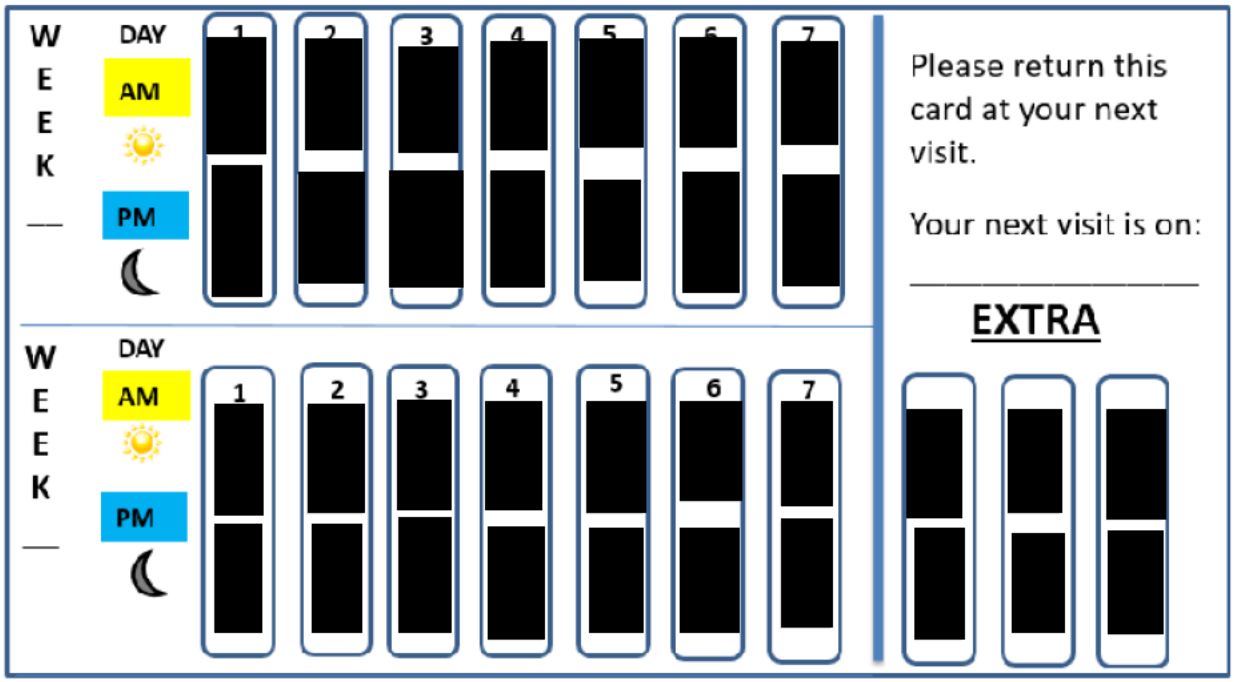
The investigators will be supplied with double-blind, pre-labeled, individually packaged blister cards (AVP-786 and placebo blister cards will be identical in appearance). Each 2-week blister

card will contain 2 panels, providing study medication for 2 weeks (14 days) of treatment, and an extra 3 days of supply (total of 34 capsules). Each panel (1-week of study medication) will consist of 2 rows of blister strips, 1 row for the morning dose and 1 row for the evening dose (Figure 1).

Three types of 2-week AVP-786 blister cards will be supplied:

- Titration Blister Card (Days 1 to 14)
  - First panel contains - AVP-786-28/4.9 and placebo for 7 days (Days 1 to 7)
  - Second panel contains - AVP-786-28/4.9 BID for 7 days (Days 8 to 14)
  - Extra medication supply - AVP-786-28/4.9 BID for 3 days
- Maintenance Blister Card (Days 15 to 85) - AVP-786-42.63/4.9 BID
- Down-Titration Blister Card - AVP-786-28/4.9 BID (down-titration allowed between Days 16 to 43; these patients will remain at this dose throughout double-blind treatment)

Figure 1: Sample Configuration of Study Medication Blister Card (17-AVP-786-206)



5.1.4. Labeling

Labels will include the protocol number, product name, medicine identification number (randomization number), an investigational drug warning, dose 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 will be provided on both panels of the card label to record patient number, visit week, and dispensing date. The study medication labels will 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 to 86°F).

5.1.6. Study Medication Administration

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

Each patient will be instructed to ingest 1 capsule of study medication orally with water BID, approximately every 12 (± 4) hours (morning and evening) (2 capsules daily). For each patient, the time each dose of study medication is ingested should be consistent throughout double-blind treatment. Study drug doses will be recorded in the study drug diary and noted in the electronic case report form (eCRF).

All study medication will be supplied and administered in a double-blind manner throughout the 12-week treatment period.

5.2. Accountability of Study Supplies

5.2.1. Receipt of Supplies

The investigator is responsible for maintaining an inventory of each shipment of study medication supplies 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 designee. Study drug supplies are for use only in this study and should not be used for any other purpose. All blister card identification numbers will be recorded and tracked at the study site using the Drug Accountability Log.

5.2.2. Record of Dispensing

Accurate recording of all study medication dispensed to patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: patient number to whom the drug was dispensed and date(s) and quantity of study drug dispensed to the patient.

Additionally, the detachable panel of the 2-panel label on each blister card will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space will be

provided on both panels of the blister card label to record patient number, visit week and dispensing date.

5.2.3. Unused Supplies

At the end of the study, all unused study medication supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or designee, 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 the ICF is signed at screening), each patient will be assigned a [redacted] patient number. [redacted]. This [redacted] number is the main identifier for each patient.

Eligible patients will be randomized to receive AVP-786 capsules or matching placebo capsules in a [redacted] ratio stratified by study site at baseline (predose, Day 1) in a double-blind manner according to a randomization scheme devised by Avanir (sponsor) or designee and managed within an IWRS. Each patient will have at least a [redacted] chance of receiving AVP-786 during double-blind treatment.

Patients randomized to receive AVP-786 will ingest a dose of AVP-786-28/4.9 and a dose of placebo for the first 7 days (Days 1 to 7) followed by AVP-786-28/4.9 BID for the next 7 days (Days 8 to 14). On Day 15, patients will receive AVP-786-42.63/4.9 BID for the remaining 10 weeks of double-blind treatment.

