Protocol Title: Clinical trial to evaluate the safety and efficacy of NRCT-101SR in Adult Attention Deficit Hyperactivity Disorder

Protocol #: NC-018

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STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- All National and Local Regulations and Guidance applicable at each site
- The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- US Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed:_____ Date: _____
Name and Title

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAQoL	Adult ADHD Quality of Life scale
ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of Daily Living
AE	Adverse Event
AISRS	ADHD Investigator Symptom Rating Scale
ALT	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANCOVA	Analysis of Covariance
API	Active pharmaceutical ingredient
ASRS	ADHD Self Report Scale
AST	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area Under Curve
bpm	Beats Per Minute
BRIEF-A	Behavior Rating Inventory Executive Function for Adults
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
bw	Total Body Weight
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBC	Complete Blood Count
CDR-SB	Clinical Dementia Rating- Sum of Boxes
CGI-S	Clinical Global Impression - Severity
CNS	Central Nervous System
CO2	Carbon Dioxide
CPK	Creatine Phosphokinase
Cr	Creatinine
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DDI	Drug-drug interaction

DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Executive Function
ET	Early Termination
eGFR	Estimated glomerular filtration rate
$eGFR_{corr}$	Corrected estimated glomerular filtration rate
EOS	End of Study
F	Fahrenheit
FAD	Full Analysis Dataset
FCSRT	Free and Cued Selective Reminding Test
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
h	Hour
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HDL	High-Density Lipoprotein
HDPE	High Density Polyethylene
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IND	Investigational New Drug

IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat (Dataset)
IU	International Units
iv	Intravenous
IRT	Interactive Response Technology
kg	Kilogram
LAR	Legally Authorized Representative
[redacted]	[redacted]
LC	Laboratory Classroom
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LM II	Logical Memory II
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligram
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
[redacted]	[redacted]
MINI	Mini International Neuropsychiatric Interview
mIU	Milli International Unit
MITT	Modified Intent-To-Treat
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
MMRM	Mixed Model for Repeated Measures
MOP	Manual of Operations
MPV	Mean Platelet Value
MRI	Magnetic Resonance Imaging
msec	Millisecond
NCS	Not Clinically Significant
NNT	Number Needed to Treat
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-Inflammatory Drugs

PACC	Preclinical Alzheimer's Cognitive Composite
PCRS	Placebo Control Reminder Script
PERMP	Permanent Product Measure of Performance
PFC	Prefrontal Cortex
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
[redacted]	[redacted]
PTSD	Post-Traumatic Stress Disorder
QTc	Corrected QT interval
r	Pearson's Correlations Coefficient
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
sTNFRII	Soluble Tumor Necrosis Factor Receptor 2
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPSA	UCSD Performance-Based Skills Assessment
US	United States
WASI-II	Wechsler Abbreviated Scale of Intelligence
WBC	White Blood Cells
[redacted]	[redacted]

1.0 PROTOCOL SYNOPSIS

1.1 Rationale for Proposed Clinical Study

NRCT-101SR is being developed for patients with neurological disorders, including neuropsychiatric disorders and cognitive decline. Studies conducted over the last two decades demonstrated that prefrontal cortex (PFC) dysfunction, underlined by glutamatergic synapse dysfunction, play a critical role in the pathophysiology of neuropsychiatric disorders, including Attention-Deficit/Hyperactivity Disorder (ADHD) (Opel, Goltermann et al. 2020) (Seidman, Biederman et al. 2011) (Duman, Aghajanian et al. 2016) (Zarate, Singh et al. 2006) (Duman 2014). In this regard, the API of NRCT-101-SR, [redacted] clinical code: NRCT-101), has been shown to increase synaptic density and the number of functional presynaptic release sites, while reducing release probability in the PFC. Systemically, NRCT-101 treatment leads to the enhancement of learning ability, working memory, and short- and long-term memory in young rats, reverses cognitive impairment in aged rats [redacted] and improves emotional regulation [redacted]

In a preliminary clinical efficacy study conducted at the [redacted] in adult ADHD subjects, NRCT-101 was shown to significantly reduce core symptoms of ADHD (AISRS and ASRS). This 12-week, single-site, open-label trial included relatively few subjects (17 enrolled and 15 in efficacy population). Importantly, NRCT-101 administration significantly improved overall function (Global Assessment of Function) and cognition, using both objective (WASI-II and CANTAB) and self-reported measurements (global executive function: BRIEF-A). Effects of NRCT-101 [redacted] were observed by the first time point at 3 weeks and maintained through the end of study at 12 weeks.

Many ADHD symptoms are problems with executive function and emotional regulation. From five preliminary single-site clinical trials in other patient populations with neuropsychiatric symptoms and/or varying degrees of cognitive impairment, NRCT-101SR was shown to improve emotional regulation in less than 1 week. Importantly, NRCT-101SR also improved executive function.

Overall, the preliminary studies show that NRCT-101SR has a strong tolerability and safety profile, with a safety database of more than 200 subjects enrolled in studies with NRCT-101 [redacted] to date.

Study NC-018 will evaluate the efficacy of NRCT-101SR in approximately 216 adult ADHD subjects across multiple sites using a parallel design. The goal of this trial is to demonstrate the safety and efficacy of 6-week administration of NRCT-101SR compared to placebo in improving functional performance and reducing core symptoms in adult ADHD subjects. Evaluation at one week will assess the rapid-acting effects of NRCT-101SR on ADHD symptoms.

1.2 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-arm design, laboratory classroom (LC) trial to assess the efficacy and safety of NRCT-101SR [redacted] compared to inactive placebo over a 6-week period in approximately 216 subjects ≥ 18 years of age with ADHD. Study population will include adult male and female subjects of all race/ethnicity with ADHD, recruited from sites across the US. All subjects will either be naïve to stimulant or non-stimulant ADHD medications, or prior to enrollment, have been off stimulants for at least 2 weeks and non-stimulants for at least 3 weeks.

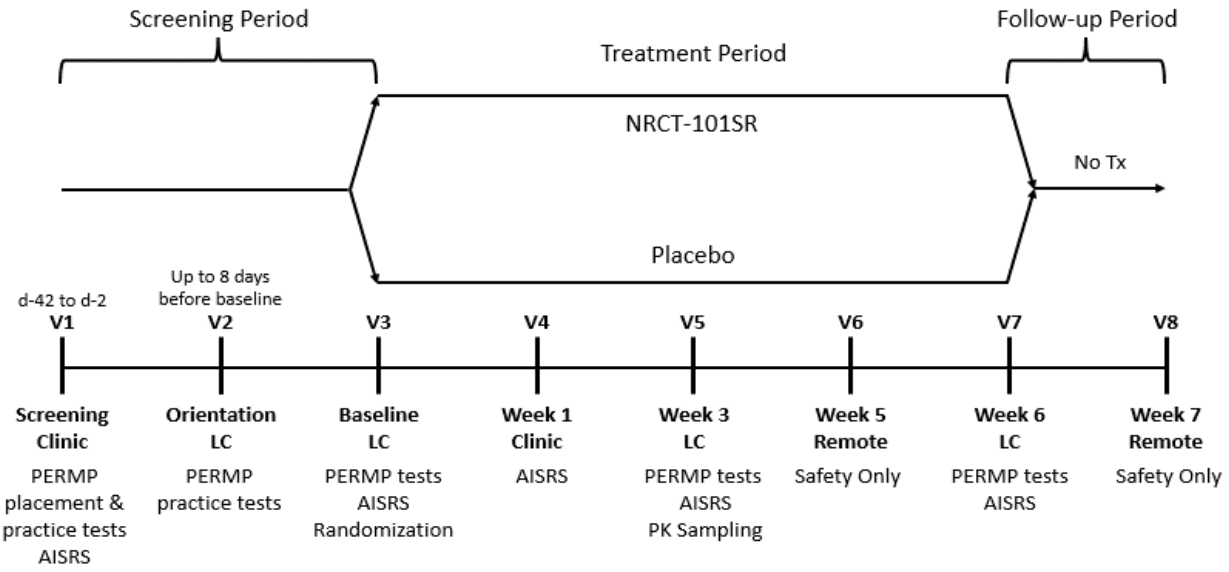
Total subject participation in the study is up to approximately 13 weeks, including a screening period (up to 6 weeks), a 6-week treatment period, and an approximate 1-week follow-up period. Each study subject will be randomized into one of two groups (1:1) to receive either active drug or placebo during the entirety of the 6-week treatment period. Within 8 days of Baseline LC visit, subjects will complete an LC Orientation Visit. At the Baseline LC visit, subjects will be randomized, assigned to a group, and dispensed study drug (first dose to be taken the next morning). The primary endpoints of the study include Permanent Product Measure of Performance (PERMP) Math Tests and the ADHD Investigator Symptom Rating Scale (AISRS). To familiarize the subjects with the PERMP, prior to the Baseline LC visit, they will complete 8 practice PERMP assessments (3 at screening and 5 at the LC Orientation visit). LC visits will be repeated at Week 3 and Week 6. Secondary and exploratory assessments will also be conducted at the Baseline, Week 3, and Week 6 LC visits. A clinic visit will be conducted at Week 1 to administer AISRS with expanded version, HADS, and BRIEF-A. Safety assessments (concomitant medications, adverse events, and suicide risk) will be conducted at all clinic and remote visits/phone calls (Week 5, and follow-up); safety labs will be conducted at screening, Week 3, and Week 6. For population PK analysis, PK sampling will be conducted at the Week 3 LC visit. Blood samples for PK will be collected prior to dosing, at 4 hours and 7 hours after dosing (with a 30-minute window). See Study Schema and Schedule of Events below.

The primary analysis will be on effects of 6-week treatment of NRCT-101SR versus placebo on performance and ADHD core symptoms in subjects with adult ADHD. The dual primary endpoints are PERMP (performance) and AISRS (core symptoms). The study will be declared successful by reaching statistical significance on either primary endpoint with adjustment for multiplicity.

Randomization will be stratified by:

- Site
- LC Cohort
- Sex (approximately equal number of male and female in the study)

1.3 Study Schema



1.4 Study Objectives and Endpoints

1.4.1 Primary Objective

1. To determine if treatment with NRCT-101SR improves objective performance and/or reduces core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the PERMP and AISRS at Week 6. The trial will be declared successful by reaching statistical significance on either primary endpoint.

1.4.2 Key Secondary Objectives

1. To determine if treatment with NRCT-101SR reduces executive function symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the BRIEF-A at Week 6
2. To determine if treatment with NRCT-101SR reduces neuropsychiatric symptoms (anxiety and depression) in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the HADS at Week 6

1.4.3 Other Secondary Objectives

1. To determine if NRCT-101SR treatment has rapid-acting effects on reducing core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AISRS at Week 1
2. To determine if NRCT-101SR treatment has same-day effects on improving objective performance in adult subjects with ADHD compared to placebo as assessed by change from pre-dose timepoint in PERMP at Week 6

3. To determine if treatment with NRCT-101SR improves quality of life in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AAQoL at Week 6
4. To determine if treatment with NRCT-101SR reduces disease severity in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the CGI-S at Week 6
5. To evaluate responder rate with NRCT-101SR compared to placebo as assessed by AISRS response and change from baseline in CGI-S at Week 6
6. To assess the population pharmacokinetics of NRCT-101SR in ADHD subjects
7. To determine if treatment with NRCT-101SR improves objective performance and/or reduces core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AISRS Expanded Version at Week 6

1.4.4 Exploratory Objectives

1. [redacted]

[redacted]

1.4.5 [redacted] objective

1. [redacted]

1.4.6 Safety Objective

1. To evaluate the safety and tolerability of NRCT-101SR compared to placebo as assessed by the incidence of adverse events, vital sign measurements, clinical laboratory evaluations, electrocardiogram (ECG) parameters, proportion of subjects who discontinue from the study due to any adverse event (tolerability), and the Columbia Suicide Severity Rating Scale (C-SSRS)

1.4.7 Study Endpoints

All primary and secondary endpoints will be evaluated as the difference between NRCT-101SR and placebo following the 6-week treatment period unless as noted.

1.4.7.1 Primary Efficacy Endpoints

1. Objective Performance: Permanent Product Measure of Performance – Correct (PERMP-C)
2. Core Symptoms: ADHD Investigator Symptom Rating Scale (AISRS)

1.4.7.2 Key Secondary Efficacy Endpoints

1. **Cognition**
   - Subjective Executive Function: Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)
2. **Neuropsychiatric Symptoms**
   - Hospital Anxiety and Depression Scale (HADS)

1.4.7.3 Other Secondary Endpoints

1. **Core Symptoms**
   - AISRS Expanded Version at Week 6
2. **Clinician Rated Scales**
   - Clinical Global Impression - Severity (CGI-S)
3. **Responder Rate**
   - The proportion of responders (≥ 25% reduction of AISRS and ≥ 2-point reduction of CGI-S from baseline to Week 6)
4. **Subjective Subject Rated Symptoms Scales**
   - Adult ADHD Quality of Life scale (AAQoL)
5. **Population PK**
   - Plasma levels of NRCT-101 [redacted] for PK modeling in ADHD subjects

1.4.7.4 Exploratory Efficacy Endpoints

1. [redacted]

[redacted]

1.4.7.6 Safety Endpoints

1. The proportion of subjects with adverse events or serious adverse events (SAEs) over the 6-week study intervention period.
2. The proportion of subjects who discontinue from the study due to any adverse event (tolerability) over the 6-week study intervention period.
3. The change relative to placebo from baseline to each post-baseline measure in labs, vitals, ECG, and C-SSRS responses.

1.5 Study Population

Study will enroll approximately 216 subjects ≥ 18 years of age with Attention-Deficit/Hyperactivity Disorder (ADHD). Study population will include male and female subjects of all race / ethnicity with ADHD, recruited from sites across the US. All subjects will either be naïve to stimulant or non-stimulant ADHD medications, or prior to enrollment, have been off stimulants for at least 2 weeks and non-stimulants for at least 3 weeks.

