PROTOCOL: NB-001-01

A RANDOMIZED, PLACEBO-CONTROLLED CROSSOVER TRIAL TO ASSESS THE SAFETY AND EFFICACY OF NB-001 IN CHILDREN AND ADOLESCENTS WITH 22Q11 DELETION SYNDROME

Version: 3.1, June 6, 2022

Sponsor:

Nobias Therapeutics, Inc.

[redacted]

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by:

[redacted]

Nobias Therapeutics, Inc. Date

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure for NB-001. I have read this protocol, NB-001-01, and agree to conduct the trial as outlined.

I understand that all information concerning NB-001 supplied to me by Nobias Therapeutics, Inc. and/or its agents, in connection with this trial and not previously published, is confidential information. This includes the Investigators' Brochure, Clinical Trial Protocol, Case Report Forms, and any other preclinical and clinical data provided by Nobias Therapeutics, Inc.

I understand that no data are to be made public or published without prior knowledge and written approval from Nobias Therapeutics, Inc.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol NB-001-01 and in accordance with the Declaration of Helsinki and most recent Good Clinical Practice (GCP; CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

I acknowledge that the Sponsor of the trial, Nobias Therapeutics, Inc., has the right to discontinue the trial at any time.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

TRIAL CONTACTS

Table 1: Trial Contact Information

Role in Trial	Name	Email and Telephone Number
Clinical Operations and Project Management	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company: Nobias Therapeutics, Inc.	
Name of Investigational Product: NB-001	
Name of Active Ingredient: (5R)-5-(pyridine-1-carbonyl)pyrrolidin-2-one monohydrate; fasoracetam monohydrate	
Protocol Number: NB-001-01	**Phase of Development:** 2
Title of Trial: A Randomized, Placebo-Controlled Crossover Trial to Assess the Safety and Efficacy of NB-001 in Children and Adolescents with 22q11 Deletion Syndrome	
Trial Centers: Approximately 3-5 trial centers located in the United States and Canada will participate in this trial.	

Objectives:

Primary:

- To assess the safety and tolerability of NB-001 during 6 weeks of treatment with NB-001 in subjects with 22q11.2 Deletion Syndrome (22q11DS)

Secondary:

- To assess the efficacy of NB-001 after 6 weeks of treatment with NB-001 using the following endpoint:
  - Clinical Global Impression (CGI)
- To assess the efficacy of NB-001 using a scale specific to the following domain/symptom of greatest impairment for each subject based upon baseline clinical assessment:
  - Anxiety (generalized anxiety disorder [GAD], social phobia [SoP], or separation anxiety disorder [SAD]);
  - Attention and executive deficits (attention deficit hyperactivity disorder [ADHD]);
  - Social interaction and repetitive tendencies (i.e., autism spectrum disorder [ASD]);
- To assess the efficacy of NB-001 using scales specific to the additional symptom domains listed above

Exploratory:

- [redacted]

Endpoints:

Primary:

- Type, frequency, severity, and causality of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), clinically significant changes from baseline in: laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings during treatment with NB-001

Secondary:

- Clinical Global Impressions-Improvement (CGI-I)
- Clinical Global Impression-Severity (CGI-S)
- Pediatric Anxiety Rating Scale (PARS)
- Attention Deficit Hyperactivity Disorder-Rating-Scale 5 (ADHD-RS-5)
- Social Responsiveness Scale, Second Edition (SRS™-2)

Exploratory:

[redacted]

Trial Design:

This is a Phase 2, randomized, placebo-controlled crossover trial to assess the safety and efficacy of NB-001 in children and adolescents with 22q11DS that manifest commonly associated neuropsychiatric conditions.

The trial is designed to allow all visits to be conducted via telephone and/or video (i.e., telemedicine) or by home health nurse. An in-person visit is required at Screening unless site or government mandates restrict this due to coronavirus disease-2019 (COVID-19). Other in-person visit(s) may occur, if indicated, based on the Investigator's clinical judgement. Subjects will be screened to confirm eligibility and then randomized in a 1:1 ratio to one of two treatment sequences: NB-001 (active drug product) followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A). During the Double-Blind Treatment Phase of the trial, the subject and/or parent/legal guardian (henceforth, 'parent/guardian') will be contacted at Day 0 to complete baseline symptom scales and will begin dosing with the investigational product (IP; NB-001 or placebo) on the morning of Day 1. Subjects or their parent/guardian will administer the IP twice daily (BID) and will be contacted at Days 0, 1, 14, 28, 42, 49, 50, 63, 77 and 91 to evaluate measures of safety and efficacy, including the completion of symptom scales. In addition, the subject and/or parent/guardian will be contacted at Days 7, 21, 35, 56, 70 and 84 to assess subject safety. Blood samples for pharmacokinetic analysis, 4β-hydroxycholesterol and plasma proline will be collected at the timepoints noted in Table 3. During the Double-Blind Treatment Phase, subjects will receive IP corresponding with their first treatment assignment for 6 weeks (Treatment Period 1), followed by an intervening wash-out period of 1 week, and then will receive their second treatment assignment for the subsequent 6-week period (Treatment Period 2). All symptom scales will be centrally and/or locally administered.

[redacted]

The subject and/or parent/guardian will be contacted for an End of Trial Visit to occur 4 weeks following the last dose of IP to assess safety. If the Investigator perceives a subject is experiencing

clinical benefit to treatment and the subject has completed the trial, provisions may be made to allow the subject to continue to receive NB-001. Details will be provided in a separate open-label extension protocol.
Sample Size Justification: A total of 30 evaluable subjects are planned for enrollment in the trial: 15 subjects in each treatment sequence. 'Evaluable' is defined as having received at least 1 dose of IP and having at least 1 post-baseline efficacy evaluation within each treatment period. Assuming a 10% dropout rate, approximately 34 subjects will be randomized into the trial. With this sample size, the trial will have approximately 80% power to establish a statistically significant treatment effect at a 2-sided alpha of 0.05 if the true mean difference (NB-001 vs. placebo) for the primary efficacy endpoint (CGI-I score) is 1 and the standard deviation is 1.25. In the event the trial is updated based on another unspecified endpoint, the sample size may be increased accordingly.
Number of Subjects (Planned): Approximately 34 subjects will be randomized; additional subjects may be enrolled, at the discretion of the Sponsor, to replace subjects who terminate early from the trial.

Diagnosis and Main Criteria for Inclusion:

Subject Inclusion Criteria:

1. The subject has a genotype with a pathologic deletion in the 22q11 region confirmed by documentation (e.g., genetic test results) available at the clinical trial site.
2. The subject is aged 6 to 17 years old, inclusive.
3. The subject has a CGI-S scale score of ≥4 (i.e., moderately, markedly, severely, or among the most extremely ill patients) at Screening. Note that the Severity score of 4 could be from a composite of 2 or more sub-threshold scores.

   And either:

   a. Psychiatric symptoms in the clinical range for **at least 1 of 3 disorders**, anxiety disorder, ADHD, or ASD, respectively, as demonstrated by score(s) at or above the following numbers ***on at least 1 of 3 scales****:*
      - PARS 5-Item Severity Score ≥12 (i.e., sum of items *2+3+5+6+7* ≥12)
      - ADHD-RS-5 Scores of 2 or 3 (i.e., "Often" or "Very Often") on at least 6 questions, with the majority of symptoms related to inattention (common in 22q11DS) rather than hyperactivity (less common in 22q11DS)
      - SRS™-2 ≥60

   OR:

   b. Psychiatric symptoms in the **subclinical range for at least 2 of 3 disorders**, anxiety disorder, ADHD, and/or ASD, respectively, as demonstrated by scores at or above the following numbers ***on at least 2 of 3 scales***:
      - PARS 5-Item Severity Score of 10 or 11 (i.e., sum of items *2+3+5+6+7*=10 or 11)
      - ADHD-RS-5 Scores of 2 or 3 (i.e., "Often" or "Very Often") on 4 or 5 questions, with the majority of symptoms related to inattention (common in 22q11DS) rather than hyperactivity (less common in 22q11DS)
      - SRS™-2 of 55-59
4. The subject has adequate renal and hepatic function indicated by:
      - Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 (per the revised Schwartz equation; Fadrowski and Furth 2011, Staples et al. 2010)
      - Serum bilirubin ≤2.5 × upper limit of normal (ULN; unless documented Gilbert's Disease); aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN
5. If the subject is female and of reproductive potential, she has a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 0.
6. If the subject is of reproductive potential, s/he agrees to abstain from reproductive cell donation, per below, and, if ever heterosexually active, to use dual effective/highly effective contraception (including at least one effective and at least one highly effective contraceptive method; Section 9.2.1) from Screening through the End of Trial Visit.
      - If the subject is female and of reproductive potential, she agrees to abstain from oocyte donation from Screening through the End of Trial Visit.
      - If the subject is male and of reproductive potential, he agrees to abstain from sperm donation from Screening through the End of Trial Visit.
7. The subject's parent/guardian understands the trial procedures and agrees to the subject's participation in the trial, as well as to the parent/guardian trial involvement, as indicated by

parent/guardian signature on the informed consent form and, if applicable, subject signature on the subject assent form.

Subject Exclusion Criteria:

1. The subject or parent/guardian is, in the opinion of the Investigator, mentally or legally incapacitated, or has significant emotional problems at the time of Screening or expected emotional problems during the conduct of the trial which would interfere with the conduct of the trial evaluations.
2. The subject has a history of psychotic symptoms, current psychotic symptoms, or a diagnosis of a psychotic disorder based on clinical assessment.
3. The subject has an intelligence quotient (IQ) score of <65 based on the WASI-II assessment. NOTE: A maximum of 3 (i.e., 10% of the total N) nonverbal subjects will be allowed in the trial on a first-come-first-served basis. (Refer to Section 13.1.)
4. The subject has a history of any illness that, in the opinion of the Investigator, might confound the results of the trial or pose an additional risk to the subject by participation in the trial.
5. The subject has clinically significant unstable or uncontrolled endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary abnormalities or diseases.
6. The subject has uncontrolled, active seizure(s), within the 3 months prior to Screening.
7. The subject has known human immunodeficiency virus (HIV), a detectable viral load for hepatitis C, or hepatitis B surface antigen indicative of chronic active infection.
8. The subject is pregnant or is a nursing mother.
9. The subject has suicidal ideation and behavior, based on Investigator assessment of the completed Columbia–Suicide Severity Rating Scale at Screening, or when repeated on Day 0 (if more than 21 days elapse between Screening and Day 1).
10. The subject is currently taking neuropsychiatric medication(s) at a dose that has not been stable for ≥3 months prior to Day 1 or psychotherapy that has not been stable for ≥3 months prior to Day 1. If the subject is taking medication(s) or receiving psychotherapy, the subject and parent/guardian must agree to continue the intervention(s) at the same dose and frequency through the End of Trial Visit.
11. The subject has received any investigational therapy (i.e., used for a non-approved indication and in the context of a research investigation) <14 days prior to the first dose of NB-001 (i.e., Day 1) or within 5 drug half-lives prior to the first dose of NB-001.
12. The subject uses illicit drugs (e.g., marijuana, amphetamines or cocaine), or has known alcohol or drug abuse or dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association 2013). Medically approved marijuana use, where usage is legal, is allowed; however, the dose and frequency of use should remain stable during trial participation.

Investigational Product, Dosage and Mode of Administration: NB-001: Two (2) 100 mg capsules will be administered orally BID with liquids or, if the subject is unable to swallow a capsule whole, capsules may be opened, and the contents sprinkled on applesauce; total daily dose: 400 mg. All subjects will receive NB-001 for 6 weeks, during Treatment Period 1 or Treatment Period 2, based upon their randomized treatment sequence: NB-001 followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A).
Duration of Treatment: Each subject will participate in the trial for up to approximately 21 weeks, including a Screening period of up to approximately 4 weeks, two 6-week treatment periods with an intervening 1-week wash-out, followed by an End of Trial Visit 4 weeks after the final dose.
Reference Therapy, Dosage and Mode of Administration: Matching placebo capsules will be administered orally BID with liquids or, if the subject is unable to swallow a capsule whole, capsules may be opened, and the contents sprinkled on applesauce. All subjects will receive placebo for 6 weeks, during Treatment Period 1 or Treatment Period 2, based upon their randomized treatment sequence: NB-001 followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A).
Statistical Methods: Full details of the statistical analyses will be provided in the Statistical Analysis Plan, which will be finalized before the database lock. Summaries of baseline patient characteristics will be presented by treatment sequence and for all subjects combined. Efficacy and safety endpoints will be summarized by treatment groups. Efficacy analyses will be conducted using the intent-to-treat principle on the full analysis set, which will include all subjects who receive at least 1 complete daily dose of IP (400 mg) and have at least 1 post-baseline efficacy evaluation within each treatment period. Safety analyses will be conducted on the safety population, which will include all subjects who receive at least 1 capsule (100 mg) of IP. Continuous variables, including ordinal variables, will be summarized with descriptive statistics (number evaluated, mean, standard deviation, median, minimum, and maximum). Categorical variables will be presented as counts and percentages within each category. As appropriate, 95% confidence intervals will be included. All statistical testing will be conducted at a 2-sided significance level of 0.05 and considered exploratory in nature. The count and percentage of subjects reporting TEAEs and TESAEs will be summarized overall, by System Organ Class, by Preferred Term within the System Organ Class, by maximum severity, onset, duration and by relationship to IP. All other safety parameters, including clinical laboratory values, vital sign measurements, and ECG interval results, will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables by treatment group. Results will be presented for the observed value and the change from baseline by time point.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and terms are used in this trial protocol.

Table 2: Abbreviations

Abbreviation or Specialist Term	Explanation
22q11DS	22q11.2 Deletion Syndrome
ADHD	attention deficit hyperactivity disorder
ADHD-RS-5	Attention Deficit Hyperactivity Disorder-Rating Scale-5
adolescents	individuals aged 12 to 17 years (inclusive)
AE	adverse event
ASD	autism spectrum disorder
$AUC_{0\text{-inf}}$	area under the concentration time-curve between zero and infinity
BID	twice daily
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
children	individuals aged 2 to less than 12 years
CL/F	apparent oral clearance adjusted for bioavailability
C_{max}	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
CRF	case report form
C-SSRS	Columbia–Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate

Abbreviation or Specialist Term	Explanation
ENR	enrolled analysis set
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
GAD	generalized anxiety disorder
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act (U.S.)
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IP	Investigational Product (NB-001 or placebo in this trial)
IQ	intelligence quotient
IRB	Institutional Review Board
MedDRA	Medical Dictionary of Regulatory Activities
mGluR	metabotropic glutamate receptor
NDA	New Drug Application
NS	Nippon-Shinyaku
OAT1	organic anion transporter 1
PARS	Pediatric Anxiety Rating Scale
PHIPA	Personal Health Information Protection Act (Ontario, Canada)
PIPEDA	Personal Information Protection and Electronic Documents Act (Canada)
PK	pharmacokinetic
PPS	per-protocol set
RANBP1	ran-specific binding protein 1
SAD	separation anxiety disorder
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set

Abbreviation or Specialist Term	Explanation
SIB	suicidal ideation and behavior
SoP	social phobia
SRS™-2	Social Responsiveness Scale, Second Edition
TEAE	treatment-emergent adverse event
TEAE-SI	treatment-emergent adverse event of special interest
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
U.S.	United States
V_{ss}/F	apparent volume of distribution adjusted for bioavailability
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition

4. INTRODUCTION

4.1. Background

22q11.2 Deletion Syndrome (22q11DS) is a contiguous gene deletion syndrome that most often occurs as a result of a *de novo* (spontaneous) deletion. The deletion can also be inherited in an autosomal dominant manner from an affected parent (McDonald-McGinn and Sullivan 2011). Chromosome 22q is characterized by the presence of chromosome-specific low copy repeats or segmental duplications, and the misalignment of low copy repeats during nonallelic homologous recombination leads to deletion of the 22q region, resulting in 22q11DS (Hacıhamdioğlu et al. 2015). 22q11DS is a rare disease as it affects 1 in approximately 2,000 to 6,000 live births, affects males and females equally, and is associated with various clinical phenotypes (Hui et al. 2020; Campbell et al. 2018).

Individuals with 22q11DS are at an increased risk for developing several psychiatric disorders; at least 60% of individuals with 22q11DS meet diagnostic criteria for at least 1 psychiatric diagnosis (Jonas et al. 2014). Anxiety disorder, attention deficit with hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) may arise early in life with manifestation of mood disorders, psychotic illness, and anxiety in adolescence and young adulthood (McDonald-McGinn et al. 2015). A study of children with 22q11DS using standardized instruments found that children could be placed into 3 groups: those with elevated anxiety with little or no depression (50%), those with elevated anxiety and depression (13%) and those with neither diagnosis (37%) (Stephenson et al. 2015). A study of 1,402 individuals with 22q11DS, ranging from 6-68 years of age demonstrated that ADHD was the most frequent disorder in children under 19 years of age (37%) and was overrepresented in males, whereas psychotic disorders were present in 41% of adults over age 25 and anxiety was frequent at all age groups but highest in children and adolescents (Schneider et al. 2014).

4.2. Rationale for Use of NB-001

While the etiology of the psychiatric symptoms of 22q11DS is complex and not fully understood, recently, attention has been directed toward the role of deficits in the glutamate system. Glutamate is one of the most widely distributed and important neurotransmitters in the brain, and its receptors, called metabotropic glutamate receptors (mGluRs), are widely expressed in the central nervous system. Evidence from animal models, pharmacology studies, and human brain and genetic studies reveal their critical roles in regulating neuronal function, especially in relation to neurological/neuropsychiatric disorders (Krystal et al. 2010; Niswender and Conn 2010).

Several genes in the 22q11.2 region deleted in 22q11DS patients are thought to play a role in glutamatergic signaling:

- Ran-specific binding protein 1 (RANBP1) is a member of the mGluR gene family whose role is believed to be stabilization of a protein complex that facilitates mGluR signaling. The RANBP1 gene is found on the q11.2 section of chromosome 22, and therefore it is, by definition, deleted in 22q11DS patients.