5.3.2. Blinding/Masking

Blinding will be maintained by providing capsules of AVP-786 and placebo that are identical in appearance. The sponsor, patients, investigators, or other study personnel will not be aware of the treatment assignment, with the exception of the IWRS manager and the designated sponsor representative who are not required to be blinded and will have access to the study drug list and the randomization code. In the event that it becomes medically necessary to identify which treatment a patient received, the blind can be broken. In that event, the investigator is to contact the sponsor's medical monitor or designee to request the unmasking of a patient.

5.4. Study Drug Compliance

Each patient will be instructed to return the study drug blister card and the paper study drug diary to each postbaseline double-blind study visit. Patients will be instructed to record daily the number of capsules taken and the time of study drug dosing in the paper study drug diary. The study drug diary will be reviewed for compliance and collected at each double-blind study visit or early termination.

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

[redacted]

[redacted]

6. STUDY ASSESSMENTS AND PROCEDURES

Samples of the efficacy and safety scales and questionnaires to be used during double-blind treatment are attached as Appendices. The proper and consistent administration of the rating scales is critical to the study objectives. In order to ensure the collection of high quality data, all study raters will receive training in the proper administration of the rating scales. In addition to training, raters must be certified in order to administer the Life History of Aggression, SCID-5-CT, OAS-M, mCGI-S and mCGI-C rating scales. Training and certification will be documented and updated as necessary. Raters must be approved by the sponsor or designee before administering the scales. Ongoing surveillance and remediation will be conducted to ensure that rater competency and consistency is maintained throughout the study. Whenever possible, each patient should have the rating scales administered by the same raters throughout the study, for consistency of ratings.

Patients will provide written consent to allow audio recordings of the applicable study assessments (at any time, the patient may withdraw consent to allow these recordings); all efforts will be taken to maintain confidentiality of the patient.

6.1. Screening Assessments

CTSdatabase and Subject Database Authorization: Clinical trial registries, such as CTSdatabase, seek to reduce duplicate enrollment by identifying duplicates before randomization. At the time of providing the Informed Consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the patient and witness the signature.

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

At the last patient contact, CTSdatabase staff will automatically close out subjects (early termination or completer) based on IWRS.

Life History of Aggression Scale: This is a 5-item scale (Appendix 3) to assess aggression, consequences/antisocial behavior and self-directed aggression, rated on a 6-point scale (0 to 5).[15] The Life History of Aggression Scale total score is considered a reliable and valid measure of a life history of overt aggression. Patients must have a score ≥ 12 on this scale at screening to continue study participation. A trained, certified clinician will administer the scale at screening only.

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a 9-item, patient self-rated questionnaire (Appendix 4) that is specific to depression.[16] The PHQ-9 will be used, in the current study, as a screening assessment to exclude patients with significant depressive symptoms; those with a PHQ-9 score ≥ 10 points at screening will be excluded from further study participation. The questionnaire will be completed by the patient (administered by a trained rater) at screening only.

Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT): The SCID-5-CT interview is a clinician-rated diagnostic assessment (Appendix 5) that will be administered at screening and will be considered a source document in this study.[17] The interview will be conducted by a trained, certified clinician with experience in the diagnosis of mental illness.

6.2. Efficacy Assessments

6.2.1. Overt Aggression Scale - Modified (OAS-M)

The OAS-M is a clinical-administered instrument (Appendix 6) that was designed to assess various manifestations of aggressive behavior in outpatients.[18] The version used in the current study was designed to evaluate the severity, type, and frequency of aggressive behavior and was adapted from 2 established instruments (Overt Aggression Scale, a scale used to assess single episodes of aggression in hospitalized psychiatric patients, and the Schedule for Affective Disorders and Schizophrenia). The OAS-M evaluates 2 domains – aggression and irritability.

The OAS-M aggression domain includes the following 4 items: verbal assault, assault against objects, assault against others, and assault against self. Each response will be scored using a 6-point scale (0 = no events within that category to 5 = most severe form of assault within that category).

The rater determines the frequency of each response (item) during the past week and the frequency of each item is multiplied by the severity level (0 to 5) that produces a raw score; this raw score is multiplied by a severity weight for that item (verbal assault x 1, assault against objects x 2, assault against others x 3, and assault against self x 3). The weighted individual item scores are added to obtain the OAS-M Total Aggression score. The severity weights were added to reduce the influence of lower severity aggressive behaviors on an overall assessment of aggression.

The OAS-M irritability domain includes the following 2 global assessment items: global subjective irritability and global overt irritability. Each response will be scored using a 6-point scale (0 = not at all to 5 = extreme). The 2 scores are added to create the OAS-M Total Irritability score (score range = 0 to 10). Patients must have an OAS-M Total Irritability score ≥ 6 at screening and baseline to qualify for randomization (at least a moderate degree of subjective irritability and overt irritability).

The OAS-M includes information regarding the number of DSM-5 A1 aggressive episodes and the number of DSM-5 A2 aggressive episodes experienced by the patient during the past week. The number of discrete IED episodes will be calculated after an interview with the patient and will be defined in accordance with the definition provided in DSM-5[2] and OAS-M Manual. Episodes identified as discrete must be separated by at least 30 minutes; episodes separated by less than 30 minutes will be considered a single episode, as defined in the OAS-M Manual.

The OAS-M will be administered by a trained, certified clinician at screening and baseline (predose on Day 1), and Days 15 (Week 2), 29 (Week 4), 43 (Week 6), 57 (Week 8), 71 (Week 10), and 85 (Week 12) or early termination. This scale should be administered by the

same rater at all visits, with the exception of baseline and Day 85 (Week 12), this scale must be administered by the same rater at these visits. The [redacted] will be reviewed by the clinician before the OAS-M is scored, in order to ensure that the ratings reflect a thorough assessment of the patient's IED symptoms.

[redacted]

6.2.3. Modified 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.[19] The Early Clinical Drug Evaluation Unit 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.[20] 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.[21,22] 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.

Patients with IED have marked impairment in aggression, anger, and irritability, and global assessments may not be sensitive to specific changes in these symptoms. In this study, the CGI scales have been modified for IED, and the clinician is explicitly instructed to rate the severity (mCGI-S) or change (mCGI-C) in the patient's IED symptoms, aggression, anger and irritability, to ensure that the global ratings specifically evaluate the target symptoms.