1.5.1 Inclusion Criteria

1. Male or female, ≥ 18 years of age at screening
2. Has a primary diagnosis of ADHD according to the DSM-5 classification, confirmed with MINI using DSM-5 probes
3. AISRS ≥ 26 at screening and baseline, and does not change by more than 25% from screening to baseline, except subjects who stop taking ADHD medication after screening may have an increase of more than 25%
4. Has a minimum score of 4 on the CGI-S at baseline
5. Must be fluent in English, and capable of reading, writing, and communicating effectively with others and willing to participate in laboratory classroom
6. Completion of at least 10 years of formal education

7. Hearing and Vision ability sufficient to complete cognitive testing, in investigator's opinion

8. Willing and able to give informed consent

9. Total Body weight (bw) ≥ 50 kg and ≤ 120 kg [redacted]

10. Naïve to stimulant or non-stimulant medications used for the treatment of ADHD or have discontinued stimulants at least 2 weeks and non-stimulants at least 3 weeks prior to randomization

1.5.2 Exclusion Criteria

Exclusions to rule out subjects with impairment likely due to something other than ADHD:

11. Subject is functioning below an age-appropriate level intellectually, as judged by the investigator.

12. Lifetime history of severe psychiatric symptoms of major depression requiring hospitalization, bipolar disorder, schizophrenia of schizoaffective disorder, hallucinations, or delusions. Severe comorbid disorders such as PTSD, severe obsessive-compulsive disorder, or other symptomatic presentation that, in the opinion of the examining physician, will contraindicate NRCT-101SR treatment or confound efficacy or safety assessments. Subjects with mild to moderate forms of social phobia or dysthymia, for instance, may be included.

13. History of seizures (other than infantile febrile seizures), any tic disorder (except transient tic disorder and subject has no episodes for at least 1 year), or a current diagnosis of Tourette's Disorder.

14. Recent history (within the past 1 year) of suspected substance abuse or dependence disorder (excluding stable nicotine use) in accordance with DSM-5 criteria. (Note: subject's average nicotine use should not be exceeded during each LC visit)

15. Current abnormal thyroid function as defined as abnormal screening thyroid stimulating hormone. Treatment for at least 3 months with a stable dose of thyroid medication is permitted.

Exclusions to rule out subjects with potential issues absorbing or metabolizing NRCT-101SR:

16. Poor kidney function; corrected estimated glomerular filtration rate (eGFRcorr) < 40 mL/min/m^2

17. History of significant gastrointestinal disorders, such as chronic diarrhea, irritable bowel syndrome, ulcerative colitis, Crohn's disease, etc.

Exclusions to rule out subjects with conditions that could affect their safety:

18. Female subjects who are pregnant and/or lactating

19. A "yes" answer to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at screening (in the past 12 months).

20. Has history of severe drug allergy or hypersensitivity to the study medication or its excipients.

21. Hypermagnesemia; magnesium > 2.5 mg/dL

22. Reproduction:

    a. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning 30 days prior to the first dose of study drug and throughout the study:

        i. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first study drug administration

        ii. Surgically sterile male partner

        iii. Simultaneous use of male condom and diaphragm with spermicide

        iv. Established hormonal contraceptive

    b. Males must:

        i. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of study drug, or

        ii. Have been surgically sterilized prior to the Screening Visit.

Exclusions to rule out subjects with conditions that could inhibit or confound the effects of NRCT-101SR or the ability of the subject to complete the study:

23. Is currently participating in another clinical trial or has participated in a clinical trial within 30 days prior to the Screening Visit.

24. Currently living in an institutional facility such as a nursing home

25. Severe physical disability not associated with cognitive function that limits ability to complete testing (e.g., severe tremor, debilitating arthritis, etc.)

26. Known history of symptomatic cardiac disease, advanced atherosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary heart disease, transient ischemic attack or stroke or other serious cardiac problems.

27. Known family history of sudden cardiac death or ventricular arrhythmia.

28. Serious or unstable clinically important systemic illness or disease that, in the judgment of the investigator, is likely to affect cognitive assessment, deteriorate, or affect the subject's safety or ability to complete the study, including hepatic (e.g., Child-Pugh grade C), renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, infectious, or hematologic disorders

29. Has previously participated in a NRCT-101SR / [redacted] investigational study

30. Investigators and their immediate family members are not permitted to participate in the study.

31. Consumes more than a weekly average of: 2 drinks / day or more than 3 drinks in any day for males; 1 drink / day or more than 2 drinks in any day for females

32. Changes in medications or doses of medication as follows:

    a. All allowed concomitant medications, supplements, or other substances must be at stable doses for at least 30 days prior to screening and must be kept as stable as medically possible during the trial. For allowed concomitant medications, any dosing change within 30 days of Screening may be allowed if, in the opinion of the investigator, it will not affect or influence study results.

1.6 Prior and Concomitant Medications

Prior treatments, defined as any treatment taken within 3 months or any ADHD drug taken within 6 months before screening, are to be recorded in the electronic case report form (eCRF) as prior medications. Concomitant treatments, defined as treatments taken after the first dose of study drug, are to be recorded in the eCRF as concomitant medications.

If a change in medication dosage occurs during the study it may lead to discontinuation from study participation unless it relates to a medication that, in the view of the study investigator and in consultation with the medical monitor, does not affect the subject’s participation in the trial or the study results. Any medication or therapy that is taken by or administered to the subject during the study should be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

After randomization, medication(s) to treat minor treatment-emergent illness(es) is generally permitted and subjects may be allowed to continue in the study after being evaluated by the clinician and discussed with the Sponsor. However, for certain classes of drugs (listed below; not inclusive of every drug and brand or generic name), subjects must follow dosing guidelines listed below (i.e., restricted medications/substances) and before Baseline visit and throughout the study, must not take ADHD stimulants for at least 2 weeks, ADHD non-stimulants for at least 3 weeks, and other prohibited substances for at least 4 weeks (or as listed below). Any subject taking these substances during the study will be evaluated by the Clinician (to be discussed with Sponsor) for ability to continue in the study.

Substance use will be collected in the eCRF at screening to document the subjects previous and current use of cannabis, nicotine/tobacco, caffeine, opioids, sedatives, and hypnotics. During LC days, caffeine is limited to one cup of coffee/caffeinated drink in the morning and one caffeinated drink at meals.

<u>The following are classes of medication used for treatment of ADHD and comorbid disorders that are prohibited during the study</u>:

- Classical drugs (CNS stimulants), including:
    - Amphetamines, Adderall, Dexamphetamine, Lisdexamphetamine, Methamphetamine, Methylphenidate, Dexmethylphenidate
- Non-classical drugs (non-stimulant), including:
    - Atomoxetine, Modafinil, Viloxazine ER
- α2 adrenoceptor agonists (non-stimulant), including:
    - Clonidine, Guanfacine
- Any Antidepressants / Anxiolytics / antipsychotics, such as (but not limited to):
    - Selective Serotonin Reuptake Inhibitor (SSRI), Amitriptyline, Bupropion, Buspirone, Clomipramine, Desipramine, Duloxetine, Imipramine, Milnacipran, Moclobemide, Nortriptyline, Reboxetine, Selegiline, Venlafaxine
- Miscellaneous other drugs
    - NMDA receptor blockers, such as Amantadine and Memantine-containing drugs (e.g., Namenda®)
    - Mood stabilizers (for example, Carbamazepine, Valproate, lithium, and Lamotrigine)

<u>Other prohibited/restricted medication/substances</u>

- Marijuana / cannabinoids
- Alcohol
    - Men: greater than weekly average of 2 drinks / day or more than 3 drinks in any day

- Women: weekly average of greater than 1 drink / day f or more than 2 drinks in any day

- Calcium channel blockers, such as:
  - Felodipine (Plendil®); Amlodipine besylate (Norvasc®)
- [redacted]

All other supplements will be allowed only at the discretion of the study principal investigator.

1.7 Study Phase

Phase 2b/3

1.8 Study Sites

There will be approximately 5-10 sites across the US.

1.9 Study Intervention

NRCT-101SR is a[redacted] hour sustained release tablet. Each tablet contains 375 or 500 mg of NRCT-101 [redacted]

[redacted]

[redacted]

Study Drug	NRCT-101SR	Placebo
Manufacturer	[redacted]	[redacted]
Dose(s)	[redacted]	Not applicable
Route	Oral	Oral
Formulation	Tablet	Tablet
Strength(s)	1) 375 mg/tablet 2) 500 mg/tablet	1) matches 375 mg active 2) matches 500 mg active
Container closure	Bottles (32 tablets)	Bottles (32 tablets)

1.10 Study Duration

Subject participation in the study will be approximately 13 weeks (up to 6 weeks for screening, 6 weeks of study drug administration and clinic visits, and one week of follow-up).

1.11 Schedule of Events

Table S1 – Schedule of Events

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/- 3 days)	Day 43	Day 50 (+/- 2 day)
Informed Consent	X							
Eligibility Review	X		X					
Randomization			X					
Demographics & Medical History	X							
Substance Abuse History	X							
Prior/Concomitant Meds	X	X	X	X	X	X	X	X
Physical Exam	X		X		X		X	
MINI with DSM-5 probes	X							
Vital Signs including weight	X	X	X		X		X	
Height	X							
Safety Labs/ Urinalysis	X		X[f]		X		X	
Urine pregnancy	X		X					
Urine Drug Screen	X		X		X		X	

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/- 3 days)	Day 43	Day 50 (+/- 2 day)
[redacted]			X				X	
ECG			X				X	
PK Sampling[a]					X			
AISRS with expanded version	X		X[g]	X[g]	X[g]		X[g]	
[redacted]			X		X		X	
CGI-S	X		X	X	X		X	
[redacted]			X		X		X	
AAQoL			X		X		X	
BRIEF-A			X	X	X		X	
HADS			X	X	X		X	
C-SSRS (Baseline/Screening version)	X							
C-SSRS (since last visit version)		X	X	X	X	X	X	X
[redacted]			X		X		X	
PERMP placement	X							
PERMP practice[c]	X	X						
PERMP			X[bg]		X[bg]		X[bdg]	
Adverse Events				X	X	X	X	X

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/- 3 days)	Day 43	Day 50 (+/- 2 day)
Study Drug Dispensation			X		X		X[e]	
Study Drug Accountability					X		X	

ET = early termination; LC = Laboratory Classroom; AISRS = ADHD Investigator Symptom Rating Scale; ECG = electrocardiogram; [redacted] CGI-S = Clinician Global Impression – Severity; [redacted] AAQoL = adult ADHD Quality of Life; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult; HADS = Hospital Anxiety and Depression Scale; C-SSRS = Columbia Suicide Severity Rating Scale; PERMP = Permanent Product Measure of Performance; PK = Pharmacokinetic (samples collected pre-dose and post-dose); [redacted]

[redacted]

2.0 INTRODUCTION

2.1 Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is considered a common neurodevelopmental disorder. Individuals with ADHD are characterized by difficulties in attention, impulsive behaviors, and overactivity. These manifestations are widely considered as the 'core symptoms' of ADHD. Other common challenges include deficits in cognitive performance, executive dysfunction, and dysfunctional emotional regulation (Shanahan, Pennington et al. 2006, Katzman, Bilkey et al. 2017, Claesdotter, Cervin et al. 2018, Silverstein, Faraone et al. 2020).

In most cases, ADHD is first diagnosed in childhood and symptoms often carry into adulthood. The estimated prevalence of adult ADHD in the US is 4.4% (~11M), with more males than females (5.4% and 3.2%, respectively) (Kessler, Adler et al. 2006). Worldwide adult ADHD prevalence is assessed to be 3.4% (Fayyad, De Graaf et al. 2007). While the cause and risk factors for ADHD remain unknown, it is evident that genetics play an important role (Thapar and Stergiakouli 2008). Other factors found to be associated with ADHD include brain injury, exposure to hazardous materials during pregnancy or at a young age, alcohol and tobacco use during pregnancy, premature delivery, and low birth weight.

Current treatments for adult ADHD are similar to treatments for childhood ADHD. The available pharmacological treatments are categorized as stimulants and non-stimulants, with the former considered as the first-line. Stimulants are designed to increase dopamine and norepinephrine neurotransmission, and include non-specific monoamine reuptake inhibitors (e.g., Adderall and amphetamine) and norepinephrine-dopaminergic reuptake inhibitors (e.g., Ritalin and Focalin). Non-stimulants are designed to act on norepinephrine neurotransmission and include norepinephrine reuptake inhibitor (Atomoxetine) and α-2 adrenergic receptor agonists (e.g., Clonidine and Guanfacine).

Generally, stimulants (both short- and long-acting) are known for improving core ADHD symptoms in 65%–75% of patients in all age groups (Pliszka 2009). However, their efficacy varies between patients, requiring trying multiple medications and doses (Kolar, Keller et al. 2008).

Non-stimulants normally do not generate immediate effects and require a longer treatment period before improving symptoms. Generally, they are significantly less effective than stimulants in reducing core ADHD symptoms (Wigal, McGough et al. 2005, Wietecha, Clemow et al. 2016). Non-stimulants, however, specifically atomoxetine, may improve quality of life (Adler, Spencer et al. 2009).

Treatment discontinuation rate is circa 30% (Steer 2005), and only 11% of adults with ADHD are treated. The main reasons patients lack treatments are tolerability issues and social stigma; side effects of stimulants are a major concern for patients and include insomnia (32%), anorexia/decreased appetite (32%), headache (30%), and nervousness (26%) (Biederman, Spencer et al. 2005, Wolraich, Hagan et al. 2019) (Greenhill, Pliszka et al. 2001). Mild increase in blood pressure and pulse were also documented in individuals treated with stimulants, generally found

not to be clinically significant. However, for adults with borderline hypertension or other cardiovascular disease, such adverse effects could impose health risk.

Non-stimulant side-effects include sleepiness, headaches, fatigue, stomachaches, nausea, erectile dysfunction, and in some medications may increase seizure probability (Kolar, Keller et al. 2008, Adler, Spencer et al. 2009).

Considering the shortcomings of the current medications, including their substantial side effects, there is a need for new drugs that will improve ADHD core symptoms, executive function and overall cognitive performance, and emotional regulation with a good tolerability profile.

