[redacted]

PROTOCOL

PRODUCT NAME:	NFC-1 (fasoracetam monohydrate)
PROTOCOL NUMBER:	MDGN-NFC1-ADHD-201
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Multicenter, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of NFC-1 in Adolescents (Ages 12-17 Years) with Genetic Disorders Impacting Metabotropic Glutamate Receptors and Attention Deficit Hyperactivity Disorder
PROTOCOL DATE:	Version v4.0, 27 Oct 2016
COORDINATING/PRINCIPAL INVESTIGATOR:	[redacted]
SPONSORED BY:	Medgenics, Inc. 435 Devon Park Drive, Bldg. 715 Wayne, PA, 19087 Phone: +1 610-254-4201 Fax: +1 610-717-3390
CONTRACT RESEARCH ORGANIZATION:	[redacted]

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: MDGN-NFC1-ADHD-201

PROTOCOL TITLE: A Multicenter, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of NFC-1 in Adolescents (Ages 12-17 Years) with Genetic Disorders Impacting Metabotropic Glutamate Receptors and Attention Deficit Hyperactivity Disorder

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted] 10-27-16
Date

Chief Science Officer
Medgenics, Inc.

[redacted] 10-27-16
Date

Vice President and Therapeutic Head, Neuroscience
Medgenics, Inc.

[redacted] 27-Oct-2016
Date

Vice President and Head Statistical Sciences and Data Management
Medgenics, Inc.

[redacted] 26-Oct-2016
Date

2. SYNOPSIS

PRODUCT NAME	NFC-1 (fasoracetam monohydrate)
PROTOCOL NUMBER	MDGN-NFC1-ADHD-201
DEVELOPMENT PHASE	Phase 2
PROTOCOL TITLE	A Multicenter, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of NFC-1 in Adolescents (Ages 12-17 Years) with Genetic Disorders Impacting Metabotropic Glutamate Receptors and Attention Deficit Hyperactivity Disorder
INDICATION	Genetic disorders impacting metabotropic glutamate receptors (mGluRs) in subjects with Attention Deficit Hyperactivity Disorder (ADHD)
OBJECTIVES	The objectives of this study are: • To assess the efficacy of NFC-1 relative to placebo in reducing the severity of symptoms associated with ADHD in adolescents with genetic disorders impacting mGluRs. • To obtain additional safety data following exposure to NFC-1 in this population.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled, parallel-group study of adolescents with ADHD who have genetic disorders impacting mGluRs. Approximately 90 subjects will receive randomized treatment with NFC-1 or placebo. Dosing will be optimized during the first 4 weeks of treatment, based on clinical response and tolerability, and maintained for an additional 2 weeks when the primary assessments of efficacy and tolerability will be performed. A follow-up telephone call will be performed at Week 7.
PLANNED NUMBER OF SUBJECTS	Ninety subjects are planned to be enrolled. It is anticipated that this will yield 80 subjects who will complete the study as planned.
STUDY ENTRY CRITERIA	**Inclusion criteria:** Subjects must fulfill all of the following requirements to enter the study: 1. Subject is male or female, ≥ 12 to ≤ 17 years of age. 2. Subject has a body mass index in the range of ≥ 15 to ≤ 35 kg/m^2. 3. Subject has ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and Version 5 of the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-5) ≥ 28 at Baseline with or without conventional ADHD therapy. 4. Subject has an intelligence quotient (IQ) > 79, based on the Wechsler Abbreviated Scale of Intelligence, second edition (WASI-II). 5. Subject has been genotyped previously and determined to have disruptive mutations in genes within the glutamate receptor metabotropic (GRM)-network as determined by the presence of copy number variations (CNVs) (GRM biomarker-positive subjects). The confirmation of a subject's positive status will be provided by the sponsor. 6. Subject is a non-smoker and/or has not used nicotine or nicotine-containing products on a weekly or more frequent basis for at least approximately 6 months. 7. Subject is judged to be in general good health, other than having ADHD, based on medical history, physical examination, vital signs measurements, laboratory safety tests, and the Columbia Suicide Severity Rating Scale (C-SSRS)

	performed at the Screening Visit and/or prior to administration of investigational product (IP). 8. Female subjects of reproductive potential will have a negative pregnancy test at Screening (serum) and prior to drug administration (urine). If sexually active, female subjects agree to use (and/or have her partner use) 2 acceptable methods of birth control beginning at least 2 weeks prior to administration of IP and throughout the study. Acceptable methods of birth control are abstinence or 2 of the following: intrauterine device, diaphragm, spermicides, cervical cap, contraceptive sponge, and condoms. 9. Subject has no clinically significant abnormality on electrocardiogram (ECG) performed at the Screening Visit and/or prior to administration of IP such as serious arrhythmia, bradycardia, tachycardia, cardiac conduction problems, or other abnormalities deemed to be a potential safety issue. 10. Parent/legal guardian and subject understand the study procedures and agree to the subject's participation in the study as indicated by parental/legal guardian signature on the subject informed consent form and subject signature on the assent form. **Exclusion criteria:** The presence of any of the following criteria excludes a subject from participating in the study: 1. Subject or parent/legal guardian is in the opinion of the investigator mentally or legally incapacitated, has significant emotional problems at the time of the Screening Visit or during the conduct of the study. 2. Subjects with a current or relevant history of comorbid major psychiatric disorders (ie, aside from ADHD), including major depression, bipolar disease, schizophrenia, pervasive development disorder, and intellectual disability. 3. Subject is currently taking a prohibited medication and/or is unwilling to wean off current ADHD medication to participate in the study 4. Subject has a history of any illness that in the opinion of the study investigator might confound the results of the study or poses an additional risk to the subject by his or her participation in the study. 5. Subject has a history of any clinically significant disease that is not currently stable. Subjects with a history of uncomplicated kidney stones may be enrolled in the study at the discretion of the investigator. 6. Subject has a known history or presence of syncope, cardiac conduction problems (eg, clinically significant heart block), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia. 7. Subject has a history of stroke, chronic seizures, or major neurological disorder which, in the opinion of the investigator, would interfere with the subject's ability to participate and/or be evaluated in the study. 8. Subject is pregnant or a nursing mother. 9. Subject has a history of aversion to blood draws that in the opinion of the investigator or parents would result in compromising the study conduct. 10. Subject has a history of physiologic difficulty in venous access that in the opinion of the investigator and parent/legal guardian would compromise study conduct. 11. Subject has a history of inability to swallow whole unadulterated capsules, which in the opinion of the investigator or parent/legal guardian would compromise study conduct. 12. Subject has a systolic or diastolic blood pressure $\geq$ the 95th percentile for his or her age.

	13. Subject consumes any alcoholic beverages on a regular basis (weekly or more often). 14. Subject consumes excessive amounts of caffeine, defined as greater than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day. 15. Subject has a history of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerability to prescription of nonprescription drugs or food. 16. Subject is currently a regular user (including "recreational use") of any illicit drugs (including marijuana) or has a history of drug (including alcohol) abuse. 17. Subject has had surgery, lost more than 5 mL/kg of blood, or participated in another investigational drug trial within 4 weeks prior to the Screening Visit. 18. Subject has a clinical laboratory abnormality that indicates clinically significant hematologic, hepatobiliary, or renal disease: a Aspartate aminotransferase/serum glutamic oxaloacetic transaminase > 2.0-times the upper limit of normal b Alanine aminotransferase/serum glutamic pyruvic transaminase > 2.0-times the upper limit of normal c Total bilirubin > 2.0-times the upper limit of normal d Hemoglobin < 9 g/dL e White blood cell count < 1,000/mm^3 f Platelet count < 100,000/mm^3 g Creatinine kinase > 300 U/L for females and > 500 U/L for males
CONCOMITANT TREATMENT	All ADHD medications will be discontinued prior to starting this study. There will be a wash-out phase of 5 days for stimulants and 14 days for atomoxetine and noradrenergic agonists. Subjects will not start any new ADHD medication during the study. Due to their potential to interfere with safety, efficacy, or tolerability assessments, the following medications are prohibited: norepinephrine reuptake inhibitors, anxiolytic or sedative hypnotic medications, antidepressants, clonidine, guanfacine, mood stabilizers (including lithium, anticonvulsants, and antipsychotics), antihypertensive agents, psychostimulants, sedating antihistamines, and investigational compounds. As NFC-1 is a potential inducer of cytochrome P450 3A4, 2B6 and 2D6, medications that are metabolized by these enzymes are prohibited.
INVESTIGATIONAL PRODUCT	Name: NFC-1 (fasoracetam monohydrate), (5R)-5-(pyridine-1-carbonyl)-pyrrolidin-2-one monohydrate, NFC-1 will be provided as white opaque size 2 capsules containing 100 mg or 200 mg NFC-1; no excipients are used. Dose, route, and frequency: 100 mg, 200 mg, and 400 mg administered orally twice daily in the fed or fasting state.
REFERENCE PRODUCT	Name: Matching placebo containing microcellulose instead of NFC-1. Dose, route, and frequency: 100 mg, 200 mg, and 400 mg administered orally twice daily in the fed or fasting state.
TREATMENT REGIMENS	Subjects will receive randomized treatment with NFC-1 or placebo. During the dose optimization phase, NFC-1 or placebo will be initiated at 100 mg twice daily and titrated weekly based on clinical response and tolerability up to a maximal dose of 400 mg twice daily. At the end of Week 4, subjects will continue with the optimized dose of NFC-1 at 100 mg, 200 mg, or 400 mg twice daily for an additional 2 weeks (maintenance phase).