- The gene PRODH is involved in the transformation of the amino-acid proline into pyrroline-5-carboxylate, which in turn is the precursor of glutamate. A deficit in *PRODH* leads to increased levels of proline, which may influence glutamate metabolism (Phang et al., 2001; Delwing et al. 2007). In a subset of patients with 22q11DS, plasma proline levels are found to be increased (Goodman et al. 2000). Variability in proline levels in 22q11DS is likely related to polymorphisms in the remaining allele of the *PRODH* gene (Bender et al. 2005). In support of this, patients with hyperprolinemia were found to have high levels of glutamate as well and high proline was found to decrease glutamate uptake in the rat brain. In 22q11DS, several studies indicate a possible relation between high proline and changes in neuropsychiatric phenotypes (Raux et al 2007; Vorstman 2009; Magnee 2011) but this observation is not consistently replicated (Evers et al 2015).
- The genes SNAP29, SEPT 5 and PI4KA are all involved in the metabolism of synaptic vesicles, the mechanism through which neurotransmitters (including glutamate) are released into the synaptic cleft (Forsyth et al. 2020).

Importantly, Wenger et al. (2016) found derangement of genes in the mGluR network at a high rate in patients with 22q11DS, and that the presence of more than 1 genetic derangement in the mGluR network increased the chances that a 22q11DS patient suffered from ASD. A non-interventional genotype/phenotype study assessing the mGluR genomic network in children and adolescents 6-17 years of age with ADHD was completed. A total of 1,894 subjects were enrolled in the study. [redacted]

NB-001 is a non-stimulant activator of multiple mGluRs. *In vitro* studies initially provided evidence that NB-001 activated mGluRs to modulate cyclic adenosine monophosphate (cAMP) activity, which is a key downstream signaling mechanism of mGluRs, in rat cerebral cortex membranes and in fetal mouse cerebral cortex primary cultured neurons (Oka et al. 1997). It is speculated that the ability of NB-001 to enhance mGluR signaling via cAMP modulation may overcome some of the signaling deficit imparted by the deletion of genes involved in glutamatergic signaling at 22q11.2 (listed above).

Animal models recapitulating certain psychiatric symptoms often found in 22q11DS have shown to be responsive to treatment with NB-001. Of particular note is the ability of NB-001 to improve performance in models of anxiety (Nijssen and Schelvis 1987) and depression (Shimidzu et al. 1997), 2 commonly found symptoms in 22q11DS patients. In addition, NB-001 was shown to improve learning in various cognition models (Ogasawara et al. 1999). These models induce learning deficits created via a variety of mechanisms (e.g., scopolamine injection, nucleus basalis of Meynert destruction, cerebral ischemia, old age), suggesting impact on a common pathway, and providing hope that learning difficulties due to ADHD and cognitive deficit might also be addressed by NB-001.

The American Professional Society of ADHD and Related Disorders defines syndromic or comorbid ADHD as patients with chromosomal microdeletions that result in high prevalence of ADHD ($\geq$1/3 of patients) and includes conditions such as 22q11DS, 16p11.2, and 15q11.2. In addition to syndromic ADHD, a large proportion of ADHD patients have comorbid symptoms of

anxiety (most common), mood disorder, depression, ASD, and bipolar symptoms, and this may account for at least 50% of the general ADHD population. In patients with 22q11DS (who often have comorbid cardiovascular abnormalities in addition to the described neuropsychiatric symptoms), stimulant drugs may not be safe, effective, and/or appropriate. To date, there is no approved medication for the combined/comorbid neuropsychiatric symptoms of 22q11DS (which may include symptoms of ADHD).

Clinical experience in syndromic/comorbid ADHD patients provides further evidence that NB-001 may have positive effects in 22q11DS. In a 5-week, open-label, single-blind, placebo-controlled study of 30 adolescents, ages 12–17 years with ADHD (Study NFC1-2014 [GREAT]), NB-001 improved Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) scores (Elia et al. 2018). Of note, patients were selected for presence of mutations in mGluR network genes, the same major pathway hypothesized to be implicated in 22q11DS.

[redacted]

Therefore, the current evidence provides strong rationale for development of NB-001 to treat the psychiatric symptoms of 22q11DS. [redacted]

Given the totality of data observed to date, including human clinical data and the high unmet medical need for treatments addressing the psychiatric symptoms of 22q11DS, the continued development of NB-001 in 22q11DS seems warranted.

4.3. Clinical Experience

[redacted]

[redacted]

4.3.1. Clinical Pharmacokinetics of NB-001

After oral administration to healthy adult males ([redacted]; Kumagai et al. 1999), NB-001 was rapidly absorbed, with time to maximum plasma concentrations typically observed around 1 hour after administration. Subsequently, plasma NB-001 concentrations declined with a half-life of approximately 4 hours. In this single dose escalation trial, NB-001 exhibited a dose proportional increase in plasma exposure (maximum plasma concentration [C_{max}] and area under the concentration time-curve between zero and infinity [$AUC_{0\text{-}inf}$]) in the dose range 50 mg to 800 mg. At the 200 mg dose level, consumption of food did not have a significant effect on NB-001 exposure. In a multiple dose PK assessment, after administration of NB-001 200 mg 3 times daily (600 mg total daily dose) for 7 days, no significant accumulation was observed. Renal clearance was the major elimination pathway of NB-001, with 80% of the administered drug recovered in the urine within 24 hours after oral administration.

[redacted]

[redacted]

Additional details are available in the Investigator's Brochure.

4.3.2. Rationale for Measuring 4β-Hydroxycholesterol in this Study

In *in vitro* and clinical studies, it has been shown that cholesterol is metabolized to 4β-hydroxycholesterol by cytochrome P450 (CYP)3A4 and 4β-hydroxycholesterol concentrations can be used as an endogenous marker for CYP3A4 activity (Bodin et al. 2001; Kanebratt et al. 2008). A comprehensive literature review has concluded that 4β-hydroxycholesterol could in fact be used as a biomarker to detect CYP3A4 induction after at least 2 weeks of treatment with a new molecular entity (Penzak and Rojas-Fernandez 2019). With regards to NB-001, *in vitro* studies with cryopreserved human hepatocytes indicate that NB-001 is not likely to be a clinically relevant inducer of CYP3A4 *in vivo*. Furthermore, archived plasma samples from a previous NB-001 dose escalation study in adolescents were retrospectively analyzed for 4β-hydroxycholesterol concentrations which did not show evidence of CYP3A4 induction indicating NB-001 is not a CYP3A4 inducer *in vivo*. Plasma samples are planned to be collected from subjects enrolled in this study for prospective analysis of 4β-hydroxycholesterol concentrations to confirm previous findings.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To assess the safety and tolerability of NB-001 during 6 weeks of treatment with NB-001 in subjects with 22q11DS

5.1.2. Secondary Objectives

- To assess the efficacy of NB-001 after 6 weeks of treatment with NB-001 using the following endpoint:
  - Clinical Global Impression (CGI)
- To assess the efficacy of NB-001 using a scale specific to the following domain/symptom of greatest impairment for each subject based upon baseline clinical assessment:
  - Anxiety (generalized anxiety disorder [GAD], social phobia [SoP], or separation anxiety disorder [SAD]);
  - Attention and executive deficits (ADHD);
  - Social interaction and repetitive tendencies (i.e., ASD);
- To assess the efficacy of NB-001 using scales specific to the additional symptom domains above

5.1.3. Exploratory Objective

- [redacted]

5.2. Endpoints

5.2.1. Primary Endpoint

- Type, frequency, severity, and causality of TEAEs, treatment-emergent serious adverse events (TESAEs), clinically significant changes from baseline in: laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings during treatment with NB-001

5.2.2. Secondary Endpoints

- Clinical Global Impressions-Improvement (CGI-I)
- Clinical Global Impression-Severity (CGI-S)
- Pediatric Anxiety Rating Scale (PARS)

- Attention Deficit Hyperactivity Disorder-Rating Scale-5 (ADHD-RS-5)
- Social Responsiveness Scale, Second Edition (SRS™-2)

5.2.3. Exploratory Endpoint

- [redacted]

6. INVESTIGATIONAL PLAN

6.1. Overall Trial Design

This is a Phase 2, randomized, placebo-controlled crossover trial to assess the safety and efficacy of NB-001 in children and adolescents with 22q11DS that manifest commonly associated neuropsychiatric conditions. (NOTE: Reference to the 'Investigator' throughout this document refers to the Principal Investigator or, if delegation of responsibilities has been documented, may apply to a sub-Investigator or other clinical trial site personnel.)

The trial is designed to allow all visits to be conducted via telephone and/or video (i.e., telemedicine) or by home health nurse. An in-person visit is required at Screening unless site or government mandates restrict this due to coronavirus disease 2019 (COVID-19). Other in-person visit(s) may occur, if indicated, based on the Investigator's clinical judgement. Subjects will be screened to confirm eligibility and then randomized in a 1:1 ratio to one of two treatment sequences: NB-001(active drug product) followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A). During the Double-Blind Treatment Phase, the subject and/or parent/legal guardian (henceforth, 'parent/guardian') will be contacted at Day 0 to complete baseline symptom scales and will begin dosing with the investigational product (IP; NB-001 or placebo) on the morning of Day 1. Subjects or their parent/guardian will administer the IP BID and will be contacted at Days 0, 1, 14, 28, 42, 49, 50, 63, 77 and 91 to evaluate measures of safety and efficacy, including the completion of symptom scales. In addition, the subject and/or parent/guardian will be contacted at Days 7, 21, 35, 56, 70 and 84 to assess subject safety. Blood samples for PK analysis, 4β-hydroxycholesterol and plasma proline will be collected at the timepoints noted in Table 3. During the Double-Blind Treatment Phase, subjects will receive IP corresponding with the first treatment assignment for 6 weeks (Treatment Period 1), followed by an intervening wash-out period of 1 week, and then will receive their second treatment assignment for the subsequent 6-week period (Treatment Period 2). All symptom scales will be centrally and/or locally administered.

The subject and/or parent/guardian will be contacted for an End of Trial Visit to occur 4 weeks following the last dose of IP to assess safety. If the Investigator perceives a subject is experiencing clinical benefit to treatment and the subject has completed the trial, provisions may be made to allow the subject to continue to receive NB-001. Details will be provided in a separate open-label extension protocol.

A schematic of the trial design is provided in Figure 1 and the Schedule of Assessments is provided in Table 3.

Figure 1: Trial Design

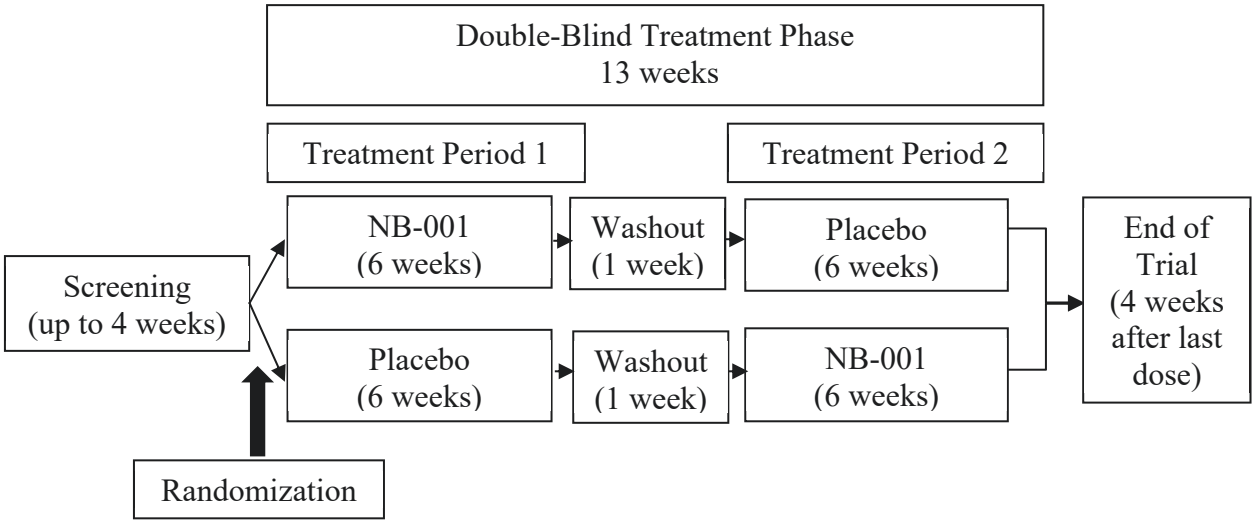

Table 3: Schedule of Assessments

	Screening Period[a]	Double-Blind Treatment Phase																End of Trial[u]
		NOTE: Grey highlights below reflect visits where a home health nurses is required to support the visit for all subjects.																
Visit/Assessment Day	**-28 to -1**	**0[l]**	**1[l]**	**7**	**14**	**21**	**28**	**35**	**42[m]**	**49[l,o]**	**50[l]**	**56**	**63**	**70**	**77**	**84**	**91/ ET[t]**	**119**
Visit Window	**4 weeks**			**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**		**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Informed Consent/Assent	X																	
Inclusion/Exclusion Criteria	X[b]	X[b]																
Demographics	X																	
Medical History	X[c]	X[c]																
Physical Examination[s]	X[v]	X							X								X	X
Vital Signs[s]	X	X	X[k]		X[k]				X		X[k]		X[k]				X	X
Clinical Laboratory Tests[d,s]	X	X							X								X	X
Serum Pregnancy Test[f,s]	X								X									X
Urine Pregnancy Test[f,s]		X			X						X		X				X	
Urine Drug Test[s]	X	X[k]			X[k]				X[k]		X[k]		X[k]				X[k]	X[k]
Sample for Centralized 22q11DS Genotype[e]	X																	
Plasma Proline Sample (fasted)[s]	X																	
12-lead ECG[s]	X	X							X								X	X
C-SSRS[i]	X	X[i]			X		X		X	X			X		X		X	X
ADHD-RS-5[g]	X	X			X		X		X	X			X		X		X	X
SRS™-2[g]	X	X			X		X		X	X			X		X		X	X
WASI-II IQ Assessment[g,h]	X																	

	Screening Period[a]	Double-Blind Treatment Phase																End of Trial[u]
		NOTE: Grey highlights below reflect visits where a home health nurses is required to support the visit for all subjects.																
Visit/Assessment Day	**-28 to -1**	**0[l]**	**1[l]**	**7**	**14**	**21**	**28**	**35**	**42[m]**	**49[l,o]**	**50[l]**	**56**	**63**	**70**	**77**	**84**	**91/ ET[t]**	**119**
Visit Window	**4 weeks**			**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**		**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
PARS[g,j]	X	X			X		X		X	X			X		X		X	X
CGI-S[g,j]	X	X			X		X		X	X			X		X		X	X
CGI-I[g,j]		X			X		X		X	X			X		X		X	X
Pharmacokinetic Sampling[s]			X[n]		X[n]						X[n]		X[n]					
Sampling for 4β-hydroxycholesterol (pre-dose)[s]			X		X						X		X					
Randomization	X[q]																	
IP Dispensed[o]	X[r]		X[r]		X		X				X		X		X			
IP Accountability and Compliance[s]				X	X	X	X	X	X	X		X	X	X	X	X	X	
Assess COVID-19/Stressor Impact		X							X								X	
Concomitant Medications and Therapies[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Adverse Events[p,s]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	[redacted]	

Abbreviations: 22q11DS = 22q11.2 Deletion Syndrome; ADHD-RS-5 = Attention Deficit Hyperactivity Disorder-Rating Scale-5; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; IP = investigational product; PARS = Pediatric Anxiety Rating Scale; SRS™-2 = Social Responsiveness Scale, Edition 2; WASI-II IQ = Wechsler Abbreviated Scale of Intelligence, Second Edition

[a] The Screening Period may occur up to 4 weeks prior to dosing (Day 1); eligibility must be determined prior to dosing. Efforts should be made to complete Screening procedures and obtain results within the first 3 weeks of the Screening Period. This will allow time to randomize the subject and ship IP in advance of dosing on Day 1. The Investigator should contact the Medical Monitor if there is a significant delay between completion of all Screening activities and Day 0 and Day 1. An in-person visit is required at Screening unless site or government mandates restrict this due to COVID-19.