2.2 Study Rationale

NRCT-101SR is being developed for patients with neurological disorders, including neuropsychiatric disorders and cognitive decline. Studies conducted over the last two decades demonstrated that prefrontal cortex (PFC) dysfunction, underlined by glutamatergic synapse dysfunction, play a critical role in the pathophysiology of neuropsychiatric disorders, including Attention Deficit Hyperactivity Disorder (ADHD) (Opel, Goltermann et al. 2020) (Seidman, Biederman et al. 2011) (Duman, Aghajanian et al. 2016) (Zarate, Singh et al. 2006) (Duman 2014). In this regard, the active pharmaceutical ingredient (API) of NRCT-101-SR – [redacted] clinical code: NRCT-101) has been shown to increase synaptic density and the number of functional presynaptic release sites, while reducing release probability in the PFC. Systemically, NRCT-101 treatment leads to the enhancement of learning ability, working memory, and short- and long-term memory in young rats, reverses cognitive impairment in aged rats (Slutsky, Abumaria et al. 2010), and improves emotional regulation (Abumaria, Yin et al. 2011, Abumaria, Luo et al. 2013).

In a preliminary efficacy study conducted at the Massachusetts General Hospital (MGH) in adult ADHD subjects, NRCT-101 was shown to significantly reduce core symptoms of ADHD (AISRS and ASRS). This 12-week, single-site, open-label trial included relatively few subjects (17 enrolled and 15 in efficacy population). Importantly, NRCT-101 administration significantly improved overall function (Global Assessment of Function) and cognition, using both objective (WASI-II and CANTAB) and self-reported measurements (global executive function: BRIEF-A). Effects of NRCT-101 [redacted] were observed by the first time point at 3 weeks and maintained through the end of study at 12 weeks.

Many ADHD symptoms are problems with executive function and emotional regulation. From five preliminary single-site clinical trials in other patient populations with neuropsychiatric symptoms and/or varying degrees of cognitive impairment, NRCT-101SR was shown to improve emotional regulation in less than 1 week. Importantly, NRCT-101SR also improved executive function.

Overall, the preliminary studies show that NRCT-101SR has a strong tolerability and safety profile, with a safety database of more than 200 subjects enrolled in studies with NRCT-101 (L-TAMS) to date.

Study NC-018 will evaluate the efficacy of NRCT-101SR in approximately 216 adult ADHD

subjects across multiple sites using a parallel design. The goal of this trial is to demonstrate the safety and efficacy of 6-week administration of NRCT-101SR compared to placebo in improving functional performance and reducing core symptoms in adult ADHD subjects. Evaluation at one week will assess the rapid-acting effects of NRCT-101SR on ADHD symptoms.

2.3 Study Population

The NC-018 study population will include male and female adults (≥ 18 years of age) with a primary diagnosis of ADHD according to the DSM-5 classification. Per FDA guidance, the diagnosis of ADHD will be confirmed using a semi-structured clinical interview assessment – the Mini International Neuropsychiatric Interview (MINI) using the DSM-5 probes for ADHD symptoms. All subjects will either be naïve to stimulant or non-stimulant ADHD medications, or prior to enrollment, have been off stimulants for at least 2 weeks and non-stimulants for at least 3 weeks.

2.4 Dose Rationale

In the preliminary efficacy studies in subjects with ADHD to evaluate cognition, the effective dosage of NRCT-101SR was determined to be [redacted] According to data from the Center for Disease Control (CDC), a total body weight range of 50-105 kg covers ~ 85% of US women and ~80% of US men.

[redacted]

2.5 Study Endpoint Rationale

2.5.1 Dual Primary Outcome Measures

The primary objectives of the study are to evaluate the clinical efficacy of NRCT-101SR versus placebo on objective performance and/or ADHD core symptoms. The study will be declared successful by reaching statistical significance on either primary endpoint with adjustment for multiplicity.

2.5.1.1 PERMP-C

Objective performance will be evaluated with the permanent product measure of performance (PERMP), a validated performance-based objective measure of attention and function. It is the standard primary outcome measure for most adult LC studies and is accepted by the FDA for assessing efficacy of an investigational new drug for ADHD (FDA 2019, Wigal 2019). PERMP Math Test covers at least five symptoms of ADHD related to attention and executive function, including initiation of activity, careless mistakes, failure to finish, easily distracted, unsustained attention, and avoidance of mentally effortful tasks. These cover symptoms likely to be improved by [redacted] Because PERMP is an objective measure with a quantifiable result, it should have reduced variability and increased sensitivity relative to other subjective measures. PERMP-correct (PERMP-C), which is the number of correctly answered math problems will serve as the primary analysis for efficacy. PERMP-attempted (PERMP-A) will also be collected and will be used to calculate PERMP-Total (PERMP-T), which is the sum of PERMP-C and PERMP-A. PERMP-A and PERMP-T will be analyzed as exploratory measures.

PERMP will be collected in an LC setting, an FDA-approved method (Wigal 2019, Childress, Cutler et al. 2022, Cutler, Childress et al. 2022). It provides a controlled environment in which ADHD symptoms are likely to occur, to allow for measurement of onset and reduction of symptoms throughout the day.

PERMP will be administered at Baseline, Week 3, and Week 6 LC visits. At each visit, there will be a pre-dose assessment followed by 6 assessments at hours 2, 4, 6, 8, 10, and 12-hours post-dose. To ensure subjects are sufficiently familiar with the administration of PERMP and to limit learning effects, practice PERMP tests will be administered at Screening visit (3x), and at an LC Orientation visit (5x).

PERMP-C will also be evaluated at Week 6 at each time point relative to the pre-dose timepoint to evaluate effects throughout the day.

2.5.1.2 AISRS

In addition to assessment of function, this study will also evaluate the effects of NRCT-101SR on reducing core symptoms of ADHD. The AISRS is an FDA-accepted clinician rated scale that assesses the core ADHD symptoms listed in DSM-5 (FDA 2019). It covers both inattentive symptoms and hyperactive/impulsive symptoms. An age-appropriate version will be used. It will be administered with the expanded version at Screening, Baseline, Week 1, Week 3, and Week 6. Assessment of AISRS at Week 6 will be a co-primary outcome measure. Sensitivity analysis of Week 1 timepoint will be conducted to evaluate rapid-acting effects of NRCT-101SR. In addition,

assessment of the AISRS expanded version at Week 6 will be evaluated as a secondary outcome measure for core symptoms.

2.6 Risks and Benefits for Subjects

While the risks of adverse events associated with NRCT-101SR are not fully known, there have been no serious adverse events considered to be related to NRCT-101[redacted]-containing study compound in any previous clinical trial. In all completed clinical trials, ranging in length from one week to 24 weeks, study subjects tolerated the study compound well. There were fewer overall adverse events reported in the active treatment group compared to placebo group. [redacted] However, gastrointestinal system events did not appear to be associated with NRCT-101 [redacted] administration. [redacted]

Blood draws are required to assess overall physical health including kidney and liver function, to evaluate target engagement, and to evaluate the drug exposure (i.e., PK). The subjects' well-being will be monitored continuously before and after the procedures.

While small, there is risk to privacy with clinical testing and data collection. Precautions will be taken to ensure that subjects are tested privately (as much as possible as some laboratory classroom assessments are meant to be done in a group), that written materials are properly stored, and that any digital materials are stored on password protected/encrypted servers/computers. All study staff who will have access to subjects and subject data will be trained in protecting human research subjects.

3.0 STUDY OBJECTIVES AND ENDPOINTS

The overall objective of the study is to evaluate the clinical efficacy and safety of NRCT-101SR relative to the placebo among adults with ADHD.

3.1 Study Objectives

3.1.1 Primary Objective

1. To determine if treatment with NRCT-101SR improves objective performance and/or reduces core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the PERMP and AISRS at Week 6.

3.1.2 Key Secondary Objectives

1. To determine if treatment with NRCT-101SR reduces executive function symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the BRIEF-A at Week 6.
2. To determine if treatment with NRCT-101SR reduces neuropsychiatric symptoms

(anxiety and depression) in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the HADS at Week 6.

3.1.3 Other Secondary Objectives

1. To determine if NRCT-101SR treatment has rapid-acting effects on reducing core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AISRS at Week 1.
2. To determine if NRCT-101SR treatment has same-day effects on improving objective performance in adult subjects with ADHD compared to placebo as assessed by change from pre-dose timepoint in PERMP at Week 6.
3. To determine if treatment with NRCT-101SR improves quality of life in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AAQOL at Week 6.
4. To determine if treatment with NRCT-101SR reduces disease severity in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the CGI-S at Week 6.
5. To evaluate responder rate with NRCT-101SR compared to placebo as assessed by AISRS response and change from baseline in CGI-S at Week 6.
6. To assess the population pharmacokinetics of NRCT-101SR in ADHD subjects.
7. To determine if treatment with NRCT-101SR improves objective performance and/or reduces core symptoms in adult subjects with ADHD compared to placebo as assessed by the change from baseline in the AISRS Expanded Version at Week 6.

3.1.4 Exploratory Objectives

1. [redacted]

[redacted]

3.1.6 Safety Objectives

1. To evaluate the safety and tolerability of NRCT-101SR compared to placebo as assessed

by the incidence of adverse events, vital sign measurements, clinical laboratory evaluations, electrocardiogram (ECG) parameters, proportion of subjects who discontinue from the study due to any adverse event (tolerability), and the Columbia Suicide Severity Rating Scale (C-SSRS).

3.2 Study Endpoints

All primary and secondary endpoints will be evaluated as the difference between NRCT-101SR and placebo following the 6-week treatment period unless as noted.

3.2.1 Primary Efficacy Endpoints

1. Objective Performance: Permanent Product Measure of Performance – Correct (PERMP-C)
2. Core Symptoms: ADHD Investigator Symptom Rating Scale (AISRS)

3.2.2 Key Secondary Efficacy Endpoints

1. **Cognition**
   - Subjective Executive Function: Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)
2. **Neuropsychiatric Symptoms**
   - Hospital Anxiety and Depression Scale (HADS)

3.2.3 Other Secondary Endpoints

1. **Core Symptoms**
   - AISRS Expanded Version at Week 6
2. **Clinician Rated Scales**
   - Clinical Global Impression – Severity (CGI-S)
3. **Responder Rate**
   - The proportion of responders (≥ 25% reduction of AISRS and ≥ 2-point reduction of CGI-S from baseline to Week 6)
4. **Subjective Subject Rated Symptoms Scales**
   - Adult ADHD Quality of Life scale (AAQoL)
5. **Population PK**
   - Plasma levels of NRCT-101 [redacted] for PK modeling in ADHD subjects

3.2.4 Exploratory Efficacy Endpoints

1. [redacted]

3.2.6 Safety Endpoints

1. The proportion of subjects with adverse events or serious adverse events (SAEs) over the 6-week study intervention period.
2. The proportion of subjects who discontinue from the study due to any adverse event (tolerability) over the 6-week study intervention period.
3. The change relative to placebo from baseline to each post-baseline measure in labs, vitals, ECG, and C-SSRS responses.

4.0 STUDY DESIGN

4.1 Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-arm design, laboratory classroom (LC) trial to assess the efficacy and safety of NRCT-101SR [redacted] compared to inactive placebo over a 6-week period in approximately 216 subjects ≥ 18 years of age with ADHD. Study population will include adult male and female subjects of all race/ethnicity with ADHD, recruited from sites across the US. All subjects will either be naïve to stimulant or non-stimulant ADHD medications, or prior to enrollment, have been off stimulants for at least 2 weeks and non-stimulants for at least 3 weeks.

Total subject participation in the study is up to approximately 13 weeks, including a screening period (up to 6 weeks), a 6-week treatment period, and an approximate 1-week follow-up period. Each study subject will be randomized into one of two groups (1:1) to receive either active drug or placebo during the entirety of the 6-week treatment period. Within 8 days of the Baseline visit, subjects will complete an LC Orientation Visit. At the Baseline LC visit, subjects will be enrolled,

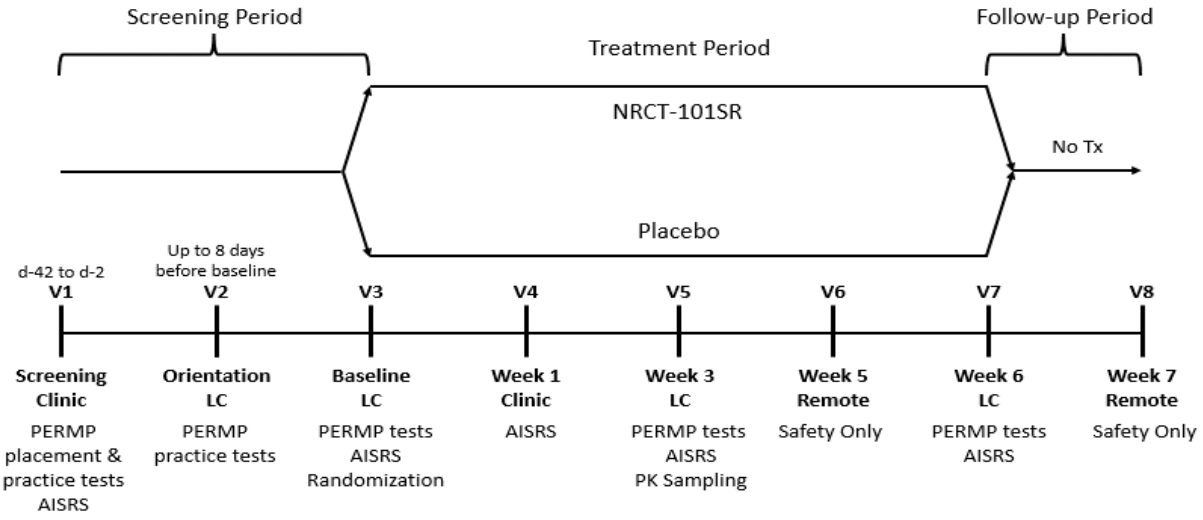
assigned to a group, and receive study drug (first dose to be taken the next morning). The primary endpoints of the study include Permanent Product Measure of Performance (PERMP) Math Tests and the AISRS. To familiarize the subjects with the PERMP, prior to the Baseline LC visit, they will complete 8 practice PERMP assessments (3 at screening and 5 at the LC Orientation visit). LC visits will be repeated at Week 3 and Week 6. Secondary and exploratory assessments will also be conducted at the Baseline, Week 3, and Week 6 LC visits. A clinic visit will be conducted at Week 1 to administer AISRS with expanded version, HADS, and BRIEF-A. Safety assessments (concomitant medications, adverse events, and suicide risk) will be conducted at all clinic and remote visits/phone calls (Week 5, and follow-up); safety labs will be conducted at screening, Week 3, and Week 6. For population PK analysis, PK sampling will be conducted at the Week 3 LC visit. Blood samples for PK will be collected prior to dosing and at 4 hours and 7 hours after dosing (with a 30-minute window). See Study Schema and Schedule of Events below.

