Psychiatric Orders in Psychoanalytic Treatment of ASD

Protocol Number*: <ASD-Psy-000>

National Clinical Trial (NCT) Identified Number: <Number, once assigned by CT.gov>

Principal Investigator*: <Yang I. Pachankis>

Sponsor: <S for Science>

Grant Title: <Project ASD>

Grant Number*: <ASD-000000>

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<17 June 2023>

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the informed consent from the participant(s) outlined in **Section 10** of the document.

INFORMED CONSENT

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance*.

Participant(s):

Signed:  Date: 

Name: 

Participant Contact Information

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: Yang Pachankis Date: May 31, 2023

Name*: Yang I. Pachankis

Title*: Principal Investigator (PI)

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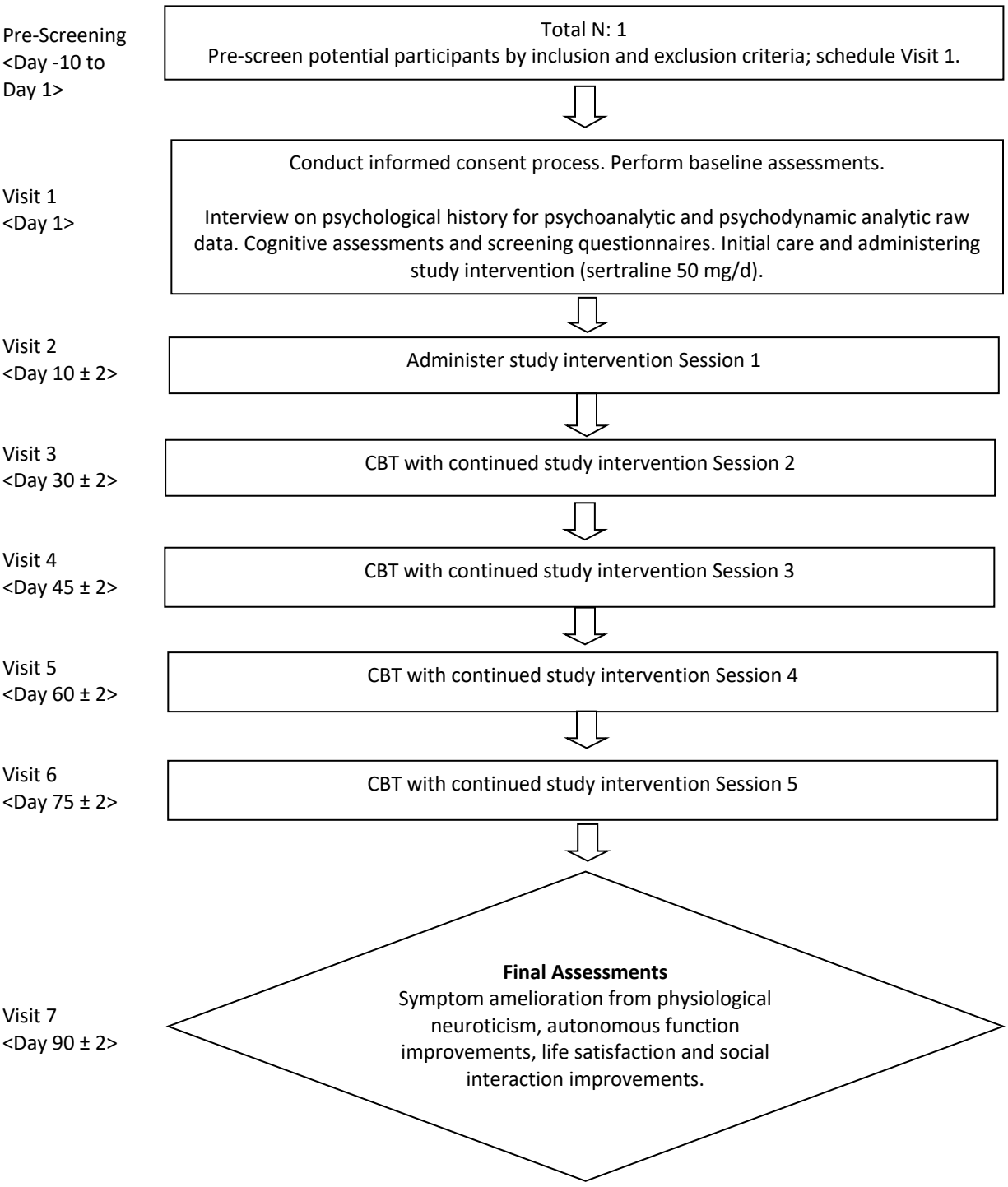
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Psychiatric Orders in Psychoanalytic Treatment of ASD
Grant Number:	ASD-000000
Study Description:	The study hypothesizes the psychoanalytic and psychodynamic determinants in psychiatric medication and its behavioral and social implications for patient care. The study is designed to advance the quality of patient care in pharmacological interventions, especially for patients with complex symptoms and characterized by autism spectrum disorder (ASD).
Objectives*:	Primary Objective: Assessing observational intervention safety. Secondary Objectives: Empirically determining psychiatric and psychological interventions according to psychodynamics and psychoanalysis.
Endpoints*:	Primary Endpoint: 11 days (11 June 2023) Secondary Endpoints: 30 days (30 June 2023)
Study Population:	The sample size is temporarily determined as the sole participant: male, 36, Han ethic Chinese with long-term residence in mainland China, recovering from autoimmune pathogenic viral detoxification.
Phase* or Stage:	Phase IV
Description of Sites/Facilities Enrolling Participants:	One site outside of the United States is organized to facilitate enrolling participant(s) in Chongqing, PRC.
Description of Study Intervention/Experimental Manipulation:	Selective Serotonin Reuptake Inhibitor (SSRI) sertraline, orally taken from 50 mg/d to 100 mg/d for 100 mg/d maintenance dose; Allosteric Serotonin Reuptake Inhibitor (ASRI) escitalopram [(1)], orally taken 5 mg/d; Selective Norephedrine Reuptake Inhibitor (SNRI) duloxetine, orally taken 20 mg/night to compensate for SSRI; Cognitive-behavioral therapy (CBT); Psychodynamic psychoanalysis.
Study Duration*:	3 months.
Participant Duration:	3 months.

1.2 SCHEMA


Pre-Screening
<Day -10 to Day 1>
Total N: 1
Pre-screen potential participants by inclusion and exclusion criteria; schedule Visit 1.
Visit 1
<Day 1>
Conduct informed consent process. Perform baseline assessments.
Interview on psychological history for psychoanalytic and psychodynamic analytic raw data. Cognitive assessments and screening questionnaires. Initial care and administering study intervention (sertraline 50 mg/d).
Visit 2
<Day 10 ± 2>
Administer study intervention Session 1
Visit 3
<Day 30 ± 2>
CBT with continued study intervention Session 2
Visit 4
<Day 45 ± 2>
CBT with continued study intervention Session 3
Visit 5
<Day 60 ± 2>
CBT with continued study intervention Session 4
Visit 6
<Day 75 ± 2>
CBT with continued study intervention Session 5
Visit 7
<Day 90 ± 2>
Final Assessments
Symptom amelioration from physiological neuroticism, autonomous function improvements, life satisfaction and social interaction improvements.

