PROTOCOL

PRODUCT NAME:	AEVI-001 (fasoracetam monohydrate)
PROTOCOL NUMBER:	**AEVI-001-ADHD-202**
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Multicenter, 2-Part, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of AEVI-001 in Children and Adolescents (Ages 6-17 Years) with Attention Deficit Hyperactivity Disorder and with or without Copy Number Variants in Specific Genes Implicated in Glutamatergic Signaling and Neuronal Connectivity
PROTOCOL VERSION AND DATE:	Version 7.0, 25 July 2018
COORDINATING/PRINCIPAL INVESTIGATOR:	[redacted]
SPONSOR:	Aevi Genomic Medicine, Inc. 435 Devon Park Drive, Suite 715 Wayne, PA, 19087 Phone: +1-610-254-4201 Fax: +1-610-717-3390
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

CONFIDENTIAL

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: **AEVI-001-ADHD-202**

PROTOCOL TITLE: A Multicenter, 2-Part, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of AEVI-001 in Children and Adolescents (Ages 6-17 Years) with Attention Deficit Hyperactivity Disorder and with or without Copy Number Variants in Specific Genes Implicated in Glutamatergic Signaling and Neuronal Connectivity

FINAL PROTOCOL: 25 July 2018

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]

[redacted] Date [redacted]

Chief Scientific Officer
Aevi Genomic Medicine, Inc.

2. EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must e-mail the Serious Adverse Event Form within 24 hours to the CRO Pharmacovigilance Department at one of the methods noted below. The Investigator should also notify the CRO Medical Monitor.

- ☐ Email: [redacted]
- ☐ Fax number: [redacted]

In the event of an SAE, the Investigator should also notify the CRO Medical Monitor. All medical personnel and their contact details can be found in the site study documentation (study binder). For protocol safety-related issues, please first contact the CRO Medical Monitor using the contact information below:

CRO Medical Contact:

Name: [redacted]

3. REASON FOR AMENDMENT

The protocol was amended to clarify the following:

- In Part B of the study, subjects may not have any of the 272 gene mutations previously implicated in glutamatergic signaling and neuronal activity. The list of excluded mutations includes the 8 gene mutations studied in Part A and an additional 264 mutations identified in an antecedent study.
- Removed the requirement for Part A of the study is positive (e.g., meets the primary endpoint) in order for Part B to be conducted.
- Pooled analyses using both parts may also be conducted, if appropriate
- The unblinded statistician is from [redacted].

4. SYNOPSIS

PRODUCT NAME	AEVI-001 (fasoracetam monohydrate)
PROTOCOL NUMBER	AEVI-001-ADHD-202
DEVELOPMENT PHASE	Phase 2
PROTOCOL TITLE	A Multicenter, 2-Part, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of AEVI-001 in Children and Adolescents (Ages 6-17 Years) with Attention Deficit Hyperactivity Disorder and with or without Copy Number Variants in Specific Genes Implicated in Glutamatergic Signaling and Neuronal Connectivity
OBJECTIVES	The primary objective of each part of this study is: To evaluate the efficacy of AEVI-001 compared with placebo in children and adolescents (6-17 years of age inclusive) with Attention Deficit Hyperactivity Disorder (ADHD) and with or without copy number variants (CNVs) in specific genes implicated in glutamatergic signaling and neuronal connectivity as measured by the change in ADHD rating scale, version 5 total score (ADHD-RS-5). The key secondary objective of each part of this study will be: To evaluate the efficacy of AEVI-001 compared with placebo using a global clinical measure of improvement, the Clinical Global Impressions – Global Improvement (CGI-I) at Visit 8/ET (Week 6/ET). Additional secondary objectives of each part of the study include: ☐ To evaluate AEVI-001 compared with placebo on response at Visit 8/ET (Week6/ET), based on the following parameters: o A ≥30% reduction from Baseline in ADHD-RS-5 total score. o Improved on the CGI-I which includes the categories of 1 (very much improved) and 2 (much improved). o Both a ≥30% reduction in ADHD-RS-5 total score and improved (1 [very much improved] and 2 [much improved]) on the CGI-I. ☐ To evaluate AEVI-001 compared with placebo on remission at Visit 8/ET (Week6/ET), based on the following parameters: o An ADHD-RS-5 total score ≤18. o A CGI-I of 1 (very much improved). o Both an ADHD-RS-5 total score ≤18 and a CGI-I of 1 (very much improved). ☐ To evaluate the efficacy of AEVI-001 compared with placebo using a global clinical measure of severity, the Clinical Global Impressions – Global Severity (CGI-S) at Visit 8 (Week 6). ☐ To evaluate the safety and tolerability of AEVI-001 compared with placebo based on occurrence of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory results, electrocardiogram (ECG) results, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Exploratory objectives of each part of the study include: ☐ To evaluate the efficacy of AEVI-001 compared with placebo on behavior as measured by the change from baseline at Visit 8 (Week 6) on Conners 3rd Edition-Parent Short form [Conners 3-P(S)].
STUDY DESIGN	This is a 2-part, 6-week, double-blind, dose-optimization, parallel-group study in children and adolescents (ages 6-17 years) with ADHD with and without CNVs in specific genes implicated in glutamatergic signaling and neuronal connectivity. Part A will include subjects determined to have one of 8 specific gene mutation(s) implicated

	in glutamatergic signaling and neuronal connectivity. Part B will be conducted and will assess subjects who do not have CNVs in any of the specific gene mutation(s) implicated in glutamatergic signaling and neuronal connectivity and may be completed at the discretion of the sponsor. Once subjects are confirmed as eligible for each part of the study, they will be randomized to one of two treatment groups (AEVI-001 or placebo) in a 1:1 ratio.
PLANNED NUMBER OF SUBJECTS	In Part A the study, 42 unique subjects are planned to be randomized to yield approximately 34 subjects who provide post-baseline efficacy data on the primary endpoint. In Part B of the study, 82 unique subjects are planned to be randomized to yield approximately 66 subjects who provide post-baseline efficacy data on the primary endpoint. Additionally, Part A of the study will include an interim analysis which will determine whether the sample size will be increased to a planned total of 64 randomized subjects. The number of planned subjects that may be randomized accounting for both study parts is approximately 146 unique subjects (Part A: approximately 64 randomized and Part B: 82 randomized).
STUDY ENTRY CRITERIA	**Inclusion criteria:** Subjects must fulfill the following requirements to be randomized into the study: 1. Subject and parent/legally authorized representative (LAR) can speak English fluently and have provided written informed consent, and assent (as applicable) for this study. 2. Subject is 6 to 17 years of age (inclusive) at the time of consent/assent. The date of signature of the informed consent/assent is defined as the beginning of the Screening Period. This inclusion criterion will only be assessed at the Screening Visit (Visit 1). 3. Subject is male or non-pregnant, non-lactating female, who if of childbearing potential agrees to comply with any applicable contraceptive requirements prior to administration of investigational product (IP). 4. Subject meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD based upon DSM-5 criteria. 5. Subject has a minimum score of ≥28 on the ADHD-RS-5 at the Baseline Visit (Visit 2). 6. Subject can swallow a capsule of investigational product whole. 7. Subject has been genotyped previously, has their identity confirmed (if required), and meets the following for the applicable part of the study: a. Part A: Determined to have a specific gene mutation(s) in one of 8 genes implicated in glutamatergic signaling and neuronal connectivity. The confirmation of a subject's positive status will be provided to the site. b. Part B: Determined not to have any of the specific genes of interest implicated in glutamatergic signaling and neuronal connectivity (N=272). The list of excluded mutations includes the 8 gene mutations studied in Part A and an additional 264 mutations identified in an antecedent study. The confirmation of a subject's negative status will be provided to the site. **Exclusion criteria:** The presence of any of the following criteria excludes a subject from being randomized into the study: 1. Subject or parent/LAR is, in the opinion of the investigator, mentally or legally

	incapacitated and/or has significant emotional problems at the time of the Screening Visit (Visit 1) which could interfere with the conduct of study evaluations. 2. Subject has a current, controlled or uncontrolled, co-morbid major psychiatric diagnosis (aside from ADHD), including an anxiety disorder, major depression, bipolar disease, schizophrenia (or any psychotic disorder), and moderate or severe intellectual disability. Mild anxiety and/or depressive symptoms that do not meet diagnostic criteria for an anxiety disorder or major depression and/or do not require treatment are not exclusionary. 3. Subject has autism spectrum disorder to include a DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder. 4. Subject has an intelligence quotient (IQ) <70 as determined by the Kaufman Brief Intelligence Test, Second Edition (KBIT-2). 5. Subject has a current or relevant history of a medical disorder that might confound the results of safety assessments conducted in the study. 6. Subject is currently taking any medication that might confound the results of safety assessments conducted in the study. 7. Subject meets DSM-5 diagnosis of conduct disorder. Oppositional defiant disorder is not exclusionary. 8. Subject is considered at risk for suicide (in the opinion of the investigator), has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. 9. Subject is either underweight or obese at the Screening Visit (Visit 1) based on Centers for Disease Control and Prevention (CDC) body mass index (BMI) for age-sex specific values. Underweight is defined as BMI-for-age and gender <5th percentile. Obese is defined as BMI-for-age and gender >97th percentile. 10. Subject's blood pressure measurements exceed the 95th percentile for age, sex, and height at the Screening Visit (Visit 1) and/or the Baseline Visit (Visit 2). 11. Subject has a known history of hypertension. 12. Subject has a known history of cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, or other serious cardiac problems. 13. Subject has a known family history of sudden cardiac death or ventricular arrhythmia. 14. Subject has any clinically significant abnormality on 12-lead ECG performed at the Screening Visit (Visit 1) and/or the Baseline Visit (Visit 2) such as serious arrhythmia, cardiac conduction problems, or other abnormalities deemed to be a potential safety issue. 15. Subject has a current or history of seizure disorder (except for infantile febrile seizures), a chronic or current tic disorder, or a current diagnosis of Tourette's Disorder. 16. Subject has a positive urine drug result at the Screening Visit (Visit 1) (except for subject's current stimulant therapy, if any) unless the Investigator can verify that the positive result at the Screening Visit (Visit 1) is attributed to medication that has been prescribed to the subject and will be discontinued

	prior to the Baseline Visit (Visit 2). In the latter instance, a positive result at the Screening Visit (Visit 1) attributed to a prescribed medication requires a re-test and a negative result to confirm subject eligibility prior to being enrolled. 17. Subject has current abnormal thyroid function at the Screening Visit (Visit 1), defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4). Treatment with a stable dose of thyroid medication for at least 3 months' prior the Screening Visit (Visit 1) is permitted. 18. Subject has a history of, been diagnosed with or is suspected to have a substance abuse or dependence disorder. 19. Subject has known or suspected intolerance or hypersensitivity to the investigational product(s), closely-related compounds, or any ingredients of the investigational product. 20. Subject has a history of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food. 21. Subject has used an investigational product, been enrolled in a clinical study (except AEVI-001-ADHD-002) including vaccines within 30 days of the Screening Visit (Visit 1). 22. Subject is a smoker or has used nicotine or nicotine-containing products once a week or on a more frequent basis. 23. Subject consumes any alcoholic beverages once a week or on a more frequent basis. 24. 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. 25. Subject was previously enrolled in another part of this study, and/or was randomized in the MDGN-001-ADHD-201 clinical study. 26. Subject has a history of difficult blood draws that in the opinion of the investigator and/or parent/LAR would potentially compromise the study conduct. 27. Subject is taking any medication at the Screening Visit (Visit 1) which is a substrate of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6, or OAT1. This excludes a subjects ADHD medication. 28. Subject has any clinically significant laboratory abnormality at the Screening Visit (Visit 1).
CONCOMITANT TREATMENT	In each part of the study, subjects may not have taken any psychotropic medication within the 28 days prior to the Screening Visit (Visit 1) other than their stimulant and/or nonstimulant medications for treatment of ADHD, and/or clonidine taken at night for sleep. Subjects may also not take any other psychotropic medication during the study. During the study, new initiation of investigational compounds, herbal therapy, sedatives, hypnotics and anxiolytics, antidepressants, antipsychotics, anticonvulsants, psychostimulants, adrenergic agents, oral corticosteroids (inhaled steroids for asthma permitted), sedating antihistamines, ephedrine and pseudoephedrine is prohibited. During the study, the initiation of new behavioral therapies is also prohibited. Additionally, any medication which is a substrate of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6 or OAT1 is prohibited during each part of the study. After completion of the Screening Visit (Visit 1) in each part of the study, eligible subjects will have their ADHD medication discontinued (if applicable). The washout

	phase will be 5 days for stimulants and 14 days for nonstimulants and/or clonidine taken at night for sleep. The investigator cannot initiate the discontinuation of ADHD therapies as part of this study without first obtaining the subject's informed consent/assent and determining a subject's eligibility.
INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION	Name: AEVI-001, also known as MDGN-001, NFC-1 and fasoracetam monohydrate, (5R)-5-(pyridine-1-carbonyl)-pyrrolidin-2-one monohydrate. Name: Matching placebo. AEVI-001 will be provided as white opaque size 1 capsules containing 100 mg or 200 mg AEVI-001. Placebo will be provided as white opaque size 1 capsules containing microcrystalline cellulose instead of AEVI-001. Dose, route, and frequency: Oral doses of 100 mg, 200 mg or 400 mg of AEVI-001 or placebo will be administered 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.] in the fed or fasted state.
COORDINATING PRINCIPAL INVESTIGATOR / PRINCIPAL INVESTIGATOR	[redacted]
PLANNED STUDY SITES	Up to 25 sites in the United States
CRITERIA FOR EVALUATION	Efficacy in each part of the study will be assessed using the ADHD-RS-5, CGI-I, CGI-S and Conners 3-P(S) scales. Safety in each part of the study will be assessed by evaluating TEAEs, vital signs measurements (including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature), measurements of weight, and responses on the C-SSRS.
STATISTICAL METHODS	Study Populations: The **Intent-to-Treat** Population of each part of the study includes all subjects who are randomized and dispensed study medication at the Baseline visit. The **Full Analysis Set** of each part of the study includes all subjects who are randomized, take at least one randomized dose of study medication during this trial, and have a valid Baseline and at least one post-Baseline follow-up assessment of the primary outcome measure - ADHD-RS-5 total score. The **Safety** Population of each part of the study includes all subjects who are randomized and take at least one randomized dose of study medication and during this trial. General Considerations: Randomization will be implemented in a 1:1 ratio using a computer-generated schedule stratified by age (6 to 12, 13 to 17 years old) and part (A, B). Each part of the study will be analyzed separately. Pooled analyses using both parts may also be conducted, if appropriate. Experimental results will be summarized with descriptive statistics and will be presented by treatment group (AEVI-001 or placebo) and overall. Continuous endpoints will be summarized by the number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum. Categorical and count endpoints will be summarized using n and the percentage of subjects in each category. All statistical tests will be 2-sided and performed at the 0.05 level of significance. All confidence intervals (CIs) will be 2-sided 95% CIs. All efficacy analyses will be

	conducted using the Full Analysis Set; all safety analyses will be conducted using the Safety Set. Primary Efficacy Endpoint: The primary outcome will be the change from baseline in the ADHD-RS-5 total score at Visit 8 (Week 6), where baseline is defined as the last ADHD RS-5 total score assessment prior to the first dose of investigational product (usually at Visit 2/Day 0). The primary efficacy analysis will be conducted using the Full Analysis Set for the change from baseline for the ADHD-RS-5 total score, including all assessments from Visit 1 (Week 1) up to Visit 8 (Week 6), using the linear mixed models repeated measures (MMRM) methods with treatment group, visit, and baseline ADHD-RS-5 total score as a covariate. Missing data will not be imputed. The primary contrast of interest will be the comparison of the AEVI-001 and placebo groups at Visit 8 (Week 6). Key Secondary Efficacy Endpoint: The key secondary efficacy measurement will be the percentage of subjects with a dichotomized CGI-I assessment of improved at Visit 8 (Week 6). A dichotomized assessment of improved includes the CGI-I categories of 1 (very much improved) and 2 (much improved), and a dichotomized assessment of not improved included all other assessed CGI-I categories (3-7). If a CGI-I score is missing at Visit 8, the missing value will be imputed by carrying forward the last post-baseline value. The percentages of subjects considered improved in the AEVI 001 and placebo groups will be compared using logistic regression methods. The logistic regression model will include terms for treatment group and baseline CGI-S score. Secondary Efficacy Endpoints: Descriptive statistics for the CGI-S score and change from baseline in CGI-S score will be presented by treatment group and visit. Finally, the dichotomized endpoints of response and remission will be presented as the percentage of subjects meeting the response or remission criteria at Visit 8/ET (Week 6/ET). Both will be scored as 1 for Response/Remission and 0 for non-Response/Remission. Response is defined as: ☐ A ≥30% reduction from Baseline in ADHD-RS-5 total score. ☐ Improved on the CGI-I which includes the categories of 1 (very much improved) and 2 (much improved). ☐ Both a ≥30% reduction in ADHD-RS-5 total score and improved (1 [very much improved] and 2 [much improved]) on the CGI-I. Remission is defined as follows: ☐ An ADHD-RS-5 total score ≤18. ☐ A CGI-I of 1 (very much improved). ☐ Both an ADHD-RS-5 total score ≤18 and a CGI-I of 1 (very much improved). Exploratory Efficacy Endpoints: Change from baseline in Conners 3-P(S) subscale scores at Visit 8/ET (Week 6/ET). In addition to prospectively defined analyses, the results of this Phase 2 study will be subjected to further exploratory analyses as supported by the data. Safety Analyses: Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment emergent AEs will

