COVER PAGE - PROTOCOL

Protocol Number:	812P412
Title:	A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered with Psychostimulants in Children and Adolescents (6 to 17 years of age) with Attention-Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
Protocol Version:	3.0
Date:	01Feb2022
NCT:	NCT04786990

TITLE PAGE

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Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
IND number:	108,864
Investigational Medicinal Product:	Viloxazine extended-release capsule
Indication:	Attention-deficit/hyperactivity disorder (ADHD)
Medical Monitor	[redacted]
Phase:	4
Protocol Version:	3.0
Date:	01Feb2022
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP) and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature	Date

Print Name

SUPERNUS PHARMACEUTICALS, INC. PROTOCOL APPROVAL PAGE

Authors:

[redacted]

Reviewers:

[redacted]

Approvers:

[redacted]

CLINICAL PROTOCOL SYNOPSIS

Sponsor: Supernus Pharmaceuticals, Inc.	
Name of Product: SPN-812 (viloxazine extended-release capsule)	**Name of Active Ingredient:** Viloxazine hydrochloride
Protocol Number: 812P412	**Phase of Development:** 4
Full Title of Study: A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered with Psychostimulants in Children and Adolescents (6 to 17 years of age) with Attention-Deficit/Hyperactivity Disorder (ADHD)	
Number of Study Sites: Up to 20 sites in the United States (US)	
Number of Subjects: Approximately 60 subjects will enroll, and approximately 50 subjects are expected to complete study	
Indication: Attention-deficit/hyperactivity disorder (ADHD)	

Objectives:

Primary Objective:

- To evaluate the safety and tolerability of AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age).

Secondary Objectives:

1. To evaluate the safety and tolerability of AM versus PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age).
2. To evaluate the efficacy of AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on:
   i. ADHD symptoms as measured by the Investigator-rated ADHD-RS-5 (IR-ADHD-RS-5).
   ii. the global assessment of severity for ADHD as measured by the Clinical Global Impression-Severity of Illness (CGI-S) scale.
   iii. the global assessment of improvement for ADHD as measured by the Clinical Global Impression-Improvement (CGI-I) scale.
   iv. sleep as measured by the Sleep Disturbance Scale for Children (SDSC).
   v. home functioning in the morning and evening as measured by the Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R).
3. To evaluate the efficacy of AM versus PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on:
   i. ADHD symptoms as measured by the IR-ADHD-RS-5.
   ii. the global assessment of severity as measured by the CGI-S scale.
   iii. the global assessment of improvement for ADHD as measured by the CGI-I scale.
   iv. sleep as measured by the SDSC.
   v. home functioning in the morning and evening as measured by the WPREMB-R.

4. To evaluate efficacy in the morning for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning Parent-Rated-ADHD-RS-5 (PR-ADHD-RS-5).
5. To evaluate efficacy in the evening for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Evening PR-ADHD-RS-5.
6. To evaluate duration of efficacy within day (morning versus evening) for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning and Evening PR-ADHD-RS-5.

Endpoints:

Primary Endpoints:

- Safety endpoints for Weeks 1-4 (AM dosing) and Weeks 5-8 (PM dosing) are adverse events (AEs), clinical safety laboratory tests, vital signs, weight, height, BMI, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Secondary Endpoints:

1. Safety endpoints for Weeks 1-4 (AM dosing) versus Weeks 5-8 (PM dosing) are AEs, clinical safety laboratory tests, vital signs, weight, height, BMI, ECGs, physical examination, and the C-SSRS.
2. Secondary endpoints for evaluating the efficacy of SPN-812 at Week 4 (AM dosing) and Week 8 (PM dosing) are:
   i. Change from baseline (CFB) in the IR-ADHD-RS-5 Total Score at Week 4 and Week 8.
   ii. CFB in CGI-S score at Week 4 and Week 8.
   iii. CGI-I score at Week 4 and Week 8.
   iv. CFB in SDSC total score and subscale scores at Week 4 and Week 8
   v. CFB in WPREMB-R total score and subscale scores at Week 4 and Week 8.
3. Secondary endpoints for evaluating the efficacy of SPN-812 Week 4 (AM dosing) versus Week 8 (PM dosing) are:
   i. CFB in the IR-ADHD-RS-5 Total Score at Week 4 versus Week 8.
   ii. CFB in CGI-S score at Week 4 versus Week 8.
   iii. CGI-I score at Week 4 versus Week 8.
   iv. CFB in SDSC total score and subscale scores at Week 4 versus Week 8
   v. CFB in WPREMB-R total score and subscale scores at Week 4 versus Week 8.
4. The CFB in the Morning PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).
5. The CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).
6. The CFB in the Morning PR-ADHD-RS-5 Total Score versus the CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).

Study Design:

This is an open-label, flexible-dose, safety study of SPN-812 in pediatric patients diagnosed with ADHD per Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5™) criteria who are experiencing an inadequate efficacy response to psychostimulant therapy. Approximately 60 subjects will enroll, and approximately 50 subjects are expected to complete this study. During screening period (up to 4 weeks), subjects will continue their psychostimulant ADHD treatment. Following the screening period, eligible subjects will receive SPN-812 with their current psychostimulant treatment for 8 weeks. The subject's parent/guardian will record a daily medication diary between screening and end of study (EOS). Total duration of the study between screening visit and EOS visit is up to 12 weeks.

At the Screening Visit (Visit 1), subjects will undergo an initial screening evaluation for eligibility including confirmation of prior ADHD diagnosis and inadequate response to current psychostimulant treatment. Subjects must washout of any prohibited medications at least 7 days prior to Baseline Visit (Visit 2, Day 1). At Visit 2, the IR-ADHD-RS-5 scale, CGI-S, SDSC, and WPREMB-R will be administered, safety evaluations will be performed, and inclusion/exclusion criteria will be reviewed to confirm eligibility.

Subject who are eligible to participate will begin dosing SPN-812 at Visit 2 (Day 1). Subjects will dose SPN-812 daily in the morning (AM) during Weeks 1-4, and then dose SPN-812 daily in the evening (PM) during Weeks 5-8. Children (6-11 years of age) will begin SPN-812 dosing at 100 mg/day during Week 1 of Treatment period and may be titrated up or tapered down in increments/decrements of 100 mg/day per week between 100 and 400 mg/day during Weeks 2 to 8 of Treatment. Adolescents (12-17 years of age) will begin SPN-812 dosing at 200 mg/day during Week 1 of Treatment period and may be titrated up or tapered down in increments/decrements of 100-200 mg/day per week between 100 and 600 mg/day during Weeks 2 to 8 of Treatment. All subjects must continue taking stable dose (mg) of psychostimulant medication at least 5 days per week during the 8-week SPN-812 treatment period. The subject's psychostimulant medication dose (mg) cannot be increased during 8-week SPN-812 treatment, but it may be decreased once; if any further adjustment is required due to safety reasons, the investigator must inform the medical monitor and sponsor. A urine drug screen will be performed at every study visit (V1-V10) to confirm use of psychostimulant medication, and (in addition to clinical laboratory testing) a single confirmatory blood sample will be collected at every study visit (V1-V10) to determine psychostimulant and viloxazine/its metabolite concentrations.

During the Treatment period, subjects will complete weekly study visits (Visits 3-10) during the Treatment Period (Days 2-57). At each post-baseline study visit, safety evaluations will be conducted, efficacy assessments (IR-ADHD-RS-5, CGI-S, CGI-I) will be administered, drug compliance will be evaluated, and subject will return bottle of study medication and receive next bottle of study medication, if required. SDSC and WPREMB-R will only be administered at Visits 6 and 10 during Treatment Period. In addition, parent/guardian must complete a 'Morning' PR-ADHD-RS-5 and 'Evening' PR-ADHD-RS-5 one or two days prior to Study Visits 2, 6, and 10. Parent/guardian will rate their child's behavior based upon interactions with their child during the morning hours in the past week and then rate their child's behavior based upon interactions with their child during the evening hours in the past week.

Subjects who discontinue early from the study will undergo safety evaluations. Subjects will receive a telephone call approximately 1 week after EOS (or last dose of SPN-812) for final safety assessments.

Duration of Subject's Participation:

Following the Screening period (up to 4 weeks), subjects will be treated with SPN-812 for 8 weeks. The total duration of the study between the screening visit and the end of the Treatment Period/EOS visit is up to 12 weeks.

Investigational Medicinal Products, Reference Therapy, Doses and Mode of Administration

Study Medication (SM): SPN-812 (viloxazine extended-release capsule)

Dose levels:

- Children (6-11 years of age): 100 to 400 mg/day; titrate at 100 mg/day per week
- Adolescents (12-17 years of age): 100 to 600 mg/day; titrate at 100 or 200 mg/day per week

Reference Therapy: not applicable

Mode of Administration: Single oral dose daily, with or without food, as either an intact capsule or sprinkling the content of capsule on one tablespoon of applesauce followed by drinking water after having ingested the SM/applesauce mix. Subjects will dose SPN-812 daily in the morning during Weeks 1-4 (AM Dosing), and then dose SPN-812 daily in the evening during Weeks 5-8 (PM Dosing).

Statistical Methodology

All statistical analyses will be based on the safety population. The Safety Population is all subjects enrolled into the study who receive at least one dose of SPN-812. Summary statistics for continuous variables will include sample size (N), mean, median, standard deviation, minimum, and maximum. Summary statistics for discrete variables will be presented in terms of frequencies and percentages in the safety population.

Each efficacy endpoint (ADHD-RS-5 [investigator-rated (IR) and parent-rated (PR)], CGI-S, CGI-I, SDSC and WPREMB-R) will be listed and summarized by group of the optimized dose, as applicable. Total scores for each efficacy scale will be summarized by dose and visit and will be examined for trends.

There are approximately 50 subjects expected to complete this study. Based on an early discontinuation rate of 20%, approximately 60 subjects would need to be enrolled. Based on a screen failure rate of 40%, approximately 100 subjects will be screened to enroll 60 subjects.

Inclusion Criteria:

1. Is male or female, 6 to ≤17 years and 9 months of age at screening.
2. Parent(s)/legal guardian(s) is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained by parent(s)/legal guardian(s) and informed assent obtained from the subject, if applicable.

4. Subject and parent(s)/legal guardian(s) are willing and able to comply with all of the procedures and requirements defined in the protocol, including parents(s)/legal guardian(s) oversight of morning and evening dosing of the SPN-812 and recording a daily medication/dosing diary for psychostimulant and/or SPN-812 during the study.
5. Has lived with the same parent(s)/legal guardian(s) at same residence for at least the last 6 months prior to screening.
6. Has a primary diagnosis of ADHD (inattentive, hyperactive, or combined presentation) confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) at screening.
7. Is currently on a single, stable psychostimulant regimen (see Inclusion Criterion 8 for definition) for treatment of ADHD with a partial, but inadequate efficacy response to at least 2 weeks of treatment with a psychostimulant (methylphenidate or amphetamine) prior to screening. An inadequate response is defined as an investigator-rated ADHD-RS-5 Total score ≥24 and a CGI-S score ≥3 (mildly ill or worse) at Screening and Baseline. Subjects taking additional medication for ADHD (e.g., nonstimulant) are excluded.
8. Is currently and expecting to continue and remain on a stable psychostimulant regimen throughout the study. A stable stimulant regimen is defined as taking dose at least 5 days per week (morning), no significant change in dose or dosing frequency at least 2 weeks prior to baseline (Visit 2), and the investigator believes the subject's psychostimulant dose is optimized.
9. Is functioning at an age-appropriate level intellectually, as judged by the Investigator.
10. Is a child (6-11 years of age) with a body weight of at least 20 kg at screening or is an adolescent (12-17 years of age) with a body weight of at least 35 kg at screening.
11. Has a resting (sitting) blood pressure (BP) and pulse rate measurement within the 95th percentile for age, sex, and height.
12. Is considered medically healthy by the Investigator via assessment of physical examination, medical and psychiatric histories, clinical laboratory tests, vital signs, and electrocardiogram (ECG).
13. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use/practice one of the following acceptable, highly effective contraceptive methods beginning during the screening period prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed during screening period prior to first dose of SM
    b. Surgically sterile male partner (e.g., vasectomized partner is sole partner)
    c. Barrier method: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    d. Established use of oral, injected, or implanted hormonal methods of contraception

    With approval by the Investigator, subjects' parents or legal guardians may select abstinence as a form of birth control if deemed more appropriate. For the purposes of this study, all females are considered to be of childbearing potential unless they are confirmed by the Investigator to be premenarchal, biologically sterile, or surgically sterile (e.g., hysterectomy with bilateral oophorectomy, tubal ligation).

14. Adolescent males, if sexually active, must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of SM, or
    b. Have been surgically sterilized prior to the Screening Visit.

Exclusion Criteria:

1. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior to screening.
2. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
3. Is a female subject who is pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable contraceptive methods throughout the study.
4. Has history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication (SPN-812).
5. Has history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. a current diagnosis of a major neurological disorder;
    b. seizures, seizure disorder or seizure-like events;
    c. history of seizure disorder within the immediate family (siblings, parents); or
    d. encephalopathy

    Note: Febrile seizures are not exclusionary and will be assessed on a case-by-case basis. If for any reason the subject received medication for a febrile seizure or has a history of complex febrile seizures, this will be exclusionary.
6. Has current diagnosis or history of major psychiatric disorders or intellectual disabilities other than ADHD per DSM-5 criteria (including schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, post-traumatic stress disorder, obsessive-compulsive disorder, severe oppositional defiant disorder, conduct disorder, and disruptive mood dysregulation disorder, and autism spectrum disorders). The following is not exclusionary:
    a. a history of mild social anxiety disorder or generalized anxiety disorder according to DSM-5 criteria;
    b. a history of mild to moderate ODD according to DSM-5 criteria;
    c. a history of Major Depressive Disorder, if he/she has not experienced a major depressive disorder episode or required psychiatric counselling; or pharmacotherapy within the 6 months prior to screening.
7. Has a known history of physical, sexual, or emotional abuse in the last year prior to screening.

8. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
9. Has a current diagnosis of drug abuse or dependence disorder within the 12 months prior to screening, has a history of drug abuse or dependence disorder or has an immediate family member living at the study participant's home who has current diagnosis drug abuse or dependence disorder (per DSM-5 criteria).
10. Evidence of suicidality (defined as either active suicidal plan/intent or active suicidal thoughts, or more than one lifetime suicide attempt) within the six months before Screening or at Screening.
11. Has positive findings on C-SSRS for suicidal ideation or behaviors at screening. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS within the 6 months prior to screening.
12. Is currently using, or has a positive result on the urine drug screening for, drugs of abuse (alcohol, amphetamine, barbiturates, benzodiazepines, cannabis [THC], cocaine, cotinine, methadone, methamphetamine [including ecstasy], methylphenidate, phencyclidine, propoxyphene, and opiates) with the exception of the psychostimulant prescribed for the treatment of ADHD.
13. Is unable to discontinue all prohibited medication at least 7 days prior to baseline.
14. Has body mass index (BMI) greater than 95th percentile for her/his appropriate age and gender (per CDC's gender specific "BMI-for-age percentiles" charts).
15. Has a current diagnosis of significant systemic disease.
16. Has uncontrolled thyroid disorder defined as thyroid stimulating hormone ≤ 0.8 x the lower limit of normal or ≥ 1.25 x the upper limit of normal for the reference laboratory range.
17. Has resting (sitting) blood pressure and pulse rate greater than the 95th percentile for age and gender.
18. Has a known personal history, or presence, of structural cardiac abnormalities, cardiovascular or cerebrovascular disease, serious heart rhythm abnormalities, syncope, tachycardia, cardiac conduction problems (e.g., clinically significant heart block or QT interval prolongation: QTc >0.44 seconds), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia.
19. Has any clinically significant abnormal clinical laboratory test, urine test, electrocardiogram (ECG) result, vital signs or physical examination finding at screening that, in the opinion of the Investigator, would interfere with the safety of the subject (see Note below).

20. Has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments.
21. Has or has had one or more medical conditions considered clinically significant/relevant by the Investigator in the context of the study (e.g., cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia, bradycardia [pulse < 70 bpm (6-11 years), pulse < 60 bpm (12-17 years)], tachycardia [pulse > 120 bpm (6-11 years); pulse > 100 bpm (12-17 years)], respiratory disease, hepatic impairment or renal insufficiency, metabolic disorder, endocrine disorder, gastrointestinal disorder, hematological disorder, infectious disorder, any clinically significant immunological condition, and/or dermatological disorder.
22. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
23. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
24. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 28 days or 5 half-lives prior to Baseline Visit (Day 1) (whichever is longer) or anticipated for the duration of the study.
25. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.
26. Has an allergy to applesauce and cannot swallow capsules whole.
27. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Note: Repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time for each test during screening period, at the discretion of the Investigator, as long as the repeat test result is available within the 28-day screening period to determine eligibility.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-IV/5	ADHD Rating Scale 4th Edition/5th Edition
ADR	Adverse drug reaction
AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomical-Therapeutic-Chemical (code)
$AUC_{0\text{-}tau}$	Area under the concentration-time curve
BMI	Body mass index
CAARS	Conners Adult ADHD Rating Scale
CFB	Change from Baseline
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity of Illness
CGI-I	Clinical Global Impression-Improvement
CI	Confidence interval
CL/F	Oral clearance
Cmax	Maximum observed concentration
CRA	Clinical Research Associate
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DDI	Drug-drug interaction
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Text Revision)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
ECI-4	Early Childhood Inventory-4
eCRF	Electronic case report form
EOS	End of study
ER	Extended-release
ET	Early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IR-ADHD-RS-5	Investigator-rated ADHD-RS-5 version
IR	Immediate release
IRB	Institutional Review Board
IWRS	Interactive web response system
LLOQ	Lower limit of quantitation
LS	Least square

MedDRA	Medical Dictionary for Regulatory Activities
MINI KID	Mini International Neuropsychiatric Interview for Children and Adolescents
OLE	Open-label extension
PK	Pharmacokinetics
PPK	Population pharmacokinetics
PP	Per protocol
PR-ADHD-RS-5	Parent-rated ADHD-RS-5 version
PT	Preferred Term
QD	Once a day
QTcF	QT interval corrected using Fridericia's method
SADR	Suspected adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDSC	Sleep Disturbance Scale for Children
SOC	System Organ Class
SOP	Standard operating procedure
SM	Study medication
SNMA	Serotonin norepinephrine modulating agent
TEAE	Treatment-emergent adverse event
USA	United States of America
Vd/F	Apparent volume of distribution
VLX	Viloxazine
WHO-DD	World Health Organization Drug Dictionary
WPREMB-R	Weekly Parent Rating of Evening/Morning Behavior-Revised
5HVLX-gluc	5-hydroxy-viloxazine glucuronide

1 INTRODUCTION

1.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric condition characterized by the existence of persistent (≥ 6 months) behavioral symptom(s) of inattention and/or hyperactivity/impulsivity that is (are) not consistent with expected level of developmental and that have an adverse impact on multiple aspects of an individual's daily life and functioning, including, but not limited to relationships with family members and others, social interactions and academic/occupational performance. ADHD is mostly identified/diagnosed in children and adolescent. As such, it has been recommended that any child between 4 and 18 years of age who exhibits symptoms of ADHD be administered a thorough, systematic assessment (and those diagnosed in childhood may likely exhibit some significant ADHD symptoms (inattention) into adulthood. Symptoms of ADHD may first be observed in younger, preschool-age children (>3 to < 6 years of age). Epidemiological data suggest that ADHD affects up to 8% of children in the United States of America (USA), while the estimated prevalence in the adult population is between 0.3% and 5% (McCann and Roy-Byrne, 2004). The standard pharmaceutical treatments for ADHD include psychostimulants, non-stimulants, and antidepressants. Stimulants (e.g., methylphenidate, amphetamine) are the first-line pharmacotherapies for the treatment of ADHD. However, 10% to 30% of patients (i.e., children and adults) do not adequately respond to stimulants or experience intolerable adverse events (e.g., decreased appetite, sleep problems, headaches) (Briars and Todd, 2016).

SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, norepinephrine reuptake inhibitor. The active substance in SPN-812 is viloxazine, whose mechanism of action is multimodal with antagonistic activity observed at 5-HT2B and agonistic activity at 5-HT2C receptors, as well as weaker antagonistic effects at ADRα1B, ADRβ2 and 5-HT7 receptors. Additionally, SPN-812 acts as a modulator with inhibitory effects at the norepinephrine reuptake transporter. Viloxazine was previously marketed in several European countries as an antidepressant as an immediate-release (IR) product. An extended-release (ER) formulation of viloxazine, SPN-812, has been developed by Supernus to prolong the release and absorption of viloxazine post-administration, thereby minimizing fluctuations in plasma drug levels and allowing longer dosing intervals for a drug with a relatively short half-life. SPN-812 was developed for potential use in the treatment of subjects with ADHD, based on the pharmacological properties and favorable safety profile and the current unmet medical need for effective long-acting, nonstimulant ADHD treatment in children and adolescents. SPN-812 is being evaluated in the current study for potential use in the treatment of ADHD in adults based on the pharmacological properties and favorable safety profile of viloxazine.

1.2 Clinical Information

The safety, pharmacokinetics (PK) and drug-drug interactions for the IR and ER formulations of SPN-812 have been evaluated in multiple Phase 1 studies in healthy adults. As of April 2019, a number of studies evaluating the efficacy and safety of SPN-812 treatment for ADHD in pediatric and adult populations have been completed, including one Phase 2 study in adults (18 to 65 years of age; 812P201), one pediatric Phase 2 in children (6 to 12 years of age; 812P202), and four pediatric Phase 3 studies, two in children (6 to 11 years of age; 812P301 and 812P303) and two in adolescents (12 to 17 years of age; 812P302 and 812P304). In addition, there is an ongoing pediatric open-label extension (OLE) safety study in children and adolescents (6 to 17 years of age; 812P310). Key findings from the completed Phase 2 and Phase 3 studies are summarized below. Additional details are provided in the SPN-812 Investigator's Brochure.

1.2.1 Phase 1 Studies

Phase 1 studies include comparison of single and two-bead SPN-812 extended release (ER) formulations to an SPN-812 immediate release (IR) formulation at single and multiple doses (812P102 and 812P103, respectively), evaluation of food and sprinkling effects (812P105), drug-drug interactions (DDIs) on CYP1A2, 2D6, and 3A4 substrates with evaluation of SPN-812 ER metabolism in CYP2D6 poor metabolizers vs. CYP2D6 extensive metabolizers (812P113.1), DDI with d-amphetamine (812P113.2), DDI with methylphenidate (812P113.3), evaluation of the effect of alcohol on SPN-812 metabolism (812P115), evaluation of the effect of renal impairment on SPN-812 metabolism (812P112.1), evaluation of multiple dose SPN-812 on QT Interval (812P117), evaluation of maximum tolerable doses and cardiac safety in a single and multiple-ascending dose study (812P120) have also been evaluated. In addition, a [14C]-labelled oral IR solution was used to examine human absorption, metabolism, and excretion (812P111).

Results from these studies demonstrated that 200 mg single dose of an extended release SPN-812 formulation resulted in a mean maximum plasma concentration (Cmax) of 1.33 µg/mL, area under the plasma concentration-time curve extrapolated to infinity (AUCinf) of 27.3 hr*µg/mL, median time to maximum concentration (tmax) of 5 hours, and a half-life of approximately 7 hours (812P103). Lower mean Cmax was observed for SPN-812 as compared to SPN-812 IR and by 48 hours overall viloxazine exposure was comparable between the two formulations. The rate of absorption of viloxazine was formulation dependent; SPN-812 exhibited a slower absorption rate than SPN-812 IR. Following multiple-dose administration of SPN-812 on consecutive days, steady-state was achieved by the second day of multiple dosing. Little systemic accumulation of viloxazine was observed as no major increase in pharmacokinetic (PK) parameters was observed following multiple administration of SPN-812 compared to single dose administration, during the same time interval.

Food and sprinkling did not affect the relative bioavailability of viloxazine following administration of SPN-812 capsules (812P105). SPN-812 interacted as a strong inhibitor

of CYP1A2, a weak inhibitor of CYP2D6, a weak inhibitor of CYP3A4; and displayed no significant differences in metabolism within CYP2D6 poor metabolizers and CYP2D6 extensive metabolizers (812P113.1). There was no DDI between SPN-812 and d-amphetamine (812P113.2) nor between SPN-812 and methylphenidate (812P113.3) In addition, there was no dose dumping observed with co-administration of alcohol with SPN-812 (812P115). Renal impairment resulted in a 1.09-fold, 1.3-fold, and 1.9-fold increase in AUC for mild, moderate, and severe renal impairment subjects receiving 400 mg SPN-812 as compared to healthy subjects (812P112.1). Multiple doses of 1800 mg (supra-therapeutic) SPN-812 did not affect cardiac repolarization as measured by QTcI and QTcF or other electrocardiographic parameters (812P117). In the single ascending/multiple ascending dose study, SPN-812 was well tolerated up to 2100 mg/day as a single dose and up to 1800 mg/day as multiple doses given once daily for 5 consecutive days. Intolerable adverse events (AEs) were not observed at doses of up to 1800 mg/day. SPN-812 at a single supratherapeutic dose had no effect on cardiac repolarization or other electrocardiographic parameters, other than slight increase in heart rate consistent with the known anticholinergic effect of viloxazine (812P120).

In the human absorption, metabolism, and excretion study, absorption of the isomers, R- and S-viloxazine, was rapid with a median Tmax of 1.0 hour and showed a 2:1 concentration ratio, respectively. Nearly 100% of the radioactive dose was recovered with approximately 90% being recovered within 24 hours of administration, demonstrating complete absorption of the drug followed by rapid elimination. The primary circulating form was SPN-812; the only metabolite found above 10% total radioactivity was de-activated hydroxylated glucuronide.

The most common AEs in the Phase 1 studies in healthy adults were somnolence and headache. Most AEs were mild; none were severe or serious. No clinically significant, study medication-related findings were observed for laboratory or electrocardiogram (ECG) tests in any study. In general, SPN-812 is considered to be well-tolerated with no safety events observed that would be unexpected for viloxazine.

1.2.2 Phase 2 Studies

The randomized, blinded, proof-of-concept Phase 1/2 study 812P201 compared an IR formulation of SPN-812 and placebo administered three times a daily in a dose range of 150 to 300 mg/day in 52 adults (26 per treatment) with ADHD. In addition to assessing the safety and tolerability of SPN-812 IR, scores of both the Investigator-rated and patient-rated Conners Adult ADHD Rating Scale (CAARS) were collected at weekly intervals during the 6-week treatment period. Treatment with SPN-812 IR showed a statistically significant reduction in median CAARS total ADHD symptom score compared to placebo. Treatment-emergent AEs were reported in 23 (88.5%) subjects in the SPN-812 IR group and in 18 (72.0%) subjects in the placebo group. The most common AEs in SPN-812 IR group were nausea, decreased appetite, headache, and insomnia. There were no clinically significant ECGs, clinical laboratory test results, vital signs, or physical examination findings in either group during the study. No serious adverse events (SAEs) or deaths occurred during the study.

