COVER PAGE - PROTOCOL

Protocol Number:	812P201
Title:	A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of SPN-812V in Adults 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:	2.0
Date:	30Jun2010
NCT:	NCT01107496

1. TITLE PAGE

Protocol Number:	812P201
Title:	A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of SPN-812V in Adults with Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor:	Supernus Pharmaceuticals, Inc. 1550 East Gude Drive Rockville, MD 20850 Phone: 301-838-2500 Fax: 301-838-2504
IND Number:	106,729
Test Drug:	Viloxazine
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Phase:	I/IIa
Release Date:	30 June 2010 / Version 2.0 09 April 2010 / Version 1.0
Good Clinical Practice (GCP) Statement	This study is to be performed in full compliance with International Conference on Harmonization (ICH) GCP and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality:	This document is confidential. It contains proprietary information of Supernus Pharmaceuticals, Inc. Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

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 and all applicable local GCP guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator	**Signature**	**Date**

2. CLINICAL PROTOCOL SYNOPSIS

Name of Company: Supernus Pharmaceuticals, Inc.		**IND Number:** 106,729
Name of Product: Viloxazine Capsules 50mg	**Name of Active Ingredient:** Viloxazine HCl	
Full Title of the Study: A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of SPN-812V in Adults with Attention Deficit Hyperactivity Disorder (ADHD)		
Investigator(s)/Center(s): Approximately 5 US centers		
Protocol Number: 812P201	**Phase of Development:** I/IIa	

Objectives:

Primary Objective:

- To determine the safety of SPN-812V in adults with ADHD

Secondary Objective:

- To determine the efficacy of SPN-812V in adults with ADHD
- To explore the single dose and steady state pharmacokinetics of SPN-812V in adults with ADHD

Study Design (Methodology): Randomized, double-blind, placebo-controlled, parallel-group

Number of Subjects: Approximately 50 subjects (25 per arm)

Criteria for Inclusion/Exclusion:

Inclusion criteria:

1. Able to provide informed consent prior to any study procedure being conducted.
2. Capable and willing to comply with study procedures.
3. Male or female aged 18 to 64, inclusive.
4. Subjects with a current diagnosis of ADHD as confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)
5. Clinical Global Impression – Severity (CGI-S) score of 4 or higher.
6. On no treatment for ADHD or willing to be withdrawn from an ongoing treatment after a washout of at least 10 days.
7. Body Mass Index (BMI) between 18.0 and 34.0 inclusive.
8. Subject must be in general good health as determined by medical history, ECG, and other analysis that, in the judgment of the Investigator, would confirm the Subject's good health.
9. Females of childbearing potential (FOCP) who, if sexually active, agree to use acceptable forms of contraception (including oral, transdermal, or implanted contraceptives; intrauterine device; female condom with spermicide; diaphragm with spermicide; cervical cap; abstinence; use of condom with spermicide by sexual partner or sterile [at least 6 months prior to SM administration] sexual partner) at least 14 days prior to start of study drug administration, throughout the study, and for 30 days following the last dose of SM.
10. Postmenopausal females with amenorrhea for at least 2 years or females who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

Exclusion Criteria

1. Current or past history of psychotic disorder or major depressive disorder with psychotic features.
2. Presence of another primary DSM-IV-TR disorder.
3. Suicidality, defined as either active suicidal plan/intent or active suicidal thoughts, in the 6 months before the Screening Visit or more than 1 lifetime suicide attempt. (The Columbia-Suicide Severity Rating Scales [C-SSRS] will be administered at each visit.)
4. Substance or alcohol abuse/dependence within previous 6 months, or a positive urine drug screen at screening or baseline prior to first dose of study medication (SM).
5. Any known or suspected significant medical or psychiatric illnesses that, in the judgment of the Investigator, may impair interpretation of study results or constitute a significant safety concern in the context of the clinical trial
6. ECG abnormalities (clinically significant according to Investigator's opinion) or vital sign abnormalities (systolic blood pressure [SBP] <90 or >140 millimeters of mercury [mmHg], diastolic blood pressure [DBP] <40 or >90mmHg, or heart rate [HR] <40 or >100 beats per minute [BPM]) at screening.
7. Clinically significant laboratory abnormalities; including presence of potential hepatic function impairment as shown by, but not limited to alanine aminotransferase (ALT/SGPT) values >2 times upper limit of normal (ULN), aspartate aminotransferase (AST/SGOT) > 2 times ULN, gamma-glutamyl transpeptidase (GGT) >3 times ULN, or total bilirubin >1.5 ULN .
8. Medications, including health food supplements judged by the Investigator to be likely to have central nervous system activity (for example, St John's Wort, gingko leaf, and melatonin), are not permitted during the study. If the subject is taking the medication prior to study entry, there must be a 7 day washout period prior to first dose of SM.
9. Lifetime history of tic disorder, Tourette's Disease, or organic brain disorder; or family history of Tourette's Disease.
10. Current or lifetime history of hyperthyroidism unless treated and stable for at least 6 months.
11. Participation in or plan to begin behavioral therapy during the study.
12. Subject has a prior history of allergy or any significant adverse reaction (including rash) to viloxazine, or any of the product components.
13. Females who are pregnant or lactating or are unwilling to use an acceptable form of contraception throughout the study.
14. Difficulty swallowing whole capsules.
15. History of seizures or risk factors for seizures (e.g., head trauma), not including febrile seizures.
16. Use of an investigational drug or participation in an investigational study within 30 days prior to first dose of SM.
17. Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.

Test Treatment, Dose, and Mode of Administration:

50mg capsules containing either SPN-812V or placebo by mouth (PO) three times per day (TID)

Duration of Treatment and Study Duration: There will be a total of 8 visits.

Visit 1: Screening

Visit 2: Baseline, randomization, and dispensation of SM

Visit 3-8: Weekly assessment

Visit 8: Final visit, Optional PK day, End of study assessments

Total subject duration on study: up to 8 weeks

Enrollment is estimated to require approximately 4 months, and the study is expected to be completed approximately 6 months after enrollment begins.

Treatment Schedule (Procedure):

Screening (Visit 1): Subjects will undergo initial screening evaluation after informed consent is obtained, including complete medical and psychiatric history, physical exam, serum pregnancy test (FOCP only), routine laboratory assessment and genetic testing for CYP2D6 enzyme activity, smoking status, and urine drug screen. Confirmation of ADHD will be performed with the CAADID and the CGI-S will be administered. Study qualification requirements will be reviewed to confirm that the subject meets all inclusion and exclusion criteria.

Baseline and Randomization and dispensation of SM (Visit 2): After a screening period of up to 14 days subjects will return to the investigational site and undergo their scheduled baseline assessment. If their eligibility to participate in the trial is confirmed, subjects will be randomized (1:1) to receive a starting dose of 1x50 mg capsule TID (150 mg/day) of either SPN-812V or placebo. Subjects will receive treatment at the 150 mg/day starting dose for one week. Dosing is to start the morning after Visit 2. Subjects who do not tolerate the starting dose will be discontinued from the study.