	be summarized by treatment group, system organ class (SOC), and preferred term. Similar summaries will be produced for AEs, serious adverse events (SAEs) and AEs leading to discontinuation. The intensity of AEs and the relationship to investigational product will also be summarized for each SOC and preferred term. Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate), weight, laboratory and ECG results will be summarized by visit using appropriate descriptive statistics. Positive responses to the C-SSRS will be reported as outlined in the statistical analysis plan.
SAMPLE SIZE DETERMINATION	For Part A of the study, 42 unique subjects are planned to be randomized to yield approximately 34 subjects who provide post-baseline efficacy data on the primary endpoint. For Part B of the study, 82 unique subjects are planned to be randomized to yield approximately 66 subjects who provide post-baseline efficacy data on the primary endpoint. In Part A, assuming an effect size of 1.0, this number will yield approximately 80% power to detect a significant difference in mean change from baseline for the ADHD-RS-5 total score at Visit 8 (Week 6) between the treatment groups, based on a 2-tailed test with α=0.05 and 1:1 randomization. In Part B, assuming an effect size of 0.7, this number will yield approximately 80% power to detect a significant difference in mean change from baseline for the ADHD-RS-5 total score at Visit 8 (Week 6) between the treatment groups, based on a 2-tailed test with α=0.05 and 1:1 randomization. Additionally, in part A of the study, an interim analysis will be performed when approximately 75% of randomized subjects have completed the study. This analysis will focus on the magnitude of placebo response and will determine whether the enrollment target should be increased to a total of 64 randomized subjects. No sample size adjustment is planned for Part B if conducted.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods in each part of the study will be as follows: ☐ Screening period: approximately 28 days. ☐ Washout or pre-baseline period: If applicable at least 14 days prior to the Baseline Visit (Visit 2) for nonstimulant medications and/or or clonidine taken at night for sleep, and/or at least 5 days prior to the Baseline Visit (Visit 2) for stimulant medications, or prior to the Baseline Visit (Visit 2) for all other subjects who do not require a washout. ☐ Treatment period: 6 weeks (±2 days) o Dose optimization phase: 4 weeks o Dose maintenance phase: 2 weeks ☐ Follow-up: 7 days (+2 days) after the last dose of IP. ☐ The maximum study duration for each subject is approximately 11 weeks. ☐ The maximum treatment duration for each subject is 6 weeks.

Table 1: Schedule of Events (Parts A and B)

	Screening Visit	Washout Period[1]	Baseline Visit	Treatment Period						Follow-up Period[6]
				Dose-optimization Phase				Dose Maintenance Phase		
Visit	**1**	**No Visit**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**No Visit**
Assessment Week	**-4**		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Assessment Day	**-28**		**0**	**7**	**14**	**21**	**28**	**35**	**42/Any**	**+7 days from last dose**
Visit Window[2]				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**+2 days**
Informed Consent/Assent	X									
Inclusion/Exclusion Review	X[5]	X	X							
Genotype result available	X									
Randomization			X							
M.I.N.I. International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid)	X									
CBCL			X							
KBIT-2	X									
Demographics	X									
Medical and Medication History	X									
Physical Exam[3]	X								X	
Weight	X[5]		X	X	X	X	X	X	X	
Height	X[5]								X	
Calculate BMI	X									
Vital Signs[4]	X[5]		X	X	X	X	X	X	X	
12-lead ECG	X[5]		X	X	X	X	X	X	X	
Hematology & Clinical Chemistry	X[5]		X	X			X		X	
Thyroid Stimulating Hormone and T4	X[5]									
Identity Confirmation[7,8]	X									

	Screening Visit	Washout Period[1]	Baseline Visit	Treatment Period						Follow-up Period[6]
				Dose-optimization Phase				Dose Maintenance Phase		
Visit	**1**	**No Visit**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**No Visit**
Assessment Week	**-4**		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Assessment Day	**-28**		**0**	**7**	**14**	**21**	**28**	**35**	**42/Any**	**+7 days from last dose**
Visit Window[2]				**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**+2 days**
Urine Drug Screen	X[5]		X	X	X	X	X	X	X	
Urinalysis	X[5]		X	X			X		X	
Serum pregnancy test[9]	X[5]								X	
Urine pregnancy test[9]			X	X	X	X	X	X		
Investigator Dose Assessment				X	X	X	X			
ADHD-RS-5			X	X	X	X	X	X	X	
CGI-S	X		X	X	X	X	X	X	X	
CGI-I				X	X	X	X	X	X	
Conners 3-P(S)	X		X				X		X	
C-SSRS Baseline Version	X									
C-SSRS Since Last Visit Version			X	X	X	X	X	X	X	
Study Drug Dispensed			X	X	X	X	X	X		
Study Drug Collected				X	X	X	X	X	X	
IWRS	X		X	X	X	X	X	X	X	
Compliance Calculation				X	X	X	X	X	X	
Adverse Event	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADHD-RS-5 = Attention Deficit Hyperactivity Disorder Rating Scale Version 5; BMI = body mass index; CBCL = Child Behavior Checklist; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; Conners 3-P(S): Conners 3rd Edition–Parent Short form; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; IWRS = interactive web response system.

[1] For subjects currently taking a nonstimulant medication for ADHD and/or or clonidine taken at night for sleep, the call should take place to allow for a 14-day washout prior to the Baseline Visit (Visit 2). For subjects receiving a stimulant medication for ADHD, the call should take place to allow for a 5-day washout prior to the Baseline Visit (Visit 2). Subjects who do not require a washout must still be contacted by phone prior to the Baseline Visit (Visit 2) being conducted.

[2] After Day 0 (Visit 2), visits at which AEVI-001 is administered should occur every 7 ± 2 days. These visits should be scheduled relative to Day 0 (Visit 2), which is the baseline visit.

[3] A complete physical examination (excluding genitourinary examination) will be performed at Visit 1 and at the completion of exposure (Visit 8/ET).

[4] Includes blood pressure, pulse rate, and respiratory rate will be measured after the subject has been in a sitting position for approximately 5 minutes. Oral or tympanic temperature will be collected at the Screening Visit (Visit 1) only.
[5] If more than 28 days have elapsed between the Screening Visit (Visit 1) and the Baseline Visit (Visit 2), clinical laboratory tests, serum pregnancy test, vital signs, height, weight, urine drug test, and ECG must be repeated and the results available and reviewed prior to proceeding with the Baseline Visit (Visit 2). Applicable inclusion and exclusion criteria must be reassessed using the results received.
[6] The follow-up call will take place 7 days (+ 2 days) after the subjects last dose of investigational product. If applicable, a subject should not be restarted on ADHD medication until the day after completion of the follow-up call.
[7] A saliva sample will be collected for identity confirmation of subjects with a previously banked saliva sample from the AEVI-001-ADHD-002 study. This requirement only applies to subjects who participated virtually in the AEVI-001-ADHD-002 study. If a subject participated in the MDGN-NFC1-ADHD-001 study, the MDGN-NFC1-ADHD-101 study or was screened on site in the AEVI-001-ADHD-002 study, a saliva sample is not required to be collected.
[8] If required, identity confirmation test result to be reviewed upon receipt to determine the subject's ability to be randomized.
[9] For all female subjects.

5. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ADHD-RS-5	Attention Deficit Hyperactivity Disorder Rating Scale Version 5
AE	adverse event
AEVI-001	also known as MDGN-001, NFC-1 and fasoracetam monohydrate
ASD	autism spectrum disorder
AUC	area under the curve
BMI	body mass index
CAG	Center for Applied Genomics
CBCL	Child Behavior Checklist
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CHOP	Children's Hospital of Philadelphia
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNV	copy number variant
Conners 3-P(S)	Conners 3rd Edition-Parent Short form
CRA	clinical research associate
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCRF	electronic case report form
EC	Ethics committee
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFIN	gene family interaction network
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

IWRS	interactive web response system
KBIT-2	Kaufman Brief Intelligence Test, Second Edition
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Affairs
mGluRs	metabotropic glutamate receptors
MMRM	mixed models repeated measures
OTC	over-the-counter
PK	Pharmacokinetic
SAE	serious adverse event
SOC	system organ class
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
$t_{1/2}$	apparent terminal half-life
T_{max}	time to maximum observed plasma concentration
US	United States

6. INTRODUCTION

6.1 Background and Rationale

Attention deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders. This neurodevelopmental disorder often persists into adulthood, causing significant life-long impairment. While for many individuals, the catecholaminergic pathway appears to play an underlying role in ADHD symptomatology, it may not be the primary pathway for all patients suffering from ADHD; other neurotransmitter systems may also be involved. In particular, there is increasing evidence to suggest that the glutamatergic system may be affected for a subset of ADHD individuals.

In various animal models of ADHD as well as human ADHD studies, the glutamatergic system has been shown to play both a direct and an indirect role. A large-scale, genome-wide study comparing copy number variants (CNVs) in ADHD patients (N=3,500) vs. healthy controls (N~13,000) demonstrated that rare, recurring CNVs impacting specific glutamate receptor metabotropic (GRM) genes occur in ADHD patients at a significantly higher frequency compared to controls (Elia et al., 2011). These CNVs appear to be highly penetrant for their effect on ADHD symptomatology. Collectively, disruptions of genes in the GRM network (as determined by the presence of CNVs) accounts for about 10% of total ADHD cases (Elia et al., 2011). These results suggest that this subset of ADHD patients with disrupted mGluR signaling/activity can be identified by genetic profiling of GRM-network genes and that the GRM network is an appropriate target for ADHD therapy.

The investigational product in this study is AEVI-001 (NFC-1, fasoracetam monohydrate), a small synthetic molecule that stimulates metabotropic glutamate receptors (mGluR). In Japan, AEVI-001 was tested in humans for stroke and vascular dementia; however, it did not meet the primary efficacy objective and development for these indications was terminated. Currently, AEVI-001 is being developed for the treatment of ADHD in subjects with CNVs in specific genes of interest in glutamatergic signaling and neuronal connectivity. AEVI-001 exerts its bioactivity through the mGluRs (Oka et al., 1997a, Oka et al., 1997b, Hirouchi et al., 2000). AEVI-001 was also found efficacious in ameliorating learning and memory impairment, which can also be interpreted in the context of improved attention span, and AEVI-001 can reduce locomotor activity, which is a correlate of hyperactivity (Ogasawara et al., 1999).

AEVI-001 was previously administered to 30 adolescents (ages 12-17) with ADHD and disruptive mutations in GRM-network genes as determined by the presence of CNVs to further establish the safety profile and to explore efficacy of AEVI-001 as a treatment for ADHD in this population (Study NFC1-2014). In this study, AEVI-001 was found to be generally safe and well tolerated. Exploratory results on the Vanderbilt Parent Rating Scale and the Clinical Global Impression-Improvement scale (CGI-I) suggested that AEVI-001 may be an effective treatment for ADHD in these adolescents with CNVs in the GRM network genes.

Additionally, in a recently completed study, AEVI-001 or placebo was administered to 97 adolescents (ages 12-17) with ADHD and disruptive mutations in GRM-network genes as determined by the presence of CNVs to assess the efficacy and AEVI-001 compared to placebo (Study MDGN-NFC1-ADHD-201). Although the study did not meet the *a priori* primary efficacy objective, subjects in the AEVI-001 group did show improvement compared to placebo subjects as measured by 3 previously defined response criteria (a reduction from Baseline of ≥30% in the

ADHD-RS-5 Total score; a CGI-I score of 1 (very much improved) or 2 (much improved) relative to Baseline; and a composite criterion that both of the other 2 criteria be met). On each of these criteria, AEVI-001 subjects were statistically significantly better than placebo subjects. AEVI-001 was also generally safe and well tolerated at doses up to 400 mg bid in the population of adolescents enrolled in this study. Post-hoc analyses examined factors such as gene mutations that were predictive of treatment response. The results of these analyses revealed 9 genes associated with robust treatment response in multiple subjects. The genes included certain GRM genes and other CNS/neurodevelopmental genes, e.g., *CNTN4*. The most frequent gene copy number variant in the study population (n=19, 19% of randomized sample) was *CNTN4*. As such, the replication of this finding is the focus of this Phase 2 study.

6.2 Clinical Experience

Previously, AEVI-001 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 tolerability, 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 AEVI-001 in these studies is presented in Table 2.

Table 2: Nippon Shinyaku Co., Ltd. Conducted Clinical Studies with AEVI-001[a]

Study Phase	Study Population	Number of Subjects	Doses Tested	Exposure	Number of Treatment-related SAEs
1	Healthy male adults	30/6[b]	25-800 mg single dose/ 200 mg/day	8 days	0
2	Adults with cerebrovascular disease	169	75-450 mg/day	8 weeks	0
2	Adults with post cerebral infarct residual symptoms	288	150 and 300 mg/day	8 weeks	0
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. One subject experience acute myocardial infarction and one subject was hospitalized for vertigo and vomiting.

Nippon Shinyaku terminated development because the phase 3 study in adults with cerebrovascular disease and dementia failed to meet the defined efficacy endpoints. Although a written report is unavailable, information in the Investigator's Brochure (IB) for this phase 3 study indicated that AEVI-001 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 creatine kinase (in 1% of the subjects).

A tolerability and single dose pharmacokinetic (PK) study of AEVI-001 in adolescents with ADHD has been completed recently in the United States (US). The 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 PK profile of AEVI-001 and metabolites, to evaluate the effect of AEVI-001 on ADHD during 4-weeks of continuous treatment (at doses up to 400 mg twice daily) following 1 week of placebo therapy and to assess long term safety for a period of up to 6 months of exposure. This study was conducted at the Jefferson University Hospital in Philadelphia, Pennsylvania. During the dose escalation phase of this study, AEVI-001 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 in the NFC1-2014 study 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 ($P < 0.001$). After completion of the study, subjects were classified into three tiers, based on their mGluR mutations. 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 open-label extension study of AEVI-001.

Finally, a double-blind, dose-optimization study of AEVI-001 in children and adolescents (ages 12-17 years) with ADHD and disruptive mutations in GRM-network genes as determined by the presence of CNVs has been completed recently in the US (MDGN-NFC1-ADHD-201). The objective of this study was to assess the efficacy and safety of AEVI-001 compared to placebo. On the primary efficacy analysis, the change in ADHD-RS-5 Total score from Baseline to the end of treatment (Visit 8/ET), there was no statistical difference between the results for the AEVI-001 group and the placebo group.

It is noted, however, that on the CGI-I, a significantly greater proportion of subjects receiving AEVI-001 were improved (26 [56.5%] subjects) compared to subjects receiving placebo (16 [32.0%] subjects). Further, for all 3 response criteria, the frequency of response vs. no response for subjects in the AEVI-001 group was significantly greater for the AEVI-001 group compared to the placebo group. Response criteria included (a) a change in ADHD-RS-5 total score from Baseline of $\geq$30%; (b) a CGI-I score of 1 (very much improved) or 2 (much improved) relative to Baseline; and (c) a composite criterion requiring that both (a) and (b) be met.