6.2.3.1. Modified Clinical Global Impression of Severity for IED (mCGI-S)

The mCGI-S (Appendix 8) is a modified version of the CGI-S scale that provides a global evaluation of the patient's IED symptoms (e.g., aggression, anger, and irritability).[19] The mCGI-S is used to measure severity of the patient's symptoms from the clinician's perspective in the context of other patients with IED. The mCGI-S responses will be scored on a 7-point scale (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients).

The mCGI-S will be administered by a trained, certified clinician at screening, baseline (predose on Day 1), and Days 43 (Week 6) and 85 (Week 12) or early termination. At these visits, the OAS-M will be administered [redacted] (when applicable) will be reviewed before this scale is scored, in order to ensure that the rating reflects a thorough assessment of the patient's IED symptoms. The patient must have a mCGI-S score ≥ 4 (at least moderately ill) at screening and baseline to qualify for randomization.

6.2.3.2. Modified Clinical Global Impression of Change for IED (mCGI-C)

The mCGI-C (Appendix 9) is a modified version of the CGI-C scale.[19] The clinician will rate the overall global change in the patient's IED symptoms (e.g., aggression, anger, and irritability) from baseline at the scheduled double-blind visits. The mCGI-C responses will be scored using a 7-point scale (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse).

The mCGI-C will be completed by a trained, certified clinician on Days 43 (Week 6) and 85 (Week 12) or early termination. At these visits, the OAS-M will be administered and the [redacted] will be reviewed before this scale is scored, in order to ensure that the rating reflects a thorough assessment of the patient's IED symptoms.

6.2.4. Modified Patient Global Impression of Severity for IED (mPGI-S)

The mPGI-S (Appendix 10) is a single-question scale that will ask patients to rate the overall global severity of their IED symptoms (e.g., aggression, anger, and irritability) using a 7-point scale (1 = normal, no symptoms; 2 = borderline symptoms; 3 = mild symptoms; 4 = moderately bad symptoms; 5 = markedly bad symptoms; 6 = severely bad symptoms; 7 = extremely bad symptoms).

The mPGI-S will be completed by the patient (administered by a trained rater) at baseline and Days 43 and 85 (Weeks 6 and 12) or early termination.

6.2.5. Modified Patient Global Impression of Change for IED (mPGI-C)

The mPGI-C (Appendix 11) is a single-question scale that will ask patients to rate the overall global change in their IED symptoms (e.g., aggression, anger, and irritability) from baseline at the scheduled double-blind visits. The mPGI-C responses will be scored using a 7-point scale (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse).

The mPGI-C will be completed by the patient (administered by a trained rater) on Days 43 and 85 (Weeks 6 and 12) or early termination.

6.2.6. Sheehan Disability Scale (SDS)

The SDS (Appendix 12) is a 3-item, patient-rated questionnaire, used to evaluate impairments in the domains of work/school, social life or leisure activities, and family life or home responsibility.[23] The patient will rate the degree of impairment in work/school, social life or leisure activities, and family life or home responsibility as a result of IED symptoms using a visual analogue scale (0 = no impairment; 1, 2, 3 = mildly; 4, 5, 6 = moderately; 7, 8, 9 = markedly; 10 = extremely).

The SDS will be completed by the patient (administered by a trained rater) at baseline (predose, Day 1), Day 43 (Week 6), and Day 85 (Week 12) or early termination.

6.2.7. Short-Form 12-Item Health Survey (SF-12)

The SF-12 (Appendix 13) is a 12-item, patient self-rated questionnaire that measures general health status and quality of life.[24] The SF-12 is a shorter version of the SF-36 that was designed for the Medical Outcomes Study, a multi-year study of patients with chronic conditions. The SF-12 is an extensively validated instrument with normative data from large numbers of individuals from both clinical samples and the general population. The SF-12 includes 12 questions that will measure the effects of health on physical functioning, role limitations due to physical health, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. These questions when combined, scored, and weighted, will result in 2 scales of mental and physical functioning and overall health-related quality of life.

The SF-12 will be completed by the patient (administered by a trained rater) at baseline (predose, Day 1) and Days 43 and 85 (Weeks 6 and 12) or early termination.

6.2.8. State-Trait Anger Expression Inventory-2 (STAXI-2)

The STAXI-2 (Appendix 14) is a 57-item, patient self-rated scale that measures the intensity of anger as an emotional state (state anger) and the disposition to experience angry feelings as a personality trait (trait anger).[25] The STAXI-2 includes a measure of state anger, trait anger, anger expression-out, anger expression-in, anger control-out and anger control, and the anger expression index (overall measure of the expression and control of anger). The state anger items will be scored using a 4-point scale (1 = not at all to 4 = very much so) to assess the intensity of anger feelings at a particular moment. The other scales will be scored using a 4-point scale to assess how frequently angry feeling are experienced, expressed, suppressed, or controlled (1 = almost never to 4 = almost always).

The STAXI-2 will be completed by the patient (administered by a trained rater) at baseline (predose, Day 1) and Days 43 and 85 (Weeks 6 and 12) or early termination.

6.3. Pharmacokinetics

Blood samples for the determination of the plasma concentrations of d6-DM, Q, and certain metabolites will be collected predose and between 2 and 4 hours postdose on Day 57 (Week 8) and Day 85 (Week 12). These samples will be collected per instructions provided by the sponsor. The date and time of each sample collection and the date and time of the last dose of study drug prior to the sample collection will be recorded on the eCRF.

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

[redacted]

6.5. Safety Assessments

6.5.1. Adverse Events

6.5.1.1. Definitions

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

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

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

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

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

Moderate: Event sufficiently discomforting to interfere with normal everyday activities

Severe: Event that is 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: 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: 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: 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: 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

6.5.1.2. Serious Adverse Events

A serious adverse event (SAE) is any AE 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. Inpatient 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 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, unless a complication occurs that meets the requirements for an AE or SAE, but must be reported on a pregnancy report form. Females who are pregnant or likely to become pregnant are excluded from this study. In the event a patient becomes pregnant during the study, study medication must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. Any pregnant patient must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., mother and fetus) must be followed-up through delivery with regard to outcome.

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

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.