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 10 ±2	Visit 3 Day 30 ±2	Visit 4 Day 45 ±2	Visit 5 Day 60 ±2	Visit 6 Day 75 ±2	Visit 7 Day 90 ±2	Unscheduled Visit
EMR Review Eligibility	X								
Informed Consent		X							
Demographics	X								
Clinical history		X	X	X	X	X	X	X	
Height & Weight	X								X
Outcome Evaluation									
Pain Assessment (Brief Pain Inventory)		X	X	X	X	X	X	X	X
Quality of Life Questionnaire		X	X	X	X	X	X	X	X
Control & Experimental Interventions – Occupational therapy	X	X	X	X	X	X	X	X	X
Adverse Events Reporting	X	X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

ASD is often accompanied by a variety of other symptoms, such as bipolar disorder, Attention Deficit Hyperactivity Disorder (ADHD), Social Anxiety Disorder (SAD), Avoidant Personality Disorder (AvPD), Obsessive Compulsive Disorder (OCD), etc. The behavioral and social complications often marginalize the population, impact on life satisfaction, undermined societal values that impact on economic and financial fairness, and so forth. Furthermore, persons with ASD are neurodiverse from standardized pharmacological and clinical cares, and are interpreted disadvantaged in the context of neurotypical treatments [(2)].

The research protocol aims to differentiate the neuropharmacological implications of ASD from its behavioral and social implications. Such a differentiation is beneficial to the quality of care for neurodiverse population, both in terms of precision treatment in medical settings, and in terms of psychotherapeutic treatment efficacy in the interpretation of behavioral and social traits.

The study protocol continues from the adverse event of the participant in NCT05711810 trial, after the positive immunological results in the NCT05839236 trial. The intervention medicine continues from Sertraline adjusted on the choice of SSRI in the previous two trials for complex post-traumatic stress disorder (CPTSD) of the participant, and its combined used with Duloxetine in the choice of SNRI for norephedrine regulations.

The hypothesized target is on the discrete psychiatric intervention centered approach to ASD treatment care. In the PRC where the study is being carried out, amphetamine class medicines are strictly prohibited and defined as illegal substances, regardless of their only proven effect for ASD patient care [(3)]. Contributed by the sociostructural elements and necessities, black market amphetamine and ketamine have not only emerged in the regime for decades, but also have become a lucrative business. Their recreational uses are also sometimes accompanied by real necessities and needs; black markets cater to the needs but guidance on the usages is based on word-of-mouth stories without professional medical assistances. There is one case the PI collected, that one person, possibly under depression contributed by PTSD, took relatively high dosage of amphetamine and ketamine, and went into a state of psychosis with overwhelming persecution mania. The study protocol, Psychiatric Orders in Psychoanalytic Treatment of ASD, is therefore designed for an evidence-based approach in treating complex psychiatric disorders with psychoanalytic guidance.

2.2 BACKGROUND

The participant started taking SNRI duloxetine 20 mg/night in Jan. 2023, and changed to SSRI sertraline 50 mg/d in Mar. 2023. The apparent psychoactive effects did not take effect until increased dosage to sertraline 100mg/d after around one week in Jun. 2023, boosted by compound pseudoephedrine. Duloxetine is planned to be added to the mix thereon.

The participant has a history in the conditions of grief with moderate separation anxiety. The participant's ASD-I is traced to early childhood, with AvPD contributed by childhood traumas and abuses. The

participant's agoraphobia can be contributed by abuses in kindergarten being locked in a small dark room for groom-sticks for hours. No claustrophobia is present but its association with the sense of helplessness while alone and especially in the dark is traced therein. ADHD can be contributed by ASD-I, while OCD can be largely contributed by childhood abuses in public school in PRC by some teachers.

The participant showed resistance to the psychological disorders, but the complex PTSD still developed through adulthood, contributing to the complex depression with panic disorder and anxiety. Borderline Personality Disorder (BPD) is therefore considered to be a derivative symptom, and the participant has a history of Stockholm Syndrome. The participant has above average aggression, and it is diagnosed to be a positive trait contributed by Stockholm Syndrome with CPTSD. This makes the AvPD more psychodynamically complicated.

There are possible risks for psychosis and schizophrenia, especially demonstrated by the adverse events from NCT05711810 and NCT05839236 trials.

Contributed by the participant's unique defense mechanisms, the sociostructural backgrounds of the psychodynamic development is considered irrelevant to the study and only the unique defense mechanism will be analyzed.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The study intervention may induce a series of physiological and psychological risks for the participant(s). It is certain that the psychodynamic and psychoanalytic facets may not totally agree with behavioral and social interventions. The medical products used for the study intervention also have established risks that may or may not be able to be complemented with the behavioral and social intervention designs. Psychoanalysis and psychodynamics will be used to mitigate the risks.

Known pharmacological risks involved with the use of SSRI and SNRI include:

- Gastric regulation risks;
- Blood pressure and heart rate elevation;
- Increased apoptosis with non-facial acnes and blood spots contributed by hypersensitivity;
- Disturbances to consciousness and eyesight;
- Hypothyroidism;
- Appetite and blood sugar changes;
- Insomnia;
- Hallucination (hearing, sensation, etc.);
- Defibration and other involuntary muscular contractions;
- Complications contributed by increased blood flow to the brain, and increased blood cholesterol;
- Interstitial fluid abnormalities;
- Liver catabolism capacities.

With the intoxicating sociostructural environment the participant is in, known physiological benefits and behavioral improvements are the sociostructural risks for the participant.

- The sociostructural stress may relapse suicidal ideation;
- Unipolar depression elevation may increase potentials for aggressive behaviors;
- There is a risk in egotism development during the behavioral interventions;
- Increased impulsivity that may lead to antisocial behaviors;
- Increased risks in social frustration;
- Panic disorder risks can be elevated by the reduction in psychiatric disorders;
- Withdrawal from medications without prior consultation with physicians or PI may worsen some symptoms.

2.3.2 KNOWN POTENTIAL BENEFITS

- Reduce immediate neurotic symptoms;
- Reducing and/or prolonging psychosis and schizophrenia risks;
- Increased apoptosis by SNRI use is positive for the participant's autoimmune detoxification;
- Ameliorate the neurological bases for suicidal ideation, but may increase the social determinant risks in suicidal ideation and sense of helplessness;
- Neuronal infection from existing autoimmune toxins;
- Increasing public awareness and governmental incentives in neurological pharmacy utility and regulations, especially in the regional context.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential risks and benefits are assessed with the participant's current circumstances:

- Gastric regulation risks are reduced by the current use of proton-pump inhibitor;
- Long-range and immediate psychiatric benefits outweigh the known risks;
- CBT will be prioritized on self-care behaviors with relation to the amelioration of neurotic symptoms;
- Social effects will emphasize on self-preservation and resilience training;
- Clinical medicines will be continued in the observational trial.

3 OBJECTIVES AND ENDPOINTS

There are complex dynamics between psychological and psychiatric methods in the determination and treatment on symptoms and causes. The psychological methods focus on the present, with a paradigm of the past for causal inference and desired outcome for future direction for intervention; the psychiatric methods seem to follow the same paths, but the physiological and neurological determinations do not necessarily agree with the patient-response-dependent consciousness practices.