The 812P202 study in children with ADHD assessed the effect of SPN-812 in reducing the symptoms of ADHD as measured by the ADHD Rating Scale IV (ADHD-RS-IV) (Johnson et al., 2020). Subjects aged 6 to 12 years were randomized in a 1:2:2:2:2 ratio of placebo or active treatment (SPN-812 100, 200, 300, or 400 mg) and received 3 weeks of titration at 100 mg/week followed by 5 weeks of maintenance dosing for a total of 8 weeks of treatment. Mean ADHD-RS-IV Total Scores improved throughout treatment in all groups. Differences in change from baseline to end of study between SPN-812 and placebo were statistically significant at the three higher SPN-812 doses ($p \leq 0.0310$) but not at the 100-mg dose. The treatment effect compared to placebo increased with the dose; however, pairwise comparisons among the four active treatment groups showed no statistically significant differences among the SPN-812 doses. All doses of SPN-812 were well tolerated with no serious or severe AEs and no clinically significant effect on laboratory values of common hematology and chemistry tests. The most common AEs were somnolence, decreased appetite, and headache.

1.2.3 Pediatric Phase 3 Studies

Four pivotal Phase 3 studies of SPN-812 for the treatment of ADHD have been completed in the pediatric population: two studies in children 6 to 11 years of age (evaluating 100 mg, 200 mg, and 400 mg) and two studies in adolescents 12 to 17 years of age (evaluating 200 mg, 400 mg, and 600 mg). As of April 2019, preliminary results are available for all four studies.

1.2.3.1 Children (6 to 11 years of age)

Study 812P301 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 100 mg/day and 200 mg/day for the treatment of ADHD in children 6 to 11 years of age (Nasser et al., 2020). The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) with SPN-812 100 mg/day or 200 mg/day led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (29.6%), 74 (48.1%), and 77 (47.8%) subjects in the placebo, SPN-812, 100 mg/day, and SPN-812, 200 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, and headache. AEs were considered to be at least possibly treatment related in 16 (10.1%), 41 (26.6%), and 56 (34.8%) subjects in the placebo, SPN-812, 100 mg/day, and SPN-812, 200 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 2 (1.3%), 5 (3.2%), and 2 (1.2%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 2 in the SPN-812, 100 mg/day treatment group and 1 in the SPN-812, 200 mg/day treatment group. All SAEs were considered unlikely related or not related to study medication. No deaths occurred during the study.

Study 812P303 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in children 6 to 11 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 8 weeks (3 weeks of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (45.6%), 56 (52.3%), and 58 (58.0%) subjects in the placebo, SPN-812, 200 mg/day, and SPN-812, 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, headache, decreased appetite, and fatigue. AEs were considered to be at least possibly treatment related in 22 (21.4%), 42 (39.3%), and 51 (51.0%) subjects in the placebo, SPN-812, 200 mg/day, and SPN-812, 400 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 3 (2.9%), 6 (5.6%), and 4 (4.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 1 in the SPN-812, 200 mg/day treatment group and 2 in the SPN-812, 400 mg/day treatment group. No deaths occurred during the study.

1.2.3.2 Adolescents (12 to 17 years of age)

Study 812P302 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 38 (36.5%), 43 (43.4%), and 56 (53.3%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, headache, fatigue and nausea. AEs were considered to be at least possibly treatment related in 20 (19.2%), 32 (32.3%), and 41 (39.0%) subjects in the placebo, SPN-812, 200 mg/day, and SPN-812, 400 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 0, 4 (4.0%), and 2 (1.9%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812, 400 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812, 200 mg/day treatment group. No deaths occurred during the study.

Study 812P304 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 400 mg/day and 600 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812, 400 mg/day for 7 weeks (2 weeks of titration followed by 5 weeks of maintenance at a

fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo; however, ADHD-RS-5 Total Score during treatment with SPN-812 600 mg/day did not showed a statistically significant improvement compared to placebo.

Throughout treatment, AEs were reported in 39 (40.2 %), 58 (58.0%), and 55 (55.6%) subjects in the placebo, SPN-812, 400 mg/day, and SPN-812, 600 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, fatigue, headache, decreased appetite, and nausea. AEs were considered to be at least possibly treatment related in 18 (18.6%), 44 (44.0 %), and 45 (45.5%) subjects in the placebo, SPN-812, 400 mg/day, and SPN-812, 600 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 1 (1.0%), 4 (4.0%), and 5 (5.1%) subjects in the placebo, SPN-812 400, mg/day, and SPN-812, 600 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812, 400 mg/day treatment group. No deaths occurred during the study.

1.2.3.3 Pediatric Open-Label Extension Safety Trial (6 to 17 years of age)

Study 812P310 is an ongoing open-label extension safety study assessing the long-term safety of SPN-812 in children (6-11 years of age) at dose of 100 to 400 mg/day and in adolescents (12-11 years of age) at dose of 100 to 600 mg/day for the treatment of ADHD. Subjects enrolled in Study 812P310 were studied in either the Phase 2 trial (812P202) or one of the four Phase 3 trials (812P301-812P304). The primary safety endpoints of the study include adverse events (AEs), clinical safety laboratory tests, vital signs, weight, height, BMI, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS). The secondary efficacy endpoints include the ADHD-RS-IV/5 Total Score and CGI-I score by visit. SPN-812 treatment during Study 812P310 are at doses between 100 to 400 mg/day (100 mg capsule) in children and at doses of 100 to 600 mg/day (100 or 200 mg capsule) in adolescents for up to 72 months. As of 31Jul2019, 1,116 pediatric subjects enrolled and 1,097 took at least one dose of open-label SPN-812 in the Study 812P310. Of the 1097 subjects with at least one dose of SM, 6 (0.5%) subjects completed the study, 411 (37.5%) subjects were ongoing, and 680 (62.0%) subjects discontinued their participation in the study. The most common reasons for study discontinuation were withdrawal by parent/guardian (19.4%), lost to follow-up, (17.7%), and withdrawal by subject (10.4%). SAEs were reported for 2.3% of subjects, and the majority of SAEs were considered as unlikely or not related to the SPN-812. AEs were mostly mild or moderate in severity, with a low discontinuation rate due to AEs. AEs that led to discontinuation of SPN-812 were reported in 6.7% of the subjects. The most common AEs that were reported in >5% of subjects included somnolence, headache, nasopharyngitis, decreased appetite, and fatigue. Nearly all subjects (98.4%) had no report of any suicidal ideation or behavior. Overall, subjects maintained normal growth in weight and height during the study. The clinical laboratory abnormalities trends were not clinically significant. Low neutrophil counts were observed in 13.5% of subjects, but were not considered clinically meaningful because they were not frequently reported as AEs; the race of the majority of these subjects was Black or African-American who had a neutrophil count that was

<1500/µL at baseline (Benign Ethnic Neutropenia). There have been no notable trends in liver function tests in this study. There were only 3 subjects with ALT >3×ULN and 2 subjects with Bilirubin >2×ULN. There were no subjects with elevated Albumin, AST, and ALP values after treatment with SPN-812. The abnormalities observed in vital signs were not considered clinically meaningful because they were not frequently reported as AEs. ECG abnormalities were not considered clinically meaningful, because they were not reported as AEs. In summary, long-term use of SPN-812 has been well-tolerated with a generally safe profile.

1.3 Study Rationale

The efficacy and safety of SPN-812 (100-600 mg/day) as a treatment for ADHD has been assessed in four pivotal pediatric Phase 3 clinical trials, including two trials in children 6-11 years of age (812P301 and 812P303) and two trials in adolescents 12-17 years of age (812P302 and 812P304). SPN-812 (100-400 mg/day) has been shown to be effective, safe and well tolerated. Of the over 1300 subjects who participated in a pivotal Phase 3 trial, there have been 1,097 pediatric subjects (6 years and older) dosed with SPN-812 (100-600 mg/day) in a long-term safety study (812P310). In addition, Supernus conducted two Drug-Drug Interaction (DDI) clinical trials in healthy adult subjects to assess the safety/tolerability of two FDA approved and most prescribed psychostimulants for the treatment of ADHD individually when co-administered with SPN-812. In Study 812P113.2, Vyvanse® (lisdexamfetamine dimesylate, 36 mg) was co-administered with SPN-812. In Study 812P113.3, Concerta® (methylphenidate, 50 mg) was co-administered with SPN-812 (viloxazine, 700 mg). The results of these two trials showed no effect of either psychostimulant on the pharmacokinetics (PK) of SPN-812 and no effect of SPN-812 on the PK of either psychostimulants. A single dose of d-amphetamine or methylphenidate co-administrated with viloxazine did not impact on the exposure of viloxazine. A single-dose administration of viloxazine co-administrated-with d-amphetamine or methylphenidate did not impact on the exposure either d-amphetamine or methylphenidate. As no relevant interactions were observed, no dose adjustment is recommended when taking either Vyvanse® or Concerta® in combination with SPN-812. All adverse events were mild in severity, and no Serious Adverse Events were reported. Altogether, SPN-812 was safe and generally well-tolerated in healthy adults when co-administered with either Vyvanse® or Concerta®.

While there have been no DDI clinical trials conducted in children/adolescents, the data from the adult clinical trials indicate that co-administered of SPN-812 with either psychostimulant (Vyvanse® or Concerta®) in children and adolescents is safe and should be well-tolerated. In summary, the rationale for this study is to assess the safety and tolerability of SPN-812 administered with a psychostimulant therapy for ADHD.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To evaluate the safety and tolerability of AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age)

2.1.1 Primary Endpoints

- Safety endpoints for Weeks 1-4 (AM dosing) and Weeks 5-8 (PM dosing) are adverse events (AEs), clinical safety laboratory tests, vital signs, weight, height, BMI, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).

2.2 Secondary Objectives

1. To evaluate the safety and tolerability of AM versus PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age).
2. To evaluate the efficacy of AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on:
   i. ADHD symptoms as measured by the investigator-rated ADHD-RS-5 (IR-ADHD-RS-5).
   ii. the global assessment of severity for ADHD as measured by the Clinical Global Impression - Severity of Illness (CGI-S) scale.
   iii. the global assessment of improvement for ADHD as measured by the Clinical Global Impression - Improvement (CGI-I) scale.
   iv. sleep as measured by the Sleep Disturbance Scale for Children (SDSC).
   v. home functioning in the morning and evening as measured by the Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R).
3. To evaluate the efficacy of AM versus PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on:
   i. ADHD symptoms as measured by the IR-ADHD-RS-5.
   ii. the global assessment of severity as measured by the CGI-S scale.
   iii. the global assessment of improvement for ADHD as measured by the CGI-I scale.
   iv. sleep as measured by the SDSC.
   v. home functioning in morning and evening as measured by the WPREMB-R.
4. To evaluate efficacy in the morning for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning Parent-Rated-ADHD-RS-5 (PR-ADHD-RS-5).

5. To evaluate efficacy in the evening for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Evening PR-ADHD-RS-5.

6. To evaluate duration of efficacy within day (morning versus evening) for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning and Evening PR-ADHD-RS-5.

2.2.1 Secondary Endpoints

1. Safety endpoints for Weeks 1-4 (AM dosing) versus Weeks 5-8 (PM dosing) are AEs, clinical safety laboratory tests, vital signs, weight, height, BMI, ECGs, physical examination, and the C-SSRS.

2. Secondary endpoints for evaluating the efficacy of SPN-812 at Week 4 (AM dosing) and Week 8 (PM dosing) are:
   i. Change from baseline (CFB) in the IR-ADHD-RS-5 Total Score at Week 4 and Week 8.
   ii. CFB in CGI-S score at Week 4 and Week 8.
   iii. CGI-I score at Week 4 and Week 8.
   iv. CFB in SDSC total score and subscale scores at Week 4 and Week 8.
   v. CFB in WPREMB-R total score and subscale scores at Week 4 and Week 8.

3. Secondary endpoints for evaluating the efficacy of SPN-812 Week 4 (AM dosing) versus Week 8 (PM dosing) are:
   i. CFB in the IR-ADHD-RS-5 Total Score at Week 4 versus Week 8.
   ii. CFB in CGI-S score at Week 4 versus Week 8.
   iii. CGI-I score at Week 4 versus Week 8.
   iv. CFB in SDSC total score and subscale scores at Week 4 versus Week 8.
   v. CFB in WPREMB-R total score and subscale scores at Week 4 versus Week 8.

4. CFB in the Moring PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).

5. CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).

6. The CFB in the Morning PR-ADHD-RS-5 Total Score versus the CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).

3 INVESTIGATIONAL STUDY PLAN

3.1 Overall Study Design and Plan

This is an open-label, flexible-dose, safety study of SPN-812 in pediatric patients diagnosed with ADHD per Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5™) criteria who are experiencing an inadequate efficacy response to psychostimulant therapy (dosed at least 5 days per week). Up to 60 subjects will enroll, and up to 50 subjects will complete this study (Figure 1).

During screening period (up to 4 weeks), subjects will continue their psychostimulant ADHD treatment (dosed at least 5 days per week). Following the screening period, eligible subjects will receive SPN-812 with their current psychostimulant treatment for ADHD for 8 weeks. The subject's psychostimulant medication dose (mg) cannot be increased during the 8-week SPN-812 treatment, however, the investigator may decrease the dose of subject's psychostimulant medication once during 8-week SPN-812 treatment; if an additional dose adjustment is needed (e.g., due to worsening of AE or start of new AE), the investigator should inform the medical monitor and study sponsor. A urine drug screen will be performed at every study visit (V1-V10) to confirm use of psychostimulant medication at visit, and (in addition to clinical laboratory testing) a single confirmatory blood sample will be collected at every study visit (V1-V10) to determine psychostimulant and/or viloxazine/its metabolite concentrations (see Section 6.6). The total duration of the study between the screening visit and the end of the treatment period/end of study (EOS) visit is up to 12 weeks.

3.1.1 Screening Period (Visit 1)

The screening period is a minimum of 7 days and a maximum of 28 days. After informed consent/assent is obtained, subjects will undergo initial screening evaluations (Section 5.1.1). Subjects with an IR-ADHD-RS-5 total score <24 or CGI-S score <3 will be excluded from study participation. Subjects with an IR-ADHD-RS-5 total score ≥24 and a CGI-S score ≥3 will be eligible to enroll if meet all other eligibility criteria. Inclusion/exclusion criteria will be reviewed to confirm the subject's eligibility. Subjects must washout of any prohibited medications at least 7 days prior to Visit 2. Subjects must continue taking stable dose of psychostimulant medication at least 5 days per week throughout the screening period, and subject's parent/guardian must record whether it was taken and date/time of each psychostimulant dose taken in a daily diary.

3.1.2 Baseline (Visit 2)

At Visit 2, a urine drug screen will be performed for all subjects and a pregnancy testing will be performed for females of childbearing potential (FOCP). If both are negative, the IR-ADHD-RS-5 scale and the CGI-S will be administered. Subjects with an IR-ADHD-RS-5 total score of <24 or CGI-S <3 will be excluded from study participation. Subjects with an IR-ADHD-RS-5 total score of ≥24 and a CGI-S score ≥3 will enroll. Safety evaluations will be performed and the IR-ADHD-RS-5 scale, CGI-S, SDSC, and WPREMB-R will be administered and inclusion/exclusion criteria will be reviewed to

confirm eligibility. Subjects who are eligible to participate will begin dosing SPN-812 dosing at Visit 2 (Day 1).

3.1.3 Treatment Period (Visits 3 to 10)

The treatment period of the study will consist of 8 weeks of adjunct SPN-812 treatment with the subject's current psychostimulant ADHD treatment. Subjects must continue taking stable dose of psychostimulant medication at least 5 days per week during the 8-week SPN-812 treatment period, and subject's parent/guardian must record whether it was taken and date/time of each psychostimulant dose taken in a daily diary (Figure 1).

Subjects will dose SPN-812 daily between Visit 2 (Day 1) and Visit 10/EOS (Day 57). Subjects will dose SPN-812 daily in the morning (AM) during Weeks 1-4, and then dose SPN-812 daily in the evening (PM) during Weeks 5-8 (Figure 1). The timing of the PM dose during Weeks 5-8 should occur approximately 12 hours (± 60 minutes) after the timing of AM dose during Weeks 1-4 (e.g., if subject dosed at 7:00AM during Weeks 1-4, they should take SPN-812 dose at or around 7:00PM). Subject's parent/guardian will record SPN-812 dosing each day in a daily diary, including date/time dose taken, SPN-812 dose (mg) and method (swallow capsule whole or sprinkle capsule contents on apple sauce) or reason dose not taken, if applicable. Children (6 to 11 years of age) will begin SPN-812 dosing at 100 mg/day during Week 1 of Treatment and may be titrated up or tapered down in increments/decrements of 100 mg/day per week between 100 and 400 mg/day. Adolescents (12 to 17 years of age) will begin SPN812 dosing at 200 mg/day during Week 1 of Treatment and may be titrated up or tapered down in increments/decrements of 100-200 mg/day per week between 100 and 600 mg/day-.

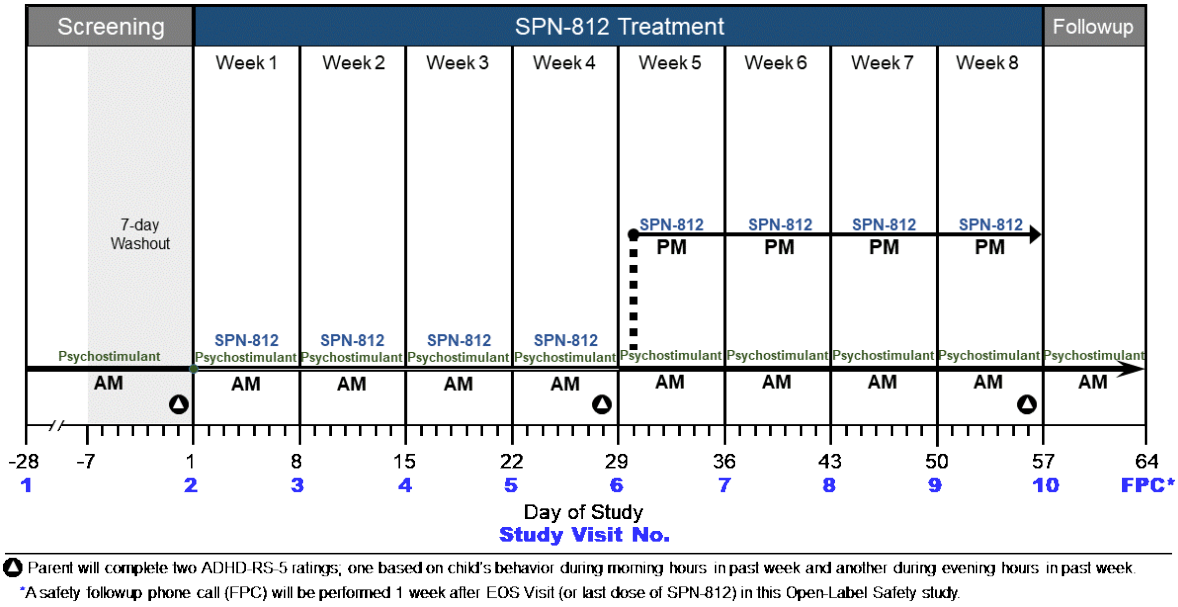
Following Baseline (Visit 2), subjects will complete weekly post-baseline study visits during the 8-week Treatment Period (Visits 3-10). At each study visit, safety evaluations (including review of AEs/concomitant medications, clinical safety laboratory tests, vital signs, weight, ECGs, and the C-SSRS) will be conducted, efficacy assessments (IR-ADHD-RS-5, CGI-S, CGI-I) will be administered, drug compliance will be evaluated, and subject will return bottle of study medication and receive next bottle of study medication, if necessary. SDSC and WPREMB-R will only be administered at Visits 6 and 10 during Treatment Period. In addition, parent/guardian/caregiver must complete a "Morning" PR-ADHD-RS-5 and "Evening" PR-ADHD-RS-5 one or two days prior to Study Visits 2, 6, and 10. Parent will rate their child's behavior based upon interactions with their child during the morning hours in the past week and then rate their child's behavior based upon interactions with their child during the evening hours in the past week.

Subjects who are non-compliant (e.g., with study procedures, dosing study medication, study visits, etc.) may be discontinued. For AEs or risks that cannot be managed using permitted concomitant medications or other protocol-specified management, SM dosing should be discontinued and an Early Termination (ET) visit conducted. Study medication dosing will otherwise continue until Week 8 (Visit 10/EOS), at which time subjects will return for final study assessments. Subjects who discontinue early from the study will undergo safety evaluations.

3.1.4 Follow-up Period

Subjects will receive a safety follow-up phone call approximately 1 week after the date of EOS Visit (or last dose of SPN-812) for final safety assessments (i.e. AEs, concomitant medications).

Figure 1 Study Schematic



Parent will complete two ADHD-RS-5 ratings, one based on child's behavior during morning hours in past week and another during evening hours in past week.
*A safety followup phone call (FPC) will be performed 1 week after EOS Visit (or last dose of SPN-812) in this Open-Label Safety study.

3.2 Rationale for Study Design

Psychostimulants are usually first line treatment for ADHD in children and adolescents. However, a small proportion of patients may not receive an adequate response to psychostimulant treatment, particularly if adverse events preclude an increase to a higher, effective dose. In such cases, an FDA-approved non-stimulant ADHD treatment may be administered with psychostimulant. In Phase 3 trials, SPN-812 has demonstrated efficacy by significantly reducing (improving) ADHD symptoms, and it has been shown to be generally safe and well tolerated when taken as a monotherapy in children and adolescents with ADHD. In addition, in Phase 1 trials in healthy adults, PK parameters (Cmax, Tmax, AUC) for either viloxazine or psychostimulant (methylphenidate or amphetamine) were not affected when a single-dose of SPN-812 was co-administered with a psychostimulant (methylphenidate or amphetamine). Therefore, in the current study, the aim is to assess the safety and efficacy of once daily SPN-812 treatment when administered with a psychostimulant in children and adolescents.

3.3 Study Population

3.3.1 Number of Subjects

Approximately 60 subjects will be enrolled, and approximately 50 subjects are expected to completed study.

3.3.2 Inclusion Criteria

1. Is male or female, 6 to ≤17 years and 9 months of age at screening.
2. Parent(s)/legal guardian(s) is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained by parent(s)/legal guardian(s) and informed assent obtained from the subject, if applicable.
4. Subject and parent(s)/legal guardian(s) are willing and able to comply with all of the procedures and requirements defined in the protocol, including parents(s)/legal guardian(s) oversight of morning and evening dosing of the SPN-812 and recording a daily medication/dosing diary for psychostimulant and/or SPN-812 during the study.
5. Has lived with the same parent(s)/legal guardian(s) at same residence for at least the last 6 months prior to screening.
6. Has a primary diagnosis of ADHD (inattentive, hyperactive, or combined presentation) confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) at screening.
7. Is currently on a stable psychostimulant regimen (see Inclusion Criterion 8 for definition) for treatment of ADHD with a partial, but inadequate efficacy response to at least 2 weeks of treatment with a psychostimulant (methylphenidate or amphetamine) prior to screening. An inadequate response is defined as an investigator-rated ADHD-RS-5 Total score ≥24 and a CGI-S score ≥3 (mildly ill or worse) at Screening and Baseline. Subjects taking additional medication for ADHD (e.g., nonstimulant) are excluded
8. Is currently and expecting to continue and remain on a stable psychostimulant regimen throughout the study. A stable stimulant regimen is defined as taking dose at least 5 days per week (morning), no significant change in dose or dosing frequency at least 2 weeks prior to baseline (Visit 2), and the investigator believes the subject's psychostimulant dose is optimized.
9. Is functioning at an age-appropriate level intellectually, as judged by the Investigator.
10. Is a child (6-11 years of age) with a body weight of at least 20 kg at screening or is an adolescent (12-17 years of age) with a body weight of at least 35 kg at screening.
11. Has a resting (sitting) blood pressure (BP) and pulse rate measurement within the 95th percentile for age, sex, and height.

12. Is considered medically healthy by the Investigator via assessment of physical examination, medical and psychiatric histories, clinical laboratory tests, vital signs, and electrocardiogram (ECG).

13. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use/practice one of the following acceptable, highly effective contraceptive methods beginning during screening period prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed during screening period to first dose of SM
    b. Surgically sterile male partner (e.g., vasectomized partner is sole partner)
    c. Barrier method: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    d. Established use of oral, injected, or implanted hormonal methods of contraception

    With approval by the Investigator, subjects' parents or legal guardians may select abstinence as a form of birth control if deemed more appropriate. For the purposes of this study, all females are considered to be of childbearing potential unless they are confirmed by the Investigator to be premenarchal, biologically sterile, or surgically sterile (e.g., hysterectomy with bilateral oophorectomy, tubal ligation).

14. Adolescent males, if sexually active, must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of SM, or
    b. Have been surgically sterilized prior to the Screening Visit.

3.3.3 Exclusion Criteria

1. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior to screening.

2. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.

3. Is a female subject who is pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable contraceptive methods throughout the study.

4. Has history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication (SPN-812).

5. Has history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. a current diagnosis of a major neurological disorder;
    b. seizures, seizure disorder or seizure-like events;
    c. history of seizure disorder within the immediate family (siblings, parents); or
    d. encephalopathy

Note: Febrile seizures are not exclusionary and will be assessed on a case-by-case basis. If for any reason the subject received medication for a febrile seizure or has a history of complex febrile seizures, this will be exclusionary.

6. Has current diagnosis or history of major psychiatric disorders or intellectual disabilities other than ADHD per DSM-5 criteria (including schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, post-traumatic stress disorder, obsessive-compulsive disorder, severe oppositional defiant disorder, conduct disorder, disruptive mood dysregulation disorder (DMDD), and autism spectrum disorders). The following is not exclusionary:
   a. a history of mild social anxiety disorder or generalized anxiety disorder according to DSM-5 criteria;
   b. a history of mild to moderate ODD according to DSM-5 criteria;
   c. a history of Major Depressive Disorder, if he/she has not experienced a major depressive disorder episode or required psychiatric counselling; or pharmacotherapy within the 6 months prior to screening
7. Has a known history of physical, sexual, or emotional abuse in the last year prior to screening.
8. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
9. Has a current diagnosis of drug abuse or dependence disorder within the 12 months prior to screening, has a history of drug abuse or dependence disorder or has an immediate family member living at study participant's' home who has current diagnosis drug abuse or dependence disorder (per DSM-5 criteria).
10. Evidence of suicidality (defined as either active suicidal plan/intent or active suicidal thoughts, or more than one lifetime suicide attempt) within the six months before Screening or at Screening.
11. Has positive findings on C-SSRS for suicidal ideation or behaviors at screening. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS within the 6 months prior to screening.
12. Is currently using, or has a positive result on the urine drug screening for, drugs of abuse (alcohol, amphetamine, barbiturates, benzodiazepines, cannabis [THC], cocaine, cotinine, methadone, methamphetamine [including ecstasy], methylphenidate, phencyclidine, propoxyphene, and opiates) with the exception of the psychostimulant stimulant prescribed for the treatment of ADHD.
13. Is unable to discontinue all prohibited medication at least 7 days prior to baseline.