In this study AEVI-001 was also generally safe and well tolerated at doses up to 400 mg bid in the population of adolescents enrolled in this study. Post-hoc analyses examined factors such as gene mutations that were predictive of treatment response. The results of these analyses revealed 9

genes associated with robust treatment response in multiple subjects. The genes included certain GRM genes and other CNS/neurodevelopmental genes, e.g., *CNTN4*. The most frequent gene copy number variant in the study population (n=19, 19% of randomized sample) was *CNTN4*. This study is in the reporting phase.

6.2.1 Clinical Pharmacokinetics

The PK of AEVI-001 has been assessed previously in Asian subjects by Nippon Shinyaku following administration of single oral doses of 50 mg, 100 mg, 200 mg (fed and fasted), 400 mg, and 800 mg AEVI-001 to healthy male adults (aged 26-48 years) in a Phase 1 dose-finding and PK study and following administration of single oral doses of 100 mg AEVI-001 after a meal to both young adults (aged 20-32 years) and elderly subjects (aged 68-79 years) in a comparative PK study. Results, summarized in Table 3, showed rapid absorption (T_{max} from 0.6 to 1.5 hours), dose-proportional increases in exposure, and an elimination half- life 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 vs. 0.7 hour) and decreased maximum observed plasma concentration (C_{max}) (4.14 vs. 5.65 µg/mL); however, no differences in area under the curve $(AUC)_{0-\infty}$ (29.3 *vs* 31.3 µg·h/mL) and elimination half-life (4.2 *vs* 4.3 h) were observed. In separate studies, similar PK parameters were obtained following administration of 100 mg AEVI-001 to healthy male adults and young adults, respectively, with T_{max} of 1.0 vs. 1.2 hours, C_{max} of 2.57 vs. 2.14 µg/mL, $AUC_{0-\infty}$ of 17.0 vs. 14.0 µg·h/mL. The apparent terminal half-life ($t_{1/2}$) was the same in both groups (4.4 hours). Compared to young adults, elderly subjects had significantly slower absorption (T_{max} of 2.1 vs. 1.2 hours, $p<0.05$), significantly higher exposure (mean C_{max} of 3.06 vs. 2.14 µg/mL, mean $AUC_{0-\infty}$ of 24.6 vs. 14.0 µg·h/mL, $p<0.01$), and slightly longer elimination half-life (5.2 vs. 4.4 hours).

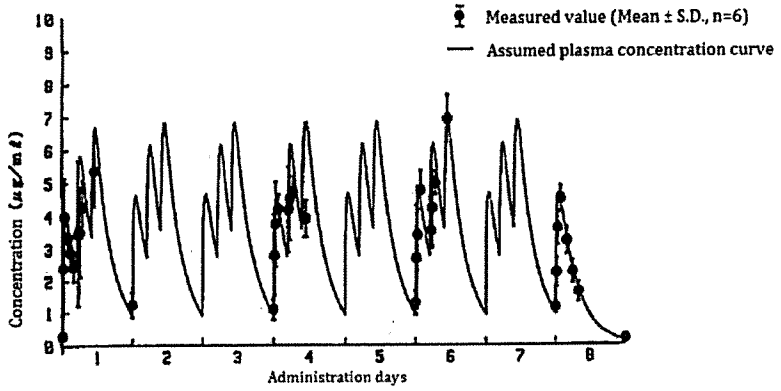
Table 3: Pharmacokinetic Parameters of AEVI-001 in Asian Subjects

Dose (mg)	N	T_{max} (h)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg-h/mL)	$t_{1/2}$ (h)
Healthy Male Adults (aged 26-48 years)					
50	6	0.6 ± 0.5	1.69 ± 0.82	7.22 ± 1.74	3.7 ± 0.9
100	6	1.0 ± 0.6	2.57 ± 0.62	16.99 ± 2.59	4.4 ± 0.6
200 (fasted)	6	0.7 ± 0.3	5.65 ± 1.54	31.34 ± 4.85	4.3 ± 0.9
200 (fed)	6	1.5 ± 0.6	4.14 ± 0.39	29.34 ± 4.05	4.2 ± 0.6
400	6	0.8 ± 0.4	10.71 ± 3.17	61.64 ± 15.02	4.2 ± 0.7
800	6	1.1 ± 0.5	20.61 ± 5.65	127.28 ± 22.53	3.8 ± 0.5
Young adults (aged 20-32 years)					
100 (fed)	7	1.2 ± 0.6	2.14 ± 0.31	14.0 ± 3.0	4.4 ± 0.7
Elderly adults (aged 68-79 years)					
100 (fed)	7	2.1 ± 1.1	3.06 ± 0.69	24.6 ± 4.4	5.2 ± 0.9

In the Phase 1 dose-finding and PK study, six healthy male adults (aged 25-36 years) were given 200 mg AEVI-001 three times daily for 8 days. PK assessments showed that the plasma concentration reached a maximum of 7 µg/mL and minimum of 1 µg/mL in steady state with

continuous administration. Measured plasma levels on days 1, 3, 5, and 7 showed good agreement with plasma concentration curves modeled from the parameters obtained after administration of single oral doses (Figure 1), showing no evidence for dose accumulation with repeated oral dosing.

Figure 1: AEVI-001 Plasma Concentration Following Continuous Administration



Note: (□) Plasma concentration as measured in the Phase 1 study and (-) as calculated by PK modeling using parameters obtained after administration of single oral doses to Asian Subjects

Measurement of AEVI-001 in urine from 0 to 8 and 8 to 24 hours after administration of single oral doses from 50 to 800 mg to healthy male adults and 100 mg to young and elderly subjects showed that approximately 80% of the administered dose was excreted in urine over 24 hours.

In a study to assess the bioequivalence of 50 mg and 100 mg tablets of AEVI-001, 14 healthy male adults (aged 20-29 years) were randomly assigned to receive either two 50 mg tablets or one 100 mg tablet of AEVI-001 under fasted conditions. After a 1-week washout, they were crossed over to the second formulation. Mean PK parameters for the 2 x 50 mg vs. 1 x 100 mg doses, respectively, showed comparable C_{max} (2.48 vs. 2.59 μg/mL) and $AUC_{0\text{-}24h}$ (15.2 vs. 14.6 μg·h/mL). Statistical evaluation using both log-transformed data and original data showed 95% confidence intervals (CIs) for the difference between dose forms of -17% to +9.9% for C_{max} and -2% to +9.8% for AUC.

6.2.1.1 Phase 1 Attention Deficit Hyperactivity Disorder Study (NFC1-2014) Pharmacokinetics Summary

The PK of AEVI-001 have been estimated following administration of single oral doses of 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg AEVI-001 to adolescent patients with ADHD (age 12-17 years). All doses were administered to groups of six patients under fasting conditions. Blood samples were collected immediately pre-dose and at 0.5, 1.0, 1.5, 2.0, 3, 4, 6, 8, 12, and 24 hours post dose. Urine was not collected.

The results demonstrate that NFC-1 is absorbed with a mean t_{max} ranging from 1.2 to 2.1 hours independent of dosage. The exposure (C_{max} or $AUC_{0-\infty}$) is approximately dose-proportional as analyzed by a non-compartmental model. The elimination half-life ($t_{½}$) was approximately 4 hours. (It is noted that the $t_{½}$ estimate for the 100 mg group was skewed by the results for Subject 111 whose individual estimate was 17.3 hours) (see Table 4). The PK parameter estimates were comparable to those reported for the Phase 1 study performed by Nippon Shinyaku.

Table 4: AEVI-001 Pharmacokinetic Parameters (Study NFC1-2014)

		Dose				
Parameter		**50 mg**	**100 mg**	**200 mg**	**400 mg**	**800 mg**
N		6	6	6	6	6
T_{max} (hrs)	Mean ± SD	1.522 ± 0.984	1.925 ± 1.189	1.336 ± 0.689	1.328 ± 0.626	1.905 ± 2.131
C_{max} (µg/mL)	Mean ± SD	1.193 ± 0.429	1.718 ± 0.647	5.072 ± 0.914	10.772 ± 2.95	20.517 ± 7.898
$AUC_{(0-\infty}$ (µg·h/mL)	Mean ± SD	6.965 ± 1.485	14.641 ± 3.461	29.92 ± 5.929	57.478 ± 12.868	134.036 ± 30.643
$t_{1/2}$ (hrs)	Mean ± SD	4.436 ± 0.716	6.989 ± 5.166	4.484 ± 0.712	4.111 ± 0.516	4.063 ± 0.51

6.2.1.2 Phase 1 Attention Deficit Hyperactivity Disorder Study (MDGN-NFC1-ADHD-101) Pharmacokinetics Summary

The PK of AEVI-001 and its metabolites (LAM-79 and LAM-163) have been estimated following administration of single oral doses of 100 mg, 200 mg, 400 mg, and 800 mg AEVI-001 to pediatric and adolescent patients with ADHD (age 6-17 years). All doses were administered to groups of 8 patients under fasting conditions. Blood samples were collected immediately pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 28 hours post dose. Urine was collected at 24 hours post dose.

Following a single oral dose of AEVI-001 at 100, 200, 400, or 800 mg to children with ADHD, AEVI-001 was rapidly absorbed into the systemic circulation with median T_{max} values ranging from 0.608 to 1.92 hours. In adolescents with ADHD, AEVI-001 was also rapidly absorbed into the systemic circulation with median T_{max} values ranging from 0.958 to 1.25 hours.

The PK exposure (C_{max} and AUC_{0-28}) of LAM-163 appeared to be slightly higher in children than that in adolescents for all doses except for the 400 mg dose, which appeared to be slightly lower in children. The ratios of children/adolescents mean C_{max} values were 1.18, 1.36, 0.787 and 2.08 for doses of AEVI-001 at 100, 200, 400 or 800 mg, respectively. Corresponding ratios of children/adolescents mean AUC_{0-28} values were 1.31, 1.33, 0.787 and 2.20.

In conclusion, the PK exposure of AEVI-001, LAM-79, and LAM-163 in children and adolescents appeared to increase as a function of AEVI-001dose in a dose proportional manner, where the 90% CI of the slopes for the log C_{max} or log AUC versus the log AEVI-001dose included the value of 1.00, except for the AUC_{0-28} which was greater than dose proportional. Conclusions from this study must be drawn cautiously because the number of patients who provided PK data in each cohort was low, ranging from 2 (adolescents given 800 mg) to 6 (children given 800 mg), with most data provided from 3-4 patients. The mean exposure (C_{max} and AUC) of AEVI-001 was similar (i.e. within 2-fold) in children and adolescents.

The PK parameter estimates from this study were also comparable to those reported for the Phase 1 study performed by Nippon Shinyaku.

Table 5: AEVI-001 Pharmacokinetic Parameters (Study MDGN-NFC1-ADHD-101)

Dose							
100 mg		200 mg		400 mg		800 mg	
Pediatric	Adolescent	Pediatric	Adolescent	Pediatric	Adolescent	Pediatric	Adolescent*
4	4	3	5	4	4	6	2
0.879±0.474	0.985±0.579	1.81±1.31	0.923±0.468	0.804±0.475	1.25±0.289	1.18±0.972	1.00
4.23±0.979	2.14±0.285	7.72±1.88	5.57±1.31	15.2±4.72	8.82±2.13	35.2±13.4	19.4
19.2±1.98	10.9±1.59	41.3±3.54	31.8±6.97	91.5±26.9	55.8±11.3	177±31.1	103
2.93±0.411	2.92±0.488	2.91±0.827	4.05±1.48	4.00±0.571	4.14±0.310	3.23±0.693	4.46

6.3 Summary of Potential Risks and Benefits

The potential benefit of study participation is that subjects with ADHD may experience a reduction in symptoms because of treatment with AEVI-001. Subjects will also understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for patients with ADHD. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to AEVI-001 and the risks of medical evaluation, including venipuncture.

A summary of the pharmaceutical properties and known potential risks of AEVI-001 is provided in the current version of the IB. The investigator must become familiar with all sections of the AEVI-001 IB before the start of the study.

7. OBJECTIVES

The primary objective of each part of this study is:

- To evaluate the efficacy of AEVI-001 compared with placebo in children and adolescents (6-17 years of age inclusive) with ADHD and with or without copy number variants (CNVs) in specific genes implicated in glutamatergic signaling and neuronal connectivity as measure by the change in ADHD-RS-5 total score.

The key secondary objective of each part of this study will be:

- To evaluate the efficacy of AEVI 001 compared with placebo using a global clinical measure of improvement, the CGI-I at Visit 8/ET (Week 6/ET).

Additional secondary objectives of each part of the study include:

- To evaluate AEVI-001 compared with placebo on response at Visit 8/ET (Week6/ET), based on the following parameters:

- A ≥30% reduction from Baseline in ADHD-RS-5 total score.
- Improved on the CGI-I which includes the categories of 1 (very much improved) and 2 (much improved).
- Both a ≥30% reduction in ADHD-RS-5 total score and improved (1 [very much improved] and 2 [much improved] on the CGI-I.

- To evaluate AEVI-001 compared with placebo on remission at Visit 8/ET (Week 6/ET), based on the following parameters:
  - An ADHD-RS-5 total score ≤18.
  - A CGI-I of 1 (very much improved).
  - Both an ADHD-RS-5 total score ≤18 and a CGI-I of 1 (very much improved).
- To evaluate the efficacy of AEVI-001 compared with placebo using a global clinical measure of severity, the CGI-S at Visit 8 (Week 6).
- To evaluate the safety and tolerability of AEVI-001 compared with placebo based on occurrence of TEAEs, vital signs, clinical laboratory results, electrocardiogram (ECG) results, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Exploratory objectives of each part of the study include:

- To evaluate the efficacy of AEVI-001 compared with placebo on behavior as measured by the change from baseline at Visit 8 (Week 6) on Conners 3rd Edition–Parent Short form (Conners 3-P(S)).

8. STUDY DESIGN

8.1 Overall Study Design and Plan

This is a phase 2, double-blind, dose optimization study designed to assess the efficacy and safety, of AEVI-001 in children and adolescents (ages 6-17 years) with ADHD with or without copy number variants in specific genes implicated in glutamatergic signaling and neuronal connectivity. In Part A of the study, approximately 42 unique subjects are planned to be randomized to yield approximately 34 subjects who provide post-baseline efficacy data on the primary endpoint. In Part B of the study, approximately 82 unique subjects are planned to be randomized to yield approximately 66 subjects who provide post-baseline efficacy data on the primary endpoint. Additionally, Part A of the study will include an interim analysis which will determine whether the sample size will be increased to a planned total of approximately 64 randomized subjects. The number of planned subjects that will be randomized accounting for both study parts is approximately 146 unique subjects (Part A: approximately 64 randomized and Part B: 82 randomized). Once subjects are confirmed as eligible for one part of the study, they will be randomized to one of two treatment groups (AEVI-001 or placebo) in a 1:1 ratio. Subjects will be stratified by age (6 to 12, 13 to 17 years old) and part (A, B) with each part of the study analyzed separately.

Subjects must be ≥6 to ≤17 years of age and have ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Subjects will have been genotyped using a microarray based technology from Illumina (Illumina, San Diego) under another Aevi protocol (MDGN-NFC1-ADHD-001, MDGN-NFC1-ADHD-101, or AEVI-001-ADHD-002).

Subjects determined to have mutations in at least one of the 8 genes of interest as determined by the presence of CNVs and who consented to future research will be considered for participation in Part A of this study. Subjects determined not to have mutations in any of 272 genes of interest and who consented to future research will be considered for participation in Part B of this study. For Part B, the list of excluded mutations includes the 8 gene mutations studied in Part A and an additional 264 mutations identified in an antecedent study.

Subjects will not be eligible if they are considered a suicide risk, have a prior diagnosis of co-morbid major psychiatric disorders (other than ADHD) or any clinically significant medical condition that would interfere with the conduct of study evaluations, are pregnant or nursing, and/or have clinically significant abnormal laboratory and/or ECG abnormalities. All subjects will provide a saliva sample at the Screening Visit (Visit 1) for identity confirmation with a previously banked saliva sample for the subject from the AEVI-001-ADHD-002 study. This requirement only applies to subjects who participated virtually in the AEVI-001-ADHD-002 study. If a subject participated in the MDGN-NFC1-ADHD-001 study, the MDGN-NFC1-ADHD-101 study, or was screened on-site for the AEVI-001-ADHD-002 study, the saliva sample is not required to be collected. If required to be performed, identity confirmation results will be reviewed prior to a subject being randomized.

