PROTOCOL TITLE:

A Phase 2, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) as an adjunctive treatment for patients with residual schizophrenia

Protocol:	15-AVP-786-202-Amendment 4	**IND:** 124525
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 25 January 2016
Drug:	AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q])	**Version:** 5.0

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NCT Number: NCT02477670
This NCT number has been applied to the document for
purposes of posting on Clinicaltrials.gov

[redacted]

Protocol Amendment 4 (Version 5.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 5.0, Amendment 4.
Study Synopsis 3.1, and 5.3.1	Study Design/ Randomization and Treatment	Clarified language on the structure of the study, randomization and treatment assignment
[redacted]		
4.1	Inclusion Criteria	Added inclusion criterion 9 to specify that patients must have a reliable informant as deemed appropriate by the investigator.
4.2	Exclusion Criteria	[redacted]
4.3	Patient Withdrawal	Revised to: patients with a QTcF change from 'pre-dose Baseline' (instead of Screening) ECG of > 60 msec at any time after Baseline are to be withdrawn from the study
5.1.6	Study Medication Administration	Clarified language on study medication administration
5.5	[redacted]	[redacted]
6.3	[redacted]	[redacted]
6.4.5	Clinical Laboratory Tests	Added HbA1c at Screening and Visit 7
Table 2	PK Blood Sampling Footer	[redacted]
Overall		Minor formatting and administrative updates

Protocol Amendment 3 (Version 4.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 4.0, Amendment 3.
4.1	Inclusion Criteria	Updated inclusion criteria #4a based on recommendation from the IRB to: If female of childbearing potential, patients must have a negative urine pregnancy test "*(all females regardless of childbearing potential will be required to submit a pregnancy test)".*
6.4.4	Pregnancy Tests	Updated language as follows: Urine pregnancy tests (beta-hCG) will be performed on *"all females regardless of childbearing potential"* at Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64), and Visit 7/Early Termination Visit (Day 85). At the Screening Visit, serum beta-hCG will be collected
Table 2	Footer	Updated footer on Table 2 to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.1	Screening Visit	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.2	Visit 1 (Baseline Visit, Day 1)	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.5	Visit 3 (Day 22 + 3-day window), Week 3	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.6	Visit 4 (Day 43 ± 3-day window), Week 6	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.9	Visit 6 (Day 64 + 3-day window); Week 9	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
6.5.1.10	Visit 7/Early Termination (Day 85 ± 3-day window), Week 12	Updated language to reflect all females will require pregnancy test regardless of childbearing potential.
Overall		Minor formatting and administrative updates

Protocol Amendment 2 (Version 3.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 3.0, Amendment 2.
4.1	Inclusion Criteria	Added clarity to inclusion #2 regarding residual schizophrenia. Added "and who meet DSM-IV-TR diagnostic criteria for residual schizophrenia."
4.1	Inclusion Criteria	Updated inclusion criteria #4 based on recommendation from the IRB to "A female is considered of childbearing potential unless she is post-menopausal (i.e., history compatible with menopause [i.e., reported lack of menses for ≥ 12 months] and no other biological/surgical cause)".
4.2	Exclusion Criteria	[redacted]
4.2	Exclusion Criteria	[redacted]
6.4	[redacted]	[redacted]
6.4.6	Electrocardiograms	Added triplicate ECGs to be performed at the Screening Visit instead of single resting ECG.
8.5	[redacted]	[redacted]
Overall		Minor formatting and administrative updates

Protocol Amendment 1 (Version 2.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 2.0, Amendment 1.
4.1	Inclusion Criteria	Added timeframe to inclusion #1 [redacted]
4.1	Inclusion Criteria	[redacted]
4.1	Inclusion Criteria	Added risperidone to the list of allowed atypical antipsychotics
4.2	Exclusion Criteria	[redacted]
4.2	Exclusion Criteria	[redacted]
6.1.7	Study Assessments and Procedures; Efficacy	[redacted]

[redacted]

Section Number	Section Title	Description
6.5.3	Vital Signs, Weight, and Height	Added Visit 2 (Day 15) and Visit 5 (Day 57). Was missing from this section but included already on the Schedule of evaluations and procedures table.
Overall		Formatting and minor administrative updates to provide consistency throughout the document

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Apathy avolition
AE	Adverse event
AIMS	Abnormal Involuntary Movements Scale
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AVP-786	Deuterated [d6]-dextromethorphan hydrobromide and quinidine sulfate combination
BAS	Barnes Akathisia Scale
BID	Twice-daily
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CaMK	Calmodulin dependent kinase phosphatase
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity of Illness
CK	Creatine kinase
CNS	Central nervous system
CRO	Contract research organization
[redacted]	[redacted] Subject Database
d6-DM	Deuterated (d6)-dextromethorphan hydrobromide
DBS	Deep Brain Stimulation
DE	Expressive deficits
DM	Dextromethorphan hydrobromide
DMP	Data Management Plan
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive treatment
EDC	Electronic data capture
EEfRT	Effort Expenditure for Reward Task
FDA	US Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice

Abbreviation	Definition
HBA1c	Glycosylated hemoglobin
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IRT	Interactive Response Technologies
LDH	Lactate dehydrogenase
MAOI	Monoamine oxidase inhibitor
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
M.I.N.I.	Mini International Neuropsychiatric Interview
mITT	Modified Intent-to-Treat
MM	Medical Monitor
MMRM	Mixed-effects model for repeated measures
NF	National Formulary
NIMH	National Institute of Mental Health
NMDA	*N*-methyl-D-aspartate
NSA-16	16-Item Negative Symptom Assessment
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PBA	Pseudobulbar affect
PCP	Phencyclidine
PD	Pharmacodynamic(s)
pH	Potential hydrogen
PK	Pharmacokinetic(s)
Q	Quinidine (sulfate)
QD	Once daily
QOL	Quality of life
QRS	The Q-R-S complex from an ECG tracing
QT	QT interval from an ECG tracing
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia's formula
RBC	Red blood cell
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical analysis plan
SAS	Simpson Angus Scale for Extrapyramidal Symptoms
SDV	Source of data verification
SGA	Second generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	Selective serotonin reuptake inhibitor
SPCD	Sequential parallel comparison design
TEAE	Treatment-emergent adverse event
TNFα	Tumor necrosis factor-alpha
ULN	Upper limit of normal
US	United States of America
USP	United States Pharmacopoeia
WBC	White blood cell
WHO	World Health Organization

PROTOCOL AGREEMENT

Protocol Title:

A Phase 2, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) as an adjunctive treatment for patients with residual schizophrenia.

Protocol Number: 15-AVP-786-202

This document is a confidential communication of Avanir Pharmaceuticals. The recipient agrees that no unpublished information contained within this document or protocol will be disclosed or published without prior consent and written approval from Avanir. An exception to this agreement may be made for the purposes of ethical or regulatory review, in which case this document may be disclosed to an Ethics Review Board or any authorized representative of a national authority as required by regulation.

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 U.S. Food and Drug Administration (FDA), or other regulatory agencies if applicable.

Principal Investigator Signature Principal Investigator Name:	Date
Avanir Representative Signature Avanir Representative Name: [redacted]	Date

STUDY SYNOPSIS

Title: A Phase 2, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) as an adjunctive treatment for patients with residual schizophrenia.

Study Objectives

The objectives of this 12-week study are to evaluate the efficacy, safety, and tolerability of AVP-786 as an adjunctive treatment compared with placebo in patients with residual schizophrenia on negative and positive symptoms and cognitive function.

Study Population

It is estimated that up to 120 patients will participate in the study at approximately 15 enrolling centers in the US.

Eligible patients for this study will be adult outpatients (between 18 and 60 years of age) who are diagnosed with schizophrenia, are clinically stable, in a residual (non-acute) phase of illness, and meet all inclusion and none of the exclusion criteria. Patients enrolled in the study will have been treated with a second generation antipsychotic (SGA) agent for at least 3 months (90 days) and on a stable dose for 1 month (30 days) prior to the Screening Visit and maintain the same dose throughout the course of the study (includes no change from Screening to Baseline/Visit 1 [Day1]). Approximately 160 patients will need to be screened (assuming a 25% screen failure rate) in order to randomize approximately 120 patients.

The diagnosis of residual schizophrenia will be based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria for schizophrenia, residual type.

An initial diagnostic assessment will be performed by the Investigator to assess if the patient meets diagnostic criteria for schizophrenia residual type according to the DSM-IV-TR using the Mini International Neuropsychiatric Interview (M.I.N.I.) version 6.0 (Appendix 3), all medical records, interviews by clinicians, and when appropriate, interviews with family or other informants. The diagnosis will be confirmed by the Investigator.

[redacted]

[redacted]

Eligible patients are to have otherwise acceptable and stable general health as required by the study protocol, and documented by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory examinations.

Eligible patients must be willing to comply with all required study procedures, attend all study visits and take the study medication as instructed.

Participants must provide a signed Informed Consent Form for the procedures in this study protocol prior to Screening.

Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, SPCD study to assess the efficacy, safety, and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) of 12 weeks duration as an adjunctive treatment in patients with residual schizophrenia. The study consists of an up to 4-week Screening period, a 12-week double-blind treatment period with 2 consecutive 6-week stages (Stage 1 and Stage 2), and a 5-day follow-up by telephone, as shown below. Daily telephone calls will be made for 5 days post the Study Exit Visit to assess any changes in health (i.e., adverse events [AEs]) and medications (i.e., concomitant medications).

Sequence	Screening	Treatment Period		Telephone Follow-up
		Stage 1	Stage 2	
Duration	Day -28 to -7 (4 weeks)	Days 1 to 42 (6 weeks)	Days 43 to 85 (6 weeks)	Days 86-90

Screening

Screening procedures must occur within approximately 4 weeks prior to randomization. The Medical Monitor (MM) or contract research organization (CRO) designee will review screening procedures for assessment of inclusion and exclusion criteria and consult with the Investigators as needed.

[redacted] and Subject Database Authorization

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

Randomization and Treatment

Stage 1

Eligible patients will be randomized in a [redacted] (active:placebo) ratio to receive either AVP-786 or matching placebo capsules. Study medication (active or placebo) will be administered orally twice daily (BID; 1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart) throughout Stage 1. Patients will be assigned to double-blind treatment for 6 weeks during Stage 1 as follows:

- Patients randomized to AVP-786 at Baseline/Visit 1 (Day 1) will receive AVP-786-[redacted] (d6-DM [redacted] mg/Q [redacted] mg) once daily (QD) in the morning and placebo in the evening for the first 7 days. Starting on Day 8, AVP-786-[redacted] will be given BID for the next 7 days until Day 14. Starting on Day 14, AVP-786 will be dose-escalated up to AVP-786-34/4.9 BID (d6-DM 34 mg/Q 4.9 mg) until the end of Stage 1 (Visit 4 [Day 43]).
- Patients randomized to placebo will receive placebo BID during the entire Stage 1 (Baseline/Visit 1 [Day 1] to Visit 4 [Day 43]).

All study medication including AVP-786-[redacted] and AVP-786-34/4.9 capsules and placebo capsules are of identical appearance in order to maintain the integrity of the blind, including during dose-escalation.

Stage 2

Patients who complete Stage 1 will be eligible to participate in Stage 2. Study medication will be administered orally BID (1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart) throughout Stage 2. Patients will be assigned to double-blind treatment for an additional 6 weeks during Stage 2 as follows:

- Patients who received AVP-786 in Stage 1 will continue to receive AVP-786 BID for the entire 6-week duration of Stage 2 (Visit 4 to Visit 7/Early Termination Visit [Day 85]) at the same dose received at the end of Stage 1.
- Patients who received placebo in Stage 1 will be further stratified into 2 subgroups ("responders" and "non-responders") on Visit 4 (Day 43) or Stage 1 Early Termination Visit based on their treatment response. Patients will be considered "responders" if their percent of change in [redacted] from Baseline. Patients who do not meet this criterion will be considered "non-responders"..

  Each placebo subgroup ("responders" and "non-responders") will then be re-randomized to receive either AVP-786 or matching placebo in a [redacted] ratio within each group as follows:

- Patients who are re-randomized to placebo will continue to receive placebo BID for the entire 6-week duration of Stage 2 (Visit 4 up to Visit 7/Early Termination Visit [Day 85]).
- Patients who are re-randomized to AVP-786 will receive AVP-786 in Stage 2 using the same dose escalation schedule used in Stage 1.

Assessments and Visits

Patients will attend a Screening Visit up to 4 weeks prior to the Baseline Visit to determine eligibility for the study. During the study, patients will attend clinic visits at Baseline/Visit 1 (Day 1), Week 2/Visit 2 (Day 15), Week 3/Visit 3 (Day 22), Week 6/Visit 4 (Day 43), Week 8/Visit 5 (Day 57), Week 9/Visit 6 (Day 64), and Week 12/Visit 7/Early Termination Visit (Day 85). Patients will receive telephone follow-up calls at Day 8 and Day 50 to inquire about AEs, concomitant medications and study drug compliance, as well as on Days 86 through 90 to inquire about AEs and concomitant medications post study treatment.

The duration of each patient's participation in this study will be approximately 12 weeks (maximum of 17 weeks including Screening period and post study exit telephone calls for 5 days).

Efficacy Measures

Primary Efficacy Measure

The primary efficacy measure is the 16-Item Negative Symptom Assessment (NSA-16) total score.