14. Has body mass index (BMI) greater than 95th percentile for her/his appropriate age and gender (per CDC's gender specific "BMI-for-age percentiles" charts).
15. Has a current diagnosis of significant systemic disease.
16. Has uncontrolled thyroid disorder defined as thyroid stimulating hormone ≤ 0.8 x the lower limit of normal or ≥ 1.25 x the upper limit of normal for the reference laboratory range.
17. Has resting (sitting) blood pressure and pulse rate greater than the 95th percentile for age and gender.
18. Has a known personal history, or presence, of structural cardiac abnormalities, cardiovascular or cerebrovascular disease, serious heart rhythm abnormalities, syncope, tachycardia, cardiac conduction problems (e.g., clinically significant heart block or QT interval prolongation: QTc >0.44 seconds), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia.
19. Has any clinically significant abnormal clinical laboratory test, urine test, electrocardiogram (ECG) result, vital signs or physical examination finding at screening that, in the opinion of the Investigator, would interfere with the safety of the subject (see Note below).
20. Has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments.
21. Has or has had one or more medical conditions considered clinically significant/relevant by the Investigator in the context of the study (e.g., cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia, bradycardia [pulse < 70 bpm (6-11 years), pulse < 60 bpm (12-17 years)], tachycardia [pulse > 120 bpm (6-11 years); pulse > 100 bpm (12-17 years)], respiratory disease, hepatic impairment or renal insufficiency, metabolic disorder, endocrine disorder, gastrointestinal disorder, hematological disorder, infectious disorder, any clinically significant immunological condition, dermatological disorder.
22. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
23. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
24. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 28 days or 5 half-lives prior to Baseline Visit (Day 1) (whichever is longer) or anticipated for the duration of the study.
25. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.

26. Has an allergy to applesauce and cannot swallow capsules whole.

27. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Note: Repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time for each test during screening period, at the discretion of the Investigator, as long as the repeat test result is available within the 28-day screening period to determine eligibility.

3.4 Completion of Study and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 10. Subjects who dose SPN-812, but who withdraw or are withdrawn from participation in the study by the Investigator before he/she finishes the study (i.e., after Visit 2 but prior to Visit 10), should complete an early termination (ET) visit. Procedures listed for Visit 10 should be completed at the ET visit.

All reasons for screening failure will be recorded. If the subject passes screening but fails eligibility at Visit 2 (Baseline), the reason(s) will also be recorded.

The Investigator(s) or subjects themselves may stop SPN-812 treatment at any time for safety or personal reasons. A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Sponsor may also withdraw the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and/or Clinical Research Associate (CRA) before the subject stops SPN-812 treatment. Subjects removed from the study for any reason will not be replaced.

Reasons for subject’s early discontinuation may include:

- Withdrawal of consent (parent/guardian)
- Withdrawal of assent (subject)
- Inclusion/Exclusion criteria
- Noncompliance
- Lack of Efficacy
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

The primary reason for subject’s early discontinuation must be recorded in the subject’s medical record and on the electronic case report form (eCRF). If subject withdraws assent or parent withdraws consent, the specific reason for withdrawal (e.g., relocating/moving [change of residence/address], personal time constraint(s) [e.g., changes in social/family/employment/health changes], loss of Interest, etc.] should be captured.

4 STUDY TREATMENT

4.1 Study Medication Identity, Packaging and Labeling

Study medication (SPN-812) are capsules supplied in labeled bottles by the Sponsor. Each bottle of SM will include capsules that contain either 100 mg or 200 mg of SPN-812 in 90-count bottles. Each bottle will be labeled with the protocol number, at a minimum.

4.2 Study Medication Administration

Study medication (SPN-812) will be administered orally once daily (QD), with or without food, as an intact capsule or by sprinkling the content of the capsule on one tablespoon of applesauce followed by drinking water after having ingested the SM/applesauce mix. The subject's parent/guardian will record a daily diary (e.g., paper or electronic source) to capture daily SPN-812 dose information, including total daily dose (mg), dosing date/time (MM/DD/YYYY, 00:00 AM/PM), administration method [e.g., subject swallowed total daily dose as intact capsule(s) or subject swallowed total daily dose as a SM/applesauce mix] and reason why no SPN-812 dose was taken or why a partial SPN-812 dose was taken, if applicable.

4.2.1 AM Dosing; Weeks 1-4 of Treatment Period

Subject will take daily SPN-812 dose in the MORNING (AM) hours during Weeks 1-4 of the Treatment period. Splitting the daily dose (e.g., taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted. A daily diary (e.g., paper or electronic source) will be used to confirm whether subject takes SPN-812 dose in the morning each day during the first 4 weeks of treatment; if it is discovered that subject has been taking daily SPN-812 dose much later in the day than expected/planned (e.g., evening) without prior Site Investigator or Sponsor approval, the medical monitor and sponsor must be informed immediately. Subject will take first AM dose of SPN-812 at Visit 2 and last AM dose of SPN-812 the morning of Visit 6.

4.2.2 PM Dosing; Weeks 5-8 of Treatment Period

Subject will take daily SPN-812 dose in the EVENING (PM) hours during Weeks 5-8 of the Treatment period. The timing of the PM dose during Weeks 5-8 should occur approximately 12 hours (± 60 minutes) after the timing of AM dose during Weeks 1-4 (e.g., if subject dosed at 7:00AM during Weeks 1-4, they should take SPN-812 dose at or around 7:00PM. Splitting the daily dose (e.g., taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted. A daily diary (e.g., paper or electronic source) will be used to confirm whether subject takes SPN-812 dose in the evening each day during the last 4 weeks of treatment; if it is discovered that subject has been taking daily SPN-812 dose much earlier in the day than expected/planned (e.g., morning/afternoon) without prior Site Investigator or Sponsor approval, the medical monitor and sponsor must be informed immediately. Subject will take first PM dose of SPN-812 the night after Visit 6 (e.g., subject will take last AM dose morning of Visit 6, Day 29, and then subject will take first PM evening of Day 30). Subject will take last PM dose of SPN-812 the night before Visit 10. Subject should continue dosing SPN-812 either at planned dose of previous week or at an

adjusted dose starting from planned dose of previous week (e.g., if 6-11 years of age, subject dosed 300 mg/day previous week, subject may resume dosing at 300 mg/day or reduce/increase dose to 200 or 400 mg/day).

4.2.3 Total Daily Dose by Age Group

Children (6-11 years of age) will begin SPN-812 dosing at 100 mg/day during Week 1 of Treatment and may be titrated up or tapered down in increments/decrements of 100 mg/day per week between 100 and 400 mg/day (Table 1). Adolescent (12-17 years of age) will begin SPN-812 dosing at 200 mg/day during Week 1 of Treatment and may be titrated up or tapered down in increments/decrements of 100-200 mg/day per week between 100 and 600 mg/day (Table 1). If an 11-year-old subject turns 12 years of age after screening, continue to dose subject and adjust subject's SPN-812 dosing as a subject 6-11 years of age. For AEs or risks that cannot be managed using permitted concomitant medications (Section 4.6) or other protocol-specified management (Section 6.3), SM dosing should be discontinued (Section 3.4).

Table 1 Study Medication Administration

Age Group	Starting Dose	Dose Range	Dose Increments for Titrating Up or Tapering Down (per week)
6-11 years	100 mg/day	100-400 mg/day	100 mg/day
12-17 years	200 mg/day	100-600 mg/day	100 or 200 mg/day

Each capsule contains either 100 mg or 200 mg SPN-812.

4.3 Method of Assigning Subjects to Treatment Arm

This is an open-label study. All eligible subjects will receive active treatment (SPN-812).

4.4 Study Medication Handling and Accountability

All SM is supplied to the Investigator by the Sponsor. SM supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with International Conference on Harmonization (ICH) E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes, but may

not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or a representative of the Food and Drug Administration (FDA). The assigned CRA will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies, including empty containers, are to be returned to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form.

4.5 Blinding

This is an open-label study.

4.6 Concomitant Medications

At screening, the subject's prior history of concomitant medication(s) (lifetime) and current concomitant medication(s) will be obtained. Subjects must continue taking stable dose of psychostimulant medication at least 5 days per week in the morning throughout study, including the screening period and 8-week SPN-812 treatment period. Every day between Visit 1 and Visit 10, the subject's parent/guardian will complete a daily medication diary (e.g., Paper or electronic) to confirm whether the prescribed psychostimulant medication dose was taken in the morning. The total daily dose (mg) of subject's psychostimulant medication cannot be increased during 8-week SPN-812 treatment, but it may be decreased once.

Subjects may not be on any prohibited medication as indicated in the inclusion/exclusion criteria. SPN-812 is a strong CYP1A2 inhibitor. Substrates with a narrow therapeutic window are prohibited during the study. Specific prohibited concomitant medications for this study include known CYP1A2 substrates (e.g., theophylline, melatonin). Subjects will undergo a washout period of prohibited medication at least 1 week (or 5 half-lives of the medication, whichever is longer) before the Baseline Visit (Day 1).
No concomitant medications are allowed during the study, with the following exceptions:

- Nutritional supplements (e.g., multivitamins, fish oil) (however, herbal supplements are prohibited)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter (OTC) therapies for minor transient ailments (e.g., acetaminophen for headache, ibuprofen for fever).
- Over-the-counter, non-sedating allergy medications and antibiotics.

All concomitant medications will be recorded in the eCRF.
Caffeine use is not prohibited during the study, however, caffeine intake will be assessed at screening, baseline and at all post-baseline study visits and recorded in the eCRF.

5 STUDY METHODS

5.1 Study Visits and Procedures

All subjects who are eligible, enroll and take the initial dose of SPN-812 will be followed according to the protocol regardless of the number of doses of SPN-812 taken, unless consent for follow-up is withdrawn. The Sponsor or the Sponsor's designee must be notified of all deviations from the protocol visit or procedures, except as noted, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. The subject's parent, legal guardian/representative or caregiver will be instructed to call study personnel to report any abnormalities during the intervals in between study visits and to come to the study site if medical evaluation is needed and as the urgency of the situation indicates. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up.

The Schedule of Events and Assessments for the study is shown in Table 2.

Table 2 Schedule of Events and Assessments

Study Period	Screening	Baseline	Treatment							EOS/ET	Follow-up phone call
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**FPC**
Day of Study	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**
Week of Study	**-4 to -1**	**–**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**–**
Study Visit Window	**–**	**–**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Signed informed consent/assent	√[a]										
MINI KID	√										
Relevant histories (social, medical, psychiatric, family psychiatric, neurological)	√										
Demographics	√										
Smoking, alcohol consumption use/history	√										
Physical examination	√[b]									√[b, c]	
Review eligibility criteria	√	√									
Blood sample for clinical safety laboratory tests	√	√	√	√	√	√	√	√	√	√	
Blood sample for Confirmatory analysis	√[d]	√[d]	√[d]	√[d]	√[d]	√[d]	√[d]	√[d]	√[d]	√[d]	
Urine sample for urinalysis	√									√	
Standard Urine drug screen	√										
Point of Care urine drug screen (Test 1)[e]		√	√	√	√	√	√	√	√	√	
Point of Care urine drug screen (Test 2 and 3)[e]	√	√	√	√	√	√	√	√	√	√	
Serum pregnancy test (FOCP only)	√										
Urine pregnancy test (FOCP only)		√	√	√	√	√	√	√	√	√	
Vital signs[f]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]	
Weight	√	√	√	√	√	√	√	√	√	√	
ECG	√	√	√	√	√	√	√	√	√	√	
Provide diary instructions to parent/guardian	√	√									
Reminder call		√[g]				√[g]				√[g]	
Review/collect PR-ADHD-RS-5		√[h]				√[h]				√[h]	
Review/Collect Dosing Diary		√[i]	√[i]	√[i]	√[i]	√[i]	√[i]	√[i]	√[i]	√[i]	
IR-ADHD-RS-5	√[j]	√[j]	√[j]	√[j]	√[j]	√[j]	√[j]	√[j]	√[j]	√[j]	

Study Period	Screening	Baseline	Treatment							EOS/ET	Follow-up phone call
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**FPC**
Day of Study	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**
Week of Study	**-4 to -1**	**–**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**–**
Study Visit Window	**–**	**–**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
CGI-S	√	√	√	√	√	√	√	√	√	√	
CGI-I			√	√	√	√	√	√	√	√	
SDSC		√				√				√	
WPREMB-P		√				√				√	
C-SSRS (Baseline)	√[k]										
C-SSRS (Since Last Visit)		√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	
Review adverse events		√[m]	√	√	√	√	√	√	√	√	√
Review concomitant medications/caffeine use	√[n]	√	√	√	√	√	√	√	√	√	√
SM dispensed		√	√	√	√	√	√	√	√		
SM returned/accountability			√	√	√	√	√	√	√	√	

ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD-RS-5 = ADHD Rating Scale 5th Edition; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity of Illness scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; FOCP = females of childbearing potential; FPC = follow-up phone call; IR-ADHD-RS-5 = investigator-rated ADHD-RS-5; MINI KID = Mini International Neuropsychiatric Interview for Children & Adolescents; PR-ADHD-RS-5 = Parent-rated ADHD-RS-5; WPREMB-R = Weekly Parent Rating of Evening and Morning Behavior-Revised; SDSC = Sleep Disturbance Scale for Children; SM = study medication.

a. To be obtained prior to performing any study procedures.
b. Includes height, excludes genitourinary system
c. Changes from Screening only
d. A confirmatory blood sample will be collected to determine psychostimulant and viloxazine/metabolite concentrations. Collect and process sample in the same manner as a Pharmacokinetic (PK) sample.
e. See Table 3 to determine which substance is being tested by Point of Care Urine Drug Screen Test 1, 2 or 3.
f. Includes orthostatic blood pressure and pulse rate, respiratory rate and oral temp. Orthostatic blood pressure and pulse rate should be assessed 5 minutes after subject has been sitting and again within 3 minutes of standing.
g. If paper version of diary is being used, a phone call should be made to parent/guardian 2-3 days prior to Study Visits 2, 6, and 10 to remind he/she to complete a "Morning" and "Evening" PR-ADHD-RS-5 prior to study visit.
h. Parent/guardian must complete a PR-ADHD-RS-5 one to two days prior to Study Visits 2, 6, and 10 to rate their child's behavior in past week, one based on interactions with their child during the morning hours and another based on interactions with their child during the evening hours.
i. If electronic diary is completed, please review data at each visit. If paper version of diary is completed, collected and enter data. Note: Only the psychostimulant dosing diary is performed during screening period prior to V2.
j. Use age-appropriate IR-ADHD-RS-5 ([redacted] [6-11yrs] or [redacted] [12-17 yrs]).
k. Use C-SSRS Baseline version per subject's age at screening ([redacted] [6-11 yrs] or [redacted] [12-17 yrs]).
l. Use C-SSRS SLV version per subject's age at screening ([redacted] [6-11 yrs] or [redacted] [12-17 yrs]).
m. Events prior to first dose of SPN-812 are Medical Hx; events after to first dose are Adverse Event.
n. Review subject's prior lifetime history of concomitant medication(s) and current concomitant medication(s).

5.1.1 Visit 1 – Screening

The following assessments will be conducted at this visit:

- Informed consent/assent form signed
- Investigator complete MINI-KID to confirm ADHD diagnosis per DSM-5
- Complete social, medical, psychiatric, neurological, and family psychiatric histories
- Demographics
- Smoking, alcohol consumption use/history
- Physical examination and height
- Blood sample for:
  - clinical safety laboratory tests (Hematology/chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
  - Serum Pregnancy Test (FOCP only)
- Urine sample for:
  - 'Standard' Urine drug screen (Table 3)
  - POC Urine Drug Screen Test 2 and Test 3 only (Table 3)
  - Urinalysis
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5 and CGI-S
- C-SSRS (age-appropriate "Children's Baseline/Screening' or 'Baseline' version)
- Review eligibility criteria
- Review concomitant medications and caffeine intake
- Provide parent/guardian with paper or electronic PR-ADHD-RS-5 and psychostimulant dosing diary and instruct them on how to complete
- Remind parent/guardian to stop prohibited medications 7 days prior to next visit.

5.1.2 Visit 2 – Baseline

The following assessments will be conducted at this visit:

- Reminder Call 2-3 days prior to visit: Parent should complete the Morning & Evening PR-ADHD-RS-5 at home, 1-2 day(s) before Baseline
- Review eligibility criteria
- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screens (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Administer the SDSC and WPREMB-R
- Investigator complete the IR-ADHD-RS-5 and CGI-S
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review/collect dosing diary and both PR-ADHD-RS-5 (Morning & Evening)

- Review concomitant medications and caffeine intake
- Review adverse events (events occurring before first SPN-812 dose, recorded as medical history; events occurring after first SPN-812 dose record as an AE).
- Instruct parent/guardian on how to record dosing diary for study medication (SPN-812) AM daily to V3; remind them to record psychostimulant dosing diary AM daily to V3
- Dispense SM; subject should take first dose of SPN-812 and record 1st dose in diary.

5.1.3 Visit 3 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S, and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Dispense SM
- Review/collect dosing diary; remind parent to record dosing diary AM daily to V4

5.1.4 Visit 4 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for: :
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Dispense SM
- Review/collect dosing diary; remind parent to record dosing diary AM daily to V5

5.1.5 Visit 5 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- Remind parent/guardian to complete Morning/Evening PR-ADHD-RS-5 before Visit 6
- SM return and accountability
- Dispense SM
- Review/collect dosing diary; remind parent to record dosing diary daily AM to V6

5.1.6 Visit 6 – Treatment Period

The following assessments will be conducted at this visit:

- Reminder Call 2-3 days prior to visit: Parent should complete the Morning & Evening PR-ADHD-RS-5 at home, 1-2 day(s) before Visit 6
- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Administer SDSC and WPREMB-R
- Investigator complete the IR-ADHD-RS-5, CGI-S, and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Dispense SM
- Review/collect dosing diary and both PR-ADHD-RS-5 (Morning & Evening)
- Remind parent/guardian to start PM dosing next day and record date and time in diary (no AM dose tomorrow morning; first PM dose tomorrow night)
- Remind parent to record dosing diary daily until V7 (AM: Psychostimulant; PM: SPN-812)

5.1.7 Visit 7 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Dispense SM
- Review/collect subject's dosing diary
- Remind parent to record dosing diary daily until V8 (AM: Psychostimulant; PM: SPN-812)

5.1.8 Visit 8 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Dispense SM
- Review/collect subject's dosing diary
- Remind parent to record dosing diary daily until V9 (AM: Psychostimulant; PM: SPN-812)

5.1.9 Visit 9 – Treatment Period

The following assessments will be conducted at this visit:

- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Investigator complete the IR-ADHD-RS-5, CGI-S and CGI-I
- C-SSRS; *Since Last Visit* (if "*Children's*" version used at screening, use "*Children's*")
- Review concomitant medications and caffeine intake
- Review adverse events
- Remind parent/guardian to complete Morning/Evening PR-ADHD-RS-5 before Visit 10
- SM return and accountability
- Dispense SM
- Review/collect subject's dosing diary
- Remind parent to record dosing diary daily until V10 (AM: Psychostimulant; PM: SPN-812)

5.1.10 Visit 10 – End of Study

The following assessments will be conducted at this visit:

- Reminder Call 2-3 days prior to visit: Parent should complete the Morning & Evening PR-ADHD-RS-5 at home, 1-2 day(s) before Visit 10
- Physical examination and height
- Blood sample for:
  - clinical safety laboratory tests (Hematology/Chemistry)
  - confirmatory analyses of psychostimulant and viloxazine and its metabolite
- Urine sample for:
  - POC Urine Drug Screen (Test 1, Test 2, and Test 3)
  - Urine Pregnancy Test (FOCP only)
  - Urinalysis
- Measure/record vital signs and weight
- Perform 12-lead ECG
- Administer SDSC and WPREMB-R
- Investigator complete the IR-ADHD-RS-5, CGI-S, and CGI-I
- C-SSRS (age-appropriate 'Since Last Visit' version)
- Review concomitant medications and caffeine intake
- Review adverse events
- SM return and accountability
- Review/collect dosing diary and both PR-ADHD-RS-5 (Morning & Evening)

5.1.11 Follow-up Phone Call (FPC)

Subjects will be contacted via telephone 1 week after EOS (or last dose of SPN-812) for the following assessments:

- Review AEs
- Review concomitant medications and caffeine intake

For subjects who discontinue/terminate early (ET Visit), EOS assessments will be performed at the ET Visit; however, efficacy assessments (IR-ADHD-RS-5, CGI-S, CGI-I, SDSC and WPREMB-R) **should not** be performed/collected if the ET Visit occurs > 7 days after the date of the subject's last dose of SM.

5.1.12 Unscheduled Visits

At the discretion of the investigator throughout the study, unscheduled visits may be conducted to perform or repeat assessments, including 12-lead ECG, measure vital signs (including orthostatic blood pressure/pulse rate, respiratory rate, and temperature) and weight, draw blood sample for hematology and/or serum chemistry and/or urine drug screen, administer age-appropriate C-SSRS ("*Since Last Visit*"; if "*Children's*" version used at screening, use "*Children's*"), perform physical examination or efficacy assessments. AEs, concomitant medications, and caffeine intake should also be assessed at all unscheduled visits. SM may also be dispensed and/or returned at unscheduled visits, if needed.

6 STUDY VARIABLES AND ASSESSMENTS

6.1 Efficacy Assessments

6.1.1 ADHD Rating Scale-5 (ADHD-RS-5)

The ADHD Rating Scale has been one of the most commonly used measures of drug efficacy in the treatment of ADHD in children, adolescents and adults. The ADHD-RS-5 is an ADHD-specific rating scale designed and validated to assess current ADHD symptomatology as described in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The scale consists of 18 items that directly correspond to the 18 DSM-5 symptoms and are further subdivided into two subscales: Hyperactivity/Impulsivity (9 items) and Inattention (9-items) (DuPaul et al., 1998a; DuPaul et al., 1998b; DuPaul, 2016). The ADHD-RS-5 scale rates the frequency and severity of each symptom on a 4-point Likert-type scale from 0 (none) to 3 (severe) and allows assessment of functional impairments linked to each symptom dimension. The ADHD-RS-5 rating scale is one of the most commonly used measures of drug efficacy in the treatment of ADHD and is a secondary outcome measure for this study.

6.1.1.1 Investigator-Rated ADHD-RS-5 (IR-ADHD-RS-5)

The ADHD-RS-5 Home Version will be administered and scored by a trained investigator (IR-ADHD-RS-5) at each weekly visit from Screening through EOS. The *IR-ADHD-RS-5 Home Version: **Child*** (Appendix 11.1.1.1) will be administered to subjects who are ***6 to 11 years of age***. The *IR-ADHD-RS-5 Home Version: **Adolescent*** (Appendix 11.1.1.2) will be administered to subjects who are 12 years of age and older. If an 11-year-old subject turns 12 years of age after screening, continue to administer the *IR-ADHD-RS-5 Home Version: **Child*** throughout the trial, regardless.

6.1.1.2 Parent-Rated ADHD-RS-5 (PR-ADHD-RS-5)

In addition, 1-2 days prior to Study Visits 2, 6, and 10 the subject's parent/guardian will complete two PR-ADHD-RS-5, one in the morning and another in the evening, as follows:

Morning Assessment: Parent will rate their child's behavior based upon interactions with their child during the morning hours in the past week. If the subject is **6 to 11 years of age**, parent will use the 'Morning' *PR-ADHD-RS-5 Home Version: **Child*** (Appendix 11.1.2.1). If the subject is ***12 years of age and older***, parent will use the 'Morning' *PR-ADHD-RS-5 Home Version: **Adolescent*** (Appendix 11.1.2.2). If an 11-year-old subject turns 12 years of age after screening, continue to administer the *'Morning' PR-ADHD-RS-5 Home Version: **Child*** throughout the trial, regardless. This can be completed on electronically diary or paper version.

Evening Assessment: Parent will then rate their child's behavior based upon interactions with their child during the evening hours in the past week. If the subject is **6 to 11 years of age**, parent will use the *'Evening' PR-ADHD-RS-5 Home Version: **Child*** (Appendix 11.1.3.1). If the subject is ***12 years of age and older***, parent will use the *'Evening' PR-ADHD-RS-5 Home Version: **Adolescent*** (Appendix 11.1.3.2). If an 11-year-old subject turns 12 years of age after screening, continue to administer the '*Evening' PR-ADHD-RS-5 Home Version: **Child*** throughout the trial, regardless. This can be completed on electronic diary or paper version.

6.1.2 Clinical Global Impression – Severity of Illness Scale (CGI-S)

The Clinical Global Impression scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (Guy, 1976; Appendix 11.2). The CGI-S is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The CGI-S is evaluated on a 7-point scale with 1 = Normal, not at all ill, 2 = Borderline Ill, 3 = Mildly Ill, 4 = Moderately Ill, 5 = Markedly Ill, 6 = Severely Ill, and 7 = Extremely Ill. Successful therapy is indicated by a lower overall score in subsequent testing.

6.1.3 Clinical Global Impression – Improvement Scale (CGI-I)

The Clinical Global Impression scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (Guy, 1976; Appendix 11.3). The CGI-I is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. The CGI-I is evaluated on a 7-point scale with 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse. Successful therapy is indicated by a lower overall score in subsequent testing.