The primary analysis will be on effects of 6-week treatment of NRCT-101SR versus placebo on performance (PERMP-C) and ADHD core symptoms (AISRS) in subjects with adult ADHD.

Randomization will be stratified by:

- Site
- LC Cohort
- Sex (approximately equal number of male and female in the study)

Figure 1 - Study Schema



4.2 Study Duration

Subject participation in the study will be approximately 13 weeks (up to 6 weeks of screening, 6 weeks of study drug administration and clinic visits, and 1 week of follow-up).

4.3 Selection of Study Population

The study will enroll approximately 216 subjects ≥ 18 years of age with ADHD. Study population will include male and female subjects of all race/ethnicity with ADHD, recruited from sites across US.

4.3.1 Inclusion Criteria

1. Male or female, ≥ 18 years of age at screening
2. Has a primary diagnosis of ADHD according to the DSM-5 classification, confirmed with MINI using DSM-5 probes
3. AISRS ≥ 26 at screening and baseline, and does not change by more than 25% from screening to baseline, except subjects who stop taking ADHD medication after screening may have increase of more than 25%
4. Has a minimum score of 4 on the CGI-S at Baseline
5. Must be fluent in English, and capable of reading, writing, and communicating effectively with others and willing to participate in laboratory classroom
6. Completion of at least 10 years of formal education
7. Hearing and Vision ability sufficient to complete cognitive testing, in investigator's opinion
8. Willing and able to give informed consent
9. Total Body weight (bw) ≥ 50 kg and ≤ 120 kg a[redacted]
10. Naïve to stimulant or non-stimulant medications used for the treatment of ADHD or have discontinued stimulants at least 2 weeks and non-stimulants at least 3 weeks prior to randomization

4.3.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria may not be enrolled in the study:

Exclusions to rule out subjects with impairment likely due to something other than ADHD:

11. Subject is functioning at an age-appropriate level intellectually, as judged by the investigator
12. Lifetime history of severe psychiatric symptoms of major depression requiring hospitalization, bipolar disorder, schizophrenia of schizoaffective disorder, hallucination, or delusions. Severe comorbid disorders such as PTSD, severe obsessive-compulsive disorder, or other symptomatic presentation that, in the opinion of the examining physician, will contraindicate NRCT-101SR treatment or confound efficacy or safety assessments. Subjects with mild to moderate forms of social phobia or dysthymia, for instance, may be included.

13. History of seizures (other than infantile febrile seizures), any tic disorder (except transient tic disorder and subject has no episodes for at least 1 year), or a current diagnosis of Tourette's Disorder
14. Recent history (within the past 1 year) of suspected substance abuse or dependence disorder (excluding stable nicotine use) in accordance with DSM-5 criteria. (Note: subject's average nicotine use should not be exceeded during each LC visit)
15. Current abnormal thyroid function as defined as abnormal screening thyroid stimulating hormone. Treatment for at least 3 months with a stable dose of thyroid medication is permitted.

Exclusions to rule out subjects with potential issues absorbing or metabolizing NRCT-101SR:

16. Poor kidney function; corrected estimated glomerular filtration rate (eGFRcorr) < 40 mL/min/m^2
17. History of significant gastrointestinal disorders, such as chronic diarrhea, irritable bowel syndrome, ulcerative colitis, Crohn's disease, etc.

Exclusions to rule out subjects with conditions that could affect their safety:

18. Female subjects who are pregnant and/or lactating
19. A "yes" answer to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at screening (in the past 12 months).
20. Has history of severe drug allergy or hypersensitivity to the study medication or its excipients.
21. Hypermagnesemia; magnesium > 2.5 mg/dL
22. Reproduction:
    a. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning 30 days prior to the first dose of study drug and throughout the study:
        i. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first study drug administration
        ii. Surgically sterile male partner
        iii. Simultaneous use of male condom and diaphragm with spermicide
        iv. Established hormonal contraceptive

b. Males must:

i. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of study drug, or

ii. Have been surgically sterilized prior to the Screening Visit.

Exclusions to rule out subjects with conditions that could inhibit or confound the effects of NRCT-101SR or the ability of the subject to complete the study:

23. Is currently participating in another clinical trial or has participated in a clinical trial within 30 days prior to the Screening Visit.
24. Currently living in an institutional facility such as a nursing home
25. Severe physical disability not associated with cognitive function that limits ability to complete testing (e.g., severe tremor, debilitating arthritis, etc.)
26. Known history of symptomatic cardiac disease, advanced atherosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary heart disease, transient ischemic attack or stroke or other serious cardiac problems.
27. Known family history of sudden cardiac death or ventricular arrhythmia.
28. Serious or unstable clinically important systemic illness or disease that, in the judgment of the investigator, is likely to affect cognitive assessment, deteriorate, or affect the subject's safety or ability to complete the study, including hepatic (e.g., Child-Pugh grade C), renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, infectious, or hematologic disorders
29. Has previously participated in a NRCT-101SR / [redacted] investigational study
30. Investigators and their immediate family members are not permitted to participate in the study.
31. Consumes more than a weekly average of: 2 drinks / day or more than 3 drinks in any day for males; 1 drink / day or more than 2 drinks in any day for females
32. Changes in medications or doses of medication as follows:

a. All allowed concomitant medications, supplements, or other substances must be at stable doses for at least 30 days prior to screening and must be kept as stable as medically possible during the trial. For allowed concomitant medications, any dosing change within 30 days of Screening may be allowed if, in the opinion of the investigator, it will not affect or influence study results.

4.4 Prior and Concomitant Medications

Prior treatments, defined as any treatment taken within 3 months or any ADHD drug taken within 6 months before screening, are to be recorded in the electronic case report form (eCRF) as prior

medications. Concomitant treatments, defined as treatments taken after the first dose of study drug, are to be recorded in the eCRF as concomitant medications.

If a change in medication dosage occurs during the study it may lead to discontinuation from study participation unless it relates to a medication that, in the view of the study investigator and in consultation with the medical monitor, does not affect the subject's participation in the trial or the study results. Any medication or therapy that is taken by or administered to the subject during the study should be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

After randomization, medication(s) to treat minor treatment-emergent illness(es) is generally permitted and subjects may be allowed to continue in the study after being evaluated by the clinician and discussed with the Sponsor. However, for certain classes of drugs (listed below; not inclusive of every drug and brand or generic name), subjects must follow dosing guidelines listed below (i.e., restricted medications/substances) and before Baseline visit and through the study, must not take ADHD stimulants for at least 2 weeks, ADHD non-stimulants for at least 3 weeks, and other prohibited substances for at least 4 weeks (or as listed below). Any subject taking these substances during the study will be evaluated by the Clinician (to be discussed with Sponsor) for ability to continue in the study.

Substance use will be collected in the eCRF at screening to document the subjects previous and current use of cannabis, nicotine/tobacco, caffeine, opioids, sedatives, and hypnotics. During LC days, caffeine is limited to one cup of coffee/caffeinated drink in the morning and one caffeinated drink at meals.

<u>The following are classes of medication used for treatment of ADHD and comorbid disorders that are prohibited during the study</u>:

- Classical drugs (CNS stimulants), including:
    - Amphetamines, Adderall, Dextroamphetamine, Lisdexamphetamine, Methamphetamine, Methylphenidate, Dexmethylphenidate
- Non-classical drugs (non-stimulant), including:
    - Atomoxetine, Modafinil, Viloxazine ER
- α2 adrenoceptor agonists (non-stimulant), including:
    - Clonidine, Guanfacine
- Any Antidepressants/ Anxiolytics / antipsychotics, such as (but not limited to):
    - Selective Serotonin Reuptake Inhibitor (SSRI), Amitriptyline, Bupropion, Buspirone, Clomipramine, Desipramine, Duloxetine, Imipramine, Milnacipran, Moclobemide, Nortriptyline, Reboxetine, Selegiline, Venlafaxine
- Miscellaneous other drugs
    - NMDA receptor blockers, such as Amantadine and Memantine-containing drugs (e.g., Namenda®)

- Mood stabilizers (for example, Carbamazepine, Valproate, lithium, and Lamotrigine)

Other prohibited/restricted medication/substances

- Marijuana / cannabinoids
- Alcohol
  - Men: greater than weekly average of 2 drinks / day or more than 3 drinks in any day
  - Women: weekly average of greater than 1 drink / day or more than 2 drinks in any day
- Calcium channel blockers, such as:
  - Felodipine (Plendil®); Amlodipine besylate (Norvasc®)
- [redacted]

All other supplements will be allowed only at the discretion of the study principal investigator.

4.5 Study Completion and Early Termination

A subject will be considered to have completed the study upon completion of the Visit 8 follow-up phone call 7 days after the Week 6 clinic visit. If a subject is discontinued at any time after

randomization into the study, the investigator will make every effort (refer to Site Operations Manual for guidance) to have the subject complete the final Visit 7 clinic visit/early termination (ET) assessments (as soon as possible after the discontinuation of study drug) as well as the Visit 8 follow-up phone call 7 days later. PERMP math tests will not be performed for the Early Termination Visit. Subjects who discontinue from the study treatment period will not be replaced.

An eCRF page should be completed for every subject who receives study drug, whether or not the subject completes the study indicating the reason for any early termination. It is important to distinguish the stopping rules between early termination of a subject from study drug and early termination of the study.

4.5.1 Stopping Rules for Subject Early Termination

Subject may be withdrawn from the study if any of the following occur:

a) Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for withdrawal. This includes serious and non-serious adverse events (SAE and NSAE) regardless of relation to the study drug.

b) Death: The subject died.

c) Withdrawal of Consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.

d) Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements, which compromises the safety of subject or data quality.

e) Lost to Follow-Up: The subject stopped coming for visits and study personnel were unable to contact the subject.

f) Other: Termination of study by sponsor.

g) ALT or AST > 3 times baseline with direct bilirubin > 2 times upper limit of normal (ULN) or international normalized ratio (INR) increased from baseline and is > 1.5 times ULN, unless the investigator in consultation with the Medical Monitor determines it is unlikely related to the study drug.

h) Creatinine > 1.8 times ULN and > 2 times baseline, unless the investigator in consultation with the Medical Monitor determines it is unlikely related to the study drug.

i) Magnesium > 3.0 mg/dL; > 1.23 mmol/L.

j) Study drug should also be discontinued in the setting of any SAE or a clinically significant grade 4 adverse event or confirmed grade 4 laboratory abnormality for an individual subject which is considered by the investigator in consultation with the Medical Monitor to be related to the study drug.

k) Intolerance to study drug.

4.5.2 Study Stopping Rules

The following are the study stopping rules which may lead to a pause in enrollment or cancellation of the study. The Medical Monitor will review the event that triggered the pause in enrollment with the Sponsor to determine study status.

a) Death in any subject in which the cause of death is assessed to be probably or definitely related to the study drug by the investigator and as confirmed by the medical monitor;

b) The occurrence in any subject of a life-threatening SAE assessed to be probably or definitely related to the study drug by the investigator and as confirmed by the medical monitor;

c) Two (2) occurrences of Grade 3 or higher (according to CTCAE scale) adverse events that are assessed to be definitely related to the study drug by the investigator and as confirmed by the medical monitor;

d) Two (2) occurrences of a clinically significant Grade 3 or higher (according to CTCAE scale) laboratory abnormality assessed to be definitely related to the study drug by the investigator and as confirmed by the medical monitor;

e) Any single SAE or ≥ grade 4 AE or laboratory abnormality unless the investigator determines it is unlikely related to the study drug and as confirmed by the medical monitor;

f) Any pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively represent a safety concern for the subject in the opinion of the investigator that are assessed to be at least possibly related to study drug and as confirmed by the medical monitor.

4.6 Study Drug

4.6.1 Details of Study Drug Administration

Information about the study drug is provided in the investigator brochure. Study drug will be provided by the Sponsor and transferred to study sites by the Sponsor. Study drug includes the active product – NRCT-101SR (375 mg and 500 mg), and corresponding placebos. NRCT-101SR is a sustained release formulation, dissolving in approximately [redacted] hours, consisting of 375 or 500 mg of [redacted] Subjects will take the study drug, via oral administration, in both morning and evening. Study drug MUST be taken immediately AFTER (within 30 minutes) eating a full meal. Study drug will be dispensed in bottles. Daily dosage will be administered as outlined in Table 1.

[redacted] Both morning and evening administrations must be taken orally within 30 minutes after eating a full meal.

[redacted]

[redacted]

4.6.2 Dosing Interruption

In consultation with the medical montitor and/or Sponsor, dosing interruptions are allowed at the discretion of the study Investigator in case of an AE occurrence believed to be related to study drug. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that dosing interruption is warranted, the Investigator should make every effort to contact the Sponsor and/or medical monitor prior to dosing interruption unless this could delay emergency treatment for the subject. If a subject's study intervention is interrupted, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the interruption must be recorded. Following study drug interruption, Investigator and Sponsor and/or medical monitor will determine whether the subject should be withdrawn from the study or study drug will be reinitiated.

Study drugs will be stored at the study center or pharmacy. It should be stored at 15ºC to 30ºC, ambient temperature.

4.6.3 Study Drug Description

NRCT-101SR (375 or 500 mg):

NRCT-101SR, 375 or 500 mg tablet is supplied as [redacted] round tablet for oral administration. In addition to 375 or 500 mg of the active ingredient, NRCT-101SR tablets contain the following inactive ingredients: [redacted]

Placebo:

Placebo tablets have the same physical appearance as the active study drug to preserve the blind. There are two placebos, one to match each of the active dosage strengths. The inactive ingredients include: [redacted]

All excipients used in the preparation of the NRCT-101SR, 375 and 500 mg and placebo tablets are compendial USP or NF grade materials, [redacted] which is composed of a mixture of compendial USP or NF grade materials. Each of the excipients have been used in FDA approved solid oral dosage forms and are listed in the FDA Inactive Ingredient Guide.

NRCT-101SR, 375 and 500 mg and placebo tablets are packaged [redacted] Each bottle contains 32 NRCT-101SR, 375 or 500 mg or placebo tablets.