Secondary Efficacy Measures

Secondary efficacy measures to further characterize the effects of AVP-786 on commonly associated features of residual schizophrenia include:

- PANSS total score, PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and pro-social factors)
- NSA-16 factor domains, global score, individual items and NSA 4 factors comprised of the 4 NSA-16 items as follows: 1) restricted speech quantity, 2) reduced emotion, 3) reduced social drive, and 4) reduced interests, as well as an overall global rating of negative symptoms
- Proportion of patients with a reduction of 20% or greater in the PANSS total score
- Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) composite score
- Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGIC) scores
- Calgary Depression Scale for Schizophrenia (CDSS) score

[redacted]

- Reward responsiveness using the frequency of hard task choices with moderate probability reward measured by the probabilistic computerized Effort Expenditure for Reward Task (EEfRT)
- [redacted]

Pharmacokinetic (PK) Measures

At Baseline/Visit 1 (Day 1, post-dose), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85), all patients will have plasma samples collected between 2 to 3 hours after the morning dose of study medication for analysis of study medication (d6-DM, its metabolites, and Q concentration levels) and plasma antipsychotic levels. [redacted]

Safety Measures

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

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

Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy analysis is the change from Baseline/Visit 1 (Day 1) to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7/Early Termination Visit (Day 85, Stage 2) of the NSA-16 total score in patients administered AVP-786 compared to patients administered placebo, using the SPCD methodology. A weighted ordinary least square test statistics combining treatment effects from Stage 1 and 2 will be used. The treatment effect in each stage will be analyzed by using a linear mixed-effects model for repeated measures (MMRM). Data from Stage 1 placebo non-responders who are re-randomized into Stage 2 will be used to estimate the Stage 2 treatment effect.

Secondary Efficacy Analyses

Secondary efficacy endpoints include: change from Baseline/Visit 1 (Day 1) to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7 (Day 85, Stage 2) for the following efficacy measures: PANSS total score; PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and prosocial factors; NSA-16 (factor domains, global score, individual items, and NSA 4 factors); proportion of patients with a 20% reduction in PANSS total score; MCCB composite score; CGI-S, CGI-C, and PGIC scores (measure change at post Baseline visits); CDSS; and EEfRT. These endpoints will be analyzed in a similar manner as the primary efficacy analysis.

[redacted]

Pharmacokinetic and Pharmacodynamic (PD) Analysis

Plasma concentrations of d6-DM, its metabolites, and Q will be measured and results will be summarized descriptively overall [redacted] Plasma antipsychotic levels will also be measured and results reported descriptively. Plasma concentration results will be used to assess the PK properties of d6-DM, its metabolites, and Q as well as potential drug interactions with co-administered antipsychotics. Additional PK/PD correlations may also be performed. Additional details will be described in the SAP.

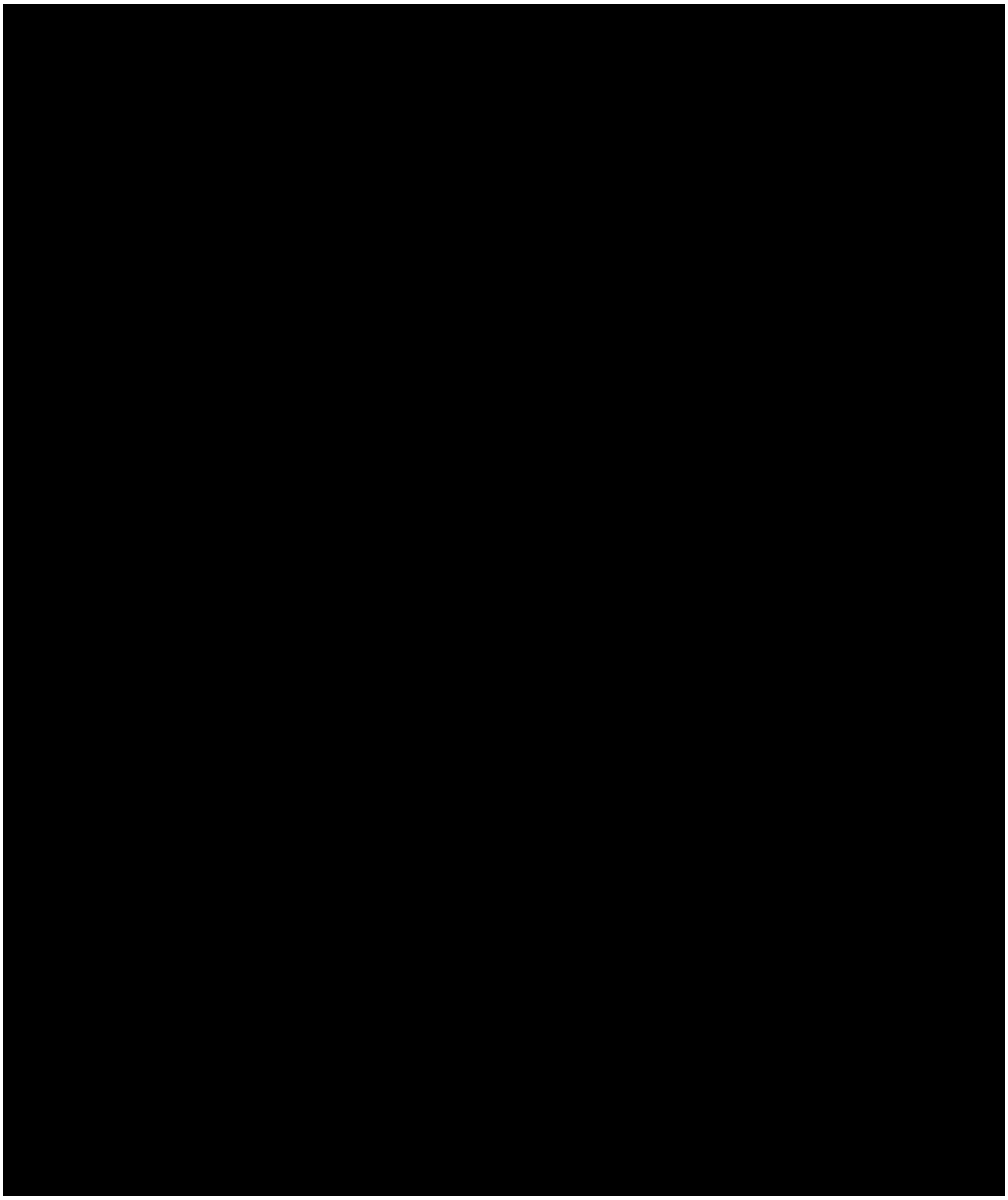
Sample Size Justification

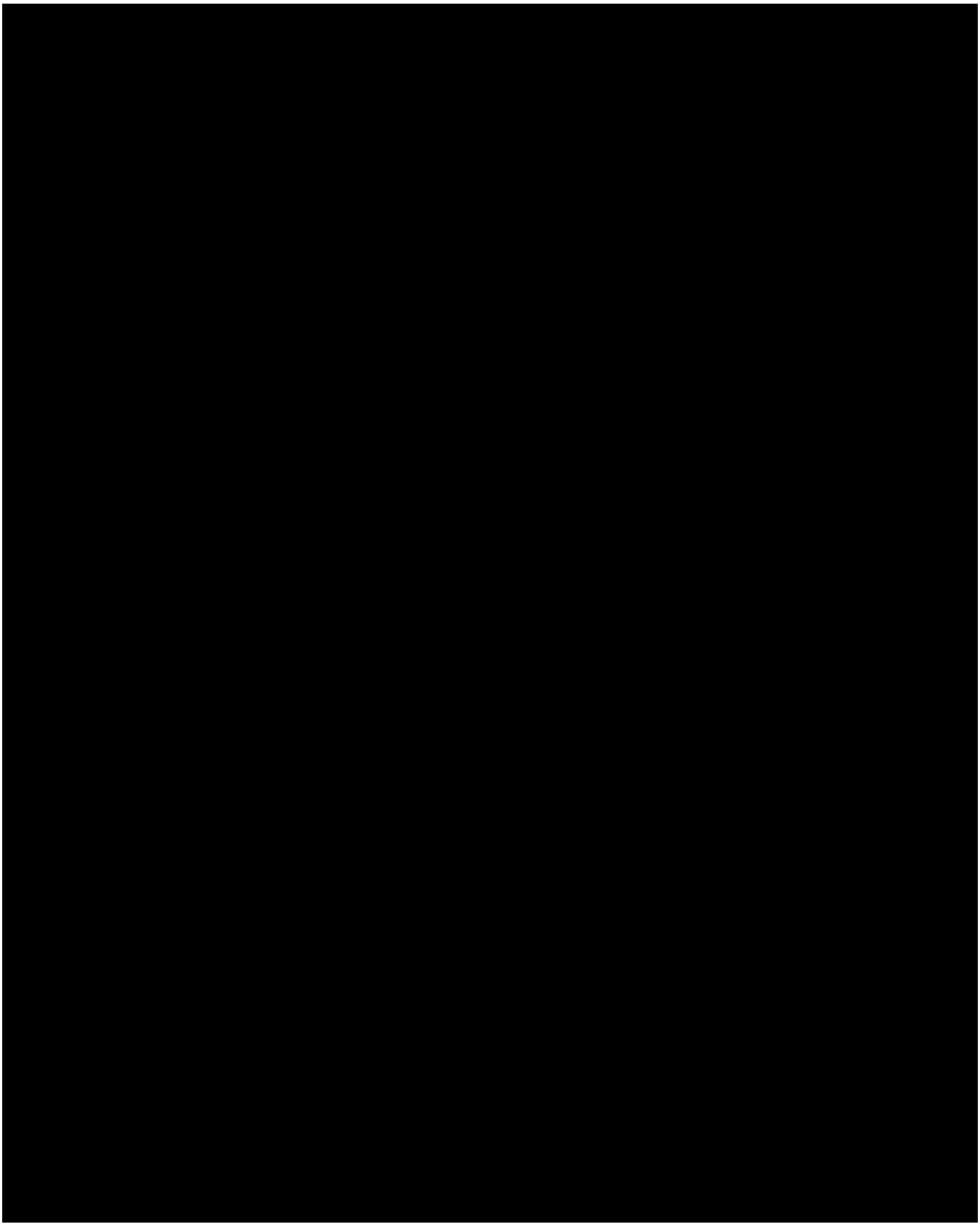
Based on published studies such as Kane et al. (1988)[1] and Buchanan, et al (2014),[2] sample size calculations were performed assuming a bivariate normal distribution for the primary endpoint.

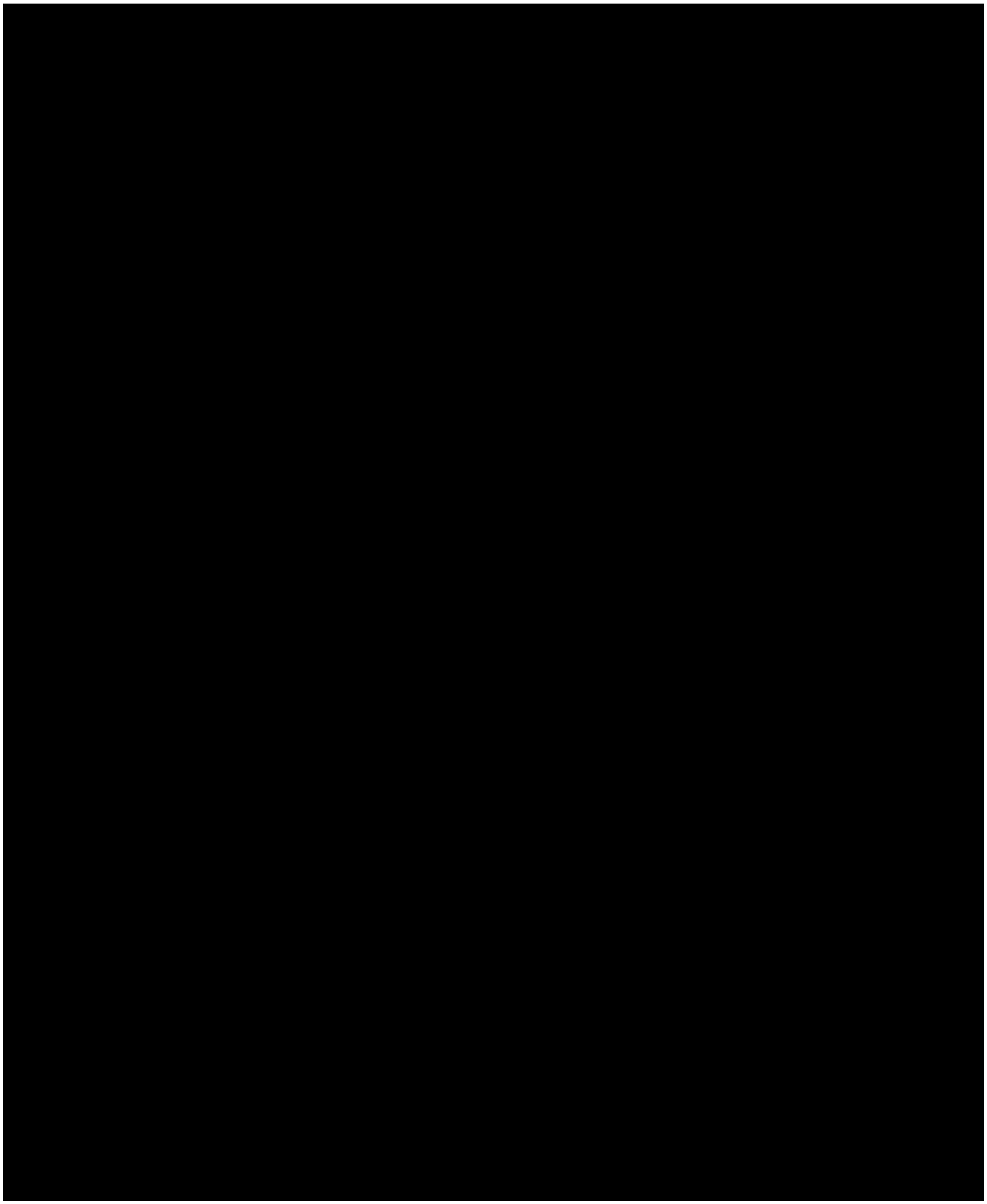
[redacted]

[redacted]

1 INTRODUCTION







2 Objectives

The objectives of this 12-week study are to evaluate the efficacy, safety, and tolerability of AVP-786 as an adjunctive treatment compared with placebo in patients with residual schizophrenia on negative and positive symptoms and cognitive function.