COORDINATING PRINCIPAL INVESTIGATOR	[redacted]
PLANNED STUDY SITES	Approximately 35 sites in North America
CRITERIA FOR EVALUATION	Response to treatment will be assessed with tools commonly used in ADHD research. These include ADHD-RS-5, Adolescent Sleep Hygiene Scale (ASHS), Screen for Childhood Anxiety-related Emotional Disorders (SCARED), and Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I). Safety and tolerability will be assessed by the frequency and severity of adverse events (AEs) as well as the evaluation of changes in clinical laboratory values, vital signs, ECG recordings, and C-SSRS.
STATISTICAL METHODS	**Efficacy:** The primary endpoint for the assessment of efficacy will be the ADHD-RS-5 score. Secondary endpoints will include the CGI-S, ASHS, and SCARED. The analysis will be based on changes from the baseline value and will test the hypothesis that there is no difference between the treatments (ie, that the difference is 0) against a 2-tailed alternative. Further exploratory analyses may be performed that include additional independent factors (eg, age, gender, and/or maintenance dose of study drug) as well as covariates that are determined to be associated with the experimental results (eg, baseline value of the dependent variable). All quantitative endpoints will be described with traditional summary statistics and tabulated by treatment group and visit. **Safety:** Adverse events will be coded with the Medical Dictionary for Regulatory Affairs (MedDRA) and tabulated by system organ class and preferred term. Adverse events will be analyzed by frequency, severity, relationship to IP, and their effect on participation in the study. Clinical laboratory values will be compared to normal ranges and flagged for levels of clinical concern. The analysis will focus on the frequencies of abnormal values as well as within-subject changes observed during the course of the study. Vital signs and ECG recordings will also be examined for changes during the study that may be attributed to exposure to IP. The C-SSRS will also be examined for changes that may be attributed to exposure to IP.
SAMPLE SIZE DETERMINATION	Enrollment of 90 subjects is expected to yield 80 subjects who complete the study as planned. Assuming an effect size of 0.7, this number will provide approximately 90% power to detect a significant difference between the treatments based on a 2-tailed $\alpha = 0.05$ comparison of mean change from Baseline.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods will be as follows: • Screening period: approximately 21 days. • Wash-out period: if applicable, up to 14 days. • Dose optimization phase: 28 days. • Dose maintenance phase: 14 days. • Follow-up: 7 days (+5 days) after the last dose of IP. • The maximum study duration for each subject is approximately 70 days. • The maximum treatment duration for each subject is 42 days.

3. TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Figures

REASONS FOR AMENDMENT

The protocol was amended due to receipt of in vitro data indicating the potential of NFC-1 to be an inducer of cytochrome P450 3A4, 2B6 and 2D6. As such, the concomitant administration of NFC-1 with drugs that are metabolized by CYP3A4, CYP2B6, or CYP2D6 could potentially reduce the therapeutic effect of those drugs. The following changes were made to the protocol:

1. Medications that may potentially be impacted by the interaction with NFC-1 are now prohibited.
2. The wording related to medication usage during the study to manage anxiety, mood disorders, ADHD, and symptoms of autism was removed as this information is repetitive with the bullet points that followed.

SUMMARY OF AMENDED SECTIONS

The text below presents the amendments made to the protocol during revision. Simple corrections of typographical errors are not presented.

Synopsis **Concomitant Treatment**

Added: As NFC-1 is a potential inducer of cytochrome P450 3A4, 2B6 and 2D6, medications that are metabolized by these enzymes are prohibited.

Section 9.12.1 **Permitted Therapies**

Text formerly read: The use of bronchodilators is allowed, if needed. Antibiotics and OTC medications that do not affect blood pressure, heart rate, or the central nervous system, which are considered necessary for the subject's welfare, may be administered at the discretion of the investigator.

Now reads: The use of **inhaled** bronchodilators is allowed, if needed. Antibiotics and OTC medications that do not affect blood pressure, heart rate, or the central nervous system, which are considered necessary for the subject's welfare, may be administered at the discretion of the investigator.

Section 9.12.2 **Prohibited Therapies**

Text formerly read: Medications used to manage anxiety or mood disorders, ADHD, and symptoms of autism are not allowed in the study, and new medications for these or other psychiatric symptoms cannot be initiated. Rescue medications will not be authorized for study participants. If subjects should require rescue medication to manage anxiety or mood disorders, ADHD, or autism spectrum disorders they will be discontinued from the study.

All ADHD medications will be discontinued prior to starting this study. There will be a wash-out phase of 5 days for stimulants and 14 days for atomoxetine and noradrenergic agonists. Study subjects will not start any new ADHD medication during the study. All ADHD medications will be discontinued prior to starting this study. Due to their potential to interfere with safety, efficacy, or tolerability assessments, the following medications are prohibited during the study:

- Norepinephrine reuptake inhibitors.
- Anxiolytic or sedative hypnotic medications.

Text now reads: All ADHD medications will be discontinued prior to starting this study. There will be a wash-out phase of 5 days for stimulants and 14 days for atomoxetine and noradrenergic agonists. Study subjects will not start any new ADHD medication during the study. Due to their potential to

interfere with safety, efficacy, or tolerability assessments, the following medications are prohibited during the study:

- **Any medication which is a substrate of CYP3A4, CYP2B6 or CYP2D6.**
- Norepinephrine reuptake inhibitors.
- Anxiolytic or sedative hypnotic medications.

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ADHD-RS-5	Attention Deficit Hyperactivity Disorder Rating Scale Version 5
AE	adverse event
ANOVA	analysis of variance
ASHS	Adolescent Sleep Hygiene Scale
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CNV	copy number variation
CRA	clinical research associate
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GRM	glutamate receptor metabotropic
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	investigational product
IQ	intelligence quotient
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version
mGluRs	metabotropic glutamate receptors
OTC	over-the-counter
PK	pharmacokinetic
PP	per-protocol
SAE	serious adverse event
SCARED	Screen for Childhood Anxiety-related Emotional Disorders
T_{max}	time to maximum plasma concentration
WASI-II	Wechsler Abbreviated Scale of Intelligence, second edition

5. INTRODUCTION

5.1 Background and Rationale

Several candidate genes related to dopamine and noradrenergic neurotransmitter systems are associated with attention deficit hyperactivity disorder (ADHD) severity and subtypes (persistence, comorbidity, functional impairment, and treatment effects), such as *DAT1*, *DRD4*, *MAO-A*, *ADRA2A*, *ADRA2C*, *NET*, and *COMT*. Recently, a large-scale, genome-wide study comparing copy number variations (CNVs) in 3,500 ADHD cases versus approximately 13,000 controls revealed that rare, recurring CNVs impacting specific glutamate receptor metabotropic (GRM) genes (ie, *GRM1, GRM5, GRM7,* and GRM8) were found in patients with ADHD at significantly higher frequencies compared to healthy controls.

Originally developed by Nippon Shinyaku Co., fasoracetam monohydrate (NFC-1, previously referred to as NS-105) is an important candidate to explore for use in restoring metabotropic glutamate receptors (mGluRs) activity in patients with ADHD exhibiting mGluR hypofunction. It has been shown to improve symptoms of depression and memory/learning in animal models. The drug activity is based on regulating the intracellular adenylyl cyclase-activity stimulated by mGluRs and works by inhibiting the brain gamma-aminobutyric acid B (GABA) receptor stimulus response and enhancing the beta-adrenergic receptor response and the acetylcholine-mediated neurologic system response (1).

Data from animal models, pharmacotherapeutic interventions, and brain and genetic studies in humans implicate glutamatergic system involvement in ADHD pathophysiology. Interventions specifically targeting this system remain to be developed even though a recent, large-scale, genome-wide study revealed that rare, recurring CNVs impacting genes in the glutamatergic network (ie, *GRM1, GRM5, GRM7,* and *GRM8*) were detected in approximately 10% of the total ADHD cases (2).

Published preclinical studies indicate that NFC-1 exerts its bioactivity through mGluRs (3, 4, 5). NFC-1 was also found to be efficacious in ameliorating learning and memory impairment, which can be interpreted in the context of improved attention span, and in reducing locomotor activity, which is a correlate of hyperactivity (6). Thus, NFC-1 may be a potentially effective therapeutic agent in the subgroup of patients with ADHD identified through genetic profiling with variants in the GRM network that the sponsor is leveraging as a biomarker indicative of the mGluR signaling pathway being disrupted.

5.2 Clinical Experience

Previously, NFC-1 was in phase 3 development for adults with cerebrovascular diseases and dementia. The previous sponsor (Nippon Shinyaku Co., Ltd.) performed the following studies:

- Phase 1 dose-finding and pharmacokinetic study in healthy volunteers.
- Phase 2 studies in subjects with residual symptoms following cerebral infarct or cerebral hemorrhage.
- Phase 3 study in subjects with cerebrovascular diseases and dementia.

Exposure to NFC-1 in these studies is presented in Table 1.

Table 1: Clinical Studies Conducted by Nippon Shinyaku Co., Ltd. with NFC-1[a]

Study Phase	Study Population	Number of Subjects	Doses Tested	Exposure	Number of Treatment-related SAEs
Phase 1	Healthy male adults	30/6[b]	25-800 mg single dose/ 200 mg/day	8 days	0
Phase 2	Adults with cerebrovascular disease	169	75-450 mg/day	8 weeks	0
Phase 2	Adults with post cerebral infarct residual symptoms	288	150 and 300 mg/day	8 weeks	0
Phase 3	Adults with cerebrovascular disease and dementia	Not available	300 mg/day	6 months to 1 year	2[c]

Abbreviation: SAE = serious adverse event

a Previously referred to as NS-105.

b A total of 30 subjects were involved in dose finding at 25 – 800 mg, a further 6 subjects were tested at the recommended dose obtained during dose finding (200 mg).

c Relationship to study treatment was categorized as unknown.

Nippon Shinyaku terminated development because the phase 3 study failed to meet the defined efficacy endpoints. Although a written report is unavailable, information in the Investigator's Brochure (IB) (1) for this phase 3 study indicated that NFC-1 was well-tolerated over 8 weeks of continuous daily dosing at doses up to 450 mg/day. The most frequently reported adverse events (AEs) were nausea (2% of subjects) and laboratory abnormalities including elevated liver function tests, including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (in 3% of the subjects each), and elevated creatinine kinase (in 1% of the subjects).