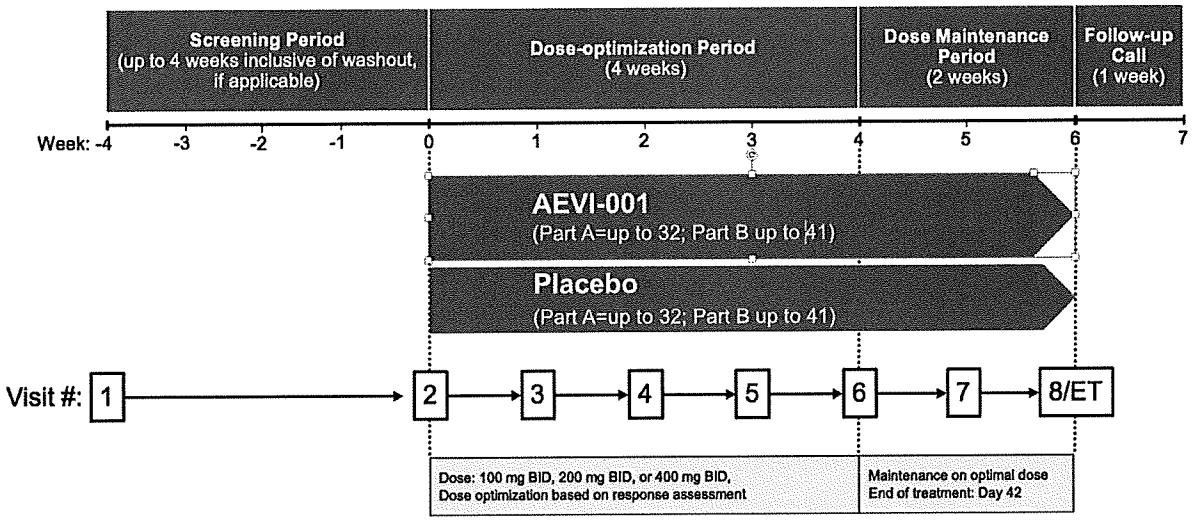
As shown in Figure 2, during both parts of the study, subjects will be randomized in a 1:1 ratio and start taking the investigational product (IP) at a dose of 100 mg twice daily on Day 1 in the morning upon awakening [7:00 a.m. to 9:00 a.m.] and in the mid-afternoon [between 3:00 p.m.to 5:00 p.m.]. Dosing will be optimized weekly (±2 days) to 100 mg, 200 mg, or 400 mg twice daily, as appropriate, over the 4 weeks of treatment (dose optimization period), 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 period). Visits during dose optimization and dose maintenance periods are to be conducted every 7 days (±2 days). Visits conducted after randomization should be scheduled relative to the Baseline Visit (Visit 2). The primary assessments of safety and efficacy will be performed weekly during the dose optimization and the dose maintenance periods. A follow-up telephone call will be performed 7 (+2 days) after the last dose of IP.

Efficacy will be assessed by evaluating the AHD-RS-5, CGI-S, CGI-I, and Conners 3-P(S) scales.

Safety will be assessed by evaluating AEs, vital sign measurements, ECGs, clinical laboratory test results, physical examination findings 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 follow-up call) will be documented.

Figure 2: Study Design (Parts A and B)



8.2 Discussion of Study Design

This efficacy and safety study is expected to evaluate an optimized dose of AEVI-001 (100mg, 200mg and/or 400mg) or placebo taken twice daily. After assessing the baseline status of the disease, the 4-week dose titration paradigm allows for individualized dose optimization. The subsequent 2-week maintenance period will allow stabilization of drug effect(s) while assessing the disease status during the treatment period. In this phase 2 study, subjects with ADHD with or without CNVs in specific genes of implicated in glutamatergic signaling and neuronal connectivity will receive AEVI-001 or placebo in a double-blind, dose optimization and subsequent dose maintenance paradigm.

8.3 Study Site(s)

The study will take place at up to 25 sites in the US.

8.4 Selection of Study Population

In Part A of the study, 42 unique subjects are planned to be randomized to yield approximately 34 subjects who provide post-baseline efficacy data on the primary endpoint. In Part B of the study, 82 unique subjects are planned to be randomized to yield approximately 66 subjects who provide post-baseline efficacy data on the primary endpoint. Additionally, Part A of the study will include an interim analysis which will determine whether the sample size will be increased to a planned total of 64 randomized subjects. The number of planned subjects that will be randomized accounting for both study parts is approximately 146 unique subjects (Part A: approximately 64 randomized and Part B: 82 randomized). Justification of this sample size is presented in Section 14.1.3.

A screening log of study candidates and a randomization log of subjects will be maintained at each study site.

8.5 Study Entry Criteria

8.5.1 Inclusion Criteria

Subjects must fulfill the following requirements to be randomized into the study:

1. Subject and parent/legally authorized representative (LAR) can speak English fluently and have provided written informed consent, and assent (as applicable) for this study.
2. Subject is 6 to 17 years of age (inclusive) at the time of consent/assent. The date of signature of the informed consent/assent is defined as the beginning of the Screening Period. This inclusion criterion will only be assessed at the Screening Visit (Visit 1).
3. Subject is male or non-pregnant, non-lactating female, who if of childbearing potential agrees to comply with any applicable contraceptive requirements prior to administration of investigational product (IP).
4. Subject meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD based upon DSM 5 criteria.
5. Subject has a minimum score of ≥28 on the ADHD-RS-5 at the Baseline Visit (Visit 2).
6. Subject can swallow a capsule of investigational product whole.
7. Subject has been genotyped previously, has their identity confirmed (if required), and meets the following for the applicable part of the study:
    a. Part A: Determined to have a specific gene mutation(s) in one of 8 genes implicated in glutamatergic signaling and neuronal connectivity. The confirmation of a subject's positive status will be provided to the site.
    b. Part B: Determined not to have any of the specific genes of interest implicated in glutamatergic signaling and neuronal connectivity (N=272). The list of excluded mutations includes the 8 gene mutations studied in Part A and an additional 264 mutations identified in an antecedent study (N=272). The confirmation of a subject's negative status will be provided to the site.

8.5.2 Exclusion Criteria

The presence of any of the following criteria excludes a subject from being randomized into the study:

1. Subject or parent/LAR is, in the opinion of the investigator, mentally or legally incapacitated, has significant emotional problems at the time of the Screening Visit (Visit 1) which could interfere with the conduct of study evaluations.
2. Subject has a current, controlled or uncontrolled, co-morbid major psychiatric diagnosis (aside from ADHD), including an anxiety disorder, major depression, bipolar disease, schizophrenia (or any psychotic disorder), and moderate or severe intellectual disability. Mild anxiety and/or depressive symptoms that do not meet diagnostic criteria for an anxiety disorder or major depression and/or do not require treatment are not exclusionary.
3. Subject has autism spectrum disorder to include a DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder.
4. Subject has an intelligence quotient (IQ) <70 as determined by the Kaufman Brief Intelligence Test, Second Edition (KBIT-2).
5. Subject has a current or relevant history of a medical disorder that might confound the results of safety assessments conducted in the study.

6. Subject is currently taking any medication that might confound the results of safety assessments conducted in the study.
7. Subject meets DSM-5 diagnosis of conduct disorder. Oppositional defiant disorder is not exclusionary.
8. Subject is considered at risk for suicide (in the opinion of the investigator), has previously made a suicide attempt, or is currently demonstrating active suicidal ideation.
9. Subject is either underweight or obese at the Screening Visit (Visit 1) based on Centers for Disease Control and Prevention (CDC) body mass index (BMI) for age-sex specific values. Underweight is defined as BMI-for-age and gender <5th percentile. Obese is defined as BMI-for-age and gender >97th percentile.
10. Subject's blood pressure measurements exceed the 95th percentile for age, sex, and height at the Screening Visit (Visit 1) and/or the Baseline Visit (Visit 2).
11. Subject has a known history of hypertension.
12. Subject has a known history of cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, or other serious cardiac problems.
13. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
14. Subject has any clinically significant abnormality on 12-lead ECG performed at the Screening Visit (Visit 1) and/or the Baseline Visit (Visit 2) such as serious arrhythmia, cardiac conduction problems, or other abnormalities deemed to be a potential safety issue.
15. Subject has a history of or a current seizure disorder (except for infantile febrile seizures), a chronic or current tic disorder, or a current diagnosis of Tourette's Disorder.
16. Subject has a positive urine drug result at the Screening Visit (Visit 1) (except for subject's current stimulant therapy, if any) unless the Investigator can verify that the positive result at the Screening Visit (Visit 1) is attributed to medication that has been prescribed to the subject and will be discontinued prior to the Baseline Visit (Visit 2). In the latter instance, a positive result at the Screening Visit (Visit 1) attributed to a prescribed medication requires a re-test and a negative result to confirm subject eligibility prior to being enrolled.
17. Subject has current abnormal thyroid function at the Screening Visit (Visit 1), defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4). Treatment with a stable dose of thyroid medication for at least 3 months prior the Screening Visit (Visit 1) is permitted.
18. Subject has a history of, been diagnosed with or is suspected to have a substance abuse or dependence disorder.
19. Subject has known or suspected intolerance or hypersensitivity to the investigational product(s), closely-related compounds, or any ingredients of the investigational product.
20. Subject has a history of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
21. Subject has used an investigational product, been enrolled in a clinical study (excluding AEVI-001-ADHD-002) including vaccines within 30 days of the Screening Visit (Visit 1).
22. Subject is a smoker or has used nicotine or nicotine-containing products once a week or on a more frequent basis.
23. Subject consumes any alcoholic beverages once a week or on a more frequent basis.

24. 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.
25. Subject was previously randomized in another part of this study, and/or was randomized in the MDGN-001-ADHD-201 clinical study.
26. Subject has a history of difficult blood draws that in the opinion of the investigator and/or parent/LAR would potentially compromise the study conduct.
27. Subject is taking any medication at the Screening Visit (Visit 1) which is a substrate of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6, or OAT1. This excludes a subjects ADHD medication.
28. Subject has any clinically significant laboratory abnormality at the Screening Visit (Visit 1).

8.6 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study with the prior approval of the CRO Medical Monitor after discussion with the Aevi Genomic Medicine, Inc. medical monitor. In the event of a rescreening, the first screening visit will be entered into the eCRF as the Screening Visit (Visit 1) and the repeat assessments entered into the eCRF as an unscheduled visit.

8.7 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 11.1.1.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons. If required, a subject whose identity is not confirmed with a previously banked saliva sample collected virtually in the AEVI-001-ADHD-002 study, will be immediately recorded as a screening failure.

The investigator also has the right to withdraw subjects from the study at any time for any reason. If a subject is withdrawn before completing the study, whenever possible the evaluations that were to be conducted at Visit 8/ET should be performed. The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- ☐ Adverse event
- ☐ Major protocol deviation
- ☐ Withdrawal by subject
- ☐ Lost to follow-up

- ☐ Lack of efficacy
- ☐ Other. If Other is selected, the investigator must specify the reason on the CRF.

8.8 Subject Replacement Criteria

Subjects who withdraw or are discontinued from the study may be replaced.

9. TREATMENTS

9.1 Identification of Investigational Product(s), Dose and Mode of Administration

The following IPs will be used in this study:

- ☐ AEVI-001 (also known as NFC-1) will be provided as white opaque size-1 capsules containing 100 mg or 200 mg AEVI-001.
- ☐ Placebo will be provided as white opaque size-1 capsules containing microcrystalline cellulose instead of AEVI-001 100 mg or 200 mg AEVI-001.
- ☐ Dose, route, and frequency (AEVI-001 or placebo): 100 mg, 200 mg, 400 mg or placebo taken twice daily orally in the fed or fasted state. The 100 mg, 200 mg or placebo doses will be administered as a single capsule, twice daily; the 400 mg dose or placebo will be administered as 2 x 200 mg capsules or 2 x placebo, twice daily.

9.2 Labeling and Packaging

All packaging and labeling operations will be performed by the sponsor or designee per Good Manufacturing Practice and Good Clinical Practice (GCP) rules. The IP will be sent to the study site by the sponsor or designee in tamper-evident, child-resistant blister cards. Labeling will be in local language and dependent upon local regulations.

9.2.1 Labeling

The blister card will have affixed a label that meets the applicable regulatory requirements and may include the following: name of compound, dosage strength, medication 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

AEVI-001 will be supplied by the sponsor and will be packaged in tamper-evident, child-resistant blister cards of 20 capsules (100 mg, 200 mg dose or matching placebo) or 40 capsules (400 mg dose administered as 2 x 200 mg capsules or 2 x placebo capsules). The packaging allows for 7±2 days between visits and includes one extra dosing day to allow for visit flexibility.

Table 6: Dispensing Blister Card Type by Visit

Dose Strength	Dispensing Visits 2-7
100 mg bid (1x100 mg bid) or placebo bid	20 count blister card (1x100 mg bid or placebo bid)

200 mg bid (1x200 mg bid) or placebo bid	20 count blister card (1x200 mg bid or placebo bid)
400 mg bid (2x200 mg bid) or placebo bid	40 count blister card (2x200 mg bid or placebo bid)

9.3 Treatments Administered

Eligible subjects will receive AEVI-001 or placebo on Day 0 and will start taking the IP at a dose of 100 mg or placebo twice daily on Day 1 in the morning upon awakening [approximately 7:00 a.m.to 9:00 a.m.] and in the mid-afternoon [approximately between 3:00 p.m.to 5:00 p.m.]. Dosing will be optimized weekly to 100 mg, 200 mg, or 400 mg or placebo 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). Visits during dose optimization and dose maintenance phases are be conducted every 7 days (±2 days). Visits conducted after randomization should be scheduled relative to the Baseline Visit (Visit 2). The primary assessments of safety and efficacy will be performed weekly throughout the study. A follow-up telephone call will be performed 7 (+2 days) after the last dose of IP.

9.4 Dispensing and Storage

The IP supplied by Aevi Genomic Medicine, Inc. is to be used exclusively in this clinical study per the instructions of this protocol. The investigator is responsible for dispensing the IP per 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 Aevi Genomic Medicine, Inc. and/or designee. Until the IP is dispensed to the subjects, it must be stored at 15 to 25°C and in a dry place in a securely locked area that is temperature monitored and 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.

An interactive web response system will be employed for this study. At a minimum IP receipt, subject visit completion, randomization, dispensing and return of IP will be recorded in the system. Additionally, the IWRS will calculate weekly compliance based on the information entered by the site.

9.5 Blinding and Unblinding Treatment Assignment

This is a double-blind study. All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment except for a specified unblinded statistician from [redacted] who will have access to the randomization code. The unblinded statistician will not otherwise participate in study procedures or data analysis prior to unblinding 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 is permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Whenever possible unblinding should be discussed with the CRO medical monitor. For emergency unblinding the Investigator will access the IWRS unblinding module. If the Investigator is not able to discuss treatment unblinding in advance, then they should notify the CRO 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 CRO medical monitor prior to unblinding the subject's treatment assignment.

If the treatment assignment is unblinded for an individual subject, the Investigator will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. The Investigator will make this decision after consultation with the CRO medical monitor.

9.6 Selection of Doses in the Study

The doses of 100 mg, 200 mg, or 400 mg or placebo taken twice daily will be administered in this study. These doses of AEVI-001 were found to be safe and well tolerated in a phase 2 study of adolescents with ADHD (MDGN-NFC1-ADHD-201).

Pharmacokinetic data from the MDGN-NFC1-ADHD-101 study were consistent with historical PK data and demonstrated a linear dose/concentration profile from 100 mg to 800 mg with a $t_{½}$ of approximately 4 hours that was independent of dose.

AEVI-001 or 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 fasted state.

9.7 Dose Adjustment Criteria

The duration of the dose-optimization phase is 4 weeks to allow for weekly titration up to the highest dose and 1 titration down to the previous dose, if necessary.

Following enrollment, all subjects will begin taking AEVI-001 or placebo and will be evaluated after approximately 7 days (± 2 days) for safety and efficacy. Subjects may be titrated weekly to the next available dose strength after approximately 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 once to the previous dose level to optimize tolerability and efficacy. Subjects unable to tolerate the lowest available dose (100 mg twice daily or placebo) will be discontinued from the study. 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:

- **Intolerable response (i.e., intolerable side effects):** Requires the subject to be tapered to a lower dose of AEVI-001 or placebo (if available). However, if this lower dose produces an intolerable response as well, the subject should be discontinued from the study.
- **Ineffective response:** Subject has not achieved a CGI-I score of <3. This response requires increasing titration of AEVI-001 or placebo 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, defined by a CGI-I score of <3, with tolerable side effects. Subjects categorized as "acceptable" may be maintained at their current dose of AEVI-001 or placebo for the remainder of the study. Subjects who are tolerating IP at the highest available dose but do not achieve an acceptable response should be continued in the study.