Study Dose Treatment Phase (Visits 3 – 8): Subjects who tolerated the starting dose will then be titrated to receive a study dose of 2x50 mg TID (300mg/day) and continue this treatment regiment for five weeks. Subjects who, after titration to the study dose, do not tolerate treatment at 300 mg/day, will be allowed, at any time, to down-titrate the dose to the 150 mg/day starting dose and continue treatment at the same dose until completion of the study. Subjects will return to the investigational site once a week to undergo safety and efficacy evaluations and to have SM compliance checked. At the end of Visit 7, the subjects who have consented to participate in the optional PK sub study will receive a drug diary to record times of all weekly doses, will be instructed to fast the night before Visit 8, and will be instructed to not take SM that morning. At Visit 8, subjects who agree to participate in the optional PK sub study will receive SM dose and will have blood drawn for PK assessments over approximately seven hours. All rating scales will be administered prior to PK dosing and blood draws. For subjects not participating in the optional PK sub study, their last dose will be taken the evening before the End of Study Visit (Visit 8).

End of Study: At the end of the Visit 8 procedures or at early termination, subjects will complete end of study assessments. Subjects will return any unused capsules and undergo safety and efficacy evaluations if not already performed as part of that visit.

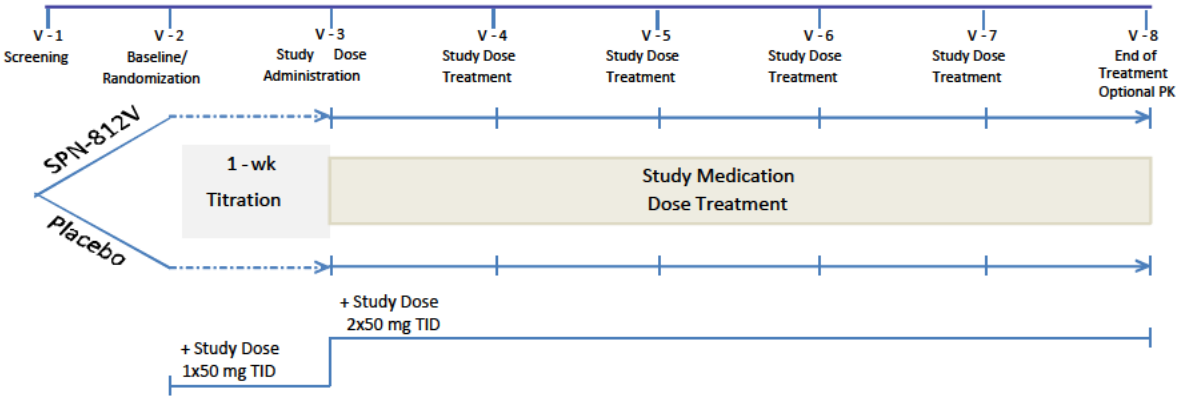
Pharmacokinetic Sampling:

Population PK data will be pooled across all subjects who participate in this optional portion of the study. On the final visit, there is an optional PK day. All subjects who wish to participate will be dosed with active SM after an overnight fast and after all efficacy assessments are completed, Blood will be drawn for quantitative PK analysis according to the following schedule (all times +/- 30 minutes):

Pre-dose and ½, 1, 2, 3, 4, 5, and 6 hours post-dose

Although draw windows are given, efforts should be made to ensure that the time interval between any two sampling timepoints is not less than 30 minutes

Figure 1. Study Schematic



Criteria for Evaluation:

Sample Size Estimation:

Approximately 50 subjects (approximately 25 per treatment group) will be randomized in the study. The sample size is not based on any statistical considerations, but it is judged adequate to provide safety, PK, and efficacy information for a proof-of-concept study.

Analysis Populations:

- Safety population: All randomized subjects who take at least one dose of SM.
- Intent-to-treat (ITT) population: The ITT population consists of all randomized subjects who took at least one dose of SM, had baseline efficacy assessment, and had at least one post-baseline efficacy assessment. The ITT population is the population for the efficacy analysis. Subjects will be analyzed according to treatment assigned.
- Restricted ITT Population: The restricted ITT population consists of all ITT population subjects with at least 1 efficacy assessment after three weeks of treatment.
- PK population – Safety population subjects with evaluable PK profile.

Safety Assessments:

- Adverse events (AEs) and serious adverse events (SAEs): incidence summary of AEs (System Organ Class [SOC], Preferred Term, Relationship, Severity)
- Clinical laboratory tests: biochemistry, hematology, and urinalysis
- Vital signs and weight: blood pressure, heart rate, respiratory rate, and body temperature; and weight
- 12-lead ECGs: normal and abnormal values
- Physical examinations: normal and abnormal findings

Drug Concentration Measurements:

The concentration of viloxazine in plasma will be determined using a validated chromatographic method.

Endpoints:

Primary Endpoints:

1. To establish the safety of SPN-812V after 6 weeks of treatment with either SPN-812V dose.

Secondary Endpoints:

1. To establish the efficacy of SPN-812V over a 5-week treatment period with SPN-812V 300 mg/day
2. To establish the initial efficacy of SPN-812V after a 1-week treatment period with SPN-812V 150mg/day.
3. To establish the effectiveness of SPN-812V over a 6-week treatment period with any SPN-812V dose.
4. To establish the clinical utility of SPN-812V after a 5-week treatment period with SPN-812V 300mg/day.
5. To establish the study subject's perception of clinical benefit of SPN-812V at endpoint after a 5-week treatment with SPN-812V at 300mg/day.
6. To explore in a population model the single dose and steady state pharmacokinetics of SPN-812V in adults with ADHD

Efficacy Measures

- Investigator-rated Conners' Adult ADHD Rating Scale (CAARS) Total ADHD Symptom Score
- Clinical Global Impression – Improvement (CGI-I)
- Self-rated Conners' Adult ADHD Rating Scale (CAARS) Total ADHD Symptom Score

Statistical Methods:

Safety Analyses

The incidence rate of AEs will be calculated by treatment group for each SOC and preferred term. The severity of the AEs and the relationship to SM will be summarized by treatment group for each SOC and preferred term.

Descriptive statistics will be presented for the results from the clinical laboratory tests, vital signs, weight, ECGs, and physical examinations. Statistical testing will be performed for some of the safety endpoints, but the resulting p-values will be used for descriptive purposes only, i.e., not for inferential purposes.

1. Incidence summary ($\geq$ 2%) of AEs (SOC, Preferred Term, Relationship, Severity) when compared to placebo after 6-week treatment with any SPN-812V dose
2. Changes from baseline in biochemistry, hematology, and urinalysis values from baseline after 6-week treatment with any SPN-812V dose
3. Percent of change from baseline in biochemistry, hematology, and urinalysis values from baseline after 6-week treatment with any SPN-812V dose when compared to placebo after 6-week treatment with any SPN-812V dose
4. Changes from baseline in blood pressure, heart rate, respiratory rate, and body temperature after 6-week treatment with any SPN-812V dose
5. Percent of change from baseline in blood pressure, heart rate, respiratory rate, and body temperature when compared to placebo after 6-week treatment with any SPN-812V dose
6. 12-lead ECGs changes from baseline after 6-week treatment with any SPN-812V dose
7. 12-lead ECGs percent of change from baseline when compared to placebo after 6-week treatment with any SPN-812V dose
8. Normal or abnormal findings on physical examinations after 6-week treatment with any SPN-812V dose
9. Rate of abnormal findings on physical examinations after 6-week treatment with any SPN-812V dose when compared to placebo after 6-week treatment with any SPN-812V dose

Efficacy Analyses

Descriptive statistics will be presented for all efficacy variables by visit and treatment group.