Behavioral characteristics are often psychiatrically symptomatic. Behavioral and social tendencies of ASD patients are largely explainable with psychiatric characteristics [4-6] instead of social determinants in early phases. The objective of the study is to utilize the physiological symptoms and its amelioration as baseline, so that the pharmacological approaches in psychiatry can be coordinated with psychological practices by

the guidance of psychoanalysis. For the qualitatively guided practice, psychometrics is designed according to the specific case.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
The primary objective is to experiment a desirable psychometric method to combine CBT with psychiatry in pharmacological practice.	The primary endpoint is set to 10 days after effective medicine dosage, and the participant experienced the first obvious psychoactive experience with positive feedback on physiological and psychological influences.	The participant's reactions to SNRI previously caused insomnia while SSRI induced narcolepsy, contributed by the combination of CPTSD and ASD. Compound pseudoephedrine (oral 180-360 mg/d) have been used for rescue therapy in conjunction with increased dosage of sertraline. The qualitative effect with psychoactive outcome proved the pharmacological choices in ameliorating CPTSD in ASD, and confirmed the unipolar nature of depression instead of bipolar phenomenon.	Gradual SSRI treatment does not interfere with norephedrine levels in dopamine-deficient and ephedrine receptor deficient patient. Compound pseudoephedrine increases the ephedrine receptors of the patient, and stimulated dopamine and norephedrine synthesis.
Secondary			
The secondary objective is to treat CPTSD with minimum impact to worsen ASD symptoms.	Secondary endpoint is established for the coordinating effects of CBT and safety procedures in complex symptom and cause's pharmacological solutions. It is defined to the 30th day of the trial.	Even though CPTSD is only symptomatic both in terms of psychiatry and psychology, not treating the symptom before treating the causes is highly risky for exacerbation of psychosis and schizophrenia risks. Secondary efficacy endpoint adopts a combination of CBT and reintroduction of SNRI to compensate for sole SSRI treatment in the ASD case.	CBT focuses on alleviating the impulsivity and aggressiveness of the participant, and potential side effects of self-destructive thoughts and behaviors by other symptoms, with the reintroduction of SNRI. SNRI will stimulate the participant's ephedrine synthesis, and henceforth, dopamine synthesis. However, uncertainty exists with the ephedrine intolerance / ephedrine receptor insensitivity of ASD.

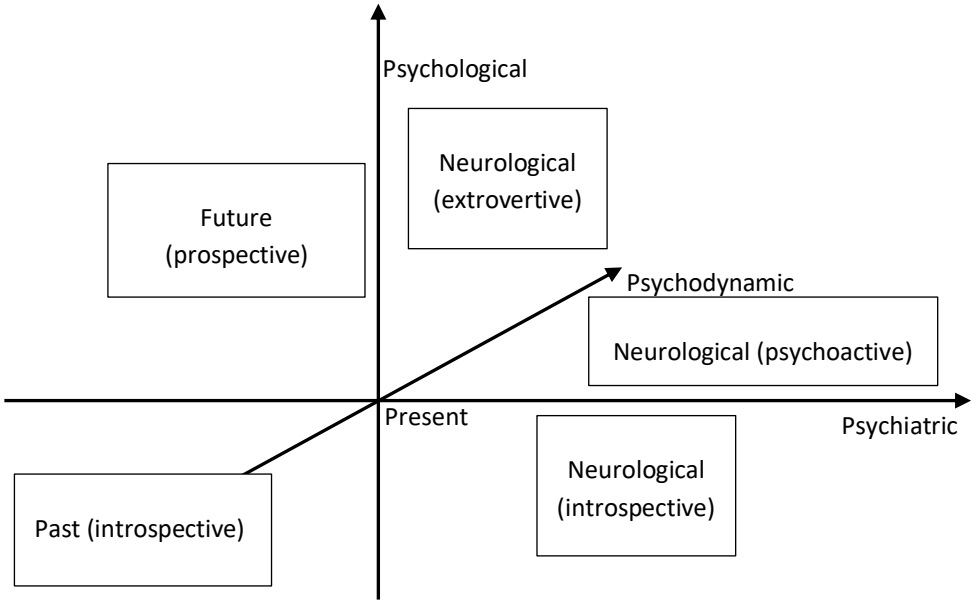
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Tertiary/ Exploratory			
Tertiary objective explores if behavioral intervention changes social cognition, or psychiatric adaptation, or both.	OCD symptoms are expected to be assuaged first, which is correlated with the social difficulties and response gaps between behavior and cognition. Subsidiary ameliorations are expected to occur with anxiety and panic disorders. These are expected to be exhibited in heart rate shift curves. Physiological ASD neurotics are expected to be assuaged with more positive social interactions and higher ephedrine-dopamine circulation rates.	CPTSD symptom treatment has been utilized to adapt positive psychodynamic motivations in social behaviors of ASD participant. Resilience strategy is built upon compensatory rewards to social defeat and punishments. Aggression is anchored with vengeance with the specific source(s) of CPTSD during trauma memory processing [(7)]. Pharmacological interventions have been adapted to the physiological symptoms during the reintegration process.	Reintegration process for CPTSD and severe depression is not only a recombination process of consciousness [(8)], but also a psychiatric and neuro-hormonal process, especially for ASD persons. Ephedrine intolerance of the specific case reduced likelihood of aggressive behaviors and mania, and the psychodynamic motivation intervention is adapted to cooperate with SNRI intervention. Psychodynamic barriers for ASD in social behaviors are balanced with the hormonal level changes.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The research adopts a multiple baseline approach for the complex psychophysiological symptoms. The multidisciplinary design's main hypothesis is the psychodynamic order of priority in its combined effects with CBT. In respect of the participant's autonomy in any societal settings, independent variable is set at the immune reflex regulation in the NCT05839236 trial, and dependent variable is set at the improvements in active and proactive social functioning of the participant, with the premise of increasing life satisfaction. For this reason in objectives, with the symptomatic emergence from the NCT05711810 trial, Sertraline is adopted as the independent variable with its effective dosage in 100 mg/d. Dosage adjustments above this dosage is considered to take effect in the dependent variables, such as OCD regulation. The other two dependent variables for Psychiatric Orders in Psychoanalytic Treatment of ASD are Duloxetine 20 mg/night and Escitalopram 5 mg/d. Therefore, the study is defined as Phase IV trial with single-arm and single site design. Half a year follow-up is designed after the completion of data collection.

The primary efficacy endpoint does not introduce any dependent variable manipulation, and only determines the independent variable, with safety control and psychodynamic history collection. The goal of CBT is discussed with the participant in the second visit, which determines the dependent variables. The secondary efficacy endpoint is set to evaluate the dependent variables, in comparison to the participant satisfaction from the primary efficacy endpoint baseline. Rationale for the design process is seen in the figure below, and CBT is designed to raise the extrovert and assertive behaviors of the participant in social and societal settings. Nature of CBT has determined that the process' control is the reference in time series of development. The control design's limitation is with the long-term risks of relapses either contributed by the participant or the changing sociostructural environment.



The study constitutes a sub-study from the NCT05839236 trial.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Even though the control is determined by the participant's self-reference, its design is valid and appropriate considering the history of suicidal ideation and active planning, with minor history of self-harm. The comparison is thus not only the physiological improvements in immune reflex regulations, but also the autonomous health behaviors of the participant. This is conformable to the study with psychotropic medicines in procedurally treating complex psychological problems. Known problem is the participant's withdrawal by the avoidance symptoms during the study phases, yet the participant's trust and partial reliance on the PI have reduced the flight risks.

4.3 JUSTIFICATION FOR INTERVENTION

The interventions are designed according to the medical and psychiatric necessities by the psychodynamic history of the participant. The data being collected from the parametric manipulations do not interfere with the natural neurodiversity of the participant, but only the behavioral-social responses and their correlations to the physiologically and neurologically relevant symptoms.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 4 intervention sessions, and the 1-month follow-up assessments.

The end of the study is defined as completion of the 1-month follow-up assessment (visits 6 & 7) shown in the Schedule of Activities (SoA), **Section 1.3**.