6.1.4 Sleep Disturbance Scale for Children (SDSC)

The Sleep Disturbance Scale for Children (SDSC) is an instrument originally developed and validated as a parent-report measure to screen for sleep disturbances in children and adolescents 6-15 years of age (Bruni et al., 1996; Appendix 11.4). It has since been validated in broader pediatric populations, 5-18 years of age (Marriner et al., 2017), including in an ADHD population (Vincent et al., 2019) The SDSC is a 26-item questionnaire from which six factor/subscale scores are generated: (1) disorders of initiating and maintaining sleep, (2) sleep breathing disorders, (3) disorders of arousal, (4) sleep-wake transition disorders, (5) disorders of excessive somnolence, and (6) sleep hyperhidrosis (or excessive sweating that's not necessarily related to heat or exercise). For item 1, the parent indicates the average sleep duration most nights on a 5-point Likert scale, where 1=*9-11 hours*, 2=*8-9 hours*, 3=*7-8 hours*, 4=*5-7 hours*, and 5=*less than 5 hours*. For item 2, the parent indicates the average sleep latency (duration of time it takes their child to fall asleep after going to bed) on a 5-point Likert scale, where 1=*less than 15 minutes*, 2=*15-30 minutes*, 3=*30-45 minutes*, 4=*45-60 minutes*, and 5=*more than 60 minutes.* Items (sleep/sleep-related problems) 3 to 26, the parent rates their child indicating the frequency with which their child has experienced any of these sleep/sleep-related problems in the past week; ratings are on a 5-point Likert scale (1 to 5), where 1=*Never*, 2=*Occasionally (once or twice per month or less),* 3=*Sometimes (once or twice per week)*, 4=*Often (3 or 5 times per week)*, and 5=*Always (daily)*. The sum of scores for these six factors/subscales yields one Total score (score ranges from 26 to 130). Raw scores can be converted to T-scores, where a T-score >70 (>95th percentile) is indicative of a clinically significant sleep problem. The parent will rate their child for each item based on the past week (7 days). It takes 5-10 minutes to complete the SDSC.

6.1.5 Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R)

The Parent Rating of Evening and Morning Behavior-Revised (PREMB-R) is a validated, 11-item scale validated for assessment of ADHD-related morning and evening behaviors (Sutton et al., 2003; Faraone et al., 2018; Appendix 11.5) that assesses at-home functioning (i.e.,

behaviors that impact activities of daily living, such as getting up and out of bed, doing or completing homework, and falling asleep) during the early morning (PREMB-R *AM*) and late afternoon/evening (PREMB-R *PM*) in children with ADHD (Sutton et al., 2003; Faraone et al. 2018). It includes surrogate measure of ADHD-related severity of impairment ("*Difficult with…*") rather than frequency of ADHD symptoms. It primarily focuses on Evening Behaviors, but includes assessment of Morning Behaviors (e.g., getting out of bed, getting ready and arguing/struggling). PREMB-R has been administered as clinician-rated (by interview) or parent rated, and it has been administered for daily (DPREMB-R) or weekly (WPREMB-R) assessments (Carlson et al 2007; Faraone et al., 2018; Wehmeier et al. 2009). For this trial, the WPREMB-R will be administered as a parent-rated to measure both morning- and evening-related functional impairment in children and adolescents in past week. Each item is rated from 0 (no difficulty) to 3 (a lot of difficulty), with the three-item WPREMB-R *AM* having a maximum score of 9, and the eight-item WPREMB-R *PM* having a maximum score of 24. It takes ~5 minutes to complete.

6.2 Safety Variables and Assessments

Safety assessments include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs and 12-lead ECGs, and the performance of physical examinations as detailed in the Schedule of Events and Assessments (Table 2).

Site Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Supernus or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subjects.

6.3 Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (GCP), an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent injuries, or exacerbation of an existing disease.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

6.3.1 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) are defined as seizure or AEs that might represent a seizure. This includes, but is not limited to syncope/syncopal episode, pseudoseizure, myoclonus, and severe muscle spasms.

6.3.2 Causality

Adverse events may be categorized as either Adverse Drug Reactions or Suspected Adverse Drug Reactions based on their relationship to SM and the degree of certainty about causality.

Suspected adverse drug reactions (SADRs) are a subset of adverse events for which there is evidence to suggest a causal relationship between the drug and the AE, i.e., there is a reasonable possibility that the drug caused the adverse event.

Adverse drug reactions (ADRs) are a subset of all SADRs for which there is reason to conclude that the drug caused the event.

6.3.3 Recording and Evaluation of Adverse Events

All subjects who are screened (Visit 1) will be questioned regarding the occurrence of AEs, which will be documented as medical history. At each contact with the subject, and beginning after first dose, the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate adverse event module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated WBC, cough, abnormal chest X-ray, etc., can all be reported as “pneumonia”.

All AEs occurring after Visit 2 and throughout the study period must be recorded. A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study medication is taken, or that worsened following first administration of study medication (SPN-812). All AEs in this study will be recorded after administration of SM, therefore all will be treatment-emergent. The clinical course of each AE should be followed for at least 30 days following the date of last dose of SM (either due to EOS or ET) or until resolution or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

The Investigator is responsible for evaluating AEs and determining the following:

- Serious vs. Non-serious: Is the event a Serious Adverse Event (SAE)?
- Causality: Was AE related or possibly related to the SM?
- Severity: How pronounced is the incapacity/discomfort caused by an AE?

6.3.4 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the

accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

6.3.5 Criteria for Assessing Causality

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a causal relationship unlikely, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- Not related: Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- Unlikely related: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on drug withdrawal may be lacking or unclear. This will be reported as a **Suspected Adverse Drug Reaction (SADR)**.
- **Definitely related**: Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the medication (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **Adverse Drug Reaction (ADR)**.

6.3.6 Serious Adverse Events

Adverse events are classified as serious or non-serious. An AE or ADR is considered "serious" if, in the view of either the investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

6.3.7 Investigator Responsibilities for Reporting SAEs/AESIs

The Site Investigator must immediately report to the Sponsor all SAEs/AESIs, regardless of whether the Investigator believes they are drug related.

All SAEs/AESIs must be reported to the Drug Safety Contact within 24 hours of first becoming aware of the SAE/AESIs. The Investigator must complete an SAE/AESIs Form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents). The investigator will keep a copy of this SAE/AESIs Report form on file at the study site.

The Site Investigator or study physician, after thorough consideration of all facts that are available, must include an assessment of causality of an AE to SM in the report to the Sponsor.

Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor, as it becomes available, using the SAE/AESIs Report Form.

The Drug Safety Contact for SAE/AESI reporting is:

[redacted]

6.3.8 Other Events Requiring Immediate Reporting

Acute suicidal crisis or clinically significant suicidal behavior or ideation should be reported to the Drug Safety Contact within 24 hours of first becoming aware of the event. Pregnancy should also be reported to the Sponsor's Drug Safety Contact within 24 hours of confirmation.

6.3.9 Sponsor Responsibilities for Reporting SAEs

The Sponsor will inform Site Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study sites submit SAE information to the Sponsor in the manner described above.

Site Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB). Investigators must also submit the safety information provided by the Sponsor to the IRB unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB.

It is the responsibility of the Sponsor to notify all participating investigators, in a written IND safety report, of any SADR that is both serious and unexpected. The Sponsor will also notify participating investigators of any findings from other sources (other studies, animal and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

6.4 Treatment-Emergent Suicidal Ideation

Prospective assessment of suicidal ideation and suicidal behavior is a mandatory part of the safety evaluations for any drug developed for a psychiatric indication (FDA Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, 2012). In this study, the initial evaluation of subjects will be conducted prior to enrollment to assess lifetime suicidal ideation and to identify subjects who must not participate in the trial due to pre-existing suicidality risk. The assessment will then be repeated at each subsequent study visit to monitor the occurrence of new suicidal and self-injurious tendencies.

6.4.1 Columbia Suicide Severity Rating Scale (C-SSRS)

Assessment of suicidal ideation and behavior will be conducted using the C-SSRS. The C-SSRS is an FDA-recommended prospective assessment instrument that directly classifies suicidal ideation and behavior events into 11 preferred categories, including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent. The instrument has been validated and used successfully in both children and adolescent patients with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating.

For subjects who are **6 to 11 years of age**, use the:

a. Children's "Baseline/Screening" version at Study Visit 1/Screening (Appendix 11.6.1)
b. Children's "Since Last Visit" version at Study Visits 2-10 (Appendix 11.6.2)
   NOTE: If child is 11 yrs old at screening, please use the Children's "Since Last Visit" version throughout their study, even at visits occurring on or after their 12th birthday.

For subjects who are **12 years of age and older**, use the:

a. "Baseline" version at Study Visit 1/Screening (Appendix 11.7.1)
b. "Since Last Visit" version at Study Visits 2-10 (Appendix 11.7.2).

6.4.2 Suicide Risk Management Plan

The protocol procedures related to clinical care of patients with treatment-emergent suicidal ideation and behavior must be implemented to ensure proper management of the event and protection of subject's safety. If a disclosure of suicidal ideation is revealed as part of the C-SSRS questionnaire or when a subject spontaneously expresses that he/she may be a threat to him/herself, the study team should be prepared to quickly evaluate the event and to determine the appropriate course of action.

6.4.2.1 Assessment of Suicide Risk

Any indication of suicidal ideation should be evaluated as soon as possible by appropriately trained staff. The Investigator is responsible for making the final judgment regarding potential suicide risk and need subsequent action.

6.4.2.2 Acute Suicidal Crisis

A person evaluated as being at high risk should be transferred to an immediate care facility. The Investigator will guide intervention as clinically indicated and follow up with the subject within 1 week and/or refer him/her to a qualified mental health professional.

6.4.2.3 Non-acute Suicidal Risk

The Investigator will conduct safety planning with the subject and will follow up within 1 week. Reference materials for subjects and caregivers should include lists of mental health organizations and professionals, outpatient behavioral services, local crisis and peer support groups and Suicide/Crisis Hotlines.

6.5 Clinical Measurements

6.5.1 Physical Examinations and Height

Physical examinations and measurement of height will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). The physical examination conducted at Screening will include assessments of all body systems, except genitourinary. Any findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical examination, only changes from baseline (Screening Visit) will be noted.

6.5.2 Vital Signs and Weight

Vital signs measurements (e.g., orthostatic blood pressure/pulse rate, oral temperature, and respiratory rate) and body weight will be obtained at every study visit as shown in the Schedule of Events and Assessments (Table 2). Orthostatic blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes and again within 3 minutes of subject standing. Vital signs may be taken at any other time, as deemed necessary by the Investigator, but must be measured as described above.

6.5.3 Screening and Clinical Safety Laboratory Assessments

Hematology and chemistry clinical laboratory tests will be performed by a central laboratory as specified in the reference binder.

Table 3 presents the clinical laboratory tests to be performed.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 2) shows the time points at which blood and urine samples will be collected.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell (WBC) count with differential
Urinalysis	Macroscopic examination[a], pH, specific gravity, protein, glucose, ketone, occult blood, WBC, nitrites, bilirubin, urobilinogen
Chemistry	**Electrolytes**: Chloride, potassium, sodium, bicarbonate
	Liver function tests: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin
	Thyroid function panel: T3, T4, TSH
	Renal function parameters: blood urea nitrogen, creatinine
	Other: glucose, Ca^{+2}, albumin, total protein
Serum Pregnancy Test	FOCP only; **Study Visit 1 only**
Urine Pregnancy Test	FOCP only; **Study Visits 2 thru 10 only**
'Standard' Urine Drug Screen	Alcohol, amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, cotinine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, tricyclic antidepressant, THC (cannabinoids); **Study Visit 1 only**
'Point of Care' Urine Drug Screen Test 1	Amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, tricyclic antidepressant, THC (cannabinoids); **Study Visits 2 thru 10 only**
'Point of Care' Urine Drug Screen Test 2	Methylphenidate; **all study visits (1-10)**
'Point of Care' Urine Drug Screen Test 3	Propoxyphene; **all study visits (1-10)**

FOCP = females of childbearing potential; WBC = white blood cell
[a] A microscopic examination will be performed on abnormal findings unless otherwise specified.

6.5.4 Electrocardiograms (ECGs)

A 12-lead ECG will be obtained at every study visits as shown in the Schedule of Events and Assessments (Table 2). Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 10 minutes. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 hours by the Investigator or qualified Sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT interval corrected using Fridericia's method).

6.6 Confirmatory Blood Sample Assessment

An additional confirmatory blood sample will be collected at each study visit (1-10) to assess concentrations of psychostimulant and viloxazine and its metabolite. Confirmatory blood samples for measurement of plasma concentrations of viloxazine (and 5-hydroxy-viloxazine glucuronide, if applicable) and of psychostimulant will be collected at any time during the Visit, shown in the Schedule of Events and Assessments (Table 2).

6.7 Screening Scales and Assessment Tools

6.7.1 Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)

The Mini-International Neuropsychiatric Interview for Children and Adolescents is a semi-structured interview designed to determine early diagnosis of affective childhood mental disorders and/or current and past episodes of psychopathology in children and adolescents 6 to 18 years of age according to DSM-5 criteria (Sheehan et al., 2010; APA, 2013; Duncan et al., 2018; Appendix 11.8).

7 STATISTICAL METHODS

7.1 General Considerations

All statistical analysis will be performed using SAS version 9.2 or higher either by Supernus or a designated CRO.

All tabulations of analysis results will include summaries for treatment arms of SPN-812 100 mg and placebo.

Where appropriate, variables will be summarized descriptively: frequency count and percentage for categorical variables; and number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables.

Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are too small for asymptotic assumptions, exact testing techniques will be used.

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the eCRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Baseline is defined as the last non-missing assessment recorded before receiving the first dose of study medication.

Complete details of the statistical analysis will be provided in a separate statistical analysis plan (SAP). The statistical analysis methods described in the SAP will supersede the statistical methods described in this protocol.

7.2 Handling of Missing Data

Missing dates for occurrence of adverse events and non-study medication use will be imputed. The details will be presented in the SAP.

7.3 Analysis Populations

The **Enrolled Population** consists of all subjects who have signed Informed Consent/Assent and have fulfilled all Inclusion/Exclusion Criteria.

The **Safety Population** consists of all subjects who enrolled in the study and receive at least one dose of SM. Subjects in the Safety Population may be analyzed according to the psychostimulant treatment that they received. The Safety population will be used for all safety and efficacy variables.

7.4 Demographics and Baseline Analysis

Demographic/baseline variables [including age, sex, ethnicity, race, height and weight, and BMI at screening, baseline IR-ADHD-RS-5 scores (Total score, Inattention subscale score, Hyperactivity/Impulsivity subscale score), the "Morning" PR-ADHD-RS-5 scores (Total score,

Inattention subscale score, “Hyperactivity/Impulsivity subscale score), the “Evening” PR-ADHD-RS-5 scores (Total score, Inattention subscale score, Hyperactivity/Impulsivity subscale score), CGI-S score, SDSC total score and subscale scores, and WPREMB-R total score and morning/evening scores] will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables. The descriptive summary will be presented by optimized dose group for Safety Population.

7.5 Subject Disposition

A disposition of subjects will include the number and percentage of subjects in each of the following categories:

- Subjects in the Enrolled Population
- Subjects in the Safety Population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized.

The reason for early discontinuation may include any of the following:

- Withdrawal of consent
- Noncompliance
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

7.6 Study Medication Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to SM. This will be calculated for each subject by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1) and multiply that by the number of capsules that the subject was instructed to take daily during the treatment period (i.e, between visits) for total daily dose planned dose (‘X’).

Duration of treatment exposure will be summarized by duration category and will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of SM compliance is defined as {(number of capsules dispensed minus number of capsules returned) / X × (date of last dose minus date of first dose + 1)}* 100%.

For subjects 6 to 11 years of age, ‘X’ may be equal to:

- 1 (1 × 100mg); or
- 2 (2 × 100mg); or
- 3 (3 × 100mg); or
- 4 (4 × 100mg)

For subjects 12 to 17 years of age, ‘X’ may be equal to:

- 1 (1 × 100mg) or (1 × 200mg); or
- 2 (2 × 200mg) or ([1 × 200mg] + [1 × 100mg]); or
- 3 (3 × 200mg) or ([2 × 200mg] + [1 × 100mg])

$$\%\ SM\ compliance = 100\ \text{x}\ \left[\frac{(\text{no. of capsules dispensed}) - (\text{no. of capsules returned})}{\text{X} \times [(\text{date of last dose}) - (\text{date of first dose}) + 1]}\right]$$

For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment.

7.7 Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO-DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the Safety Population.

7.8 Primary Analysis

All primary and secondary analyses will be based on the Safety Population. Evaluation of safety will be performed for the safety population. Safety data that will be evaluated include concomitant medications, AEs, clinical laboratory results, vital signs, ECGs, and findings from the physical examinations. Suicidal ideation and suicidal behavior will be measured by C-SSRS.

All summary tables related to safety analyses will use the safety population.

7.8.1 Primary Safety Analysis

Safety analyses will be performed by optimized dose group based on the Safety Population.

The incidence rate of AEs will be calculated by treatment arm for each System Organ Class (SOC) and Preferred Term (PT). The severity of the AEs and the relationship to SM will be summarized by treatment arm for each SOC and PT.

AEs will be summarized using discrete summaries at the subject and event level by SOC and PT, and by severity and relationship separately for each treatment arm. Verbatim description and Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for all AEs will be contained in the subject data listings.

Clinical laboratory values will be summarized by visit by treatment arm using descriptive statistics. For quantitative laboratory parameters, both actual values and change from Screening values will be summarized.

Vital signs will be summarized by visit by treatment arm using descriptive statistics. Both actual values and CFB will be summarized.

ECG results will be summarized by visit by treatment arm using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).

7.8.2 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each group of doses. Similarly, treatment-emergent AEs will be summarized by severity and relationship separately. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the subject data listings.

All AEs occurring throughout the study period will be recorded. Treatment-emergent AEs (TEAEs) will be collected starting after the first dose of SM (Visit 1) to the end of the study. These AEs include those that emerge during treatment or worsen in severity during treatment. These AEs will be tabulated, listed and analyzed.

TEAE incidence tables will be listed and summarized by the group, if applicable, of optimized dose (100, 200, 300, 400, 500 or 600 mg/day) the subject received. The incidence rates for all SADRs will also be summarized as described for all TEAEs.

Listings (and tabular summaries, if warranted) of deaths, other SAEs, and other significant TEAEs, including TEAEs resulting in treatment discontinuation, will be provided.

7.8.3 Clinical Laboratory Values

Clinical laboratory values for hematology and chemistry will be summarized by visit and by group of optimized dose (100, 200, 300, 400, 500, 600 mg/day) received using descriptive statistics. For quantitative laboratory parameters, both actual values and change from Baseline values will be summarized.

Laboratory test results will be assigned a low, normal, high (LNH) classification according to whether the values were below (L), within (N), or above (H) the laboratory parameters' reference ranges provided by the central laboratory. By subject-listings of all abnormal laboratory values, i.e., those with L or H classification will be provided.

7.8.4 Vital Signs, Height, Weight and BMI

Vital signs will be summarized by the group, if applicable, of the optimized doses (100, 200, 300, 400, 500, 600 mg/day) the subject received using descriptive statistics. Both actual values and changes from the Baseline to final visit will be summarized. Descriptive summary statistics (mean, SD, median, and range) for vital signs' data, height, weight, and BMI will be evaluated.

7.8.5 Electrocardiogram (ECG) Results

Tabular summaries of the quantitative ECG parameters and the overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant) will be presented by group of the optimized doses (100, 200, 300, 400, 500, 600 mg/day). The QT will be corrected using Fridericia's method.

ECG results will be summarized by visit and by group, if applicable, of optimized doses using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative

ECG parameters, including the overall ECG finding). For quantitative ECG parameters, both actual values and change from Baseline values will be summarized

7.8.6 Concomitant medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO-DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented

7.8.7 C-SSRS

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The “Non-suicidal Self-injurious Behaviors” category will be captured separately. The summary will be presented by group of optimized dose (100, 200, 300, 400, 500, 600 mg/day) the subject received and if applicable by visit.

7.9 Efficacy Analysis

Where applicable, each of the efficacy assessments/scales variable (IR-ADHD-RS-5, CGI-S, CGI-I, ‘Morning’ and ‘Evening’ PR-ADHD-RS-5, SDSC, and WPREMB-R) will be listed and summarized by group, if applicable, of optimized dose. Total score for the ADHD-RS-5, as well as the Hyperactivity/Impulsivity and Inattention subscale score, will be summarized by optimized dose and visit and will be examined for trends.

7.10 Sample Size and Power Considerations

There is no consideration for power or sample size determination in this open-label study. There are approximately 50 subjects expected to complete this study. Based on an early discontinuation rate of 20%, approximately 60 subjects would need to be enrolled. Based on a screen failure rate of 40%, approximately 100 subjects will be screened to enroll approximately 60 subjects.

7.11 Interim Analysis

No interim analysis will be performed.

7.12 Pharmacokinetic Analyses

No pharmacokinetic analyses other than summary statistics of plasma concentrations of psychostimulant (methylphenidate and amphetamine) and viloxazine and its metabolite obtained from confirmatory blood sampling (Section 6.6).

8 DOCUMENTATION

8.1 Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

8.2 Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor, and IRB must be notified promptly.

Changes to the protocol which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor or CRO will send a letter to the IRB detailing such changes.

8.3 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor’s Quality Assurance team or qualified designee, which is an independent function from the study conduct team.

8.3.1 Data Collection

The primary source document will be the subject’s medical record. If separate research records are maintained by the Investigator(s), both the medical record and the research record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF completion instructions that are provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of GCP.

8.3.2 Clinical Data Management

Data from eCRFs and other external data (e.g., laboratory data) will be entered into or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

8.3.3 Database Quality Assurance

In accordance with the vendor's procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. The procedure for handling missing data will be addressed in the Statistical Analysis Plan (SAP). Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

8.3.4 Bioanalytical Sample Handling

The concentrations of amphetamine, methylphenidate, viloxazine and 5-HVLX-gluc in plasma will be determined using validated achiral chromatographic tandem mass spectrometry methods. The analytical range for plasma concentrations are reported as free base. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures may be included in the clinical study report. Bioanalytical sample analysis may be performed by the Bioanalytical group at Supernus Pharmaceuticals (Rockville, MD).

8.4 Retention of Records

The Investigator has the responsibility to retain all study "essential documents", as described in ICH E6 for at least two years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB correspondence). The Investigator must obtain written permission from Supernus prior to the destruction of any study document.

8.5 Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by

a regulatory authority, the Investigator must inform the Sponsor and the CRO immediately that this request has been made.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 Code of Federal Regulation (CFR) 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

8.6 Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until all Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

8.7 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

8.8 Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

8.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

9 ETHICS

9.1 Institutional Review Boards

The IRB that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the ICF will be reviewed and approved by the appropriate IRB before subjects are enrolled. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

9.2 Ethical Conduct of the Study

This study will be conducted in accordance with SOPs from both the Sponsor and the CRO. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent/Assent and IRB regulations).
- Local, national legal guidelines.

9.3 Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor).

Contact persons at the Sponsor and the CROs are listed in the reference binder provided to each investigational site. The study will be monitored by qualified personnel from the Sponsor or their designees, such as the CROs, for their respective sites. Medical writing, data management, and statistical analyses may be performed by the CROs. Laboratory tests will be conducted by a central laboratory as designated in the reference binder.

9.4 Subject Information and Consent

The Investigator (or designee) will inform the subject (and the subject’s parent or legal guardian/representative) of all aspects pertaining to the subject’s participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and subject’s parent or legal guardian/representative must sign and date the ICF before the subject can participate in the

study. The subject's parent or legal guardian/representative will be given a copy of the signed and dated ICF and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject's parent or legal guardian/representative that consent, regarding study participation, may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use the amended ICF (including ongoing subjects).