All significance tests will be performed at the 0.05 level.

As down titration from 300mg to 150mg is allowed for subjects who cannot tolerate the maintenance dose, those subjects will be treated as part of the 300mg arm while analyzing the data.

Primary Efficacy Analyses

The primary efficacy measure is the investigator-rated CAARS Total ADHD Symptom Score which is the sum of the Inattention and Hyperactivity/Impulsivity subscales (18 items rated on 4-point scale).

The changes from baseline to the endpoint in the investigator-rated CAARS Total ADHD Symptom Scores will be compared between the two treatment groups using the Wilcoxon rank-sum test or the two-sample t-test. To confirm the results (sensitivity analysis), a mixed model repeated measures (MMRM) analysis will be conducted. MMRM analysis will contain fixed effect terms for treatment, investigative site, visit, and interaction between treatment and visit. The model will include post-baseline values of the investigator-rated CAARS Total ADHD Symptom Score as the dependent variable with a random patient effect and baseline investigator-rated CAARS Total ADHD Symptom Score as a covariate and will use an unstructured covariance.

Secondary Efficacy Analyses

1. Initial efficacy of SPN-812V starting dose (150 mg/day) when compared to placebo as measured by changes in the investigator-rated CAARS Total ADHD Symptom Score from baseline at week 1 of treatment with starting dose will be analyzed with Wilcoxon rank-sum test or two-sample t-test
2. Effectiveness of any SPN-812V dose when compared to placebo as determined by the weekly changes in the Clinical Global Impression – Improvement (CGI-I) score from baseline severity for 6-week treatment will be plotted as mean CGI-I change versus visit and analyzed using Wilcoxon rank-sum test or two-sample t-test
3. Clinical utility of SPN-812V study dose (300 mg/day) when compared to placebo as determined by the investigator's assessment of the changes in the CAARS score from baseline at week 2, 3, 4, 5, and 6 of treatment will be analyzed with Wilcoxon rank-sum test or two-sample t-test
4. Study subject's perception of clinical benefit of SPN-812V study dose (300 mg/day) when compared to placebo as determined by changes in the self-rated CAARS score from baseline at endpoint after 5-week treatment will be analyzed with Wilcoxon rank-sum test or two-sample t-test

Subgroup Analyses for Efficacy

Subgroup analyses for efficacy will be performed on categories of the following measures:

- Sex
- Race

for the ITT population for the investigator-rated CAARS Total ADHD Symptom Score. Subgroup analyses will also be carried out for the following subscales

- investigator-rated CAARS inattention subscale score
- investigator-rated CAARS hyperactivity/impulsivity subscale score

that together make up the CAARS Total ADHD Symptom Score

Pharmacokinetic and/or Pharmacodynamic Analyses: Population PK data will be pooled across all subjects who participate in this optional portion of the study and analyzed using nonlinear mixed-effects modeling methods. The objective of the population PK analyses is to derive individual-specific estimates of apparent oral clearance (CL/F) but not to fully characterize the PK of this formulation of Viloxazine.

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4. LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the plasma concentration versus time curve
AUC_{ss}	area under the concentration-time curve at steady state
BUN	blood urea nitrogen
CAARS	Conners' Adult ADHD Rating Scale
CAADID	Conners' Adult ADHD Diagnostic Interview for DSM-IV
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-S	Clinical Global Impression – Severity of Illness
CGI-I	Clinical Global Impression – Global Improvement
CL/F	apparent oral clearance
CRA	Clinical Research Associate
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scales
CRO	Contract Research Organization
C_{ss} avg	average steady-state concentration
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Text Revision
ECG	electrocardiogram
FOCP	Females of Childbearing Potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	intent to treat
LNH	Low, normal, high
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PK-PD	pharmacokinetic-pharmacodynamic
PO	orally
PR	Interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium
QRS	QRS complex refers to ventricular depolarization in the measurement of electrical activity of the myocardium
QT	Interval from ventricular depolarization and repolarization in the measurement of electrical activity of the myocardium
QTc	QT, corrected
QTcF	QT corrected using Fridericia's method
RBC	red blood cell

SAE	serious adverse event
SM	study medication
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
TESS	Treatment-emergent signs and symptoms
TID	three times per day
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5. ETHICS

5.1. Institutional Review Boards / Independent Ethics Committees

A list of the Institutional Review Board(s) (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 informed consent form (ICF) will be reviewed and approved by the IRB before subjects are screened for entry. Verification of the IRB's unconditional approval of the protocol will be transmitted to the Sponsor prior to the shipment of SM to the investigational site. The Investigators or Sponsor will submit periodic reports and inform the IRB of any reportable adverse events (AEs) per International Conference on Harmonization (ICH) guidelines and IRB standards of practice.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of the Sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

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 Good Clinical Practices (GCP) (CPMP/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) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

5.3. Subject Information and Consent

The Investigator (or designee) will inform subjects of all aspects pertaining to the subject's participation in the study. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and the subject must sign and date the ICF before the subject can participate in the study. The subject 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 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 informed consent form (including ongoing subjects).

A separate ICF will be given for the optional PK portion of the study. The above procedures will be followed in obtaining this consent.

6. INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the Sponsorship of Supernus Pharmaceuticals Inc. (Supernus) at approximately 5 investigational sites in the US.

Contact persons at the Sponsor and the contract research organization(s) (CRO) are listed in the Regulatory Binder provided to each site.

Contact information for the Safety Contact and Medical Monitor can be found listed in the Regulatory Binder provided to each site.

The study will be monitored by qualified personnel identified by the Sponsor. Data management, statistical analyses, safety, pharmacovigilance, and medical writing will be the responsibility of the CRO.

7. INTRODUCTION

Viloxazine was previously marketed as an antidepressant in several European countries, since the 1970's, and is currently under development by the Sponsor as SPN-812V, for its potential utility in treating adult attention deficit hyperactivity disorder (ADHD). Viloxazine is a racemate and Supernus plans to develop the compound as such. Supernus intends to carry out this preliminary safety and proof of concept study in adult ADHD patients using an immediate release formulation that will support future development of a modified release formulation to facilitate compliance and possibly improve tolerability.

Similar to tricyclic antidepressants and atomoxetine, viloxazine is an inhibitor of the reuptake of norepinephrine, but may also enhance the release of serotonin from neuronal stores. Clinical efficacy in Major Depressive Disorder has been shown at daily doses of 300 to 600 mg. Thorough published pharmacological and clinical summaries of the product are found in the reviews of Pinder et al., 1977 and Ban et al., 1980.

Supernus development thesis is based on the current unmet medical need for effective long-acting non-stimulant treatment for ADHD in adults. Viloxazine can offer a compelling alternative to the use of scheduled substances to control ADHD thus limiting patients' exposure to agents with potential for substance abuse.