The half-a-year follow-up has the potential in overturning the study validity if severe relapses occur.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. The individuals need to be autistic;
2. For children, informed assent and parental informed consent to participate in the study;
3. Stated willingness to comply with all study procedures and lifestyle considerations (see **Section 5.3, Lifestyle Considerations**) and availability for the duration of the study;
4. Males and females; Age 18-70;
5. Self-reported diagnosis of ASD, or documented diagnosis of ASD;
6. Willingness to adhere to the Psychiatric Orders in Psychoanalytic Treatment of ASD regimen;
7. Not currently practicing CBT and have not participated in a class or program on CBT within the last 12 months.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. ASD-3 is currently not being considered for the resource limitations of the study;
2. Participation in another CBT treatment or intervention study within 12 months;
3. Presence of conditions or diagnosis of psychosis, delusions, and/or schizophrenia;
4. Activity restrictions that limit one's ability to engage in physical activities.

5.3 LIFESTYLE CONSIDERATIONS

Abstain from alcohol and risky sexual behaviors.

5.4 SCREEN FAILURES

N/A.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

No cost or compensation is designed for participant recruitment.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Baseline intervention without experimental manipulations is conducted in the primary efficacy endpoint. The secondary efficacy endpoint eases in the dependent variable experimental manipulations, and determine the maintenance dosage in the following endpoint(s).

6.1.2 ADMINISTRATION AND/OR DOSING

The study interventions are administered by the participants on a daily basis, assigned by the PI. At least two sessions after the secondary efficacy endpoint are considered a complete / full-dose intervention, with accompanying CBT. CBTs are conducted in-person.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Fidelity of the interventions are dependent on the PI's interactions with the participants, and the PI will train the participants' health behaviors through the CBTs, serving as the tracking method.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Refer to **Section 6.2.1**.

6.5 CONCOMITANT THERAPY

For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications. Medication usage will be assessed at each study visit and documented in the relevant Case Report Form (CRF).

For the participant enrolled from the NCT05839236 trial, the interventions from the trial is defined as concomitant therapy in this study.

6.5.1 RESCUE THERAPY

Compound pseudoephedrine (oral 180-360 mg/d, maximum 7 days' section per month) have been introduced as rescue therapy without dextroamphetamine supplies.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from particular study intervention(s) but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is

identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives;
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**);
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study;
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 2 weeks, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary,

a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file;
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Physical examination-based assessments will be performed on the suitability conditions of the participants in the study, mainly in consideration of infectious diseases, physiological movability and injuries, etc. Psychoanalytic assessments on basic psychological performance and social functioning will be performed, with interviews and satisfaction questionnaires.

8.2 SAFETY ASSESSMENTS

Safety assessments are conducted in the primary efficacy endpoint and when the participants need to cease the medications. Hostility elements have to be prioritized on major depressive disorder (MDD) for safety conduct of the study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are defined as risks that may lead to the immediate death or incapacitation of the participant(s), or those that are foreseeable to lead to premature death or incapacitation in the long range, if not properly dealt with at present.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in ASD and neurology will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make

a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

AEs and SAEs are typically reported by the PI or participants to the PI directly. The PI has the duty to prioritize solutions for AEs, and if SAEs are beyond the control of the PI, immediate contact with the IRB is mandated. Study reporting should be completed within one month after the occurrence(s) of AEs and SAEs, and archived to the IRB.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The PI is responsible to inform the participants in foreseeable AEs and SAEs, so that the participants can directly contact the PI if any signs of AEs and SAEs emerge.

8.3.8 EVENTS OF SPECIAL INTEREST

The participants are required to report to the PI on a weekly basis regarding the psychoactive experiences associated with the medicine dosage. Reflections are required from the participants in these experiences' influence to their modes and behaviors, in order to prevent their introspective tendencies of substance reliance and abuse. The PI is responsible to report to the IRB on the evaluations of the participants' risks in substance abuse and violent tendencies.

8.3.9 REPORTING OF PREGNANCY

N/A.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor/funding agency within one month of the investigator becoming aware of the event;
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within one month of the investigator becoming aware of the problem;
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), and the supporting agency head (or designee) within one month of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary efficacy endpoint is analyzed according to the Bell curve of memory [9] illustrated in **Section 4.1**. The PI hypothesized that the ASD participant's physiological symptoms are contributed by ephedrine intolerance, and the hypothesis is confirmed by the compound pseudoephedrine's effect in treating the participant's narcolepsy. The participant responded well in the three errand-purposed outdoors activities, with one of them partially social. The social activity reduced the interpersonal anxiety level of the participant, contributed by positive interactions with energetic spirit. The participant reports higher confidence for social interactions after the event.

With positive change from the primary efficacy endpoint, it is further hypothesized that the combined use of SNRI with SSRI will induce similar effects in enhancing the ephedrine receptor capacities, and the amino acids circulation. Risks for hyperactivity is monitored during the secondary endpoint, together with CBT for socially induced dopamine generation stimulation with behavioral experimental manipulation according to the daily activities of the participant. It is hypothesized that mode balance and daily energy of the participant will be optimized during the secondary endpoint with the parallel dosage optimization.

9.2 SAMPLE SIZE DETERMINATION

Sample size is defined as the neurotic symptoms of the participant. Details of the neurotic symptom orders are seen in **Section 9.4.5**. Theoretical sampling is conducted and organized by the end of the primary efficacy endpoint.

The psychodynamic goals of CBT are to align the participant's introvert characteristics with extrovert characteristics, so that participant's social functioning does not conflict with inherent psychomotor traits. For this experimental manipulation goal, a set of questionnaires is designed for CBT and psychometric evaluation. The questionnaire and statistical approach are seen in **Section 9.4.1**.

Due to the dependence of the treatment goals on the psychoanalytic and psychodynamic elements of the participant, and the intersubjective nature of psychoanalytic method, the sample size and statistical components are qualitative other than quantitative in nature.

Satisfaction questionnaire and interviews are used to determine the power level and Type I error rate according to the coordinate seen in **Section 4.1**. The quantification of qualitative elements adopts the numerical value of x and y axes in an aggregated reporting, with power level set to 90% according to the projective baseline codetermined by the psychoanalyst and the participant, as a goal orientated perspective.

In this way, any UP can be anticipatory with the psychodynamic behavioral analysis falling in the second to fourth quadrants in the coordinate system, constituting safety, interim, and exploratory analyses respectively seen in **Sections 9.4.4**, **9.4.6**, and **9.4.9**.

9.3 POPULATIONS FOR ANALYSES

N/A.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The questionnaire collecting statistical data is social behavioral orientated, and designed into sections of social situations, inherent dispositions, and inherent vulnerabilities. The full annotated questionnaire is seen below:

Behavioral Satisfaction Questionnaire

Social Situations*

(*X score total range -150 to + 140; except for additive scores, other can be calculated in orders of proportion.)