Research has also been conducted on NFC-1 in adolescents with ADHD. The recently completed NFC1-2014 trial was a 30-subject phase 1b study that evaluated adolescents with ADHD and disruptions in the mGluR gene network. The objectives of the study were to evaluate the safety, tolerability, and single-dose pharmacokinetic (PK) profile of NFC-1 and to evaluate the effect of NFC-1 on ADHD during 4 weeks of continuous treatment (at doses up to 400 mg twice daily) following 1 week of placebo therapy.

The study was conducted at the Jefferson University Hospital in Philadelphia, Pennsylvania. Subjects were classified into three tiers, based on their mGluR mutations. During the dose escalation phase of this study, NFC-1 was well tolerated with no treatment-related serious adverse events (SAEs) reported. All AEs were mild to moderate, and the most frequently reported treatment-emergent adverse events (TEAEs) were headaches in 17/30 subjects (56.7%),

fatigue in 9/30 subjects (30.0%), upper abdominal pain in 7/30 subjects (23.3%), and irritability in 6/30 subjects (20.0%).

In addition to several exploratory measures, efficacy was assessed using the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales, and the Vanderbilt Parent Assessment Score. Clinical improvement, based on the CGI-S, CGI-I, and Vanderbilt scores, was demonstrated in analyses of all subjects. Improvement in the mean scores after 4 weeks of active treatment was observed as follows: CGI-S scores decreased from 3.97 to 3.00 ($P < 0.001$), CGI-I scores decreased from 3.83 to 2.24 ($P < 0.001$), and the Vanderbilt score decreased from 29.1 to 22.5 ($P < 0.001$). Improvement was greatest in the Tier-1/Tier-2 mGluR mutation positive subjects ($P < 0.001$). In this group, 80% of the subjects were deemed to be responders (defined as at least a 25% improvement in the Vanderbilt Score). Approximately half of the participants opted to participate in the currently ongoing open-label extension study of NFC-1.

5.3 Summary of Potential Risks and Benefits

The potential benefits of study participation are that mGluRs mutation-positive subjects with ADHD (1) may experience a reduction in symptoms as a result of treatment with NFC-1 and (2) will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for patients with genetic disorders impacting mGluRs together with ADHD. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to NFC-1 and the risks of medical evaluation, including venipuncture.

A summary of the pharmaceutical properties and known potential risks of NFC-1 is provided in the current version of the IB (1). The investigator must become familiar with all sections of the NFC-1 IB before the start of the study.

6. OBJECTIVES

The objectives of this study are:

- To assess the efficacy of NFC-1 relative to placebo in reducing the severity of symptoms associated with ADHD in adolescents with genetic disorders impacting mGluRs.
- To obtain additional safety data following exposure to NFC-1 in this population.

7. STUDY DESIGN

7.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, parallel-group phase 2 study of adolescents to compare the safety and efficacy of NFC-1 with that of placebo. Approximately 90 male and female subjects will receive randomized treatment with NFC-1 or placebo to obtain 80 subjects that complete the study as planned. Subjects must be ≥ 12 to ≤ 17 years of age and have ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and Version 5 of the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-5) > 28 at Baseline with or without conventional ADHD therapy.

Subjects will not be eligible if they are mentally or legally incapacitated, have significant emotional problems, have a prior diagnosis of co-morbid major psychiatric disorders or any clinically significant medical condition that would interfere with the conduct of study evaluations, are pregnant or nursing, and/or have abnormal laboratory values that indicate clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary abnormalities or diseases.

As shown in Figure 7.1, subjects will be randomly assigned to receive either NFC-1 or placebo on Day -1 and will start taking the investigational product (IP) at a dose of 100 mg twice daily on Day 1. Dosing will be optimized to 100 mg, 200 mg, or 400 mg twice daily, as appropriate, over the 4 weeks of treatment (dose optimization phase), based on clinical response and tolerability. If the subject tolerates a dose well, the dose will be maintained for an additional 2 weeks (dose maintenance phase) when the primary assessments of efficacy and tolerability will be performed. A follow-up telephone call will be performed at Week 7.

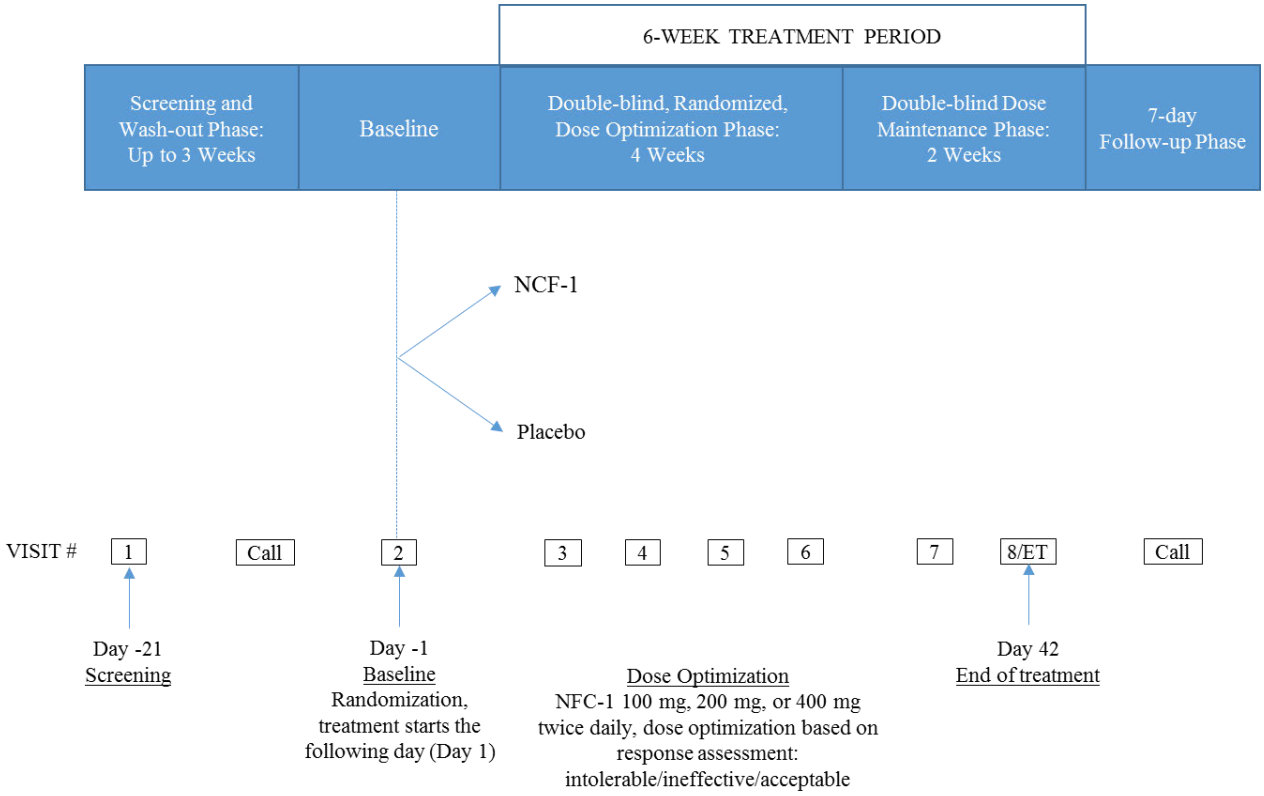
Approximately 45 subjects will be randomly assigned to each treatment group. The duration of study participation is expected to be 70 days.

Efficacy will be assessed by the ADHD-RS-5 score, CGI-I, CGI-S, Adolescent Sleep Hygiene Scale (ASHS), and Screen for Childhood Anxiety-related Emotional Disorders (SCARED).

Safety will be assessed by evaluating AEs, physical examination findings, vital sign measurements, electrocardiograms (ECGs), clinical laboratory test results, and Columbia Suicide Severity Rating Scale (C-SSRS) scores.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through the posttreatment visit) will be documented.

Figure 7.1: Study Design



Abbreviation: ET = early termination

7.2 Discussion of Study Design

The randomized, double-blind, parallel group design chosen for this study is standard for the head-to-head comparison of treatments. After assessing the baseline status of the disease (in the absence of study drug), the 4-week dose titration paradigm allows for individualized dose optimization. This is the norm for pharmacological interventions in neuropsychiatric indications. The subsequent 2-week maintenance period will allow stabilization of drug effect(s) prior to assessing the disease status at the end of the treatment (ie, the primary endpoint in this study).

7.3 Study Site(s)

The study will take place at approximately 35 sites in the United States. Each site is anticipated to screen a sufficient number of subjects to be able to randomize approximately 2-3 subjects. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrollment.

8. SUBJECT POPULATION

8.1 Selection of Study Population

Approximately 90 subjects will be randomized. It is anticipated that this will yield 80 subjects who will have completed the study as planned. Justification of this sample size is presented in Section 13.2.

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site.

8.2 Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets all of the following criteria:

1. Subject is male or female, ≥ 12 to ≤ 17 years of age.
2. Subject has a body mass index in the range of ≥ 15 to ≤ 35 kg/m^2.
3. Subject has ADHD as defined by DSM-5 and ADHD-RS-5 ≥ 28 at Baseline with or without conventional ADHD therapy.
4. Subject has an intelligence quotient (IQ) > 79, based on the Wechsler Abbreviated Scale of Intelligence, second edition (WASI-II).
5. Subject has been genotyped previously and determined to have disruptive mutations in genes within the GRM-network as determined by the presence of CNVs (GRM biomarker-positive subjects). The confirmation of a subject's positive status will be provided by the sponsor.
6. Subject is a non-smoker and/or has not used nicotine or nicotine-containing products on a weekly or more frequent basis for at least approximately 6 months.
7. Subject is judged to be in general good health, other than having ADHD, based on medical history, physical examination, vital signs measurements, laboratory safety tests, and the C-SSRS performed at the Screening Visit and/or prior to administration of IP.
8. Female subjects of reproductive potential will have a negative pregnancy test at Screening (serum) and prior to drug administration (urine). If sexually active, female subjects agree to use (and/or have her partner use) 2 acceptable methods of birth control beginning at least 2 weeks prior to administration of IP and throughout the study. Acceptable methods of

birth control are abstinence or 2 of the following: intrauterine device, diaphragm, spermicides, cervical cap, contraceptive sponge, and condoms.