6.5.1.3. Reporting

Patients will be queried regarding AEs at each study visit after screening. The investigator will assess and record all reported AEs. Any AE reported after the last dose of study drug will be followed-up until 30 days. Patients will receive a safety follow-up telephone call 7 days after the last dose of study drug to query regarding any AEs experienced since that visit.

A death occurring during the study, or which comes to the attention of the investigator within 30 days after the last dose of study drug whether considered treatment-related or not, must be reported to the sponsor.

For all SAEs, including an abnormal laboratory test value assessed as clinically significant, the investigator should consult with the sponsor's medical monitor or designated representative as needed and report any SAE by fax/email form as detailed below no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of the event, start date, stop date, intensity, frequency, relationship to study drug, action taken regarding study drug, any treatment required, and outcome to date. These details must be recorded on the clinical study AE report form that is provided. This form should be transmitted by fax and the details given by telephone to the contact numbers below.

SAE reporting by FAX or e-mail correspondence
FAX: [redacted]
E-ma [redacted]

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

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

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

6.5.2. Physical and Neurological Examinations

Physical and neurological examinations will be performed at screening (Day -28 to Day -1), and Day 85 (Week 12). 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.

6.5.3. Vital Signs Measurements

Vital sign measurements, including orthostatic blood pressure and pulse rate, respiratory rate (breaths/minute) (recorded only sitting), and body temperature (ºF) (recorded only sitting), will be recorded at each study visit. Blood pressure and pulse will be measured after a patient has been sitting for at least 5 minutes (each measurement will be taken twice in the same position and recorded) and after approximately 3 minutes of standing.

Weight will be recorded at baseline (predose, Day 1) and Day 85 (Week 12) only.

6.5.4. Clinical Laboratory Tests

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

Screening Tests

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

Routine Clinical Laboratory Tests

The routine clinical laboratory tests will be performed non-fasting during the screening period, Day 57 (Week 8), and Day 85 (Week 12) (within 3 hours postdose) or early termination.

- Chemistry panel - calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, creatine kinase, gamma-glutamyl transferase, triglycerides, total protein, and total cholesterol; additionally, glycosylated hemoglobin (HbA1c) will be measured at screening and Day 85 (Week 12) or early termination only
- Hematology panel - red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology
- Urinalysis - pH, specific gravity, protein, glucose, ketones, blood, leucocyte esterase, nitrates, and microscopic appearance

Any patient 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.

Urine Drug Screen

- UDS – Urine screen for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and marijuana metabolites will be performed at screening and baseline; patients with a positive UDS may be excluded from further study participation after a discussion with the medical monitor. Additionally, the UDS will be repeated on Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12) or early termination.

6.5.5. Pregnancy Tests

Urine pregnancy test will be performed at all study visits only for females of childbearing potential. Patients with a positive pregnancy test must be discontinued from the study.

All female patients of childbearing potential should be instructed to use appropriate birth control methods until 30 days after the last dose of study drug. Females of childbearing potential are defined as any female 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.

6.5.6. Electrocardiograms

A resting 12-lead ECG will be performed at each study visit; the screening, ECG will be performed in triplicate. On Day 1 (baseline) and Day 43 (Week 6), an ECG recording will be performed predose and between 2 and 3 hours postdose (± 15 minutes) after ingesting the morning dose of study drug in the clinic; on Days 15 and 85 (Weeks 2 and 12), the ECG will be obtained between 2 and 3 hours (± 15 minutes) postdose in the clinic (no predose ECG will be obtained at these time points).

The ECG equipment will be provided to the study center by the central reader. The ECG assessment will be recorded at the study center and will include general findings, including heart rate (beats/minute), QRS complex and PR and QTc intervals. Results will be provided by the central reader to the investigators within 24 hours; ECG data will be transferred automatically from the central reader into the sponsor's database monthly. Any ECG abnormality present at screening will be recorded as medical history. Any changes from the ECG status at screening that are deemed to be clinically significant by the investigator should be captured as AEs.

Any clinically significant abnormal ECG should be discussed with the medical monitor and, if necessary, the ECG should be repeated within approximately 1 week. In addition, any patient with a QTcF interval > 500 msec (unless due to ventricular pacing) or a QTcF interval increase from the predose baseline ECG (Day 1) > 60 msec at any time after randomization, will be withdrawn from the study.

6.5.7. Sheehan Suicidality Tracking Scale (S-STS)

A measurement of suicidality, a term referencing suicidal ideas or suicidal behaviors, is required by regulatory agencies in psychiatric patients participating in clinical studies. The S-STS (Appendix 15) is a measure of suicidal ideation and suicidal behaviors, and will serve as an ongoing assessment of suicidality (i.e., suicidal thinking and behavior) during this study. The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors. Each item of the S-STS is scored by the clinician using a 5-point scale (0 = not at all; 1 = a little; 2 = moderately; 3 = very; 4 = extremely).[26] The S-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. The S-STS takes approximately 5 to 10 minutes to administer. At screening, the timeframe for the items will be 'in the past 6 months' and for all other visits, the timeframe will be 'since the last visit'.

The S-STS will be completed by a trained clinician at each study visit or early termination. Whenever possible, the same rater should administer the S-STS at these 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, who is also a psychiatrist, must provide necessary intervention to manage suicidal ideation and refer the patient to their primary physician.

6.6. Schedule of Evaluations and Procedures

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

6.6.1. Description of Study Procedures

At each study visit, a member of the study 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.

6.6.1.1. Screening Visit (Days -28 to -1, + 2-day window)

The following procedures will be performed at screening (within 28 days prior to Day 1). In the event that a patient is rescreened, a new ICF must be signed, a new patient number will be assigned, and all screening procedures must be repeated.