[b] Review Inclusion/Exclusion Criteria and confirm eligibility prior to randomizing the subject, prior to dispensing IP, and on Day 0 (prior to first dose on Day 1).
[c] Medical history will be documented during Screening and updated on Day 0 to confirm trial eligibility. Any confirmed Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnoses should be documented as medical history.
[d] Clinical laboratory tests include hematology, serum chemistry, urinalysis and Other: eGFR, as described in Table 5.
[e] A blood sample will be collected for centralized confirmation of the subject's 22q11DS genotype. If any blood remains from the collected sample, it will be stored and may be used for future research. (Refer to Section 12.1.5.) The subject and/or parent/guardian have the option to decline future research on any remnant blood sample.
[f] Females of childbearing potential only.
[g] When possible, to be completed in consecutive order as listed here in Table 3.
[h] The WASI-II IQ Assessment should be one of the final clinical assessments completed during Screening and as near as possible to Day 0.
[i] After Screening, the C-SSRS will be performed remotely by the local rater via telephone or video (i.e., telemedicine). The C-SSRS should be repeated on Day 0 if more than 21 days elapse between its completion during Screening and Day 1.
[j] Performed remotely by central raters via telephone or video (i.e., telemedicine). A rating of the PARS, CGI-S and/or CGI-I by the local rater is optional. When possible local raters may participate in the telephone or video PARS interview and/or asynchronously review the PARS interview audio recording to complete their PARS rating. In order to complete the CGI-S and/or CGI-I rating, the local rater must participate in the PARS interview or review the audio recording of the PARS interview. The CGI-I and CGI-S scales will be the last rating scale assessment performed at each visit indicated above. CGI-I assessments at Assessment Days 14, 28, 42 and 49 should use the Assessment Day 0 CGI-S baseline rating as reference for change. CGI-I assessments at Assessment Days 63, 77, 91 and 119 should use the Assessment Day 49 CGI-S baseline rating as reference for change. (Refer to Section 11.1)
[k] Performed only if clinically indicated (i.e., subject exhibits signs or symptoms that require further evaluation), or as deemed necessary by the Investigator.
[l] Day 0 and Day 1 may occur on the same calendar date so long as the procedures required for Day 0 (baseline) are completed prior to subject dosing. Similarly, Day 49 and Day 50 may be combined to occur on the same calendar date so long as the procedures required for Day 49 are completed at the end of the wash-out period and prior to dosing. Note that pre-dose samples are required on Day 1 and Day 50.
[m] Day 42 will be the last day of dosing for Treatment Period 1. The last assessment of Treatment Period 1 should be completed before the wash-out which, generally, will start on Day 43 and proceed through Day 49. The subject will start Treatment Period 2 and resume dosing on Day 50.
[n] Days 1 and 14 pharmacokinetic (PK) samples and Days 50 and 63 PK samples will be collected pre-dose (morning), then at 1 and 4 hours post-dose.
[o] Dosing will be paused from Days 43-49 (generally), during the wash-out period. No capsules will be taken during this time.
[p] Adverse Event (AE) recording will occur from the time of signing the informed consent form and, if applicable, the subject assent form, and through the End of Trial Visit. Home health nurses may supplement the reporting of AEs and Concomitant Medications during home visits; however the Investigator's assessment will supersede that of the home health nurse. Only the Investigator will assign AE *Relationship* to IP. AEs will be followed until resolution or until deemed stable by the Investigator.
[q] Randomization will occur after all Screening procedures are complete and the subject is determined to be eligible for the study.
[r] Once the subject is randomized, IP will be sent to the subject's home with instructions to begin dosing on the morning of Day 1 (with guidance from the home health nurse who will collect pre-dose samples on Days 1, 14, 50 and 63, as noted above). Additional IP shipments with supply for approximately 2 weeks of dosing will be sent to the subject or parent/guardian and subjects will be instructed to begin dosing from new supply on Days 15, 29, 50, 64 and 78.
[s] Procedures and assessments will be performed, laboratory samples collected, AEs and concomitant medications recorded, and IP accountability and dispensation recorded by home health nurses and/or the Investigator.
[t] The end of treatment assessments will be performed at the Day 91 Visit, or if the subject withdraws from the study prior to Day 91 (i.e., early termination), as soon as possible after the last dose of IP.
[u] The End of Trial Visit will be performed 4 weeks after the last dose of IP to assess safety. If the Investigator perceives a clinical benefit to any subject who completes the trial, provisions may be made to allow the subject to continue to receive NB-001 and the End of Trial Visit/Assessment Day 119 will not be required. Details will be provided in a separate open label extension protocol.
[v] The physical exam at Screening will include a measurement of height.
[redacted]

6.2. Number of Subjects

Approximately 34 subjects will be randomized; additional subjects may be enrolled, at the discretion of the Sponsor, to replace subjects who terminate early from the trial.

6.3. Treatment Assignment

Subjects will be randomized in a 1:1 ratio and in a double-blind manner (Section 9.4) to one of two treatment sequences: either NB-001 (active drug product) followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A).

6.4. Dose Adjustment Criteria

Dose adjustments in this trial are discouraged. However, if there is evidence of intolerance at the current dose, and the subject is experiencing clinical benefit, a dose reduction and/or drug holiday followed by re-introduction of study drug at a reduced dose may be considered after consultation with the Medical Monitor.

6.5. Criteria for Trial Termination

The Sponsor reserves the right to discontinue the trial at any time for either clinical research or administrative reasons and to discontinue participation by an individual Investigator or clinical trial site for poor enrollment or noncompliance. All subjects will be followed for safety assessments through the requisite follow-up period. If the Investigator perceives a clinical benefit to any subject who completed the trial, provisions may be made to allow the subject to continue to receive NB-001. Details will be provided in a separate open label extension protocol.

The Sponsor will instruct the Investigators to notify their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of discontinuation of a clinical trial site or the trial and the reason(s) for doing so.

The reason for terminating recruitment or the trial, at a clinical trial site, or altogether, may include:

- Review of TEAE/TESAE data shows an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial;
- The clinical trial site has failed to enroll subjects at an acceptable rate;
- The protocol requirements, including Good Clinical Practice (GCP), have not been adhered to;
- Sponsor decision; and/or
- Administrative reasons.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all of the following subject inclusion criteria to be eligible to participate in the trial:

1. The subject has a genotype with a pathologic deletion in the 22q11 region confirmed by documentation (e.g., genetic test results) available at the clinical trial site.
2. The subject is aged 6 to 17 years old, inclusive.
3. The subject has a CGI-S scale score of ≥4 (i.e., moderately, markedly, severely, or among the most extremely ill patients) at Screening. Note that the Severity score of 4 could be from a composite of 2 or more sub-threshold scores.

   And either:

   a. Psychiatric symptoms in the clinical range for **at least 1 of 3 disorders**, anxiety disorder, ADHD, or ASD, respectively, as demonstrated by score(s) at or above the following numbers ***on at least 1 of 3 scales***:
      - PARS 5-Item Severity Score ≥12 (i.e., sum of items *2*+*3*+*5*+*6*+*7* ≥12)
      - ADHD-RS-5 Scores of 2 or 3 (i.e., "Often" or "Very Often") on at least 6 questions, with the majority of symptoms related to inattention (common in 22q11DS) rather than hyperactivity (less common in 22q11DS)
      - SRS™-2 ≥60

   OR:

   b. Psychiatric symptoms in the **subclinical range for at least 2 of 3 disorders**, anxiety disorder, ADHD, and/or ASD, respectively, as demonstrated by scores at or above the following numbers ***on at least 2 of 3 scales***:
      - PARS 5-Item Severity Score of 10 or 11 (i.e., sum of items *2*+*3*+*5*+*6*+*7*=10 or 11)
      - ADHD-RS-5 Scores of 2 or 3 (i.e., "Often" or "Very Often") on 4 or 5 questions, with the majority of symptoms related to inattention (common in 22q11DS) rather than hyperactivity (less common in 22q11DS)
      - SRS™-2 of 55-59
4. The subject has adequate renal and hepatic function indicated by:
   - Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 (per the revised Schwartz equation; Fadrowski and Furth 2011; Staples et al. 2010)
   - serum bilirubin ≤2.5 × upper limit of normal (ULN), unless documented Gilbert's Disease; aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN
5. If the subject is female and of reproductive potential, she has a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 0.
6. If the subject is of reproductive potential, s/he agrees to abstain from reproductive cell donation, per below, and, if ever heterosexually active, to use dual effective/highly

effective contraception (including at least one effective and at least one highly effective contraceptive method; Section 9.2.1) from Screening through the End of Trial Visit.

- If the subject is female and of reproductive potential, she agrees to abstain from oocyte donation from Screening through the End of Trial Visit.
- If the subject is male and of reproductive potential, he agrees to abstain from sperm donation from Screening through the End of Trial Visit.

7. The subject's parent/guardian understands the trial procedures and agrees to the subject's participation in the trial, as well as to the parent/guardian trial involvement, as indicated by parent/guardian signature on the informed consent form (ICF) and subject signature, if applicable, on the subject assent form.

7.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from trial participation:

1. The subject or parent/guardian is, in the opinion of the Investigator, mentally or legally incapacitated, or has significant emotional problems at the time of Screening or expected emotional problems during the conduct of the trial which would interfere with the conduct of the trial evaluations.
2. The subject has a history of psychotic symptoms, current psychotic symptoms, or a diagnosis of a psychotic disorder based on clinical assessment.
3. The subject has an intelligence quotient (IQ) score of <65 based on the WASI-II assessment. NOTE: A maximum of 3 (i.e., 10% of the total N) nonverbal subjects will be allowed in the trial on a first-come-first-served basis. (Refer to Section 13.1.)
4. The subject has a history of any illness that, in the opinion of the Investigator, might confound the results of the trial or pose an additional risk to the subject by participation in the trial.
5. The subject has clinically significant unstable or uncontrolled endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary abnormalities or diseases
6. The subject has uncontrolled, active seizure(s), within the 3 months prior to Screening.
7. The subject has known human immunodeficiency virus (HIV), a detectable viral load for hepatitis C, or hepatitis B surface antigen indicative of chronic active infection.
8. The subject is pregnant or is a nursing mother.
9. The subject has SIB, based on Investigator assessment of the completed C-SSRS at Screening, or when repeated on Day 0 (if more than 21 days elapse between Screening and Day 1).
10. The subject is currently taking neuropsychiatric medication(s) at a dose that has not been stable for ≥3 months prior to Day 1 or psychotherapy that has not been stable for ≥3 months prior to Day 1. If the subject is taking medication(s) or receiving psychotherapy,

the subject and parent/guardian must agree to continue the intervention(s) at the same dose and frequency through the End of Trial Visit.

11. The subject has received any investigational therapy (i.e., used for a non-approved indication and in the context of a research investigation) <14 days prior to the first dose of NB-001 (i.e., Day 1) or within 5 drug half-lives prior to the first dose of NB-001.
12. The subject uses illicit drugs (e.g., marijuana, amphetamines, or cocaine), or has known alcohol or drug abuse or dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association 2013). Medically approved marijuana, where usage is legal, is allowed; however, the dose and frequency of use should remain stable during trial participation.

7.3. Subject Withdrawal Criteria

7.3.1. Withdrawal Criteria

A subject and/or parent/guardian may withdraw their consent for subject participation in this trial at any time without prejudice. The Investigator must withdraw any subject from the trial who requests, or whose parent/guardian requests the subject to be withdrawn. A subject's participation in the trial may also be discontinued at any time at the discretion of the Investigator, in accordance with his/her clinical judgement. The reason for withdrawal will be documented. Reasons for withdrawal from the trial may include, but are not limited to, the following:

- Symptomatic deterioration (clinical deterioration suggesting that no further benefit from treatment is likely);
- Request of the subject or parent/guardian
- Development of any adverse event (AE), condition, intercurrent illness, injury, medical or psychiatric condition, or SIB, or desired use of an experimental therapy, other therapy or change in dose of a concomitant medication that is likely to interfere with the subject's safety, the overall assessment, or the trial procedures;
- Subject noncompliance, defined as inability or unwillingness to complete the procedures defined in the Schedule of Assessments (Table 3), multiple missed doses (with the exception of those authorized by the Medical Monitor, see Section 6.4), or missed or late trial visits, especially without a commitment to remedy or visible improvement in the behavior;
- Pregnancy or desire to become pregnant;
- Investigator's decision;
- Withdrawal of consent;
- Subject is lost to follow up (i.e., the Investigator is unable to contact the subject and/or parent/guardian after several documented attempts);
- Death.

7.3.2. Notification of Subject Withdrawal and Subject Termination Procedures

The Investigator must notify the Sponsor as soon as possible if any subject prematurely discontinues from the trial. The date when the subject is withdrawn from the trial and the primary reason(s) for discontinuation must be recorded in the case report form (CRF). A subject will be considered "lost to follow-up" only after reasonable, documented attempts to reach the parent/guardian prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a subject fails to return for required trial visits or discontinues from the trial.

If a subject is withdrawn from the trial early (regardless of the cause), all of the Day 91/Early Termination (ET) Visit evaluations are to be performed at the time of withdrawal (i.e., as soon as possible after the last dose of IP), to the extent possible. After completion of the Day 91/ET Visit, subjects will be followed for an additional 4-week period. All procedures and assessments noted in Table 3 for the End of Trial Visit will be performed 4 weeks after the last dose of IP to assess safety.

7.3.3. Subject Replacement

At the discretion of the Sponsor, subjects who discontinue from the trial early may be replaced.

8. TRIAL PROCEDURES

8.1. Visit Windows

Screening assessments (including review of results) should be completed within 28 days. Day 0 and Day 1 may occur on the same calendar date so long as the procedures required for Day 0 are completed prior to subject dosing. Similarly, Day 49 and Day 50 may be combined to occur on the same calendar date so long as the procedures required for Day 49 are completed at the end of the wash-out period and prior to dosing. Note that pre-dose samples are required on Day 1 and Day 50.

Otherwise, visits during the Double-Blind Treatment Phase should be scheduled to occur as noted on the schedule in Table 3 and, if necessary, may be conducted ±3 days from the target Visit/Assessment Day. When scheduling subject visits, the Visit/Assessment Day should be calculated to occur using Day 1 (during Treatment Period 1) as the anchored reference point (i.e., not based on the prior visit date) for Dosing Period 1. Similarly during Treatment Period 2, Visit/Assessment Days should be calculated to occur using Day 50 as the anchored reference point. For subjects who terminate early, end of treatment assessments (e.g., Day 91/ET Visit) should be completed as soon as possible after the last dose of IP.

8.2. Telemedicine and Home Health Nurse Visits

Due to considerations regarding the COVID-19 global pandemic, this trial is designed to allow all visits to be conducted via telephone and/or video (i.e., telemedicine) or by home health nurse, unless an in-person visit is indicated based on Investigator's clinical judgement. An in-person visit is required at Screening unless site or government mandates restrict this due to COVID-19. Procedures to be performed by telemedicine or by home health nurse are outlined in Table 3.

Additionally, clinical efficacy scales will be performed by a central and, where possible (i.e., optional), a local rater. Wherever possible, the same central and (if applicable) local rater will complete all assessments for a given subject throughout the subject's trial participation.

8.3. Screening Visit(s)

During Screening, the potential subject and the parent/guardian will receive an explanation of the purpose and nature of the trial. If, after careful consideration of the pros and cons of trial participation, they agree to participate, the parent/guardian will be asked to review and sign the ICF and, if applicable, the subject will sign the subject assent form, prior to any trial-related procedures. Screening procedures will be performed only after documented informed consent and, if applicable, subject assent are obtained.

The Screening Period allows for up to 4 weeks for each of the Screening procedures to be performed and results obtained; detailed assessments are outlined in Table 3. Efforts should be made to complete Screening procedures and obtain results within the first 3 weeks of the Screening Period, when possible. This will allow time to randomize the subject and ship IP in advance of dosing on Day 1. The Investigator should contact the Medical Monitor if there is a significant delay between completion of all Screening activities and Day 0/Day 1.

8.3.1. Subject Numbering

All subjects who consent/assent to participate in the study will be assigned a unique 3-digit Screening identification (ID) number. The Screening ID will consist of the site's single-digit number (i.e., 1, 2, 3), followed by a unique 2-digit number assigned sequentially in the order screened and beginning with 01 (e.g., 201, 202). Screening ID numbers will not be re-used unless a subject is rescreened in which case the subject will maintain his/her original Screening ID number.

Each subject will also be assigned a unique 3-digit randomization number after all Screening procedures are complete and the subject is determined to be eligible for the study. The subject randomization number will be obtained via the electronic data capture (EDC) system. The subject's Screening ID number along with randomization number (e.g., 201-456) will serve as the Subject Number and will be used as the subject identifier and recorded in the source documentation, CRFs, study drug dispensation records, and other identifying documents throughout the study.

8.3.2. Re-Screening Procedures

Re-screening may be allowed under certain circumstances (e.g., recent minor illness) if the Investigator feels that the reason for screen failure has resolved and after discussion with the Medical Monitor or designee. It will not be necessary to repeat centralized 22q11DS genotype sampling for subjects who are rescreened. The re-screening time interval for other assessments will be at the discretion of the Medical Monitor and may exceed 28 days from time of initial screening to randomization.

8.3.3. Screening Failures

Any subject who does not meet all of the Inclusion Criteria and none of the Exclusion Criteria will be considered a Screening Failure. The primary reason for Screening Failure will be documented.

8.4. Day 91 / Early Termination Visit

The end of treatment assessments noted in Table 3 will be performed at the Day 91/ET Visit, or if the subject withdraws from the study prior to Day 91, as soon as possible after the last dose of IP.

8.5. End of Trial Visit

All procedures and assessments noted in Table 3 for the End of Trial Visit will be performed approximately 4 weeks after the last dose of IP to assess safety.

If the Investigator perceives a clinical benefit to any subject who completes the trial, provisions may be made to allow the subject to continue to receive NB-001 and the End of Trial Visit/Assessment Day 119 will not be required. Details will be provided in a separate open-label extension protocol.

8.6. Unscheduled Visits

An unscheduled visit may be performed as clinically indicated or deemed necessary by the Investigator. The date and reason for the unscheduled visit, as well as the procedures performed, will be documented. The performance of special testing (i.e., other than the per-protocol testing) should be discussed in advance with the Medical Monitor or designee, if the subject's clinical status allows.

8.7. Provisions for COVID-19 Pandemic

Due to the possibility of trial interruption by the COVID-19 pandemic, each clinical trial site participating in this trial will be asked to prepare and file a Pandemic Risk and Mitigation Plan with their IRB/IEC outlining handling of various protocol requirements including, but not limited to:

- Appropriate safety follow-up of subjects
- Study assessments to be done remotely (i.e., telemedicine) vs. in-clinic or at local facilities
- IP shipments to/from subject/parent/guardian
- Remote data monitoring capabilities (e.g., access to source records)

8.7.1. Period of Applicability

These COVID-19 pandemic guidelines only apply during any public health emergencies related to COVID-19 that are declared by government authorities in the countries where the clinical trial sites are located.

8.7.2. COVID-19 Symptoms

If any individual subject reports any flu-like symptoms, fevers and/or respiratory problems, the Investigator should determine if the subject has been, or should be, tested for COVID-19.

8.7.3. Maintaining Protocol Requirements, Including Schedule of Activities

Exposure to, or instances of, a confirmed positive result for COVID-19 will not mandate early termination of a subject from the trial. Continued participation in the trial will be at the discretion of the Investigator.