Table 1 - Details of Study Drug

[redacted]

Subjects will take their first dose of NRCT-101SR or corresponding placebo the following day after the Baseline LC Visit and will continue morning and evening administration until the Week 6 visit. On the days of LC visits at week 3 and week 6, subjects will not take their daytime dose until arriving at the clinic and are instructed to do so by the study staff. Every effort should be made to take dosages at the same times each day.

Table 2 - Dosage Schedule [redacted]

[redacted]			Daily total	Total Tablets
Dosage	750 mg AM	750 mg PM	1,500 mg	4
[redacted]				
Dosage	1,000 mg AM	1,000 mg PM	2,000 mg	4

4.6.4 Study Drug Assignment

Eligibility must be confirmed (inclusion and exclusion criteria) for entry into this study. At the Baseline LC Visit, subjects will be assigned to one of two study arms (NRCT-101SR or placebo). Computer-generated randomization codes for each study arm will be assigned through IRT, with restrictions on total number of subjects assigned to each group, thereby limiting imbalance in numbers between groups. Randomization will be stratified by site and LC cohort to esnure approximately equal number of those on NRCT-101SR and placebo, and sex to ensure approximately equal numbers of male and female subjects in NRCT-101SR and placebo groups. At randomization, the subject will automatically be assigned by IRT unique subject bottle numbers from the available stock on-site. The IP dispensation, accountability and destruction status will be maintained in the IRT system. The subject randomization status will also be maintained in the IRT system.

If for any reason, after signing the informed consent form, the subject (who has passed screening) fails to be randomized, the reason for not being randomized should be recorded in the source documents and eCRF. Until the trial is concluded, the randomization codes will be blind to the study subjects as well as research coordinators, raters, and sponsor. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's study drug assignment unless this could delay emergency treatment for the subject. If a subject's study drug assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded. The Investigator is encouraged to maintain the blind as much as possible. The actual study drug assignment must NOT be disclosed to the subject and/or other study personnel including other site personnel, monitors, the sponsor or their delegates or project office staff; nor should there be any written or verbal disclosure of the randomization code or corresponding study drug assignment in any of the corresponding subject documents. Unblinding should not necessarily be a reason for study drug discontinuation.

4.6.5 Study Drug Packaging and Blinding

Initial study drug supply will be provided to sites by sponsor and resupply will be provided as needed per subject randomization at that site. Each bottle contains 32 tablets and enough bottles will be dispensed to subjects at their scheduled study visits to provide enough study drug until their next scheduled visit, including the allowed visit window.

An IRT system will be used to randomize subjects to either the active or placebo study drug as well as maintain blinding of the study drug assignment. In the event of an SAE, Neurocentria, in consultation with the investigator and medical monitor, will decide whether to unblind a given subject's study drug assignment, except in circumstances where the investigator believes it is in the subject's best medical interest to do so immediately.

The randomization codes will be stored electronically in a secure manner, which are only accessible to the designated unblinded study team member(s).

4.6.6 Study Drug Inventory and Accountability

Sponsor will ship the study drug as an overnight shipment to the site per the Certificate of Analysis document. Sites are required to verify receipt of the shipment within the IRT system by recording the bottles received and any damage or temperature excursions noted. The sites are required to notify the Sponsor if a temperature excusion occurs or the shipment contains damaged study drug so it can be quarantined as needed per Sponsor requirements. The study drug will be stored at the site per protocol. Sites needs to maintain a daily temperature monitoring log where the study drug is stored. The Sponsor and/or Contract Research Organization (CRO) needs to be notified immediately in case of any temperature excursion.

The investigator must keep an accurate accounting of the number of study drug bottles that are delivered to the site, dispensed to subjects, returned to the investigator by the subject, and returned to the sponsor or other disposition during and at the completion of the study, as recorded in the IRT system. The study drug is to be used in accordance with the protocol by subjects who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study drug received at the site before final disposition. At the end of the study, or as directed, all unused study drug will be returned to the sponsor.

4.6.7 Study Drug Compliance

Study drug is dispensed at the Baseline LC Visit and the Week 3 Visit during the study. Study drug bottles must be returned at Week 3 and Week 6 visits, as compliance will be assessed by tablet counts. Noncompliance is defined as taking less than 80% or more than 120% of study drug between each clinic visit. Subjects who are noncompliant with administration of study drug should be counseled about the study drug administration requirements at the scheduled visits, and documentation of counseling should be kept along with the source documents. Discontinuation for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

4.7 Overview of Study Visits

Total subject participation in the study is up to approximately 13 weeks, including a screening period (up to 6 weeks), a 6-week treatment period, and an approximate 1-week follow-up period:

- Screening period of up to 6 weeks: The Screening visit will include obtaining ICF signature and review of eligibility criteria per screening visit assessments. During the screening period, there will be an LC Orientation Visit to familiarize the subjects with the LC day. The LC

Orientation Visit should be within 8 days of the Baseline LC visit. The Baseline LC visit should be no more than 42 days from the original screening visit.

- Treatment period of 6 weeks: During the treatment period, study subjects will receive either NRCT-101SR or placebo. After the Baseline visit, there is one clinic visit (Week 1) and two LC visits (Week 3 and Week 6.). A remote visit will occur at Week 5. During the remote visit, concomitant medications, adverse events, and suicide risk information will be collected.
- Follow-up period: One week following last administration of study drug at the Week 6 clinic visit, concomitant medications, adverse events, and suicide risk will be assessed via a phone call with subjects.

Unless otherwise indicated, all assessments will be performed by the investigator or designated study personnel. At the investigator's discretion, subjects may attend unscheduled visits for evaluation of reported adverse events and laboratory retesting, as necessary. Subjects that meet the criteria for withdrawal from the study should make every effort (refer to the Site Operations Manual for guidance) to complete the Early Termination and Follow-Up visit assessments.

4.7.1 Rationale for Study Visits

This study is a parallel design planned for 6 weeks of administration of NRCT-101SR, a sustained release tablet formulation with the API [redacted] or 6 weeks of placebo. Previous studies in adult ADHD subjects and subjects with neuropsychiatric symptoms and/or cognitive impairment show effects of [redacted] within 1-6 weeks. Specifically, in adult ADHD subjects, reduction in ADHD symptoms and improvement in quality of life and cognition are observed by 3 weeks and maintained through 12 weeks of [redacted] administration. Evaluations at 3 and 6 weeks should be sufficient to observe effects of NRCT-101SR on ADHD symptoms and cognition.

In support of safety for 6 week administration of NRCT-101SR, Sponsor has conducted 7 efficacy clinical trials with study drug containing [redacted] ranging from one week to 24 weeks. Five of these clinical trials were 8-24 weeks in length, including a 12 week study in subjects with Adult ADHD (NC-004). In these trials, safety assessments (physical exam, ECG, and safety labs) were conducted as part of in-clinic visits at baseline, every 6-12 weeks during the study, and at the end of study visit. These studies provide relevant safety information for the population and support safety of at least 6 week exposure of NRCT-101SR.

In previous studies, effects on emotional regulation and overall mood have been observed by approximately [redacted] of NRCT-101SR administration and effects on ADHD symptoms were observed at the first timepoint of [redacted]. [redacted] Administration of AISRS at Week 1 will allow for evaluation of rapid-acting effects of NRCT-101SR compared to placbeo. This is an important assessment considering most other non-stimulant ADHD drugs may require up to 4-6 weeks for clinically meaningful effects (Wietecha, Clemow et al. 2016).

In line with previous studies, all safety assessments in this study will be performed at 6 weeks with additional evaluations done in clinic and on the phone at interim timepoints. A follow-up phone call one week after cessation of study drug will evaluate AEs, concomitant medications, and

suicidal risk. Considering the short half-life of NRCT-101SR ([redacted] hour), one week should be sufficient time to evaluate any effects of study drug cessation.

4.7.2 Schedule of Events

The procedures to be performed throughout the study are outlined in the Schedule of Events (Table 3).

Table 3 - Schedule of Events

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/-3 days)	Day 43	Day 50 (+/-2 day)
Informed Consent	X							
Eligibility Review	X		X					
Randomization			X					
Demographics & Medical History	X							
Substance Abuse History	X							
Prior/Concomitant Meds	X	X	X	X	X	X	X	X
Physical Exam	X		X		X		X	
MINI with DSM-5 probes	X							
Vital Signs including weight	X	X	X		X		X	
Height	X							
Safety Labs/Urinalysis	X		X[f]		X		X	
Urine pregnancy	X		X					
Urine Drug Screen	X		X		X		X	

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/-3 days)	Day 43	Day 50 (+/-2 day)
[redacted]			X				X	
ECG			X				X	
PK Sampling[a]					X			
AISRS with expanded version	X		X[g]	X[g]	X[g]		X[g]	
[redacted]			X		X		X	
CGI-S	X		X	X	X		X	
[redacted]			X		X		X	
AAQoL			X		X		X	
BRIEF-A			X	X	X		X	
HADS			X	X	X		X	
C-SSRS (Baseline/Screening version)	X							
C-SSRS (since last visit version)		X	X	X	X	X	X	X
[redacted]			X		X		X	
PERMP placement	X							
PERMP practice[c]	X	X						
PERMP			X[bg]		X[bg]		X[bdg]	
Adverse Events				X	X	X	X	X

Schedule of Events	**Screening**	**LC Orientation**	**Baseline (LC)**	**Week 1 (clinic)**	**Week 3 (LC)**	**Weeks 5 (remote)**	**Week 6 or ET (LC)**	**Week 7 Follow-up (remote)**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/-3 days)	Day 43	Day 50 (+/-2 day)
Study Drug Dispensation			X		X		X[e]	
Study Drug Accountability					X		X	

ET = early termination; LC = Laboratory Classroom; AISRS = ADHD Investigator Symptom Rating Scale; ECG = electrocardiogram; [redacted]; CGI-S = Clinician Global Impression - Severity; [redacted]; AAQoL = adult ADHD Quality of Life; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult; HADS = Hospital Anxiety and Depression Scale; C-SSRS = Columbia Suicide Severity Rating Scale; PERMP = Permanent Product Measure of Performance; PK = Pharmacokinetic (samples collected pre-dose and post-dose); [redacted]

[redacted]

4.7.3 Study Procedures

4.7.3.1 Screening Visit: Visit 1 (day -42 to day -2)

The assessments during the screening phase will determine the subjects' eligibility for the study and their ability to comply with protocol requirements by completing all screening assessments.

The following procedures will be performed and recorded during the screening period:

- Obtain informed consent from study subject
- Review inclusion and exclusion criteria for eligibility. Any subject that does not meet inclusion/exclusion criteria may be rescreened with Sponsor approval
- Confirm ADHD diagnosis (MINI with DSM-5 probes)
- Administer AISRS with expanded version
- Administer CGI-S
- Urine pregnancy and drug screen
- Evaluate Demographic information (age, sex, race, ethnicity) and medical history including significant medical illnesses and conditions, including history of diabetes, hypertension, and smoking, etc.
- Collect substance abuse history
- Collect Prior and Concomitant medications information (also reference the prohibited medications/substances list)
- Physical exam
- Vital signs and body weight
- Measure height (cm)
- Administer the C-SSRS, Baseline/Screening version
- Administer PERMP placement and practice tests (x3)
- Collect samples for Safety Labs, including urinalysis

Formula for calculating Corrected eGFR (eGFRcorr)

To allow for comparison between individuals, eGFR is typically normalized to body surface area (BSA) because high filtration rates are needed for people with larger bodies to maintain the same amount of clearance as people with smaller bodies. Typically, 1.73 m^2, the BSA of the average size male, is used when calculating eGFR, resulting in final eGFR units of mL/min/1.73m^2. However, when normalizing to a set BSA, values may be erroneously high for people with a BSA greater than average and erroneously low for people with a BSA lower than average. To avoid this problem, eGFR should be corrected using the following calculation:

$$eGFR_{corr} = \frac{eGFR * 1.73}{BSA},$$

where

$$BSA = 0.007184 * weight_{(kg)}{}^{0.425} * Height_{(cm)}{}^{0.725}$$

$eGFR_{corr} < 40$ mL/min/m^2 is exclusionary.

4.7.3.2 LC Orientation Visit: Visit 2 (Day -8 to day -1)

- Review prior and concomitant medications
- Administer C-SSRS, since last visit version
- Administer PERMP practice tests (x5)
- Vital signs and body weight

4.7.3.3 Baseline LC Visit: Visit 3 (day 1)

Baseline visit must begin in the early morning to allow adequate time to complete all procedures.

Since meals are required prior to administration of study drug, meals will be provided at this visit as per the LC schedule (refer to LC manual) to replicate what will be done on Week 3 and Week 6 LC visits.

- Review of eligibility criteria for subject randomization
- Review concomitant medications
- Physical examination
- Vital signs and body weight
- Urine Pregnancy and drug screen
- [redacted]
- Electrocardiogram
- Administer PERMP per LC schedule (refer to LC manual) and provide PCRS* prior to administration of first PERMP math test of the day
- Administer AISRS with expanded version (provide PCRS* prior to administration)
- [redacted]
- Administer CGI-S
- [redacted]
- Administer AAQoL

- Administer BRIEF-A
- Administer HADS
- Administer C-SSRS, since last visit version
- [redacted]
- Collect samples for Safety Labs, including urinalysis (Does not need to be collected if screening visit results are within 30 days of the Baseline visit. However, samples may still be collected to confirm subject eligibility as needed)

Provide the subject with study drug for home use with first dose taken the following morning (provide written and verbal instructions on how to take the product).

* PCRS will be administered only once per visit prior to PERMP or AISRS assessments whichever occurs first.

4.7.3.4 Week 1 Clinic Visit: Visit 4 (+/- 1 day)

A clinic visit will be conducted at Week 1 (± 1 day). During this visit, the following procedures will be conducted:

- Review concomitant medications
- Review adverse events
- Administer AISRS with expanded version (provide PCRS prior to administration)
- Administer CGI-S
- Administer BRIEF-A
- Administer HADS
- Administer C-SSRS, since last visit version

4.7.3.5 Week 3 LC Visit: Visit 5

Prior to arriving at clinic, subjects should NOT have taken study drug. Subject will take study drug at LC visit when instructed, within 30 minutes after eating a meal.