1. The investigator will provide the patients and/or their legally authorized representatives with informed consent and will explain the rationale for the study, providing ample time for the patients and/or their legally authorized representatives to ask questions.
2. Authorization form will be completed and patient information will be entered into CTSdatabase.
3. Medical history, including patient demographics, any prior and concomitant medications (including over-the-counter [OTC], vitamins, and herbal supplements) or nondrug therapies will be reviewed and recorded.
4. Inclusion/exclusion criteria (eligibility form) will be reviewed.
5. Vital signs will be measured and recorded.
6. Physical and neurological examination will be performed.
7. Resting 12-lead ECG will be performed in triplicate.
8. Blood and urine specimen will be collected for safety laboratory assessments, including TSH and HbA1c.
9. Urine sample will be collected for UDS.
10. Urine pregnancy test will be performed for females of childbearing potential only.
11. Other assessments will be completed: Life History of Aggression, SCID-5-CT, PHQ-9, S-STS, OAS-M, and mCGI-S (OAS-M will be administered before the mCGI-S).
12. Review assessments to verify that patients are eligible to continue study participation.
13. Issue the [redacted] and train the patient on its use. Patients will be instructed to complete the [redacted], each evening before bedtime.

Following screening procedures for assessment of inclusion and exclusion criteria, a protocol eligibility form will be submitted to the medical monitor for approval. Patients deemed eligible by the investigator and the medical monitor will return for the baseline visit (Day 1). Patients having ECG findings or laboratory test results outside of the reference normal range that the investigator considers as clinically significant, and that may place the patient at a higher risk for study participation, will be discontinued (not randomized).

6.6.1.2. Baseline Visit (Day 1)

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

Baseline (predose):

1. Inclusion/exclusion criteria will be reviewed, eligibility will be reconfirmed, and eligibility form will be completed.
2. Review the [redacted] to ensure that each patient had at least 3 IED days (at least 1 IED episode on each day) per week for the 2 consecutive weeks, directly preceding baseline, with 70% compliance during that time frame (assessed by the investigator).
3. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
4. Vital signs, including weight, will be measured and recorded.
5. Resting 12-lead ECG will be performed.
6. Urine pregnancy test will be performed for females of childbearing potential only.
7. Urine sample will be collected for UDS.
8. Blood sample will be collected for [redacted]
9. The following efficacy assessments will be completed: OAS-M, mCGI-S, mPGI-S, SDS, SF-12, and STAXI-2 (OAS-M will be completed and the [redacted] will be reviewed before the mCGI-S is administered).
10. S-STS safety assessment will be completed.
11. 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 a study medication kit number via IWRS.

Study Drug Dosing:

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

Postdose:

1. Resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) postdose.
2. Patient will be queried regarding any postdose AEs.
3. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the study drug blister card in the morning and 1 capsule from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours). For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the dose on that day will be ingested in the clinic.

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind

patients to complete the [redacted] each evening before bedtime. Patients will also be instructed to consult with the study site prior to taking any non-study medications and to return the study drug blister card and the study drug diary at each double-blind visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.3. Visit 2 (Day 15/Week 2 ± 2-day window)

In the morning of Day 15, the following procedures will be performed.

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
2. Vital signs will be measured and recorded.
3. Urine pregnancy test will be performed for females of childbearing potential only.
4. Collect and review study drug diary and study drug blister card.

Study Drug Dosing:

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

Postdose:

1. [redacted] will be reviewed; investigator assessment of IED days and the OAS-M will be completed.
2. S-STS safety assessment will be completed.
3. Resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) postdose.
4. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the blister card in the morning and 1 capsule from the bottom row [PM] of the study drug blister card in the evening, approximately every 12 hours ± 4 hours) until the next visit. For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the morning dose will be ingested in the clinic.

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind patients to complete the [redacted] each evening before bedtime. Patients will be instructed to consult with the study site prior to taking any non-study medications and to return the study drug blister card and the study drug diary at each double-blind visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.4. Visit 3 (Day 29/Week 4 ± 2-day window)

In the morning of Day 29, the following procedures will be performed.

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
2. Vital signs will be measured and recorded.
3. Urine pregnancy test will be performed for females of childbearing potential only.
4. Urine sample will be collected for UDS.
5. Study drug diary and the study drug blister card will be collected and reviewed.

Study Drug Dosing:

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

Postdose:

1. [redacted] will be reviewed; investigator assessment of IED days and the OAS-M will be completed.
2. S-STS safety assessment will be completed.
3. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the study drug blister card in the morning and 1 capsule from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next visit. For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the morning dose will be ingested in the clinic.

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind patients to complete the [redacted] each evening before bedtime. Patients will be instructed to consult with the study site prior to taking any non-study medications and to return the study drug blister card and the study drug diary at each double-blind study visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.5. Visit 4 (Day 43/Week 6 ± 2-day window)

In the morning of Day 43, the following procedures will be performed.

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).

2. Vital signs will be measured and recorded.
3. Resting 12-lead ECG will be performed.
4. Urine pregnancy test will be performed for females of childbearing potential only.
5. Study drug diary and study drug blister card will be collected and reviewed.

Study Drug Dosing:

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

Postdose:

1. [redacted] will be reviewed and the following efficacy assessments will be completed: OAS-M, investigator assessment of IED days, mCGI-S, mCGI-C, mPGI-S, mPGI-C, SDS, SF-12 and STAXI-2 (OAS-M will be completed and the [redacted] will be reviewed before the mCGI-S and mCGI-C scales are administered).
2. S-STS safety assessment will be completed.
3. Resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) postdose.
4. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the study drug blister card in the morning and 1 capsule from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) until the next visit. For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the morning dose will be ingested in the clinic.

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind patients to complete the [redacted] each evening before bedtime. Patients will also be instructed to consult with the study site prior to taking any non-study medications and to return the study drug blister card and the study drug diary at each double-blind study visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.6. Visit 5 (Day 57/Week 8 ± 2-day window)

In the morning of Day 57, the following procedures will be performed.

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
2. Vital signs will be measured and recorded.

3. Blood sample for pharmacokinetic analysis and safety laboratory assessments (hematology and chemistry) will be collected.
4. Urine sample for urinalysis and UDS will be collected.
5. Urine pregnancy test will be performed for females of childbearing potential only.
6. Study drug diary and the study drug blister card will be collected and reviewed.

Study Drug Dosing:

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

Postdose:

1. The [redacted] will be reviewed; investigator assessment of IED days and the OAS-M will be completed.
2. S-STS safety assessment will be completed.
3. Blood sample for pharmacokinetic analysis will be collected between 2 and 4 hours postdose.
4. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the stud drug blister card in the morning and 1 capsule from the bottom row [PM] of the study drug blister card in the evening, approximately every 12 hours ± 4 hours) until the next visit. For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the morning dose will be ingested in the clinic.