3 Study Design and Rationale

3.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, SPCD study of 12 weeks duration, consisting of an up to 4-week Screening period, a 12-week double-blind treatment period with 2 consecutive stages (Stage 1 and Stage 2), and a 5-day follow-up by telephone, as shown below. Post study exit follow-up telephone calls will be made for 5 days to assess any changes in health (i.e., adverse events [AEs]) and medications (i.e., concomitant medications).

Sequence	Screening	Treatment Period		Telephone Follow-up
		Stage 1	Stage 2	
Duration	Days -28 to -7 (4 weeks)	Days 1 to 42 (6 weeks)	Days 43 to 85 (6 weeks)	Days 86-90

3.1.1 Screening

Screening procedures must occur within approximately 4 weeks (28 days) prior to randomization. The Medical Monitor (MM) or contract research organization (CRO) designee may review Screening procedures for assessment of inclusion and exclusion criteria in consultation with the Investigators.

3.1.1.1 [redacted] *and Subject Database Authorization*

Clinical trial registries, such as the [redacted] Subject Database [redacted], seek to reduce duplicate enrollment by identifying duplicates before randomization.[2] At the time of providing the Informed Consent Form (ICF) for the study, the Investigator or designee will explain the Institutional Review Board (IRB)-approved subject database authorization form to the patient and witness the signature.

During Screening, site staff that have received training, login information, and access to [redacted] will enter the patient study identification (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 patient participating in another study within 30 days or (3) the patient matches with a patient who has *pre*-screened at another site.

At the last patient contact, site staff will access [redacted] again, enter the patient study ID and the nature of the last contact (i.e., early termination or completer).

3.1.2 Stage 1

The Baseline/Visit 1 (Day 1) marks the start of Stage 1 of the study.

Eligible patients will be randomized at Baseline/Visit 1 (Day 1) in a [redacted] (active:placebo) ratio to receive either AVP-786 capsules or matching placebo capsules. Study medication will be administered orally BID (1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart) throughout Stage 1. Patients will be assigned to double-blind treatment for 6 weeks during Stage 1 as follows:

- Patients randomized to AVP-786 at Baseline/Visit 1 (Day 1) will receive AVP-786-[redacted] (d6-DM [redacted] mg/Q [redacted] mg) once daily (QD) in the morning and placebo in the evening for the first 7 days. Starting on Day 8, AVP-786-[redacted] will be given BID for the next 7 days until Day 14. Starting on Day 14, AVP-786 will be dose-escalated up to AVP-786-34/4.9 BID (d6-DM 34 mg/Q 4.9 mg) until the end of Stage 1 (Visit 4 [Day 43]).
- Patients randomized to placebo will receive placebo BID during the entire Stage 1 (Baseline/Visit 1 [Day 1] to Visit 4 [Day 43]).

All study medication including AVP-786-[redacted] and AVP-786-34/4.9 capsules and matching placebo capsules are of identical appearance [redacted] in order to maintain the integrity of the blind, including during dose-escalation.

3.1.3 Stage 2

Patients who complete Stage 1 will be eligible to participate in Stage 2 of the study. Study medication will be administered orally BID (1 capsule in the morning and 1 capsule in the evening, approximately 12 hours apart) throughout Stage 2. Patients will be assigned to double-blind treatment for an additional 6 weeks during Stage 2 as follows.

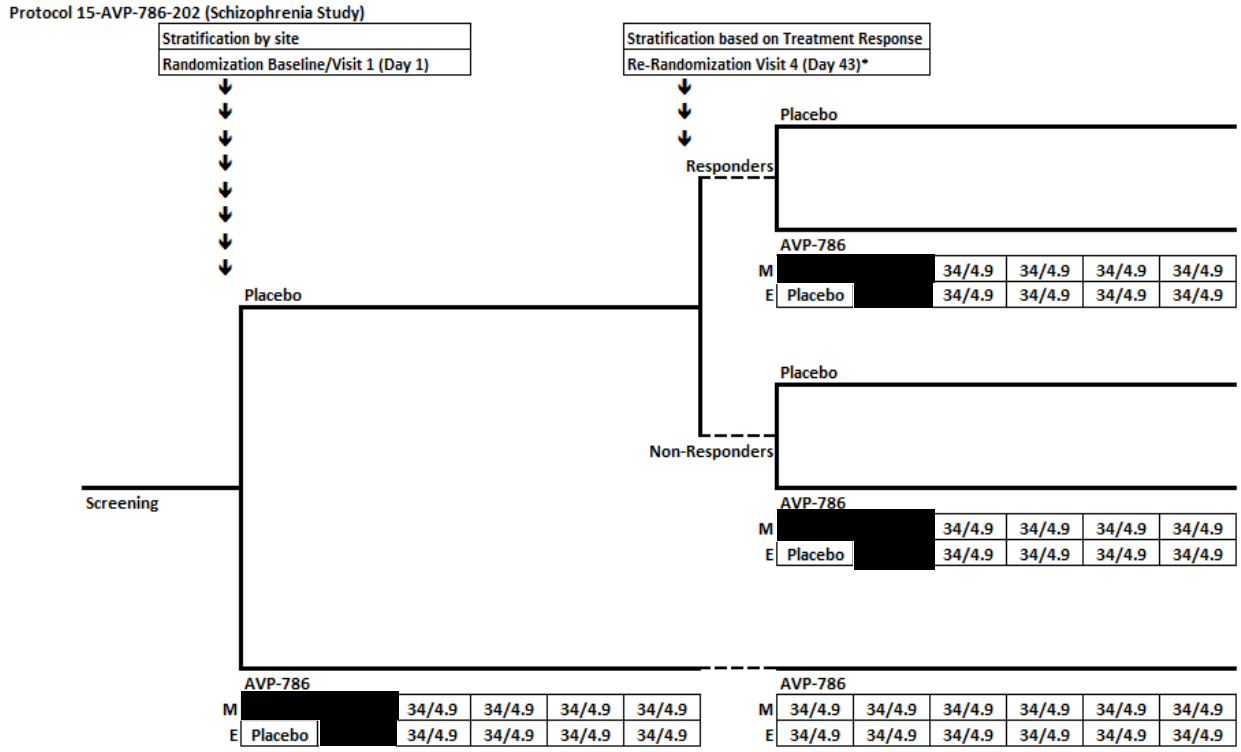
- Patients who received AVP-786 in Stage 1 (Baseline/Visit 1 [Day 1] to Visit 4 [Day 43]), will continue to receive AVP-786 BID for the entire 6-week duration of Stage 2 (Visit 4 to Visit 7/Early Termination Visit [Day 85]) at the same dose as at the end of Stage 1.
- Patients who received placebo in Stage 1 will be further stratified into 2 subgroups ("responders" and "non-responders") on Visit 4 (Day 43) or Stage 1 Early Termination Visit based on their treatment response. Patients will be considered "responders" if their percent of change in [redacted] from Baseline. Patients who do not meet this criteria will be considered "non-responders".

  Each placebo subgroup ("responders" and "non-responders") will then be re-randomized to receive either AVP-786 or matching placebo in a [redacted] ratio within each group.

- Patients who are re-randomized to placebo will continue to receive placebo BID for the entire 6-week duration of Stage 2 (Visit 4 to Visit 7/Early Termination Visit [Day 85]).
- Patients who are re-randomized to AVP-786 will receive AVP-786 in Stage 2 using the same dose escalation schedule used in Stage 1.

A schematic of the study is shown in Figure 1.

Figure 1 STUDY SCHEMATIC



3.2 Visits

Patients will attend a Screening Visit up to 4 weeks (28 days) prior to the Baseline Visit to determine eligibility for the study. During the study, patients will attend clinic visits at Baseline/Visit 1 (Day 1), Week 2/Visit 2 (Day 15), Week 3/Visit 3 (Day 22), Week 6/Visit 4 (Day 43), Week 8/Visit 5 (Day 57), Week 9/Visit 6 (Day 64) and Week 12/Visit 7/Early Termination Visit (Day 85). Patients will also receive telephone follow-up calls at Days 8 and 50 to inquire about AEs and study drug compliance. In addition, post study exit follow-up telephone calls will be made daily on Days 86 to 90 to assess any changes in health (i.e., AEs) and medication (i.e., concomitant medications).

The assessments planned for Visit 7 should be performed in the event of a patient withdrawing prematurely from the study. In this case, the visit is referred to as the "Early Termination Visit."

The duration of each patient's participation in this study will be approximately 12 weeks (maximum of 17 weeks including Screening phase and post study exit telephone calls for 5 days).

4 Study Population

It is estimated that approximately 120 patients will participate in the study at approximately 15 centers in the US.

Eligible patients for this study will be adult outpatients (between 18 and 60 years of age) who are diagnosed with schizophrenia, are clinically stable, in a residual (non-acute) phase of illness, and meet all the inclusion criteria and none of the exclusion criteria. Patients enrolled in the study will have been treated with a second generation antipsychotic (SGA) agent for at least 3 months (90 days) and on a stable dose for 1 month (30 days) prior to the Screening Visit and maintain the same dose throughout the course of the study (includes no change from Screening to Baseline/Visit 1 [Day1]). Approximately 160 patients will need to be screened (assuming a 25% screen failure rate) in order to randomize approximately 120 patients.

The diagnosis of residual schizophrenia will be based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR).

An initial diagnostic assessment will be performed by the Investigator to assess if the patient meets diagnostic criteria for schizophrenia according to the DSM-IV-TR using the Mini International Neuropsychiatric Interview (M.I.N.I.) version 6.0 (Appendix 3), all medical records, interviews by clinicians, and when appropriate, interviews with family or other informants. The diagnosis of schizophrenia will be confirmed by the Investigator.

4.1 Inclusion Criteria

1. Males and females 18 to 60 years of age, inclusive, at time of informed consent.
2. Patients who meet DSM-IV-TR diagnostic criteria for schizophrenia using the M.I.N.I. version 6.0 and who meet DSM-IV-TR diagnostic criteria for residual schizophrenia.
3. [redacted]
4. If female of childbearing potential, patients must
   a) have a negative urine pregnancy test (all females regardless of childbearing potential will be required to submit a pregnancy test), and
   b) not be nursing or planning a pregnancy for the duration of the study through 30 days after the last dosing visit, and
   c) be abstinent or willing to use a reliable method of birth control from the Screening Visit, and continue with the same method until 28 days after the last dosing visit

[redacted]

Reliable methods of contraception that meet the study requirements are:

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

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

Females of childbearing potential who are abstinent can enroll in the study.

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

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

5. Patients currently receiving atypical antipsychotics (oral and long acting intramuscular injectables) within the dose guidance from the USPI for the treatment of schizophrenia disorder (e.g., SGAs like olanzapine, risperidone, paliperidone, quetiapine, aripiprazole and lurasidone) are eligible provided they have been treated with the medication for at least 3 months (90 days), the dose has been stable for at least 1 month (30 days) prior to the Screening Visit (includes no change from Screening to Baseline/Visit 1 [Day1]), and there has been no inpatient psychiatric hospitalization in the past 4 months prior to Screening.

6. [redacted]

7. [redacted]

[redacted]

[redacted]

8. Patients who are capable, according to the Investigator, and have signed and received a copy of the ICF after the nature and risks of study participation had been fully explained to them.
9. Patients must have a reliable informant as deemed appropriate by the investigator.

4.2 Exclusion Criteria

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

1. [redacted]
2. Patients with current major depressive disorder (MDD) at the Screening Visit [redacted]

[redacted]

[redacted]

10. Patients currently using anticholinergic medications or within 1 month (30 days) prior to Baseline for treatment of AEs associated with antipsychotic medications.

[redacted]

15. Patients who have had an inpatient psychiatric hospitalization within 4 months of Screening.
16. Patients with clinically significant laboratory abnormalities (hematology, chemistry, and urinalysis) or with safety values of potential clinical concern or with AST or ALT > 2 x ULN at the Screening Visit.

[redacted]

[redacted]

4.3 Patient Withdrawal

Patients will be advised verbally and in the 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. Patients may withdraw from the study at any time and for any reason, and are not obligated to provide the reason.

The Investigator or Sponsor may discontinue a patient from the study in the event of an inter-current illness, AE, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product (IP), and follow-up with the patient regarding any unresolved AEs.

Any reason for withdrawal given (or the failure to provide a reason) must be recorded in the source documentation and on the patient's electronic case report form (eCRF).

Patients who present a QTcF > 500 msec (unless due to ventricular pacing) or a QTcF change from the pre-dose Baseline ECG of > 60 msec at any time after Baseline are to be withdrawn from the study. The QTcF values will be recorded and assessed for clinical significance.

Patients who start a prohibited concomitant medication, psychotherapy, or somatic therapy (light therapy, repetitive transcranial magnetic stimulation, and other non-invasive brain stimulation techniques) during the study may need to be withdrawn from the study. The decision to withdraw the patient will be made on a case-by-case basis in conjunction with the MM.