If, in the opinion of the investigator, the "acceptable" dose is well tolerated and the subject would potentially receive additional symptom reduction, the dose may be increased to the next dosage strength.

If, in the opinion of the investigator, the subject experiences unacceptable tolerability, the dose of AEVI-001 or placebo may be reduced (if available) by 1 dose level (to the previous dose). If the subject tolerates the dose reduction and maintains symptom control, the subject may be maintained at that reduced dose for the remainder of the study.

Only 1 dose reduction is permitted during the dose optimization phase of the study. Once a dose has been reduced no further changes to the dose will be allowed. Visit 5 will be the last visit at which titration (increase or reduction) can occur. Once a subject has reached an optimal dose, this dose should be maintained during the remainder of the dose optimization phase and will be the dose received during the dose maintenance phase (2 weeks). Subjects who are unable to tolerate AEVI-001 or placebo will be discontinued. A 7-day (+2 days) follow-up call will occur after the last dose of IP.

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.

9.8 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 allow IP access to any person except those named as subinvestigators on the US Food and Drug Administration (FDA) Form FDA 1572 and designated study personnel. An IWRS will be used during this study to help account for IP information at a site and subject level. The investigator will not dispense IP to anyone other than to the intended subject/LAR. The investigator will not dispense the IP from any study locations other than those listed on Form FDA 1572. Investigational product 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 received in a damaged container, this information must be documented and reported to Aevi Genomic Medicine, Inc. and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (partly used, unused, and empty packaging [e.g., blister cards]) must be left in the original packaging and returned to the sponsor or designee for destruction per directions provided by the Sponsor.

9.9 Permitted and Prohibited Therapies

All non-study therapies including but not limited to OTC, non-pharmacological and behavioral treatments received within 28 days prior to the Screening Visit (Visit 1) and through the follow-up phone call must be recorded on the appropriate eCRF page.

9.9.1 Prior Therapies

Prior treatment includes all treatment received within 28 days of the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate eCRF page.

9.9.2 Concomitant Therapies

Concomitant therapies refer to all therapies taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

9.9.3 Permitted Therapies

In both parts of the study, ongoing behavioral therapies, including individual cognitive behavioral therapy, group cognitive behavioral therapy, social effectiveness training, ADHD behavioral therapy, or applied behavioral analysis are allowed during the study and must be maintained at the same frequency/intensity as at the Screening Visit (Visit 1). The initiation of new behavioral therapies during the study is not allowed.

The use of inhaled bronchodilators is allowed, if needed. Antibiotics and over-the-counter (OTC) medications that do not affect blood pressure, heart rate, or the central nervous system and are considered necessary for the subject's welfare, may be administered at the discretion of the investigator provided they are not substrates of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6 or OAT1. Non-sedating antihistamines such as Allegra® are allowed, as are OTC nonstimulant cold remedies such as guaifenesin. The use of inhaled steroids (corticosteroids) for asthma is allowed.

Acceptable methods of birth control are abstinence or 2 of the following: intrauterine device, diaphragm, spermicides, cervical cap, contraceptive sponge, and condoms. The use of oral, implantable, hormonal and/or injectable contraceptives is not permitted in this study as they are a substrate of excluded cytochrome P450 enzymes noted in Section 9.9.4.

9.9.4 Prohibited Therapies

In both parts of the study, any concomitant medication which is a substrate of CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6, or OAT1 is prohibited in this study. Subjects may not have taken any psychotropic medication within the 28 days prior to the Screening Visit (Visit 1) other than their stimulant and/or nonstimulant medications taken for ADHD and/or or clonidine taken at night for sleep. After completion of the Screening Visit (Visit 1), eligible subjects will have their ADHD medication discontinued (if applicable). The washout phase will be 5 days for stimulant medications and 14 days for nonstimulant medications and/or or clonidine taken at night for sleep. The investigator cannot initiate the discontinuation of ADHD therapies as part of this study without first obtaining the subject's informed consent/assent and determining a subject's eligibility.

Initiation of any new psychotropic medication during the study is not allowed. A change in frequency/intensity of behavioral therapies ongoing at the Screening Visit (Visit 1) or the initiation of new behavioral therapies during the study is also not allowed.

During the study, new initiation of investigational compounds, herbal therapy, sedatives, hypnotics and anxiolytics, antidepressants, antipsychotics, anticonvulsants, psychostimulants, adrenergic agents, oral corticosteroids (inhaled steroids for asthma is permitted), sedating antihistamines, ephedrine and pseudoephedrine is prohibited.

Subjects receiving an excluded therapy within the 28 days prior to the Screening Visit (Visit 1) will be ineligible for study participation. At the discretion of the Sponsor, subjects receiving excluded therapies during the study may be ineligible for continuation in the study.

9.10 Treatment after End of Study

After the end of the study, defined as completion of the follow-up call, each subject will be treated per standard clinical practice.

10. STUDY PROCEDURES

The parent / legally authorized representative will provide written informed consent and subjects will assent (as applicable) before any study-related procedures are initiated.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Table 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, ±2 days of the originally scheduled date. Visits should not be skipped during the study.

10.1 Study Periods and Visits

10.1.1 Screening (Visit 1, Day -28)

The subject must be screened within 28 days before randomization in the study. The following procedures will be performed at the Screening Visit (Visit 1):

- ☐ Obtain written informed consent/assent.
- ☐ Review inclusion/exclusion criteria.
- ☐ Collect demographic information.
- ☐ Record medical/medication history including documentation of CNV in specific gene of interest.
- ☐ Perform a physical examination.
- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate, oral or tympanic temperature, weight and height. Refer to Section 20 for instructions on how to calculate blood pressure percentile for age, sex and height to determine that the subjects blood pressure does not exceed the 95th percentile.
- ☐ Calculate body mass index (BMI). Refer to Section 20 for instructions on how to calculate BMI to determine that the subject is not underweight or obese based on CDC BMI for age-sex specific values.
- ☐ Collect blood and urine samples required for clinical laboratory tests to include: hematology, serum chemistry, thyroid stimulating hormone (TSH), T4, urinalysis, urine drug screen, and serum pregnancy test (females only).
    a. A subject with a positive urine drug result at the Screening Visit (Visit 1) attributed to a prescribed medication requires a re-test and a negative result to confirm subject eligibility prior to the Baseline Visit (Visit 2). This does not apply to a positive result due to a subject's current stimulant therapy for a comorbid diagnosis of ADHD.

- ☐ If required, collect a saliva sample for identity confirmation of subject with a previously banked saliva sample collected in the AEVI-001-ADHD-002 study. The results are to be reviewed prior to randomization to confirm subject eligibility.
    a. If required, any subject whose identity is not confirmed with a previously banked saliva sample collected virtually in the AEVI-001-ADHD-002 study, will be immediately recorded as a screening failure.
    b. If a subject participated in the MDGN-NFC1-ADHD-001 study, the MDGN-NFC1-ADHD-101 study, or was screened on-site for the AEVI-001-ADHD-002 study, a saliva sample is not required to be collected.
- ☐ Perform 12-lead ECG.
- ☐ Conduct clinician completed assessments:
    - o M.I.N.I. International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid)
    - o KBIT-2
    - o CGI-S
    - o C-SSRS Baseline Version
- ☐ Collect parent completed assessment:
    - o Conners 3-P(S)
- ☐ Access interactive web response system (IWRS)
- ☐ Assess and record concomitant medications and adverse events (AEs).

Instruction for rescreening subjects who initially fail study entry criteria are described in Section 8.6.

If more than 28 days have elapsed between the Screening Visit (Visit 1) and the Baseline Visit (Visit 2), the following procedures must be repeated and the repeat Screening Visit (Visit 1) results available and reviewed prior to proceeding with the Baseline Visit (Visit 2):

- ☐ Collect blood and urine samples required for clinical laboratory tests to include: hematology, serum chemistry, thyroid stimulating hormone (TSH), T4, urinalysis, urine drug screen, and serum pregnancy test (females only).
- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate, oral or tympanic temperature, height and weight.
- ☐ Perform 12 lead ECG.
- ☐ Access interactive web response system (IWRS).

Applicable inclusion and exclusion criteria must be reassessed using the results received.

10.1.2 Washout or Pre-Baseline Period

During the screening period, the parent/LAR will receive a telephone call to initiate washout (after eligibility has been confirmed and if a washout is if required) and to schedule the Baseline Visit (Visit 2). For subjects receiving a stimulant medication for ADHD, the call should take place to

allow for a 5-day washout prior to the Baseline Visit (Visit 2). For subject's current taking a nonstimulant medication for ADHD and/or or clonidine taken at night for sleep, the call should take place to allow for a 14-day washout prior to the Baseline Visit (Visit 2). Subjects who do not require a washout must still be contacted by phone prior to the Baseline Visit (Visit 2) being conducted.

The following will be completed for all subjects:

1. Review inclusion/exclusion criteria.
2. Assess and record concomitant medication and newly occurring AEs since the last evaluation.
3. Schedule the Baseline Visit (Visit 2).

10.1.3 Baseline (Visit 2, Day 0)

Subjects will attend a Baseline Visit (Visit 2) on the day before starting study treatment (Day 0). Subjects who remain eligible for the study will be given AEVI-001 at the initial dose of 100 mg twice daily to begin treatment the following day (Day 1).

The following procedures will be performed at the Baseline Visit (Visit 2).

- ☐ Review inclusion/exclusion criteria.
- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate and weight. Refer to Section 20 for instructions on how to calculate blood pressure percentile for age, sex and height to determine that the subjects blood pressure does not exceed the 95th percentile.
- ☐ Collect blood and urine samples required for clinical laboratory tests to include: hematology, serum chemistry, urine drug screen and urinalysis. The results are to be reviewed upon receipt to confirm continued participation in the study.
    a. A subject with a positive urine drug result at the Screening Visit (Visit 1) attributed to a prescribed medication requires a re-test and a negative result to confirm subject eligibility prior to the Baseline Visit (Visit 2). This does not apply to a positive result due to a subject's current stimulant therapy for a comorbid diagnosis of ADHD.
- ☐ Perform urine pregnancy test (for female subjects only).
- ☐ Perform 12-lead ECG.
- ☐ Conduct clinician completed assessments:
    - o ADHD-RS-5
    - o CGI-S
    - o C-SSRS Since Last Visit Version
- ☐ Conduct parent completed assessments:
    - o Child Behavior Checklist (CBCL)
    - o Conners 3-P(S)

- ☐ Access IWRS.
- ☐ Randomization
- ☐ Dispense IP blister card at the initial dose level of 100mg or placebo twice daily with instructions to begin taking the IP the following day in the morning upon awakening [7:00 a.m.to 9:00 a.m.] and again in the mid-afternoon [between 3:00 p.m.to 5:00 p.m.].
- ☐ Assess and record concomitant medications and AEs.

10.1.4 Dose Optimization Phase (Visit 3-6, Days 7-28 [± 2 days])

Subjects will be treated with a 100 mg dose or placebo twice daily at the next scheduled dosing timepoint, for approximately a week. During the 4-week dose-optimization phase, subjects will be administered 100, 200, 400 mg or placebo twice daily based on dose assessments performed by the investigator.

Subjects will attend a visit for evaluation by the investigator weekly during the dose optimization phase. During these visits, the investigator will assess the tolerability and efficacy of the subject's current AEVI-001 or placebo dose, and categorize their response as intolerable, ineffective, or acceptable (see Section 9.7 for the dose adjustment criteria). Based on this categorization, the subjects will be dispensed the next appropriate dose of AEVI-001 or placebo, to begin taking at the next dosing timepoint.

The following procedures will be performed at these visits.

- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate and weight.
- ☐ Collect blood and urine samples required for clinical laboratory tests to include: hematology, serum chemistry and urinalysis (Visits 3 and 6 only) and urine drug screen (Visits 3-6). The results of the should be reviewed upon receipt to confirm continued participation in the study. hematology, serum chemistry and urinalysis (Visits 3 and 6 only).
    a. Any subject with a positive urine drug result at Visits 3-6 must be discussed with the CRO medical monitor to confirm continued participation in the study.
- ☐ Perform urine pregnancy test (for female subjects only).
- ☐ Perform 12-lead ECG.
- ☐ Conduct clinician completed assessments:
    - o ADHD-RS-5
    - o CGI-S
    - o CGI-I
    - o C-SSRS Since Last Visit Version
- ☐ Collect parent completed assessment:
    - o Conners 3-P(S) (Visit 6 only)
- ☐ Subject returns empty or partially filled IP blister card(s).

- ☐ Assess subject compliance with IP. Compliance will be calculated within IWRS with doses not returned assumed to be taken. Weekly compliance is defined as 80-100%. A subject who is non-compliant at a given visit should be retrained by the site to secure compliance with dosing. If a subject remains non-compliant after being retrained they may be discontinued from the study. All instances of non-compliance are to be discussed with the Medical Monitor. Additionally, a subject who is >100% compliant in any week should be queried to confirm whether they took an extra dose(s) on a given day than was prescribed (e.g, subject assigned to take 1 capsule bid for a total of two capsules but they instead took 2 capsules bid for a total of 4 capsules). If this occurs, the overdose would be reported per Section 12. The compliance formula is shown below:

  (# of capsules taken / # of capsules that should have been taken) x 100

- ☐ Conduct Investigator dose assessment.
- ☐ Access IWRS.
- ☐ Dispense IP blister card(s) at the appropriate dose level, with instructions to begin taking the IP at the next dosing timepoint.
- ☐ Assess and record concomitant medications and AEs.

10.1.5 Dose Maintenance Phase (Visit 7, Day 35 [± 2 days])

Subjects will attend the visit for evaluation by the investigator. During this visit, the investigator will assess the tolerability and efficacy of treatment with AEVI-001 or placebo. The subjects will be dispensed the same dose of AEVI-001 or placebo during this phase as was taking at Visit 6. and instructed to begin taking at the next dosing timepoint.

The following procedures will be performed at the visit.

- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate, and weight.
- ☐ Perform urine pregnancy test (for female subjects only).
- ☐ Collect urine sample required for urine drug screen. Any subject with a positive urine drug result at Visits 7 must be discussed with the CRO medical monitor to confirm continued participation in the study.
- ☐ Perform 12-lead ECG.
- ☐ Conduct clinician completed assessments:
  - o ADHD-RS-5
  - o CGI-S
  - o CGI-I
  - o C-SSRS Since Last Visit Version
- ☐ Subject returns empty or partially filled IP blister card(s).
- ☐ Assess subject compliance with IP. Compliance will be calculated within IWRS with doses not returned assumed to be taken. Weekly compliance is defined as 80-100%. A subject

who is non-compliant at a given visit should be retrained by the site to secure compliance with dosing. If a subject remains non-compliant after being retrained they may be discontinued from the study. All instances of non-compliance are to be discussed with the Medical Monitor. Additionally, a subject who is >100% compliant in any week should be queried to confirm whether they took an extra dose(s) on a given day than prescribed (e.g, subject assigned to take 1 capsule bid for a total of two capsules but they instead took 2 capsules bid for a total of 4 capsules). If this occurs, the overdose would be reported per Section 12. The compliance formula is shown below:

(# of capsules taken / # of capsules that should have been taken) x 100

- ☐ Access IWRS.
- ☐ Dispense IP blister card(s) as the appropriate dose level, with instructions to begin taking the IP at the next scheduled timepoint.
- ☐ Assess and record concomitant medications and AEs

10.1.6 Study Completion / Early Termination (Visit 8/Early Termination [ET], Day 42/Any [± 2 days])

Subjects will attend a visit for final evaluation by the investigator after 6 weeks of treatment or upon decision to discontinue from the study. During this visit, the investigator will make a final assessment of tolerability and efficacy of treatment with AEVI-001 or placebo.

The following procedures will be performed at these visits.