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind patients to complete the [redacted] each evening before bedtime. Patients will also be instructed to consult with the study site prior to taking any non-study medications and to return the study drug diary and study drug blister card at each double-blind study visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.7. Visit 6 (Day 71/Week 10 ± 2-day window)

In the morning of Day 71, the following procedures will be performed.

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
2. Vital signs will be measured and recorded.
3. Urine pregnancy test will be performed for females of childbearing potential only.

4. Study drug diary and study drug blister card will be collected and reviewed.

Study Drug Dosing:

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

Postdose:

1. [redacted] will be reviewed; investigator assessment of IED days and the OAS-M will be completed.
2. S-STS safety assessment will be completed.
3. Study drug diary and study drug blister card will be dispensed.

Patient Instructions

Patients will be instructed to ingest study drug BID (1 capsule from the top row [AM] of the blister card in the morning and 1 capsule from the bottom row [PM] of the study drug blister card in the evening, approximately every 12 hours ± 4 hours) until the next visit. For the next study visit, patients will be reminded not to ingest their morning dose of study drug at home on that day instead the morning dose will be ingested in the clinic. Patients will be reminded to bring the [redacted] to the next study visit (final assessment).

The investigator and/or study coordinator will provide patients with detailed instructions regarding study procedures, including how to complete the study drug diary, and to remind patients to complete the [redacted] each evening before bedtime. Patients will also be instructed to consult with the study site prior to taking any non-study medications and to return the study drug diary and study drug blister card at each double-blind study visit. These requirements will be reviewed in-person, and patients will be queried at the end of each double-blind visit to be certain they understand what is required of them.

6.6.1.8. Visit 7 (Day 85/Week 12 ± 2-day window)/Early Termination

In the morning of Day 85, the following procedures will be performed:

Predose:

1. Patient will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and herbal supplements).
2. Vital signs, including weight, will be measured and recorded.
3. Physical and neurological examination will be performed.
4. Urine pregnancy test will be performed for females of childbearing potential only.
5. Urine sample will be collected for urinalysis and UDS.
6. Blood sample for pharmacokinetic analysis will be collected.
7. Study drug diary and study drug blister card will be collected and reviewed.
8. [redacted] will be retrieved.

Study Drug Dosing:

Last dose of study drug will be administered from the AM strip of the study drug blister card brought in by the patient, regardless of the time of day, for those patients who complete double-blind treatment (not those who prematurely discontinue).

Postdose:

1. [redacted] will be reviewed; the following efficacy assessments will be completed: OAS-M, investigator assessment of IED days, mCGI-S, mCGI-C, mPGI-S, mPGI-C, SDS, SF-12, and STAXI-2 (OAS-M will be completed and the [redacted] will be reviewed before the mCGI-S and mCGI-C are administered).
2. S-STS safety assessment will be completed.
3. Resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) postdose.
4. Blood sample for hematology and chemistry, including HbA1c, will be collected within 3 hours postdose.
5. Blood samples for the pharmacokinetic analysis will be collected between 2 and 4 hours postdose.
6. At the last patient contact, site staff will access CTSdatabase, enter the patient study ID and the nature of the last contact (i.e., early termination or completer).

Any previously reported and unresolved 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 drug.

Procedures for Early Termination: Patients who discontinue treatment are required to complete study procedures as listed above, within 48 hours whenever possible, of the last dose of study drug. For these patients, study drug will not be administered in the clinic on that day and, therefore, there is no specific time frame for the 12-lead ECG and the blood/urine specimen collection (clinical laboratory tests, UDS, or pharmacokinetics).

6.6.1.9. Safety Telephone Contact (Day 8/Week 1 + 2-day window)

Patients will receive a safety telephone contact to assess AEs and query regarding concomitant medications; patients who experience AEs may need to return to the clinic for an unscheduled visit for safety assessments.

6.6.1.10. Safety Follow-up Telephone Contact (+ 2-day window)

Patients will receive a safety telephone contact to assess AEs, 7 days after the last dose of study drug.

7. DATA MANAGEMENT

7.1. Data Collection

The sponsor or designated representative (e.g., 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 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 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 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. 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 have view access only.

This study will use an [redacted]) that will be completed daily by the patient; [redacted]

8. STATISTICAL METHODS

8.1. Analysis Populations

Three analysis populations will be evaluated including the modified intent-to-treat (mITT), per-protocol (PP), and safety populations, as defined below:

mITT - patients who ingest at least 1 dose of study medication and have at least one postbaseline primary efficacy assessment; this 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 - patients with no significant protocol deviation that may impact the efficacy evaluations. Patients in PP will be included in the treatment group based on the actual treatment received.

Safety - patients who ingest study medication; this population will be used for the safety analyses. 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 will be the change from baseline to Week 12 in the OAS-M Total Aggression score.

Secondary efficacy endpoints:

The secondary efficacy endpoints will be the change from baseline to Week 12 in the following measures (raw score for mCGI-C and mPGI-C):

- OAS-M Total Irritability
- OAS-M - individual items for the Aggression and Irritability
- [redacted] - IED days, IED episodes, IED severity, and patient's distress
- IED days - investigator assessment
- OAS-M - number of discrete IED episodes
- mCGI-S
- mCGI-C
- mPGI-S
- mPGI-C

- SDS
- SF-12
- STAXI-2

8.3.2. Primary Efficacy Analysis

The primary efficacy endpoint will be the change from baseline to Week 12 in the OAS-M Total Aggression score, using the mITT population.

For the primary efficacy endpoint, the null hypothesis is that there is no treatment effect and will be tested against the alternative that there is a treatment effect. The treatment effect will be analyzed using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data. The model will include fixed effects for treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, and baseline value. The OAS-M Total Aggression scores are highly skewed and, in general, not normally-distributed; a log-transformation will be applied first before using the MMRM. The analysis on the original scale will be the sensitivity analysis.

8.3.3. Secondary Efficacy Analyses

Secondary efficacy endpoints include the change from baseline to Week 12 for the secondary efficacy measures described above, and will be analyzed in a similar manner to the primary endpoint or as appropriate.

Detailed analyses for the primary and secondary efficacy endpoints will be specified in the statistical analysis plan (SAP) prior to unblinding the study.