- Review concomitant medications
- Review of adverse events
- Physical examination
- Vital signs and body weight
- Collect samples for Safety Labs, including urinalysis
- Urine drug screen
- Administer PERMP per LC schedule (refer to LC manual) and provide PCRS* prior to administration of first PERMP math test of the day

- Collect PK samples (pre-dose and at hours 4 and 7 post-dose with a 30-minute window for completion of sampling)
- Administer study drug in clinic (morning and evening doses)
- Administer AISRS with expanded version (provide PCRS* prior to administration)
- [redacted]
- Administer CGI-S
- [redacted]
- Administer AAQoL
- Administer BRIEF-A
- Administer HADS
- Administer C-SSRS, since last visit version
- [redacted]
- Provide subject with study drug for home use (provide written and verbal instructions on how to take the product).
- Perform study drug accountability

* PCRS will be administered only once per visit prior to PERMP or AISRS assessments whichever occurs first.

4.7.3.6 Week 5 Remote Visit: Visit 6 (+/- 3 days)

A remote visit will be conductedat Week 5 (± 3 days). During this visit, the following procedures will be conducted:

- Review concomitant medications
- Review adverse events
- Administer C-SSRS, since last visit version

4.7.3.7 Week 6 LC Visit/ET: Visit 7

Prior to arriving at clinic, subjects should NOT have taken study drug. Subject will take study drug at LC visit when instructed, within 30 minutes after eating a meal as per the LC manual. For those subjects that have discontinued study drug, the following procedures excluding PERMP will be conducted as soon as possible after discontinuation of the study drug.

- Review concomitant medications
- Review of adverse events
- Physical examination
- Vital signs and body weight

- Collect samples for Safety Labs, including urinalysis
- Urine drug screen
- [redacted]
- Electrocardiogram
- Administer PERMP per LC schedule (refer to LC manual) and provide PCRS* prior to administration of first PERMP math test of the day
- Administer study drug in clinic (morning and evening doses)
- Administer AISRS with expanded version (provide PCRS* prior to administration)
- [redacted]
- Administer CGI-S
- [redacted]
- Administer AAQoL
- Administer BRIEF-A
- Administer HADS
- Administer C-SSRS, since last visit version
- [redacted]
- Perform study drug accountability

* PCRS will be administered only once per visit prior to PERMP or AISRS assessments whichever occurs first.

4.7.3.8 Week 7 Remote Follow-up Visit: Visit 8 (+/- 2 days)

- Review concomitant medications
- Review adverse events
- Administer C-SSRS, since last visit version

4.7.4 LC Visit Days

During the LC visit day, subjects will be grouped in cohorts where they will complete scheduled PERMP math tests and other assessments throughout the day. Subjects' activities, behavior, and function will be monitored. Cohorts may contain 10-12 subjects; any cohort size smaller or larger requires sponsor approval.

AEs and con meds will be reviewed, and vitals will be collected at these visits. A pre-dose PERMP math test will be administered as well as a total of 6 post-dose PERMP math tests throughout the day, approximately every two hours. In between PERMP math tests, subjects will complete other

assessments per the schedule of events. Study drug will be provided according to the dosing schedule. Refer to the LC manual for more detailed information on the LC schedule.

An LC Orientation Visit is scheduled to familiarize the subjects with the LC visit days (Baseline, Week 3, and Week 6). The orientation day is similar to the other LC visit days except the time between PERMP administrations is shorter (a minimum of 20 minutes apart from start to start). Refer to the LC manual for more details.

4.8 Efficacy Assessments

4.8.1 Dual Primary Efficacy Assessments

4.8.1.1 Permanent Product Measure of Performance (PERMP)

The Permanent Product Measure of Performance (PERMP) is a skill adjusted math test. It is a series of 10-minute age-appropriate math tests consisting of five pages of 80 math problems each. The level of difficulty is established during a pretest administered at the screening visit. There is one of four difficulties that the subject is assigned to for the duration of the study (difficulty level assignment can be changed prior to the first baseline timepoint if difficulty is determined to be considerably too easy or too difficult).

PERMP-C is the number of math problems answered correctly in a 10-minute session and typically ranges from 0-400 with higher scores indicating better performance. The PERMP total score (PERMP-T) is the sum of the number of math problems attempted (PERMP-A) plus the number of math problems answered correctly (PERMP-C). The PERMP-T scores typically range from 0-800 with higher scores indicating better performance.

To limit learning effects, subjects will complete practice PERMP tests at screening and the LC Orientation Visit. Placement and practice PERMP tests are administered as follows (refer to the LC manual for more details):

- Screening
    - Placement test
    - 3 practice tests (with a minimum of 20 minutes apart from start to start)
- LC Orientation Day
    - 5 practice tests administered during the classroom period according to LC schedule (with a minimum of 20 minutes apart from start to start)

PERMP tests for analysis will be administered at Baseline, Week 3 and Week 6 LC visits.

For each LC visit, PERMP tests will be administered pre-dose and at 2, 4, 6, 8, 10, and 12-hours post dose. For analysis, the average of PERMP-C scores at the post-dose timepoints at the Baseline LC visit (however, no dosing) will serve as the baseline value. For evaluation of effects, the average of the PERMP-C scores at the post-dose timepoints at Weeks 3 and 6 will be used.

4.8.1.2 ADHD Investigator Symptom Rating Scale (AISRS)

The ADHD Investigator Symptom Rating Scale (AISRS) consists of 18 items scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms) with a total score ranging from 0 to 54. Each item has multiple prompts; the highest score that is generated from each prompt should be used as the score for that item. Responses from the 18 items will be used to assess the primary efficacy endpoint for AISRS. The expanded version has an additional 13 accessory questions which will be used to assess a secondary endpoint. Evaluations will be based on symptoms over the week prior to the administration.

The AISRS with expanded version will be administered at Screening, Baseline, Week 1, Week 3, and Week 6 to evaluate effects of NRCT-101SR on core ADHD symptoms. Administration of AISRS at Week 1 will allow for evaluation of rapid-acting effects of NRCT-101SR compared to placbeo.

4.8.1.3 Placebo-Control Reminder Script (PCRS)

The Placebo-Control Reminder Script (PCRS)© Hassman and Cohen, 2019, Version 5.0 educates clinical study subjects of key causes of the placebo and nocebo effects, namely the tempering of study expectations, reminding study subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with previous providers. To do this, the PCRS informs subjects that they are to be honest about their symptoms, site staff have no expectations of symptom improvement or worsening and will not be disappointed if they feel better, worse or the same, and asks subjects to explain in their own words its content to ensure comprehension. Per the instructions on the PCRS, site staff will read the script verbatim immediately before administering the AISRS with expanded version at the Week 1, 3 and 6 visits as well as the first PERMP test at the Week 3 and 6 visits. The PCRS is read to each subject typically taking about 3 minutes to read. The PCRS has been empirically found to significantly manage (reduce) the placebo and nocebo effects (Cohen, Hassman et al. 2021).

4.8.2 Key Secondary Efficacy Assessments

4.8.2.1 Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)

The BRIEF-A is a standardized self-report measure of executive functions/self-regulation in an everyday environment. It includes 75 items with nine overlapping clinical scales including inhibit, self-monitor, plan/organize, shift, initiate, task monitor, emotional control, working memory, and organization of materials. All items are rated in terms of frequency on a 3-point scale (0 = never, 1 = sometimes, 2 = often). Raw scores for each scale are summed for an overall summary score – the Global Executive Composite (GEC) - and T scores (mean = 50, standard deviation = 10) are determined. BRIEF-A will be administered at baseline, Week 1, Week 3, and Week 6.

4.8.2.2 Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 items, divided into two 7 item subscales: anxiety (HADS-A) and depression (HADS-D). HADS-A questions reflect a state of generalized anxiety and HADS-D focuses on the concept of anhedonia. Subjects will rate each of the questions on a 4-point scale

ranging from 0 (absence) to 3 (extreme presence). Scores will be derived by summing responses for each of the two subscales or for the scale as a whole, and the total score is out of 42, with higher scores indicating higher severity of symptoms. HADS will be administered at baseline, Week 1, Week 3 and Week 6.

4.8.3 Other Secondary Efficacy Assessments

4.8.3.1 Clinical Global Impression - Severity (CGI-S)

The CGI-S is a brief assessment tool that measures clinician's impression of illness severity. Evaluation includes information from the subject and may include information from the subject's medical history, physical exam, or other ratings done at screening. CGI-S assesses the severity of the subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). CGI-S will be administered at screening, baseline, and Weeks 1, 3 and 6.

4.8.3.2 Adult ADHD Quality of Life Scale (AAQoL)

The AAQoL is a 29-item self-reported scale evaluating aspects of quality of life in ADHD patients. It consists of a total score of 4 subscales, including life productivity, psychological health, life outlook, and relationship. Items are scored on a 5-point scale ranging from 1 (not at all/never) to 5 (extremely/very often). Raw scores are transformed to a 0 to 100 scale with higher scores indicating a better quality of life. AAQoL will be administered at baseline and Weeks 3 and 6.

4.9 Exploratory Assessments

4.9.1 [redacted]

[redacted]

4.9.3 Exploratory [redacted]

[redacted]

4.10 Safety Assessments

4.10.1 Physical Exam

A general physical examination is to be performed by a qualified health care practitioner as designated by and trained on the protocol by the PI. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Delegation of Authority Log. Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and central nervous system. Any clinically significant changes after the first dose of the study drug and up to the last study procedure must be recorded on the AE eCRF. Height without shoes will be recorded in cm at screening.

A physical exam will be performed at screening, baseline, and Week 3 and 6 clinic visits.

4.10.2 Vital Signs and Body Weight

Vital signs and body weight may be collected by a qualified health care practitioner as designated by and trained on the protocol by the PI. Vital signs will include body temperature (°F), respiratory rate (per minute), sitting radial pulse rates (beats per min – bpm), and sitting systolic and diastolic blood pressures (mmHg). Vital signs are to be collected after subject has been sitting for at least 5 minutes. Body weight without shoes will be recorded in kilograms whenever vital signs are recorded.

Vital signs and body weight will be evaluated at screening, LC Orientation Visit, baseline, Week 3, and Week 6.

4.10.3 Electrocardiogram

Standard 12-lead ECGs will be taken to identify a multitude of cardiac disease processes and examine any changes throughout study participation. ECG is to be collected by a qualified health care practitioner as designated by and trained on the protocol by the PI. The following parameters need to be collected - heart rate, cardiac rhythm, PR interval, QRS interval, QT interval, and QTc

interval.The ECG needs to be reviewed by the study physician and/or appropriately-trained specialist to rule out any clinically significant abnormal findings. Any clinically significant abnormal findings on the ECG after the first dose of study drug must be recorded on the AE eCRF.

ECG will be evaluated at baseline and Week 6 clinic visit.

4.10.4 Columbia Suicide Severity Rating Scale (C-SSRS)

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is the C-SSRS. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior. The scale can be completed as an interview or as a self-report.

At the Screening Visit, the C-SSRS Baseline/Screening version will be administered. This version is used to assess suicidality over the participant's lifetime and the last 12 months.

At all other visits, the Since Last Visit version of the C-SSRS will be administered. This version of the scale assesses suicidality since the subject's last visit.

If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the subject during the administration of the C-SSRS, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the subject's safety. The site must ensure that the subject is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. For visits post the Baseline visit, the investigator in consultation with the Sponsor will determine whether the subject should remain on study drug.

It is recommended that a medically licensed physician, nurse, nurse practitioner, or physician assistant assess the C-SSRS. All evaluators must be certified to perform the C-SSRS. Certification is required prior to performing the C-SSRS.

The C-SSRS will be administered at all Visits (including remote visits).

4.10.5 Adverse Events

All AEs occurring or worsening after the subject takes the first dose of study drug and up to the last study visit will be recorded in the AE eCRFs. The definition of adverse events and reporting requirements of adverse events are explained in the Adverse Event Reporting section. The evaluation for safety includes determination of percentage of subjects who reported adverse events between the active treatment group and placebo group in the study.

Tolerability will be calculated as the proportion of subjects who discontinue from the study due to any adverse event. An Odds Ratio will be calculated as the ratio of the tolerability in the NRCT-101SR group to the tolerability in the placebo group.

AEs will be reviewed at all visits (including remote visits) beginning at the Baseline LC Visit.

4.10.6 Laboratory Parameters

4.10.6.1 Safety Labs - Blood

General safety laboratory testing will be performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified central laboratory, Eurofins, using standard clinical pathology methods.

The following blood tests are completed as part of safety labs.

- *Complete Blood Count (CBC) with differential*: RBC, WBC, Hgb, hematocrit (Hct), MCV, MCH, MCHC, RDW, Platelets, MPV and absolute cell counts.
- *Chemistry and metabolic panel:* Alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, magnesium, potassium, sodium, total bilirubin, total protein, and creatine phosphokinase (CPK).

The samples will be collected and analyzed using routine methods per the central laboratory's guidelines. In the event of an unexplained clinically significant abnormal laboratory test value, the test should be repeated immediately at an unscheduled visit and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Safety labs will be performed at Screening, Baseline, Week 3, and Week 6 Visits. Baseline safety labs do not need to be collected if screening visit results are within 30 days of the Baseline visit. However, samples may still be collected to confirm subject eligibility as needed.

4.10.6.2 Urinalysis

Urine pregnancy tests and urinalyses will be performed at the study sites.

- Urinalysis is performed in clinic as part of the safety labs at screening, baseline, week 3 and week 6 including:
  - pH of freshly voided specimen, specific gravity, protein, glucose, ketones, blood, nitrite, bilirubin, urobilinogen using a dipstick
  - microscopic examination will only be performed at the central laboratory if results from two consecutive tests noted above are abnormal; sites will send the abnormal sample to the central laboratory for further examination
- Other urine tests
  - Pregnancy: to be performed at screening and baseline in clinic using a pregnancy dipstick
  - drug screen: to be performed in clinic using a dipstick at Screening, Baseline, Week 3 and 6 visits; includes a 10-panel drug screen for cocaine, amphetamines, methamphetamines, tetrahydrocannabinol, methadone, opioids, phencyclidine, barbiturates, benzodiazepines, and tricyclic anti-depressants

4.11 Additional study assessments

4.11.1 Specialty Laboratory Assessments

[redacted]

4.11.2 MINI with DSM-5 Probes

The ADHD module (Module Q) of the MINI will be administered at Screening to confirm the subject has a diagnosis of Adult ADHD. The questionnaire will be administered electronically.