According to your own circumstances, please answer the following questions with the past experiences you have: (if one or more applies to you, please order them by frequency)

1. Typically, I am: -- Active and reactive social behavior.

- Welcoming and open to strangers; -- +5 (additive)
- Discrete towards strangers; -- +5 (additive)
- Hostile or distrust to strangers; -- -10
- Insensitive to strangers; -- 0
- Courteous to strangers; -- -2
- Have negative feelings towards strangers; -- -4
- Fearing strangers may have negative feelings towards me; -- -4
- Try to ignore strangers; -- -6
- Try to keep away from strangers. -- -8

2. In a social setting, I often: -- Social cognition.

- Easily recognize or remember persons by their faces and names; -- +10
- May recognize or remember some persons who try to draw attention in a crowd; -- +6
- May recognize or remember some persons that I'm interested in; -- +3
- Can remember people I knew but limited in recognizing new people; -- 0
- Can remember people I knew and have a hard time recognizing new people; -- -4
- May not remember all the people, but can recognize persons by introductions; -- -2
- May not remember all the people, and have a hard time recognize new people; -- -6

- May not remember all the people, and confused about who they are when they meet me; -- -8
- Do not remember any people at all. -- -10

3. In a social setting, I typically: -- Active and reactive social behavior.

- Pretend to be someone else for specific purposes; -- -2
- Just be myself regardless of the occasions; -- 0
- Cater to other people according to how I am perceived; -- -4
- Completely lost about who I am; -- -10
- Enjoy myself and don't care about other people. -- -7

4. When I meet someone new in public, I often: -- Active and reactive social behavior.

- Actively come forth and greet; -- +10
- Only greet with who comes to me; -- +5
- Try to avoid eye contact with people I don't know; -- -5
- Run away from any people I don't know coming towards me; -- -8
- Only greet by introduction with someone I know; -- 0
- Feel being intruded. -- -10

5. When I meet someone new in small gatherings, I often: -- Active and reactive social behavior.

- Actively come forth and greet; -- +10
- Only greet with who comes to me; -- +5
- Try to avoid eye contact with people I don't know; -- -5
- Run away from any people I don't know coming towards me; -- -8
- Only greet by introduction with someone I know; -- 0
- Feel being intruded. -- -10

6. When I meet someone new online, I often: -- Active and reactive social behavior.

- Pretend to be someone else for specific purposes; -- +5
- Just be myself and see; -- +10
- Cater to other people according to how I am perceived; -- -5
- Waiting for someone to greet me; -- 0
- Feel being intruded. -- -10

7. Usually, I: -- Active and reactive social behavior.

- Have specific preferences on people's certain characteristics; -- +5
- Have specific dislikes on people's certain characteristics; -- -5
- Have both specific preferences and dislikes; -- +10
- No certain patterns; -- 0
- Don't like other people. -- -10

8. When there is somebody I'm fond of, I usually: -- Active and reactive social behavior.

- Directly talk to that person; -- +10
- Find someone to introduce me to that person; -- +5
- Try to draw that person's attention to me; -- 0
- Avoid direct contact with that person; -- -2
- Keep it to myself and don't get influenced; -- -5
- Keep it to myself but feel bothered. -- -10

9. Usually, I have: -- Social cognition.

- Many different friends at the same time; -- +10
- Only the friends I know since childhood; -- -5
- Only a few friends in specific periods of my life; -- +5
- No friends at all. -- -10

10. What I value in friendship: -- Social cognition.

- Have specific social values to me; -- +10
- Being kind and looks after me; -- -2
- I can look after; -- +5
- Have specific traits or talents; -- +8
- Follows my lead; -- +2
- Knows me well with little effort for communication; -- -5
- Do things for me as I ask; -- -8
- Don't have any special preferences; -- 0
- I don't want any friends. -- -10

11. If I don't like a person, I: -- Active and reactive social behavior.

- Directly tell the person; -- +10
- Tell other people except for that person; -- +2
- Try to avoid meeting that person; -- 0
- Secretly sabotage on that person; -- -5
- Confront that person either verbally or physically; -- -8
- Keep it to myself without hard feelings; -- +5
- Keep it to myself but still bothers me; -- -2
- Don't have any person I dislike. -- -10

12. To my friends, I think I am: -- Social cognition.

- Usually leader in a group; -- +5
- The devoted follower; -- -5
- The peace-maker; -- 0
- The listener; -- +8
- The invisible person; -- -8

- The one who always have something to say or express; -- -2
- The organizer or planner; -- +2
- The one who everybody dislikes but still in the group; -- -10
- The most adorable one with everyone's attention. -- +10

13. I usually get comments from my friends that I: -- Social cognition.

- Am too clingy; -- -1
- Don't listen to them; -- 0
- Am too self-centered; -- -3
- Am a people-pleaser; -- -5
- Am caring, kind, and / or responsible; -- +10
- Am eccentric; -- -7
- Sometimes make them feel afraid; -- -9
- Don't care about them / am distant; -- -4
- Am unpredictable; -- -6
- Feel like a parent; -- +5
- Feel like a child; -- -2
- Clever / intelligent; -- +8
- Stupid / moron; -- -8
- Stubborn / inflexible; -- +2
- They never tell me how they think about me. -- -10

14. In schools or work places, I often: -- Active and reactive social behavior.

- Get elected in leadership positions; -- +10
- Being assigned to leadership positions by people in authority; -- +5
- Follow the leaders and rules without questions; -- 0
- Rebel against the leaders and / or rules for no reason; -- -10

- Rebel against the leaders and / or rules whenever I see them unfit; -- +4
- Follow the leaders and rules even when I feel them not adequate / wrong; -- -6
- Don't draw much attention and do my own work; -- +1
- Do my own work while make collaborations; -- +6
- Seek approval by the leadership / authorities; -- -4
- Seek approval from my peers; -- -2
- Trick other people because it makes me happy; -- -8
- Trick other people because I think it's good for them; -- -1
- Try to do good whether or not I am in the leadership position; -- +8
- Try to compete with my peers. -- +2

15. In the formal settings, I often: -- Sociopathy screening.

- Try to fit in the formalities / customs / procedures; -- 0
- Try to make connections and seek favors; -- -5
- Try to understand the whys, hows, and whats; -- +10
- Get completely lost; -- -8
- Deliberately go against the formalities; -- -10
- Don't like the formal settings but quietly follow to avoid troubles; -- +5
- Don't like the formal settings but quietly follow to satisfy others. -- +2

Inherent Dispositions* -- Positivity and resilience in social behaviors.

*(Y score total range -200 to +195. It mainly evaluates the hormonal and cognitive attributions to behaviors. Some elements need to be assessed cross-sectionally to render a full evaluation.)

Reflecting on the social circumstances, why do you think you behaved in certain ways? Please answer the following questions according to your innermost feelings; if one or more applies to you, please order them by your gut feelings with descending order from what makes you most to least comfortable:

16. What pleases my mind the most is:

- Sports with competitive and cooperative elements; -- +10

- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -4
- Family love and taking care of them; -- +2
- Friends doing interesting things together; -- +8
- The beauty and comfort of natural environment; -- +8
- The convenience of cities with a place for myself; -- 0
- Sexual attractions; -- +4
- The diversity of culture and arts; -- +6
- Knowledge about nature and mysteries behind them; -- +6
- Knowing more about myself and others with questions of what is human; -- -6
- Helping others; -- -4
- Taking control on the environment and things around me; -- -2
- Taking control on the people around me; -- -8
- Doing as told. -- -10

17. What makes me feel energetic is:

- Sports with competitive and cooperative elements; -- +10
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- 0
- Family love and taking care of them; -- +4
- Friends doing interesting things together; -- +8
- The beauty and comfort of natural environment; -- +6
- The convenience of cities with a place for myself; -- -6
- Sexual attractions; -- +2
- The diversity of culture and arts; -- +6
- Knowledge about nature and mysteries behind them; -- +6
- Knowing more about myself and others with questions of what is human; -- -2

- Helping others; -- +2
- Taking control on the environment and things around me; -- -4
- Taking control on the people around me; -- -8
- Doing as told. -- -10