9. Subject has no clinically significant abnormality on ECG performed at the Screening Visit and/or prior to administration of IP such as serious arrhythmia, bradycardia, tachycardia, cardiac conduction problems, or other abnormalities deemed to be a potential safety issue.
10. Parent/legal guardian and subject understand the study procedures and agree to the subject's participation in the study as indicated by parental/legal guardian signature on the subject informed consent form and subject signature on the assent form.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if the subject meets any of the following criteria:

1. Subject or parent/legal guardian is in the opinion of the investigator mentally or legally incapacitated, has significant emotional problems at the time of the Screening Visit or during the conduct of the study.
2. Subjects with a current or relevant history of comorbid major psychiatric disorders (ie, aside from ADHD), including major depression, bipolar disease, schizophrenia, pervasive development disorder, and intellectual disability.
3. Subject is currently taking a prohibited medication and/or is unwilling to wean off current ADHD medication to participate in the study.
4. Subject has a history of any illness that in the opinion of the study investigator might confound the results of the study or poses an additional risk to the subject by his or her participation in the study.
5. Subject has a history of any clinically significant disease that is not currently clinically stable. Subjects with a history of uncomplicated kidney stones may be enrolled in the study at the discretion of the investigator.
6. Subject has a known history or presence of syncope, cardiac conduction problems (eg, clinically significant heart block), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia.
7. Subject has a history of stroke, chronic seizures, or major neurological disorder which, in the opinion of the investigator, would interfere with the subject's ability to participate and/or be evaluated in the study.
8. Subject is pregnant or a nursing mother.
9. Subject has a history of aversion to blood draws that in the opinion of the investigator or parents would result in compromising the study conduct.
10. Subject has a history of physiologic difficulty in venous access that in the opinion of the investigator and parent/legal guardian would compromise study conduct.
11. Subject has a history of inability to swallow whole unadulterated capsules, which in the opinion of the investigator or parent/legal guardian would compromise study conduct.
12. Subject has a systolic or diastolic blood pressure $\geq$ the 95th percentile for his or her age.
13. Subject consumes any alcoholic beverages on a regular basis (weekly or more often).
14. Subject consumes excessive amounts of caffeine, defined as greater than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day.

15. Subject has a history of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerability to prescription of nonprescription drugs or food.
16. Subject is currently a regular user (including "recreational use") of any illicit drugs (including marijuana) or has a history of drug (including alcohol) abuse.
17. Subject has had surgery, lost more than 5 mL/kg of blood, or participated in another investigational drug trial within 4 weeks prior to the Screening Visit.
18. Subject has a clinical laboratory abnormality that indicates clinically significant hematologic, hepatobiliary, or renal disease:
    a Aspartate aminotransferase/serum glutamic oxaloacetic transaminase > 2.0-times the upper limit of normal
    b Alanine aminotransferase/serum glutamic pyruvic transaminase > 2.0-times the upper limit of normal
    c Total bilirubin > 2.0-times the upper limit of normal
    d Hemoglobin < 9 g/dL
    e White blood cell count < 1,000/mm^3
    f Platelet count < 100,000/mm^3
    g Creatinine kinase > 300 U/L for females and > 500 U/L for males

8.3 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol violations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4 Subject Replacement Criteria

Once randomized, subjects who discontinue from the study will not be replaced.

9. TREATMENTS

9.1 Identification of Investigational Product(s)

The following IPs will be used in this study:

- NFC-1 will be provided as white opaque size-2 capsules containing 100 mg or 200 mg NFC-1; no excipients are used.
- Dose, route, and frequency (NFC-1): 100 mg, 200 mg, and 400 mg administered orally twice daily in the fed or fasting state.
- Matching placebo will be provided as white opaque size-2 capsules containing microcellulose instead of NFC-1.
- Dose, route, and frequency: Placebo for 100 mg, 200 mg, and 400 mg administered orally twice daily in the fed or fasting state.

9.2 Labeling and Packaging

All packaging and labelling operations will be performed by the sponsor according to Good Manufacturing Practice and Good Clinical Practice (GCP) rules. The IP will be sent to the study site by the sponsor or designee. Labelling will be in local language and dependent upon local regulations.

9.2.1 Labeling

The bottle will have affixed a label that meets the applicable regulatory requirements and may include the following: subject identifier, name of compound or placebo, dosage strength, lot identifier, protocol number, specified number of capsules, caution statement ("New Drug – Limited by United States Law to Investigational Use"), storage conditions, and sponsor identification.
The investigator will be asked to save all empty packaging or packaging containing unused capsules for final disposition by the sponsor.

9.2.2 Packaging

NFC-1 and placebo will be supplied by the sponsor. NFC-1 will be packaged in high-density polyethylene bottles of 20 capsules. NFC-1 and placebo will be packaged so that the investigator, the study clinic personnel, and subjects are blinded to study treatment.

9.3 Treatments Administered

Eligible subjects will be randomized to either NFC-1 or placebo for 6 weeks of treatment; a 4-week stepwise dose-optimization period will be followed by a 2-week maintenance period.

NFC-1 or placebo will be administered twice daily for a maximum of 6 weeks. At Baseline, randomized subjects will receive blinded IP to begin treatment the following day at a dose of 100 mg twice daily. Doses will be optimized to 100 mg, 200 mg, or 400 mg twice daily over the following 4 weeks as determined by the investigator's assessment of clinical response and tolerability to IP. Additional dose adjustments will not be allowed after Week 4, and if well tolerated, subjects will be maintained at their Week-4 dose.

The objective of this period is to ensure subjects are titrated to an optimal dose of IP based upon the investigator's review of efficacy, AEs, and clinical judgment.

9.4 Dispensing and Storage

The IP supplied by Medgenics is to be used exclusively in this clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his/her signature. A copy of this receipt must be kept by the investigator, and another copy will be stored at Medgenics and/or [redacted]. Until the IP is dispensed to the subjects, it must be stored at 20-25°C and in a dry place in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The storage area will be accessible only to those persons authorized by the investigator to dispense the IP.

9.4.1 Interactive Web Response System for Investigational Product Management

An Interactive Web Response System (IWRS) will be employed in this study to register and randomize subjects, maintain the blind during the study, provide a mechanism for unblinding, dispense and manage investigational product, and track final subject disposition (ie, study completion or discontinuation).

A user manual with specific functions and instructions for the IWRS will be provided to the site.

9.5 Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to NFC-1 or placebo. The randomization schedule will be computer-generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through the central IWRS as subjects are entered into the study.

The randomization schedule will be prepared by [redacted] in advance of study initiation. All efforts will be made to ensure the integrity of the study blind up until the final database has been locked. No one involved in study conduct will have access to the randomization schedule prior to that event. No subject will be randomized into this study more than once.

9.6 Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician from [redacted] who will have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis prior to unblinding of the study data to all study related personnel.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study personnel will access the IWRS unblinding module. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all

cases that are not emergencies, the investigator should discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

9.7 Selection of Doses in the Study

Doses of 100 mg, 200 mg, or 400 mg twice daily will be administered in this study. These doses were found to be safe and well tolerated in a phase 1 study of adolescents with ADHD.

Previous PK studies in both healthy adults (aged 26 to 48 years) and young adults (aged 20 to 32 years) showed an elimination half-life ($t_{½}$) of about 4 hours. In view of the short half-life, twice daily dosing is expected to provide a more consistent pharmacologic effect throughout the day.

Administration of single oral doses of 100 mg NFC-1 after a meal to young adults (aged 20 to 32 years) showed rapid absorption (time to maximum plasma concentration [T_{max}] from 0.6 to 1.5 hours), dose-proportional increases in exposure, and a $t_{½}$ of 3.7 to 4.4 hours in healthy male adults. Comparison of doses administered under fed and fasted conditions to healthy male adults showed that food caused slower absorption (T_{max} of 1.5 versus 0.7 hours) and decreased the maximum observed plasma concentration (C_{max}) (4.14 versus 5.65 µg/mL), but no difference in the area under the plasma concentration-time curve extrapolated from time 0 to infinity ($AUC_{0-\infty}$) (29.3 versus 31.3 µg h/mL) and $t_{½}$ (4.2 versus 4.3 hours). In separate studies, similar PK parameters were obtained following administration of 100 mg NFC-1 to healthy male adults and young adults, respectively, with T_{max} of 1.0 versus 1.2 hours, C_{max} of 2.57 versus 2.14 µg/mL, $AUC_{0-\infty}$ of 17.0 versus 14.0 µg h/mL, and $t_{½}$ of 4.4 versus 4.4 hours.

Preliminary evaluation of PK data from the recent adolescent PK study is consistent with previous PK data and demonstrated a linear dose/concentration profile with a $t_{½}$ of approximately 4 hours.

9.8 Selection of Timing of Dose for Each Subject

NFC-1 or matching placebo is to be taken orally twice daily during the treatment period (in the morning upon awakening [7:00 a.m.to 9:00 a.m.] and in the mid-afternoon [between 3:00 p.m.to 5:00 p.m.]) and can be taken in the fed or fasting state.

9.9 Dose Adjustment Criteria

The duration of the dose-optimization period is 4 weeks to allow for up-titration to the highest dose and no more than one down-titration to the previous dose, if necessary.