4.11.3 PK Sampling

For pharmacokinetic analyses, evaluation of NRCT-101SR blood concentrations will be performed using a validated assay at a contract laboratory designated by the sponsor. Samples from a minimum of 120 subjects will be analyzed by the lab. Samples will be collected at the Week 3 visit at the pre-dose, 4- and 7-hour post-dose timepoints (with a 30-minute window for completion of sampling).

5.0 ADVERSE EVENT REPORTING

Throughout the course of the study, all AEs will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, seriousness, severity, action taken, outcome and relationship to the studydrug. AEs and SAEs will be collected from the time of first dose through the last follow-up visit at Week 7. All events prior to this will be documented as medical history. If AEs occur, the first concern will be the safety of the study subjects. All AEs should be followed by the investigator until resolved or stable.

5.1 Definitions and Criteria

5.1.1 Adverse Events

Per International Conference on Harmonization (ICH) E2A: An AE is "any untoward medical occurrence in a patient or clinical investigation patient administered apharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. 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."

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. Only the medical condition should be recorded as an AE in the AE eCRF. Any medications given as a result of treating the AE should be recorded on the Concomitant Medications eCRF.

5.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not meet the above criteria but may be considered serious when, based upon appropriate medical judgment, that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Suicidal ideation and behavior will be monitoried via C-SSRS throughout the study. While not necessarily considered a serious adverse event, throughout the trial, an affirmative response on the C-SSRS may require a referral to a trained mental health professional, an emergency psychiatrist evaluation, or other relevant resource.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours’ duration may be rated as severe but may not be considered serious.

5.1.3 Unexpected Adverse Reactions

An unexpected adverse reaction (UAR) is a reaction for which the nature or severity is not consistent with the applicable information in the Investigator’s Brochure. Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected.” Specific examples would be (a) acute renal failure as a labeled UAR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in the Reporting Procedures and Requirements section.

5.1.4 Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or that has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study drug
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

5.2 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the study drug:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study drug.

5.2.1 Intensity

Each AE will be classified according to the following criteria (Table 4):

Table 4 - Criteria for Intensity Grading of Adverse Events (CTCAE Severity Grading)

Grade 1 Mild:	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of dailing living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3 Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4 Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

5.2.2 Relationship

The investigator will evaluate the causal relationship of each AE to a study drug and/or to a study procedure (e.g., venipuncture or ECG evaluation) and record that relationship on the appropriate CRFs. Causality will be assessed considering whether the AE is reasonably related to the study drug or procedure or whether the AE is not reasonably related to the study drug or procedure considering the definitions in Table 5.

Table 5 - Criteria used for Determining Causality of Adverse Events to Study Drug Administration

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

When assessing the relationship to the study drug, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping suspect the study drug, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

5.3 Reporting Procedures and Requirements

5.3.1 Adverse Events

Adverse events occurring from when the subject signs the ICF until the last study visit will be recorded in the eCRFs. Any AEs occurring before the start of study drug administration (ie, before the first dose of the study drug) will be recorded in the medical history. Any sign, symptom, or disease present before starting the administration of the study drug are only considered AEs if they worsen after starting the administration.

If the investigator detects an AE in a study subject after the last scheduled follow-up visit and considers the event at least possibly related to prior study drug administration, the investigator is to report it to the sponsor.

The investigator should report all AEs on the AE eCRF and within source documentation, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., “common cold” or “upper respiratory infection” rather than by the symptoms “runny nose, cough, mild fever”) and should be assessed for the attributes described in the Assessing Intensity and Relationship Section.

5.3.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (refer to the Serious Adverse Events Section). If the AE is considered serious, the investigator should report this event to Neurocentria or their designee as outlined below and to the institutional review board (IRB) according to its standard operating procedures.

If the investigator detects an SAE in a study subject after the last scheduled follow-up visit and considers the SAE at least possibly related to prior study drug use, the investigator is to report it to the sponsor.

All information about SAEs will be collected and reported digitally via an electronic form. The investigator should complete the initial report within 24 hours of becoming aware of the SAE. At minimum, the initial report should include the following information:

1. Event
2. Protocol Number
3. Subject number, initials, and date of birth

4. Study drug
5. Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and for reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports). The sponsor or its designee will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

The sponsor must report in an IND safety report any Suspected Unexpected Serious Adverse Reactions (SUSARs) defined as a suspected adverse reaction to study drug (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the criterion below:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three criterion, it should not be submitted as an IND safety report. SUSARs will be reported to regulatory authorities within 7 calendar days for life threatening and fatal events, or 15 calendar days for all others. These timeframes begin with the first notification of the event from the reporting investigator to the sponsor (or designee), which represents the start of the regulatory clock (Day 0).

The sponsor (or designee) will also provide all investigators with a safety letter describing the SUSAR. The information will be provided by e- mail within 15 calendar days from Day 0.

5.3.3 Pregnancy

Each female subject should be instructed to inform the investigator immediately if she becomes pregnant at any time between the start of study screening until 30 days after the last administration of study drug. All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Follow-up information regarding the outcome of the pregnancy will be required to be reported on the pregnancy notification form.

6.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

6.1 Data Management Considerations

Electronic CRFs (eCRFs) will be employed for this study. Data will be entered into electronic CRFs within 3 business days by the investigator and/or the investigator's dedicated site staff. Queries are to be responded to in a similar fashion. Data entered onto eCRFs are stored on a secure server and accessed via a secure website. The EDC system will be designed and validated by Neurocentria prior to activation for data entry by sites. The investigator must review data entered and electronically sign the eCRFs to verify their accuracy.

This study will utilize EDC, a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. EDC software provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of subject data, and variations of data exporting/importing.

Access to the EDC system for data entry or review will require documentation of training. Data are collected within the EDC system to which the sponsor and site monitors have "read only" access. eCRF data will be reviewed routinely by sponsor and/or sponsor designated monitors.

6.1.1 Data Clarification

Sponsor and/or sponsor delegates may have questions or note discrepancies on entered data, as referred to as queries. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The sponsor and its delegates are the only parties that can generate a Manual Query. Entered data that falls outside parameters set by sponsor according to protocol may also create a System Generated Query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the time changes were made, and reason for change. If changes are made to a previously electronically signed eCRF, the investigator must confirm the changes and re-sign the page.

The statistical analysis of these data will be performed by the sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary. Data management details will be outlined in a separate data management plan.

6.2 Statistical Considerations

The statistical analysis will be undertaken by the sponsor or its representative.

A detailed Statistical Analysis Plan (SAP) will be finalized and signed before database lock, before the randomization code for all subjects is broken, and before analysis of the study is carried out. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

6.2.1 Statistical Methods

Descriptive summaries of variables by treatment group will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated by treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment group. All statistical comparisons will be tested at two-sided alpha=0.05; however, only those included in the multiplicity algorithm will be considered for significance.

6.2.2 Power/Sample Size Analysis

Previous studies of ADHD drugs using PERMP as the primary endpoint showed improvement of ~10% with effect sizes approximately 0.4-0.7 (Wigal, Brams et al. 2010, Wigal, Brams et al. 2011, Wigal, Childress et al. 2018). In one study, Wigal et. al. reported a mean difference between treatment and placebo of 23.4 with a standard deviation of approximately 40.5 (effect size = 0.58) (Wigal, Brams et al. 2010). The effect size of currently approved ADHD drugs on reduction of core symtpom measurements is approxmatly 0.5-1.0 (Cortese, Adamo et al. 2018).

To determine expected effect size for this study, Sponsor considered the effects of treatment on performance and core symptom reduction separately. In several previous studies with study drug, a cognitive performance evaluation was adminsitered with an improvement of approximatley 10% with active treatment. Typically, a 10% net improvement over placebo in PERMP is observed with ADHD drugs, with an effect size of approximatley 0.7 (Wigal, Brams et al. 2010, Wigal, Brams et al. 2011, Wigal, Childress et al. 2018). For reduction of core symptoms, NC-004 study showed reduction of AISRS with study drug was approximately 25%. With an estimated starting AISRS score of approximately 35 points, a 25% improvement is approximatley -8 to -9 points. Since the standard deviation of change for AISRS is approximately 13.5 (Spencer, Adler et al. 2010), the effect size is approximately 0.65. Based on this, Sponsor conservatively estimates an effect size of 0.5 for PERMP and AISRS in this study.

Sample size estimates for power = 85% were calculated using the following assumptions:

- 1:1 randomization ratio between placebo and NRCT-101SR
- Two-sample t test
- Two sided alpha = 2.5%
- Effect size = 0.5

Based on these, the total sample size for 85% power = 172. Due to the dual pimary outcomes and alpha control adjustment, an alpha of 0.025 is utilized and power is based on the above assumptions for PERMP; it is possible that the overall power, taking into account the additional primary of AISRS, is greater than 85%.To account for attrition increased variaiblity due to dropout, a total of approximately 216 subjects (108 in each treatment group) are planned for 85% power.

6.2.3 Analysis Populations

The analysis populations will include the following:

- The Safety Population will include all subjects who receive at least one dose of study drug. Subjects will be analyzed as treated.
- The Intent-To-Treat (ITT) population will include all subjects who are randomized. Subjects will be analyzed as randomized. The ITT population is the primary population for the efficacy analyses.
- The Modified Intent-To-Treat (MITT) population will include all subjects who are randomized, receive at least one dose of study drug, and have at least one non-missing post-baseline efficacy measurement (PERMP-C or AISRS). Subjects will be analyzed as randomized.
- The Per Protocol (PP) population will include all subjects in the mITT population who did not incur a protocol violation that impacts the efficacy evaluation. Subjects will be analyzed as randomized.

6.2.4 Protocol Deviations

Summaries of key protocol deviations are to be maintained on the study protocol deviation log. Protocol deviations should be collected and grouped into different categories, such as:

−those who entered the study even though they did not satisfy the entry criteria;

−those who met withdrawal criteria during the study but were not withdrawn;

−those who received the wrong study drug, incorrect dose, or who had poor study drug compliance;

−those who received an excluded concomitant treatment.

Major protocol violations will be determined by the principal investigator and sponsor prior to the unblinding of data and will lead to exclusion from the PP population.

6.2.5 Subject Disposition

The number of screening failures, study completers, and early terminations will be summarized. The number of subjects in each analysis popualtion will also be summarized.

6.2.6 Demographic and Baseline Characteristics

The baseline data will be summarized using the Safety, MITT, ITT, and PP populations.

6.2.7 Measurement of Study Drug Compliance

Compliance is defined as taking at least 80% but not more than 120% of study drug between each clinic visit. Subjects will return all bottles and unused tablets at each clinic visit. The number of tablets taken divided by the number of tablets the subject should have taken in between visits multiplied by 100% will be used to calculate study drug compliance.

6.3 Efficacy Analyses

6.3.1 Dual Primary Estimand #1 PERMP-C

- **Population**

The target population is adults with ADHD as defined by the inclusion/exclusion criteria.

- **Variable**

This primary efficacy endpoint is defined as the change from Baseline to Week 6 in mean PERMP-C score over course of the visit (post-dose).

- **Intercurrent Events**

A hybrid approach of treatment policy and hypothetical strategy will be used to address intercurrent events of study discontinuation. No special data handling will be used for other intercurrent events, such as subjects who initiate concomitant medications. Likewise, subjects that discontinue treatment but return for the Week 6 visit will have those data analyzed as reported. Subjects that discontinue the study due to adverse events and lack of efficacy and consequently have missing data at Week 6 are assumed to be representative of subjects that would not continue to use the drug outside of a clinical trial and their missing values following discontinuation will be imputed using multiple imputation based off the distribution of placebo values at the matching time point, conditioned on the observed data (including baseline) and sex. All other missing values (both intermittent and following study discontinuation will be imputed using multiple imputation assuming that they are missing at random, conditioned on the observed data (including baseline) and sex. Sensitivity analyses will explore the results under different analysis assumptions.

- **Population-Level Summary**

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 6 from the primary analysis model. See below for details.

6.3.2 Dual Primary Estimand #2 AISRS

- **Population**

The target population is adults with ADHD as defined by the inclusion/exclusion criteria.

- **Variable**

This primary efficacy endpoint is defined as the change from Baseline to Week 6 in AISRS score.

- **Intercurrent Events**

A hybrid approach of treatment policy and hypothetical strategy will be used to address intercurrent events study discontinuation. No special data handling will be used for other intercurrent events, such as subjects who initiate concomitant medications. Likewise, subjects that discontinue treatment but return for the Week 6 visit will have those data analyzed as reported. Subjects that discontinue the study due to adverse events and lack of efficacy and consequently have missing data at Week 6 are assumed to be representative of subjects that would

not continue to use the drug outside of a clinical trial and their missing values following discontinuation will be imputed using multiple imputation based off the distribution of placebo values at the matching time point, conditioned on the observed data (including baseline) and sex. All other missing values (both intermittent and following study discontinuation) will be imputed using multiple imputation assuming that they are missing at random, conditioned on the observed data (including baseline) and sex. Sensitivity analyses will explore the results under different analysis assumptions.

- **Population-Level Summary**

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 6 from the primary analysis model. See below for details.

6.3.3 Primary Efficacy Endpoint – PERMP-C and AISRS

6.3.3.1 Primary Efficacy Endpoint #1

The first primary efficacy endpoint is the change in PERMP-C from baseline to Week 6 in those receiving NRCT-101SR compared to those receiving placebo. The primary analysis population will be the ITT population.

PERMP is a timed (10-minute sessions) performance-based assessment for evaluating function in ADHD subjects. PERMP-C is the number of math problems answered correctly and typically ranges from 0-400 with higher scores indicating better performance. The PERMP total score (PERMP-T) is the sum of the number of math problems attempted (PERMP-A) and the number of math problems answered correctly (PERMP-C). The PERMP-T scores typically range from 0-800 with higher scores indicating better performance. At each visit where collected (Baseline, Week 3, and Week 6), PERMP-C from six post-dose time points (2, 4, 6, 8, 10, and 12 hours) will be averaged to get the PERMP-C score for analysis.