Patients who withdraw prior to study completion for any reason will be asked to return to the clinic to complete the Visit 7 (Early Termination) assessments.

If the patient withdraws from the study and consent for disclosure of further information is withdrawn then no further evaluations may be performed and no additional data may 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.

For information on termination of the study refer to Section 9.11.

5 Study Treatments

5.1 Treatments Administered

All medication used in this study will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

5.1.1 Description of Study Medications

Clinical study medication will be provided as hard, [redacted] gelatin capsules [redacted].

Three different capsule strengths will be provided, as follows:

- AVP-786-[redacted] (d6-DM [redacted] mg/Q [redacted] mg)
- AVP-786-34/4.9 (d6-DM 34 mg/Q 4.9 mg)
- AVP-786 Placebo, with the same excipients as the study medication

5.1.2 Composition of Study Medications

AVP-786 and matching placebo will be supplied as a solid oral dosage form (gelatin capsule). AVP-786 will contain [redacted] mg or 34 mg of d6-DM in combination with 4.9 mg of Q. [redacted]

Table 1 Composition of Investigational Products

Ingredient	AVP-786 (d6-DM [redacted] mg/Q [redacted] mg) (mg)	AVP-786 (d6-DM 34 mg/Q 4.9 mg) (mg)	Placebo (mg)
d6-dextromethorphan hydrobromide	[redacted]	34.0	0
Quinidine sulfate USP, EP		4.9	0
Croscarmellose sodium NF, EP		[redacted]	
Microcrystalline cellulose NF, EP			
Colloidal silicone dioxide NF, EP			
Magnesium stearate NF, EP			
Total			
Capsule: Hard gelatin capsules, [redacted] (average weight)			
Total Weight			

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

5.1.3 Packaging

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

5.1.4 Labeling

All labels will contain the protocol number, material ID number, product name (AVP-786), blister card number, an investigational drug warning, dosing instructions to take 1 capsule in the morning and 1 capsule in the evening, storage conditions, and company name. The blister card label will consist of 2 panels, with 1 detachable panel that will be removed and kept with the site's study records (e.g., affixed to the study medication dispensing log page or patient source records) at the time of dispensing. Space is provided on both panels of the card label to record patient number, dispensing date and assigned treatment week. All IP labels comply with all applicable federal and local regulations.

5.1.5 Storage of Clinical Supplies

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

5.1.6 Study Medication Administration

All patients will receive AVP-786 or matching placebo according to the material ID number assigned by an interactive response technologies (IRT) system randomization scheme. Designated staff at each site will dispense study medication. The patient will self-administer the study medication, except on visit days when study medication will be administered in the presence of site personnel. Patients are to be advised **NOT** to take the morning dose of study medication on the day of their study visits. When self-administering, patients will be instructed to take the study medication approximately every 12 hours orally with water (morning and evening).

Stage 1: At Baseline/Visit 1 (Day 1) and Visit 3 (Day 22), study medication will be dispensed and administered as follows:

- Baseline/Visit 1 (Day 1): AVP-786 or placebo patients will be dispensed a 3-week blister card labeled for the morning and evening doses. Patients will be administered 1 capsule from the AM blister card in the morning and 1 capsule from the PM blister card in the evening, approximately 12 hours apart until their next scheduled visit (Visit 3 [Day 22]). The cards will be assigned such that patients randomized to active treatment will escalate the dose. All other patients (i.e., those remaining on placebo treatment) undergo a dummy escalation (required to take cards in strict order) to maintain blinding.
- Visit 3 (Day 22): AVP-786 or placebo patients will be dispensed a 3-week blister card containing cards labeled for the morning and evening doses. Patients will be administered 1 capsule from the AM blister card in the morning and 1 capsule from the PM blister card in the evening, approximately 12 hours apart until their next scheduled visit (Stage 2, Visit 4 [Day 43]).

Stage 2: At Visit 4 (Day 43) and Visit 6 (Day 64), study medication will be dispensed and administered as follows:

- Visit 4 (Day 43): AVP-786 or placebo patients will be dispensed a 3-week blister card labeled for the morning and evening doses. Patients will be administered 1 capsule from the AM blister card in the morning and 1 capsule from the PM blister card in the evening, approximately 12 hours apart until their next scheduled visit (Visit 6 [Day 64]). The cards will be assigned such that patients re-randomized from placebo to active treatment will escalate the dose. All other patients (i.e., those remaining on AVP-786 treatment or placebo treatment) will undergo a dummy escalation (required to take cards in strict order) to maintain blinding.
- Visit 6 (Day 64): AVP-786 or placebo patients will be dispensed a 3-week blister card labeled for the morning and evening doses. Patients will be administered 1 capsule from the AM blister card in the morning and 1 capsule from the PM blister card in the evening, approximately 12 hours apart until their next scheduled visit (Visit 7 [Day 85]).

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

5.2 Accountability of Study Supplies

5.2.1 Receipt of Supplies

IP will be shipped by the Sponsor direct to the study sites.

The Investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The Investigator will verify the accuracy of the information. All IP supplied is for use only in this study and should not be used for any other purpose. All blister card material ID numbers will also be recorded and tracked at the site using a drug accountability log.

5.2.2 Record of Dispensing

Accurate recording of all IP dispensing for individual patients will be made in the appropriate section of the patient's drug accountability records. This document will contain the following information: (i) the patient number to whom the drug was dispensed; (ii) the date(s) and quantity of the drug dispensed to the patient; and (iii) the blister card material ID number assigned to the patient via IRT system.

Additionally, the detachable panel of the 2-panel label on each card will be removed and kept with the site's study records (e.g., affixed to a study medication patient drug dispensing log page) at the time of dispensing. Space is provided on both panels of the card label to record patient number, dispensing date and visit week.

5.2.3 Unused Supplies

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

5.3 Methods of Assigning Patients to Treatment Groups

5.3.1 Randomization

Upon entry into the study (after ICF is signed at the Screening Visit), all patients will be assigned a patient number. [redacted]

[redacted]

[redacted]

Stage 1

Eligible patients will be randomized into the study in a [redacted] (active:placebo) ratio to receive either AVP-786 capsules or matching placebo capsules at Baseline/Visit 1 (Day 1, Stage 1) in a double-blind manner according to a randomization scheme devised by Avanir or its representative and managed within an IRT system.

Stage 2

Re-randomization will occur for patients who were assigned to placebo in Stage 1. The patient number will not be re-assigned; it will remain the same in both stages of the study.

1. Patients who receive placebo in Stage 1 will be further stratified into 2 sub-groups ("responders" and "non-responders") based on their treatment responses. Patients will be considered "responders" if their percent of change in [redacted] from Baseline. Patients who do not meet this criterion will be considered "non-responders." Patients within each placebo sub-group will be re-randomized in a [redacted] (active:placebo) ratio to receive either AVP-786 or matching placebo capsules.
2. Patients who receive placebo and who drop out early in Stage 1 will also be assigned a re-randomization treatment in the same manner as the other placebo patients. Their "responders" and "non-responders" status will be based on their treatment responses using measurements at their Early Termination Visit.
3. Patients who receive AVP-786 in Stage 1 will not be re-randomized and will continue to receive the same dose of AVP-786 for the entire duration of Stage 2.

5.3.2 Blinding/Masking

All study medication, including AVP-786 capsules and placebo capsules, are of identical appearance in order to maintain the integrity of the blind, including during dose escalation. Neither the Sponsor, patients, Investigators, nor other study personnel will be aware of a patient's treatment assignment. In the event that it becomes medically necessary to identify which treatment a patient has received, the blind can be broken. In that event, the Investigator is to make all attempts to contact Avanir's MM or representative to request the unblinding of a patient. The IRT manager is not required to be blinded, and he or she will have access to the study medication list and the randomization code.

5.4 Patient Compliance

Patients will be instructed to bring any used and unused study medication and empty blister packs to the clinic on Days 15, 22, 43, 57, 64, and 85 (Visits 2-7). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses.

6 Study Assessments and Procedures

6.1 Efficacy

Examples (for reference only) of all of the scales and questionnaires that will be used during the study can be found in the Appendices (Section 11).

6.1.1 16-Item Negative Symptom Assessment (NSA-16)

The NSA-16 (Appendix 1) is considered a valid and reliable measure of the presence, severity, and range of negative symptoms associated with schizophrenia; it has high interrater and test–retest reliability across languages and cultures.[50,51] The NSA-16 uses a 5-factor model to describe negative symptoms: (1) Communication, (2) Emotion/affect, (3) Social involvement, (4) Motivation, and (5) Retardation. These factors, assessed through a structured interview, are comprehensive and well-defined to help standardize assessment. As a truncated version of the 25-item NSA, the NSA-16 still captures the multidimensionality of negative symptoms but can be completed in approximately 15 to 20 minutes.[51] The NSA-4[52] is comprised of the 4 NSA-16 items as follows: 1) restricted speech quantity, 2) emotion: reduced range, 3) reduced social drive, and 4) reduced interests, as well as an overall global rating of negative symptoms.

The NSA-16 evaluation will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination Visit (Day 85).

6.1.2 Positive and Negative Syndrome Scale (PANSS)

The PANSS (Appendix 2) is a 30-item clinical scale that has been extensively used as a reliable and valid measure for negative symptom trials.[50] Each item is scored for "1" (absent) to "7" (extremely severe). Three subscales can be derived: the Positive Subscale, the Negative Subscale and the General Psychopathology Subscale. Outpatients will need to identify a reliable informant (e.g., case manager, social worker, family member) who spends sufficient time with them to be able to provide information to PANSS raters.

The PANSS subscale descriptions are provided below:

- Negative Subscale: N1-N7
- Positive Subscale: P1-P7
- General Psychopathology Subscale: G1-G16
- Prosocial Factors:
    - G16. Active social avoidance
    - N2. Emotional withdrawal
    - N4. Passive/apathetic social withdrawal

- N7. Stereotyped thinking
- P3. Hallucinatory behavior
- P6. Suspiciousness/persecution

- Marder Negative Factors:
  - N1. Blunted affect,
  - N2. Emotional withdrawal
  - N3. Poor rapport
  - N4. Passive/apathetic social withdrawal
  - N6. Lack of spontaneity and flow of conversation
  - G7. Motor retardation
  - G16. Active social avoidance
- Excitement Component:
  - P4. Excitement
  - P7. Hostility
  - G4. Tension
  - G8. Uncooperativeness
  - G14. Poor Impulse Control

The PANSS evaluation will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination Visit (Day 85).

6.1.3 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.[53] The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI comprises 2 companion 1-item measures, the CGI-S (Severity) and CGI-C (Change). The CGI forms can be completed in less than 1 minute by an experienced rater.

6.1.3.1 Clinical Global Impression - Severity (CGI-S)

The CGI-S (Appendix 5) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients

who have the same diagnosis.[54] Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, among the most extremely ill patients.

The CGI-S evaluation will be performed at Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

6.1.3.2 Clinical Global Impression - Change (CGI-C)

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

The CGI-C evaluation will be performed at Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85). At Day 43 (Visit 4), the CGIC will be completed to assess change from the Baseline Visit (Day 1). At Day 85 (Visit 7), the CGIC will be completed to assess change from Day 43 (Visit 4) and change from the Baseline Visit (Day 1).

6.1.3.3 Patient Global Impression – Change (PGIC)

The PGIC (Appendix 4) is a 7-point (1–7), patient-rated scale used to assess treatment response as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

The PGIC evaluation will be performed at Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

6.1.4 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS (Appendix 7) is a 9-item scale derived from the Hamilton Depression Scale (Ham-D) that is designed to assess depression specifically in patients with schizophrenia.[55] Unlike the Ham-D, the CDSS does not contain depressive symptoms that overlap with negative symptoms of schizophrenia, such as anhedonia and social withdrawal. The CDSS has shown excellent psychometric properties. Each item on the scale is scored as 0, Absent; 1, Mild; 2, Moderate; or 3, Severe. The CDSS score is obtained by adding each of the item scores. A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

The CDSS evaluation will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64) and Visit 7/Early Termination Visit (Day 85).

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

The MCCB (Appendix 8) is the standard tool for assessing cognitive change in trials of cognitive-enhancing agents in schizophrenia. The MCCB[56] is intended to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders. The MCCB includes 10 tests that measure 7 cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving and Social Cognition.

The MCCB evaluation will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85). The MCCB should be conducted at approximately the same time of day (+/- 2 hours) and preferably in the AM. Alternate versions of the battery will be used at different visits to decrease the learning confound.

6.1.6 Effort Expenditure for Reward Task (EEfRT)

The Effort Expenditure for Rewards Task EEfRT[57] is a multi-trial computerized task in which participants are given an opportunity on each trial to choose between 2 tasks that differ in difficulty level and are associated with varying levels of monetary reward. This task examines probabilistic learning in response to variable reward schedules and effort expended (button pushing) for reward. Probability is manipulated in the EEfRT, because like mobilization of effort, probability discounting appears to be highly predictive of negative symptoms. Additionally, the inclusion of a probability manipulation improves the overall ecological validity of the task, as most real-world choices that require motivation are usually associated with some level of uncertainty in the outcome. The EEfRT reliably measures drug effects on willingness to expend effort in relation to amount of reward or probability of reward. For example, amphetamine increased effort in response to low- and moderate probability rewards.[58] Whereas reward salience and behavioral response have been linked to dopamine release in the striatum, glutamatergic input to midbrain dopamine neurons via NMDA receptors is also required for reward conditioning.[59] We will use the ratio of hard task choices with moderate probability reward as our outcome measure for negative symptoms.