This Phase I/IIa study seeks to evaluate the safety and tolerability of an immediate release formulation of viloxazine given three times per day (TID) at a dose of 150 or 300mg/day in adults. A randomized, multicenter, parallel group, double-blind, placebo-controlled dose-ranging study design will be used. 50 subjects will be randomized; assuming a 20% dropout rate, it is anticipated that 40 subjects will complete the study. Subjects will be monitored regularly for safety endpoints.

Study Rationale

Epidemiological data suggest that ADHD affects up to 8% of children in the USA while the estimated prevalence in the adult population is between 0.3 to 5%. (McCann, 2004). The increased recognition of ADHD as a disorder affecting adults has led investigators to focus on identifying pharmacological treatments for this age group. While stimulants, like methylphenidate, and amphetamine derivatives, are highly effective in ADHD with low risk of tolerance, they have significant adverse effects and a potential for abuse and illicit trafficking (Popper, 2000). Although stimulants are the mainstay of ADHD pharmacotherapy, atomoxetine is an FDA-approved non-stimulant selective noradrenergic re-uptake inhibitor considered a useful option for patients at risk of substance abuse, as well as for those who have co-morbid anxiety or tics, or who do not wish to take a controlled substance (Garnock-Jones, 2009-2010). Antidepressant drugs have also been shown to be effective in the treatment of ADHD (Slatkoff and Greenfield, 2006). According to the literature, antidepressants with a wide range of receptor actions, efficacy, and side effects, including tricyclic antidepressants, noradrenergic, dopaminergic and 5-HT re-uptake inhibitors, can be helpful in controlling the ADHD symptoms. For instance reboxetine – an antidepressant registered in Europe with a mechanism of action supposedly very similar to viloxazine – has been claimed to have comparable efficacy to methylphenidate (Cohen-Yavin, 2009). Finally, the recently FDA-approved alpha-2 adrenergic agonist, guanfacine, has demonstrated efficacy in reducing hyperactivity and impulsivity in ADHD patients (Popper, 2000).

After publishing fundamental research to clarify the mechanism of action of stimulants in ADHD, Arnsten, one of the key experts in this area, has summarized past and new results of neurobiological research on ADHD (Arnsten, 2006, 2009), suggesting an important role for prefrontal cortex (PFC) dysfunction. The PCF is critical for regulating so-called executive functions and for controlling attention and behavior. Regulation of behavior is accomplished through networks of interconnected pyramidal cells which serve to store goals and rules guiding an individual's actions. The networks interact with each other and are highly dependent on their neurochemical environment. In particular, small changes in the catecholamines (norepinephrine) or dopamine can have marked effects on the PCF function. It is not surprising that all drugs effective in ADHD, regardless of their mechanisms of action, modulate norepinephrine and dopamine release and optimize their concentrations at alpha (2A)-receptors and D (1) receptors respectively. Serotonin has also been implicated in behavior modulation as suggested by some preclinical evidence generated in a rodent ADHD model. Research conducted in young rats with neonatal hyperactivity induced by 6- hydroxydopamine (6-OHDA) lesioning indicates that behavioral effects of stimulants are mediated by release of both NE and serotonin (Davids, 2002). These findings support the clinical testing of potential ADHD therapies that increase activity of the abovementioned neuromodulators.

The pharmacological similarity of viloxazine to other agents with proven efficacy in ADHD provides the rationale for a clinical trial to test preliminarily its effectiveness in this indication. While viloxazine inhibitory action on serotonin re-uptake appears to be weak, the drug does potentiate serotonin-mediated functions in mouse and rat (Ref: Lippman and Pugsley, 1976), and that feature might add interest to its pharmacological profile.

Finally, the extensive human use of this product for depression has not generated any major safety concerns. Formulated as an extended-release product to overcome the molecule's short half life, viloxazine may represent a novel approach to a polymorphic disease, for which more therapeutic options are still deemed necessary (Wigal, 2009).

8. STUDY OBJECTIVES

Primary Objective

The primary objective is to determine the safety of SPN-812V in adults with ADHD.

Secondary Objectives

The secondary objectives of this study are:

- To determine the efficacy of SPN-812V in adults with ADHD
- To explore the single dose and steady state pharmacokinetics of SPN-812V in adults with ADHD.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan

This will be a multicenter, randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy in adults with ADHD. The target subjects are healthy male or female adults aged 18 to 64 years, inclusive, with a diagnosis of ADHD. A total of fifty subjects will be enrolled at approximately 5 sites in the US. Subjects will be randomized (1:1) to one of two treatment groups, SPN-812V or placebo.

The study will consist of a Screening Period (within 14 days prior to randomization) and a Dosing Period of 6 weeks,. The total subject duration in the study will be up to 8 weeks as illustrated in Figure 1.

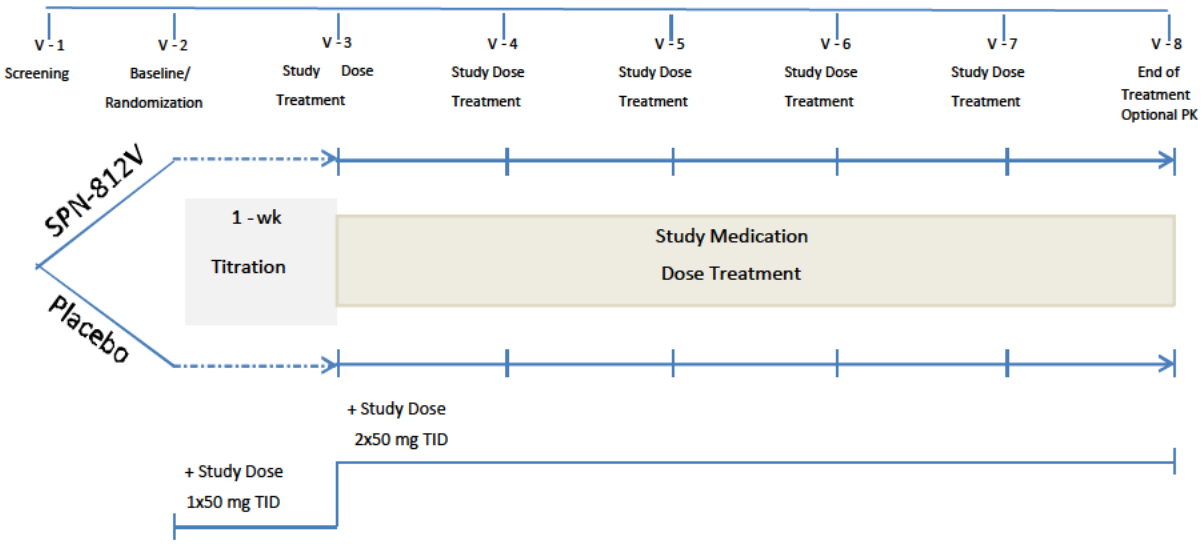

Figure 1. Study Schematic

9.1.1. Screening Period

Screening will take place within 14 days prior to randomization to determine subjects' eligibility to participate in the study. No screening or study-specific assessments may be performed until written informed consent has been obtained. Screening procedures will be performed to determine each subject's eligibility to participate in the study and may be carried out over more than one visit during the Screening Period. Abnormal results on laboratory tests may be repeated once at the discretion of the Investigator during the Screening Period.