10 REFERENCES

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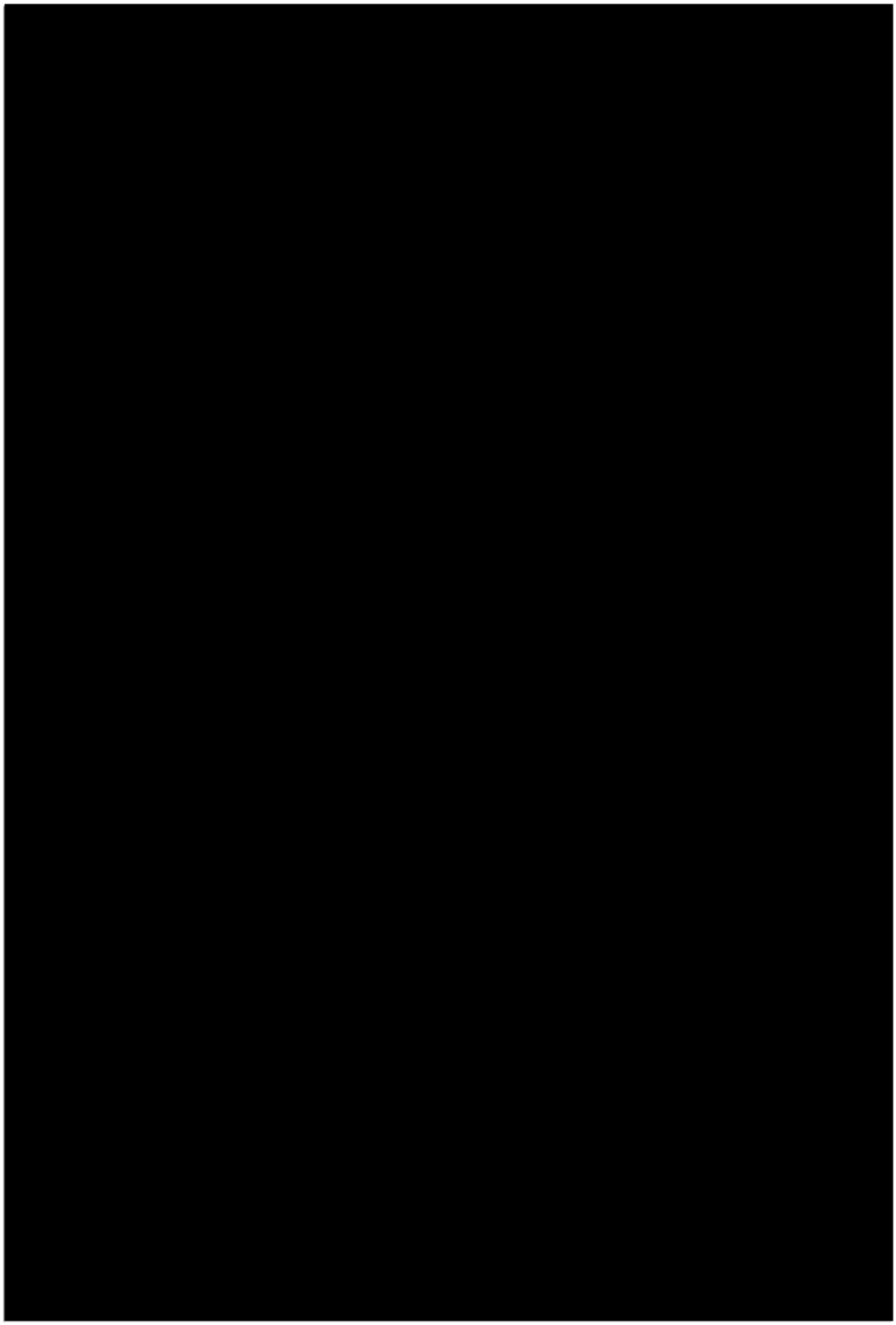
11 APPENDIX:

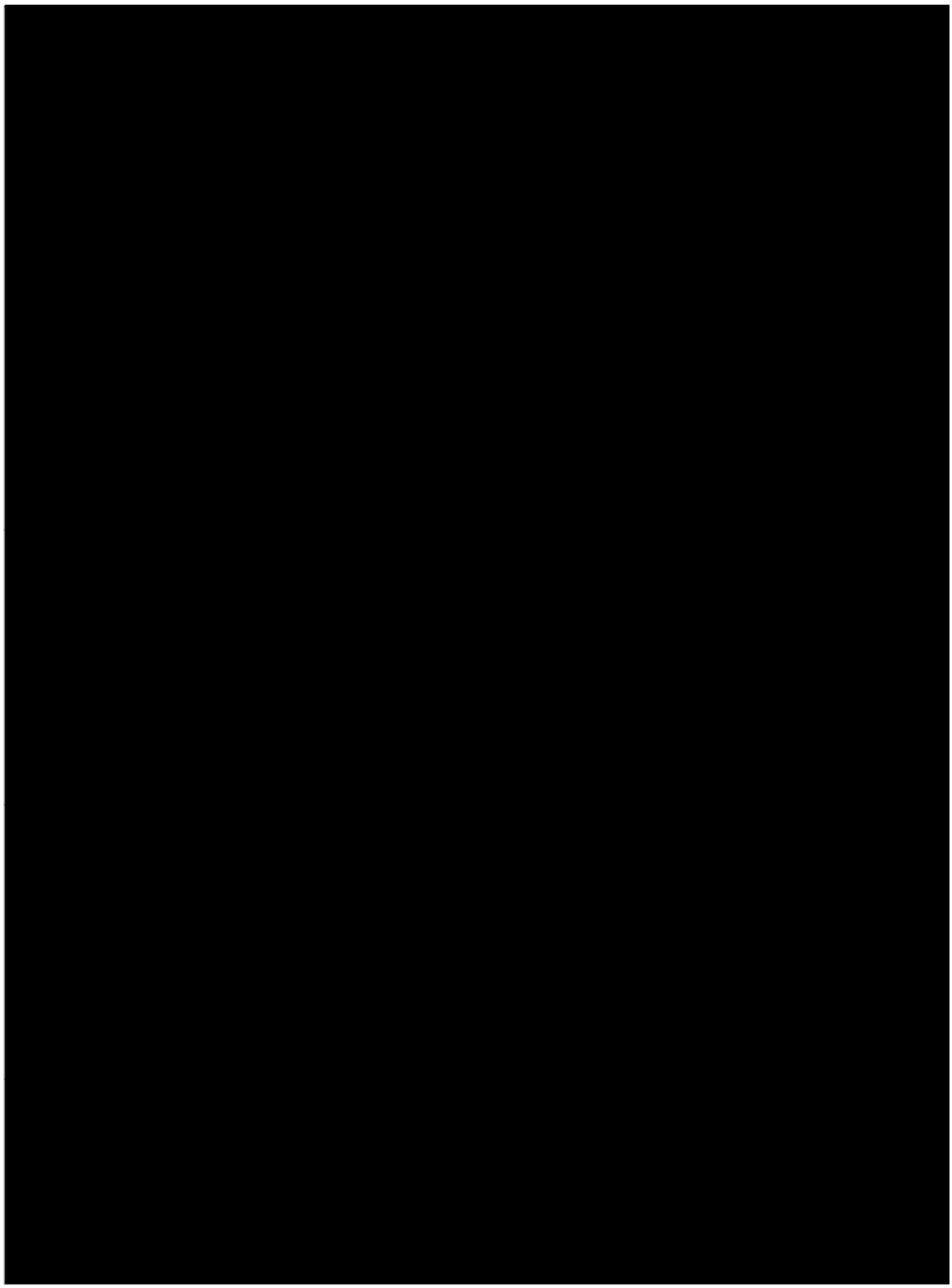
11.1 ADHD-RS-5

11.1.1 Investigator-rated ADHD-RS-5 Home Version

11.1.1.1 IR-ADHD-RS-5 Child Version [6-11 years old]

.





11.1.1.2 IR-ADHD-RS-5 Home Version: Adolescent [12-17 years old]

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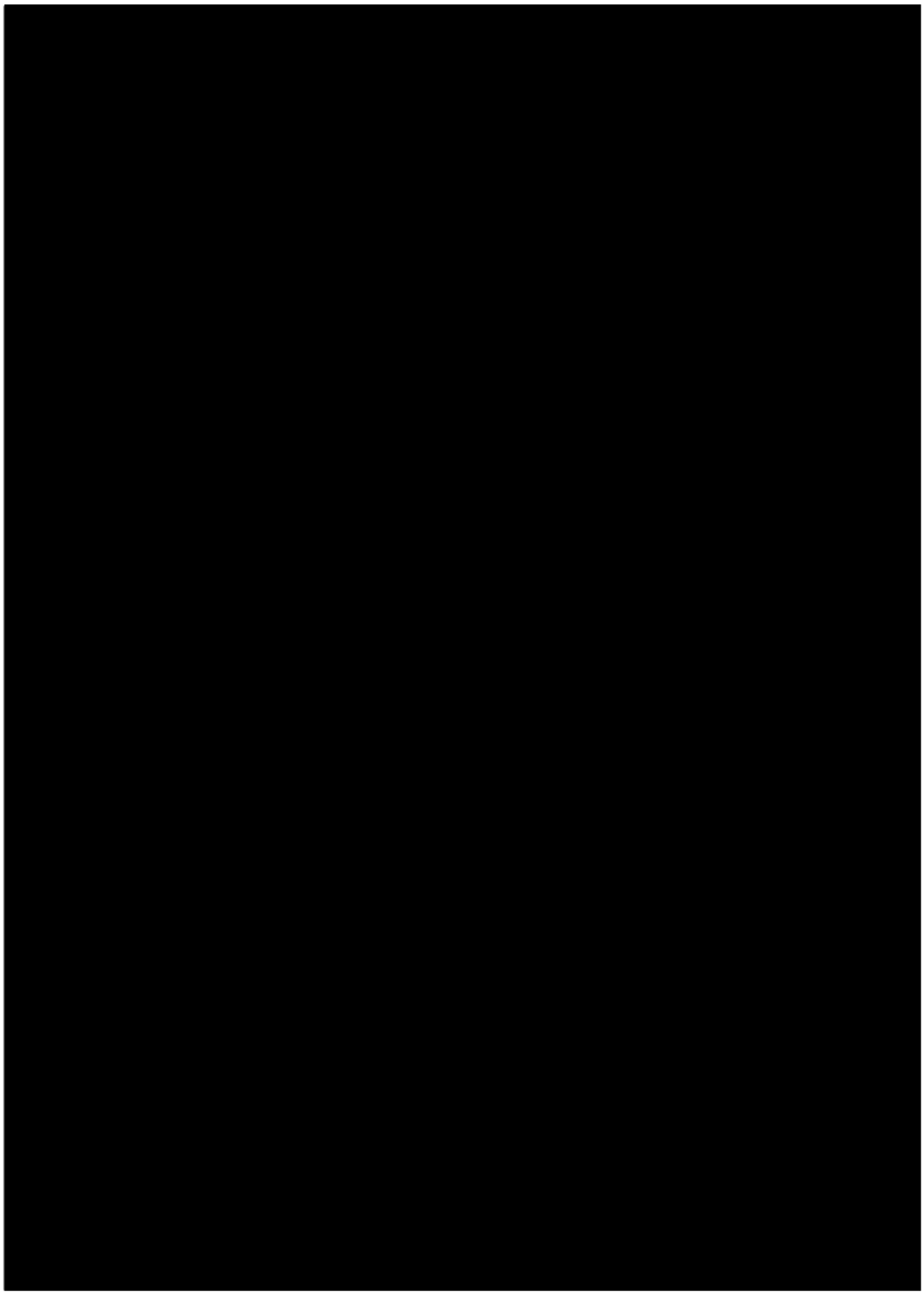
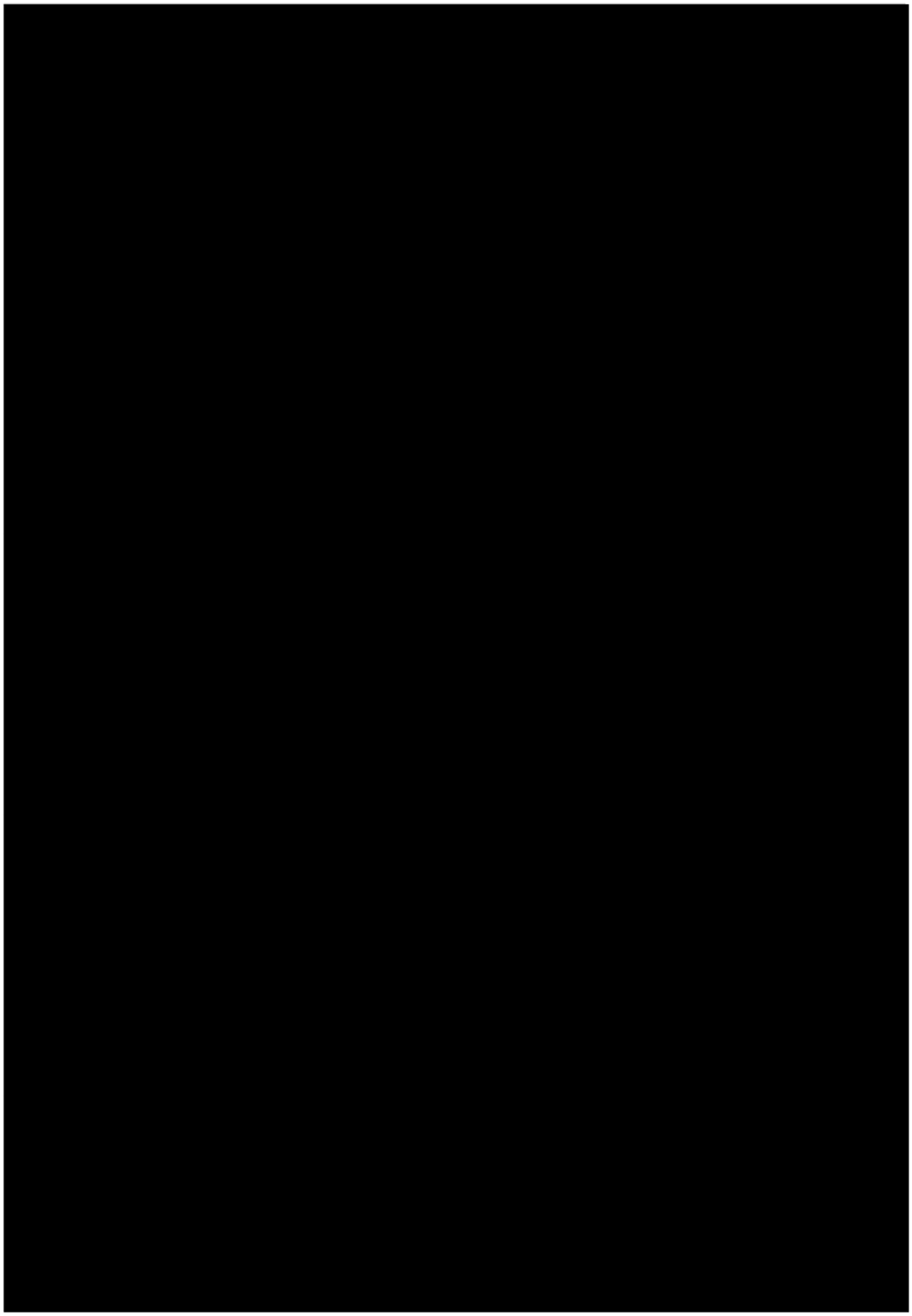
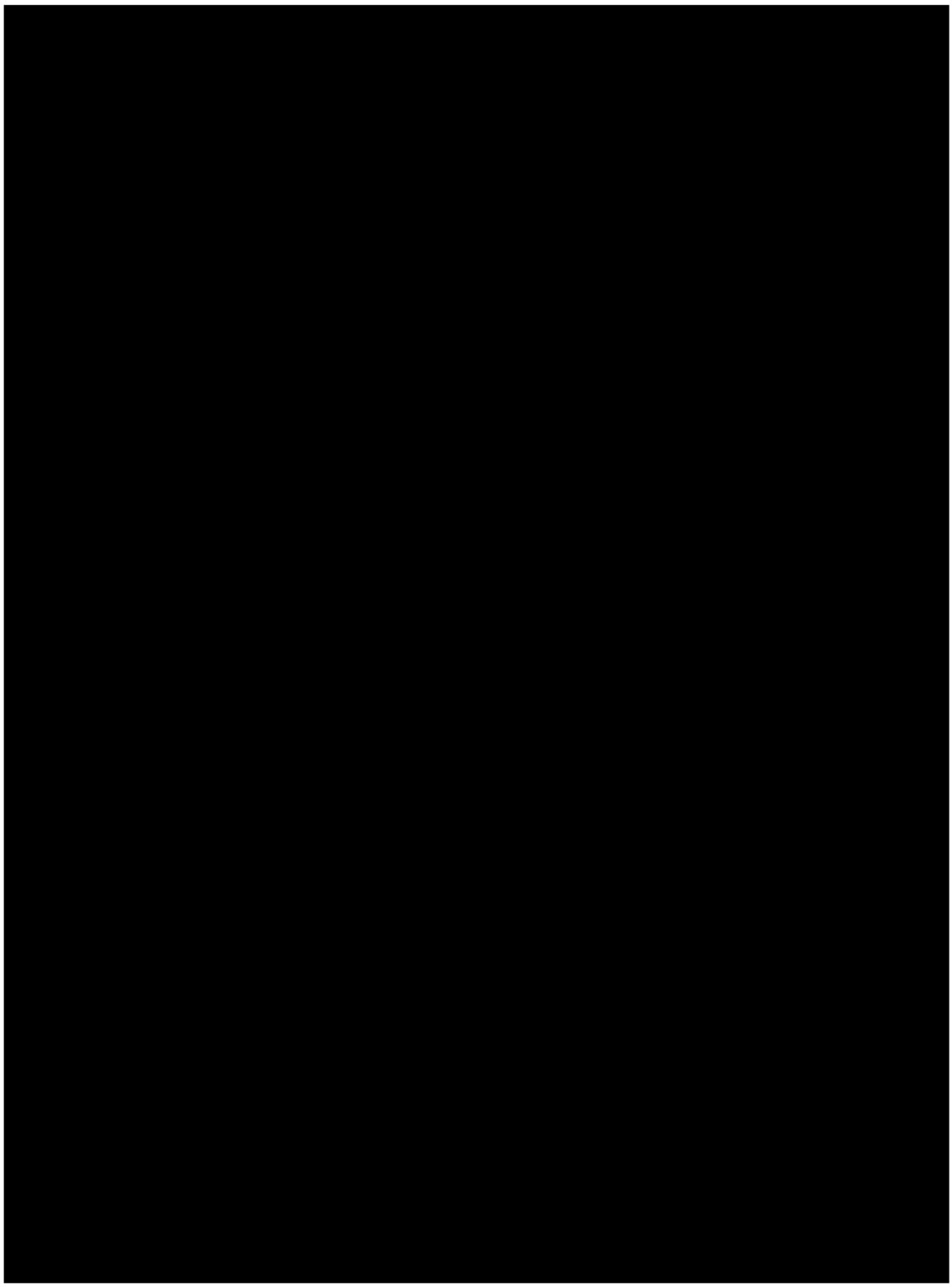
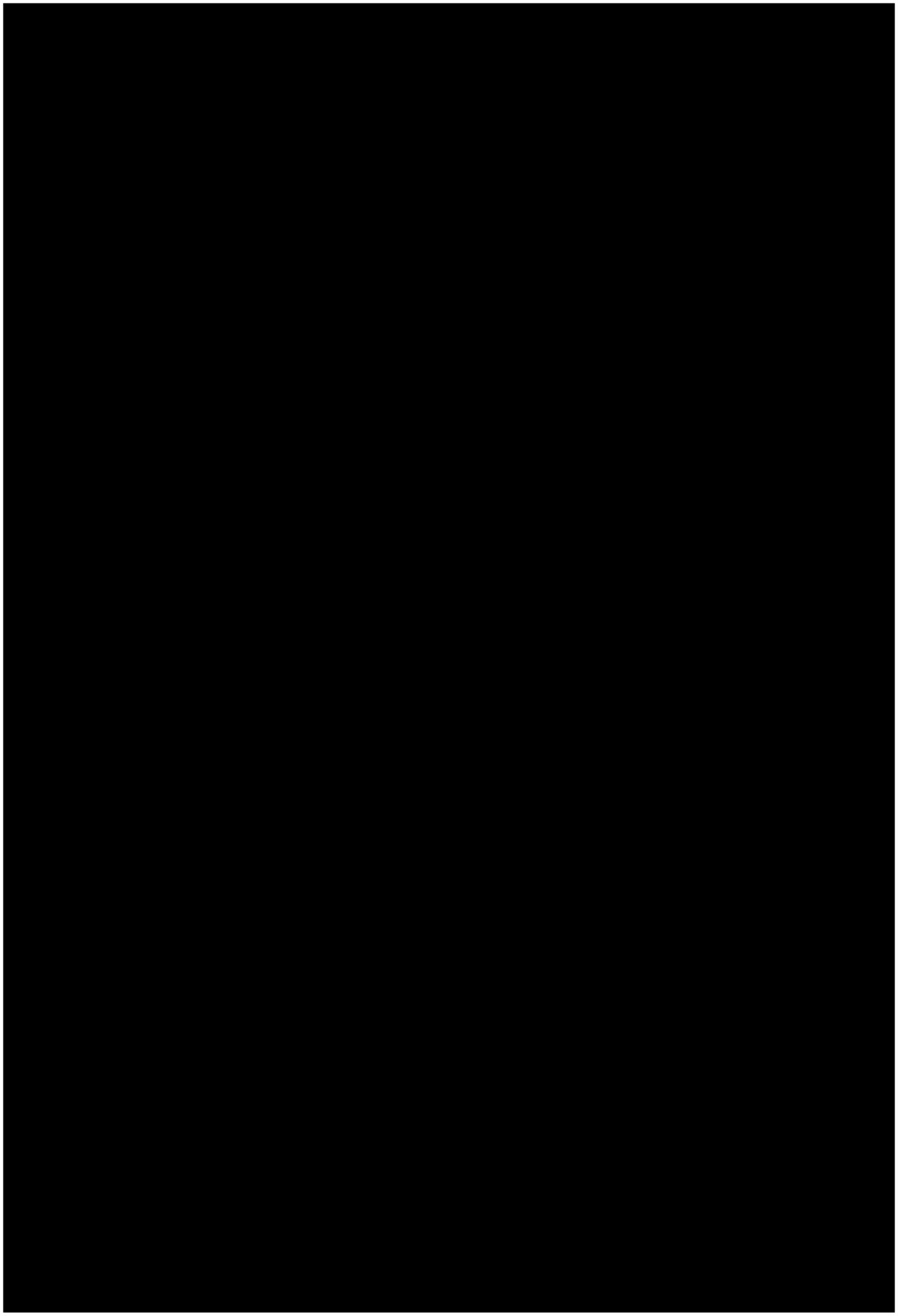




11.1.2 'MORNING Parent-rated ADHD-RS-5 Home Version

11.1.2.1 'Morning' PR-ADHD-RS-5 Child [6-11 years old]





11.1.2.2 'Morning' PR-ADHD-RS-5 Adolescent [12-17 years old]