The EEfRT evaluation will be performed at Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

[redacted]

[redacted]

6.2 Pharmacokinetics (PK)

At Baseline/Visit 1 (Day 1, post-dose), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85) all patients will have plasma samples collected between 2 and 3 hours after the morning dose of study medication for analysis of study medication (d6-DM, its metabolites, and Q concentration levels). The time when the patient was administered the dose of study medication and the time of the blood draw will be recorded on the eCRF. Plasma samples will be separated by centrifugation and then stored in accordance with the study lab manual until assayed at the analytical unit.

6.4 Safety

6.4.1 Adverse Events

6.4.1.1 Definitions

An AE is any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time ICF is signed, including inter-current illness, which occurs during the course of a clinical study 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).

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. An overdose must be reported irrespective of outcome even if toxic effects were not observed.

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

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

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

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

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

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

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

Related: the event follows a reasonable temporal sequence from the time of drug administration; **and** follows a known response pattern to the study medication; **and** cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

6.4.1.2 Serious Adverse Events

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

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

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

The terms "cancer" and "overdose" may not always be 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., the mother and the 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 his last dose of study medication or study completion, whichever is greater.

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

6.4.1.3 Reporting

Patients will be queried regarding AEs starting with the Baseline Visit (Visit 1, Day 1) until the end of the study (Days 1, 14, 22, 43, 57, 64, and 85 [Visits 1–5 including the 2 telephone follow-up calls at Day 14 and Day 50, and the post-study follow-up calls at Days 85 through 90]). The Investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication and up until 30 days after receiving the last dose of study medication will be followed up until resolution (patient's health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

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

For all SAEs, including an abnormal laboratory test value, the Investigator should consult with Avanir's MM as needed and report any SAE by fax/e-mail form no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to test drug, action taken regarding test drug, treatment required, and outcome to date. These details must be recorded on the clinical study AE 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-mail: [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 IRB will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

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

In the event of an unexplained abnormal laboratory test result found to be clinically significant by the Investigator, the test should be repeated and followed up until test values have either returned to the patient's baseline (pretreatment) range and/or until an adequate explanation of the abnormality is found.

6.4.2 Physical and Neurological Examinations

The examination should include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The physical and neurological examinations should be performed by the same person each time, whenever possible.

Physical and neurological examinations abnormalities determined by the Investigator, including those that are determined 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.

Physical and neurological examinations will be performed at Screening (Day –28 to Day –1) and at the discretion of the Investigator at the subsequent visits. If a subsequent physical exam is performed after the Screening Visit, then the Investigator should document any clinically significant finding on the AE form.

6.4.3 Vital Signs, Weight, and Height

At Screening (Day –28 to Day –1), orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed. Supine BP and HR will be measured after a patient has rested for at least 5 minutes in the supine position. Each measurement will be taken twice in the same position and recorded. After the measurement of supine BP and HR, the patient will stand still for up to 3 minutes and a single measurement of standing BP and HR will be recorded within these 3 minutes of standing. Respiratory rate (breaths/minute), body temperature, height and weight will also be recorded.

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

At all subsequent visits, the supine/semi-recumbent SBP and DBP and HR (bpm), after at least 5 minutes of rest, will be taken and recorded twice. Respiratory rate (breaths/minute), body temperature, and weight will also be recorded.

The vital signs and weight will be recorded at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 2 (Day 15), Visit 3 (Day 22), Visit 4 (Day 43), Visit 5 (Day 57), Visit 6 (Day 64), and Visit 7/Early Termination Visit (Day 85).

Height will be recorded only at Screening (Day –28 to Day –1).

[redacted]

6.4.4 Pregnancy Tests

All female patients of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication (See Section 4.1).

Urine pregnancy tests (beta-hCG) will be performed on all females regardless of childbearing potential at Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64), and Visit 7/Early Termination Visit (Day 85). At the Screening Visit, serum beta-hCG will be collected.

6.4.5 Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at Screening (Day –28 to Day –1), Visit 4 (Day 43), and Visit 7/Early Termination Visit (Day 85).

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen [BUN], serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], creatine kinase [CK], gamma-glutamyl transferase [GGT], triglycerides, total protein, total cholesterol, and glycosylated hemoglobin [HbA1c, at Screening and Visit 7]).
- Hematology (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology).
- Urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, urobilinogen, nitrites, leucocytes, and blood). Microscopic analysis will be performed on those samples that are positive for blood, protein, leucocyte esterase or nitrates.
- Urine screen for presence of alcohol and substances of abuse - PCP, benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, and opiates. (Screening Visit only).
- Thyroid function tests TSH, T3, T4 (Screening Visit only)

Any patients with clinically significant abnormal laboratory test results may be required by the MM to have a repeat test 1 week later or sooner, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry. Non-eCRF data including, but not limited to, laboratory tests and results, will be sent to the Sponsor, CRO, or representative by data transfer from the central laboratory.

6.4.6 Electrocardiograms

ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute) QRS complex and PR and QTc intervals (milliseconds). Results will be provided by the central reader to the Investigators within 72 hours and any significant findings will be reported within 24 hours. ECG abnormalities 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 recorded as AEs. Any clinically significant abnormal ECG should be discussed with the study MM and, if necessary, be repeated within a 1-week period. Non-eCRF data including, but not limited to, ECG tests and results, will be sent to the Sponsor, CRO, or representative by data transfer from the central reader.

A resting 12-lead ECG will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 4 (Day 43), and Visit 7/Early Termination Visit (Day 85). Triplicate ECGs will be performed at Screening. At Baseline/Visit 1 (Day 1) and Visit 4 (Day 43), 2 ECGs will be performed; one prior to study medication dosing and one 2 to 3 hours after dosing.

6.4.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Appendix 9) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the NIMH Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

The C-SSRS evaluation will be performed at Screening (Day –28 to Day –1), Baseline/Visit 1 (Day 1), Visit 3 (Day 22), Visit 4 (Day 43), Visit 6 (Day 64), and Visit 7/Early Termination Visit (Day 85).

6.4.8 Simpson Angus Scale for Extrapyramidal Symptoms (SAS)

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

The SAS evaluation will be performed at Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

6.4.9 Barnes Akathisia Scale (BAS)

The BAS (Appendix 11) consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity.

The BAS is scored as follows:

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

The BAS evaluation will be performed at Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

6.4.10 Abnormal Involuntary Movements Scale (AIMS)

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

The AIMS evaluation will be performed at Baseline/Visit 1 (Day 1), Visit 4 (Day 43) and Visit 7/Early Termination Visit (Day 85).

6.5 Schedule of Evaluations and Procedures

A schedule of evaluations and procedures is provided in Table 2.

[redacted]

Table 2 Study Schedule of Evaluations and Procedures

				Stage 1				Stage 2				
Procedure	**Visit:**	**Screening**	**Baseline Visit 1**	**Telephone[7]**	**Visit 2[2]**	**Visit 3[1]**	**Visit 4[2]**	**Telephone[7]**	**Visit 5[2]**	**Visit 6[1]**	**Visit 7/ ET [2,4]**	**Post Exit Telephone[7]**
	Study Day:	**Day -28 to -7**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 43**	**Day 50**	**Day 57**	**Day 64**	**Day 85**	**Day 86-90**
	Study Week:	**Week -4 to -1**		**Week 1**	**Week 2**	**Week 3**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 12**	
Informed Consent Form signed		X										
[redacted]		X									X	
Medical History		X										
M.I.N.I. Exam		X										
Inclusion and Exclusion		X	X									
Randomization / (re-randomization)			X				X					
Physical Examination		X										
Resting 12-lead ECG		X[6]	X[6]				X[6]				X[6]	
Chemistry, Hematology, and Urinalysis[3]		X					X				X	
Pregnancy Test[3]		X	X			X	X			X	X	
[redacted]			X[5]									
Plasma Antipsychotic Levels		X					X				X	
PK and [redacted]			X[5]				X[5]				X[5]	
Review of Adverse Events			X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Record Vital Signs/Weight[9]		X	X		X	X	X		X	X	X	
NSA-16		X	X			X	X			X	X	
PANSS		X	X			X	X			X	X	
MCCB[10]		X	X				X				X	
CGI-S			X				X				X	
CDSS		X	X			X	X			X	X	
CGI-C							X				X	
PGIC							X				X	
RDoC Task (EEfRT)			X				X				X	
Side Effects Scales (AIMS, BAS, SAS)			X				X				X	
C-SSRS		X	X		X	X	X		X	X	X	
[redacted]												
Dispense Study Medication			X			X	X			X		
Dose in Clinic			X		X	X	X		X	X	X	
Review and/or Return Unused Study Medication				X[8]	X	X	X	X[8]	X	X	X	

1 Visits 3 and 6 have a +3 day window.
2 Visits 2, 4, 5, and 7 have a +/- 3 day window.
3 Urinary (beta-hCG) test will be performed for all females regardless of of childbearing potential (serum beta-hCG at Screening only). Fasting glucose and lipids will be measured at Screening, Visit 4 and Visit 7.
4 Final visit or Early Termination Visit for patients who withdraw prior to study completion.
5 PK blood draws will be taken 2-3 hours post-dose for Baseline and Visits 4 and 7. [redacted]
6 Electrocardiogram will be performed prior to dosing and 2-3 hours post-dosing for Visits 1 and 4. Post-dose only for Visit 7. Triplicate ECGs at Screening only.
7 Telephone call will have a +3 day window. Post study exit calls will be daily for 5 days to assess any changes in health (AEs)/concomitant medications.
8 Patient will be asked if they have taken their medications as directed during telephone calls at Days 8 and 50.
9 Height will be measured at Screening only.

[10] The MCCB should be conducted at approximately the same time of day (+/- 2 hours) and preferably in the AM. After the Screening Visit, patients who use sedatives/hypnotics or benzodiazepine medications on a prn basis should not take any of these medications the day of, or the day before, the assessment of cognitive function by MCCB. Patients who are on stable dose regimens of sedatives/hypnotics or benzodiazepine medications should take their medication as prescribed.

6.5.1 Description of Study Procedures

Patients will be seen in the clinic for a Screening Visit within 28 days of dosing (Day 1) to assess eligibility for the study. Patients will be randomized after eligibility is confirmed on Day 1.

At certain visits throughout the study, site staff will be required to enter information into the IRT system. Further instructions will be provided in the IRT Site Manual.

6.5.1.1 Screening Visit (Days –28 to –1)

The following procedures will be performed at Screening (within 28 days prior to Day 1):

1. The Investigator or delegated site staff will provide the patients with informed consent documents and will explain the rationale for the study, providing ample time for patients to ask questions.
2. Authorization form completed and patient information will be entered into [redacted].
3. Patients will be assessed for inclusion and exclusion criteria.
4. Medical history, including patient demographics, and any concomitant medications use (including over-the-counter [OTC] medications, vitamins, and supplements) will be reviewed and recorded.
5. Psychiatric history will be recorded and M.I.N.I. exam will be conducted.
6. Physical and neurological examination will be conducted.
7. Orthostatic BP and HR measurements will be performed. Supine BP and HR will be measured after a patient has rested for at least 5 minutes in the supine position. Each measurement will be taken and recorded twice. After the measurement of supine BP and HR, the patient will stand still for up to 3 minutes and a single measurement of standing BP and HR will be recorded within these 3 minutes of standing. Respiratory rate (breaths/minute), body temperature, height and weight will also be recorded.
8. In addition, the following tests will be completed:
   a) NSA-16
   b) PANSS
   c) MCCB
   d) CDSS
   e) C-SSRS
9. A serum pregnancy test will be performed on all females regardless of childbearing potential.

10. A blood and/or urine specimen will be collected for:
    a) Clinical laboratory assessments
    b) Plasma antipsychotic levels
11. Triplicate 12-lead ECGs will be performed at Screening.
12. Patient information will be recorded in the IRT system.

Patient Instructions

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

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

6.5.1.2 Visit 1 (Baseline Visit, Day 1); Stage 1

The Baseline/Visit 1 (Day 1) visit should occur in the morning.

Before dosing the following procedures will be performed at Baseline/Visit 1 (Day 1):

1. Inclusion/exclusion criteria will be reviewed.
2. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
3. Patients will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements). In addition, confirmation that patient did not take prn sedatives/hypnotics or benzodiazepine medications on date of visit or day before.
4. In addition:
    a) NSA-16
    b) PANSS
    c) MCCB
    d) CGI-S
    e) CDSS
    f) EEfRT
    g) C-SSRS
    h) AIMS

i) BAS

j) SAS

k) [redacted]

5. A urine pregnancy test will be performed on all females regardless of childbearing potential.
6. A blood specimen will be collected for [redacted] (shipped frozen).
7. A resting 12-lead ECG will be performed prior to dosing.
8. Visit information along with PANSS total score will be entered in the IRT system

Patients will be randomized once it is determined that they satisfy all of the inclusion and none of the exclusion criteria (on the basis of the Screening and Baseline assessments described above) and will be assigned with a study medication card number via IRT.

Study Medication Dosing:

The FIRST dose of study medication will be administered at the clinic regardless of the time of day.

After Dosing:

1. A PK sample will be collected between 2 and 3 hours post dosing.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) post dosing.
3. Sufficient study medication will be dispensed for a 21-day (3-week) treatment period.

Patient Instructions

The Investigator will give patients detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient. Patients will be instructed to take the study medication BID (1 capsule from the blister labeled AM in the morning and 1 capsule from the blister labeled PM in the evening, approximately every 12 hours) for 21 days (3 weeks). Patients will also be instructed to bring to the clinic any used and unused study medication at each study visit.