However, the Medical Monitor should be notified of any suspected or confirmed positive cases of COVID-19 in a subject or parent/guardian. The Investigator and the Medical Monitor will make a case-by-case decision regarding the assessments, procedures, and samples that are appropriate to continue, taking into consideration precautions for all clinical trial personnel who may come into contact with the subject or his/her family (e.g., home health nurse). Similarly, the subject and parent/guardian will be notified of any clinical trial personnel who test positive for COVID-19 and to whom the subject and/or parent/guardian may have been or may be exposed.

8.7.4. Documentation of COVID-19 Related Guidelines or Other Measures

It is important to document the reason for implementing any COVID-19 contingency measures. Such documentation should include details on how restrictions related to COVID-19 led to the use of these contingency measures during trial conduct, the duration of those changes, which subjects were impacted, and how those subjects were impacted. When adopting or implementing these guidelines, Investigators should make every effort to minimize any impacts on trial integrity. If any additional changes are required that are not covered in these guidelines, Investigators should act according to local guidelines and regulations, but above all to assure the safety of subjects, maintaining compliance with GCP, and minimizing risks to trial integrity. Any changes made should be appropriately documented as protocol deviations.

In advance of any data analyses or planned database locks, the Sponsor will ensure that the impact from trial visit changes is assessed and will revise the Statistical Analysis Plan (SAP) accordingly.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Product

Table 4 provides a summary of the IP to be administered, including the routes of administration.

Table 4: Investigational Product

	Investigational Product	
Product Name:	NB-001	Placebo
Dosage Form:	Capsule	Capsule
Unit (Capsule) Dose	100 mg	Not applicable
BID Dose	200 mg	Not applicable
Total Daily Dose	400 mg	Not applicable
Dosing Frequency	BID	BID
Route of Administration	Oral	Oral
Dosing Instruction	Take whole with liquids or open and sprinkle contents of capsules on applesauce.	Take whole with liquids or open and sprinkle contents of capsules on applesauce.
Physical Description	White hard-gelatin capsule, Size 1	White hard-gelatin capsule, Size 1
Manufacturer	[redacted]	[redacted]

Abbreviation: BID = twice daily

9.2. Concomitant Medications and Procedures

All medications taken within 30 days prior to the Screening visit through the End of Trial Visit, and any changes to concomitant medication dosing during the trial, will be recorded, including use of over-the-counter oral supplements, e.g., iron or a multi-vitamin, (including Vitamin D/Calcium supplement), calcium carbonate (i.e., antacid), melatonin, arnica and cannabidiol. Subjects taking neuropsychiatric medications must have been taking a stable dose for ≥3 months prior to the Day 1 visit and must agree to continue to take these and all other medications s/he may be taking at the start of the trial at the same dose and frequency through the End of Trial Visit. Subjects taking hormonal contraceptives for birth control, must have been taking a stable dose for ≥3 months prior to the Day 1 visit and must agree to continue to take them at the same dose and frequency through the End of Trial Visit. Subjects are discouraged

from starting new prescription or over-the-counter oral supplements during their participation in the trial.

Medications excluded prior to and during the trial include another investigational therapy within 14 days prior to the first dose (Day 1) of NB-001 or within 5 drug half-lives prior to the first dose of NB-001.

NB-001 is an *in vitro* inhibitor of organic anion transporter 1 (OAT1). Examples of OAT1 substrates are adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine and zidovudine. Patients taking OAT1 substrates with a narrow therapeutic index should be monitored carefully while being dosed with NB-001.

9.2.1. Contraception

Dual effective/highly effective contraception is required for any subject of reproductive potential who is ever heterosexually active.

Dual effective/highly effective contraception is defined as a combination of at least TWO forms of contraception, including at least one effective and at least one highly effective contraceptive method.

Effective forms of contraception include:

- Condom (male or female*) with or without a spermicidal agent
  *If using condoms as the form of effective contraception, the subject may use a male condom OR a female condom for each heterosexual act. Combined use of a male condom AND a female condom is never permissible, due to the risk of condom failure with combined male/female condom use.
- Cervical cap with a spermicidal agent
- Diaphragm with a spermicidal agent
- Sponge with a spermicidal agent

Highly effective forms of contraception include:

- Long-Acting Reversible Contraception placed at least 1 month prior to study enrollment (e.g., intrauterine device or etonogestrel contraceptive implant)
- Hormone-based contraceptive started at least 3 months prior to study enrollment (e.g., birth control pills, shots, patches, intravaginal rings)
- Female surgical sterilization (e.g., uterine tubal ligation/occlusion or partial salpingectomy) at least 3 months prior to study enrollment
- Male surgical sterilization (e.g., vasectomy) at least 3 months prior to study enrollment

9.3. Treatment Compliance

The Investigator should monitor the subject's IP dosing compliance on an ongoing basis, as confirmed by IP accountability. If the Investigator has concerns about a subject's dosing compliance, s/he should discuss this with the subject and/or parent/guardian, assess the reasons and whether the subject is likely to remain non-compliant. The Medical Monitor should be notified of any potential dosing compliance issues.

Dose adjustments in this trial are discouraged. However, if there is evidence of intolerance at the current dose, and the subject is experiencing clinical benefit, a dose reduction and/or drug holiday followed by re-introduction of study drug at a reduced dose may be considered after consultation with the Medical Monitor (see Section 6.4).

Subjects will be instructed to retain all bottles of IP, even if empty, and to return the bottles with any unused capsules to the home health nurse at each visit noted in Table 3. The Investigator will perform IP accountability and will follow-up with subjects to retrieve any IP supplies that have not been returned. The subject and/or parent/guardian will be instructed to take note of any missed doses and, if possible, to document this information and to report it at the time of their next visit.

9.4. Randomization and Blinding

This is a randomized, double-blind, crossover trial. Therefore, every subject will receive NB-001 and placebo. However, the subject and parent/guardian, the Investigator, clinical trial site personnel, home health nurses, centralized rater(s), and the Sponsor will be blinded to treatment sequence assignment.

Subjects will be randomized at the conclusion of the Screening Visit, after confirmation of trial eligibility. Randomization will occur in a 1:1 ratio to one of two treatment sequences: NB-001 followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A). The randomization scheme will be generated using a computer program and verified for accuracy using strict quality control procedures. Each IP bottle will be labeled with a unique bottle number which will correspond to the randomization code and blinded treatment assignment.

In the event of a medical emergency in which it is important for the treating physician to know the treatment assignment, the blind may be broken by the Investigator. When possible (i.e., if time allows), the Investigator will contact the Medical Monitor, or designee, prior to accessing the treatment code for the subject. Instructions for emergency unblinding of treatment codes by the Investigator will be provided separately.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

NB-001 is (5R)-5-(pyridine-1-carbonyl)pyrrolidin-2-one monohydrate; also known as fasoracetam monohydrate. Each NB-001 capsule contains 100 mg of the active ingredient. The capsules are size 1 and white in color.

Placebo capsules contain excipients only and match the NB-001 capsules in appearance.

10.2. Investigational Product Packaging and Labeling

NB-001 and matching placebo will be supplied to the Investigator or designee in blinded plastic bottles, each containing 40 capsules. Each bottle will be labeled with the protocol number, storage conditions, dosing instructions, the federal cautionary statement, a unique bottle number and the Sponsor name and address. Prior to dispensing IP to the subject, the Investigator or designee will annotate the label to include the subject number, Visit/Assessment, and date dispensed. Two bottles will be dispensed at each clinic visit noted in Table 3.

10.3. Investigational Product Storage

Until dispensing to the subject, NB-001 and placebo bottles will be stored in a locked and limited access area at room temperature (15-25°C). The subject and parent/guardian will be informed of appropriate storage requirements.

10.4. Investigational Product Preparation

NB-001 and placebo capsules require no preparation prior to dosing.

10.5. Investigational Product Administration

NB-001 or placebo capsules will be administered orally to the subject. Subjects will take 2 capsules BID, 2 in the morning and 2 in the evening (i.e., 4 capsules daily). The subject should begin dosing for Treatment Period 1 on the morning of Day 1, after collection of pre-dose samples. If Day 0 and Day 1 are combined, the Investigator should schedule the combined Day 0/Day 1 visit early enough in the morning to ensure all Day 0 procedures are completed, pre-dose samples collected, and the total daily dose is taken (2 capsules, BID; 4 capsules total), in that order. Similarly, the subject should begin dosing for Treatment Period 2 on the morning of Day 50 after collection of pre-dose samples. If Day 49 and Day 50 are combined, the Investigator should ensure that the procedures required for Day 49 are completed at the end of the wash-out period and prior to pre-dose sample collection and dosing.

Capsules may be either swallowed whole or, if the subject is unable to swallow a capsule whole, it may be opened, and its contents sprinkled on applesauce. If the subject can swallow the capsules intact, sufficient liquids should be taken to swallow the capsule. If dosing is delayed, the subject should take the dose as soon as remembered with a minimum of 4 hours between doses. For example, if the subject forgets to take the morning dose and takes it upon

remembering in the afternoon, the subject should wait at least 4 hours before taking his/her evening dose. Missed doses should be reported to the Investigator.

Dosing will be paused from Days 43-49, during the wash-out period. No capsules will be taken during this time. The wash-out period may be extended beyond one week (and within reason) to accommodate the subject's schedule, after consultation with the Clinical Research Associate (CRA) or Medical Monitor.

10.6. Investigational Product Accountability

Both NB-001 and placebo will be provided in quantities sufficient for subject enrollment. Subjects and parents/guardians will be instructed to return all IP bottles, including empty bottles and bottles containing unused capsules, at each visit noted in Table 3, and the Investigator or designee will review the record of returned IP and assess compliance.

The Sponsor and Investigator will ensure that records of IP inventory and accountability are maintained throughout the trial. IP supplies and records must be readily available for inspection by the Sponsor or its representatives and regulatory authorities at any time.

10.7. Investigational Product Handling and Disposal

All unused IP will be recorded by the Investigator and reconciled by the Clinical Research Associate (CRA) on an ongoing basis throughout the trial. The Sponsor will provide instructions regarding IP disposal.

11. ASSESSMENTS OF EFFICACY

All symptom scales included in this section are either "clinician rated" or may be proctored by a local clinician, and will be administered centrally and, when possible (i.e., optional), locally, i.e., by the clinical trial Investigator or delegate, via telemedicine. The telemedicine sessions may be recorded, and the central and local assessments conducted concurrently or, for the local rater, asynchronously (after review of the audio recording). Assessment will be conducted by licensed clinicians, defined as a Doctor of Medicine, Doctor of Osteopathic Medicine, licensed psychologist with a PhD or PsyD, or highly trained BA or MA level raters under PhD/MD supervision as otherwise approved by the Sponsor. Scoring guidelines for the rating scales will be provided in a separate document. Whenever possible, the same central and, if applicable, local rater should administer all scales to a given subject and/or parent/guardian at each visit throughout the subject's participation in the trial. The parent/guardian and clinician should be available to answer any questions that the raters may have. Efforts should be made, when possible, to complete assessments in the same, consecutive order at each visit and as listed in Table 3.

In addition to the validated rating scales below, the subject and/or parent/guardian will be asked about the impact on the subject by the COVID-19 pandemic or other stressors and/or significant changes in the subject's life that may impact behavior, positively or negatively.

11.1. Clinical Global Impression Scales

The CGI scales will be performed by a central rater and, when possible, by a local rater and will be the last assessment performed at each visit. A rating of the CGI-S and/or CGI-I by the local rater is optional. In order to complete the CGI-S and/or CGI-I rating, the local rater must participate in the PARS interview or review the audio recording of the PARS interview. CGI-I assessments at Assessment Days 14, 28, 42 and 49 should use the Assessment Day 0 CGI-S baseline rating as reference for change. CGI-I assessments at Assessment Days 63, 77, 91 and 119 should use the Assessment Day 49 CGI-S baseline rating as reference for change. When possible, the same central and, if applicable, local raters will complete all CGI scales for a given subject throughout the subject's trial participation.

The CGI-S scale will be used to establish the degree of disease severity for each subject. The CGI-I scale will be used as an outcome measure for estimating level of functioning in response to treatment. The clinician's global assessments of the severity of the symptoms and changes in symptoms from baseline (Day 0 or Day 49, per above) will be based on reports from the subject and/or parent/guardian, and minimal direct observation (Guy 1976; Busner and Targum 2007).

The CGI-S scale will be administered at Screening and Day 0 prior to dosing, and at additional visits noted in Table 3, to rate the severity of the subject's condition on a 7-point scale ranging from 1 (Normal, not at all ill) to 7 (Among the most extremely ill subjects) (Appendix 1). At the visits noted in Table 3, the central and, if applicable, the local rater will assess the subject's improvement relative to his/her symptoms at baseline (Day 0 or Day 49, per above) using a CGI-I assessment, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) (Appendix 2).

Administration of the CGI scales is estimated to take 10 to 20 minutes.

11.2. Pediatric Anxiety Rating Scale

The PARS is a clinician-rated instrument for assessing, over time, the severity of anxiety symptoms that are associated with common DSM-5 (American Psychiatric Association 2013) anxiety disorders (GAD, separation anxiety disorder, and social phobia [SoP) in subjects aged 6 to 17 years. The clinician will interview both the subject and the parent/guardian to complete this assessment at the visits described in Table 3.

The PARS includes 2 sections. The first section is a 50-item symptom checklist, which the clinician rates as present or absent during the past week. The second section is comprised of 7 severity/impairment items that are rated on a 6-point Likert scale. The 7 severity/impairment items reflect the severity/impairment of all symptoms noted in Section 1 of the PARS (during the previous week) (Research Units on Pediatric Psychopharmacology Anxiety Study Group 2002). The PARS is provided in Appendix 3.

Administration of the PARS is expected to take 20 to 30 minutes and will be completed by the central rater and, when possible, by a local rater. A rating of the PARS by the local rater is optional. When possible local raters may participate in the PARS interview via telemedicine and/or asynchronously review the PARS interview audio recording to complete their PARS rating.

11.3. Attention Deficit Hyperactivity Disorder-Rating Scale-5

The ADHD-RS-5 will be administered at the visits noted in Table 3 to document the subject's ADHD symptoms over the previous week. The ADHD-RS-5 Home Version is a parent/guardian-reported scale that was developed to measure the behaviors of children with ADHD, with separate forms for children (ages 5-10 years) and adolescents (11-17 years). The ADHD-RS-5 consists of 18 items designed to reflect the symptomatology of ADHD based on the DSM-5 criteria (American Psychiatric Association 2013). Each item will be scored on a scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54.

The 18 items may be grouped into 2 subscales: inattention and hyperactivity/impulsivity. The Inattention subscale raw score is computed by summing the item scores for Items 1 through 9 and the Hyperactivity–Impulsivity subscale raw score is computed by summing the item scores for Items 10 through 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 (Appendix 4) (DuPaul et al. 2016).

Administration of the ADHD-RS-5 is expected to take 10 to 15 minutes and will be proctored by the local rater.

11.4. Social Responsiveness Scale, Second Edition

The SRS™-2 identifies the presence and severity of social impairment within the autism spectrum and differentiates it from that which occurs in other disorders. It is a 65-item, parent-

completed questionnaire which incorporates 5 content areas of social deficits: social awareness, social cognition, social communication, social motivation, and autistic mannerisms. The SRS™-2 should be administered as described in Table 3, is estimated to take about 15-20 minutes to complete, and will be proctored by the local rater. (Appendix 5) (Constantino et al. 2003; Constantino and Gruber 2005).

12. ASSESSMENTS OF SAFETY

12.1. Safety Parameters

12.1.1. Demographic/Medical History

A complete demographic and medical history will be obtained at Screening. Medical history will be updated on Day 0, prior to dosing on Day 1, to confirm trial eligibility. Any confirmed DSM-5 diagnoses (American Psychiatric Association 2013) should be documented.

12.1.2. Vital Signs

Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature and will be performed after the subject has been at rest in the seated position for at least 5 minutes. Vital signs will be assessed at the Screening Visit and as clinically indicated per Table 3.

12.1.3. Physical Examinations

A complete physical examination will be performed at the Screening Visit, Day 0, Day 42, Day 91/ET Visit, and End of Trial Visit, and will include an assessment of the following body systems: height (at the Screening Visit only); general appearance; weight; mental status; head, eyes, ears, nose, and throat; dermatologic; cardiovascular; respiratory; gastrointestinal; musculoskeletal; and neurological at Screening. Additional body systems may be examined at the Investigator's discretion. An abbreviated, clinically focused physical examination based on the Investigator's clinical judgement will be administered at all other assessment intervals or as clinically indicated. Any clinically significant abnormality should be reported on the AE CRF page, as appropriate.

12.1.4. Electrocardiograms

A 12-lead ECG in triplicate will be obtained at the at the Screening Visit, Day 0, Day 42, Day 91/ET Visit, and End of Trial Visit, with the subject in a supine position following at least a 5-minute rest. The Investigator will review and report the results of each ECG; the reviews on Days 42 and 91 will include a comparison of each ECG to the baseline (i.e., Day 0) ECG. Any clinically significant abnormality should be reported as an AE, as appropriate.

12.1.5. Laboratory Assessments

The clinical laboratory tests (chemistry, hematology, and urinalysis) that will be performed are shown in Table 5. Samples will be obtained at the Screening visit, Day 0, Day 42, Day 91/ET Visit, and End of Trial Visit.

Table 5: Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Total bilirubin Total protein Albumin Glucose Carbon dioxide Blood urea nitrogen Creatinine Sodium Potassium Chloride Calcium	Hemoglobin Hematocrit Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Erythrocyte count Leukocyte count Neutrophil count and percentage Lymphocyte count and percentage Monocyte count and percentage Eosinophil count and percentage Basophil count and percentage Platelet count	Glucose Protein Specific gravity pH Nitrite Bilirubin Urobilinogen Ketone Blood Leukocyte esterase **Other** eGFR (at Screening only; using the revised Schwartz equation; Fadrowski and Furth 2011, Staples et al. 2010)

eGFR = estimated glomerular filtration rate

Other laboratory tests will include serum and urine pregnancy tests (β-human chorionic gonadotropin) in females of childbearing potential, and urine drug tests (amphetamines/methamphetamines, benzodiazepines, cannabinoids, cocaine, opiates).