Additional screening procedures will include review of medical and psychiatric history, including confirmation of ADHD diagnosis and smoking history; assessment of suicide risk; assessment of demographic and baseline characteristics; full physical examination; measurement of vital signs, height and weight; ECG; sample collections for hematology, biochemistry, CYP2D6 enzyme activity screening, urinalysis, urine drug screen and serum pregnancy test (FOCP only); prior and concomitant medication information will also be collected.

9.1.2. Dosing Period

Subjects who meet the requirements for study participation will be randomized and proceed to the Dosing Period which will last 6 weeks. Approximately 50 subjects will be randomized at a 1:1 ratio, using a centralized randomization system, to either SPN-812V or placebo. The first dose of SM should be taken the morning after the randomization visit.

At the baseline and randomization visit, baseline safety and efficacy assessments will be performed. Inclusion/Exclusion criteria should be re-assessed at this visit. Concomitant medication information will be collected. FOCP will be given a urine pregnancy test. SM will be dispensed.

Each week after randomization, subjects will return to the study site for monitoring of AEs, and the administration of safety tests and efficacy scales. Procedures to be performed are collection

of vital signs and weight, PK blood sampling at Visit 8 (optional, if subjects wish to participate), and an ECG at Visit 4. Assessments of concomitant medications, suicide risk, and SM compliance and dispensation will be performed. Subjects who have consented to participate in the optional PK sub study will be given a diary at Visit 7 on which to record time of SM doses taken prior to Visit 8. Subjects who are participating in the optional PK sub study will be given all efficacy assessments prior to blood draws or dosing on the PK day. For subjects not participating in the optional PK sub study, their last dose will be taken the evening before the End of Study Visit (Visit 8).

9.1.3. End of Study Visit/Early Termination

At the end of Visit 8, or prior to early discontinuation, subjects will undergo end of study assessments. AEs will be monitored, and safety tests and efficacy scales will be administered unless assessments were performed earlier in the visit. The procedures to be performed will include physical examination, collection of vital signs, weight, ECG, blood collection for hematology and chemistry, urine collection for urinalysis, drug screen, and pregnancy test (for FOCP). Assessments of concomitant medications and SM compliance will be performed.

9.2. Discussion of Study Design, Including Choice of Treatment Groups and Appropriateness of Measurements

This will be a randomized, double-blind, multicenter, parallel group, placebo-controlled safety and tolerability study in adults with ADHD. The target subjects are healthy male and female adults aged 18 to 64 years, inclusive, with a diagnosis of ADHD. 50 subjects will be randomized; assuming a 20% dropout rate, it is anticipated that 40 subjects will complete the study.

Blinding to treatment will be employed to reduce potential bias during data collection and evaluation of endpoints. Randomization will be used in this trial to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The primary objective of this Phase I/IIa study is to evaluate the safety of SPN-812V in these subjects. Safety will be assessed by the monitoring of AEs, vital signs, clinical laboratory tests, physical examinations, and ECGs.

The secondary endpoints of this study are:

1. To establish the efficacy of SPN-812V over a 5-week treatment period with SPN-812V 300 mg/day
2. To establish the initial efficacy of SPN-812V after a 1-week treatment period with SPN-812V 150mg/day.
3. To establish the effectiveness of SPN-812V over a 6-week treatment period with either SPN-812V dose.
4. To establish the clinical utility of SPN-812V after a 5-week treatment period with SPN-812V 300mg/day.
5. To establish the study subject's perception of clinical benefit of SPN-812V at endpoint after a 5-week treatment with SPN-812V at 300mg/day.

6. To explore in a population model the single-dose and steady state pharmacokinetics of SPN-812V in adults with ADHD.

To determine the drug effect on reducing ADHD symptoms, the CAARS will be utilized. The CGI Scale will be administered to reflect drug effect on global functioning. These efficacy assessments will be performed at all study visits. Subjects who have agreed to participate in the optional PK sub study will have the efficacy assessments performed prior to blood being drawn and dosing for the PK sub study.

Randomization will be used in this trial to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

9.3. Selection of Study Population

This study population was selected to evaluate SPN-812V safety and efficacy in adults, aged 18 to 64 years old, inclusive, with ADHD. In this study 50 subjects will be randomized at approximately 5 US sites.

9.3.1 Inclusion Criteria

Subjects meeting all of the following criteria may be included in the study:

1. Able to provide informed consent prior to any study procedure being conducted.
2. Capable and willing to comply with study procedures.
3. Male or female aged 18 to 64, inclusive.
4. Subjects with a current diagnosis of ADHD as confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)
5. Clinical Global Impression – Severity (CGI-S) score of 4 or higher.
6. On no treatment for ADHD or willing to be withdrawn from an ongoing treatment after a washout of at least 10 days.
7. Body Mass Index (BMI) between 18.0 and 34.0 inclusive
8. Subject must be in general good health as determined by medical history, ECG, and other analysis that, in the judgment of the Investigator, would confirm the Subject's good health.
9. Females of childbearing potential (FOCP) who, if sexually active, agree to use acceptable forms of contraception (including oral, transdermal, or implanted contraceptives; intrauterine device; female condom with spermicide; diaphragm with spermicide; cervical cap; abstinence; use of condom with spermicide by sexual partner or sterile [at least 6 months prior to SM administration] sexual partner) at least 14 days prior to start of study drug administration, throughout the study, and for 30 days following the last dose of SM.
10. Postmenopausal females with amenorrhea for at least 2 years or females who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

9.3.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Current or past history of psychotic disorder or major depressive disorder with psychotic features.
2. Presence of another primary DSM-IV-TR disorder.
3. Suicidality, defined as either active suicidal plan/intent or active suicidal thoughts in the 6 months before the Screening Visit or more than 1 lifetime suicide attempt. (The Columbia-Suicide Severity Rating Scales [C-SSRS] will be administered at each visit.)
4. Substance or alcohol abuse/dependence within previous 6 months, or a positive urine drug screen at screening or baseline prior to first dose of study medication (SM).
5. Any known or suspected significant medical or psychiatric illnesses that, in the judgment of the Investigator, may impair interpretation of study results or constitute a significant safety concern in the context of the clinical trial
6. ECG abnormalities (clinically significant according to Investigator's opinion) or vital sign abnormalities (systolic blood pressure [SBP] <90 or >140 millimeters of mercury [mmHg], diastolic blood pressure [DBP] <40 or >90mmHg, or heart rate [HR] <40 or >100 beats per minute [BPM]) at screening.
7. Clinically significant laboratory abnormalities; including presence of potential hepatic function impairment as shown by, but not limited to alanine aminotransferase (ALT) values >2 times upper limit of normal (ULN), aspartate aminotransferase (AST) > 2 times ULN, gamma-glutamyl transpeptidase (GGT) >3 times ULN, or total bilirubin >1.5 ULN .
8. Medications, including health food supplements judged by the Investigator to be likely to have central nervous system activity (for example, St John's Wort, gingko leaf, and melatonin), are not permitted during the study. If the subject is taking the medication prior to study entry, there must be a 7 day washout period prior to first dose of SM.
9. Lifetime history of tic disorder, Tourette's Disease, or organic brain disorder; or family history of Tourette's Disease.
10. Current or lifetime history of hyperthyroidism unless treated and stable for 6 months.
11. Participation in or plan to begin behavioral therapy during the study.
12. Subject has a prior history of allergy or any significant adverse reaction (including rash) to viloxazine, or any of the product components.
13. Females who are pregnant or lactating or are unwilling to use an acceptable form of contraception throughout the study.
14. Difficulty swallowing whole capsules.
15. History of seizures or risk factors for seizures (e.g., head trauma), not including febrile seizures.
16. Use of an investigational drug or participation in an investigational study within 30 days prior to first dose of SM.
17. Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.