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

6.5.1.3 Telephone Follow-up (Day 8); Stage 1

Patients will be called and asked if they have had any changes in their medications, experienced any AEs and have taken their study medication as instructed since the Baseline Visit. Patients

should also be asked if they have any questions/concerns regarding adhering to the medication regimen. They will also be asked to return their study medication cards at the next visit.

6.5.1.4 Visit 2 (Day 15 ± 3 day window), Week 2; Stage 1

The visit should occur within the 3-day window as described. The following procedures will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications
3. C-SSRS
4. Study medication review
5. Study medication will be administered from the AM strip of the blister card brought in by the patient.

Patients will be asked to return their study medication cards for review by the site during this visit. Sites will check for dosing compliance and return the study medication cards to the patient to use until the next scheduled visits. (New medication cards should not be dispensed at this visit).

6.5.1.5 Visit 3 (Day 22 + 3-day window), Week 3; Stage 1

The visit should occur in the morning. The patient is advised NOT to take the morning dose of study medication prior to the clinic appointment. If the patient has taken the morning dose on the same day as the visit then the patient should be asked to return the following day to complete the study visit procedures.

Before dosing the following procedures will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications
3. A urine pregnancy test will be performed on all females regardless of childbearing potential.
4. In addition:
    a) NSA-16
    b) PANSS
    c) CDSS

    d) C-SSRS

[redacted]

5. Returned and unused study medication will be accounted for compliance.
6. Visit information along with PANSS total score will be entered in the IRT system.

Study Medication Dosing:

The FIRST dose of NEW study medication will be administered from the assigned blister pack at the clinic regardless of the time of day.

After Dosing:

1. Sufficient study medication will be dispensed for a 21-day (3-week) treatment period.

Patient Instructions

Patients will be instructed to take the study medication BID (1 capsule from the blister labeled AM in the morning and 1 capsule from the blister labeled PM in the evening, approximately every 12 hours) for 21 days (3 weeks). Patients will also be instructed to bring to the clinic any used and unused study medication at each study visit.

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

6.5.1.6 Visit 4 (Day 43 ± 3-day window), Week 6; Stage 1

The visit should occur in the morning. The patient is advised NOT to take the morning dose of study medication prior to the clinic appointment. If the patient has taken the morning dose on the same day as the visit then the patient should be asked to return the following day to complete the study visit procedures.

Before dosing the following will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications
3. A urine pregnancy test will be performed on all females regardless of childbearing potential.
4. In addition:
    a) NSA-16
    b) PANSS
    c) MCCB
    d) CGI-S
    e) CDSS

[redacted]

f) CGI-C

g) PGIC

h) EEfRT

i) C-SSRS

j) AIMS

k) BAS

l) SAS

m) [redacted]

5. Returned and unused study medication will be accounted for compliance.
6. A resting 12-lead ECG will be performed prior to dosing.
7. Visit information along with PANSS total score will be entered in the IRT system

Patients will either continue to use AVP-786 or be re-randomized to receive either AVP-786 or matching placebo (see Section 3.1).

Study Medication Dosing:

The FIRST dose of NEW study medication will be administered from the assigned blister pack at the clinic regardless of the time of day.

After Dosing:

1. A blood/urine specimen will be collected for:
    a) Clinical laboratory assessments
    b) Plasma antipsychotic levels
    c) PK sample 2-3 hours (± 15 minutes) post dosing (shipped frozen)
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) post dosing.
3. Sufficient study medication will be dispensed for a 21-day (3-week) treatment period.

Patient Instructions

Patients will be instructed to take the study medication BID (1 capsule from the blister card labeled AM in the morning and 1 capsule from the blister card labeled PM in the evening, approximately

every 12 hours) for 21 days (3 weeks). Patients will also be instructed to bring to the clinic any unused study medication at each study visit.

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

6.5.1.7 Telephone Follow-up (Day 50); Stage 2

Patients will be called and asked if they have had any changes in their medications, experienced any AEs and have taken their study medication as instructed since the Baseline Visit. Patients should also be asked if they have any questions/concerns regarding adhering to the medication regimen. They will also be asked to return their study medication cards at the next visit.

6.5.1.8 Visit 5 (Day 57 ± 3 day window); Week 8; Stage 2

The visit should occur within the 3-day window as described. The following procedures will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications
3. C-SSRS
4. Study medication review
5. Study medication will be administered from the AM strip of the blister card brought in by the patient.

Patients will be asked to return their study medication cards for review by the site during this visit. Sites will check for dosing compliance and return the study medication cards to the patient to use until the next scheduled visits. (New medication cards should not be dispensed at this visit).

6.5.1.9 Visit 6 (Day 64 + 3-day window); Week 9; Stage 2

The visit should occur in the morning. The patient is advised NOT to take the morning dose of study medication prior to the clinic appointment. If the patient has taken the morning dose on the same day as the visit then the patient should be asked to return the following day to complete the study visit procedures.

Before dosing the following procedures will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications

[redacted]

3. A urine pregnancy test will be performed on all females regardless of childbearing potential.
4. In addition:
    a) NSA-16
    b) PANSS
    c) CDSS
    d) C-SSRS
4. Returned and unused study medication will be accounted for compliance.
5. Visit information along with PANSS total score will be entered in the IRT system

Study Medication Dosing:

The FIRST dose of NEW study medication will be administered from the assigned blister pack at the clinic regardless of the time of day.

After Dosing:

1. Sufficient study medication will be dispensed for a 21-day (3-week) treatment period.

Patient Instructions

Patients will be instructed to take the study medication BID (1 capsule from the blister card labeled AM in the morning and 1 capsule from the blister card labeled PM in the evening, approximately every 12 hours) for 21 days (3 weeks). Patients will also be instructed to bring to the clinic any unused study medication at each study visit.

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

6.5.1.10 Visit 7/Early Termination (Day 85 ± 3-day window), Week 12; Stage 2

This visit will take place in the morning.

The assessments scheduled for this visit are also to be performed if patients withdraw from the study early. In this case the visit is termed the "Early Termination Visit" and patients should attempt to return to the clinic 7 days after they were withdrawn if possible. If not within 7 days, patients should still make every attempt to return for a final exit visit.

Before dosing the following will be performed:

1. Supine/semi-recumbent BP and HR (measured twice); respiratory rate (breaths/minute), body temperature, and weight will also be recorded.
2. AEs and concomitant medications

[redacted]

3. A urine pregnancy test will be performed on all females regardless of childbearing potential.
4. In addition:
    a) NSA-16
    b) PANSS
    c) MCCB
    d) CGI-S
    e) CDSS
    f) CGI-C (The CGIC will be completed to assess change from Day 43 [Visit 4] and change from the Baseline Visit [Day 1]).
    g) PGIC
    h) EEfRT
    i) C-SSRS
    j) AIMS
    k) BAS
    l) SAS
    m) [redacted]
5. Returned and unused study medication will be accounted for compliance.
6. Visit information along with PANSS total score will be entered in the IRT system

Study Medication Dosing:

The LAST dose of study medication will be administered from the assigned blister pack at the clinic regardless of the time of day.

After Dosing:

1. A blood/urine specimen will be collected for:
    a) Clinical laboratory assessments
    b) Plasma antipsychotic levels
    c) PK sample 2-3 hours (± 15 minutes) post dosing (shipped frozen)
2. A resting 12-lead ECG will be performed 2-3 hours (± 15 minutes) post dosing.

3. At the last patient contact, site staff will access [redacted], enter the patient study ID and the nature of the last contact (i.e., early termination or completer).

6.5.1.11 Post Study Exit Daily Telephone Follow-up (Days 86-90); Stage 2

Patients will be called daily for 5 days post the study exit visit and asked if they have had any changes in their health, experienced any AEs or changes to their medications since their final visit.

Any AE previously reported and not yet resolved at the time of this visit, will be followed-up until resolution (patient's health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

Any newly reported AE after receiving and up to 30 days after the last dose of study medication will be followed up until resolution (patient's health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event).

[redacted]

7 Data Management

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 authorized designee. All study-site personnel must use a password-protected user account to enter, review, or correct study data. Electronic signature procedures shall comply with the CFR Title 21 Part 11. Passwords will be strictly confidential.

All eCRF data will be exported from the 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 (SDV) of the data recorded in the EDC system with source documents at the clinical study sites according to the DMP 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 AEs will be coded using a current version of Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications using a current version of the World Health Organization (WHO) Drug Dictionary. The Sponsor or representative will perform a medical safety review of the coding.

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

8 Statistical Methods

8.1 Analysis Populations

Modified Intent-to-Treat (mITT) Population: The mITT population is defined as all randomized patients who had at least one post-Baseline NSA-16 efficacy assessment. The mITT population will be used for all analyses of efficacy. Patients will be included in the treatment group to which they were randomized, regardless of treatment received.

Intent-to-Treat (ITT) Population: The ITT population includes all randomized patients. The ITT population will be used for exploratory efficacy analyses.

Safety Population: The safety population includes all patients who received 1 or more doses of study treatment. The safety population will be used for all analyses of safety and patients will be included in the treatment group based on treatment received.

8.2 Demographic and Baseline Characteristics

Baseline characteristics, such as demographics, will be summarized by treatment group for the ITT and mITT populations.

8.3 Efficacy Analysis

The primary and secondary efficacy endpoints are assessed throughout the study.

8.3.1 Study Endpoints

Efficacy Measures

Primary Efficacy Measures:

The primary efficacy measure is the NSA-16 total score.

Secondary Efficacy Measures:

Secondary efficacy measures include the following:

- PANSS total score, PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and prosocial factors)
- NSA-16 factor domains, global score, individual items, and NSA-4 (four NSA-16 items include: 1) restricted speech quantity, 2) reduced emotion, 3) reduced social drive, and 4) reduced interests, as well as an overall global rating of negative symptoms.)
- Proportion of patients with a reduction of 20% or greater in the PANSS total score
- MCCB composite score
- CGI-S, CGI-C, and PGIC scores

- CDSS
- EEfRT

8.3.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline/Visit 1 to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7(Day 85, Stage 2) on the NSA-16 total score. The primary efficacy analysis will be based on the SPCD method using a weighted ordinary least square test statistics combining treatment effects from Stage 1 and 2.[2,48] Data from Stage 1 placebo non-responders who are re-randomized into Stage 2 will be used to estimate Stage 2 treatment effect.

The null hypothesis is that there is no treatment effect in Stage 1 or Stage 2 and it will be tested against the alternative that there is a treatment effect in at least 1 of the 2 stages. The treatment effect in each stage will be estimated by 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 as a covariate. An unstructured covariance model will be used.

8.3.3 Secondary Efficacy Analyses

Secondary efficacy endpoints include: change from Baseline to Week 6/Visit 4 (Day 43, Stage 1) and from Week 6/Visit 4 (Day 43) to Week 12/Visit 7 (Day 85, Stage 2) for the following efficacy measures: PANSS total score; PANSS subscales (positive, negative, general psychopathology, Marder negative factors, excitement component, and prosocial factors); NSA-16 (factor domains, global score, individual items, and NSA-4 factors); proportion of patients with 20% reduction in PANSS total score; MCCB composite score; CGI-S, CGI-C, and PCIG scores (measures change at post Baseline visits); CDSS; and EEfRT. These endpoints will be analyzed in a similar manner as the primary efficacy analysis.

[redacted]

8.4 [redacted]

[redacted]

8.5 Plasma Antipsychotic Levels

Plasma antipsychotic levels will be summarized descriptively.

[redacted]

8.6 Safety and Tolerability Analysis

Safety and tolerability will be assessed by the following measurements: AEs, vital signs, weight, urine pregnancy tests, clinical laboratory assessments, resting 12-lead ECGs, C-SSRS, AIMS, BAS, and SAS.

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

8.6.1 Adverse Events

AEs will be coded using the MedDRA. The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAEs). TEAEs are those AEs that occur after the first dose of study medication up until 30 days after last dose.

8.6.2 Vital Signs and ECGs

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

8.6.3 Clinical Laboratory Values

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

8.6.4 Data and Safety Monitoring Board

A data and safety monitoring board will not be used for this study.

8.6.5 Interim Analysis

An interim analysis of efficacy is not planned; however, may be carried out. If so, the protocol will be amended to provide details.

8.7 Sample Size Justification

Based on published studies such as Kane et al. (1988)[1] and Buchanan, et al (2014),[2] sample size calculations were performed assuming a bivariate normal distribution for the primary endpoint. [redacted]

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9 Administrative Procedures

9.1 Institutional Review Board Approval

IRBs must meet the guidelines set out by the US 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 the laws and regulations of the US (see Appendix 13 Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 14.

9.2 Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed consent will be obtained from the patient.

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

9.3 Quality Assurance

9.3.1 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.

9.3.2 Monitoring

Throughout the course of 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 patient's authorized representative for study procedures and for the release of

medical records to the Sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the Investigator explaining why the patient was unable to provide assent. 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.

9.3.3 Medical Monitoring

Throughout the course of the study, the MM may verify eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (e.g., AE/SAE, laboratory, and ECG) and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

9.4 Electronic Case Report Forms

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

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The EDC vendor will provide user-specific access to the live (production) eCRF once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

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

All investigators will be provided with copies of the eCRFs for their site on a CD-ROM at the end of the study.

9.5 Record Retention

To enable evaluations and/or audits from regulatory authorities or Avanir, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls 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 becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Avanir should be prospectively notified. The study records must be transferred to a designee acceptable by Avanir, such as another Investigator, another institution, or to Avanir. The Investigator must obtain Avanir's written permission before disposing of any records, even if retention requirements have been met.

9.6 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.

9.7 Data Handling

The eCRF data will be entered by trained study-site personnel. Queries will be issued as outlined in the DMP and clinical monitoring plan and should be resolved by the investigational center in a timely manner. The eCRF data will be reviewed for completeness and accuracy and electronically signed by the Investigator or authorized designee.