- ☐ Perform a physical examination.
- ☐ Collect vital sign measurements including blood pressure, pulse rate, respiratory rate, weight, and height.
- ☐ Collect blood and urine samples required for clinical laboratory tests to include: hematology, serum chemistry, urinalysis urine drug screen, and serum pregnancy test (for female subjects only). The results of the should be reviewed upon receipt.
- ☐ Perform 12-lead ECG.
- ☐ Conduct clinician completed assessments:
  - o ADHD-RS-5
  - o CGI-S
  - o CGI-I
  - o C-SSRS Since Last Visit Version
- ☐ Collect parent completed assessment:
  - o Conners 3-P(S)
- ☐ Subject returns empty or partially filled IP blister card(s).
- ☐ Access IWRS.

- ☐ Assess subject compliance with IP. Compliance will be calculated within IWRS with doses not returned assumed to be taken. Weekly compliance is defined as 80-100%. A subject who is >100% compliant in any week should be queried to confirm whether they took an extra dose(s) on a given day than prescribed for that week (e.g, subject assigned to take 1 capsule bid for a total of two capsules but they instead took 2 capsules bid for a total of 4 capsules). If this occurs, the overdose would be reported per Section 12. The formula is shown below:

  (# of capsules taken / # of capsules that should have been taken) x 100

- ☐ Assess and record concomitant medications and AEs.

10.1.7 Follow-up Call (7 days [+2 days] after the last dose of Investigational Product)

At Day 7 (+ 2 days) after the last dose of IP, caregivers will receive a telephone call to assess and record concomitant medication and newly occurring AEs and the outcome of ongoing AEs since the last evaluation.

10.2 Study Duration

The overall study duration of each part of the study is expected to be approximately 11 weeks (including up to 28 days of screening, 6 weeks of treatment, and a follow-up period of 7 days (+2 days).

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

1. Screening period: approximately 28 days.
2. Open-label treatment period: 6 weeks inclusive of,
   a. Dose-optimization phase: 4 weeks.
   b. Dose Maintenance phase: 2 weeks.
3. Follow-up: 7 days (+2 days) after the last dose of IP.

The maximum study duration for each subject is approximately 11 weeks.

The maximum treatment duration for each subject is 6 weeks.

10.3 Assessments

10.3.1 Psychological Screening Evaluations

10.3.1.1 M.I.N.I. International Neuropsychiatric Interview for Children and Adolescents

The M.I.N.I. Kid is a short, structure diagnostic interview designed to assess psychiatric disorders per DSM-5 criteria (Sheehan et al., 1998).

Time of administration = 30-45 minutes.

10.3.1.2 Kaufman Brief Intelligence Test, Second Edition (KBIT-2)

The Kaufman Brief Intelligence Test, Second Edition (Kaufman et al, 2004) is designed to measure both the verbal and nonverbal intelligence in children and adults (ages 4 years, 0 months through 90 years, 11 months) using a brief, individual format. The assessment includes 3 subtests; 2 classified as verbal and 1 as nonverbal. Administration of the KBIT-2 yields a Verbal Score, Nonverbal Score, and IQ Composite.

Time of administration: 15-30 minutes.

10.3.1.3 Child Behavior Checklist

The Child Behavior Checklist (CBCL) was designed to address the problem of defining child behavior problems. The checklist assesses the behavioral problems and social competencies of children as reported by parents using a standardized format. The CBCL can be self-administered or administered by an interviewer and consists of items related to behavior problems. Each item is scored on a 3-point scale ranging from not true to very true or often true of the child. Additionally, there are social competency items used to obtain parents' reports of the amount and quality of their child's participation in specific tasks and activities.

Time of administration: 30 minutes.

10.3.2 Efficacy

All scales included in Section 10.3.1 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, licensed psychologist with a PhD, or as otherwise approved by the sponsor or designee. At a given site, the assessments and other evaluations may be recorded for reliability purposes.

10.3.2.1 Attention Deficit Hyperactivity Disorder Rating Scale 5 (ADHD-RS-5)

The ADHD-RS-5 (DuPaul et al, 2016) will be used as the primary outcome measure. The ADHD-RS-5 will be administered at each visit, beginning at the Baseline Visit (Visit 2) 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 and consists of 18 items designed to reflect the symptomatology of ADHD based on the Diagnostic and) 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 score is computed by summing the item scores for Items 1–9. The Hyperactivity-Impulsivity subscale 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 (CGI-I) and Severity (CGI-S) Scales

The CGI-I will be used as a key secondary outcome measure and the CGI-S as a secondary outcome measure to estimate level of functioning in response to treatment with AEVI-001 or placebo. It is a clinician's global assessments of the severity of the symptoms and changes in symptoms from baseline based on reports from parents, subjects, and minimal direct observation. This assessment will guide the investigator during dosing adjustments.

Starting at the Screening Visit (Visit 1), a CGI-S scale is performed to rate 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).

From Visits 3-7 (or ET) the investigator will assess the subject's improvement relative to their symptoms at Baseline (Visit 2) using a CGI-I assessment, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

Time of administration: 10-20 minutes.

10.3.2.3 Conners 3rd Edition-Parent Short form (Conners 3- P(S)

The Conners 3–P(S) is a parent completed assessment that has been used to obtain the parent's observations about the behavior of their child. The scale was designed to assess ADHD and the most common co-morbid problems in children and adolescents aged 6 to 18 years old. The scale includes 45 questions that are scored on 4-point scale ranging from 0 (Not true at all) to 3 (Very much true). The scale has 5 content scales which include Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Functioning, Defiance/Aggression, and Peer/Family Relations.

Time of administration: 10-20 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, physical examination findings, and C-SSRS.

10.3.3.1 Clinical Laboratory Safety Assessments

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 (Table 1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, 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. Screening Visit (Visit 1) only: thyroid stimulating hormone and T4
Urinalysis	pH, specific gravity, blood, glucose, protein, ketones.
Urine/serum pregnancy test	For all women.
Urine drug screen	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids, propoxyphene, and methadone.

Laboratory specimens will be analyzed at the central laboratory per their collection and processing requirements. The urine pregnancy test will be performed at the site.

Sampled Blood Volume

The sampled blood volume for this study is shown below:

Table 7: Sampled Blood Volume per Subject

Type	Volume per sample	Sample number	Total
Safety			
Clinical chemistry	3.5 mL	6*	21 mL
Hematology	2 mL	6*	12 mL
Total (up to)			**33 mL**

*If more than 28 days have elapsed between the Screening Visit (Visit 1) and the Baseline Visit (Visit 2), an additional blood draw will be required.

Identity Confirmation Test to be Performed

If required, a subject will provide a saliva sample at the Screening Visit (Visit 1) for identity confirmation with a previously banked saliva sample of the subject collected virtually in the AEVI-001-ADHD-002 study. A short tandem repeat analysis of the saliva sample will be undertaken. If a subject participated in the MDGN-NFC1-ADHD-001 study, the MDGN-NFC1-ADHD-101 study, or was screened on-site for the AEVI-001-ADHD-002 study, the saliva sample is not required to be collected.

Saliva Sample Collection and Analysis

If required, two milliliters of saliva will be collected in a designated collection vehicle (Oragene•Dx) per the manufacturer's instructions which will be review with the parent/LAR. The instructions are also included in Section 20 of this protocol.

If a subject participated in the MDGN-NFC1-ADHD-001 study, the MDGN-NFC1-ADHD-101 study, or was screened on-site for the AEVI-001-ADHD-002 study, the saliva sample is not required to be collected.

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 site and/or 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 per the applicable regulations.

Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this study will be provided by the central laboratory. They will be regarded as the reference ranges on which decisions will be made for the specific site.

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 subject's source documentation.

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, as necessary, and reported as AEs and followed, as described in Section 11.1.1.

All measurements described in this section are recognized standard methods.

Evaluation of Identity Confirmation Result

If required, a subject's whose identity is not confirmed with a previously banked saliva sample collected virtually from the AEVI-001-ADHD-002 study, will be immediately recorded as a screening failure.

10.3.3.2 Clinical Examinations

Blood Pressure, Pulse Rate, Respiratory Rate and Temperature

Blood pressure, pulse rate and respiratory rate will be measured at times specified in the schedule of events. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE. Temperature (oral or tympanic) will be collected at the Screening Visit (Visit 1) only.

The blood pressure percentile for age, sex and height is to be calculated at the Screening Visit (Visit 1) and the Baseline Visit (Visit 2) to confirm that the subject does not exceed the 95th percentile. Refer to Section 20 for instruction how to calculate blood pressure percentile for age, sex and height.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be documented and used throughout the study for all subjects. In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after approximately 5 minutes of rest in the sitting position.

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be comfortably seated, with the legs uncrossed, with feet flat on the floor, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum).

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for approximately 5 minutes. All ECG recordings will be identified with the subject number, subject initials, date, and time of the recording and a copy will be included with the subject's source documentation.

Twelve-lead ECGs will be performed at the times specified in the schedule of events. All ECGs will be performed using the equipment supplied by the central ECG vendor.

Electronic ECG tracings will be analyzed by the central ECG vendor for the calculation of reported values for the following ECG tests: heart rate, PR interval, RR interval, QRS duration, and QT interval, corrected QT interval using the Bazett formula (QTcB), corrected QT interval using the Fridericia formula (QTcF), and evaluator interpretation. In addition, the investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and recorded in the eCRF.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time to achieve precise ECG recordings. One complete recording, including a 10-second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording and if not valid, it should be repeated. All ECGs collected are to be entered into the eCRF. In the event of more than one ECG, the first valid ECG will be recorded as the ECG for the visit in question and all others entered in the eCRF as unscheduled assessments.

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 CRO medical monitor and reported as AEs and followed, as described in Section 11.1.1.

Physical Examination, Height, Weight and Body Mass Index

A complete physical examination (excluding the genitourinary examination) will be performed at the Screening Visit (Visit 1) before potential exposure to the IP and at Visit 8/ET at the completion of exposure. Any clinically significant physical examination findings are to be and reported as AEs and followed, as described in Section 11.1.1.

Weight will be collected at the Screening Visit (Visit 1) through Visit 8/ET. Height will be collected at the Screening Visit (Visit 1) and at Visit 8/ET. Body mass index will be calculated at the Screening Visit (Visit 1) to confirm that the subject is not underweight or obese based on CDC BMI for age-sex specific values. Refer to Section 20 for instructions how to calculate BMI to determine BMI for age-sex percentile.

10.3.3.3 Columbia Suicide Severity Rating Scale

The C-SSRS 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 sponsor-approved licensed clinician who is medically responsible for the subject. A clinician is defined as a doctor of medicine, doctor of osteopathic medicine, or licensed psychologist with a PhD unless otherwise approved by the sponsor. The C-SSRS has a "baseline" version which will be completed at the Screening Visit (Visit 1) and a "Since Last Visit" version that will be completed at Visits 2 through 8/ET. There is 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 (i.e., yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors (Posner, 2011).

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 11.2.1.

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, ask about, and/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. ADVERSE EVENTS

11.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

11.1.1 Adverse Event Collection

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 related to the product. An AE will be considered treatment emergent if it occurs after the first dose of IP and within 3 days of a subjects last dose of IP.

All AEs are collected from the time of the informed consent is signed until the follow-up call is completed as stated in Section 10.1.7. This includes events occurring during the screening phase of the study, regardless of whether investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate

AE pages in the eCRF and in source documents. In addition, to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the source documents and AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variable have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of an event(s) can be documented.

11.1.2 Severity of Adverse Events

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of a pre-treatment events, after initiation of investigational product must be recorded as new AEs. For example, if the subject experiences mild, intermittent headaches prior to dosing with IP however the headache intensity increases to moderate after the first dose of IP, a new AE of moderate intermittent headaches is to be recorded in the source documents and eCRF.

The medical assessment of clinical severity of an AE will be determined using the following definitions:

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 11.1.4.3.

11.1.3 Relationship Categorization

A physician investigator must make the assessment of relationship to IP for each AE. The investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the IP. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, the AE should be categorized per the guidelines below. The causality assessment must be documented in the source document and the eCRF (Table 8).

Table 8: Assessment of Relationship to Investigational Product

Relationship	Description
Not Related	Exposure to IP has not occurred. *OR* The administration of IP and the occurrence of the AE are not reasonably related in time *OR* The AE is considered likely to be related to an etiology other than the use of the IP, that is, there are no facts/evidence or arguments to suggest a causal relationship to the IP.
Possibly Related	The administration of the IP and the occurrence of the AE are reasonably related in time. *AND* The AE could not be explained equally well by factors or causes other than exposure to IP
Probably Related	The administration of IP and the occurrence of the AE are reasonably related in time. *AND* The AE is more likely explained by exposure to IP than by other factors or causes.

11.1.3.1 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

*See Section 11.1.5.

11.1.4 Serious Adverse Events

11.1.4.1 Investigational Product Safety Information

The IB is the reference document for safety information pertaining to this study. The IB is provided separately.

11.1.4.2 Reporting of Serious Adverse Events

Initial and follow-up SAE reports must be completed by the investigator or designee and sent to the CRO within 24 hours of the first awareness of a SAE. The investigator or designee must complete, sign and date the appropriate SAE form and verify the accuracy of the information against corresponding source documents. This information is to be sent to the CRO Pharmacovigilance Department by one of the following methods:

- ☐ E-mail: [redacted]
- ☐ Fax number: [redacted]

11.1.4.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence, whether considered to be related to IP or not, 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.*

11.1.4.4 Serious Adverse Event Collection Time Frame

All SAEs, regardless of the relationship to study, are collected from the time the parent/ LAR or subjects signs the informed consent until the subject's last visit (office or telephone contact). The investigator or designee must report all SAEs promptly to CRO within 24 hours of first becoming aware of the event.

Any SAE(s), regardless of relationship to study, discovered by the investigator at any interval after study has completed must be reported to CRO within 24 hours of the first awareness of the event. Please see individual study site documentation (study binder) for forms and contact details.

11.1.4.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date symptoms resolve or the event is considered chronic. In the case of hospitalization, the hospital admission and discharge dates are considered respectively, the onset and resolution date of the SAE.

Any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE or following the resolution date of the SAE must be recorded as an AE.

11.1.5 Fatal Outcome

Fatal should only be selected as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE.

Any AE that results in the subject's death must have fatal checked as an outcome with the date of death recorded as the resolution date. AEs resulting in death must be reported within 24 hours as a SAE, if not already reported as such.

For other AEs, ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

11.2 Special Considerations

11.2.1 Adverse Events of Special Interest

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

- Suicidal ideation.

11.2.2 Pregnancy

All females 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. Females should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted on every female prior to administration of IP and at every post-baseline visit. A female who is found to be pregnant at the Visits 1 or 2 will be excluded from the study and considered to be a screening failure. A female who is found to be pregnant after Visit 2 is required to be discontinued from the study and the ET visit assessments performed as soon as possible after learning of the pregnancy.

The investigator must report the pregnancy of any female (study participant or female partner of male study participant) who becomes pregnant during IP treatment or within 7 days of discontinuing the IP. The pregnancy must be reported within 24 hours of learning of the pregnancy to the CRO 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.

The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Pregnancy Data Collection 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.

11.2.3 Reporting to Regulatory Agency, Institutional Review Board/Ethics Committee (EC) and Site

The sponsor or its designee is responsible for notifying the relevant regulatory authorities and if applicable, US central institutional review board (IRB) of related, unexpected SAEs.

In addition, the sponsor and the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the development program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his/her site, as required.

12. ABUSE, MISUSE, OVERDOSE AND MEDICATION ERROR

Abuse, misuse, overdose, or medication error, of IP, defined below (Table 9), must be reported to the sponsor using the SAE reporting procedures outlined above whether or not they result in an AE/SAE. The 24-hour reporting period from time of first awareness does not apply to an abuse, misuse, overdose or medication error event(s) unless the abuse, misuse, overdose or medication error event results in a SAE.

Table 9: Definition of Abuse, Misuse, Overdose, and Medication Error

Category	Definition
Abuse	Persistent of sporadic intentional intake of IP when used for a non-medical purpose (for example, to get high, for potential psychoactive effects) in a manner that would be detrimental to the individual and/or society
Misuse	Intentional use of IP other than as directed or indicated at any dose. This includes where IP is not used as directed at the dose prescribed in the protocol.
Overdose	Intentional or unintentional intake of a dose of IP exceeding the dose prescribed to the subject as part of the clinical trial.
Medication Error	Error made in prescribing, dispensing, administration and/or use of IP. Medication errors are reportable to the sponsor or its designee if it involves: Administration and/or use of an unassigned treatment (for example, incorrect IP kit used by subject) Administration and/or use of expired IP

Missing doses are not considered a medication error event and do not need reporting. NOTE: An abuse, misuse, overdose or medication error event can meet more than one category.