9.4. Study Methods

9.4.1. Schedule of Visits and Procedures

Table 1. Schedule of Visits and Procedures presents the schedule of visits and procedures for the study.

Table 1. Schedule of Visits and Procedures

Study Phase	Screening Period	Dose Treatment Period (Visit window +/- 2 days)		End of Study [b]
Activity	Visit 1 Up to 14 Days Prior to Visit 2	Visit 2	Visits 3 – 8	
Informed Consent [a]	X			
Medical and Psychiatric History and Demographics	X			
Physical Exam	X			X
ECG (12-lead)	X		X [c]	X
Vital Signs [d]	X	X	X	X
Hematology	X			X
Urinalysis and drug screen	X			X
CYP2D6 Enzyme Activity Screening	X			
Serum Chemistry	X			X
Serum Pregnancy Test (for FOCP only)	X			X
Urine Pregnancy Test (for FOCP only)		X		
CAADID	X			
CGI	X	X	X	X
C-SSRS	X	X	X	X
CAARS [e]		X	X	X
Concomitant Medication	X	X	X	X
Randomization		X		
SM Dispensed		X	X	
SM Diary Dispensed			X [f]	
Optional SM Administered On-Site [g]			X	
Optional PK Blood Sampling			X [h]	
Adverse Events			X	X [i]

a To be obtained prior to any study procedures being performed.

b To be performed at the end of Visit 8 (unless done previously during Visit 8), or at early discontinuation.

c At Visit 4 only

d Heart rate, seated blood pressure, temperature, and respiratory rate will be measured at every visit. The vital signs readings will be performed within approximately 10 minutes prior to the scheduled blood draws, where applicable. Height will be taken at screening and weight will be assessed at each visit.

e CAARS self-report done only at Visits 2 and 8, CAARS investigator-report done at Visits 2-8

f At Visit 7 to record SM taken prior to Visit 8. Diary to be collected at Visit 8.

g Dose to be administered on-site after the pre-dose draw and an overnight fast at Visit 8; subjects may eat 2 hours after dosing.

h At Visit 8, subjects who wish to participate will be dosed after an overnight fast and have a series of PK samples drawn. Samples will be taken pre-dose, and at Hours ½, 1, 2, 3, 4, 5, and 6.

i Any subject who experiences an adverse event (whether serious or non-serious) or has a clinically significant abnormal laboratory test value(s) will be followed by the Investigator at appropriate intervals based on the severity and nature of the event, until resolved, or when the condition is assessed as stable, causality other than the SM has been found, or the subject is referred to another health care professional.

9.4.1.1. Screening Period

A Screening Period will take place within 14 days prior to the first dose administration to determine subjects' eligibility to participate in the study. If needed, screening may take place over more than 1 visit. Prior to conducting any screening procedures, written informed consent must be obtained from the subject.

The procedures to be performed will include:

- Informed consent process
- Medical and psychiatric history, including smoking history
- Demographics
- Administration of CAADID for confirmation of ADHD diagnosis
- Administration of CGI-S
- Administration of C-SSRS
- Assessment of inclusion/exclusion criteria
- Physical examination
- ECG (12-lead)
- Vital signs, height, and weight
- Laboratory tests (including hematology, clinical chemistry, and urinalysis)
- Urine drug screen
- Serum pregnancy test (for FOCP)
- Assessment of prior and concomitant medications

9.4.1.2. Baseline and Randomization

Once subjects have been adequately screened and it is determined the subject is eligible for the study, the subject will return for the baseline and randomization visit.

The procedures to be performed will include:

- Changes in medical and psychiatric history since last visit (AE collection starts after first dose)
- Administration of CGI-S
- Administration of CAARS, both investigator-rated and self-rated versions
- Administration of C-SSRS
- Vital signs and weight
- Urine pregnancy test (for FOCP)
- Assessment of concomitant medications
- Randomization

- SM dispensed

9.4.1.3. Dose Treatment Period

9.4.1.3.1. Visits 2-7

Dosing Schedule:

- The first dose of SM should be taken the morning following the randomization visit.
- Following dosing for a week at the starting dose of 150mg SPN-812V or placebo (1 capsule TID), subjects will be titrated to and maintained at the 300mg SPN812-V or placebo dose level (2 capsules TID) for 5 weeks.
- Subjects in the highest dose group will be permitted to down titrate to the starting dose at the Investigator's discretion in consultation with the Medical Monitor. Subjects who still cannot tolerate study medication after one down-titration should be removed from the study. Visits will occur on a weekly basis (+/- 2 days).

The following evaluations will be performed:

- AEs assessed (monitoring begins after first dose of SM)
- Administration of CGI-I
- Administration of CAARS, investigator-rated version at each visit, self-rated version only at Visit 8
- Administration of C-SSRS
- Vital signs and weight
- ECG (12-lead) (Visit 4 only)
- Assessment of concomitant medications
- SM returned and dispensed, assessment of compliance
- SM time recordation diary dispensed to subjects who have consented to participate in the PK sub study (Visit 7)
- Subjects who will participate in the optional PK sub study at Visit 8 will be reminded to not eat or take SM prior to coming to the clinic the morning of Visit 8

9.4.1.3.2. Visit 8

The following evaluations will be performed:

- AEs assessed
- Administration of CGI
- Administration of CAARS, investigator-rated and self-rated versions
- Administration of C-SSRS
- Vital signs and weight

- Assessment of concomitant medications
- SM returned, assessment of compliance
- SM time recordation diary collected

PK Sub study Procedures: All efficacy assessments will be done first.

- Subjects who agree to participate in the optional PK sub study will be given 2 x 50mg SPN-812V on-site in the morning, unless the subject had been down-titrated, in which case, the subject will receive 1 x 50mg SPN-812V on-site in the morning.

- Subjects must arrive after an overnight fast and may eat two hours after dosing. The subject will have a pre-dose PK draw taken, will be dosed, and will have PK draws taken at ½, 1, 2, 3, 4, 5, and 6 hours post-dose. There is a 30 minute window on all draw times, but they may be used only so that there is at least one hour between each sampling time after the ½ hour post-dose draw.

9.4.1.4. Final Visit/Early Termination

The following evaluations will be performed during the final visit or at early discontinuation (assessments completed at Visit 8 will not be repeated):

- Administration of CGI
- Administration of CAARS, investigator-rated version at Visits 2-8, self-rated version at Visit 8 only
- Administration of C-SSRS
- Physical examination
- ECG (12-lead)
- Vital signs and weight
- Laboratory tests (including hematology, clinical chemistry, and urinalysis)
- Urine drug screen
- Serum pregnancy test (for FOCP)
- Assessment of concomitant medications
- SM returned, assessment of compliance
- AEs assessed

9.4.2. Efficacy Assessments

Investigator-rated Conners' Adult ADHD Rating Scale (CAARS)
This assessment will be administered at study visits 2 - 8.