9.8 Laboratory Procedures

Each individual site laboratory will collect clinical laboratory samples for analysis. Instructions for specimen evaluation and transport to a central laboratory will be provided at the time of study initiation.

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

Protocol modifications must be prepared by a representative of Avanir or the Investigator, and reviewed and approved by Avanir. All major changes must be addressed and when appropriate, justified in the Background and/or Study Design section of the protocol.

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

9.12 Confidentiality of Study Documents and Patient Records

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

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

9.13 Reports

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

9.14 Publications

It is anticipated that a report of this study will be published in the scientific literature by the Sponsor. The Investigator will not seek to arrange for publication of any of the information or

results from the study in any scientific journal, or other publication or by way of lecture without Avanir's prior review and written consent.

9.15 Audits/Inspections

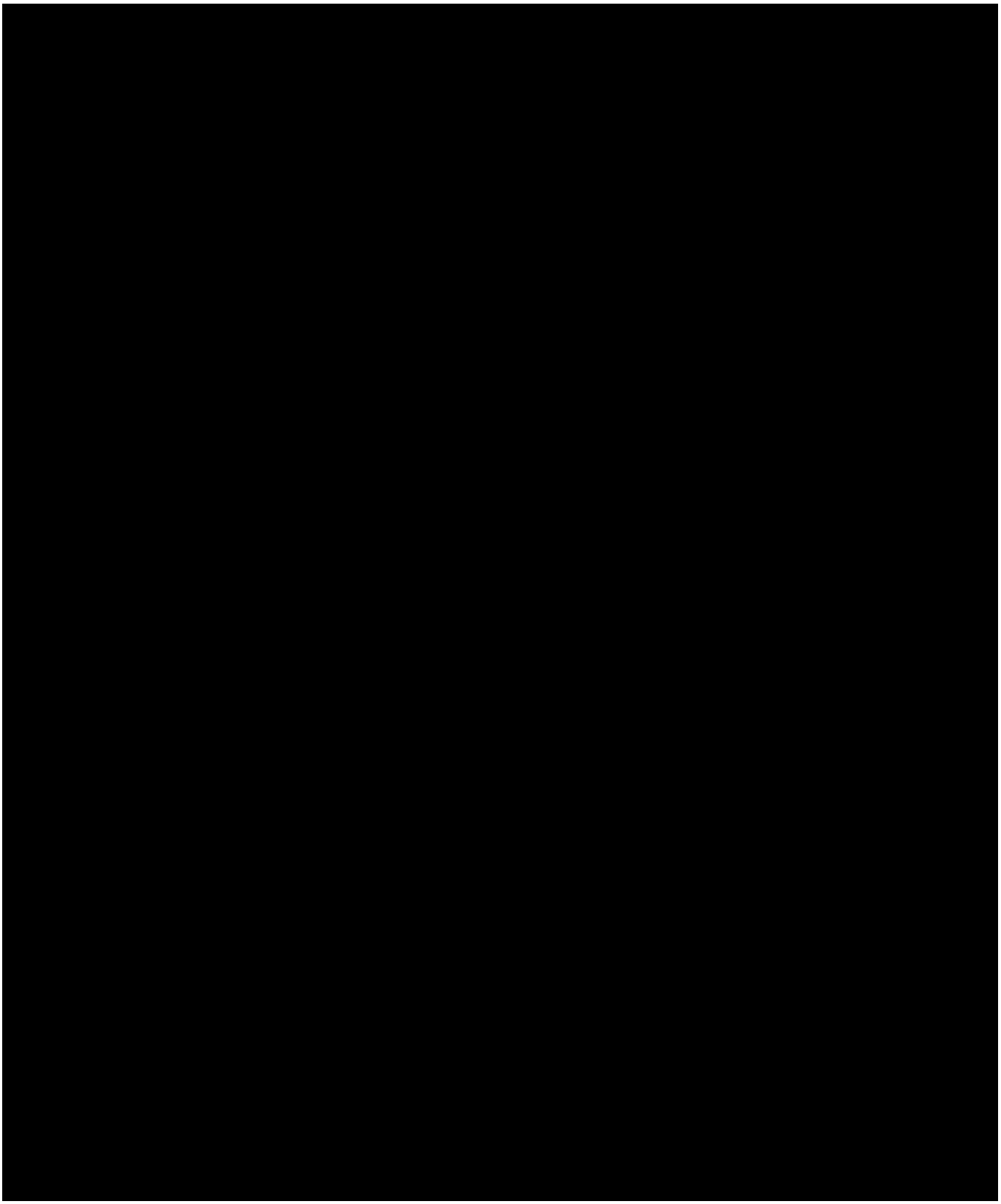
The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from Avanir or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents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

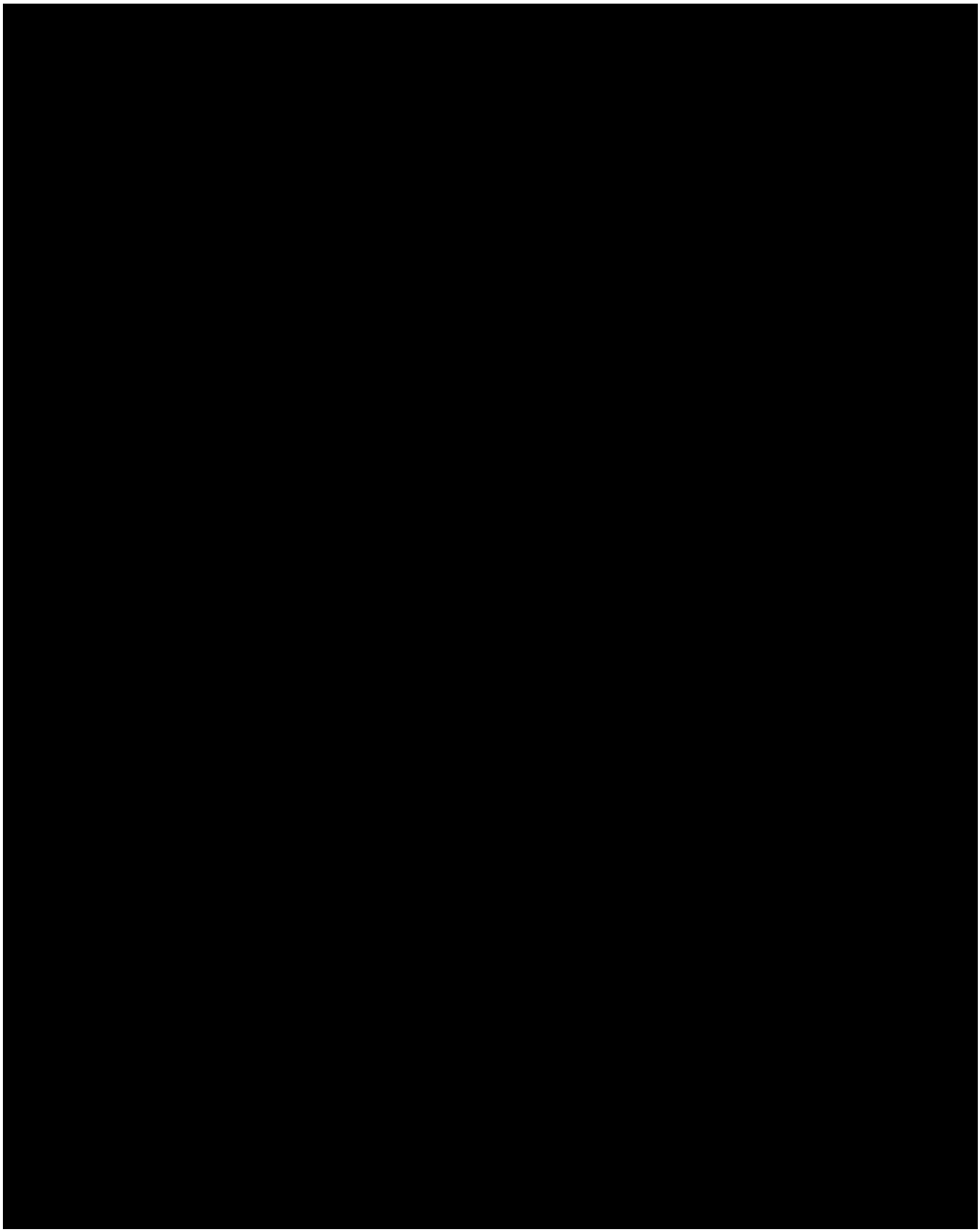
The inspector from the regulatory authority will be especially interested in the following items:

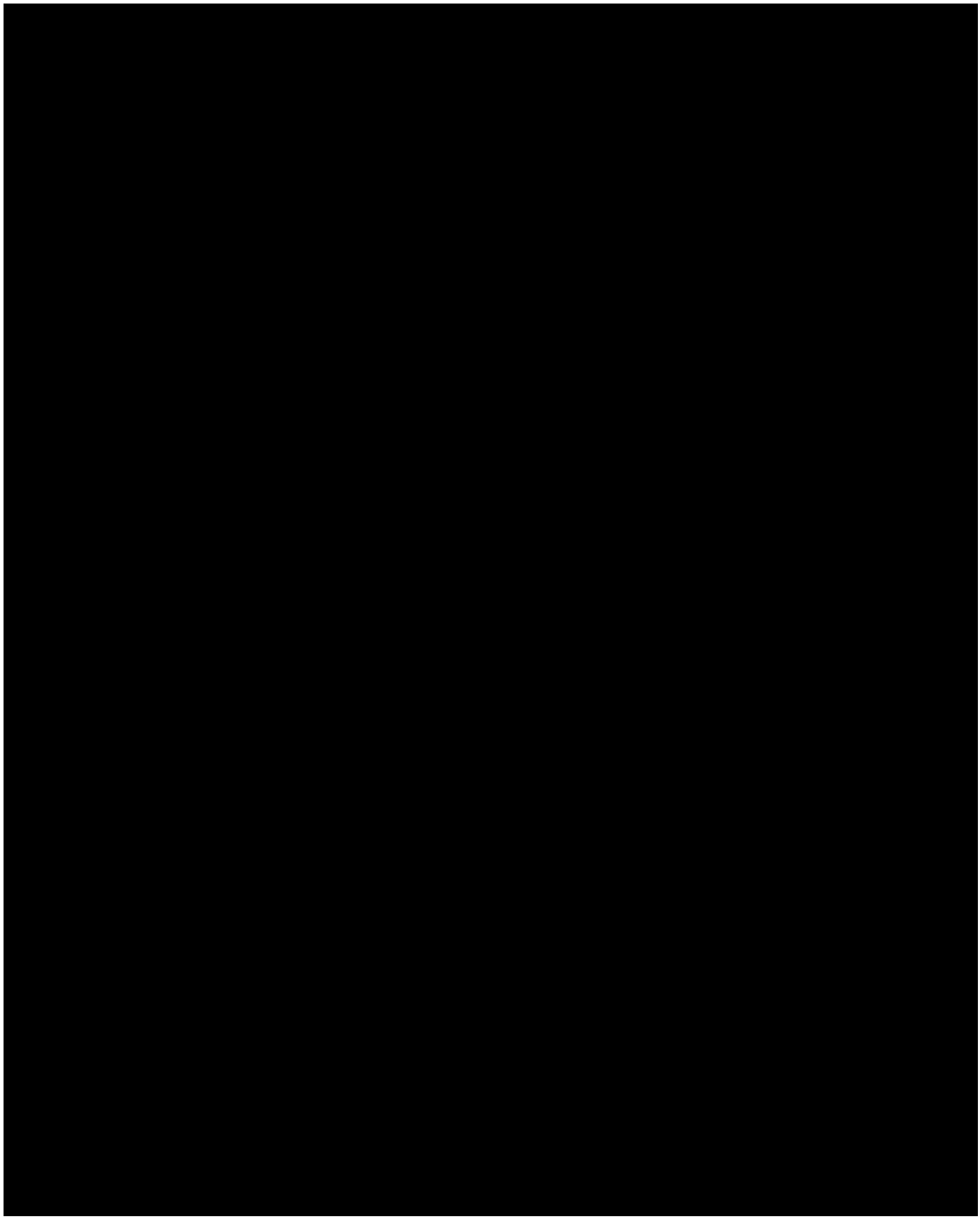
1. Visits from the Sponsor's representatives
2. IRB approval(s)
3. Study medication accountability
4. Study protocol and amendments
5. ICFs of the patient (if capable of providing ICF, according to the Investigator) or patient's authorized representatives
6. Assent of the patients (if capable of providing assent, according to the Investigator)
7. Medical records supportive of eCRF data
8. Reports to the IRB and the Sponsor
9. Record retention