8.4. Pharmacokinetic Analysis

Plasma concentrations of d6-DM, Q, and certain metabolites will be measured and results will be summarized descriptively overall [redacted]. Plasma concentration results will be used to assess the pharmacokinetic properties of d6-DM, Q, and certain metabolites. Additional pharmacokinetic correlations may also be performed. Additional details will be described in the SAP.

[redacted]

8.6. Safety Analysis

Safety will be assessed by the following measurements: AEs, physical and neurological examination, vital signs including orthostatic measurements, urine pregnancy test, clinical laboratory assessments (chemistry, hematology, and urinalysis), resting 12-lead ECG, concomitant medications, and S-STS.

Safety analysis will consist of data summaries and tabulated by treatment group.

8.6.1. Adverse Events

Adverse events will be coded using the 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). A TEAE is defined as an AE that occurred after the first dose of study drug through 30 days after the last dose.

8.6.2. Vital Signs and Electrocardiograms

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

8.6.3. Clinical Laboratory Values

Laboratory parameters will be summarized using descriptive statistics. Shift tables showing the pattern of change in the normal range value between screening and end of treatment as increased, decreased, or no change will be produced.

8.7. Data and Safety Monitoring Board

The sponsor will appoint a Data and Safety Monitoring Board (DSMB) for the periodic review of available study data to monitor the safety of all patients randomized into this study.

The DSMB will include an independent group of experts that advises the sponsor and the study investigators. The members of the DSMB will each serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, and (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study.

The DSMB will consider study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking, and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

8.8. Interim Analysis

An interim analysis may be performed and will be prespecified in the SAP.

8.9. Sample Size Calculation

Sample size calculation was performed based on the results of a previous 12-week study of fluoxetine vs. placebo in patients with IED; the observed OAS-M aggression score effect size was approximate 0.45 taking into account a 45% discontinuation rate.[1] For the current study, the

planned sample size of 150 patients (75 per group) will have approximately 80% power to detect a treatment effect size of 0.45 in the comparison of AVP-786 vs. placebo with a 2-sided type I error α=0.05. If the effect size is assumed to be 0.50, the power is approximately 85%.

9. ADMINISTRATIVE PROCEDURES

9.1. Institutional Review Board Approval

The IRBs must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB 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 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 laws (Appendix 16 Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is provided in Appendix 17.

9.2. Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. Signed informed consent must be obtained from each patient (if the patient is capable in the judgment of the investigator to provide informed consent) or their legally authorized representative prior to patient entry into the study; no screening procedure will be conducted until the informed consent is signed.

The patient will be properly informed of the purpose of the study and alerted to any anticipated AE that may be encountered with the study medication. The patient will be provided with a copy of their signed ICF.

9.3. Study Drug Diary

The study drug diary will be reviewed at each double-blind study visit after baseline by clinical study personnel for confirmation of the number of capsules taken and the time of study drug dosing. The study personnel are responsible for ensuring that (1) patients properly record study drug dosing data into the study drug diary and (2) transcribing the study drug diary recordings into the eCRF. The study drug diary will be collected at each study visit after baseline, and the originals will be maintained at the site as source documents.

9.4. Electronic Case Report Forms

For each patient enrolled who has provided 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 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. Any data changes in the EDC system once the data have 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 completed eCRFs for their site on a 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 study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

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

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

9.6. Record Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, 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), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or the sponsor. The investigator must obtain written permission from the sponsor 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. Guidelines for Good Clinical Practice

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

9.10. Conditions for Amending the Protocol

Protocol modification to ongoing studies that 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 the sponsor and the investigator.

Protocol modifications must be prepared by a representative of the sponsor or the investigator, and reviewed and approved by the sponsor.

All protocol modifications must be reviewed and approved by the appropriate IRB 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.

9.11. Conditions for Terminating the Study

Both the sponsor and the 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, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

9.12. Confidentiality of Study Documents and Patient Records

The investigator must assure that the patient's anonymity will be maintained. On eCRFs or other documents, including audio recordings, submitted to the sponsor, 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 the sponsor, for example, patients' signed ICFs, should be maintained by the investigator in strict confidence.

9.13. 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 the sponsor's prior review and written consent.