A sample will be collected at Screening for centralized 22q11DS genotype testing to confirm diagnostic homogeneity of the trial population. Results of this test will not be required prior to randomization of each subject as historical or local records confirming diagnosis will be adequate to establish trial eligibility.

Reports containing these laboratory test results will be generated by the laboratory performing the test. Laboratory values outside of the normal range will be assessed for clinical significance by the Investigator.

Abnormal laboratory tests may be repeated at the discretion of the Investigator or Sponsor.

Other laboratory tests may be performed by the Investigator, as deemed necessary, to evaluate, or ensure the safety of, a subject. The performance of special testing (i.e., other than the protocol-defined testing) that the Investigator deems necessary should be discussed in advance with the Medical Monitor, if the subject's clinical status allows.

A blood sample to assess serum proline levels will be collected as described in Table 3. There is evidence that proline affects glutamatergic neurotransmission. PRODH, a protein coding gene, encodes the enzyme proline dehydrogenase, which is involved in the transformation of the amino-acid proline into pyrroline-5-carboxylate, which in turn is the precursor of glutamate. In a subset of patients with 22q11DS, plasma proline levels are found to be increased (Goodman et al. 2000). Variability in proline levels in 22q11DS is likely related to polymorphisms in the remaining allele of the PRODH gene (Bender et al. 2005). In 22q11DS, several studies indicate a

possible relation between high proline and changes in neuropsychiatric phenotypes (Raux et al. 2007; Vorstman et al. 2009; Magnee et al. 2011) but this observation is not consistently replicated (Evers et al. 2015).

If any blood remains from the sample collected for centralized confirmation of 22q11DS genotype, the remnant blood samples will be stored per the federal (and/or local) regulations that govern the laboratory's processes on biological sample (and laboratory report) retention. Additionally, if a new protocol and informed consent form are developed to investigate the remnant samples, these documents will be submitted for IRB and/or EC approval and the subject and/or parent/guardian will be required to provide documented informed consent for additional analyses of the samples. Table 3. At the time of signing the initial ICF for this trial, NB-001-01, the subject and/or parent/guardian will have the option to decline future research on any remnant blood sample.

Blood samples for PK analysis and 4β-hydroxycholesterol will be collected at the timepoints noted in Table 3.

12.1.6. Columbia–Suicide Severity Rating Scale

Consistent with Food and Drug Administration (FDA) Guidance, Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, (FDA 2012), the C-SSRS is used to evaluate SIB. The scale consists of 10 categories with binary responses (yes/no) to assess the subject's suicidal thoughts. An additional question regarding self-injurious behavior without suicidal intent will be evaluated with a binary response (yes/no). The overall suicidal ideation score is a composite endpoint based on categories of suicidal ideation, suicidal behavior, and SIB. The C-SSRS will be used at the visits noted in Table 3 to evaluate the subject's suicidal tendencies. Subjects with suicidal tendencies at Screening (or Day 0, if more than 21 days elapse between Screening and Day 1), based on Investigator assessment, will be excluded according to the Exclusion Criteria (Section 7.2). Investigator guidelines for managing a subject with SIB will be provided separately (Posner et al. 2011).

The C-SSRS is provided in Appendix 6 and administration of the C-SSRS is expected to take 15 to 20 minutes.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

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

Pre-existing events that increase in frequency or severity in nature during or as a consequence of use of an IP will also be considered as AEs. Any medical condition or clinically significant laboratory abnormality with an onset date before the date of ICF signature is pre-existing and

should be documented as medical history. Any AE that occurs between the date of ICF signature and the date/time of first IP administration will be considered a pre-treatment-emergent AE. Any AE that occurs after the date/time of first IP administration will be considered a TEAE.

Often, a clinically significant laboratory value is an abnormal laboratory value that is accompanied by a sign or symptom. Typically, a diagnosis or set of clinical signs and symptoms including abnormal laboratory value(s) is captured as the AE term (e.g., anemia). However, in the absence of a diagnosis, a clinically significant laboratory abnormality may be captured as an AE term (e.g., elevated alanine aminotransferase). All laboratory values, including abnormal values, will be reported during the trial.

12.2.1.2. Serious Adverse Event

An AE is considered serious if it results in any of the following outcomes or circumstances:

- Death
- Life-threatening
  - The term life threatening in the definition of "serious" refers to an event in which the subject was at immediate 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.
- Inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization for elective intervention for a pre-existing condition that did not worsen from baseline is not considered an AE.
- Persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of a subject

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations. Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious adverse events (SAEs) when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of Terms

Life-threatening: An AE is life-threatening if it places the subject at immediate risk of death from the event as it occurred (i.e., it does not include an event that, had it occurred in a more severe form, might have caused death). For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug induced hepatitis can be fatal.

Hospitalization: An AE requiring hospitalization should be considered an SAE. Hospitalization scheduled for an elective procedure or treatment of a pre-existing condition that has not worsened during participation in the trial (e.g., elective surgery for a pre-existing condition that

has not worsened), or for a routine clinical procedure that is not the result of an AE is not considered an SAE. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either serious or non-serious, according to the defined criteria. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or in the emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Disability/incapacity: An AE is disabling or incapacitating if the event results in a substantial disruption of a subject's ability to conduct normal life functions.

12.2.1.2.1. Reporting Serious Adverse Events

Any AE that is assessed as serious, whether or not it is related to the IP, must be reported by the Investigator to the Medical Monitor within 24 hours of knowledge of the event and documented on the SAE CRF. An initial SAE CRF should be completed with the available information, even if additional information will be needed to fully document the event. All additional information relevant to the SAE must be provided to the Medical Monitor as soon as possible. Relevant medical records, including, as applicable, hospital records and autopsy reports, should be obtained by the Investigator and provided to the Medical Monitor.

In the event of a fatal or life-threatening SAE, any required information for the initial report must be provided and expedited to the Medical Monitor to allow for regulatory reporting by the Sponsor within 7 calendar days of the Investigator’s initial report.

The Investigator will follow an SAE until it resolves, the Investigator feels the event is stable and chronic in nature, or the subject is lost to follow-up. All follow-up information relevant to the SAE must be provided to the Medical Monitor within 24 hours of the Investigator’s receipt of this information.

SAEs will be reported from the time of signing the ICF and, if applicable, the subject assent form, and through the End of Trial Visit.

SAEs should be reported on the SAE CRF in the EDC system:

12.2.1.3. Treatment-Emergent Adverse Event of Special Interest

A treatment-emergent adverse event of special interest (TEAE-SI) is an AE of scientific and medical concern specific to the Sponsor’s study drug/device or program, which may warrant ongoing monitoring and/or rapid communication by the investigator to the sponsor or designee. Such an event might warrant further investigation in order to characterize and understand it.

TEAEs-SI in this trial will include: development of psychotic symptoms, SIB, seizure, overdose with untoward medical sequalae, and confirmed cases of COVID-19. Such events will require expedited reporting to the Sponsor within 24 hours of knowledge of the event.

12.2.2. Overdose

Any instance of overdose (suspected or confirmed, accidental or intentional, with or without untoward sequelae, and irrespective of whether or not the IP was involved) must be reported by the Investigator to the Medical Monitor by telephone or email within 24 hours of knowledge of the event. An overdose with no associated signs or symptoms will not be classified as an AE or SAE but should be reported to the Medical Monitor. Any signs or symptoms of overdose should be documented as an AE or SAE (as applicable); an overdose associated with an SAE should be reported according to the SAE reporting procedures.

In the case of an overdose, the subject will be monitored closely and managed with supportive care. Any symptoms will be treated according to the Investigator's standard practices.

12.2.3. Pregnancy

If a female subject becomes pregnant at any time following the first dose of IP through the End of Trial Visit, the Investigator must notify the Medical Monitor within 24 hours of learning of the pregnancy by completing the Pregnancy CRF in the EDC system. IP will be discontinued, and the subject will be withdrawn from the trial. Female subjects will be instructed to report a pregnancy that occurs within 90 days of the End of Trial Visit. The Investigator must report the pregnancy to the Medical Monitor within 24 hours or as soon as possible after learning of it. Any premature terminations of pregnancy, including elective/therapeutic and/or spontaneous abortions, must be reported to the Medical Monitor. Each pregnancy will be followed to its conclusion. For pre-term or term deliveries, the status of the mother and child after delivery must be reported to the Medical Monitor by updating the Pregnancy CRF in the EDC system. Although pregnancy occurring in a clinical trial is not considered to be an AE or SAE, any pregnancy complication will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion (i.e., miscarriage), a medically-recommended therapeutic abortion, and an ectopic pregnancy will always be reported as an SAE. In the event of a pregnancy-associated AE or SAE, the AE or SAE should be reported by adding the appropriate event term(s) to the AE CRF in the EDC system.

12.2.4. Relationship to Investigational Product

After careful medical consideration, the Investigator will assess the relationship of the AE to the IP according to the following categories:

- Not related: A causal relationship between IP and the AE can be easily ruled out (e.g., based on the temporal relationship, absence of a reasonable pathophysiologic mechanism, or direct evidence of actual cause). An alternate etiology must be documented in the source record.
- Related: An AE that is most likely caused by the IP, per Investigator assessment. Rechallenge is not required to fulfill this definition.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then the AE should be considered "related" to IP.

12.2.5. Recording Adverse Events

All reported AEs will be documented, including events that are spontaneously reported by a subject and/or parent/guardian. AEs may also be elicited by asking each subject (and/or parent/guardian) a general, non-directed question such as “How are you feeling?” or “How have you been feeling since the last visit?” Directed questioning and examination will then be done, as appropriate. Generally, in this population, AEs should be elicited from the parent/guardian in consultation with the subject.

A full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious, if applicable, should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction. Whenever feasible, the AE should be documented as a medical diagnosis (highest possible level of integration). When this is not possible, the AE should be documented in terms of the signs and/or symptoms observed by the Investigator and/or reported by the subject and/or parent/guardian.

Information documented will include the diagnosis or succinct description of the AE, the date of onset and the date of resolution (if applicable), severity, seriousness, relationship to IP, action taken with respect to IP, and the outcome. It is the responsibility of the Investigator to document all AEs that occur, in accordance with the guidelines above, whether or not they are considered to be related to the IP. AEs will be reported from the time of signing the ICF and, if applicable, the subject assent form, and through the End of Trial Visit.

The Investigator is responsible for reporting AEs and SAEs to the reviewing IRB/IEC in accordance with the IRB/IEC’s standard procedures.

12.2.6. Adverse Event Severity

The severity of each AE/SAE will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Dictionary, Version 5.0, which is available for download: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. which provides the following scale:

- **Grade 1/Mild**; asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated
- **Grade 2/Moderate**; minimal, local or noninvasive intervention indicated OR limiting age- appropriate instrumental activities of daily living
- **Grade 3/Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated OR disabling OR limiting self care activities of daily living
- **Grade 4/Life-threatening** consequences OR urgent intervention indicated
- **Grade 5/Death** related to AE

It remains important to distinguish between serious and severe AEs. Severity is a measure of intensity (e.g., mild, moderate, or severe myocardial infarction). Seriousness is defined by the criteria under Section 12.2.1.2 and is based on subject/event outcome or action criteria usually

associated with events that pose a threat to a subject's life or functioning. An AE of severe intensity may not be considered serious. Assignment of an AE as 'Serious' (not severity) serves as a guide for defining regulatory reporting obligations.

13. OTHER STUDY ASSESSMENTS

13.1. Wechsler Abbreviated Scale of Intelligence, Second Edition

Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II), is an abbreviated measure of cognitive intelligence designed for individuals 6 to 90 years of age. It is primarily used in clinical, psychoeducational, and research settings and was developed to quickly and accurately estimate cognitive intelligence when administration of a full battery is not feasible or necessary (McCrimmon and Smith 2012; Wechsler 2013).

The WASI-II should be administered and interpreted by a qualified rater with appropriate training and certification; the same person should administer and interpret the results of the measure. Nonverbal subjects will complete only the Perceptual Reasoning component of the WASI-II. For all subjects, a minimum IQ score of 65 is required for participation in the trial.

If feasible, and to minimize administration of this assessment where other criteria may exclude the subject, the WASI-II should be one of the final clinical assessments completed during Screening and as near as possible to Day 0. The WASI-II is provided in Appendix 7 and administration time is approximately 30-45 minutes.

14. DETERMINATION OF PLASMA NB-001 AND 4B-HYDROXYCHOLESTEROL CONCENTRATIONS

14.1. NB-001 Concentrations in Plasma

Blood samples for determination of NB-001 plasma concentrations will be collected at the time points noted in Table 3. On PK assessment days, the morning dose of NB-001 should be administered during the visit with the home health nurse.

NB-001 plasma concentrations will be compared between subjects, based upon dosing conditions, within this trial (i.e., subjects taking intact NB-001 capsules versus subjects taking NB-001 sprinkled on applesauce) and to historical data. Only PK samples collected during active NB-001 treatment for each subject will be analyzed after all subjects have completed the trial.

NB-001 concentration and other relevant data from this trial may be pooled with data from other studies for nonlinear mixed effects modelling and reported separately.

Collection of Samples for Plasma Concentrations on Days 1, 14, 50, 63		**Example Schedule**
Pre-dose	Collect PK and 4B-hydroxycholesterol samples	9:45 am
Administer Morning Dose		10:00 am
1-hour Post-dose	Collect PK sample	11:00 am
4 hours Post-dose	Collect PK sample	2:00pm
Administer Evening Dose		6:00 pm

PK = pharmacokinetic(s)

14.2. 4B-Hydroxycholesterol Concentrations in Plasma

Blood samples for the determination of concentrations of 4β-hydroxycholesterol, an endogenous biomarker for CYP3A4 induction, will be collected pre-dose at the visits noted in Table 3. Changes, if any, in 4β-hydroxycholesterol concentrations 2 weeks after the start of IP in subjects assigned to active and placebo arms will be used in the assessment of CYP3A4 induction potential of NB-001.

14.3. Sample Handling

PK and 4β-hydroxycholesterol sample collection, processing, and shipping instructions will be provided separately in the Laboratory Manual.

15. STATISTICS

This section provides a summary of key reporting and statistical analytic methods of the trial data. A detailed description of these concepts, including modifications to the methods described below, will be given in the SAP and will be finalized before the database lock. Any deviations from the SAP will be reported in the clinical study report.

15.1. Analysis Sets

The following analysis sets will be used in the trial:

- Enrolled Analysis Set (ENR): The ENR consists of all subjects who meet all eligibility criteria and receive at least 1 complete daily dose (400 mg) of IP.
- Full Analysis Set (FAS): The FAS consists of ENR subjects who have at least 1 valid post-baseline efficacy evaluation within each treatment period. Subjects will be analyzed based on the treatment to which they were randomized. Subsets in the FAS are referred to as evaluable subjects.
- Safety Analysis Set (SAS): The SAS consists of all subjects who receive at least 1 capsule (100 mg) of IP. Subjects will be analyzed based on treatment received.
- Per Protocol Analysis Set (PPS): The PPS consists of FAS subjects who do not have major protocol deviations. Subjects will be analyzed based on the treatment received.

Efficacy analyses will be conducted using the FAS, with sensitivity analyses performed using the PPS.

15.2. General Procedures

Trial population and baseline data collection (e.g., subject disposition and demographics) will be presented by treatment sequence and for all subjects combined. Efficacy and safety endpoints will be summarized by treatment group.

Continuous variables will be summarized with descriptive statistics (number evaluated, mean, standard deviation, median, minimum, and maximum). Categorical variables will be presented as counts and percentages within each category. As appropriate, 95% confidence intervals will be included.

15.3. Sample Size

A total of 30 evaluable subjects, with 15 subjects in each treatment sequence, are planned for enrollment in this trial. The sample size is chosen to guarantee approximately 80% power for demonstrating a statistically significant treatment effect at a 2-sided alpha of 0.05 if the true mean difference (NB-001 versus placebo) for the CGI-I score at the end of each treatment period is 1 and the standard deviation is 1.25. This sample size calculation is based on the paired t-test.

15.4. Efficacy Analyses

All statistical testing will be based on a 2-sided significance level of 0.05 and will be considered exploratory in nature. Efficacy results will be analyzed by treatment group. Data collected at

post-baseline evaluation time points will be combined across the 2 treatment periods depending on the treatment received, based on the following:

The baseline value will be the last measurement reported prior to the first dose of any IP at Day 1 during Treatment Period 1 or Day 50 during Treatment Period 2 and will be further defined in the SAP.

The treatment effect on the continuous efficacy endpoints, i.e., CGI-I and CGI-S and other efficacy endpoints, will be evaluated using mixed-effects models. A model will be defined for each endpoint to include treatment, visit, treatment-by-visit interaction, period and sequence as fixed effects, subject nested within sequence as a random effect, and the baseline value as a covariate. The within-subject errors will be modeled using an unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If a model fails to converge, other covariance structures will be evaluated until model convergence is met.

Each efficacy endpoint will be first evaluated within the subset of subjects with the corresponding significant domain/symptom of greatest impairment, e.g., the treatment effect on the PARS will be assessed within the subset where the symptom of greatest impairment is anxiety. Additional analyses of the efficacy endpoints will be performed in the overall subject population.

A supportive analysis of the efficacy endpoints measured on an ordinal scale, including the CGI-I and CGI-S will be performed by comparing the treatment groups using a Wilcoxon signed-rank test at each post-baseline evaluation.

An overall treatment effect evaluation will be performed using the global test for multiple endpoints (O'Brien 1984; Dmitrienko and Tamhane 2009). This test relies on pooling the evidence of effectiveness across several endpoints and will be employed for assessing the evidence to support the global alternative hypothesis that NB-001 is uniformly better than placebo in the mean changes in the PARS, ADHD-RS-5, and SRS^{TM}-2 scores (treated as 1 instrument).

Efficacy summaries will be based on observed data only and no explicit imputation to account for missing data will be performed.

Additional details of analysis methods to be applied to the efficacy endpoints will be described in the SAP.