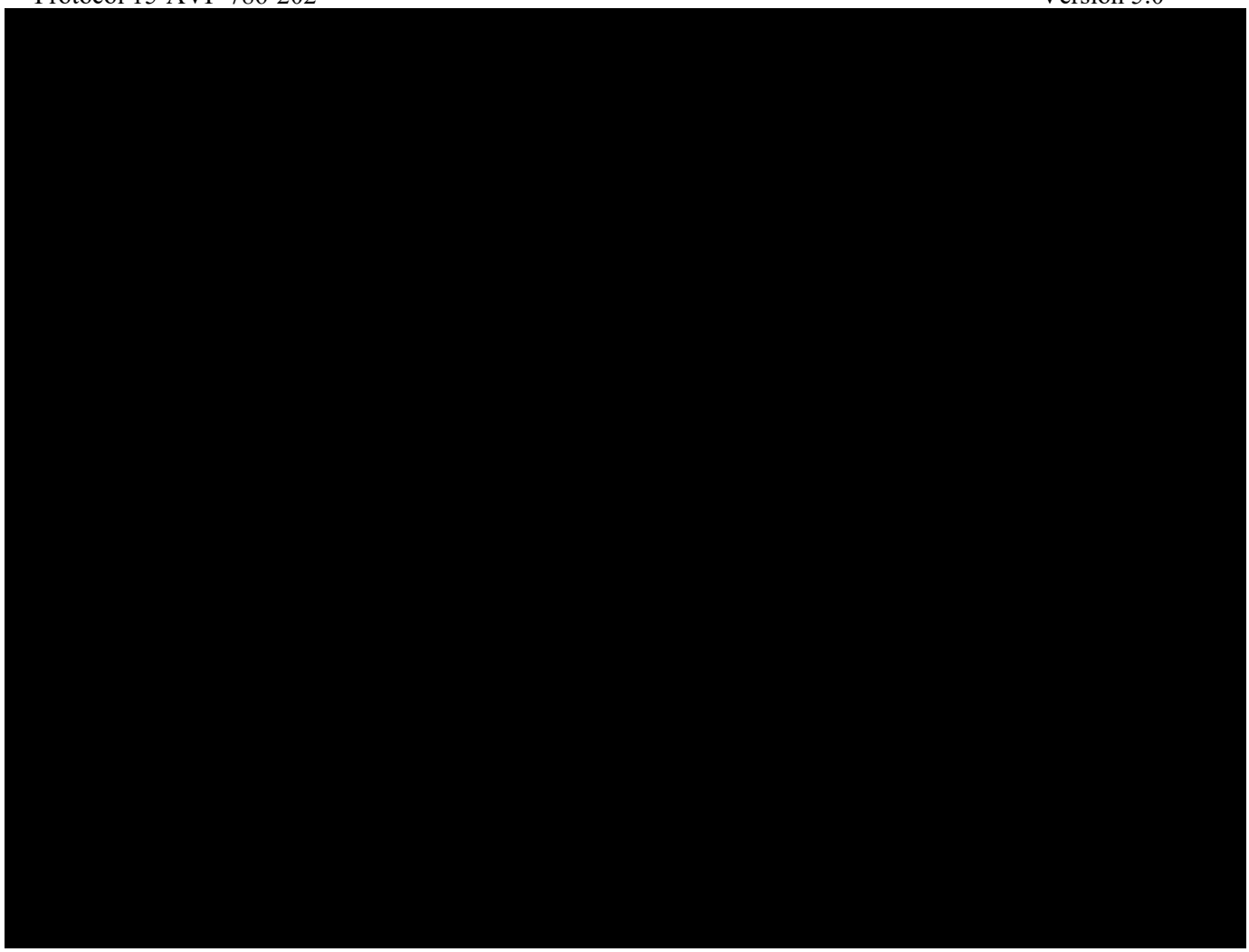
The Sponsor will be available to help Investigators prepare for an inspection.

10 REFERENCES









11 Appendices

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Appendix 13: Investigator Responsibility

Appendix 14: World Medical Association Declaration Helsinki

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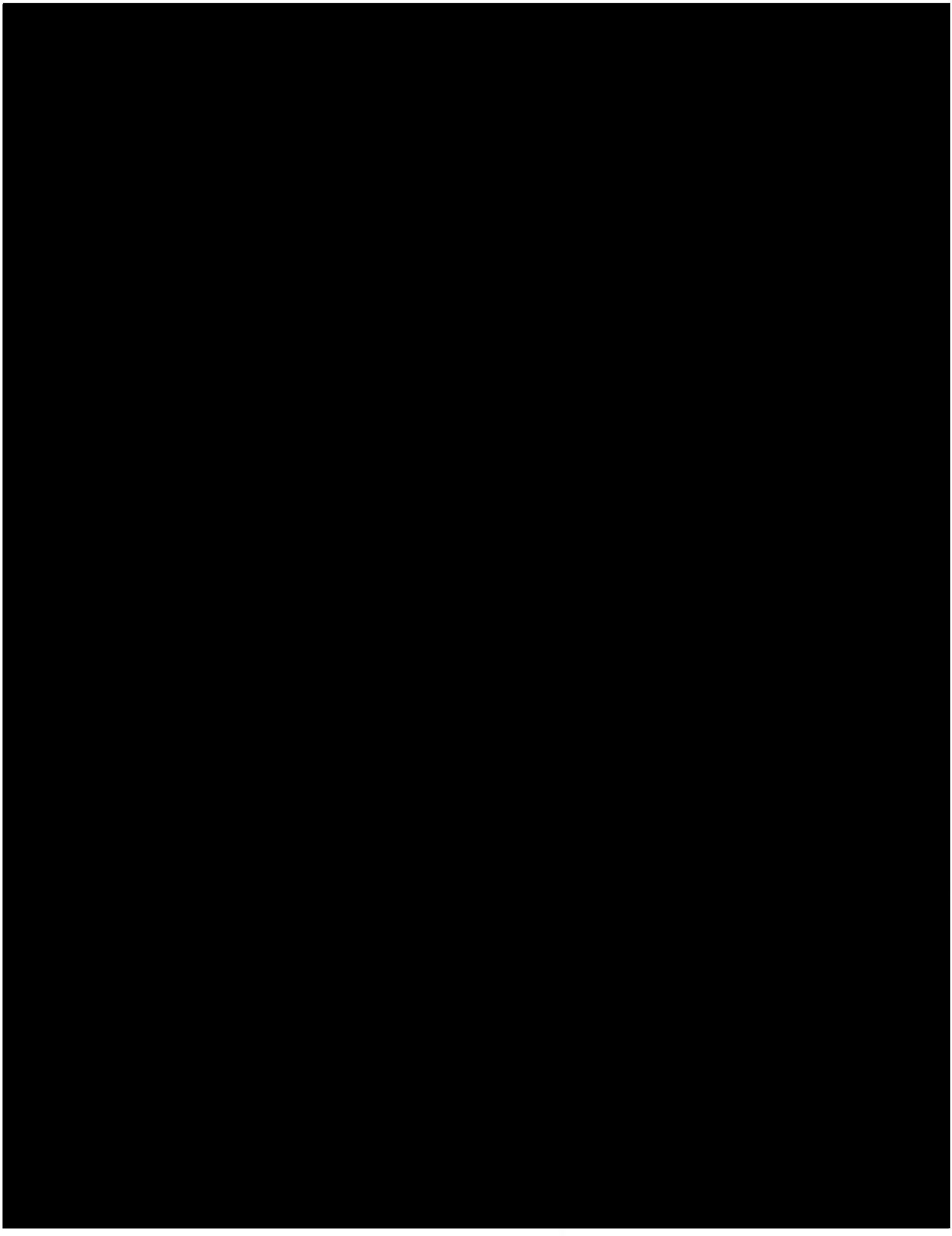

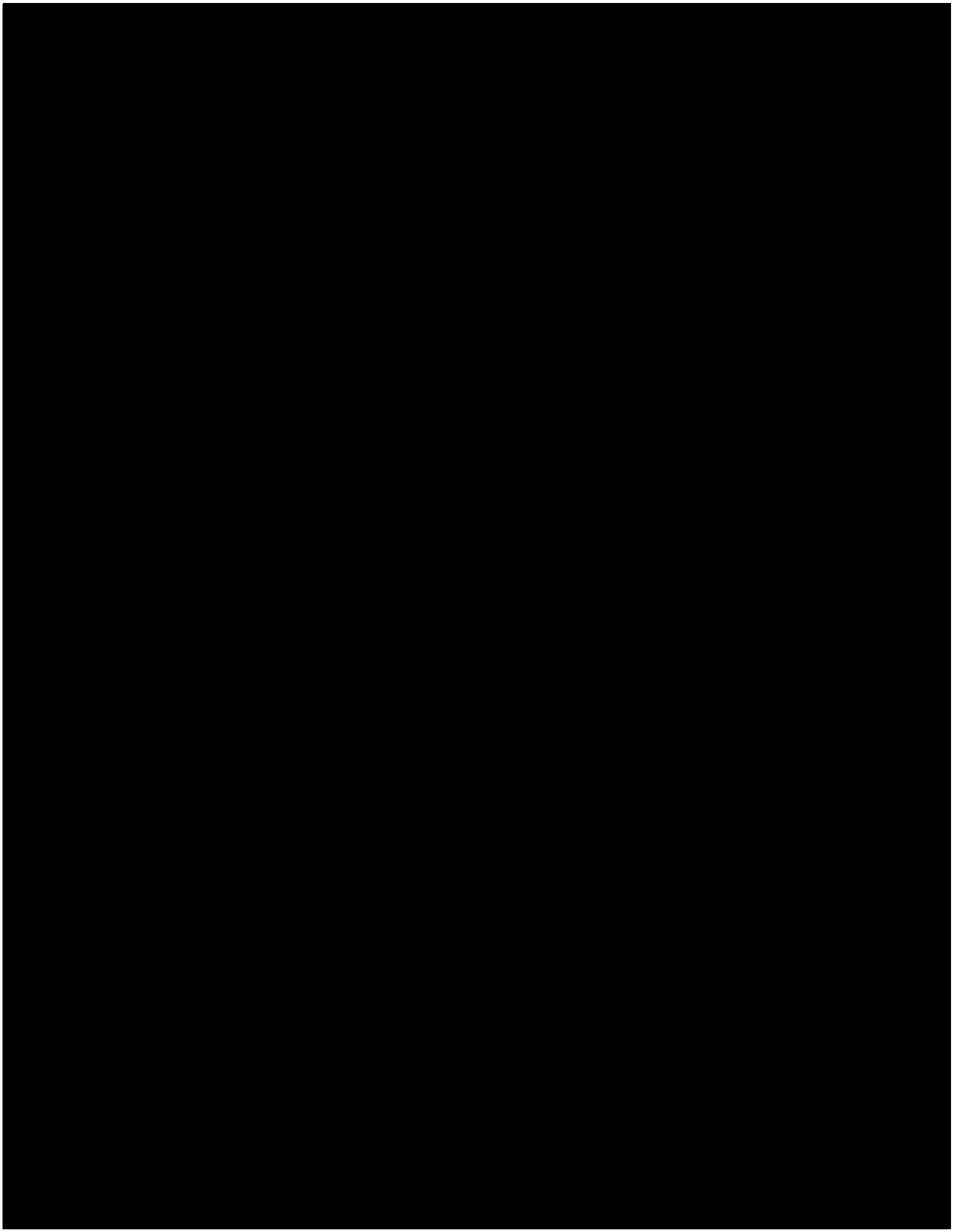

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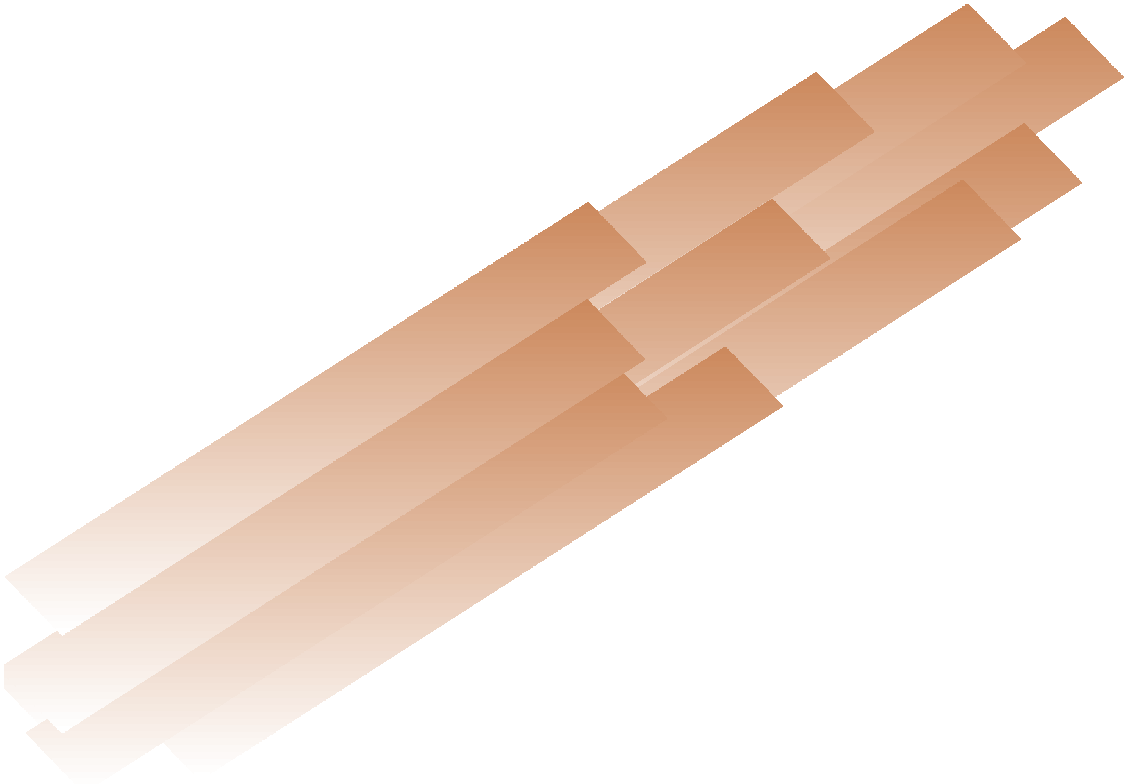
Appendix 13: Investigator Responsibility

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448,
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 1996
ICH

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

Appendix 14: World Medical Association Declaration Helsinki

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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