Subjects will be instructed to take NFC-1 or placebo each morning upon awakening (at 7:00 a.m. to 9:00 a.m.) and in the mid-afternoon (3:00 p.m. to 5:00 p.m.). On Day 1, all subjects will begin taking NFC-1 or placebo and will be evaluated after 7 days (± 2 days) for tolerability and effectiveness. Subjects may be titrated weekly to the next available dose strength after 7 days (± 2 days) on the previous dose, based on the overall response of the subject. Additionally, if needed, a subject may be down-titrated to the previous dose level in order to optimize tolerability and efficacy. Subject response will be categorized by the investigator as 1 of 3 conditions and associated actions, with titration continuing until an "acceptable response" is achieved. These conditions are defined as follows:

Intolerable response (ie, intolerable side effects): Requires the subject to be tapered to a lower dose of NFC-1 (if available). However, if this lower dose produces an intolerable response as well, the subject should be discontinued from the study.

Ineffective response: The subject is not showing a significant reduction in symptoms, and requires increasing titration of NFC-1 to the next available dose strength, provided tolerability is acceptable, followed by weekly evaluation.

Acceptable response: A response is defined as acceptable if it shows a significant reduction in symptoms with tolerable side effects. Subjects categorized as "acceptable" may be maintained at their current dose for the remainder of the optimization period. Subjects who are tolerating study medication at the highest available dose but do not achieve an acceptable response should continue in the trial at that dose.

Further, if the "acceptable" dose is well tolerated and, in the opinion of the investigator, the subject would potentially receive additional symptom reduction, the dose may be increased to the next higher dose level.

If the subject experiences unacceptable intolerability, in the opinion of the investigator, the dose may be reduced (if available) by 1 dose level (to the previous dose). If the subject tolerates the dose reduction well and maintains symptom control, the subject may be maintained at that reduced dose for the remainder of the optimization period (through Visit 6).

Only 1 dose reduction is permitted during the optimization period. Visit 5 will be the last visit at which titration can occur. Once a subject has reached an optimal dose, this dose will be maintained for the remainder of the dose-optimization phase of the study (through Visit 6). Subjects who are unable to tolerate the IP will be discontinued. After the dose optimization period, subjects will continue to receive the current optimized dose of IP for an additional 2 weeks. A 7-day follow-up call will occur after discontinuing study treatment.

Subjects who discontinue because they are unable to tolerate the IP must complete all early termination (ET) visit assessments required during the last study visit. These subjects will also receive a 7-day follow-up call after discontinuing study treatment.

9.10 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the US Food and Drug Administration (FDA) Form FDA 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on Form FDA 1572. IP(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed; is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to Medgenics and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (partly used, unused, and empty packaging [eg, bottles]) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.11 Treatment Compliance

Treatment compliance with IP regimens will be assessed by study personnel via capsule counts of returned medication and by questioning the subject, if necessary, at every post-baseline visit. A subject who is not compliant (taken < 80% or > 100% of IP) will be counseled at each visit on

the importance of taking IP as instructed. A subject who is noncompliant on 3 consecutive visits will be discharged from the study.

9.12 Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter [OTC] medications) will be recorded in the source document and on the appropriate eCRF.

9.12.1 Permitted Therapies

Ongoing behavioral therapies, including individual cognitive behavioral therapy, group cognitive behavioral therapy, social effectiveness training, ADHD behavioral therapy, or applied behavioral analysis are allowed and must be maintained at the same frequency/intensity as at Screening. The initiation of new behavioral therapies is not allowed.

The use of inhaled bronchodilators is allowed, if needed. Antibiotics and OTC medications that do not affect blood pressure, heart rate, or the central nervous system, which are considered necessary for the subject's welfare, may be administered at the discretion of the investigator. The administration of all such medication must be recorded in the appropriate section of the source documentation and eCRF. Non-sedating antihistamines such as Allegra® are allowed, as are OTC non-stimulant cold remedies such as guaifenesin.

The use of inhaled steroids (corticosteroids) for asthma is allowed.

9.12.2 Prohibited Therapies

All ADHD medications will be discontinued prior to starting this study. There will be a wash-out phase of 5 days for stimulants and 14 days for atomoxetine and noradrenergic agonists. Study subjects will not start any new ADHD medication during the study. Due to their potential to interfere with safety, efficacy, or tolerability assessments, the following medications are prohibited during the study:

- Any medication which is a substrate of CYP3A4, CYP2B6 or CYP2D6.
- Norepinephrine reuptake inhibitors.
- Anxiolytic or sedative hypnotic medications.
- Antidepressants, tricyclic antidepressants , selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors including atomoxetine (Strattera).
- Clonidine.
- Guanfacine.
- Mood stabilizers (including lithium, anticonvulsants, and antipsychotics).
- Antihypertensive agents.
- Psychostimulants.
- Sedating antihistamines.
- Investigational compounds.
- All herbal preparations.
- Cough/cold preparations containing stimulants.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study, at the discretion of the investigator and sponsor.

9.13 Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice. In order to support a subject's transition from the clinical trial, after care and medical oversight will be covered in the amount of $250.00 per month for a total of up to 3 months. Payment will be made to the site to ensure appropriate medical oversight of the subject during titration and to cover costs for prescribed medication within the allotted total.

10. STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 17.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible, ideally within 2 days of the originally scheduled date.

10.1 Study Periods and Visits

10.1.1 Screening and Wash-out

10.1.1.1 Screening (Visit 1, Day -21 [± 2 days])

The subject must be screened within 21 days [± 2 days] before enrollment in the study. The following procedures will be performed at Screening:

1. Obtain written informed consent/assent.
2. Perform a psychiatric evaluation Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL).
3. Conduct the WASI-II brief IQ test (IQ should be > 79).
4. Conduct ADHD-RS-5 evaluation.
5. Conduct CGI-S evaluation.
6. Review inclusion/exclusion criteria.
7. Collect demographic information.
8. Record medical and medication history including confirmation from the sponsor that each subject has been determined to have disruptive mutations in genes within the GRM-network as determined by the presence of CNVs (GRM biomarker-positive subjects).
9. Perform a physical examination including vital signs (resting blood pressure, heart rate, and respiratory rate), weight, and height.
10. Collect blood and urine for clinical laboratory tests: hematology, serum chemistry, and urinalysis.
11. Perform 12-lead ECG.
12. Perform a serum pregnancy test (for females of childbearing potential only).
13. Perform urine drug test.
14. Conduct C-SSRS evaluation.
15. Access IWRS.
16. Assess and record concomitant medication and ongoing AEs.

If more than 23 days have elapsed between the Screening Visit and the Baseline Visit the following procedures must be repeated and the results available and reviewed prior to proceeding with the Baseline Visit:

- Collect blood and urine for clinical laboratory tests: hematology, serum chemistry, and urinalysis.
- Perform a serum pregnancy test (for females of childbearing potential only).
- Measure vital signs (resting blood pressure, heart rate, and respiratory rate) and weight.
- Perform 12-lead ECG.
- Perform urine drug test.

10.1.1.2 Wash-out Period

Caregivers will receive a telephone call no later than at Day -14 (± 2 days) before the scheduled day of treatment initiation to confirm that stimulant and/or non-stimulant therapies for ADHD are being washed out.

The following details will be recorded:

1. Review inclusion/exclusion criteria.
2. Assess and record concomitant medication and newly occurring AEs since the last evaluation.

Subjects who do not require a washout call must still be contacted by phone prior to the Baseline visit being conducted.

10.1.2 Baseline (Visit 2, Day -1 [± 2 days])

Subjects will attend a baseline visit (Day -1) on the day before starting study treatment (Day 1). Subjects who remain eligible for the study will be given blinded IP at the initial dose (100 mg twice daily) to begin treatment the following day (Day 1).

The following procedures will be performed at Visit 2:

1. Review inclusion/exclusion criteria.
2. The subject will be randomized to NFC-1 or placebo via IWRS.
3. Measure vital signs (resting blood pressure, heart rate, and respiratory rate) and weight.
4. Perform 12-lead ECG.
5. Perform a urine pregnancy test (for females of childbearing potential only).
6. Conduct ADHD-RS-5 evaluation.
7. Conduct CGI-S evaluation.
8. Conduct ASHS evaluation.
9. Conduct SCARED evaluation.
10. Conduct C-SSRS evaluation.
11. Access IWRS.
12. Dispense IP at initial dose level of 100 mg twice daily with instructions to begin taking the IP the following day.
13. Assess and record concomitant medication and newly occurring AEs since the last evaluation.

10.1.3 Double-blind Treatment Period

The double-blind treatment period will comprise a dose optimization phase of 28 days and a subsequent dose maintenance phase of 14 days.

10.1.3.1 Dose Optimization Phase (Visit 3, Day 7 [± 2 days], Visit 4, Day 14 [± 2 days], Visit 5, Day 21 [± 2 days], and Visit 6, Day 28 [± 2 days])

Subjects will take 100 mg NFC-1 or placebo twice daily from Study Day 1. During the 4-week dose-optimization phase, subjects will be administered 100 mg, 200 mg, or 400 mg IP twice daily based on dose assessments performed by the investigator.

Subjects will attend a visit for evaluation by the investigator on the last day of each week of treatment during the optimization phase. Subjects will undergo the same evaluations at the end of each of the 4 weeks of the dose-optimization phase. During these visits, the investigator will assess the tolerability and efficacy of the subject's current IP dose, and categorize their response as intolerable, ineffective, or acceptable. Based on this categorization, the subjects will be dispensed the next appropriate dose of the IP, to begin taking at the next scheduled dosing timepoint (see Section 9.9 for the definition of the dose adjustment criteria).

The following procedures will be performed at Visit 3 (Day 7 [± 2 days]), Visit 4 (Day 14 [± 2 days]), Visit 5 (Day 21 [± 2 days]), and Visit 6 (Day 28 [± 2 days]):

1. Measure vital signs (resting blood pressure, heart rate, and respiratory rate) and weight.
2. Collect blood and urine for clinical laboratory tests: hematology, serum chemistry, and urinalysis (at Visit 3 only).
3. Perform 12-lead ECG.
4. Perform a urine pregnancy test (for females of childbearing potential only).
5. Conduct ADHD-RS-5 evaluation.
6. Conduct CGI-I evaluation.
7. Conduct C-SSRS evaluation.
8. Access IWRS.
9. Conduct dose assessment and dispense the IP at the appropriate dose level, with instructions to begin taking the provided IP at the next scheduled dosing timepoint.
10. Subject returns unused IP.
11. Assess subject compliance using returned IP.
12. Assess and record concomitant medication and newly occurring AEs since the last evaluation.