15.5. Safety Analyses

AEs will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory activities (MedDRA). TEAEs will be mapped to IP by comparing the event onset to the date of first dose of IP within each treatment period. Incidence rates for TEAEs will be

summarized by system organ class and preferred term by treatment group. In addition, TEAEs will be summarized by severity and relationship to IP by treatment group. Subjects will be counted once at each level of summation (i.e., overall, by system organ class, and by preferred term). Summaries by relationship to IP will count a subject once at each level of summation based on the closest relationship; summaries by severity will count a subject once at each level of summation using the highest severity reported. As this is a crossover trial in which subjects are randomized to one of two treatment sequences: NB-001 followed by placebo (treatment sequence A/P) or placebo followed by NB-001 (treatment sequence P/A), all subjects who receive at least one dose of IP (NB-001 or placebo) in treatment period will be included in summaries of TEAE data for both NB-001 and placebo, according to the treatment being taken at the time of TEAE onset. A detailed description of the planned TEAE analyses will be presented in the SAP.

All other safety parameters including clinical laboratory values, vital sign measurements, and ECG interval results will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables by treatment group. Results will be presented for the observed value and the change from baseline by time point.

15.6. Interim Analysis

An interim analysis is not planned for this trial.

15.7. Independent Data Monitoring Committee

An Independent Data Monitoring Committee is not planned for this trial.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Trial Monitoring

The Sponsor is responsible for ensuring the proper conduct of the trial with respect to ethics, protocol adherence and clinical trial site procedures, integrity of the data, and applicable laws and/or regulations, including International Conference on Harmonization (ICH) GCP. Trial monitoring will be conducted by the Sponsor or designee at regular intervals during the trial and following completion of the trial. Trial monitors (i.e., CRAs) will communicate with the Investigator via visits to the clinical trial site, telephone calls, and other communication methods in order to review the progress of the trial. During the monitoring visits, the following aspects of the trial conduct will be carefully reviewed: parent/guardian informed consent and subject assent, subject recruitment, compliance with trial procedures and ICH GCP, source data verification, AE and SAE documentation and reporting, quality of the data, IP disposition records, Investigator's Site File and acceptability of the facilities. The Investigator must make him/herself available to meet with the trial monitor and make all trial data accessible to the clinical monitor, other authorized representatives of the Sponsor, members of the IRB, and regulatory inspectors. The ICF signed by the parent/guardian must indicate the possibility for review of the data by these authorized individuals/entities. Monitoring visits may be conducted remotely, if required, in response to the COVID-19 pandemic.

16.2. Data Management

All subject-related data will be documented in the CRFs using an EDC system in a confidential fashion, with the subject identified by subject number and initials only.

All the information required by the protocol must be documented and any omissions explained. The Principal Investigator must review all CRF entries for completeness and accuracy. Source documents, including all demographic and medical information, CRFs, and the parent/guardian ICF and, if applicable, assent for each subject in the trial must be maintained by the Principal Investigator. All information in the CRFs must be traceable to the original source documents. Examples of source documents include hospital records, office visit records, physician notes, consulting physician notes, laboratory reports, IP inventory records, subject dosing data, and diaries. Records may be written in hard copy or in an electronic medical records system. The Principal Investigator must maintain the original source document records for each subject for the length of time required by the Sponsor (Section 19.2).

Concomitant medications will be coded using the current (at the start of the trial) version of World Health Organization Drug Global (the international reference for medicinal product information), which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the current (at the start of the trial) version of the MedDRA.

16.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB may visit the clinical trial site to perform audits or inspections, including source data verification. The purpose

of an inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

16.4. Institutional Review Board/Independent Ethics Committee

Before initiation of the trial, the Investigator must submit the protocol, Investigator's Brochure, ICF, subject assent form, and any written materials that will be made available to the subject to an IRB/IEC complying with applicable regulations and the provisions specified in the ICH guidelines for approval. Written IRB/IEC approval of the noted documents must be obtained prior to initiation of the trial at the relevant investigational site(s).

The Investigator is responsible for reporting the following to the IRB/IEC:

- SAEs in accordance with IRB/IEC regulations
- Significant findings that become known during the course of the trial that might affect the willingness of subjects to continue to participate
- Protocol, ICF and subject assent form amendments prior to the implementation of the change (except where necessary to eliminate apparent immediate hazards to the subjects)
- Trial progress reports at least once per year, if applicable
- Notification of trial completion or termination

In accordance with reporting requirements, the Investigator will also promptly report all changes in research activity and all unanticipated problems involving risk to subjects or others to the IRB/IEC. Additionally, the Investigator will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subject(s).

17. QUALITY CONTROL AND QUALITY ASSURANCE

This trial will be conducted in accordance with the Declaration of Helsinki and most recent GCP guidelines (CPMP/ICH/135/95), 21 Code of Federal Regulations (CFR) Part 312 and all applicable regulatory requirements.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 16.3 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final trial protocol, including the final version of the ICF and subject assent form, must be approved or given a favorable opinion in writing by an IRB/IEC, and the Investigator must submit written IRB/IEC approval to the Sponsor before enrolling subjects into the trial.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB/IEC upon receipt of protocol amendments and annually, as local regulations require.

The Investigator is responsible for reporting AEs and SAEs to the reviewing IRB in accordance with the IRB's standard procedures. The Investigator is also responsible for providing the IRB/IEC with expedited reports of any unexpected serious adverse drug reactions from any other trial conducted with the IP. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

18.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and applicable regulatory requirements. In addition, in the United States (U.S.), the Investigators will follow U.S. Department of Health and Human Services regulations regarding the Health Information Portability and Accountability Act (HIPAA; 45 CFR 164). Canadian Investigators will adhere to federal privacy legislation, Personal Information Protection and Electronic Documents Act (PIPEDA, S.C. 200, c. 5), and provincial (Ontario) privacy legislation, Personal Health Information Protection Act (PHIPA). Each Investigator will ensure that appropriate health care and necessary referrals for appropriate health care are provided for their subjects throughout the trial.

18.3. Written Informed Consent and Assent

No subject will be admitted into this trial until the Investigator (or designee) has obtained legally effective informed consent from the subject's parent/guardian and, if applicable, assent from the subject. The Investigator shall seek such consent only under circumstances that provide the prospective subject and/or parent/guardian with sufficient opportunity to consider whether or not to participate in the trial. Informed consent must be obtained without coercion, undue influence, or misrepresentation of the potential benefits or risks that might be associated with participation in the trial.

Informed consent encompasses all oral and written information given to the subject and/or parent/guardian about the trial and the trial materials. This includes the consent form signed by the parent/guardian and, if applicable, the assent form signed by the subject, the instructions for use of trial materials that are provided to the subject, and any other information provided to the subject. All such information that is given to the subject and/or parent/guardian must be in a language that is understandable to the individual. The information will not include any language

in which the subject and/or parent/guardian is made to waive any of their rights or which releases or appears to release the Investigator, the Investigator's institution, or the Sponsor from liability for negligence.

Informed consent will be documented by the use of a written consent form that is signed by the parent/guardian and the Investigator (or designee). If an assent is applicable, the assent will be signed by the subject and the Investigator (or designee). A copy of the signed consent form and, if applicable, the subject assent form will be offered to the subject and parent/guardian. The original signed consent and assent forms for each subject will be kept at the clinical trial site. The consent form must include each of the basic and additional elements of informed consent described in 21 CFR Part 50.25 and must describe each of the risks or discomforts to the subject that have been identified by the Sponsor as reasonably foreseeable.

18.4. Subject Confidentiality

The confidentiality of all subjects consented into this trial will be protected to the fullest extent possible. Subjects' clinic records may be audited by the Sponsor, FDA personnel, or other individuals authorized in writing by the Sponsor to audit the trial. However, trial subjects will not be identified by name on any CRF, or on any other documentation sent to the Sponsor or other organizations involved in this trial, and will not be reported by name in any report or publication resulting from data collected in this trial.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

The Sponsor will be allowed to conduct visits to the investigational facilities for the purpose of monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the IP storage area, IP inventory, IP accountability records, subject medical charts, trial source documents, and other records relative to trial conduct.

19.2. Retention of Records

In the U.S., the signed original ICF and assent (if applicable) form for each subject and originals of all trial documentation (e.g., IP inventory forms, subject clinic records, original laboratory reports, guidebooks) will be retained by the Investigator for a minimum of 2 years after FDA approval or withdrawal of a New Drug Application (NDA). If an NDA is not submitted within 5 years of the last follow-up visit, the Investigator may request permission, in writing, from the Sponsor to destroy the records. In accordance with Canadian law, site(s) in Canada will maintain trial records for a minimum of 25 years. No records may be destroyed without written permission from the Sponsor.

20. PUBLICATION POLICY

The Sponsor is responsible for preparing a clinical study report based on the results of this trial. The Sponsor's publication policy will be detailed in the Investigator's Clinical Research Agreement.

The following publication principles will be considered:

- Clinical Trial Registries (e.g., clinicaltrials.gov): A description of the trial and relevant design elements (e.g., basic design, objectives and endpoints, sample size, trial population, and key inclusion/exclusion criteria) and results (when available) will be published online in a manner consistent with applicable regulatory guidelines.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the trial databases and the analyses conducted.
- Single Center Publication and Additional Publications: This is a multicenter trial and is designed to be published with complete data from all the trial sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter trial and that the trial was not intended, or statistically powered, for data presentation by a single trial site.
- Nobias Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this trial to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days before submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies, or chemical formulae) may still need to remain confidential.

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22. APPENDICES

Appendix 1: Clinical Global Impression-Severity

Severity

Considering your total clinical experience with this particular population, how impaired is the patient at this time?

0. Not assessed
1. Normal, not at all impaired
2. Borderline impaired
3. Mildly impaired
4. Moderately impaired
5. Markedly impaired
6. Severely impaired
7. Among the most extremely impaired patients

Appendix 2: Clinical Global Impression-Improvement

Global Improvement

Rate total improvement whether or not in your judgement it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has he/she changed?

8. Not assessed
9. Very much improved
10. Much improved
11. Minimally improved
12. No change
13. Minimally worse
14. Much worse
15. Very much worse

Appendix 3: Pediatric Anxiety Rating Scale

PEDIATRIC ANXIETY RATING SCALE (PARS)

SYMPTOM CHECKLIST

Instructions: Fill in the blanks with "1" (yes), "2" (no), or "9" (other, e.g., unable or unwilling to answer)

SOCIAL INTERACTIONS or PERFORMANCE SITUATIONS	Parent	Child	Rater
1. Has fear of and/or avoids participating in group activities.	_____	_____	_____
2. Has fear of and/or avoids going to a party or social event.	_____	_____	_____
3. Has fear of and/or avoids talking with a stranger.	_____	_____	_____
4. Has fear of and/or avoids talking on the phone.	_____	_____	_____
5. Reluctant or refuses to talk in front of a group.	_____	_____	_____
6. Reluctant or refuses to write in front of other people.	_____	_____	_____
7. Reluctant or refuses to eat in public.	_____	_____	_____
8. Reluctant or refuses to use a public bathroom.			
9. Reluctant or refuses to change into gym clothes or bathing suit with others present.	_____	_____	_____
SEPARATION			
10. Worry about harm happening to attachment figures.	_____	_____	_____
11. Worry about harm befalling self, including the fear of dying.	_____	_____	_____
12. Distress when separation occurs or is anticipated.	_____	_____	_____
13. Fear or reluctance to be alone.	_____	_____	_____
14. Reluctance or refusal to go to school or elsewhere.			
15. Complaints of physical symptoms when separation occurs or is anticipated.	_____	_____	_____
16. Reluctance or refusal to go to sleep alone.	_____	_____	_____
17. Reluctance or refusal to sleep away from home.	_____	_____	_____
18. Nightmares with a separation theme.	_____	_____	_____
19. Clings to parent, or follows parent around the house.	_____	_____	_____
GENERALIZED			
20. Excessive worry about everyday or real-life problems.	_____	_____	_____
21. Restlessness or feeling keyed-up or on edge.	_____	_____	_____
22. Easily fatigued.	_____	_____	_____
23. Difficulty concentrating or mind going blank.	_____	_____	_____
24. Irritability.	_____	_____	_____
25. Muscle tension or nonspecific tension.	_____	_____	_____
26. Sleep disturbance, especially difficulty falling asleep.	_____	_____	_____
27. Dread or fearful anticipation (nonspecific).			
SPECIFIC PHOBIA			
28. Animal: Specify _____	_____	_____	_____
29. Natural environment: (e.g., heights, storms) Specify: _____	_____	_____	_____
30. Blood-injection-injury: Specify: _____	_____	_____	_____
31. Situational (e.g., airplane, elevator): Specify:			

ACUTE PHYSICAL SIGNS & SYMPTOMS

32. Blushing.	_____	_____	_____
33. Feels paralyzed.	_____	_____	_____
34. Trembling or shaking.	_____	_____	_____
35. Feels dizzy, unsteady, lightheaded or going to pass out.	_____	_____	_____
36. Palpitations or pounding heart.	_____	_____	_____
37. Difficult breathing.	_____	_____	_____
(sensation of shortness of breath, smothering or choking).	_____	_____	_____
38. Chills or hot flashes.	_____	_____	_____
39. Sweating.	_____	_____	_____
40. Feels sick to stomach, nausea or abdominal distress.	_____	_____	_____
41. Recurrent urge to go to bathroom.	_____	_____	_____
42.Chest pain or discomfort.	_____	_____	_____
43. Paresthesias			
(numbness or tingling sensation in fingers, toes, or perioral region).	_____	_____	_____
44. Problems swallowing or eating.	_____	_____	_____

OTHER

45. Crying spells when in anxiety-provoking situations.	_____	_____	_____
46. Temper tantrums when in anxiety-provoking situations.	_____	_____	_____
47. Needs to flee certain anxiety-provoking situations.	_____	_____	_____
48. Keeps distance from other people.	_____	_____	_____
49. Fear of losing control or going crazy.	_____	_____	_____
50. Derealization (feeling of unreality)			
or depersonalization (detached from oneself).	_____	_____	_____

OTHER SYMPTOMS (ATYPICAL ANXIETY)	**parent**	**child**	**rater**
51. Anxiety about changes in routine	_____	_____	_____
52. New situations (places, events, activities)	_____	_____	_____
53. Change in daily schedules			
54. Worry about losing access to specific interest	_____	_____	_____
55. Somatic symptoms in social settings	_____	_____	_____
56. Efforts to escape social situations	_____	_____	_____
57. Increased irritability before or during social situations	_____	_____	_____
58. Insistence on certain behaviors in the absence of clear desire to prevent feared outcome.			

Other anxiety symptoms: Specify: _____

Specify: _____

Specify: _____

SEVERITY ITEMS

Instructions: For each item circle the number that best characterizes the patient during the past week.

		Code
1. Overall Number of Anxiety Symptoms (Circle code for past week only)		
	Not applicable	8
	Does not know	9
	No symptoms	0
	1 symptom	1
	2-3 symptoms	2
	4-6 symptoms	3
	7-10 symptoms	4
	More than 10 symptoms	5
2. Overall Frequency of Anxiety Symptoms		
	Not applicable	8
	Does not know	9
	No symptoms	0
	1 or 2 days a week	1
	3 or 4 days a week	2
	5 or 6 days a week	3
	Daily	4
	Several hours every day	5
3. Overall Severity of Anxiety Feelings		
	Not applicable	8
	Does not know.	9
	None. No anxious symptoms.	0
Minimal	Very transient discomfort. Not clinically significant.	1
Mild	Transient discomfort that is mildly disturbing. Borderline clinical significance. Intermediate between 1 and 3.	2
Moderate	Clearly nervous when anticipating or confronting the anxiety-provoking situation(s). Often unable to overcome these feelings. These feelings impact on well-being.	3
Severe	Very distressed when anxious or when anticipating or confronting the anxiety-provoking situation (s). Usually unable to overcome this feeling. Intermediate between 3 and 5.	4
Extreme	Feels wretched when anticipating or confronting anxiety-provoking situation(s). Often or almost totally unable to overcome this fear. Very marked impact on well-being.	5

4. Overall Severity of Physical Symptoms of Anxiety

	Not applicable	8
	Does not know	9
	None. No physical symptoms of anxiety.	0
Minimal	Very transient physical symptoms of anxiety. Symptoms are not, or are hardly noticeable by others. Not clinically significant.	1
Mild	Few physical symptoms: no lasting impact.	2
	Borderline clinical significance. Intermediate between 1and 3.	
Moderate	Persistent physical symptoms of anxiety, especially during exposure to the feared situation(s). Symptoms are noticeable by others and significantly interfere with his/her ability to function in the situation.	3
Severe	Marked physical symptoms of substantial clinical significance. Intermediate between 3 and 5.	4
Extreme	Severe and persistent physical symptoms of anxiety, especially during exposure to the feared situations(s). Symptoms are very obvious to others and often result in inability to function in the situation.	5

5. Overall Avoidance of Anxiety-Provoking Situations

NOTE: Rate all avoidance here; include school, home, activities, etc. in rating

	Not applicable	8
	Does not know	9
	None. Does not avoid the anxiety-provoking situation(s).	0
Minimal	Very occasionally avoids the anxiety-provoking situation(s). Avoided situation(s) is/are not critical to his/her well-being.	1
Mild	Avoids anxiety-provoking situation(s) some of the time but no important situation is consistently avoided. Borderline clinical significance. Intermediate between 1 and 3.	2
Moderate	Avoid anxiety-provoking situation(s) frequently. At least one important situation is avoided.	3
Severe	Avoids anxiety-provoking situation most of the time or more than one important situation is consistently avoided. Intermediate between 3 and 5.	4
Extreme	Avoids all or almost all anxiety-provoking situations.	5