Clinical Global Impression (CGI)
This assessment will be administered at all study visits.

Self-rated Conners' Adult ADHD Rating Scale (CAARS)
This assessment will be administered at study visits 2 and 8.

9.4.3. Pharmacokinetic Measurements

On the morning of Visit 8, all subjects who wish to participate in the optional PK day will arrive at the clinic after an overnight fast and will have all efficacy assessments administered first. The subjects then will have a pre-dose PK sample taken, and be administered either 2 x 50mg SPN-812V capsules or will be administered 1 x 50mg SPN-812V capsule for subjects who underwent dose reduction. PK sampling will occur pre-dose and at 0.5, 1, 2, 3, 4, 5, and 6 hours post-dose. Although there is a 30 minute window on draw times, efforts should be made to ensure that the time interval between any two sampling timepoints is not less than 30 minutes. Subjects may eat two hours after dosing.

SPN-812V concentrations in plasma samples will be determined by the Sponsor using a validated chromatographic method. The amount of blood to be drawn at each timepoint to determine the plasma concentrations of SPN-812V is 4mL. Information regarding sample collection, handling, and shipping procedures will be detailed in a separate manual.

Single dose administration of viloxazine hydrochloride (100mg) to ten healthy volunteers resulted in mean C_{max} near 1800 ng/mL for viloxazine at a mean T_{max} ~100 min post-dose and with elimination half-life ~3 hr (Vandel B. et al., "Pharmacokinetics of viloxazine hydrochloride in man," European Journal of Drug Metabolism and Pharmacokinetics, 1982, Vol 7, pp. 65-68). Timepoints were chosen on the basis of these data to inform both absorption and elimination phases of the viloxazine time course while minimizing the sampling burden on patients. The design of the study provides both first-dose (in placebo group) and steady state (in active group) observations, albeit in parallel treatment groups.

9.4.4. Safety Assessments

Safety assessments during the study will consist of AE and SAE monitoring, weight, clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs, as detailed in section 9.4.1.

9.4.4.1. Adverse Events

As defined by the ICH Guideline for GCP, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, 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 or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test (e.g., ECG or X-ray) 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.

AEs fall into the categories of “non-serious” and “serious”. 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.

AEs or SAEs that are ongoing at the subject’s last study visit must be followed until resolution or if, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

9.4.4.1.1. Reporting of Adverse Events

All subjects will be closely questioned regarding the occurrence of AEs.

For subjects who receive SM, all AEs (learned of through spontaneous reports or subject interview) will be collected starting from the first dose of SM until the end of the study. All AEs will be collected on the AE Case Report Form (CRF). All SAEs will be reported to the Sponsor.

A cluster of signs and symptoms that results from a single cause may be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal chest X-ray, etc. can all be reported as “pneumonia”).

9.4.4.1.2. Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he/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 (see Section 9.4.4.2. for the definition of an SAE).

9.4.4.1.3. Criteria for Assessing Causality

The question of the relationship of an AE to SM should be determined by the Investigator or study physician after thorough consideration of all facts that are available. Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations. The causal relationship of an AE to SM will be assessed according to the following criteria (based on World Health Organization [WHO] definitions):

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or suspected.

- **Not suspected:** The temporal relationship of the AE to SM administration makes a **causal relationship unlikely**, or other drugs, therapeutic interventions, or underlying conditions provides 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:** Reasonable time sequence to administration of SM, but event could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Definitely related:** Plausible time relationship to SM administration; event cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenological, using a satisfactory rechallenge procedure if necessary.

9.4.4.2. Serious Adverse Events

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

- results in death;
- is life-threatening (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.);

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the SM)
- is a medically important event or reaction (see below)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or seizures that do not result in hospitalization, or development of drug dependency or drug abuse. These events may be considered to need rapid reporting by the Sponsor to regulatory authorities (see Section 9.4.4.2.2.).

Any new SAEs reported by the subject that occur after the first dose of SM and until the end of the study will be collected. SAEs that are ongoing at the subject's last study visit must be followed until resolution or if, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

9.4.4.2.1. Reporting of SAEs

All SAEs must be reported to the Safety Contact person(s) within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE Form, including a detailed description of the SAE and all other information available (e.g., hospital records, autopsy reports and other relevant documents). The Investigator must inform the IRB about such AEs in accord with ICH guidelines and the practices of the governing IRBs (Section 5.1.).

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 Form.

Safety Contact persons and all contact information are listed in the Site Manual and/or Regulatory Binder provided to each investigational site.

9.4.4.2.2. Other Events Requiring Immediate Reporting

The Investigator must report a pregnancy that occurs in a subject during a clinical study to the Medical Monitor within 24 hours of first becoming aware of the event. The Investigator should discuss the case with the Medical Monitor; the Investigator must follow any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

9.4.4.2.3. Expedited Reporting

The Sponsor will inform 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 investigational sites submit SAE information to the Sponsor (or designee) in the manner described above.

9.4.4.3. Laboratory Measurements

Clinical laboratory tests will be performed by a central laboratory. Information regarding collecting, handling, and shipping samples will be detailed in a separate manual. The Schedule of Visits and Procedures (Table 1. Schedule of Visits and Procedures) shows the time points at which blood and urine will be collected for clinical laboratory tests.

For subjects who participate in the optional PK portion of the study, a total of approximately 32mL (8 PK blood draws $\times$ 4mL) of blood/subject will be taken during the course of the study for the purpose of PK samples, in addition to 29mL (2 blood draws for clinical chemistry $\times$ 14.5mL) required for laboratory tests for all subjects. A complete list of all clinical laboratory assessments is presented in Table 2. Clinical Laboratory Assessments.

Laboratory personnel contact information and laboratory sample shipment information and instructions are listed in the Site Manual and/or Regulatory Binder provided to each investigational site.

Table 2. Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell count (RBC) Platelet count White blood cell count (WBC) (with differential)	Albumin Alkaline phosphatase Alanine transaminase (ALT) Aspartate transaminase (AST) Bilirubin- Total and Direct Blood urea nitrogen (BUN) Calcium Chloride Cholesterol- Total, HDL and LDL Creatinine Creatine phosphokinase (CPK) Gamma-glutamyl transpeptidase (GGT) Glucose Inorganic phosphorous Potassium Sodium Total protein Triglycerides Uric acid	Ketones Protein Specific gravity Glucose pH
Other tests		
Urine drug panel for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabinoids, methadone, opiates, phencyclidine, propoxyphene, and alcohol) Urine pregnancy test (for FOCP) CYP2D6 enzyme activity (poor, intermediate and ultra rapid metabolizers)		

Abnormal lab findings may be confirmed if necessary by one repeated testing at the discretion of the Investigator. Any laboratory abnormality may qualify as an AE in the Investigator's judgment.

9.4.4.4. Vital Signs, Height, and Weight Measurements

Vital sign measurements (HR, blood pressure, temperature, and respiratory rate) will be obtained at all visits as designated on the Schedule of Visits and Procedures (Table 1. Schedule of Visits and Procedures). Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. Height and weight will be obtained at the Screening Visit and weight will be collected at all visits as designated on the Schedule of Visits and Procedures (Table 1. Schedule of Visits and Procedures).