10.1.3.2 Dose Maintenance Phase (Visit 7, Day 35 [± 2 days], Visit 8, Day 42 [± 2 days], or Early Termination) Evaluation

At Day 35 and Day 42 or ET of the study, the following procedures will be performed:

1. Perform a physical examination and measure height (at Visit 8/ET only).
2. Measure vital signs (resting blood pressure, heart rate, and respiratory rate) and weight.
3. Collect blood and urine for clinical laboratory tests: hematology, serum chemistry, and urinalysis (at Visit 8/ET only).
4. Perform 12-lead ECG.
5. Perform a urine pregnancy test (for females of childbearing potential only).

6. Conduct ADHD-RS-5 evaluation.
7. Conduct CGI-S evaluation (at Visit 8/ET only).
8. Conduct CGI-I evaluation.
9. Conduct ASHS evaluation (at Visit 8/ET only).
10. Conduct SCARED evaluation (at Visit 8/ET only).
11. Conduct C-SSRS evaluation.
12. Access IWRS.
13. Subject returns unused IP.
14. Assess subject compliance using returned IP.
15. Assess and record concomitant medication and newly occurring AEs since the last evaluation.

10.1.4 7-day Follow-up Call

At Day 49 (+ 5 days), caregivers will receive a telephone call to assess and record concomitant medication and newly occurring AEs since the last evaluation.

10.2 Study Duration

The overall study duration is expected to be 70 days (including up to 21 days of screening inclusive of a maximum 14 days of wash-out, approximately 42 days of treatment, and a follow-up period of approximately 7 days).

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening period: approximately 21 days.
2. Wash-out period: if applicable, up to 14 days.
3. Dose optimization phase: 28 days.
4. Dose maintenance phase: 14 days.
5. Follow-up: 7 days (+5 days) after the last dose of IP.

The maximum study duration for each subject is approximately 70 days.

The maximum treatment duration for each subject is 42 days.

10.3 Assessments

10.3.1 Screening

10.3.1.1 Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime

The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R) and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria. Probes and objective criteria are provided to rate individual symptoms.

The primary diagnoses assessed with the K-SADS-PL include, but are not limited to: major depression, dysthymia, mania, bipolar disorders, schizoaffective disorders, panic disorder, agoraphobia, separation anxiety disorder, avoidant disorder of childhood and adolescence, simple phobia, social phobia, overanxious disorder, generalized anxiety, obsessive compulsive disorder, ADHD, conduct disorder, and oppositional defiant disorder.

The K-SADS-PL will be administered by the investigator, by interviewing the parent or caregiver, the child, and finally achieving summary ratings, which include all sources of information (parent or legal caregiver, child, school, chart, and other).

Time of administration: 90 minutes

10.3.1.2 Wechsler Abbreviated Scale of Intelligence

The WASI-II is administered by the investigator. It comprises a 4 sub-test form (vocabulary, similarities, block design, matrix reasoning) and yields 3 scales:

- Full Scale IQ-4 score: estimate of generalized cognitive ability.
- Verbal Comprehension Index score: measure of crystallized abilities.
- Perceptual Reasoning Index score: measure of nonverbal fluid abilities and visuomotor/coordination skills.

Time of administration: 30 minutes

10.3.2 Efficacy

All scales included in Section 10.3.2 that are described as "clinician rated" are to be completed by the principal investigator or a delegated subinvestigator who is a licensed clinician. A licensed clinician is defined as a doctor of medicine, doctor of osteopathic medicine, or licensed psychologist with a PhD or another individual that is approved by the sponsor or designee. All raters are to be approved by the sponsor or designee.

10.3.2.1 Attention Deficit Hyperactivity Disorder Rating Scale Version 5

The ADHD-RS-5 (7) will be used as the primary measure. This parent-reported clinician-rated scale will be administered at each visit, beginning at Screening to capture the ADHD symptoms within each study week. The ADHD-RS-5 is a parent-reported/clinician-rated scale that was developed to measure the behaviors of children with ADHD, and comes in a Home Version and a School Version, with separate forms for children (ages 5-10 years) and adolescents (11-17 years); it consists of 18 items designed to reflect the symptomatology of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) DSM-5 criteria. Each item will be scored on a range of 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54. The 18 items may be grouped into 2 subscales: inattention and hyperactivity/impulsivity. The Inattention subscale raw score is computed by summing the item scores for Items 1–9. The Hyperactivity–Impulsivity subscale raw score is computed by summing the item scores for Items 10–18. Additionally, the ADHD-RS-5 incorporates 2 impairment scales keyed to the inattention and hyperactivity–impulsivity dimensions, which allow the clinician to assess the extent to which ADHD-related problems adversely affect the home and/or school functioning of children and adolescents

Time of administration: 10-15 minutes

10.3.2.2 Clinical Global Impression-Improvement and Severity Scales

The CGI-I and CGI-S scales will be used as a secondary outcome measure for estimating level of functioning in response to NFC-1 treatment. These scales record the investigator's global assessment of the severity of the symptoms and changes in symptoms from Baseline based on reports from parents, subject, and minimal direct observation (8). This assessment will guide the investigator during dosing adjustments.

A CGI-S scale captures the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) (Table 2) on Baseline (Visit 2) and at Visit 8/ET.

At each visit from Visit 3 to Visit 8/ET, the investigator will assess the improvement of the subject's illness severity on the 7-point CGI-I scale ranging from 1 (very much improved) to 7 (very much worse) (Table 2).

The CGI-based assessments have been used to evaluate efficacy of ADHD medications (9), where they have general consistency and reliability.

Time of administration: 10-20 minutes.

Table 2: Clinical Global Impression Scales

SEVERITY – CGI-S	
Normal, not at all ill	1
Borderline mentally ill	2
Mildly ill	3
Moderately ill	4
Markedly ill	5
Severely ill	6
Amongst the most extremely ill patients	7

IMPROVEMENT – CGI-I	
Very much improved	1
Much improved	2
Minimally improved	3
No change	4
Minimally worse	5
Much worse	6
Very much worse	7

Abbreviations: CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity

10.3.2.3 Adolescent Sleep Hygiene Scale

The ASHS is a self-report questionnaire assessing sleep practices theoretically important for optimal sleep in adolescents aged ≥ 12 years of age. It assesses physiological (eg, evening caffeine consumption), cognitive (eg, thinking about things that need to be done at bedtime), emotional (eg, going to bed feeling upset), sleep environment (eg, falling asleep with the lights on), sleep stability (eg, different bedtime/wake time pattern on weekdays and at weekends), substance use (eg, evening alcohol use), daytime sleep (eg, napping), and having a bedtime routine.

The ASHS will be assessed at Baseline (Visit 2) and Visit 8/ET.

Time of administration: 10 minutes.

10.3.2.4 Screen for Childhood Anxiety-related Emotional Disorders

The SCARED is a child self-report instrument for ages 8-18 years used to screen for childhood anxiety disorders including general anxiety disorder, separation anxiety disorder, panic disorder, and social phobia. In addition, it assesses symptoms related to school phobias.

The SCARED consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders. The scale has good internal consistency, test-retest reliability, and discriminant validity, and it is sensitive to treatment response.

The SCARED will be assessed at Baseline (Visit 2) and Visit 8/ET.

Time of administration: 10 minutes.

10.3.3 Safety

Safety and tolerability assessments will include the frequency and severity of AEs as well as the evaluation of changes in clinical laboratory values, vital signs, ECG recordings, and C-SSRS.

10.3.3.1 Clinical Laboratory Safety Assessments

10.3.3.1.1 Clinical Laboratory Tests to be Performed

Samples for the following clinical laboratory tests will be collected at the time points specified in the schedule of events (Section 17.1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential.
Serum chemistry	Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, creatine kinase, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid.
Urinalysis	pH, specific gravity, blood, glucose, protein, ketones.
[Urine/serum] pregnancy test	For women of childbearing potential only.
Urine drug screen	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids, propoxyphene and methadone.

Blood samples will be collected as specified in the study laboratory manual.

Laboratory specimens will be analyzed at the central laboratory as specified in the study laboratory manual.

10.3.3.1.2 Biological Markers

Not applicable.

10.3.3.1.3 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

10.3.3.1.4 Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this study will be provided by the responsible laboratory and submitted to Medgenics, Inc. prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his/her assessment of the clinical relevance in the appropriate eCRF.

All laboratory values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the medical monitor and reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.3.2 Clinical Examinations

10.3.3.2.1 Vital Signs

Vital signs, including heart rate, respiratory rate, and systolic and diastolic blood pressure will be measured after the subject has been in a sitting position for 5 minutes.

10.3.3.2.2 Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, subject initials, date, and time of the recording and will be attached to the subject's eCRF.

All ECG values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the medical monitor and reported as AEs and followed, as described in Section 11.2.5.

10.3.3.2.3 Physical Examination

A complete physical examination (excluding the genitourinary examination) will be performed at Visit 1 before potential exposure to the IP and at Visit 8 at the completion of exposure.

10.3.3.3 Columbia Suicide Severity Rating Scale

The C-SSRS (10) is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The interview and rating for the C-SSRS must be completed by a licensed clinician and is medically responsible for the subject. A licensed clinician is defined as a doctor of medicine, doctor of osteopathic medicine, or licensed psychologist with a PhD. The C-SSRS has a "baseline" version which will be completed at Screening (Visit 1) and a "Since Last Visit" version that will be completed at all subsequent visits. There are a maximum of 19 items to be completed: 7 that are required, 10 potential additional items if there is a positive response to a required item, and 2 items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

Time of administration = 10 minutes.