The change from baseline in PERMP-C scores at the Week 3 and Week 6 visits will be compared between the treatment and placebo groups.

The null hypothesis is that there is no significant effect of study drug type (NRCT-101SR versus placebo) on change in PERMP-C. The alternative hypothesis is that there is a significant effect of study drug type (NRCT-101SR versus placebo) on change in PERMP-C controlling for appropriate covariates and cofactors. Alpha ≤ 0.05 will be used as criteria for rejecting the null hypothesis and accepting the alternative hypothesis (see section 6.3.9 Multiplicity).

The primary efficacy endpoint will be analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment group (NRCT-101SR and placebo), time (week 3, and week 6), the treatment-by-visit interaction, site (possibly using pooled sites), and sex. Baseline PERMP-C value will be included as a covariate. The outcome variables will be the PERMP-C change from baseline to each timepoint; the primary comparison will be the contrast between treatment groups at Week 6. An unstructured within-subject covariance matrix will be utilized along with Kenward-Rogers denominator degrees of freedom. Should this fail to converge under the standard Newton-Raphson algorithm, the Fisher

scoring method will be attempted, followed by alternative methodology given in Lu, Mehrotra (Lu and Mehrotra 2010). In the unlikely event that none of these converge, the following structures will be attempted in order with the first to converge being selected: first-order ante dependence, heterogeneous first-order autoregressive, heterogeneous compound symmetry, and compound symmetry; sandwich estimator will be utilized for each.

LS means and differences across the twenty MI reps (see missing data imputation below) will be combined using SAS procedure MIANALYZE (Rubin, 1976). Significance testing will be based on least-squares means and two-sided 95% confidence intervals will be presented.

6.3.3.2 Primary Efficacy Endpoint #2

The second primary efficacy endpoint is the change in AISRS from baseline to Week 6 in those receiving NRCT-101SR compared to those receiving placebo. The primary analysis population will be the ITT population.

The null hypothesis is that there is no significant effect of study drug type (NRCT-101SR versus placebo) on change in AISRS. The alternative hypothesis is that there is a significant effect of study drug type (NRCT-101SR versus placebo) on change in AISRS controlling for appropriate covariates and cofactors. Alpha ≤ 0.05 will be used as criteria for rejecting the null hypothesis and accepting the alternative hypothesis (see section 6.3.9 Multiplicity).

The change from baseline in AISRS will be analyzed using an MMRM similar to the primary efficacy endpoint #1. However the analysis of AISRS will also include values collected at week 1 and will not require averaging within visit since it is collected only once at each visit.

6.3.5 Missing Data Imputation

Missing values for subjects in the ITT population will be imputed via multiple imputation (MI). When the study medication is discontinued due to lack of efficacy (LOE) or due to an adverse event (AE), missing values will be imputed drawing from the placebo distribution at the matching time points, conditioned on the obsevered data under the assumption that they are missing not at random (MNAR), with a covariate for sex. If the study medication was discontinued for any other reason (including impacts from the COVID-19 pandemic), values will be imputed within treatment group using MI under the assumption that they are missing at random (MAR) with covariates sex and observed values recorded at each time point. For the purposes of the imputation algorithm, AE discontinuations due solely to COVID and COVID sequelae will be included in the MAR imputation grouping. Subjects that withdraw due to COVID and have an independent, unrelated, adverse event that also results in study discontinuation will be included in the MNAR imputation grouping (with all other AE withdrawals other than the aforementioned COVID exclusion). The MAR approach will also be applied for sporadic missing values (prior to discontinuation). The MI process will use twenty repeats in the analysis datasets generated.

The steps will be as follows:

1. Intermittent missing values for both completers and dropouts prior to discontinuation will be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure.

2. For subjects that do not discontinue for LOE or AEs, a MAR imputation will be applied: the monotone missing values will be imputed with the SAS MI procedure using the monotone regression method. Baseline and the post-baseline scores at each visit will be included as covariates as well as sex; imputation will be done within treatment group. This will also apply for subjects that complete, but have their final value missing.

3. For subjects that discontinue for LOE or AEs, values will be imputed using the placebo group as reference. Missing values will be imputed with the SAS MI procedure using the monotone regression method. Baseline and the post-baseline scores at each visit will be included as covariates as well as sex.

Subjects that discontinue study drug or early terminate from the study but provide data will have all observed data used.

6.3.6 Secondary Efficacy Analysis

Secondary efficacy endpoints include:

Key Secondary Efficacy Endpoints

- BRIEF-A
- HADS

Other Secondary Efficacy Endpoints

- CGI-S
- Responder Rate
- AAQoL
- AISRS Expanded Version

The change from baseline in the above secondary efficacy endpoints will be analyzed using an MMRM similar to the primary efficacy endpoint. For all endpoints, the time point of primary interest is week 6.

Responder rate will be summarized descriptively and analyzed with a logistic regression model, providing odds ratio and 95% confidence interval. The number needed to treat (NNT) will be estimated by taking the reciprocal of the risk difference, i.e.,

$$NNT_{responders} = \frac{100}{\%responders_{NRCT-101SR\ group} - \%responders_{Placebo\ group}}$$

6.3.7 Other Endpoints

[redacted]

[redacted]

6.3.8 Sensitivity and Supportive Analyses

Efficacy analyses (primary, key secondary, other secondary, and other endpoints) will also be performed using the mITT and PP populations as sensitivity analyses. The multiple imputation techniques will investigate inclusion of dropouts for lost to follow up and unspecified reasons among those utilizing the placebo distribution. A tipping point analysis will also be performed. Supportive analyses include analyses at Week 1 and Week 3 utilizing the MMRMs described above, including additional covariates in the models (e.g., age, sex, ADHD subtype score, prior ADHD medication and time of withdrawal prior to enrollment, neuropsychiatric symptoms as measured by HADS and [redacted] etc.), and subgroup analyses for the efficacy endpoints. Because PERMP is collected multiple times per visit, additional analyses will be performed comparing within visit timepoints (e.g., pre-dose vs. post-dose).

[redacted]

6.3.9 Multiplicity

The dual primary endpoints and key secondary efficacy endpoints will be tested with control for multiplicity. All tests will be two-sided. An alpha recycling approach will be utilized to maintain alpha = 0.05 and pass alpha to secondary endpoints.

1. The 0.05 alpha will be split equally and 0.025 allocated to each of the dual primary endpoints (change from Baseline to Week 6 in PERMP-C and in AISRS). The smaller p-value of the dual primary efficacy endpoints will be tested at the 0.025 level.
2. If the endpoint with the smaller p-value is not significant at 0.025, all testing will halt and all p-values will be declared non-significant.
3. If significant at 0.025, it will be declared successful and its 0.025 alpha passed to the second of the dual primary endpoints.
4. If the second of the dual primary endpoints is not significant at alpha=0.05, it will be declared non-significant, all testing will halt and all subsequent p-values will be declared non-significant; success will only be declared on the stronger endpoint (step 3).
5. If the second of the dual primary endpoints is significant at alpha=0.05, it will be declared significant and the remaining alpha=0.05 passed to the key secondary endpoints.
6. If the first key secondary endpoint (BRIEF-A) is significant at alpha=0.05, its 0.05 alpha will be passed to the second key secondary endpoint (HADS).
7. No additional adjustments for multiplicity will be applied to any of the other endpoints; p-values will be reported, but will be purely nominal.

6.4 Safety Analyses

Safety variables include adverse events, laboratory test results, ECG results, vital sign measures as well as change in C-SSRS responses completed throughout the study. Tolerability will be

calculated as the propotion of subjects in each group who discontinue from the study due to any adverse event. For tolerability, an Odds Ratio will be calculated comparing the tolerability in the NRCT-101SR group to the tolerability in the placebo group. 95% confidence intervals will be reported for the Odds Ratio.

6.4.1 Extent of Exposure

Extent of exposure will be described by whether the subject took any study drug along with the number of days of exposure (last date of dosing minus first day of dosing plus 1). If the date of last dosing is completely missing, then the date of last dosing will be taken for analysis purposes as the date the relevant study drug was last dispensed. If only the month of the last dose is recorded, the first day of the month will be assumed as the last dosing date.

6.4.2 Adverse Events

All AEs will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Affairs (MedDRA).

The incidence of treatment-emergent AEs (TEAEs) (number and percent of subjects reporting the AE at least once during the study), serious adverse events (SAEs), TEAEs related to study drug, SAEs related to study drug, and TEAEs leading to study discontinuation will be summarized by study drug.

A TEAE is defined as any AE that has an onset on or after the dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug.

The incidence of TEAEs and study drug administration-related TEAEs will also be summarized by maximum severity and most-related relationship to study drug by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of subjects reporting an event. In counting the number of events reported, a continuous event, i.e., reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same subjects will be counted as multiple events.

6.4.3 Electrocardiographic Data

A list of subjects with abnormal 12-lead ECG parameters will be presented. Baseline and change-from-baseline in ECG parameters (heart rate, cardiac rhythm, RR interval, QRS interval, uncorrected QT interval, and QTc interval) will be summarized at the Week 6 post-baseline time point. QT will be corrected using Fridericia's correction (QTcF): $QTC = QT/RR^{1/3}$. Accepted definitions for outliers (e.g., frequency counts of interval changes from baselines ≥ 30 and ≥ 60 msec; QTc > 500 msec and QTc > 480 msec with change from baseline QTc > 60 msec) will be utilized as well as analyses of central tendency of active study drug vs placebo and active dose vs placebo.

6.4.4 Vital Signs

Summary statistics for the absolute vital sign value and the changes from baseline will be presented by treatment group for each visit.

Any incidence of clinically meaningful changes in heart rate (beats per minute), blood pressure (mmHg) and/or respiration (breaths per minute) will be summarized. A clinically meaningful change will be determined and at the discretion of the investigator. Vital signs are to be collected after subject has been sitting for at least 5 minutes.

6.4.5 C-SSRS

The questions of the C-SSRS will be presented in a listing of all responses for any subject with emergent increase in ideation or any suicidal behavior.

6.4.6 Laboratory Data

Mean changes from baseline at each post-baseline time point for each numeric laboratory variable will be presented. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables for the baseline and follow-up measurements will be presented.

6.5 PK Analysis

Population PK modeling, for those receiving NRCT-101SR, will be conducted on plasma levels of threonic acid at pre-dose and 4 and 7 hours post-dose (with a 30-minute window) using appropriate structural modeling and covariates.

6.6 Interim Analyses

No interim analyses are planned.

7.0 STUDY MANAGEMENT

7.1 Ethics and Consent

7.1.2 Regulations and Guidelines

The study will be performed in accordance with this protocol, ICH guidelines for Good Clinical Practice (GCP), the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki. These guidelines are on file at Neurocentria, Inc.

7.1.3 Institutional Review Board/Independent Ethics Committees

Conduct of the study must be approved by an appropriately constituted institutional review board (IRB). Approval is required for the study protocol, protocol amendments, informed consent forms (ICFs), subject information sheets, and advertising materials. No study drug will be shipped to a site until written IRB authorization has been received by the sponsor or its representative. Sponsor/site representative will comply with the IRB requirements on submissions of adverse event reports, continuing review reports and major protocol deviation reports. Sites using a local IRB are required to submit all the IRB approved documents to Sponsor or their designee for review.

7.1.4 Informed Consent

Before the start of the trial, the investigator will submit an informed consent form (ICF) and any other material to be provided to subjects to their IRB for review and approval. This review and approval will be documented and stored on site. The principal investigator or a designated representative will provide the sponsor or its representative with a blank copy of the IRB-approved ICF before the start of the study.

For each eligible study subject , a signed ICF will be obtained before any protocol-related activities are initiated. As part of the subject consenting procedure, the investigator or a designated site representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject and legally authorized representative (LAR; if applicable) are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects and LARs (if applicable) will be asked to read and review the consent form.

All questions should be answered to subject's (or LAR's if applicable) satisfaction by the study Investigator or the delegated site staff, before signing the ICF. Subjects should be informed that they may withdraw from the study at any time.

Subject (or LAR if applicable) must sign the ICF prior to starting any study procedures being done specifically for this trial. Copies of the signed ICF will be provided to the subject (or LAR if applicable).

7.2 IRB and Investigator Responsibilities:

The protocol and the ICF template must be reviewed and approved by a properly constituted IRB before study start. Properly constituted IRB is defined in ICH Guideline for Good Clinical Proactive E6 (R1), section 3. A signed and dated statement that the protocol and informed consent have been reviewed and approved by the IRB must be given to Neurocentria before study initiation. Prior to study start and any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and give access to all relevant data and records to Neurocentria and designated representatives.

The investigator is also responsible for ensuring that all persons assisting with the trial are adequately qualified, and informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. 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 for review and approval, (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).

The IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB and, if applicable, between a coordinating investigator and the IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

Investigators will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

7.3 Confidentiality

Subject names or initials will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document before being supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, institutional review boards (IRBs), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The investigator will maintain on-site a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

7.4 Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at a site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate, has excessive protocol and/or outcome measure administration deviations may be discontinued. Should the study be terminated and/or a site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the sponsor or its representative.

7.5 Study Documentation

By signing a copy of Form FDA 1572, the principal investigator assures the sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the sponsor’s written approval.

7.6 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include on-site

visits, telephone communication and remote monitoring to assure that the investigation is conducted according to the protocol, standard operating procedures, Guidelines of Good Clinical Practice, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Note that a variety of original documents, data, and records will be considered as source documents in this study. The eCRF itself is not to be used as a source document under any circumstances.

Sponsor, medical advisors, and clinical research associates (CRAs) or assistants may request to witness subject assessments (in person or via video/audio recordings) conducted by study clinicians or study coordinators at one or more on-site study visits occurring as part of this protocol. These recordings will be used to evaluate the quality of the data obtained and ensure consistency among clinicians administering these assessments. The recordings may be retained for up to 5 years. The investigator and appropriate site personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution.

The study may be audited by the sponsor, its designee or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its designee, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

7.7 Retention of Records

The investigator must arrange for retention of study records for 2 years after the investigational product's new drug application (NDA) is approved or the IND is withdrawn/abandoned, as required by FDA regulations. The investigator should take measures to prevent accidental or premature destruction of these documents.

7.8 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative.

8.0 REFERENCES

[redacted]

[redacted]