13. DATA MONITORING COMMITTEE

Not applicable.

14. STATISTICS

Each part of the study will be analyzed separately. Pooled analyses using both parts may also be conducted, if appropriate.

14.1 Study Endpoints

14.1.1 Efficacy

In each part of the study, the primary outcome will be the change from baseline in the ADHD-RS-5 total score at Visit 8 (Week 6), where baseline is defined as the last ADHD RS-5 total score assessment prior to the first dose of investigational product (usually at Visit 2/Day 0).

The primary efficacy analysis will be conducted using the Full Analysis Set for the change from baseline for the ADHD-RS-5 total score, including all assessments from Visit 3 (Week 1) up to Visit 8 (Week 6), using the linear mixed models repeated measures (MMRM) methods with treatment group, visit, and baseline ADHD-RS-5 total score as a covariate, and interaction of the baseline ADHD-RS-5 total score with the visit included in the model. Missing data will not be imputed.

The primary contrast of interest will be the comparison of the AEVI-001 and placebo groups at Visit 8 (Week 6).

Key Secondary Efficacy Endpoint

The key secondary efficacy measurement will be the percentage of subjects with a dichotomized CGI-I assessment of improved at Visit 8 (Week 6). A dichotomized assessment of improved includes the CGI-I categories of 1 (very much improved) and 2 (much improved), and a dichotomized assessment of not improved included all other assessed CGI-I categories (3-7). If missing CGI-I data are present at Visit 8, the missing score will be imputed by carrying forward the last post-baseline value.

The percentages of subjects considered improved in the AEVI-001 and placebo groups will be compared using logistic regression methods. The logistic regression model will include terms for treatment group and baseline CGI-S score.

Secondary Efficacy Endpoints

Descriptive statistics for the CGI-S score and change from baseline in CGI-S score will be presented by treatment group and visit.

Finally, the dichotomized endpoints of response and remission will be presented as the percentage of subjects meeting the response or remission criteria at Visit 8/ET (Week 6/ET). Both will be scored as 1 for Response/Remission and 0 for non-Response/Remission. Response is defined as:

- A ≥30% reduction from Baseline in ADHD-RS-5 total score.
- Improved on the CGI-I which includes the categories of 1 (very much improved) and 2 (much improved).
- Both a ≥30% reduction in ADHD-RS-5 total score and improved (1 [very much improved] and 2 [much improved] on the CGI-I.

Remission is defined as follows:

- An ADHD-RS-5 total score ≤18.
- A CGI-I of 1 (very much improved).
- Both an ADHD-RS-5 total score ≤18 and a CGI-I of 1 (very much improved).

Exploratory Efficacy Endpoints

Change from baseline in Conners 3-P(S) subscale scores at Visit 8 (Week 6).

14.1.2 Safety

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Affairs and will be summarized by system organ class (SOC) and preferred term. 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 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.

14.1.3 Sample Size Determination

For part A of the study, 42 unique subjects are planned to be randomized to yield approximately 34 subjects who provide post-baseline efficacy data on the primary endpoint. Assuming an effect size of 1.0, this number will yield approximately 80% power to detect a significant difference in mean change from baseline for the ADHD-RS-5 total score at Visit 8 (Week 6) between the treatment groups, based on a 2-tailed test with α=0.05 and 1:1 randomization. In part A of the study, an interim analysis will be performed when approximately 75% of randomized subjects have completed the study. The sample size could be increased to 64 randomized subjects.

For part B of the study, 82 unique subjects are planned to be randomized to yield approximately 66 subjects who provide post-baseline efficacy data on the primary endpoint. Assuming an effect size of 0.7, this number will yield approximately 80% power to detect a significant difference in mean change from baseline for the ADHD RS-5 total score at Visit 8 (Week 6) between the treatment groups, based on a 2-tailed test with α=0.05 and 1:1 randomization.

14.2 Analysis Populations

This study will have the following populations of interest:

- The **Intent-to-Treat** Population includes all subjects who are randomized and dispensed study medication at the Baseline visit.
- The **Full Analysis Set** includes all subjects who are randomized, take at least one dose of randomized study medication during this trial, and have a valid Baseline and at least one post-Baseline follow-up assessment of the primary outcome measure - ADHD-RS-5 total score.
- The **Safety** Population includes all subjects who are randomized and take at least one of randomized study medication during this trial.

14.3 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 (SAP) for this study. The SAP will be finalized prior to database lock.

14.3.1 Study Subjects and Demographics

14.3.1.1 Disposition and Withdrawals

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

14.3.1.2 Protocol Deviations

All subject data will be reviewed for the occurrence of protocol deviations. Prior to database lock, all protocol deviations will be reviewed and classified with respect to the potential to influence experimental outcomes.

14.3.1.3 Demographics and Other Baseline Characteristics

The analysis of demographic and baseline data will be performed for the safety population. 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, and clinical laboratory tests.

14.3.2 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by dose administered and by the number and percentage of subjects taking each medication. Prior medications will be summarized by dose administered and by the number and percentage of subjects taking each medication. Medications will be coded per the World Health Organization Drug Dictionary (WHO-DD) preferred term.

14.3.3 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 overall and by visit. Based on capsule counts, the number of doses administered will be expressed as the proportion of doses scheduled by week and overall. Doses not returned will be assumed taken for the purposes of calculating compliance. Additionally, compliance will be calculated within IWRS. A subject will be considered non-compliant if their overall compliance is less than 80% or greater than 120%. This assessment will be completed at the end of the study.

14.3.4 Efficacy Analyses

All efficacy measures will be described with standard summary statistics. Continuous variables will be summarized by N, the mean and standard deviation, and categorical variables will be summarized by the number and percent of subjects in each category. The analysis of response rate will be performed after randomized subjects have completed their final visit. This will be calculated as the proportion of the Full Analysis Set population who achieve responder status. The response rate will be expressed as a percentage with an accompanying 95% CI. Comparisons of dichotomized responses between treatment groups will be based on odds ratios and associated 95% CIs resulting from the logistic regression model.

14.3.5 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 14.2). Safety variables include TEAEs, clinical laboratory values, vital signs, ECG results, and C-SSRS results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

14.3.5.1 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Affairs (MedDRA). The incidence of TEAEs will be summarized by treatment group, system organ class (SOC), and preferred term. An AE will be considered treatment emergent if it occurs after the first dose of IP and within 3 days after a subjects last dose of IP. Similar summaries will be produced for SAEs and AEs leading to discontinuation. The intensity of AEs and the relationship to investigational product will also be summarized for each SOC and preferred term.

14.3.5.2 Clinical Laboratory Evaluations

Descriptive summaries for all reported values and change from baseline values will be summarized by laboratory test category, treatment group, and visit.

14.3.5.3 Vital Signs and Electrocardiograms

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

14.3.5.4 Columbia Suicide Severity Rating Scale

The incidence of suicidal ideation/behavior at any time will be summarized by treatment group.

14.3.6 Interim Analysis

In part A of the study, an interim analysis will be performed when approximately 75% of randomized subjects have completed the study. This analysis will focus on the magnitude of placebo response and will determine whether the enrollment target should be increased to a total of 64 randomized subjects. No sample size adjustment is planned for Part B if conducted.

The interim analysis will require unblinding of patient-level data and will be conducted by an independent statistician having no other involvement in the analysis or conduct of this study. The analysis will be limited to evaluation of ADHD-RS-5 data (i.e., the primary outcome). To maintain the integrity of the experimental blind, only qualitative results will be shared with the sponsor.

15. 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.

15.1 Sponsor and Investigator Responsibilities

15.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 17). The sponsor reserves the right to withdraw a subject from the study (Section 8.7), to terminate participation of a study site at any time (Section 15.5), and/or to discontinue the study (Section 15.4).

Aevi Genomic Medicine, Inc. agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study per the study protocol.

15.1.2 Investigator Responsibilities, Protocol Adherence and Investigator Agreement

By signing the Investigator's Agreement in Section 19, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to adhere to the protocol as detailed in this document.

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 (e.g., 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 Aevi Genomic Medicine, Inc. 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 may 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.

Per local laws and regulations, the investigator, sponsor or sponsor designee will communicate with the IRB/EC to ensure accurate and timely information is provided throughout the study.

15.2 Study Documents

All documentation and material provided by Aevi Genomic Medicine, Inc. for this study are to be retained in a secure location and treated as confidential material.

15.2.1 Case Report Forms

By signing the Investigator's Agreement in Section 19, the investigator agrees to complete the eCRFs and maintain source documentation as part of the case histories for all subjects who sign an informed consent form.

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 per the completion guidelines provided by the sponsor or its designee. All data will have separate source documentation; no data will be recorded directly into the eCRF.

The eCRFs will be signed by the investigator or a subinvestigator to whom this authority has been delegated. These signatures serve to attest that the information contained in the eCRF is accurate and true.

15.2.2 Recording, and Retention of Source Data and Study Documents

All study information must be recorded in the subject's medical records and no data will be recorded directly onto the eCRF. Data 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 reports and notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

15.3 Data Quality Control

Aevi Genomic Medicine, Inc. and its designees will perform quality control checks on this clinical study.

15.3.1 Access to Study and Source Documents

Aevi Genomic Medicine, Inc. and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB/EC, having access to the source data (for example, subject's medical records, appointment books, original laboratory reports, radiographic exams and reports, etc.)

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 Aevi Genomic Medicine, Inc. 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 eCRFs will be described for the study personnel as part of training. 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 19, 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 Aevi Genomic Medicine, Inc. or designee auditors or inspectors from IRBs/ECs or regulatory agencies to review records and to assist the inspectors in their duties, if requested.

15.3.2 Data Management

Aevi Genomic Medicine, Inc. 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 the designee's standard operating procedures. Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated eCRF, self-evident correction conventions, 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 will be described.

15.3.3 Quality Assurance Audit / Inspection

This study may be subject to audit by Aevi Genomic Medicine, Inc. or designee. The audits undertaken will check compliance with GCP guidelines. Aevi Genomic Medicine, Inc. 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 per 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.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator will/must notify Aevi Genomic Medicine, Inc. immediately.

15.4 Study Termination

The study may be terminated at Aevi Genomic Medicine, Inc. discretion at any time and for any reason.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will return all investigational product, containers, and other study materials to the sponsor.

15.5 Study Site Closure

At the end of the study, all study sites will be closed. Aevi Genomic Medicine, Inc. 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.

15.5.1 Record Retention

It is the investigator's responsibility for maintaining adequate and accurate study and medical records. The investigator shall retain and preserve 1 copy of all data generated during the study, specifically including, but not limited to, those defined by ICH 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 must notify the sponsor in writing of her/his intent to move and/or destroy any study material. Approval from the sponsor must be granted prior to any action being taken.

15.5.2 Sample Retention

Not applicable.

15.6 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Aevi Genomic Medicine, Inc. 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.

15.7 Use of Information and Publication

All information concerning AEVI-001, Aevi Genomic Medicine, Inc. operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Aevi Genomic Medicine, Inc. or designee to the investigator and not previously published, is considered confidential and remains the sole property of Aevi Genomic Medicine, Inc. Case report forms also remain the property of Aevi Genomic Medicine, Inc. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Aevi Genomic Medicine, Inc. in connection with the continued development of AEVI-001 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 Aevi Genomic Medicine, Inc. Publication or other public presentation of AEVI-001 data resulting from this study requires prior review and written approval of Aevi Genomic Medicine, Inc. Abstracts, manuscripts, and presentation materials should be provided to Aevi Genomic Medicine, Inc. 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 Aevi Genomic Medicine, Inc. has reviewed and commented on such a presentation or manuscript for publication.

16. PUBLIC POSTING OF STUDY INFORMATION

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigator information (e.g. site name, investigator name, site location, site contact information).

17. ETHICAL AND LEGAL CONSIDERATIONS

17.1 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.

17.2 Subject Information and Informed Consent

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subjects or parent/LAR before any activity or procedure is undertaken that is not part of routine care including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's LAR, as applicable, is requested to sign and date the subject informed consent form or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, included but not limited to: the objectives, potential benefits and risks, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (such as a complete set of subject information sheets and fully

executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national requirements) prior to the study start that another party (such as the sponsor or coordinating principal investigator) is responsible for this action. If the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

17.3 Institutional Review Board or Ethics Committees

A properly constituted, valid IRB/EC according to local laws and regulations must review and approve the protocol, the investigator's informed consent document, and related subject information and any other study materials requiring review (such as recruitment information) before the start of the study.

Until written approval by the IRB has been received by the investigator, no subject may undergo any study procedure solely for determining eligibility for this study. Investigational product will not be released until the sponsor or its designee has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve and provide documentation of favorable opinion/approval of any revisions to informed consent documents and amendments to the protocol unless there is a subject safety issue.

Depending on location (outside EU or inside EU) the IRB/EC will be apprised of the progress of the study and of any changes made to the protocol at least yearly. This may be done by the investigator (outside EU and in some cases, inside EU) or the sponsor (in some cases inside EU). These updates include information on any serious or significant AEs.

Upon study completion, the investigator will provide the IRB/EC with final report/summary as required.

17.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after where the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from sponsor or subsidiaries such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consulting or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 (b) (1998).

17.5 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations and guidelines.

After subjects have consented to participate in a study, the sponsor and/or its representatives reviews their medical records and data collected as part of the study. These records and data may be reviewed by others including the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB/EC which gave the approval for the study, third parties with whom the sponsor may develop, register or market the investigational product. The sponsor and its representatives will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, the initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of data.

The results of the studies, containing the subjects' unique identifying number, relevant medical records and possibly initials and dates of birth, will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where the study is conducted. The purpose of such transfer would include supporting regulatory submissions, to conduct new data analyses to publish or present the study results or to answer questions asked by regulatory or health authorities.

18. REFERENCES

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.

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.

Hadley D, Wu ZL, Kao C, et al. The impact of the metabotropic glutamate receptor and other gene family interaction networks on autism. Nat Commun. 2014;5:4074.

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. European Journal of Pharmacology 387 (2000)9-17.

Kaufman, A. S., & Kaufman, N. L. (2004). Kaufman Brief Intelligence Test, Second Edition. Bloomington, MN: Pearson, Inc.

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. Pharmacology Biochemistry and Behavior 1999 Sept; 64(1): 41–52.

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 Research. 754(1997);121-130.

Oka M, Itoh Y, Shimidzu T, Tatsumi S, Ma F, Ukai Y, Yoshikuni Y, Kimura K. A novel cognition enhancer NS-105 modulates adenylate cyclase activity through metabotropic glutamate receptors in primary neuronal culture. Naunyn-Schmiedeberg's Arch Pharmcol (1997) 356:189-196.

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.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 1998;59(suppl 20):22-33.

19. ATTACHMENTS

INVESTIGATOR'S AGREEMENT

PROTOCOL NUMBER:	AEVI-001-ADHD-202
PROTOCOL TITLE:	A Multicenter, 2-Part, 6-Week, Double-blind, Randomized, Placebo-controlled, Parallel-design Study to Assess the Efficacy and Safety of AEVI-001 in Children and Adolescents (Ages 6-17 Years) with Attention Deficit Hyperactivity Disorder and with or without Copy Number Variants in Specific Genes Implicated in Glutamatergic Signaling and Neuronal Connectivity
FINAL PROTOCOL:	25 July 2018

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 Aevi Genomic Medicine, Inc. and designee 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: _____

20. APPENDICES

STUDY-SPECIFIC REQUIREMENTS

All assessments under license are provided in the study file.

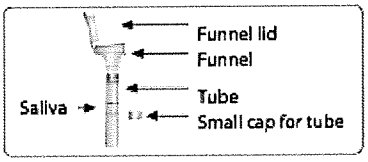
Assessment	**Version for AEVI-001-ADHD-202**
Attention Deficit Hyperactivity Disorder Rating Scale, Version 5	2016
Centers for Disease Control Body Mass Index and Stature	http://nccd.cdc.gov/dnpabmi/Calculator.aspx
Child Behavior Checklist	2001
Clinical Global Impression of Severity	1976
Clinical Global Impression of Improvement	1976
Columbia Suicide Severity Rating Scale, Baseline	Version 1/14/2009
Columbia Suicide Severity Rating Scale, Since Last Visit	Version 1/14/2009
Conners 3rd Edition Parent Short form	2008
Kaufman Brief Intelligence Test, second edition	2004
M.I.N.I International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid)	Version 7.0.2 dated 8/8/2016
National Heart, Lung Blood Institute	https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf

INSTRUCTIONS FOR SALIVA SAMPLE COLLECTION

ORAgene®·Dx
OGD-500/510

USER INSTRUCTIONS

Read all instructions prior to collection



Collection precautions:

Do NOT eat, drink, smoke or chew gum for 30 minutes before giving your saliva sample.