10.3.3.4 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 11.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition (worsening of a pre-existing condition is considered an AE).

Events occurring in subjects treated with placebo or during treatment-free periods of the study are also considered AEs.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an IP, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE is one for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

11.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  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 which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly.
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.*
- Is an important medical event.
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. 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.*

11.1.4 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.5 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of IP (NFC-1 or placebo) and not more than 7 days after the last administration of IP.

11.2 Management of Adverse Events

Adverse events will be collected from the time of signing informed consent form (ICF) through the Follow-up Visit or Early Termination Visit, whichever occurs first.

11.2.1 Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild:	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe:	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.3.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.3.

11.2.2.3 Action(s) Taken

Action(s) taken may consist of:

Dose increased:	An indication that a medication schedule was modified by addition; either by changing the frequency, strength or amount.
Dose not changed:	An indication that a medication schedule was maintained.
Dose reduced:	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount.
Drug interrupted:	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn:	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable:	Determination of a value is not relevant in the current context.
Unknown:	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved.
- Recovered/resolved with sequelae.
- Recovering/resolving.
- Not recovered/not resolved.
- Fatal*.
- Unknown.

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are listed below.

Not related:	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (eg, no temporal relationship to drug administration, because the drug was administered after onset of event;

	investigation shows that the drug was not administered; another cause was proven).
Unlikely related:	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events or underlying disease provide plausible explanations.
Possibly related:	An AE with a reasonable time sequence to administration of the IP, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related:	An AE occurring in a plausible time relationship to IP administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

The AE relationship to IP will be assessed separately by the investigator and Medgenics.

11.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. The period of observation for the study is described in Section 11.2.

- AE name or term.
- When the AE first occurred (start date and time).
- When the AE stopped (stop date and time or an indication of "ongoing").
- Severity of the AE.
- Seriousness (hospitalization, death, etc.).
- Actions taken.
- Outcome.
- Investigator opinion regarding the AE relationship to the IP.

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may continue in the study/should be withdrawn from the study and the reason must be documented in the eCRF. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, or for which continued administration of IP is not reasonable in view of the potential benefit to subject, the investigator must decide whether to stop the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double- or triple-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 7 days after the last dose of the IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate eCRF.

11.2.6 Notification

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing, signing, and dating the SAE pages, verifying the accuracy of the information recorded on the SAE pages with the corresponding source documents and eCRF, and sending the SAE pages to the [redacted] Pharmacovigilance Department by one of the following methods:

- Email: [redacted].
- FAX number: [redacted]

The written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number.
- Reporter (study site and investigator).
- Subject's study number.
- Subject's year of birth.
- Subject's gender.
- Date of first dose of IP.
- Date of last dose of IP, if applicable.
- Adverse event term.
- Date of occurrence of the event.
- A brief description of the event, outcome to date, and any actions taken.
- The seriousness criteria(on) that were met.
- Concomitant medication at onset of the event.
- Relevant past history information.
- Relevant laboratory test findings.
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?").
- Whether and when the investigator was unblinded as to the subject's treatment assignment.

Any missing or additional relevant information concerning the SAE should be provided to the recipient(s) of the initial information as soon as possible on a follow-up SAE Report Form together with the following information: AE, date of occurrence, subject ID, study ID, IP, and site number. This will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the [redacted] Pharmacovigilance Department using a follow up request form. The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his/her health authorities, institutional review boards (IRBs), principal and coordinating investigators, study investigators, and institutions.

11.2.6.2 Non-serious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by [redacted] to Medgenics.

11.3 Special Considerations

11.3.1 Adverse Events of Special Interest

The following events will be considered as AEs of special interest during this study:

- Psychosis.
- Suicidal ideation.

Based on the population under study, and their age, suicidal ideation will be considered as an AE of special interest.

11.3.2 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy within 24 hours of learning of the pregnancy to [redacted] Pharmacovigilance using the Pregnancy Data Collection Form via the same fax and email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an Exposure in Utero form/other designated form provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero Form/other designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

12. DATA SAFETY MONITORING BOARD

No Data Safety Monitoring Board will be required.

13. STATISTICS

13.1 Study Endpoints

13.1.1 Primary Efficacy Endpoint

The primary endpoint for the assessment of efficacy will be the ADHD-RS-5 score. The analysis will be based on changes from the baseline value and will test the hypothesis that there is no difference between the treatments (ie, that the difference is 0) against a 2-tailed alternative.

13.1.2 Secondary Efficacy Endpoints

Secondary endpoints will include the CGI-I, CGI-S, and other assessment scales. Further exploratory analyses will examine the effect of covariates such as dose-level and age. All quantitative endpoints will be described with traditional summary statistics and tabulated by treatment group and visit.

13.1.3 Safety Endpoints

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Affairs (MedDRA) and tabulated by system organ class and preferred term. Adverse events will be analyzed by frequency, severity, relationship to IP, and their effect on participation in the study.

Clinical laboratory values will be compared to normal ranges and flagged for levels of clinical concern. The analysis will focus on the frequencies of abnormal values as well as within-subject changes observed during the course of the study.

Vital signs and ECG recordings will also be examined for changes during the study that may be attributed to exposure to IP.

The C-SSRS will also be examined for changes that may be attributed to exposure to IP.

13.2 Sample Size Determination

Enrollment of 90 subjects is expected to yield 80 subjects who complete the study as planned. Assuming an effect size of 0.7, this number will provide approximately 90% power to detect a significant difference between the treatments based on a 2-tailed $\alpha = 0.05$ comparison of mean change from Baseline.

13.3 Analysis Populations

The design of this study yields 3 main populations of scientific interest.

The Safety Population will consist of all subjects who are randomized into the study and receive any amount of IP.

The Intent-to-Treat (ITT) Population will be composed of all subjects who are randomized into the study.

The occurrence of significant protocol deviations may lead to the exclusion of some subjects from specific analyses, thereby yielding a Per-protocol (PP) Population.

Specific subgroups of these populations may also be evaluated as warranted by the experimental results.

Membership in the analysis populations will be determined prior to unblinding.

13.4 Statistical Analyses

This section presents a summary of the planned statistical analyses. Additional details regarding data handling, analytical methods, and presentation of results will be found in the Statistical Analysis Plan for this study. The Statistical Analysis Plan will be finalized prior to database lock.

13.4.1 Study Subjects and Demographics

13.4.1.1 Disposition and Withdrawals

The disposition of all subjects enrolled in this study will be fully described with respect to their randomization status and ultimate discontinuation. Subjects who discontinue the study will be summarized with the reason for discontinuation.

13.4.1.2 Protocol Deviations

All subject data will be reviewed for the occurrence of protocol deviations. Prior to database lock, all protocol deviations will be reviewed in a blinded fashion and classified with respect to the potential to influence experimental outcomes. The results of this review may lead to enumeration of a PP Population, as described in Section 13.3.

13.4.1.3 Demographics and Other Baseline Characteristics

The analysis of demographic and baseline data will be performed for all study populations.

Demographic variables include age, gender, race, ethnicity, height, and weight. Baseline subject characteristics to be summarized will include medical history, physical examination, ECG assessment, C-SSRS evaluation, an IQ test (WASI-II), and clinical laboratory tests.

Prior and concomitant medications will be summarized by treatment group and by the number and percentage of subjects taking each medication. Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.4.2 Exposure and Compliance

Exposure to IP will be summarized for all participating subjects. Subjects will be described with respect to cumulative exposure as well as categorized by the highest dose received.

Compliance with study medication will be determined for each subject. Based on capsule counts, the number of doses administered will be expressed as the proportion of doses scheduled. Compliance will be assessed independently for each phase of the study (ie, dose optimization and maintenance).

13.4.3 Efficacy Analyses

All efficacy measures will be described with standard summary statistics. Continuous variables will be summarized by N, mean, and standard deviation, and categorical variables by the number and percent of subjects in each category. Where appropriate, estimates will be presented with 95% confidence intervals.

Efficacy analyses will attempt to quantify the effects of treatment with NFC-1 relative to placebo. The null hypothesis of no difference between active and placebo will be tested against a 2-tailed alternative with a type-I error rate of 0.05.

13.4.3.1 Primary Analysis

The primary analysis will focus on the effect of treatment on ADHD, as indicated by the ADHD-RS-5. The change in ADHD-RS-5 will be derived as the difference between the last post-treatment value and that recorded at the Baseline visit. The analysis of the change will employ a 1-way analysis of variance (ANOVA) model with a term for treatment (active or placebo). Depending on the fit of the single-factor model, subsequent exploratory analyses may be performed that include additional independent factors (eg, age, gender, and/or maintenance dose of study drug) as well as covariates that have been determined to be associated with experimental results (eg, baseline value of the dependent variable). Results of these exploratory analyses will be presented as estimates for all factors included in the model with corresponding 95% confidence intervals and associated levels of statistical significance.

This analysis will be performed with primary focus on the ITT Population.

13.4.3.2 Secondary Analyses

Secondary efficacy analyses will examine the effects of the treatment on changes observed in other efficacy measures (ie, CGI-S, ASHS, and SCARED). These analyses will model the overall or total scale scores and will employ the same general approach as for the primary analysis. All secondary efficacy measures will be treated as continuous measurement scales and analyzed by the ANOVA methods described above.

Results of the CGI-I assessment will also be dichotomized and presented for each week of treatment. CGI-I scores of 1 or 2 will be combined into a single group labelled "Improved" and scores of 3 to 7 will be combined and labelled "No Improvement." The observed proportions of "Improved" subjects will be compared between treatment groups at each week of the study.

In addition, analysis of the weekly results from ADHD-RS-5 and CGI-I will be evaluated for evidence of trend over time. This analysis will employ a linear mixed-effects model with repeated measures on each subject. Terms for the model will be selected as described for the primary analysis.