6. Interference with Family Relationships and/or Performance at Home

	Not applicable	8
	Does not know	9
	None. No interference.	0
Minimal	Very transient interference. No impact on relationships with family members or performance (tasks, etc.) at home.	1
Mild	Slight impact on relationships or performance outside of the home. Borderline clinical significance. Intermediate between 1 and 3.	2
Moderate	Clear interference. Either performance of tasks at home or frequency or quality of interaction with family members is affected: he/she might withdraw from interaction, or might be avoided/rejected by family members, or might have many conflicts with them.	3
Severe	Marked interference in relationships with family members and/or performance at home. Of substantial clinical significance. Intermediate between 3 and 5.	4
Extreme	Totally or almost totally unable to maintain appropriate family relationship and/or function at home.	5

7. Interference with Peer and Adult Relationships &/or Performance Outside of Home.

NOTE: Out-of-home functioning includes school (not avoidance), activities, etc

	Not applicable	8
	Does not know	9
	None. No interference.	0
Minimal	Very transient interference. No impact on relationships with peers or teachers or other adults outside of the home. No impact on functioning outside of home, e.g., attending and performing group activities.	1
Mild	Slight impact on relationships or performance outside of the home. Borderline clinical significance. Intermediate between 1 and 3.	2
Moderate	Clear interference. Either performance outside of the home or frequency or quality of peer or adult interactions is affected: he/she might withdraw from interaction, or might be avoided/rejected by peers or adults, or might have conflicts with them.	3
Severe	Marked interference in relationship with peers or adults \ outside of home and/or performance outside of home. Of substantial clinical significance. Intermediate between 3 and 5.	4
Extreme	Totally or almost totally unable to maintain appropriate peer or adult relationship and/or function outside of home.	5

PARS total score _____

Appendix 4: Attention Deficit and Hyperactivity Disorder-Rating Scale-5

Attention and Behavior Rating Form, Home Version: Child (English)

Child's name: _____ Sex: M F Age: _____ Grade: _____

Completed by: Mother ___ Father ___ Guardian ___ Grandparent ___

Please select the answer that *best describes your child's behavior over the past 6 months.*

How often does your child display this behavior?	Never or Rarely	Sometimes	Often	Very Often
Fails to give close attention to details or makes careless mistakes in schoolwork or during other activities	0	1	2	3
Has difficulty sustaining attention in tasks or play activities	0	1	2	3
Does not seem to listen when spoken to directly	0	1	2	3
Does not follow through on instructions and fails to finish schoolwork or chores	0	1	2	3
Has difficulty organizing tasks and activities	0	1	2	3
Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework)	0	1	2	3
Loses things necessary for tasks or activities (e.g., school materials, pencils, books, eyeglasses)	0	1	2	3
Easily distracted	0	1	2	3
Forgetful in daily activities (e.g., doing chores)	0	1	2	3

How much do the nine behaviors in the previous question cause problems for your child:	No Problem	Minor Problem	Moderate Problem	Severe Problem
Getting along with family members	0	1	2	3
Getting along with other children	0	1	2	3
Completing or returning homework	0	1	2	3
Performing academically in school	0	1	2	3
Controlling behavior in school	0	1	2	3
Feeling good about himself/herself	0	1	2	3

(continued)

Attention and Behavior Rating Form, Home Version: Child (English) *(page 2 of 2)*

How often does your child display this behavior?	Never or Rarely	Sometimes	Often	Very Often
Fidgets with or taps hands or feet or squirms in seat	0	1	2	3
Leaves seat in situations when remaining seated is expected	0	1	2	3
Runs about or climbs in situations where it is inappropriate	0	1	2	3
Unable to play or engage in leisure activities quietly	0	1	2	3
"On the go," acts as if "driven by a motor"	0	1	2	3
Talks excessively	0	1	2	3
Blurts out an answer before a question has been completed	0	1	2	3
Has difficulty waiting his or her turn (e.g., while waiting in line).	0	1	2	3
Interrupts or intrudes on others	0	1	2	3

How much do the nine behaviors in the previous question cause problems for your child:	No Problem	Minor Problem	Moderate Problem	Severe Problem
Getting along with family members	0	1	2	3
Getting along with other children	0	1	2	3
Completing or returning homework	0	1	2	3
Performing academically in school	0	1	2	3
Controlling behavior in school	0	1	2	3
Feeling good about him-/herself	0	1	2	3

Attention and Behavior Rating Form, Home Version: Adolescent (English)

Child's name: _____ Sex: M F Age: _____ Grade: _____

Completed by: Mother ___ Father ___ Guardian ___ Grandparent ___

Please select the answer that *best describes your teenager's behavior over the past 6 months.*

How often does your child display this behavior?	Never or Rarely	Sometimes	Often	Very Often
Fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities	0	1	2	3
Has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during conversations or lengthy reading)	0	1	2	3
Does not seem to listen when spoken to directly	0	1	2	3
Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	0	1	2	3
Has difficulty organizing tasks and activities	0	1	2	3
Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; preparing reports)	0	1	2	3
Loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)	0	1	2	3
Easily distracted	0	1	2	3
Forgetful in daily activities (e.g., doing chores, running errands, returning calls, keeping appointments)	0	1	2	3

How much do the nine behaviors in the previous question cause problems for your teenager:	No Problem	Minor Problem	Moderate Problem	Severe Problem
Getting along with family members	0	1	2	3
Getting along with other teenagers	0	1	2	3
Completing or returning homework	0	1	2	3
Performing academically in school	0	1	2	3
Controlling behavior in school	0	1	2	3
Feeling good about himself/herself	0	1	2	3

(continued)

Attention and Behavior Rating Form, Home Version: Adolescent (English) *(page 2 of 2)*

How often does your teenager display this behavior?	Never or Rarely	Sometimes	Often	Very Often
Fidgets with or taps hands or feet or squirms in seat	0	1	2	3
Leaves seat in situations when remaining seated is expected	0	1	2	3
Runs about or climbs in situations where it is inappropriate or feels restless	0	1	2	3
Unable to play or engage in leisure activities quietly (e.g., is unable to be or is uncomfortable being still for an extended period of time)	0	1	2	3
"On the go," acts as if "driven by a motor"	0	1	2	3
Talks excessively	0	1	2	3
Blurts out an answer before a question has been completed	0	1	2	3
Has difficulty waiting his or her turn (e.g., while waiting in line).	0	1	2	3
Interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may intrude into or take over what others are doing)	0	1	2	3

How much do the nine behaviors in the previous question cause problems for your teenager:	No Problem	Minor Problem	Moderate Problem	Severe Problem
Getting along with family members	0	1	2	3
Getting along with other teenagers	0	1	2	3
Completing or returning homework	0	1	2	3
Performing academically in school	0	1	2	3
Controlling behavior in school	0	1	2	3
Feeling good about himself/herself	0	1	2	3

Appendix 5: Social Responsiveness Scale, Second Edition

School-Age Form

Response Sheet

SRS™ 2

Social Responsiveness Scale, Second Edition

John N. Constantino, MD

WPS unlocking potential

Child and Rater Information

Child s name	Gender	Date of rating	Assessment ID
	☐ Male ☐ Female		
School or clinic		Child s age in years	Grade
Rater s name	Relationship to rated individual		
	☐ Mother ☐ Father ☐ Other custodial adult ☐ Teacher ☐ Other specialist		

Instructions: For each question, please circle the number that best describes this child s behavior **over the past 6 months**	Not True	Sometimes True	Often True	Almost Always True
1. Seems much more fidgety in social situations than when alone.	1	2	3	4
2. Expressions on his or her face don t match what he or she is saying.	1	2	3	4
3. Seems self-confident when interacting with others.	1	2	3	4
4. When under stress, he or she shows rigid or inflexible patterns of behavior that seem odd.	1	2	3	4
5. Doesn t recognize when others are trying to take advantage of him or her.	1	2	3	4
6. Would rather be alone than with others.	1	2	3	4
7. Is aware of what others are thinking or feeling.	1	2	3	4
8. Behaves in ways that seem strange or bizarre.	1	2	3	4
9. Clings to adults, seems too dependent on them.	1	2	3	4
10. Takes things too literally and doesn t get the real meaning of a conversation.	1	2	3	4
11. Has good self-confidence.	1	2	3	4
12. Is able to communicate his or her feelings to others.	1	2	3	4
13. Is awkward in turn-taking interactions with peers (for example, doesn t seem to understand the give-and-take of conversations).	1	2	3	4
14. Is not well coordinated.	1	2	3	4
15. Is able to understand the meaning of other people s tone of voice and facial expressions.	1	2	3	4
16. Avoids eye contact or has unusual eye contact.	1	2	3	4
17. Recognizes when something is unfair.	1	2	3	4

continued on next page

Instructions: For each question, please circle the number that best describes this child s behavior **over the past 6 months**	Not True	Sometimes True	Often True	Almost Always True
18. Has difficulty making friends, even when trying his or her best.	1	2	3	4
19. Gets frustrated trying to get ideas across in conversations.	1	2	3	4
20. Shows unusual sensory interests (for example, mouthing or spinning objects) or strange ways of playing with toys.	1	2	3	4
21. Is able to imitate others actions.	1	2	3	4
22. Plays appropriately with children his or her age.	1	2	3	4
23. Does not join group activities unless told to do so.	1	2	3	4
24. Has more difficulty than other children with changes in his or her routine.	1	2	3	4
25. Doesn t seem to mind being out of step with or "not on the same wavelength" as others.	1	2	3	4
26. Offers comfort to others when they are sad.	1	2	3	4
27. Avoids starting social interactions with peers or adults.	1	2	3	4
28. Thinks or talks about the same thing over and over.	1	2	3	4
29. Is regarded by other children as odd or weird.	1	2	3	4
30. Becomes upset in a situation with lots of things going on.	1	2	3	4
31. Can t get his or her mind off something once he or she starts thinking about it.	1	2	3	4
32. Has good personal hygiene.	1	2	3	4
33. Is socially awkward, even when he or she is trying to be polite.	1	2	3	4
34. Avoids people who want to be emotionally close to him or her.	1	2	3	4
35. Has trouble keeping up with the flow of a normal conversation.	1	2	3	4
36. Has difficulty relating to adults.	1	2	3	4
37. Has difficulty relating to peers.	1	2	3	4
38. Responds appropriately to mood changes in others (for example, when a friend s or playmate s mood changes from happy to sad).	1	2	3	4
39. Has an unusually narrow range of interests.	1	2	3	4
40. Is imaginative, good at pretending (without losing touch with reality).	1	2	3	4
41. Wanders aimlessly from one activity to another.	1	2	3	4
42. Seems overly sensitive to sounds, textures, or smells.	1	2	3	4
43. Separates easily from caregivers.	1	2	3	4
44. Doesn t understand how events relate to one another (cause and effect) the way other children his or her age do.	1	2	3	4
45. Focuses his or her attention to where others are looking or listening.	1	2	3	4
46. Has overly serious facial expressions.	1	2	3	4
47. Is too silly or laughs inappropriately.	1	2	3	4
48. Has a sense of humor, understands jokes.	1	2	3	4
49. Does extremely well at a few tasks, but does not do as well at most other tasks.	1	2	3	4

ontinued on next page

Instructions: For each question, please circle the number that best describes this child s behavior **over the past 6 months**	Not True	Sometimes True	Often True	Almost Always True
50. Has repetitive, odd behaviors such as hand flapping or rocking.	1	2	3	4
51. Has difficulty answering questions directly and ends up talking around the subject.	1	2	3	4
52. Knows when he or she is talking too loud or making too much noise.	1	2	3	4
53. Talks to people with an unusual tone of voice (for example, talks like a robot or like he or she is giving a lecture).	1	2	3	4
54. Seems to react to people as if they are objects.	1	2	3	4
55. Knows when he or she is too close to someone or is invading someone s space.	1	2	3	4
56. Walks in between two people who are talking.	1	2	3	4
57. Gets teased a lot.	1	2	3	4
58. Concentrates too much on parts of things rather than seeing the whole picture. For example, if asked to describe what happened in a story, he or she may talk only about the kind of clothes the characters were wearing.	1	2	3	4
59. Is overly suspicious.	1	2	3	4
60. Is emotionally distant, doesn t show his or her feelings.	1	2	3	4
61. Is inflexible, has a hard time changing his or her mind.	1	2	3	4
62. Gives unusual or illogical reasons for doing things.	1	2	3	4
63. Touches others in an unusual way (for example, he or she may touch someone just to make contact and then walk away without saying anything).	1	2	3	4
64. Is too tense in social settings.	1	2	3	4
65. Stares or gazes off into space.	1	2	3	4

Appendix 6: Columbia-Suicide Severity Rating Scale

Children's Baseline/Screening:

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* _____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe	Most Severe
Frequency *How many times have you had these thoughts?* *Write response*_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____	____

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS—Children's Baseline/Screening (Version 6/23/10)
Page 2 of 2

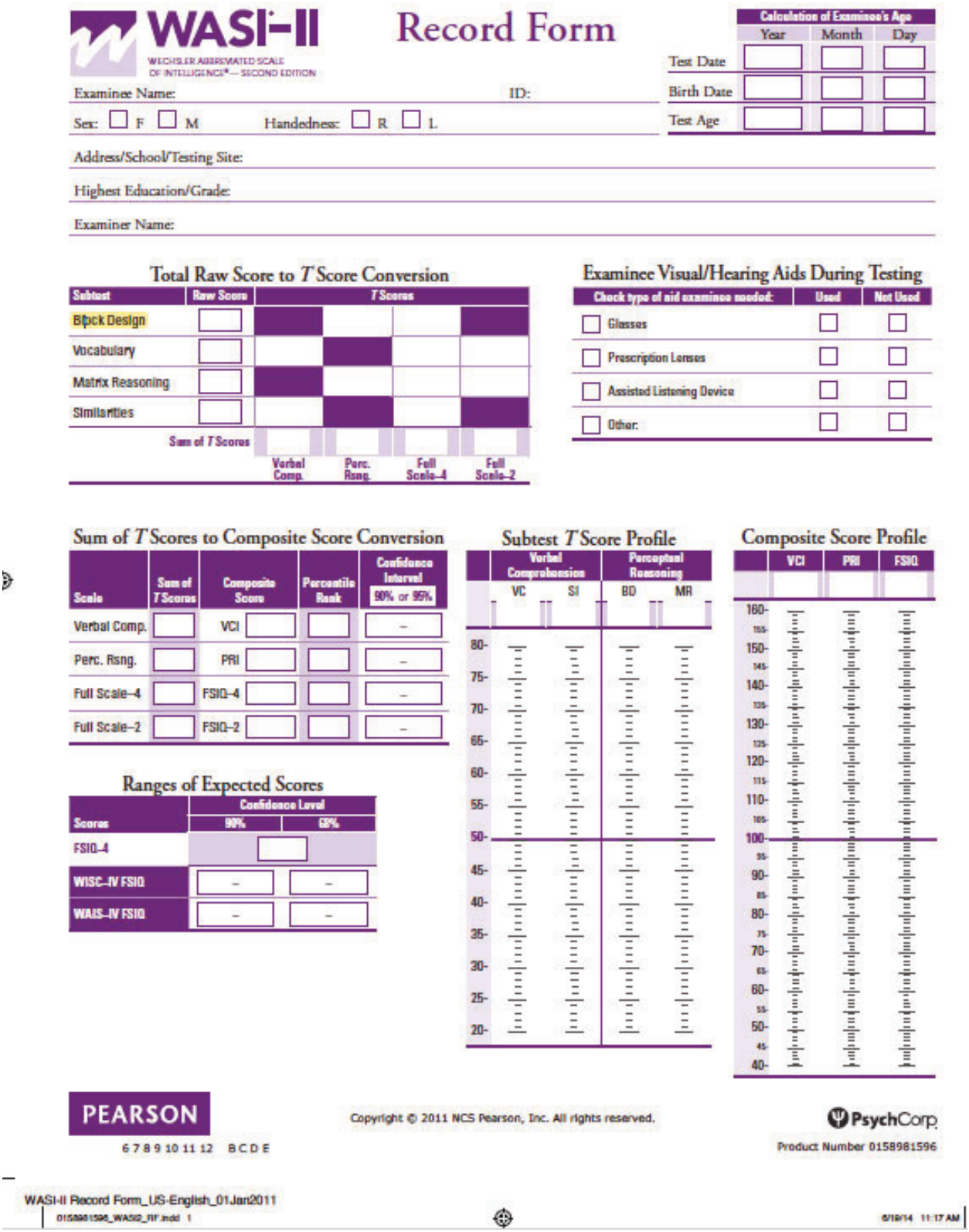
Children's Since Last Visit (Post-baseline):

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 7: Weschler Abbreviated Scale of Intelligence – Second Edition



WASI-II
WECHSLER ABBREVIATED SCALE OF INTELLIGENCE®—SECOND EDITION

Record Form

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Examinee Name: ID:

Sex: ☐ F ☐ M Handedness: ☐ R ☐ L

Address/School/Testing Site:

Highest Education/Grade:

Examiner Name:

Total Raw Score to *T* Score Conversion

Subtest	Raw Score	*T* Scores			
Block Design					
Vocabulary					
Matrix Reasoning					
Similarities					
Sum of *T* Scores					
		Verbal Comp.	Perc. Rsng.	Full Scale–4	Full Scale–2

Examinee Visual/Hearing Aids During Testing

Check type of aid examinee needed:	Used	Not Used
☐ Glasses	☐	☐
☐ Prescription Lenses	☐	☐
☐ Assisted Listening Device	☐	☐
☐ Other:	☐	☐

Sum of *T* Scores to Composite Score Conversion

Scale	Sum of *T* Scores	Composite Score	Percentile Rank	Confidence Interval 90% or 95%
Verbal Comp.		VCI		–
Perc. Rsng.		PRI		–
Full Scale–4		FSIQ–4		–
Full Scale–2		FSIQ–2		–

Ranges of Expected Scores

Scores	Confidence Level 90%	68%
FSIQ–4		
WISC–IV FSIQ	–	–
WAIS–IV FSIQ	–	–

Subtest *T* Score Profile

Verbal Comprehension		Perceptual Reasoning	
VC	SI	BD	MR

80 75 70 65 60 55 50 45 40 35 30 25 20

Composite Score Profile

VCI	PRI	FSIQ

160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40

PEARSON
6 7 8 9 10 11 12 B C D E

PsychCorp
Product Number 0158981596

WASI-II Record Form_US-English_01Jan2011
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1. Block Design

(Time limit: See item)

Start — Ages 6–8: Item 1; Ages 9–90: Item 3

Reverse — Ages 9–90: Does not obtain a perfect score on *either* Item 3 or Item 4, administer the preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue — After 2 consecutive scores of 0.