Do NOT remove the plastic film from the funnel lid.

Intended use: For the collection of human DNA from saliva samples.

Contents: Kit contains stabilizing liquid.

Warnings and precautions: Wash with water if stabilizing liquid comes in contact with eyes or skin. Do NOT ingest. See MSDS at www.dnagenotek.com.

Small cap, choking hazard.

Storage: 15°C – 30°C

Summary and explanation of the kit:

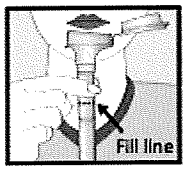
Oragene·Dx is a self-collection kit that provides the materials and instructions for collecting and stabilizing saliva specimens.

Label legend:

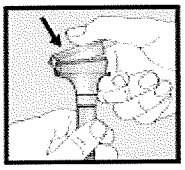
- Consult instructions for use
- Collect saliva only (for use)
- In vitro diagnostic medical device
- Catalog number
- CE Mark
- Caution, consult instructions for use
- Storage instructions
- Authorized Representative
- Manufacturer

Procedure:

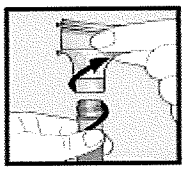
Most people take between 2 and 5 minutes to deliver a saliva sample following steps 1 to 5.



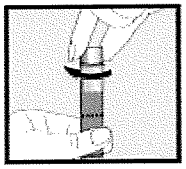
1 Spit into funnel until the amount of liquid saliva (not bubbles) reaches the fill line shown in picture #1.



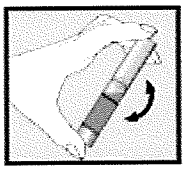
2 Hold the tube upright with one hand. Close the funnel lid with the other hand (as shown) by firmly pushing the lid until you hear a loud click. The liquid in the lid will be released into the tube to mix with the saliva. Make sure that the lid is closed tightly.



3 Hold the tube upright. Unscrew the funnel from the tube.



4 Use the small cap to close the tube tightly.



5 Shake the capped tube for 5 seconds. Discard or recycle the funnel.

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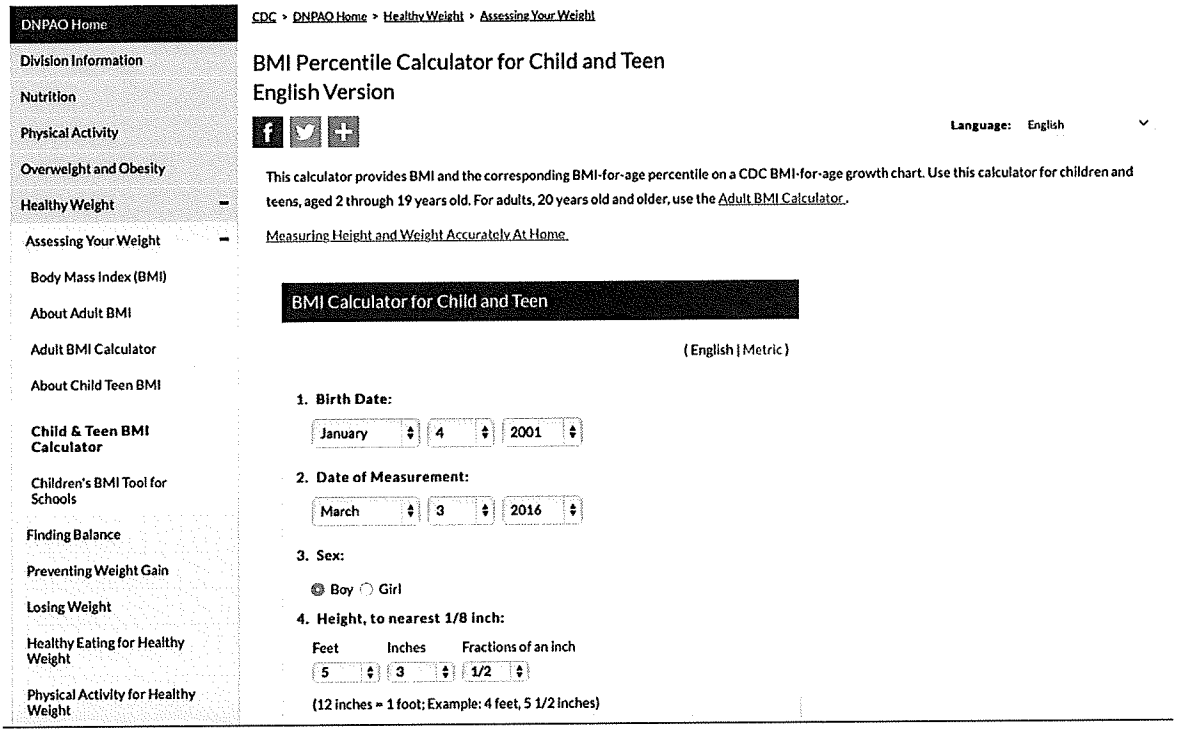
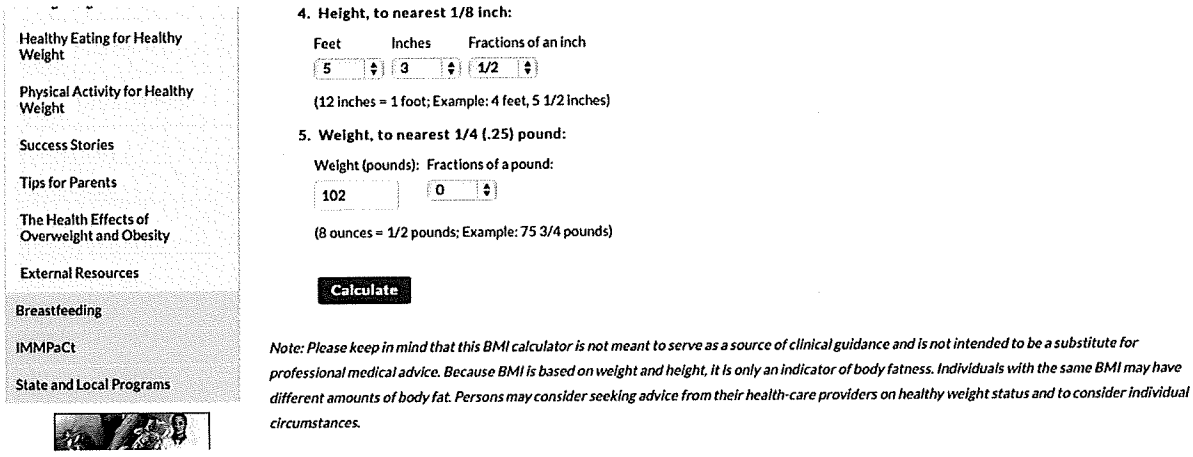
INSTRUCTIONS FOR CALCULATING BODY MASS INDEX AT SCREENING VISIT (VISIT 1)

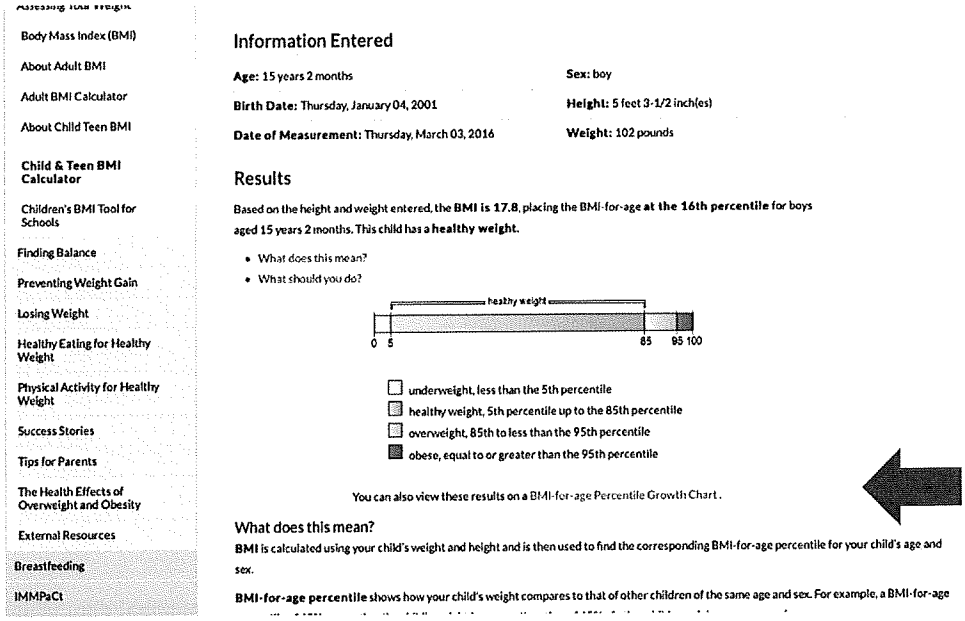
1. Log on to the CDC website: http://nccd.cdc.gov/dnpabmi/Calculator.aspx
2. Enter in the potential subject's data



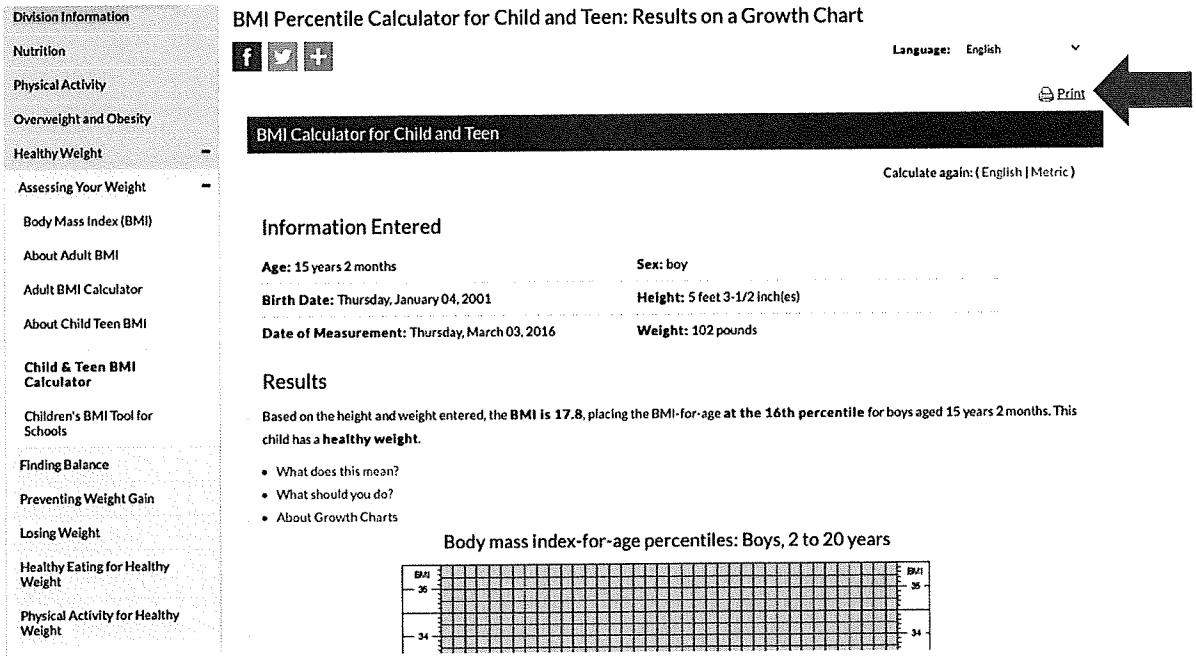
3. Click the "Calculate" button toward the bottom of the page



4. Scroll to middle of calculation summary page to click on hyperlink to view results as BMI for age Percentile Growth Chart.



5. Print BMI for age Percentile Growth Chart output for placement with study source documents. Please label all pages with subject initials and subject study screening number.



INSTRUCTIONS FOR CALCULATING BLOOD PRESSURE PERCENTILE FOR AGE, SEX AND HEIGHT

1. Identify the correct table for the subject's sex from the 2 tables provided below.
2. Find the subject's height percentile as calculated using the CDC information for Girls or Boys via:

   http://reference.medscape.com/calculator/height-age-percentile-girls

   http://reference.medscape.com/calculator/height-age-percentile-boys

   a. Enter age as years using decimals to represent fraction of months beyond birth year, e.g. 16.5 is 16 years and 6 months.

   b. Enter height in inches using decimals to represent fraction of inch, e.g. 54.5 inches for 54 inches and one half inch.

   c. Print page with result for filing in subject's study source documents labelling with subject initials and subject screening number.
3. Find the subject's age row on the blood pressure within the appropriate sex table. If the subject has yet to reach their next birth date, the current age is to be used.
4. Locate the subject's height percentile under the systolic section (column) of the chart within the subject's age row. If the subject is between percentiles, use the values in the lower percentile column. E.g. if the subject has a height measuring to the 48th percentile, use the column for the 25th percentile. When the percentile of height is $\leq$ 5th percentile, se the values for the 5th percentile.
5. Identify if the subject's systolic blood pressure is $\leq$ 95th percentile and enter the outcome of this check in the subject's source documentation.
6. Find subject's height percentile under the diastolic section (column) of the chart within the subject's age row.
7. Identify if the subject's diastolic blood pressure is $\leq$ 95th percentile and enter the outcome of this check in the subject's source documentation.
8. Confirm that both the diastolic and systolic blood pressure values are $\leq$ 95th percentile.

   If the subject is ABOVE the 95th percentile value for their sex, age and height percentile, they are not eligible for the study and are to be screen failed.

   OR

   If the subject is $\leq$ 95th percentile value for their sex, age and height percentile, they are eligible for the study and may continue in the screening process.

Blood Pressure Levels for Boys by Age and Height 95th Percentile

Systolic BP (mmHg)

Age (Year)	Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th
6	109	110	112	114	115	117	117
7	110	111	113	115	117	118	119
8	111	112	114	116	118	119	120
9	113	114	116	118	119	121	121
10	115	116	117	119	121	122	123
11	117	118	119	121	123	124	125
12	119	120	122	123	125	127	127
13	121	122	124	126	128	129	130
14	124	125	127	128	130	132	132
15	126	127	129	131	133	134	135
16	129	130	132	134	135	137	137
17	131	132	134	136	138	139	140

Diastolic BP (mmHg)

Age (Year)	Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th
6	72	72	73	74	75	76	76
7	74	74	75	76	77	78	78
8	75	76	77	78	79	79	80
9	76	77	78	79	80	81	81
10	77	78	79	80	81	81	82
11	78	78	79	80	81	82	82
12	78	79	80	81	82	82	83
13	79	79	80	81	82	83	83
14	80	80	81	82	83	84	84
15	81	81	82	83	84	85	85
16	82	83	83	84	85	86	87
17	84	85	86	87	87	88	89

https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf

Blood Pressure Levels for Girls by Age and Height 95th Percentile

Systolic BP (mmHg)

Age (Year)	Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th
6	108	109	110	111	113	114	115
7	110	111	112	113	115	116	116
8	112	112	114	115	116	118	118
9	114	114	115	117	118	119	120
10	116	116	117	119	120	121	122
11	118	118	119	121	122	123	124
12	119	120	121	123	124	125	126
13	121	122	123	124	126	127	128
14	123	123	125	126	127	129	129
15	124	125	126	127	129	130	131
16	125	126	127	128	130	131	132
17	125	126	127	129	130	131	132

https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf

Diastolic BP (mmHg)

Age (Year)	Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th
6	72	72	73	74	74	75	76
7	73	74	74	75	76	76	77
8	75	75	75	76	77	78	78
9	76	76	76	77	78	79	79
10	77	77	77	78	79	80	80
11	78	78	78	79	80	81	81
12	79	79	79	80	81	82	82
13	80	80	80	81	82	83	83
14	81	81	81	82	83	84	84
15	82	82	82	83	84	85	85
16	82	82	83	84	85	85	86
17	82	83	83	84	85	85	86