18. What makes me feel hesitant about is: (Additive within threshold)

- Sports with competitive and cooperative elements; -- -8
- Sports that focus on myself, such as gym; -- -10
- Family love and being taken care of; -- +10
- Family love and taking care of them; -- -2
- Friends doing interesting things together; -- -8
- The beauty and comfort of natural environment; -- -6
- The convenience of cities with a place for myself; -- +2
- Sexual attractions; -- -6
- The diversity of culture and arts; -- -2
- Knowledge about nature and mysteries behind them; -- -2
- Knowing more about myself and others with questions of what is human; -- -2
- Helping others; -- 0
- Taking control on the environment and things around me; -- -4
- Taking control on the people around me; -- +4
- Doing as told. -- +8

19. What makes me feel challenging is: (mindful of psychodynamic interpretations and adjustment of score method, such as the second option can be positive if self-challenging other than reluctance challenging)

- Sports with competitive and cooperative elements; -- +6
- Sports that focus on myself, such as gym; -- -8

- Family love and being taken care of; -- -4
- Family love and taking care of them; -- +5
- Friends doing interesting things together; -- -10
- The beauty and comfort of natural environment; -- -6
- The convenience of cities with a place for myself; -- +4
- Sexual attractions; -- +2
- The diversity of culture and arts; -- -2
- Knowledge about nature and mysteries behind them; -- -2
- Knowing more about myself and others with questions of what is human; -- +2
- Helping others; -- -4
- Taking control on the environment and things around me; -- -4
- Taking control on the people around me; -- -5
- Doing as told. -- 0

20. What makes me feel powerful is:

- Sports with competitive and cooperative elements; -- +8
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -8
- Family love and taking care of them; -- +5
- Friends doing interesting things together; -- +3
- The beauty and comfort of natural environment; -- +5
- The convenience of cities with a place for myself; -- +3
- Sexual attractions; -- -2
- The diversity of culture and arts; -- +2
- Knowledge about nature and mysteries behind them; -- +5
- Knowing more about myself and others with questions of what is human; -- +5
- Helping others; -- 0

- Taking control on the environment and things around me; -- +2
- Taking control on the people around me; -- -10
- Doing as told. -- -5

21. What makes me feel weak is:

- Sports with competitive and cooperative elements; -- -8
- Sports that focus on myself, such as gym; -- -10
- Family love and being taken care of; -- +6
- Family love and taking care of them; -- -5
- Friends doing interesting things together; -- -10
- The beauty and comfort of natural environment; -- -3
- The convenience of cities with a place for myself; -- +2
- Sexual attractions; -- -5
- The diversity of culture and arts; -- 0
- Knowledge about nature and mysteries behind them; -- -4
- Knowing more about myself and others with questions of what is human; -- +4
- Helping others; -- -2
- Taking control on the environment and things around me; -- -2
- Taking control on the people around me; -- +10
- Doing as told. -- +8

22. What makes me feel rewarding is:

- Sports with competitive and cooperative elements; -- +10
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -10
- Family love and taking care of them; -- -4
- Friends doing interesting things together; -- +6

- The beauty and comfort of natural environment; -- +8
- The convenience of cities with a place for myself; -- +4
- Sexual attractions; -- -4
- The diversity of culture and arts; -- +8
- Knowledge about nature and mysteries behind them; -- +8
- Knowing more about myself and others with questions of what is human; -- +8
- Helping others; -- +4
- Taking control on the environment and things around me; -- +2
- Taking control on the people around me; -- -8
- Being able to do what are told to. -- -6

23. What makes me feel devotional is:

- Sports with competitive and cooperative elements; -- +8
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -4
- Family love and taking care of them; -- -4
- Friends doing interesting things together; -- +2
- The beauty and comfort of natural environment; -- +4
- The convenience of cities with a place for myself; -- 0
- Sexual attractions; -- -6
- The diversity of culture and arts; -- +6
- Knowledge about nature and mysteries behind them; -- +6
- Knowing more about myself and others with questions of what is human; -- +6
- Helping others; -- +2
- Taking control on the environment and things around me; -- -2
- Taking control on the people around me; -- -8

- Being able to do what are told to. -- -10

24. What makes me feel triumphant is:

- Sports with competitive and cooperative elements; -- +10
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -8
- Family love and taking care of them; -- -6
- Friends doing interesting things together; -- -4
- The beauty and comfort of natural environment; -- +6
- The convenience of cities with a place for myself; -- +4
- Sexual attractions; -- -4
- The diversity of culture and arts; -- 0
- Knowledge about nature and mysteries behind them; -- +8
- Knowing more about myself and others with questions of what is human; -- +8
- Helping others; -- +2
- Taking control on the environment and things around me; -- +2
- Taking control on the people around me; -- -8
- Being able to do what are told to. -- -10

25. What makes me feel invincible is:

- Sports with competitive and cooperative elements; -- +10
- Sports that focus on myself, such as gym; -- +10
- Family love and being taken care of; -- -10
- Family love and taking care of them; -- +4
- Friends doing interesting things together; -- -4

- The beauty and comfort of natural environment; -- +2
- The convenience of cities with a place for myself; -- -2
- Sexual attractions; -- 0
- The diversity of culture and arts; -- +8
- Knowledge about nature and mysteries behind them; -- +8
- Knowing more about myself and others with questions of what is human; -- +8
- Helping others; -- +2
- Taking control on the environment and things around me; -- +6
- Taking control on the people around me; -- -8
- Being able to do what are told to. -- -6

Inherent Vulnerabilities* -- Negativity and risks in social behaviors.

*(Y score total range -200 to +195. It mainly evaluates the hormonal and cognitive attributions to behaviors. Some elements need to be assessed cross-sectionally to render a full evaluation.)

Reflecting on the social circumstances, why do you think you behaved in certain ways? Please answer the following questions according to your innermost feelings; if one or more applies to you, please order them by your gut feelings with descending order from what makes you most to least uncomfortable:

26. What usually comes before my feeling of excitement:

- Anger; -- -8
- Impulsion; -- -2
- Inspiration; -- +7
- Fear / dread; -- +8
- Happiness / joy; -- +10
- Hope; -- +5
- Relief; -- 0
- Ambition; -- +1
- Malice / vengeance; -- -6

- Trust; -- +6
- Eagerness; -- -4
- Curiosity; -- +2
- Fulfillment; -- +3
- Drained; -- -10
- Calmness. -- +4

27. What makes me feel afraid is:

- Sports with competitive and cooperative elements; -- -8
- Sports that focus on myself, such as gym; -- -8
- Family love and being taken care of; -- 0
- Family love and taking care of them; -- -6
- Friends doing interesting things together; -- -2
- The beauty and comfort of natural environment; -- -4
- The convenience of cities with a place for myself; -- +2
- Sexual attractions; -- -10
- The diversity of culture and arts; -- -6
- Knowledge about nature and mysteries behind them; -- -6
- Knowing more about myself and others with questions of what is human; -- -6
- Helping others; -- -2
- Taking control on the environment and things around me; -- -4
- Taking control on the people around me; -- -2
- Being taken control of. -- +10

28. What makes me feel vulnerable is:

- Sports with competitive and cooperative elements; -- -6

- Sports that focus on myself, such as gym; -- -8
- Family love and being taken care of; -- +8
- Family love and taking care of them; -- -4
- Friends doing interesting things together; -- -4
- The beauty and comfort of natural environment; -- -2
- The convenience of cities with a place for myself; -- +2
- Sexual attractions; -- -4
- The diversity of culture and arts; -- -6
- Knowledge about nature and mysteries behind them; -- -6
- Knowing more about myself and others with questions of what is human; -- -6
- Helping others; -- 0
- Taking control on the environment and things around me; -- -8
- Taking control on the people around me; -- +10
- Being taken control of. -- -10