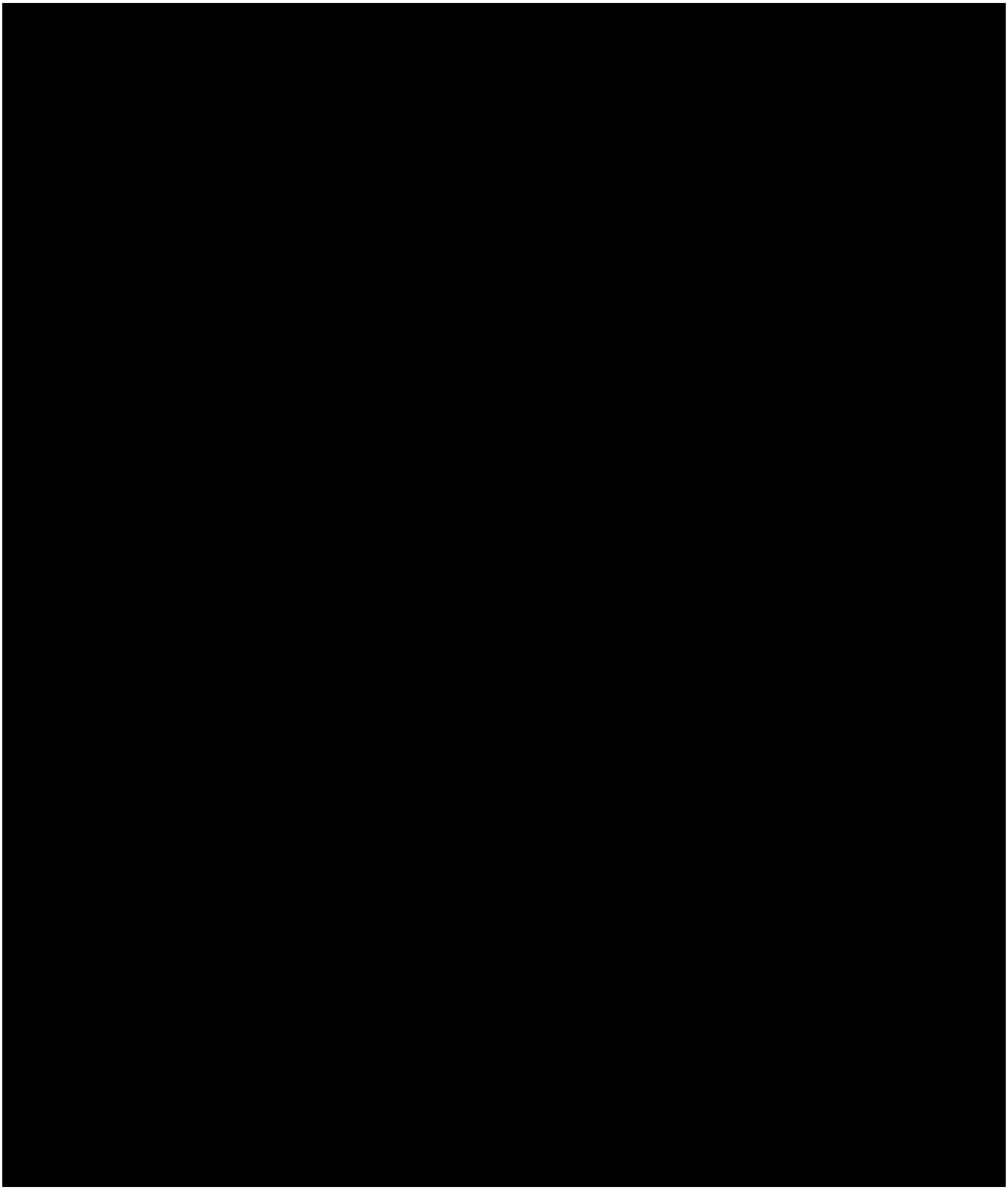
9.14. Audits/Inspections

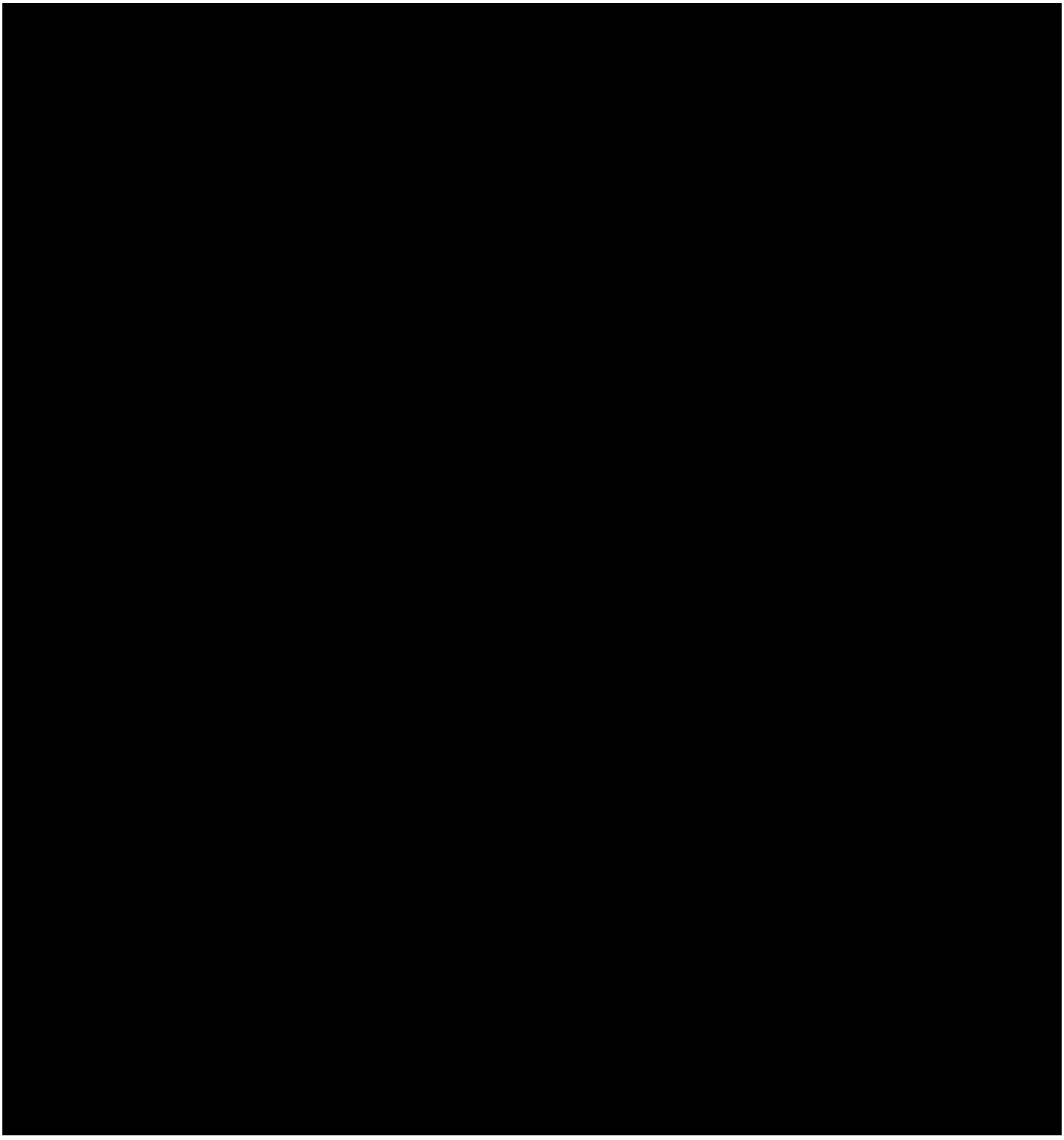
The investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee from the sponsor or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source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

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

- Visits from the sponsor's representatives
- IRB approval
- Study medication accountability
- Study protocol and amendments
- ICFs of the patient (if capable of providing ICF, according to the investigator) or patient's legally authorized representative
- Medical records supportive of eCRF data
- Reports to the IRB and the sponsor
- Record retention

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





11. APPENDICES

Appendix 1: [redacted]
Appendix 2:
Appendix 3:
Appendix 4:
Appendix 5:
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Appendix 7:
Appendix 8:
Appendix 9:
Appendix 10:
Appendix 11:
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