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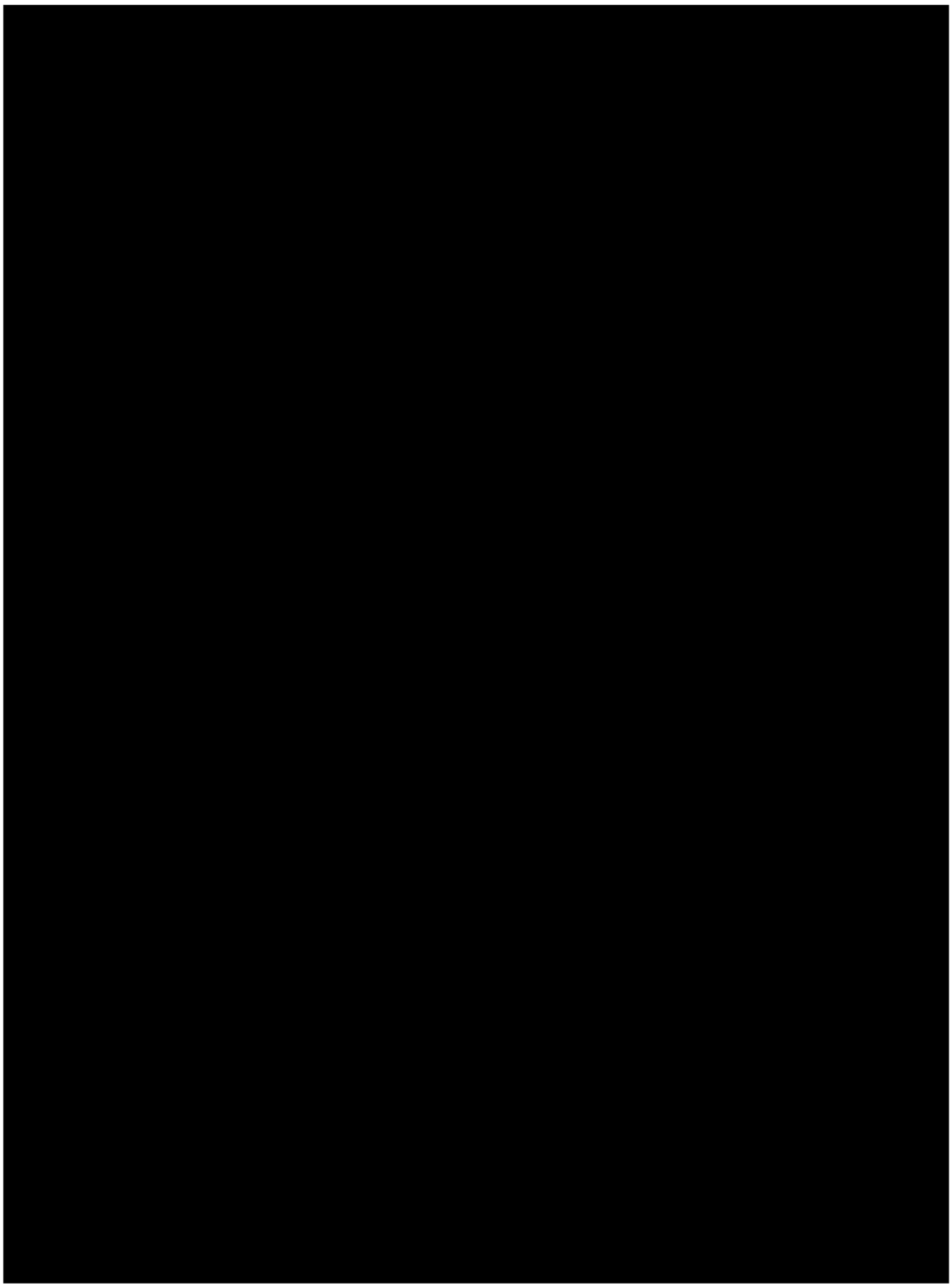
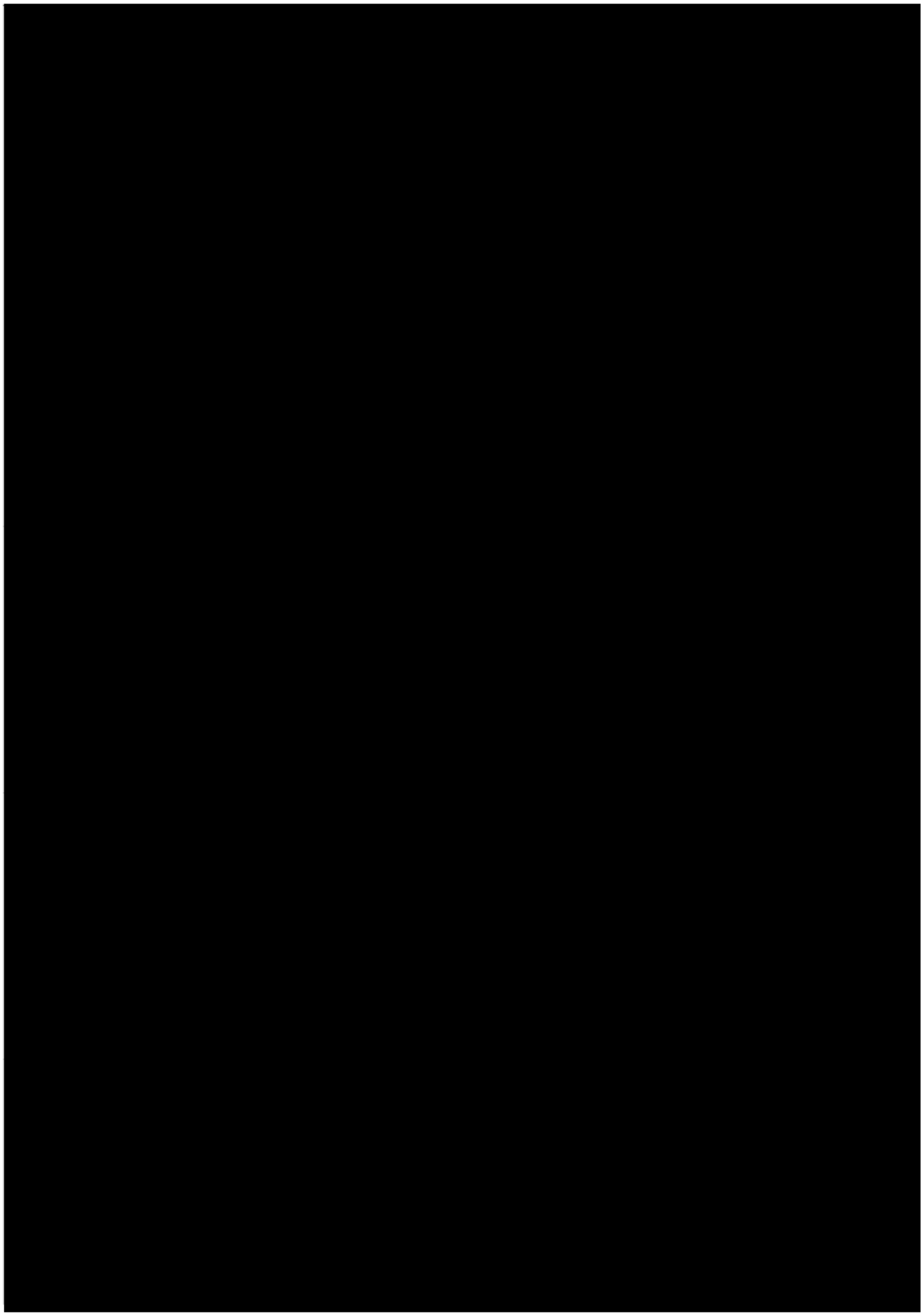
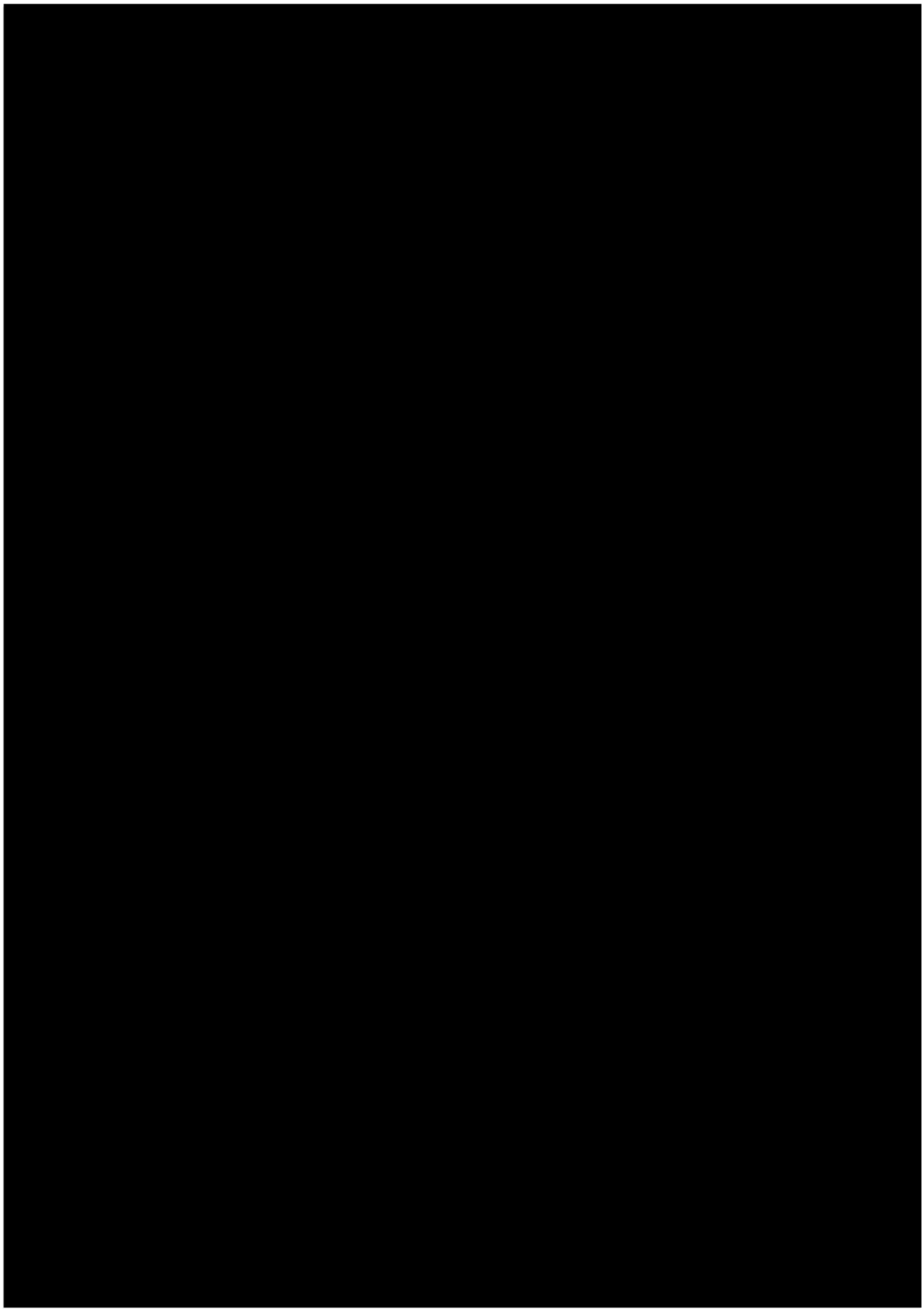
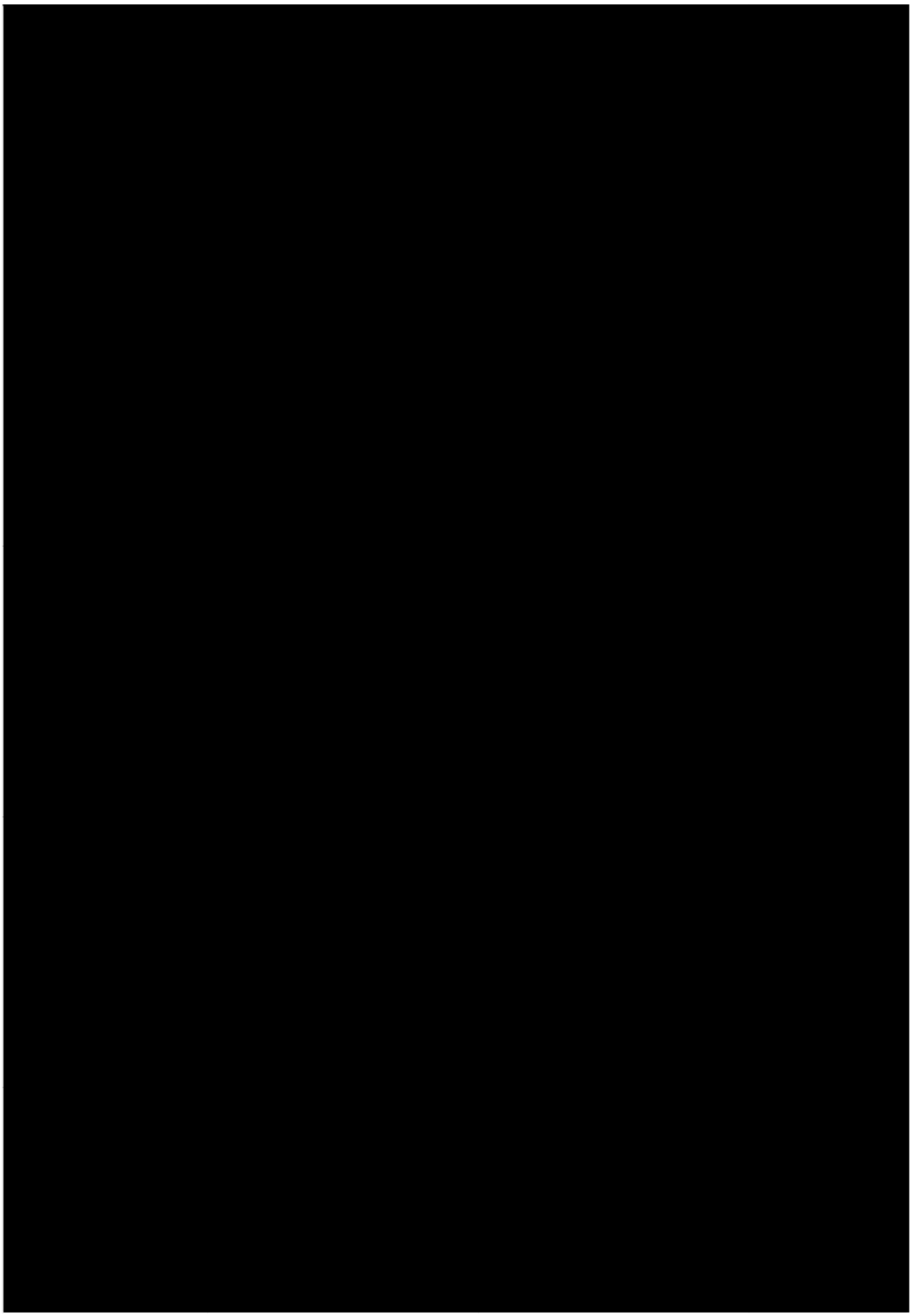




11.1.3 'EVENING' Parent-rated ADHD-RS-5 Home Version

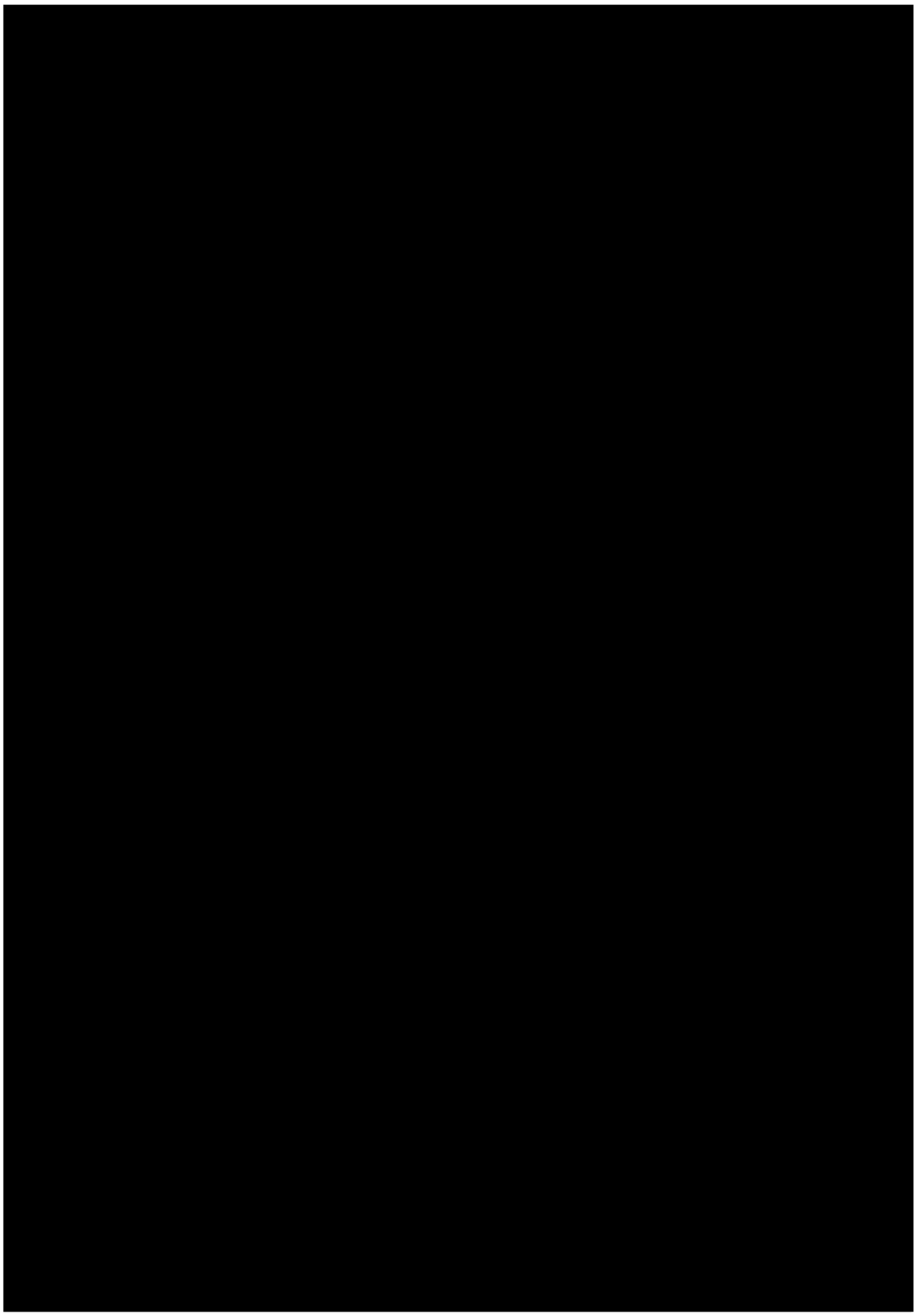
11.1.3.1 'Evening' PR-ADHD-RS-5 Child [6-11 years old]

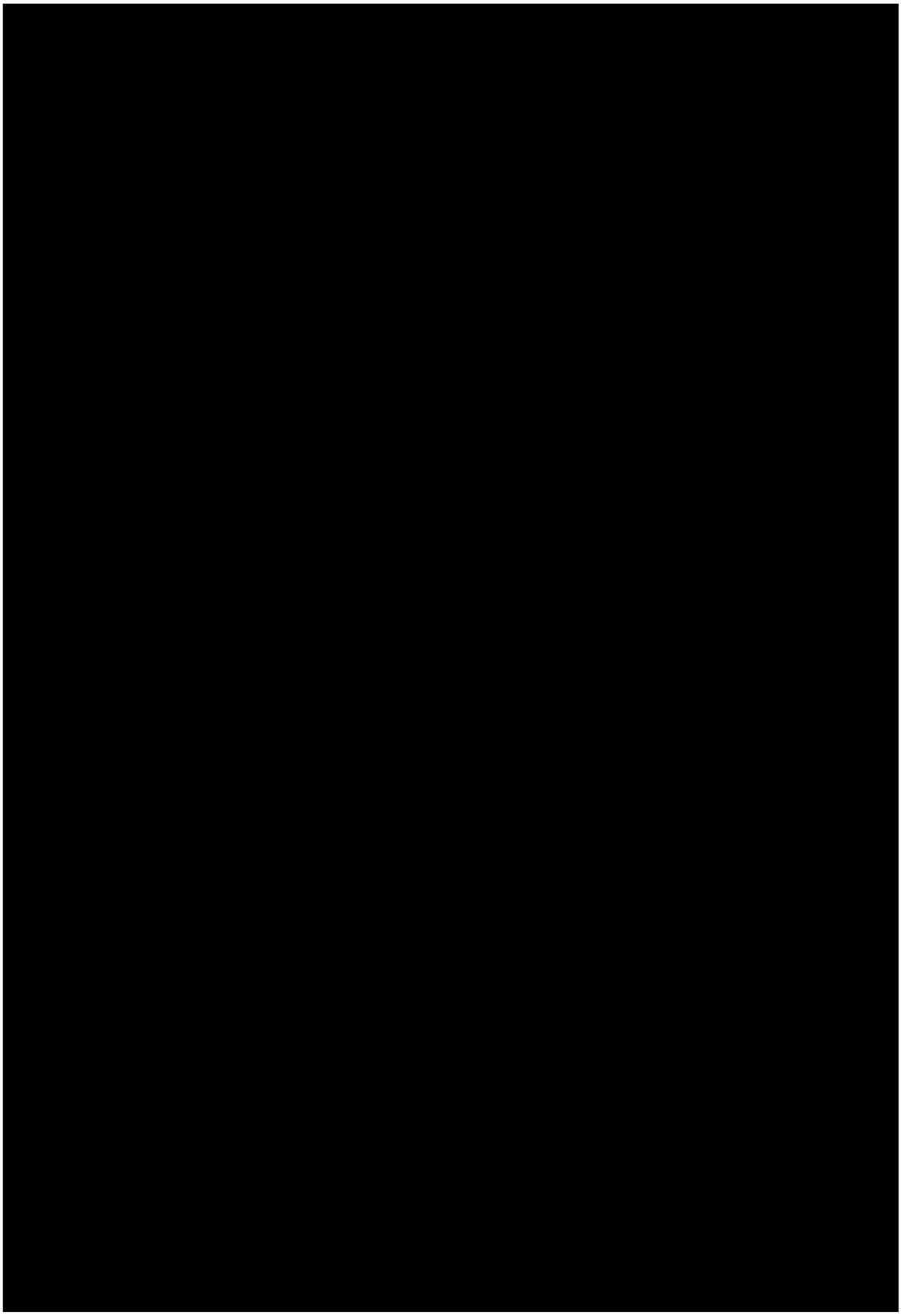




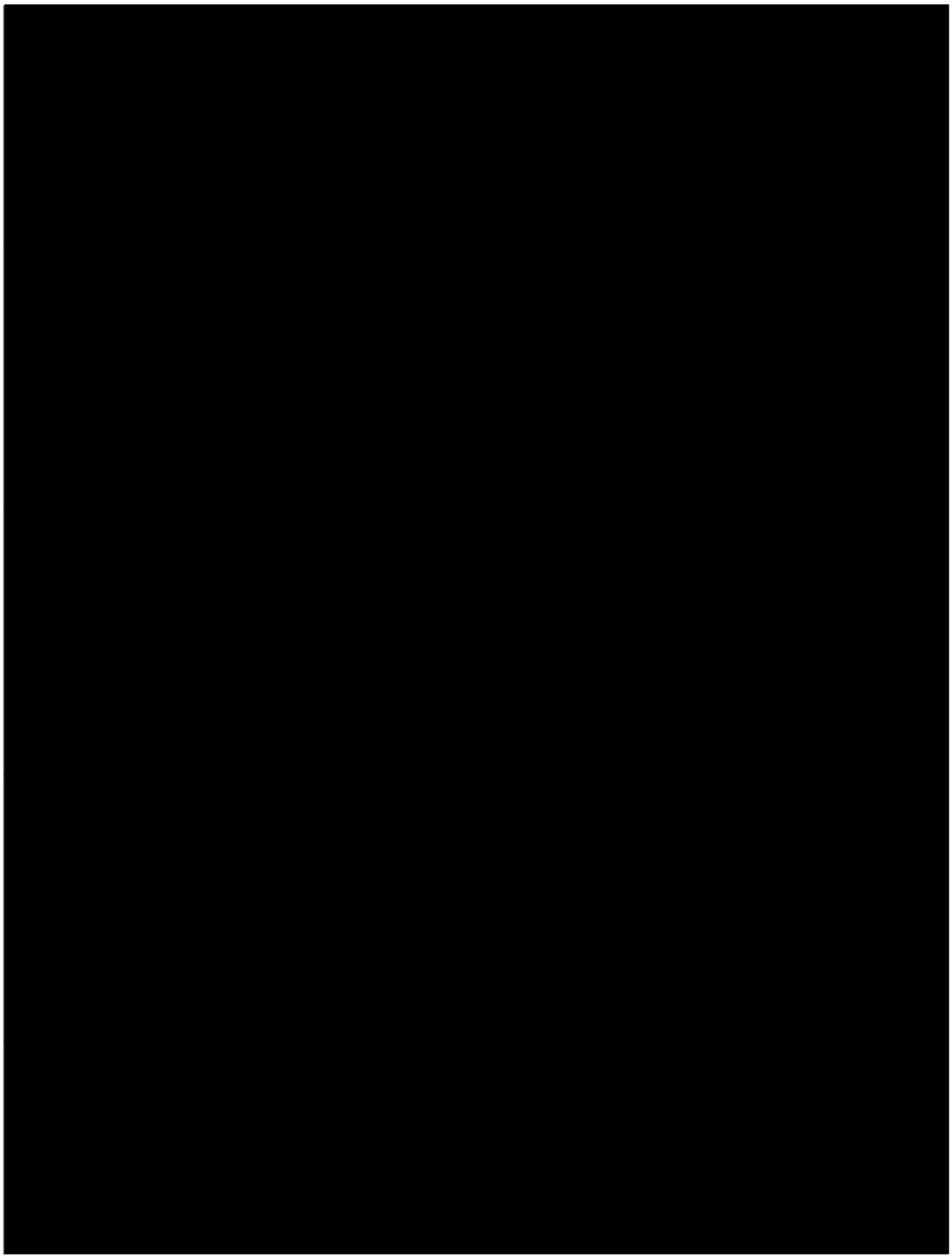
11.1.3.2 'Evening' PR-ADHD-RS-5 Adolescent [12-17 years old]

.

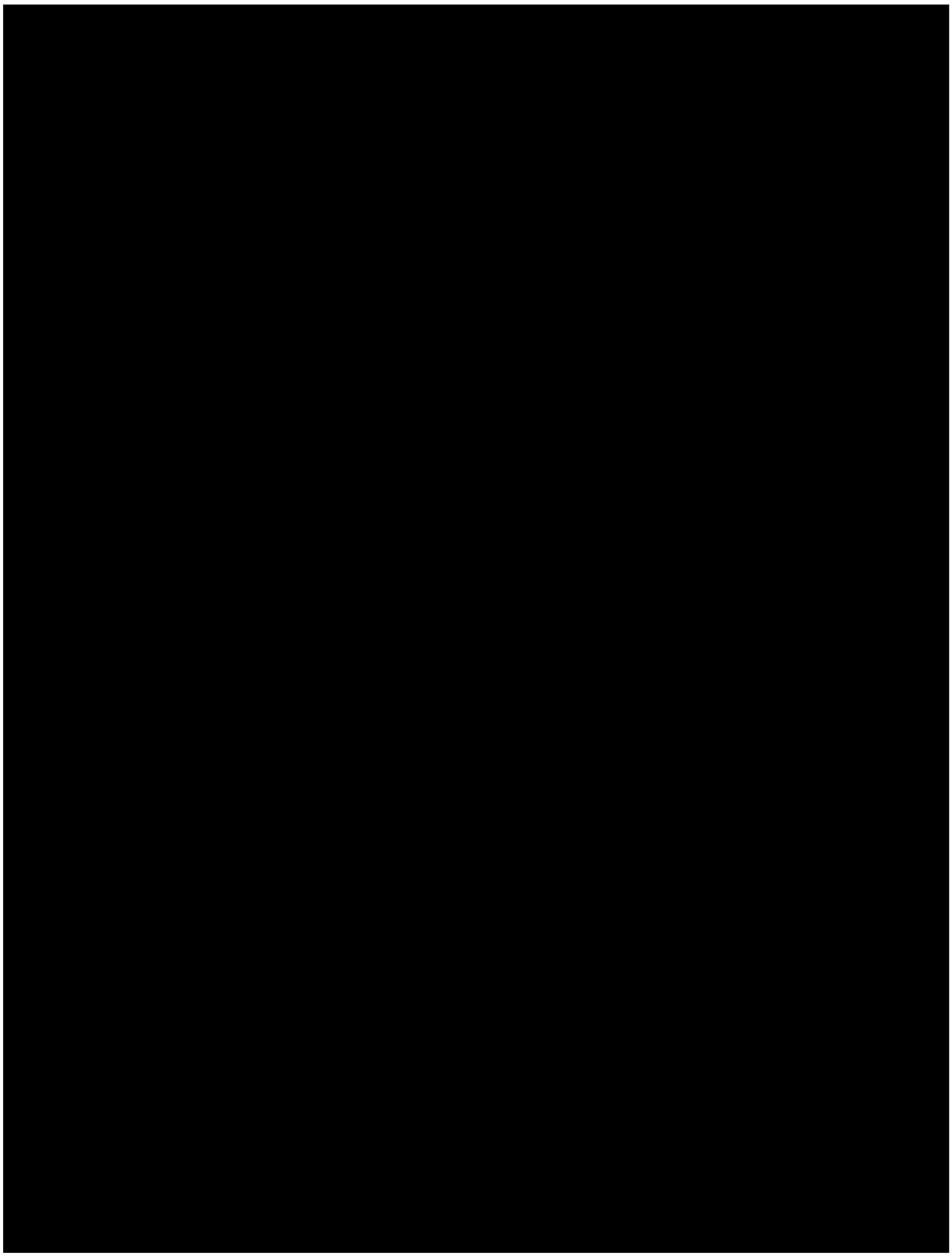




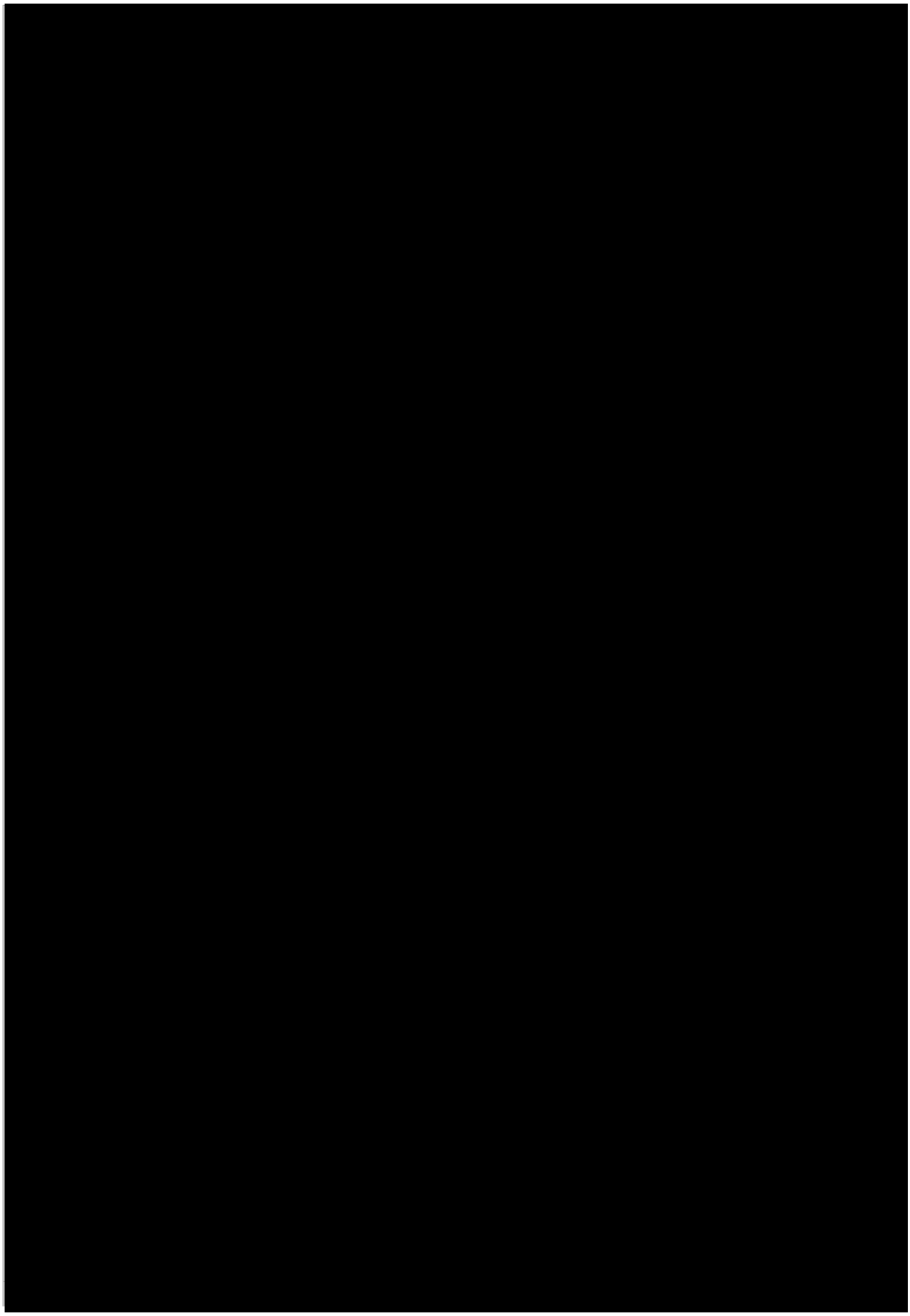
11.2 Clinical Global Impression – Severity of Illness (CGI-S)