29. What makes me feel defeated is: (score adjustments reference question 31)

- Sports with competitive and cooperative elements; -- -6
- Sports that focus on myself, such as gym; -- -8
- Family love and being taken care of; -- +5
- Family love and taking care of them; -- -4
- Friends doing interesting things together; -- -2
- The beauty and comfort of natural environment; -- -4
- The convenience of cities with a place for myself; -- 0
- Sexual attractions; -- -4
- The diversity of culture and arts; -- -2
- Knowledge about nature and mysteries behind them; -- -2

- Knowing more about myself and others with questions of what is human; -- 0
- Helping others; -- -4
- Taking control on the environment and things around me; -- -6
- Taking control on the people around me; -- -8
- Being taken control of. -- -10

30. What makes me feel lonely is:

- Sports with competitive and cooperative elements; -- -10
- Sports that focus on myself, such as gym; -- +2
- Family love and being taken care of; -- +4
- Family love and taking care of them; -- +6
- Friends doing interesting things together; -- -8
- The beauty and comfort of natural environment; -- +2
- The convenience of cities with a place for myself; -- -6
- Sexual attractions; -- -8
- The diversity of culture and arts; -- 0
- Knowledge about nature and mysteries behind them; -- -4
- Knowing more about myself and others with questions of what is human; -- -2
- Helping others; -- -2
- Taking control on the environment and things around me; -- +8
- Taking control on the people around me; -- +2
- Being taken control of. -- +10

31. I would definitely take revenge if the following is sabotaged:

- Sports with competitive and cooperative elements; -- -4
- Sports that focus on myself, such as gym; -- 0
- Family love and being taken care of; -- -6

- Family love and taking care of them; -- +6
- Friends doing interesting things together; -- -2
- The beauty and comfort of natural environment; -- +4
- The convenience of cities with a place for myself; -- +2
- Sexual attractions; -- -8
- The diversity of culture and arts; -- +4
- Knowledge about nature and mysteries behind them; -- +4
- Knowing more about myself and others with questions of what is human; -- +4
- Helping others; -- +8
- Taking control on the environment and things around me; -- -4
- Taking control on the people around me; -- -8
- Personal freedom. -- +10

32. Sometime I sabotage the following myself:

- Sports with competitive and cooperative elements; -- -6
- Sports that focus on myself, such as gym; -- -10
- Family love and being taken care of; -- +2
- Family love and taking care of them; -- 0
- Friends doing interesting things together; -- -8
- The beauty and comfort of natural environment; -- -2
- The convenience of cities with a place for myself; -- -4
- Sexual attractions; -- -8
- The diversity of culture and arts; -- -2
- Knowledge about nature and mysteries behind them; -- -2
- Knowing more about myself and others with questions of what is human; -- -2
- Helping others; -- -4
- Taking control on the environment and things around me; -- +4

- Taking control on the people around me; -- +8
- Being taken control of. -- +10

33. Usually, I am more:

- Forgiving; -- +8
- Vengeful; -- -2
- Grudge-holding; -- -8
- Forgetful; -- -4
- Demanding of people; -- 0
- Hostile against what I don't like about; -- -10
- Tolerant; -- +5
- Ignorant; -- -6
- Over-protective; -- +2
- Open. -- +10

34. Towards myself, I am more:

- Forgiving; -- +8
- Vengeful; -- -8
- Grudge-holding; -- -6
- Forgetful; -- +6
- Demanding of myself; -- -4
- Hostile against what I don't like about myself; -- -10
- Tolerant; -- +2
- Ignorant; -- -2
- Self-protective; -- +4
- Open. -- +10

35. I feel like:

- Others don't know me well enough; -- -8
- Others know too much about me; -- +2
- I don't know too much about others; -- +6
- I know too much about others; -- -6
- I want others to know more about me; -- +4
- I don't want others to know too much about me; -- -4
- I want others to know something together that is not about us; -- +10
- I want to hide in places others don't see me; -- -10
- I want to be in the spotlight and be loved; -- 0
- I want everybody being loved equally; -- +10
- I want others to feel loved; -- +8
- I want to feel that I am loved. -- -2

The questionnaire is supplementary with psychoanalytic interviews in collecting psychodynamic data. Type I error is defined with the inherent vulnerabilities score changes with CBT, and statistical significance conducting to inherent dispositions and social situations, logarithmically. Some specifically designed questions will be used to assess safety analyses, and the psychodynamic analyses compose of interim analyses for the study design. The scoring method behind the questionnaire is not definitive, and the interview tones and analyses further determine the meaning behind each question as an integrated dynamic.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

From the screening questionnaire, the participant's ASD is major contribution to the inherent vulnerabilities. The participant attributes liabilities to himself with social functioning, and a mixed state of self-protection and social interactions exists, whereby the self-protective mechanism mainly serves for protecting himself from self-demanding behaviors that can lead to self-attack.

There is a low maturity of the participant on protecting himself in social situations from the inherent vulnerabilities, with a consciousness of fighting back only by passive responsiveness. No trace of aggression is noticed in inherent dispositions, but no violent behavior is excluded when being trespassed.

The open attitude of the participant's is contributive to the troubles brought about by ASD. Familial, intimate, and familiar relationships are the core inherent dispositions of the participant. The stereotypical limited interests in ASD are present. AvPD is psychodynamically contributed by ASD and OCD. The participant is not conscious that his limited interests can be contributed by OCD. Even though ADHD may

have improved appearances in social situations from the traits, social avoidance is still a barrier for the participant. Considering the suicidal ideation and planning history, the primary efficacy endpoint has brought the participant to the upper fourth and lower first quadrant of neurologically introspective and psychoactive state seen in **Section 4.1**.

The questionnaire is designed in a y-axis with the social situation score and x-axis with the inherent disposition and vulnerability scores. Each question is score from 0 to ± 10, and adds together by axes. The participant scored x+21 y+32, in a relatively positive spectrum. The positive score of the y axis, however, is mainly contributed by inherent dispositions instead of inherent vulnerability, indicating to the lack of resilience of the participant. The dependence on social safety network is a negative sign concerning psychological resilience and psychodynamics in positive social behaviors. The aim of the secondary efficacy endpoint is therefore set to prioritize psychological resilience and diversify the psychodynamic motivations of the participant. Primary endpoint analyses hypothesize the psychological etiological cause of the participant's migraine originates from the lack of psychodynamic motivations, both on a physiological and psychoanalytic basis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
- *Describe how each secondary endpoint is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, mediation or moderation analyses, multilevel modeling, MANOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors or effect size*
- *For group- or cluster- randomized trials and individually randomized group-treatment trials, describe how the analyses will reflect the expected positive within-group correlation and how any heterogeneity in that correlation that may be expected among study arms as a function of the study design*
- *Describe details to check assumptions required for certain types of analyses (e.g., checks on assumptions of normality, transformations or, when appropriate, nonparametric tests)*
- *Describe the Populations for which the analysis will be conducted as discussed in **Section 9.3, Populations for Analyses***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, non-adherence and lost to follow-up*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

9.4.4 SAFETY ANALYSES

Safety analyses mainly assess the self-hostility elements related to MDD, and hostility towards others. The CBT will prioritize destructive behaviors and cognitive elements thereof for the safety of the participant, hence the study.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Geometric mean data of the participant's blood pressures and heart rate are collected from the NCT05839236 trial throughout May 2023 with 50 mg/d sertraline: 110 (7.88%), 74 (8.83%), and 85 (13.98%).