Stop — Ages 6–8: After Item 11.

Record & Score — Items 1–4: Score 0, 1, or 2 points. Items 5–12: Score 0, 4, 5, 6, or 7 points.

		Design	Presentation Method	Time Limit	Completion Time		Constructed Design		Score				
6–8	1.	Examinee / Examiner	Model and Picture	30"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	2.		Model and Picture	30"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
9–90	3.		Model and Picture	45"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	4.		Model and Picture	45"	Trial 1	Trial 2	Trial 1	Trial 2	0	1	2		
	5.		Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	6.		Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	7.		Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	8.		Picture	60"					0	21–60 4	16–20 5	11–15 6	1–10 7
	9.		Picture	120"					0	71–120 4	46–70 5	31–45 6	1–30 7
	10.		Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
	11.		Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
6–8 STOP	12.		Picture	120"					0	61–120 4	46–60 5	36–45 6	1–35 7
	13.		Picture	120"					0	101–120 4	81–100 5	56–80 6	1–55 7

Maximum Raw Score
Ages 6–8: 57
Ages 9–90: 71

Block Design Total Raw Score ☐

2. Vocabulary

Start
Ages 6–90: Item 4

Reverse
Ages 6–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in **reverse** order until two consecutive perfect scores are obtained.

Discontinue
After 3 consecutive scores of 0.

Stop
Age 6: After Item 22.
Ages 7–11: After Item 25.
Ages 12–14: After Item 28.

Record & Score
Items 1–3: Score 0 or 1 point.
Items 4–5: Score 0 or 2 points.
Items 6–31: Score 0, 1, or 2 points.
See the Manual for sample responses.

	Item	Response	Score
	1. Fish		0 1
	2. Shovel		0 1
	3. Shell		0 1
6–90	†4. Shirt		0 2
	5. Car		0 2
	6. Lamp		0 1 2
	7. Bird		0 1 2
	8. Tongue		0 1 2
	9. Pet		0 1 2
	10. Lunch		0 1 2
	11. Bell		0 1 2
	12. Calendar		0 1 2
	13. Alligator		0 1 2
	14. Dance		0 1 2

†If the examinee provides a 2-point response that requires feedback or gives an incorrect (0 point) response, provide corrective feedback as instructed in the Manual.

continue

WASI–II Record Form 3

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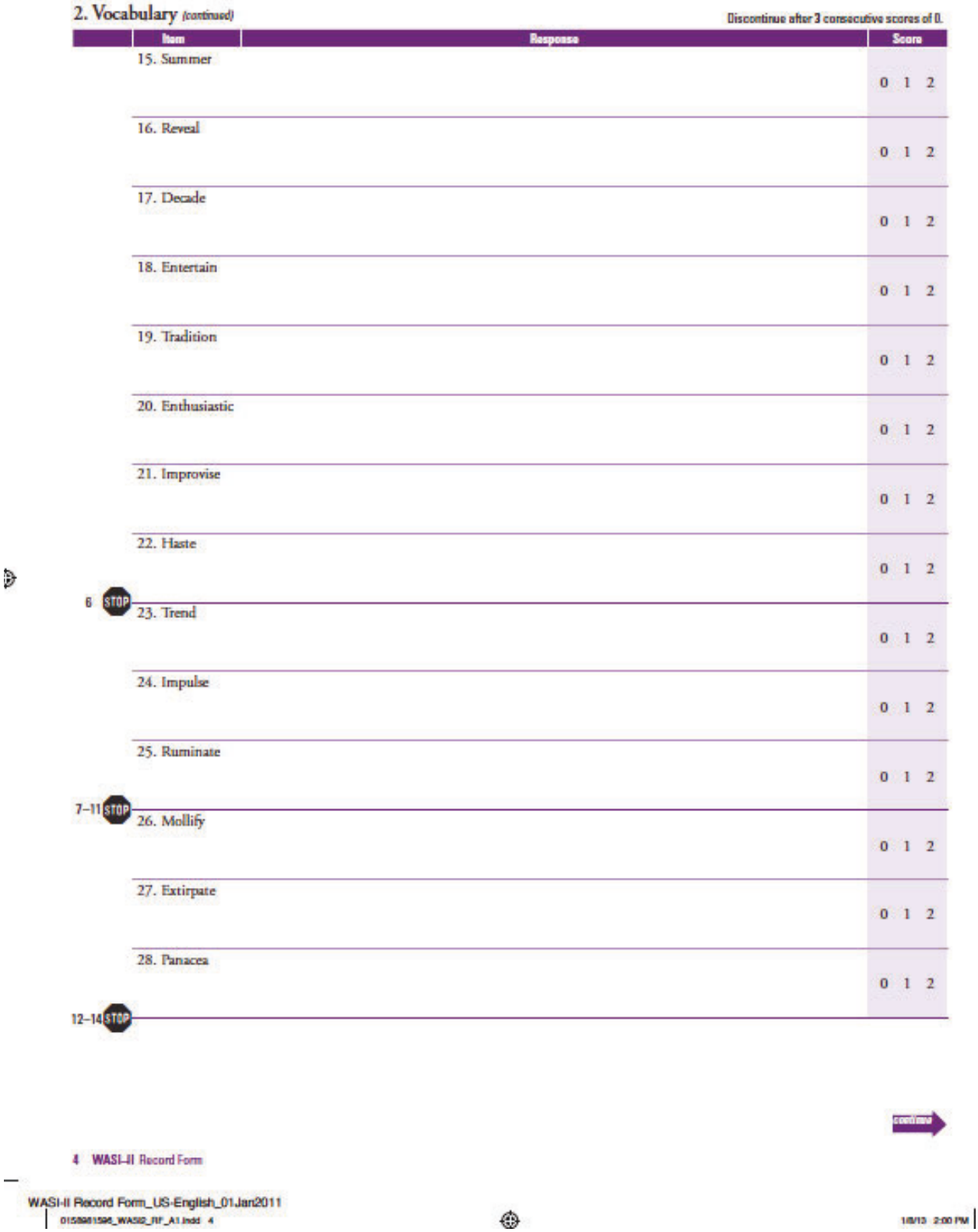

2. Vocabulary (continued)

Discontinue after 3 consecutive scores of 0.

	Item	Response	Score
	15. Summer		0 1 2
	16. Reveal		0 1 2
	17. Decade		0 1 2
	18. Entertain		0 1 2
	19. Tradition		0 1 2
	20. Enthusiastic		0 1 2
	21. Improvise		0 1 2
	22. Haste		0 1 2
6 STOP	23. Trend		0 1 2
	24. Impulse		0 1 2
	25. Ruminate		0 1 2
7–11 STOP	26. Mollify		0 1 2
	27. Extirpate		0 1 2
	28. Panacea		0 1 2
12–14 STOP			

4 WASI-II Record Form

WASI-II Record Form_US-English_01Jan2011

2. Vocabulary (continued)

Discontinue after 3 consecutive scores of 0.

Item	Response	Score
29. Perfunctory		0 1 2
30. Insipid		0 1 2
31. Pavid		0 1 2

Maximum Raw Score
Age 6: 41
Ages 7–11: 47
Ages 12–14: 53
Ages 15–90: 59

Vocabulary Total Raw Score ____

3. Matrix Reasoning

Start
Ages 6–8: Sample Items A & B, then Item 1
Ages 9–90: Sample Items A & B, then Item 4

Reverse
Ages 9–90: Does not obtain a perfect score on either Item 4 or Item 5, administer the preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue
After 3 consecutive scores of 0.

Stop
Ages 6–8: After Item 24.

Record & Score
Score 0 or 1 point.
Correct responses are in color.

	Item	Response	Score
6–90	SA.	1 **2** 3 4 5	
	SB.	1 2 **3** 4 5	
6–8	1.	1 **2** 3 4 5	0 1
	2.	**1** 2 3 4 5	0 1
	3.	1 2 **3** 4 5	0 1
9–90	4.	**1** 2 3 4 5	0 1
	5.	1 2 3 4 **5**	0 1
	6.	**1** 2 3 4 5	0 1
	7.	1 2 **3** 4 5	0 1
	8.	1 2 **3** 4 5	0 1
	9.	1 2 3 **4** 5	0 1
	10.	1 **2** 3 4 5	0 1
	11.	1 2 **3** 4 5	0 1
	12.	1 2 3 **4** 5	0 1
	13.	**1** 2 3 4 5	0 1
	14.	1 2 3 **4** 5	0 1
	15.	1 **2** 3 4 5	0 1
	16.	1 2 3 4 **5**	0 1
	17.	1 2 3 **4** 5	0 1
	18.	1 **2** 3 4 5	0 1
	19.	1 2 3 **4** 5	0 1
	20.	1 **2** 3 4 5	0 1
	21.	1 2 **3** 4 5	0 1
	22.	1 2 **3** 4 5	0 1
	23.	**1** 2 3 4 5	0 1
6–8 STOP	24.	1 2 3 **4** 5	0 1
	25.	1 2 3 **4** 5	0 1
	26.	1 **2** 3 4 5	0 1
	27.	1 2 3 4 **5**	0 1
	28.	1 2 3 4 **5**	0 1
	29.	**1** 2 3 4 5	0 1
	30.	1 **2** 3 4 5	0 1

Maximum Raw Score
Ages 6–8: 24
Ages 9–90: 30

Matrix Reasoning Total Raw Score ____

4. Similarities

Start
Ages 6–8: Item 1
Ages 9–90: Item 4

Reverse
Ages 9–90: Does not obtain a perfect score on either Item 4 or Item 5, administer the preceding items in reverse order until two consecutive perfect scores are obtained.

Discontinue
After 3 consecutive scores of 0.

Stop
Ages 6–8: After Item 22.

Record & Score
Items 1–3: Score 0 or 1 point. Correct responses are in color.
Items 4–5: Score 0 or 2 points.
Items 6–24: Score 0, 1, or 2 points. See Manual for sample responses.

	Picture Item	Response	Score	Picture Item	Response	Score	Picture Item	Response	Score
6–8	†1.	1 2 **3** 4	0 1	2.	1 2 3 **4**	0 1	3.	1 **2** 3 4	0 1

	Verbal Items	Response	Score
9–90	§† 4. Green–Blue		0 2
	§† 5. Square–Triangle		0 2
	6. Cow–Bear		0 1 2
	7. Shirt–Jacket		0 1 2
	8. Pen–Crayon		0 1 2
	9. Hat–Umbrella		0 1 2
	10. Airplane–Bus		0 1 2
	11. Door–Window		0 1 2
	12. Child–Adult		0 1 2

§If the examinee provides a response that suggests he or she does not understand the task, provide the specified prompts in the Manual.
†If the examinee provides a 2-point response that requires feedback or provides an incorrect (0 point) response, provide corrective feedback as instructed in the Manual.

continue

4. Similarities (continued)

Discontinue after 3 consecutive scores of 0.

Verbal Items	Response	Score
13. Shoulder–Ankle		0 1 2
14. Love–Hate		0 1 2
15. Smooth–Rough		0 1 2
16. Hand–Flag		0 1 2
17. Wall–Line		0 1 2
18. Heat–Wind		0 1 2
19. More–Less		0 1 2
20. Shadow–Echo		0 1 2
21. Tradition–Habit		0 1 2
22. Peace–War		0 1 2
23. Time–Progress		0 1 2
24. Memory–Practice		0 1 2

6–8 STOP

Maximum Raw Score
Ages 6–8: 41
Ages 9–90: 45

Similarities Total Raw Score

WASI–II Record Form 7

WASI-II Record Form_US-English_01Jan2011

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1/8/15 2:00 PM

WASI-II
WECHSLER ABBREVIATED SCALE OF INTELLIGENCE®— SECOND EDITION

Examinee Name: Age:

Parent/Guardian Name:

Examiner Name:

Record Form

Behavioral Observations

Referral source/Reason for referral/Presenting complaint(s)

Physical appearance

Language (e.g., first/native language, other language, English fluency, expressive and receptive language ability, articulation)

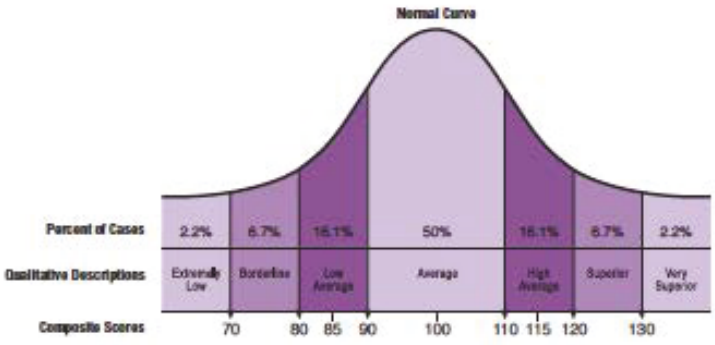
Attention and concentration

Attitude toward testing (e.g., rapport, eager to speak, working habits, interest, motivation, reaction to success/failure)

Affect/Mood

Unusual behaviors/Verbalizations (e.g., perseverations, stereotypic movements, bizarre and atypical verbalizations)

Other notes



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800.627.7271 www.PearsonClinical.com

WASI-II Record Form_US-English_01Jan2011
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Appendix 8: Protocol Version 2.0 – Summary of Changes

[redacted]

Section	Version 1.0	Version 2.0
[redacted]	[redacted]	[redacted]

Section	Version 1.0	Version 2.0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Version 1.0	Version 2.0
		ASD, respectively, as demonstrated by scores at or

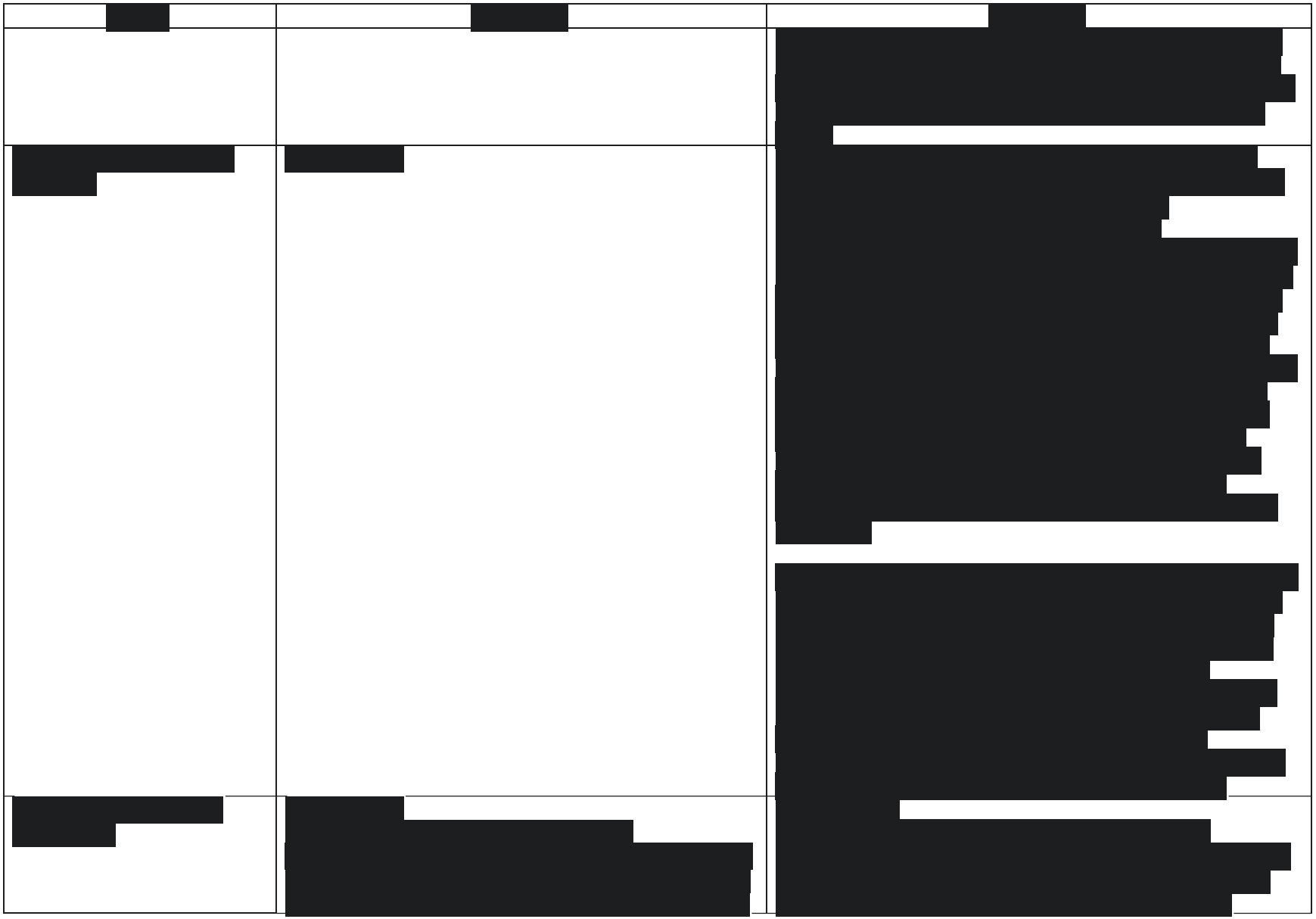
Section	Version 1.0	Version 2.0
[redacted]	[redacted]	[redacted]

Section	Version 1.0	Version 2.0
Table 3	[redacted]	[redacted]

Section	Version 1.0	Version 2.0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Version 1.0	Version 2.0
Section		

Appendix 9: Protocol Version 3.0 – Summary of Changes



REVISION HISTORY

[redacted]

DOCUMENT ELECTRONIC SIGNATURES

[redacted]