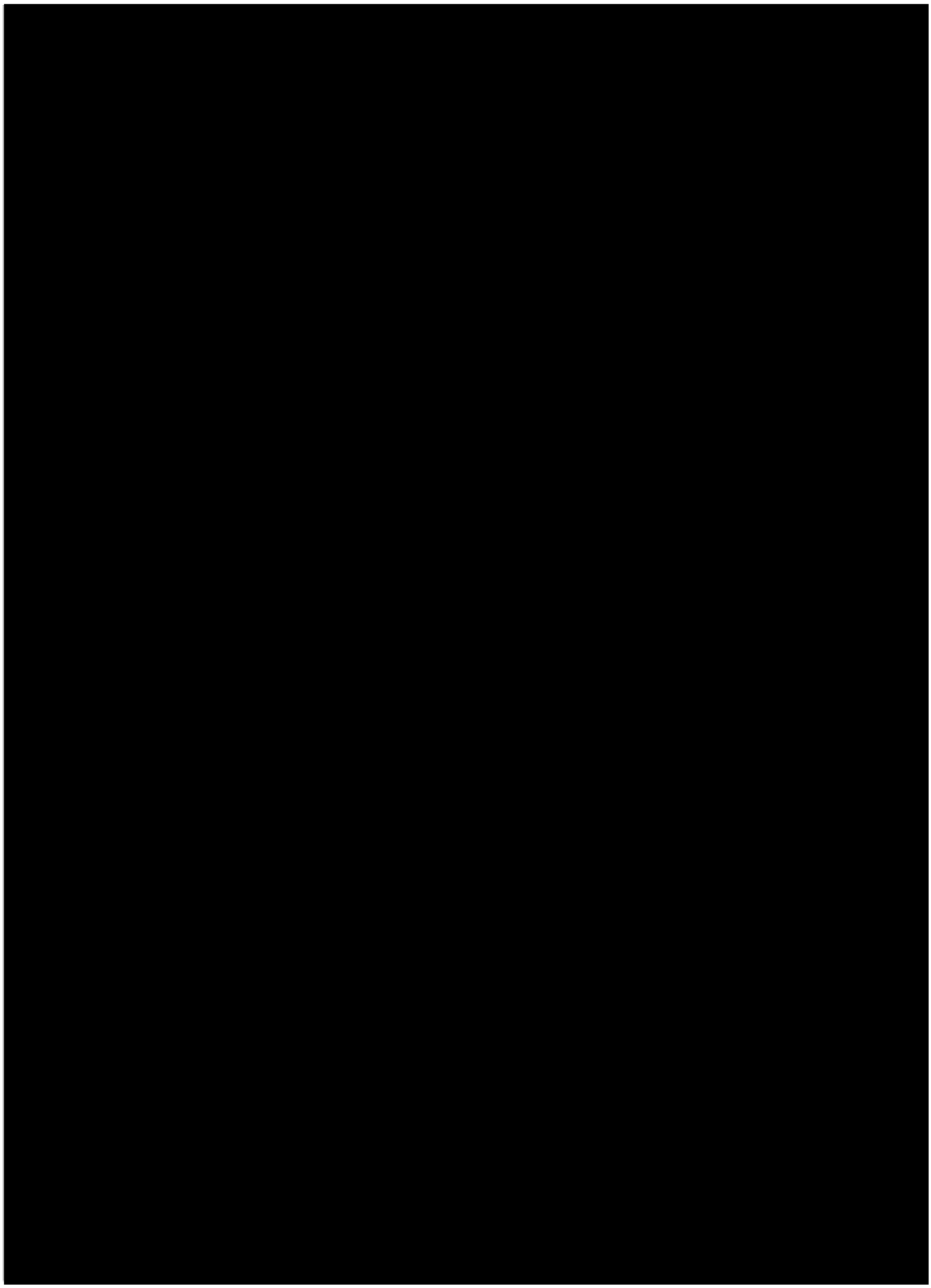
11.3 Clinical Global Impression – Improvement (CGI-I)

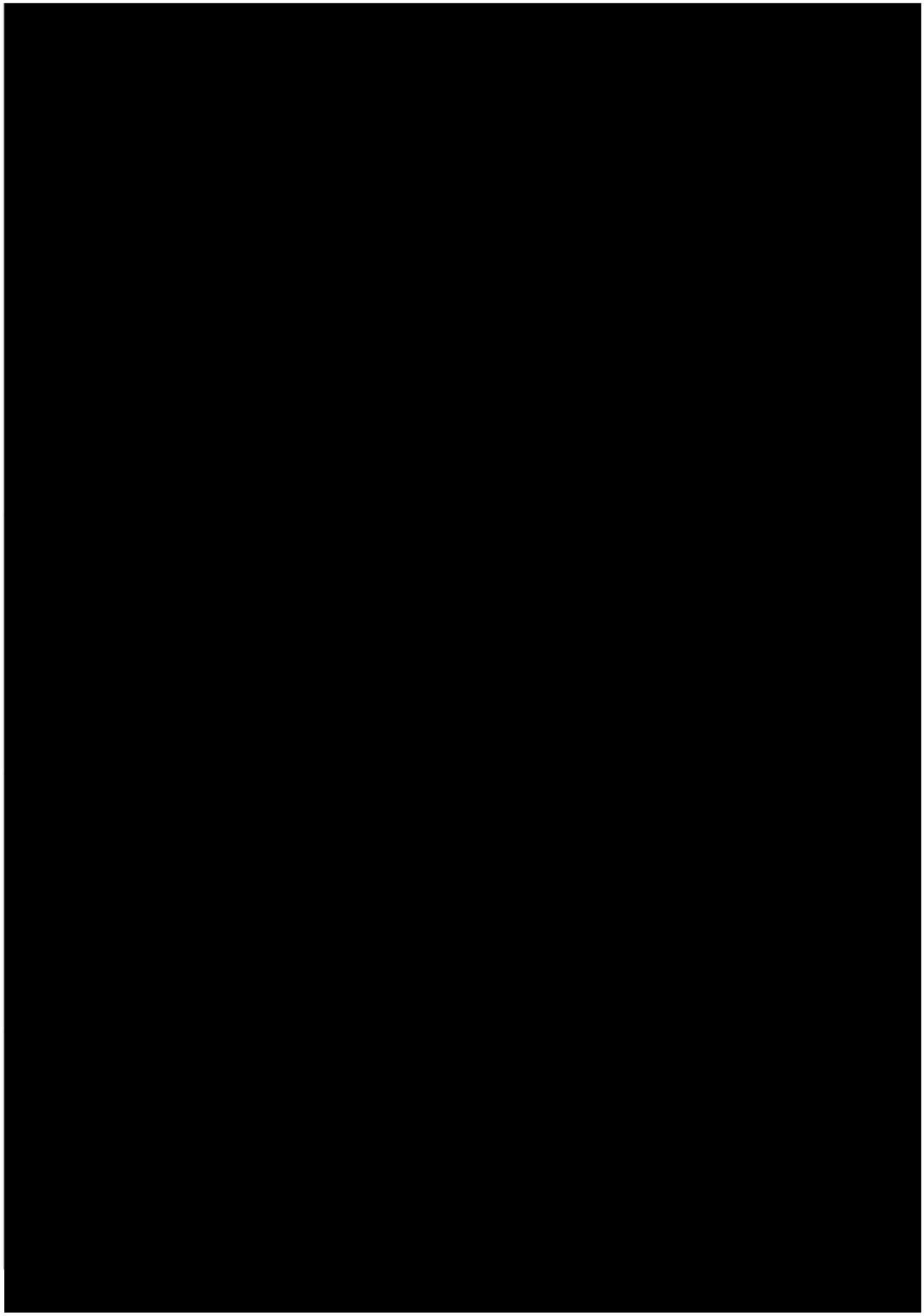


11.4 Sleep Disturbance Scale for Children (SDSC)



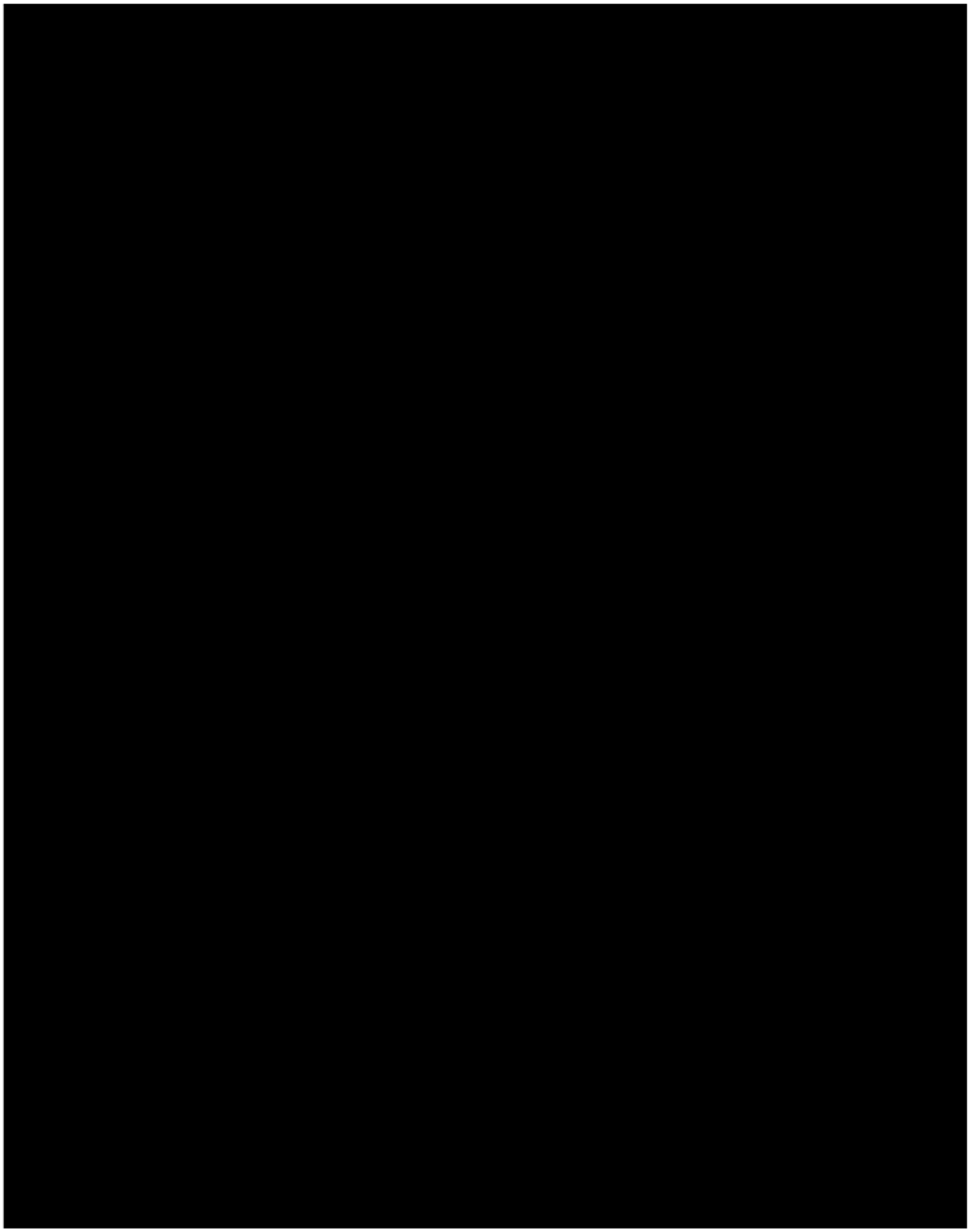
11.5 Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R)

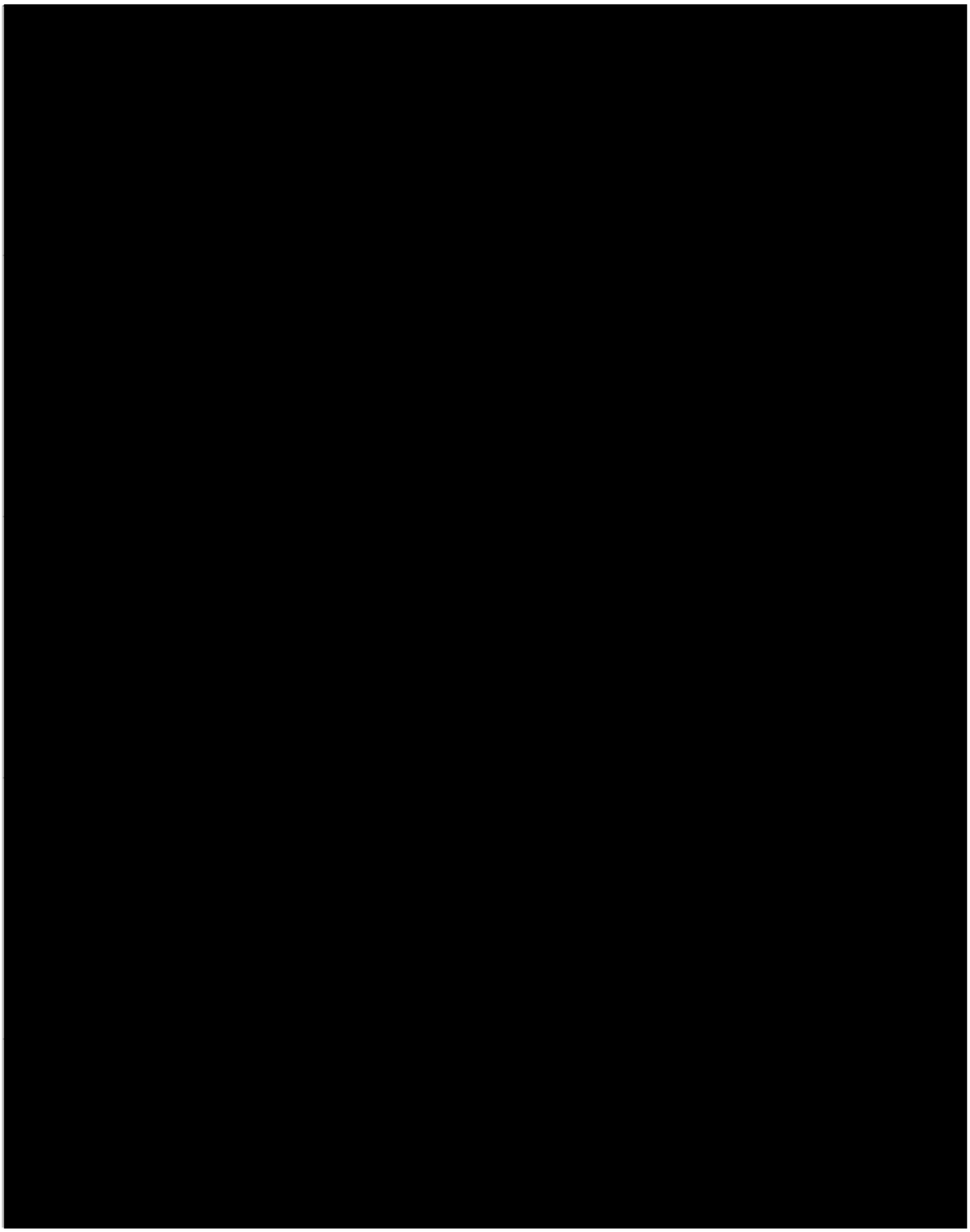


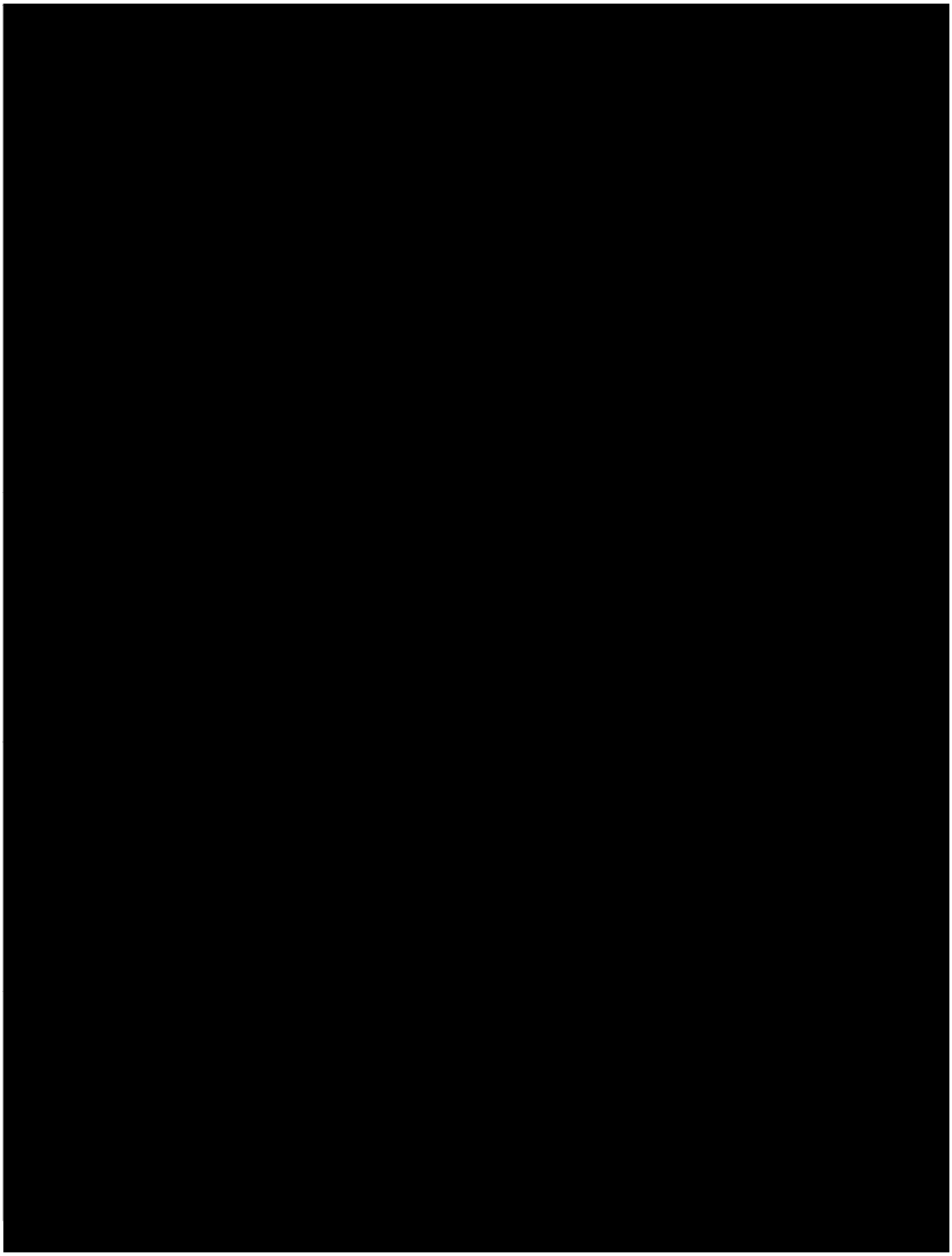


11.6 C-SSRS: 6-11 years old

11.6.1 C-SSRS; Children's "Baseline/Screening" Version







11.6.2 C-SSRS; Children's "Since Last Visit" Version

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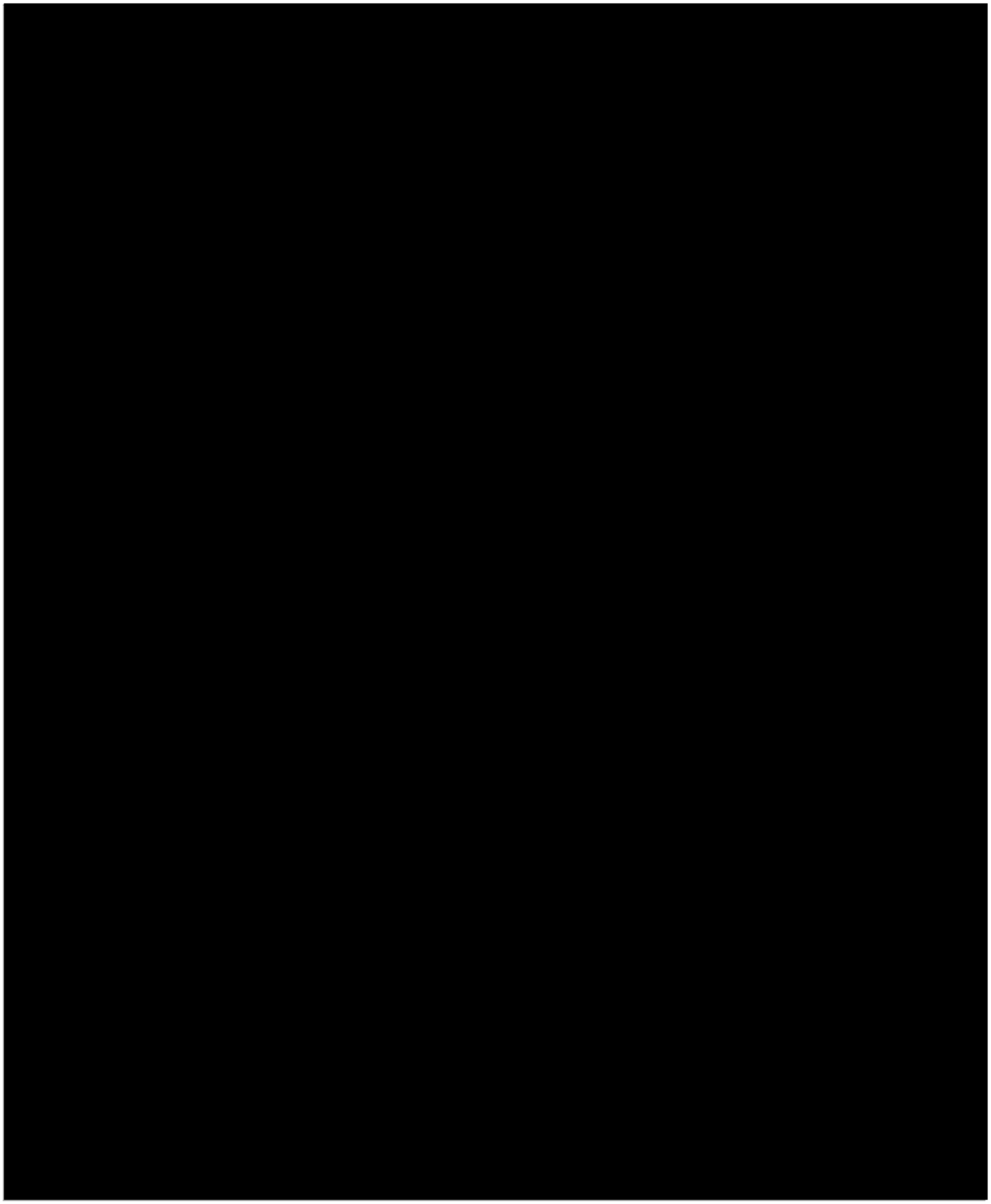
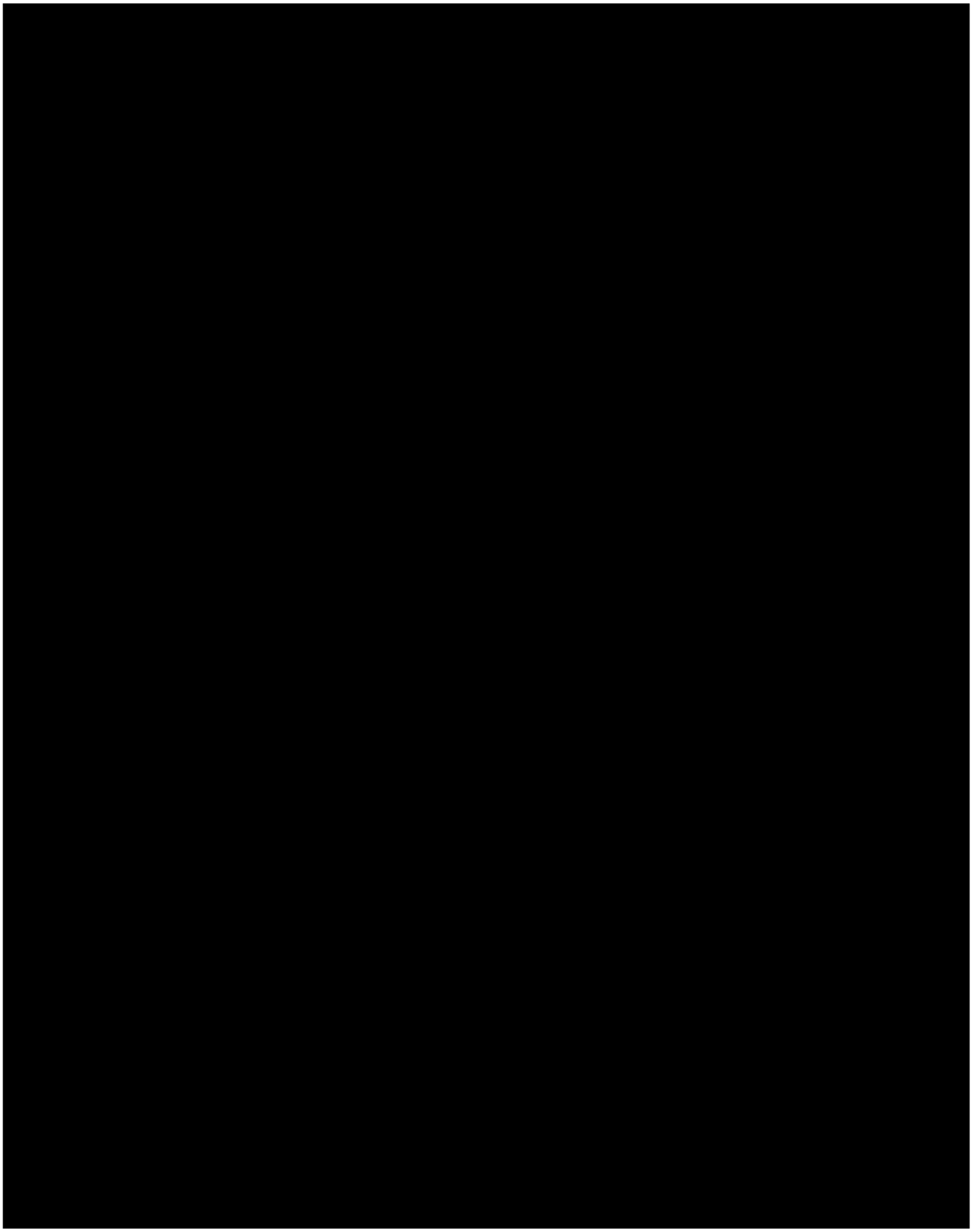
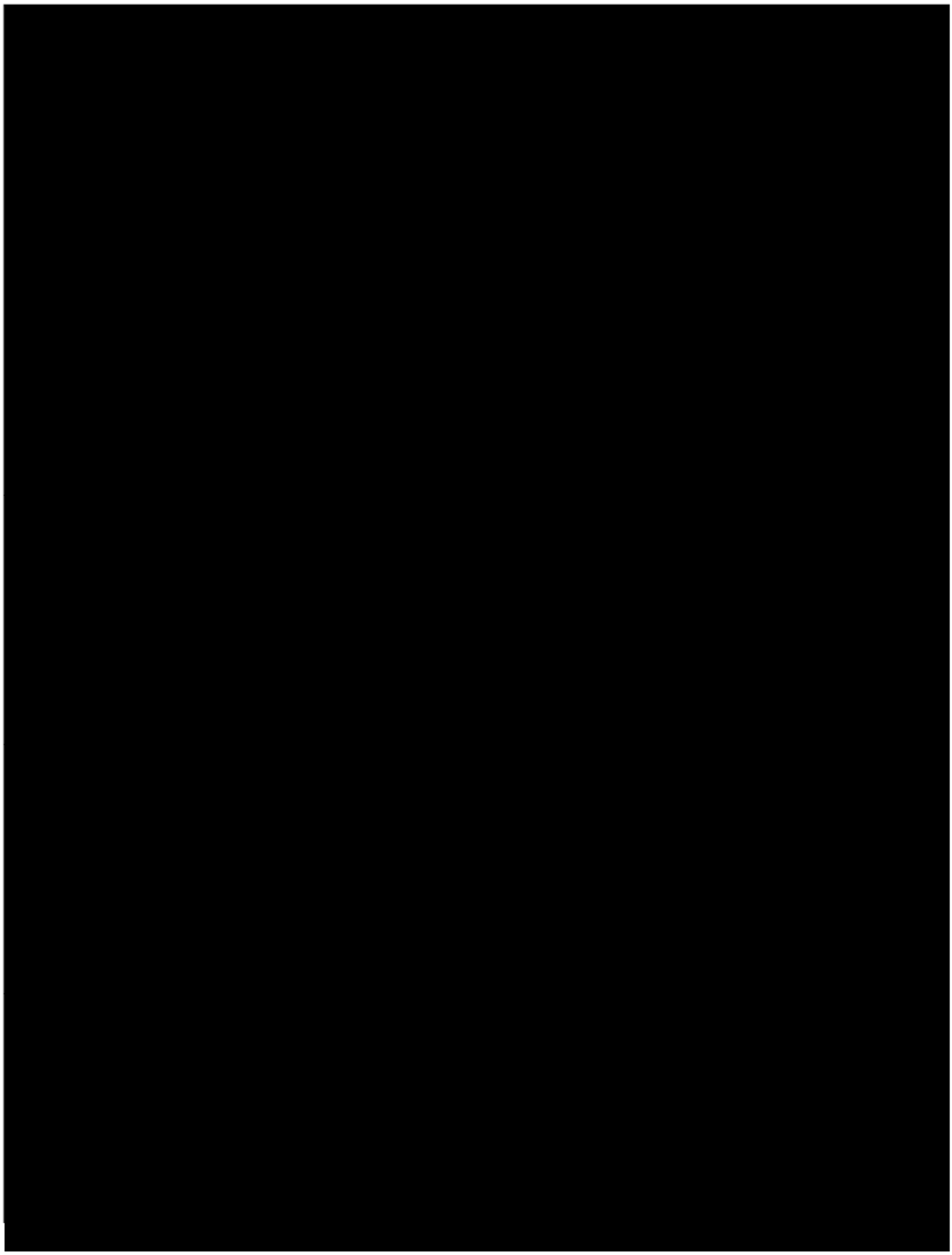