Psychiatric Order of Hierarchy					
Symptom	Neurology	Characterization	Traits	Social Effects	Side Effects
ASD	Cause	Psychiatric	Avoidance	Negative (reactive)	Separation anxiety Grief Victimization* Stereotypical Restricted Stupor* Echolalia
CPTSD	Mixed	Psychiatric Psychological (responsive)	Avoidance* Fear Panic Anxiety Aggression*	Negative (reactive)	Ego-dystonic* Restricted Echopraxia Pressured speech Paranoid*
Anxiety	Effect	Psychological (mixed)	Fear Impulsivity*	Negative (proactive)	Psychomotor retardation* Dysprosody Pressured speech Paranoid
MDD	Mixed	Mixed	Suicidal	Negative (mixed)	Psychomotor retardation* Aggression* Antisocial Expansive Negativism Alogia Dysprosody Paranoid

OCD	Effect	Psychological (mixed)	PTSD (reactive)* ADHD (active)	Positive (reactive)	Anxiety Depression* Panic Expansive Negativism Aggression Pressured speech Paranoid*
ADHD	Cause	Psychological (proactive)	Avoidance* Depersonalization* Derealization* Avolition Anosognosia* Alexithymia*	Mixed	Labile* Negativism Psychomotor agitation
Panic Disorder	Effect	Psychological (proactive)	Physiological	Negative (reactive)	Alogia Dysprosody
AvPD	Effect	Psychological (passive-reactive)	Anhedonia*	Negative (proactive)	Avolition
Agoraphobia	Effect	Mixed (passive-reactive)	Fear Panic Anxiety Avoidance	Negative (reactive)	Depression
BPD	Mixed	Psychological (proactive, reactive, and responsive)	ASD Isolation*	Negative (mixed)	Dissociation*
* Traits that may worsen suicidal ideation.					

Behavioral Traits				
Symptom	Origin	Psychiatric Order	Association to ASD	Association to CPTSD
Fear	CPTSD Agoraphobia ASD OCD Panic	2	2	3
Impulsivity	ADHD-CPTSD ASD Anxiety MDD OCD Panic	3	1	4
BPD	MDD ASD OCD ADHD Agoraphobia	6	5	2

	CPTSD			
Agoraphobia	Panic AvPD Anxiety CPTSD ASD	4	6	1
AvPD	ADHD ASD BPD Panic MDD CPTSD	1	3	1
OCD	CPTSD ASD	5	4	3

The baseline descriptive analysis is co-determined by the questionnaire and psychoanalysis.

9.4.6 PLANNED INTERIM ANALYSES

Interim analyses will be conducted according to the CBT visits. Priority in interim analyses is outlined in **Sections 8.2** and **9.4.4**. The interim analyses plan implies that primary and secondary efficacy endpoint data will be analyzed parallel to the study progress, seen in **Sections 9.4.2** and **9.4.3**. Prima facie determination of Type I error is analyzed in primary efficacy endpoint, and will be revisited at the conclusion of the trial. Unless with significant UP leading to lost-in-follow-up, safety analyses on the participants' behavioral tendencies will not affect the trial's decision of continuation. Only the safety analyses concerning medication AEs and SAEs may lead to determinations in trial suspension, such as increased frequency and severity of headache / migraine during the process combined with CBT. If CBT fulfillment is not satisfactory, but medication intervention is considered valid, adjustments will be made on CBT. The severity and extent of psychological and psychodynamic elements of the participants will constitute the exploratory analyses, whereby the latter becomes the element in CBT for the psychologist and psychoanalyst.

9.4.7 SUB-GROUP ANALYSES

N/A.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be tabulated according to the procedural goals of CBT with psychoanalysis. Prima facie tabulation is seen in **Section 9.4.5**.

9.4.9 EXPLORATORY ANALYSES

The order of planned exploratory analyses is:

1) Aggressive and hostile behaviors related to MDD;
2) Psychodynamic roots of destructive and / or self-destructive behaviors;
3) Cognitive elements behind psychodynamic behaviors;
4) Paths in aligning positive psychodynamic and cognitive elements with social active behaviors;

5) Resilience strategies for building resilience on negative psychodynamic and cognitive elements of responsive behaviors in social activities / situations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. Participant consent is signed below the confidentiality statement at the start of this document.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The participant is informed by the PI on the study design, and has read this document drafted after tailored discussions.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations);
- Data that are not sufficiently complete and/or evaluable;
- Determination that the primary endpoint has been met;
- Determination of futility.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on Open Science Framework. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by data research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Open Science Framework.

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored on the staff computers. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Open Science Framework, for use by other researchers including those outside of the study. Permission to transmit data to the Open Science Framework is included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the Open Science Framework.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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No external funding has been obtained for the study.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the IRB.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:

- On-site monitoring will be conducted by the PI on a twice-a-week basis;
- Independent audits will not be conducted.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the study protocol and statistical analysis document and ClinicalTrials.gov. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the

study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to the IRB. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with Open Science publication and data sharing policies and regulations.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A.

10.3 ABBREVIATIONS AND SPECIAL TERMS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ASD	Autism Spectrum Disorder
AvPD	Avoidant Personality Disorder
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CPTSD	Complex Post-Traumatic Stress Disorder
CRF	Case Report Form
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IDE	Investigational Device Exemption

IRB	Institutional Review Board
MDD	Major Depressive Disorder
MOP	Manual of Procedures
NCT	National Clinical Trial
OCD	Obsessive Compulsive Disorder
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAD	Social Anxiety Disorder
SAE	Serious Adverse Event
SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
1.0	2023-06-01	This is the first version of the protocol.	Basic information and design.
1.1	2023-06-11	This is the first version of the protocol, and statistical analysis plans are furnished with the primary efficacy endpoint data.	Furnishing statistical designs.
1.2	2023-06-17	This is the first version of the protocol, and primary efficacy endpoint is filled.	Procedural and interim analyses organization.

11 REFERENCES

1. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? Int Clin Psychopharmacol. 2014 Jul;29(4):185-96.

2. Parellada M, Penzol MJ, Pina L, Moreno C, González-Vioque E, Zalsman G, et al. The neurobiology of autism spectrum disorders. European Psychiatry. 2020;29(1):11-9.

3. Martin D, Le JK. Amphetamine. StatPearls. Treasure Island (FL)2023.

4. Marco EJ, Hinkley LB, Hill SS, Nagarajan SS. Sensory processing in autism: a review of neurophysiologic findings. Pediatr Res. 2011 May;69(5 Pt 2):48R-54R.

5. Schalbroeck R, van Velden FHP, de Geus-Oei L-F, Yaqub M, van Amelsvoort T, Booij J, et al. Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [18F]-FDOPA PET/CT study. Translational Psychiatry. 2021;11(1).

6. Trevisan DA, Foss-Feig JH, Naples AJ, Srihari V, Anticevic A, McPartland JC. Autism Spectrum Disorder and Schizophrenia Are Better Differentiated by Positive Symptoms Than Negative Symptoms. Frontiers in Psychiatry. 2020;11.

7. Purnell LR, Graham ACJ, Bloomfield MAP, Billings J. Reintegration interventions for CPTSD: a systematic review. Eur J Psychotraumatol. 2021;12(1):1934789.

8. Joseph ED. The Consciousness of Being Conscious. Journal of the American Psychoanalytic Association. 2016;35(1):5-22.

9. Pachankis YI. Dictatorial Psychopathological Commination in Server-Side Public Mental & Psychological Menace. Biomedical Science and Clinical Research. 2023;2(2):173-84.