Secondary analyses will focus on the ITT Population. However, analyses of the PP Population may be performed if warranted by the data.

13.4.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 13.3). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory values, vital signs, ECG results, C-SSRS, and physical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.4.4.1 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class (SOC) and preferred term. Treatment-emergent AEs will be presented as the number and proportion of subjects reporting each event. Similar summaries will be produced for post-treatment AEs, SAEs, AEs leading to termination, and AEs with at least a possible relationship to the IP. The intensity of AEs and the relationship to the IP will also be summarized for each SOC and preferred term.

13.4.4.2 Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from baseline values will be presented by treatment group for each study visit.

The number of subjects with clinical laboratory values below, within, or above normal ranges, at each study visit will be tabulated (shift tables) for each clinical laboratory analyte by treatment group.

13.4.4.3 Vital Signs and Electrocardiograms

Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate), and ECG results will be summarized by visit and treatment group using appropriate descriptive statistics. The number and percentage of subjects with abnormal ECG findings will be summarized by treatment group for each study visit.

13.4.4.4 Columbia Suicide Severity Rating Scale

The C-SSRS score will be summarized by visit and treatment group using descriptive statistics.

13.4.4.5 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

13.4.5 Interim Analysis

No interim analysis is planned for this study.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

14.1 Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Medgenics agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement in Section 17.2, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 GCP and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (eg, subinvestigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, IPs, and their specific duties within the context of the study. Investigators are responsible for providing Medgenics with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.2 Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study upon agreement with the medical monitor.

14.4 Study Documents

All documentation and material provided by Medgenics for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Investigator's Regulatory Documents

The regulatory documents are listed in the Study Manual.

The regulatory documents must be received from the investigator and reviewed and approved by Medgenics or its designee before the study site can initiate the study and before Medgenics will authorize shipment of IP to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the NFC-1 IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.2 Electronic Case Report Forms

By signing the Investigator's Agreement in Section 17.2, the investigator agrees to complete the eCRFs and maintain source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRFs used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF according to the completion guidelines provided by the sponsor or its designee.

The eCRFs may be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.3 Source Documents

All information recorded in the eCRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5 Data Quality Control

Medgenics and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Medgenics and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Medgenics personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the eCRF with the source documents.
- Consenting procedures.
- AE procedures.
- Storage and accountability of IP and study materials.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement in Section 17.2, the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area, and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Medgenics or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.5.2 Data Management

Medgenics or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Medgenics or designee. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit.
- Audit of computer database quality control.
- Audit of clinical report quality control.

Medgenics or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Medgenics immediately.

14.6 Study Termination

The study may be terminated at Medgenics' discretion at any time and for any reason.

14.7 Study Site Closure

At the end of the study, all study sites will be closed. Medgenics may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines.
- Inadequate subject enrollment.

14.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

14.7.2 Sample Retention

Not applicable.

14.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Medgenics. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(ies) having jurisdiction over the conduct of the study.

14.9 Use of Information and Publication

All information concerning NFC-1, Medgenics' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Medgenics or designee to the investigator and not previously published, is considered confidential and remains the sole property of Medgenics. Case report forms also remain the property of Medgenics. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Medgenics in connection with the continued development of NFC-1 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Medgenics. Publication or other public presentation of NFC-1 data resulting from this study requires prior review and written approval of Medgenics. Abstracts, manuscripts, and presentation materials should be provided to Medgenics for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Medgenics has reviewed and commented on such a presentation or manuscript for publication.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the protocol, the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 1996 Version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the study is conducted.

See Appendix B for regulations and guidelines.

15.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

15.3 Approval by Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the Medgenics monitor before shipment of

investigational drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Medgenics, IRB Approval Form, or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by Medgenics before implementation. This written approval will consist of a completed IRB approval form or written documentation from the IRB containing the same information.

15.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and Medgenics.

16. REFERENCES

1. NFC-1 Investigator's Brochure, 2015.
2. Elia J, Glessner JT, Wang K, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nat Genet. 2011;44(1):78-84.
3. Oka M, Itoh Y, Tatsumi, S, Ma FH, Ukai Y, Yoshikuni Y, Kimura KA. A novel cognition enhancer NS-105 modulates adenylate cyclase activity through metabotropic glutamate receptors in primary neuronal culture. Naunyn Schmiedebergs Arch Pharmacol. 1997;356(2):189-96.
4. Oka M, Itoh Y, Shimidzu T, Ukai Y, Yoshikuni Y, Kimura K. Involvement of metabotropic glutamate receptors in Gi- and Gs-dependent modulation of adenylate cyclase activity induced by a novel cognition enhancer NS-105 in rat brain. Brain Res. 1997;754(1-2):121-30.
5. Hirouchi M, Oka M, Itoh Y, Ukai Y, Kimura K. Role of metabotropic glutamate receptor subclasses in modulation of adenylyl cyclase activity by a nootropic NS-105. Eur J Pharmacol. 2000;387(1):9-17.
6. Ogasawara T, Itoh Y, Tamura M, Mushiroi T, Ukai Y, Kise M, Kimura K. Involvement of cholinergic and GABAergic systems in the reversal of memory disruption by NS-105, a cognition enhancer. Pharmacol Biochem Behav. 1999;64(1):41-52.
7. DuPaul GJ, Power TJ, Anastopoulos AD, and Reid R. ADHD Rating Scale—5 for Children and Adolescents Checklists, Norms, and Clinical Interpretation. Guildford Press. 2016.
8. Busner J, Targum SD. The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry (Edgmont). 2007;4(7):28-37.
9. Goodman DW. Lisdexamfetamine dimesylate (vyvanse), a prodrug stimulant for attention-deficit/hyperactivity disorder. PT. 2010;35(5):273-87.
10. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

17. ATTACHMENTS

17.1 Schedule of Events

	Screening	Wash-out Call	Baseline	Treatment Period						7-day Follow-up Call[a]
				Dose Optimization				Dose Maintenance		
Visit	**1**	**No Visit**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**No Visit**
Assessment Day	**-21**	**-14**	**-1**	**7**	**14**	**21**	**28**	**35**	**42**	**49**
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**+ 5 days**
Informed consent/ assent[b]	✓									
Psychiatric evaluation (K-SADS-PL)	✓									
WASI-II (brief IQ test)	✓									
Inclusion/exclusion criteria	✓	✓ (review)	✓ (review)							
Demographics	✓									
Randomization			✓							
Medical and medication history[c]	✓									
Physical examination	✓								✓	
Vital signs (resting blood pressure, heart rate, and respiratory rate)	✓[g]		✓	✓	✓	✓	✓	✓	✓	
Height (calibrated stadiometer)	✓								✓	
Weight (calibrated scale)	✓[g]		✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory test	✓[g]			✓					✓	
12-lead ECG	✓[g]		✓	✓	✓	✓	✓	✓	✓	
Serum pregnancy test (females of childbearing potential)	✓[g]									
Urine pregnancy test (females of childbearing potential)			✓	✓	✓	✓	✓	✓	✓	
Urine drug test	✓[g]									
Investigator dose assessment				✓	✓	✓	✓			

	Screening	Wash-out Call	Baseline	Treatment Period						7-day Follow-up Call[a]
				Dose Optimization				Dose Maintenance		
Visit	**1**	**No Visit**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**No Visit**
Assessment Day	**-21**	**-14**	**-1**	**7**	**14**	**21**	**28**	**35**	**42**	**49**
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**+ 5 days**
ADHD-RS-5	✓		✓	✓	✓	✓	✓	✓	✓	
CGI-S[d]	✓		✓						✓	
CGI-I[e]				✓	✓	✓	✓	✓	✓	
ASHS			✓						✓	
SCARED			✓						✓	
C-SSRS	✓		✓	✓	✓	✓	✓	✓	✓	
Access IWRS[f]	✓		✓	✓	✓	✓	✓	✓		
Study drug dispensed			✓	✓	✓	✓	✓	✓		
Study drug returned				✓	✓	✓	✓	✓	✓	
Compliance				✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Abbreviations: ADHD-RS-5 = Attention Deficit Hyperactivity Disorder Rating Scale Version 5, ASHS = Adolescent Sleep Hygiene Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ET = early termination, IQ = intelligence quotient, IWRS = interactive web response system, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version, SCARED = Screen for Childhood Anxiety-related Emotional Disorders, WASI-II = Wechsler Abbreviated Scale of Intelligence, second edition

a Caregivers will receive a follow-up telephone call from a study staff member 7 days after the last visit to collect information about any ongoing AEs and concomitant medication.

b Informed consent to be completed by a duly authorized subject representative. Assent is to be provided by subject where required.

c Medical and medication history including confirmation from the sponsor that each subject has been determined to have disruptive mutations in genes within the GRM-network as determined by the presence of CNVs (GRM biomarker-positive subjects).

d The CGI–S rates illness severity on the following 7-point scale: 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill subjects.

e The CGI-I requires the investigator to assess how much the subject's illness has improved or worsened: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

f IWRS will assign treatment numbers and will also manage all logistical aspects of treatments (eg, drug resupply and expiry dates).

g If more than 23 days have elapsed between the Screening Visit and the Baseline Visit clinical laboratory tests, serum pregnancy test, vital signs and weight, urine drug test, and ECG must be repeated and the results available and reviewed prior to proceeding with the Baseline Visit.

17.2 Investigator's Agreement

PROTOCOL NUMBER:	MDGN-NFC1-ADHD-201
PROTOCOL TITLE:	A Multicenter, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of NFC-1 in Adolescents (Ages 12-17 Years) with Genetic Disorders Impacting Metabotropic Glutamate Receptors and Attention Deficit Hyperactivity Disorder
FINAL PROTOCOL:	27 Oct 2016

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Medgenics and [redacted] during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an IP during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

APPENDICES

A. Study-specific Requirements

B. Regulations and Good Clinical Practice Guidelines

A. Study-specific Requirements

All diagnostic scales are available under license at the study centers.

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/products/guidelines.html