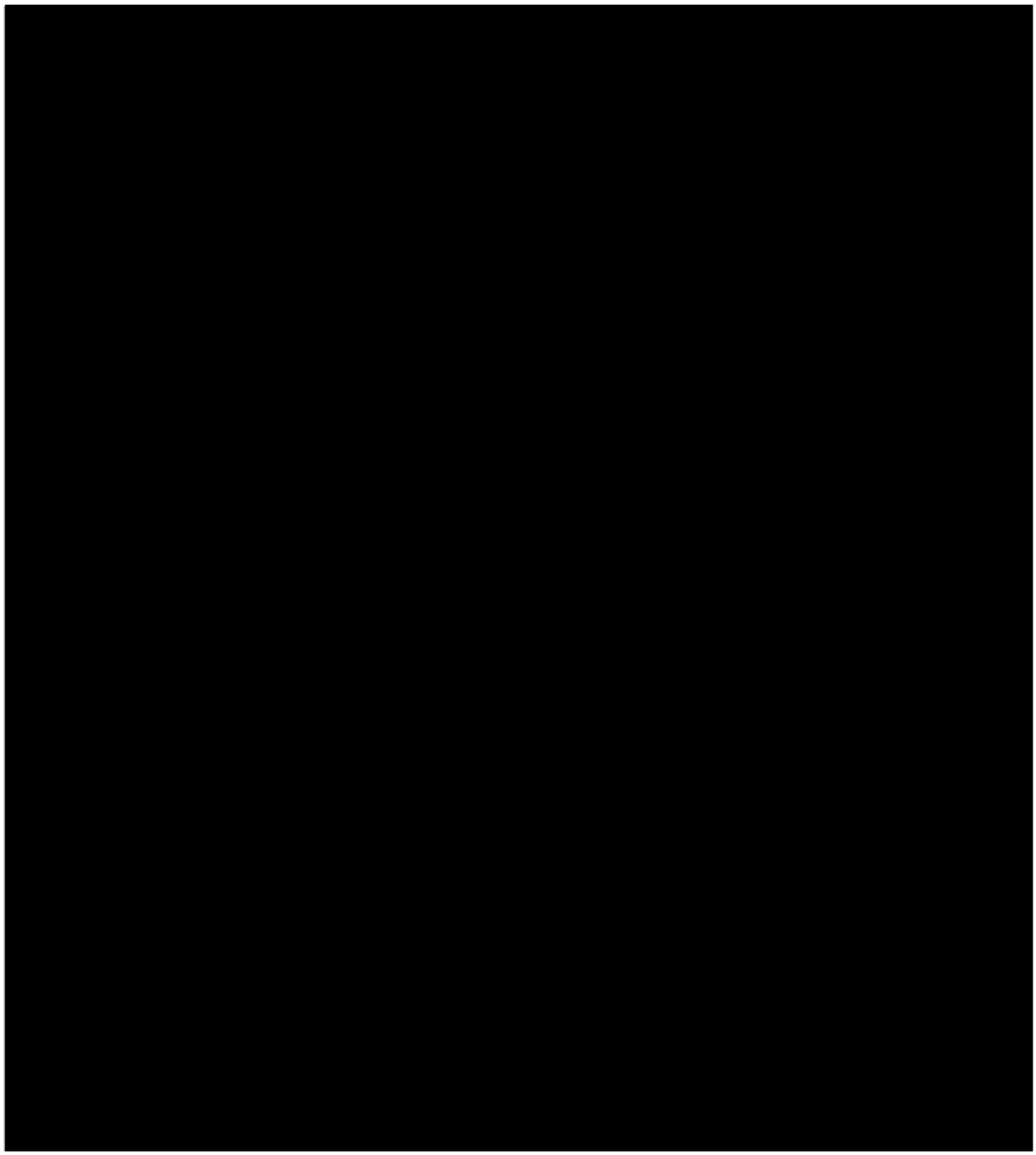


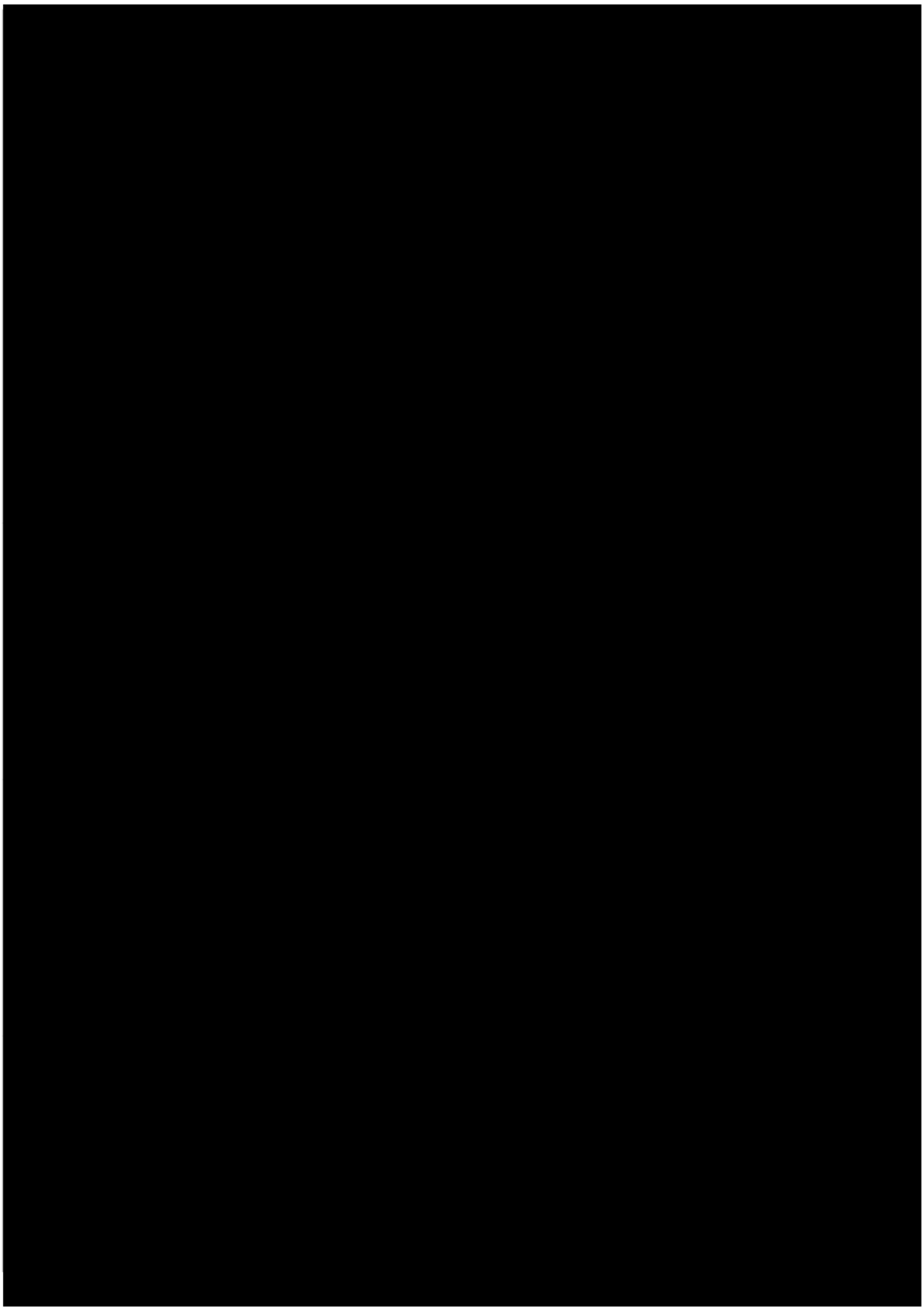


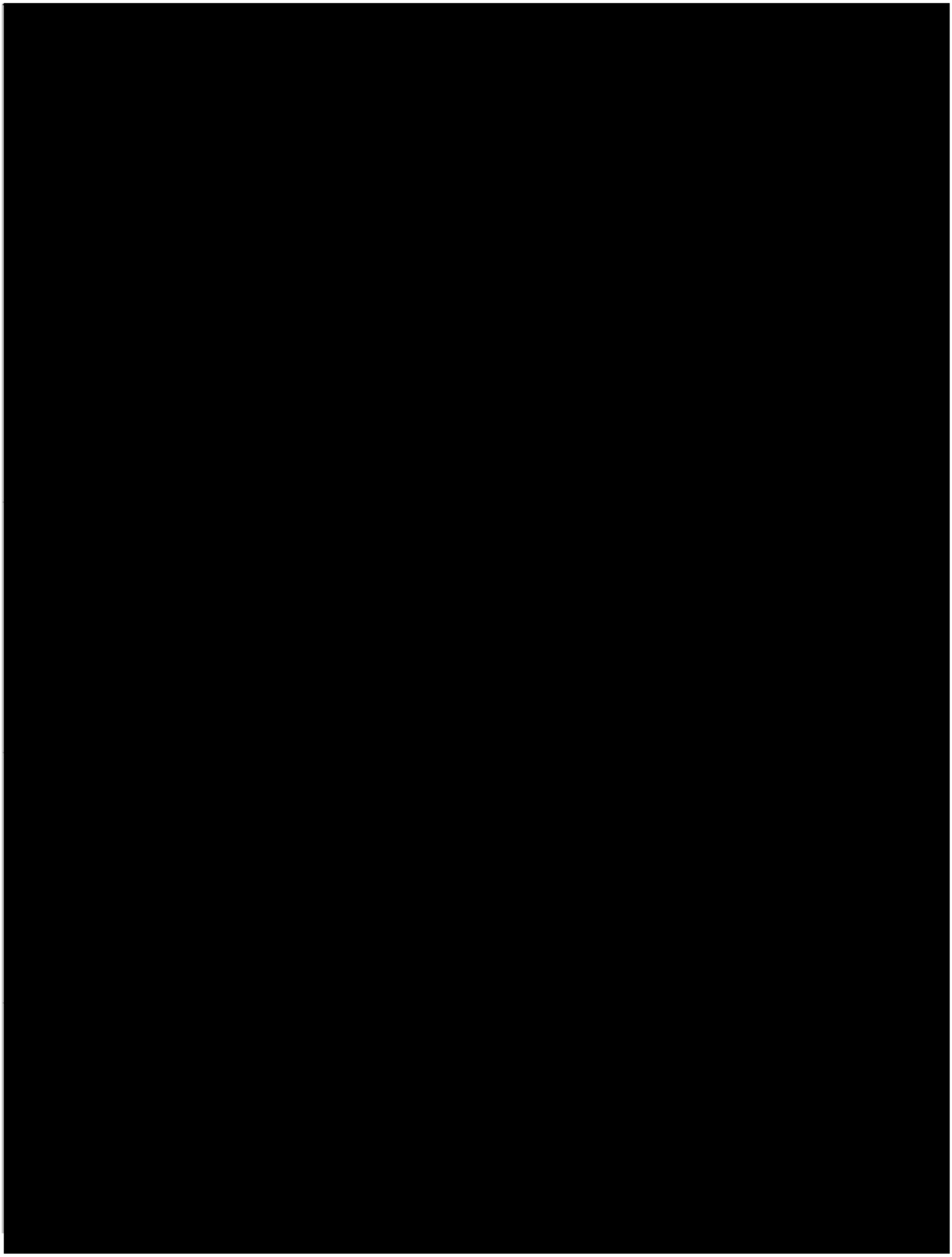
11.7 C-SSRS: 12-17 years old

11.7.1 C-SSRS; "Baseline" Version

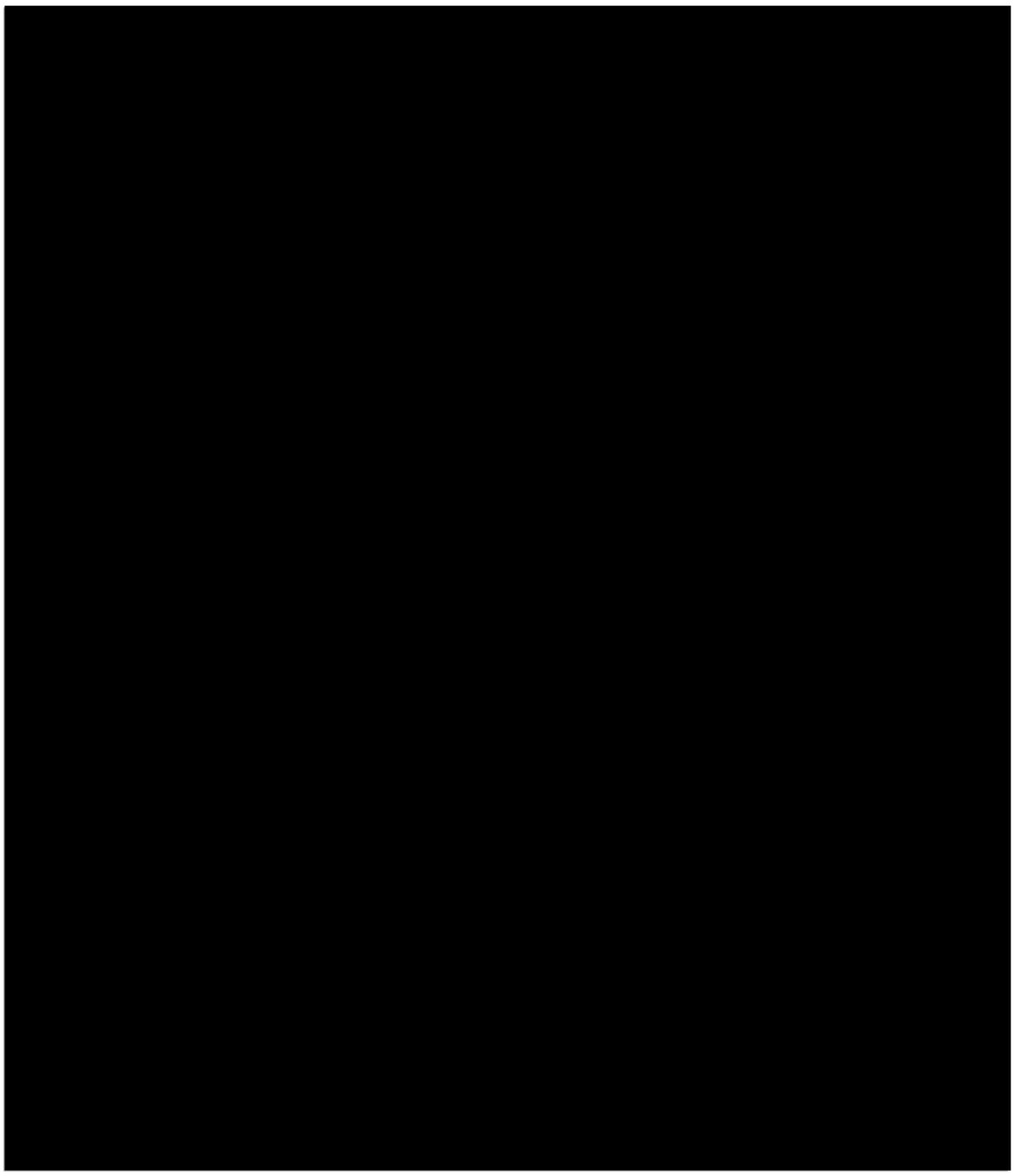
.

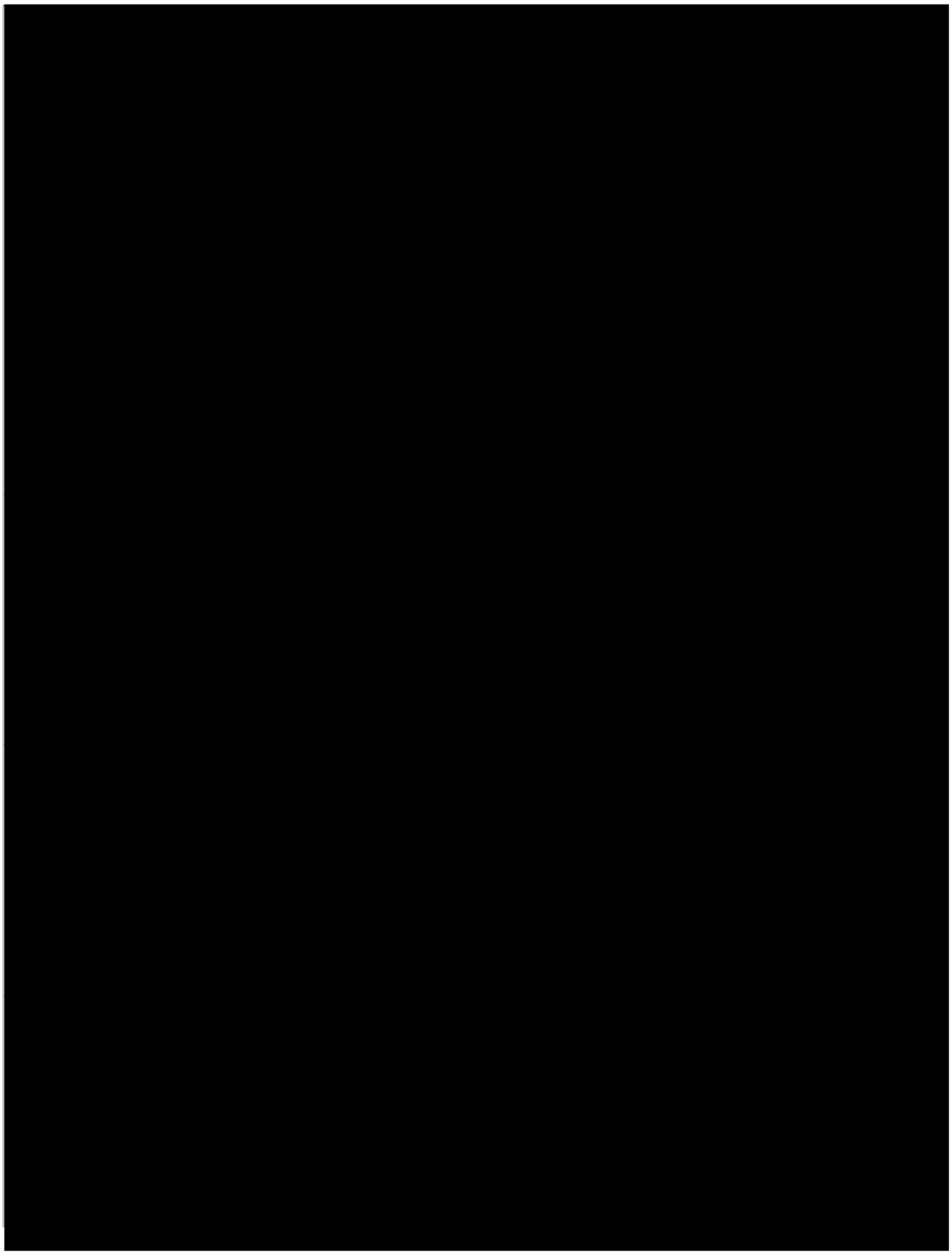


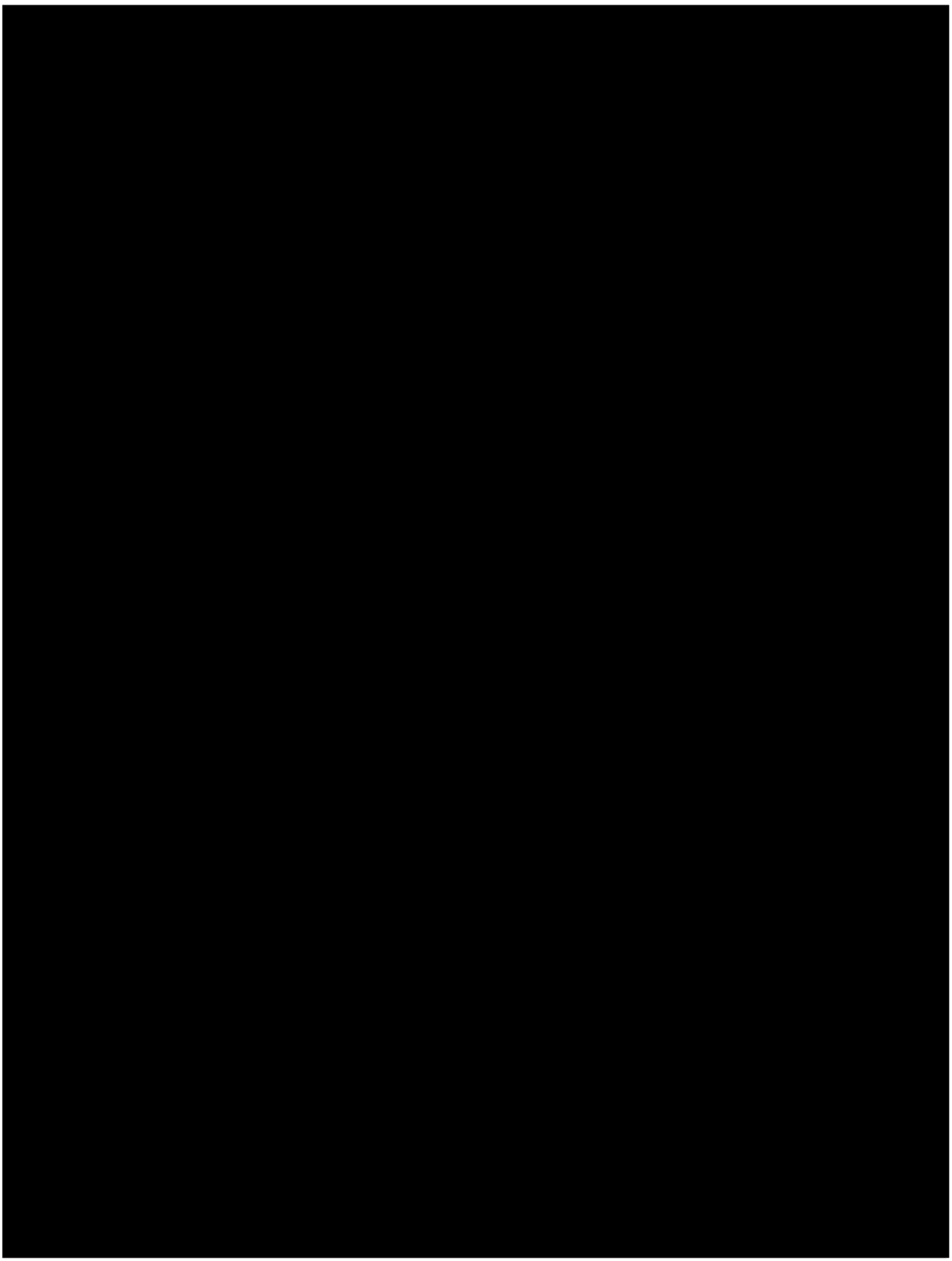




11.7.2 C-SSRS; "Since Last Visit" Version







11.8 MINI-KID

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