9.4.4.5. Medical, Psychiatric History and Physical Examinations

Medical and psychiatric history, including smoking history, will be taken at the screening visit. Physical examinations will be performed at the Screening Visit and Final Visit as designated on the Schedule of Visits and Procedures (Table 1. Schedule of Visits and Procedures).

9.4.4.6. Electrocardiograms (ECGs)

ECGs (12-lead) will be obtained at the Screening Visit, Visit 4, and the Final Visit as designated on the Schedule of Visits and Procedures (Table 1. Schedule of Visits and Procedures). Additional ECGs may be performed at other times if deemed necessary.

The ECG will be recorded while the subject is resting in a supine position. 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 corrected using Fridericia's method).

9.4.5. Completion/Discontinuation of Subjects

Subjects will be permitted to leave the study at any time. Subjects can be withdrawn from the study in any of the following circumstances:

- SAE or an AE
- Administrative reasons (e.g., sponsor decision)
- Withdrawal of consent/assent
- If the subject becomes pregnant
- If it is in the best interest of the subject, in the opinion of the Investigator
- Termination of the study

When an event such as a family emergency, a transient illness (such as a cold) unrelated to SM, or a remediable act of non-compliance prevents a subject from participating in a scheduled visit, but the subject wishes to continue in the study, the Investigator will attempt to reschedule the visit and retain the subject in the study on a case by case basis, rather than discontinue the subject’s participation.

If a subject is prematurely discontinued from participation in the study for any reason after SM administration, the Investigator must make every effort to perform the Final Visit assessments.

9.5. Treatments

9.5.1. Treatments Administered

SM will be dispensed at each visit during the Randomization and Dose Treatment Periods. Subjects will receive a bottle at each visit containing the correct number of 50mg (or placebo) capsules, which is a sufficient number of capsules for dosing until the next visit. The SM will be taken by the subject orally, three times per day during waking hours, with at least 4 hours between doses (morning, noon, and evening).

At Visit 8, subjects who agree to participate in the optional PK sub study will be given 2 x 50mg SPN-812V capsules on-site in the morning, unless the subject had been down-titrated, in which case, the subject will receive 1 x 50mg SPN-812V capsule on-site in the morning. Note: all subjects who participate in the optional PK sub study will be given active SPN-812V capsule(s) in this portion. For subjects not participating in the optional PK sub study, their last dose will be taken the evening before the End of Study Visit (Visit 8).

9.5.2. Identity of Study Medication

SM are supplied as size 0 white opaque capsules by the Sponsor in labeled bottles. There will be 50 capsules per bottle. Labels will bear the protocol number, product code, and batch number. SM will be repackaged each week into a weekly supply by the unblinded site staff member who will be dispensing the blinded medication. The site number, subject number, subject initials, and the number of capsules to be taken at each dose per day, will be handwritten on the labels by the unblinded staff member who will be dispensing the blinded medication.

9.5.3. Handling of Study Medication

All SM will be 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 labels. The Investigator must maintain an accurate record of the shipment and dispensing of the SM in an accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of SM dispensed to each subject must be available for inspection at any time. The assigned unblinded CRA will review these documents on one or more visits to the investigational site.

All SM supplies are to be used only for this protocol and not for any other purpose. The Investigator must not destroy any SM labels or any partly used or unused SM supply. At the conclusion of the study and as appropriate during the course of the study, the Investigator will return all used and unused SM containers and a copy of the completed SM accountability log to the Sponsor.

9.5.4. Study Medication Accountability

The Investigator, who will be blinded, will delegate responsibility to a qualified unblinded study staff member who will be responsible for the accountability of all clinical supplies (receipt, dispensing, inventory, record keeping, and return) following Sponsor

instructions and must adhere to GCP guidelines as well as municipal, state, and federal regulations.

Under no circumstances will the Investigator or the delegated unblinded staff member 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 in the study.

An accurate and timely record of the receipt of all clinical supplies, dispensing of SM to the subject, collection of unused supplies returned by the subject at each visit, and subsequent return of unused SM to the Sponsor must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM dispensing/return reconciliation log, (c) SM accountability log, and (d) all shipping service receipts. All forms will be provided by the Sponsor. Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. Discrepancies on SM accountability must be documented and addressed by the delegated unblinded staff member.

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). All unused SM, including empty containers, are to be returned to the Investigator by the subject or parent or LAR, and ultimately to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. Upon completion of SM accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, SM that is to be returned to the Sponsor must be shipped following all local regulatory and shipment laws. Forms and information that could unblind the study must be maintained such that the Investigator and blinded study staff are not unblinded.

9.5.5. Method of Assigning Subjects to Treatment Groups

The randomization for this study will be managed centrally; specific instructions to conduct subject randomization will be provided in a separate document to all investigational sites.

A randomization scheme will be generated using a pseudo-random number generator in a computer program. The method avoids bias by use of a chance mechanism. The randomization scheme assigns Treatment 1 or Treatment 2 to each randomization number in a 1:1 ratio.

Upon admission to the study, subjects will be assigned a 4-digit screening number, in the order that they are entered. Subjects who subsequently meet all eligibility criteria will be assigned a 6-digit randomization number. The first 3 digits will refer to the site, and the last 3 will refer to the subject-specific number, which will be assigned according to the randomization scheme.

Once a randomization number has been assigned, no attempt should be made to use that number again, if, for example, a subject is withdrawn. All subjects are randomized only once.

Note: all subjects who participate in the optional PK substudy will be given active SPN-812V capsule(s) in this portion.

9.5.6. Removal of Subjects from Therapy or Assessment

The Investigator or subjects themselves may stop SM treatment at any time for safety or personal reasons. If possible, a subject who discontinues treatment will be followed for end of study protocol-specified visits and procedures. A subject removed from the study for any reason may not be replaced.

9.5.7. Dosing Schedule

At the Baseline and Randomization Visit, subjects will be randomized to Treatments 1 or 2 and will initiate dosing. Once the target dose is reached, maintenance treatment will continue for 6 weeks. Down titration to the starting dose is allowed for subjects who cannot tolerate the maintenance dose, at the discretion of the Investigator in consultation with the Medical Monitor. Subjects who cannot tolerate study drug after dose-reduction should be removed from the study.

At Visit 8, subjects who agree to participate in the optional PK sub study will be administered efficacy assessments prior to dosing. Then, subjects will be given 2 x 50mg SPN-812V on-site in the morning, unless the subject had been down-titrated, in which case, the subject will receive 1 x 50mg SPN-812V on-site in the morning.

9.5.8. Method of Administration

Capsules should be swallowed whole and not crushed or chewed. The SM will be administered three times per day, with at least 4 hours between doses (morning, noon, and evening). When possible, doses should be administered at the same times each day. If a dose is missed, it should be taken as soon as possible unless it is within 30 minutes of the next dose; in this case the subject should skip the missed dose and return to the regular schedule thereafter.

9.5.9. Blinding

The appropriate SM, according to randomization, will be placed into bottles to be dispensed to the subject by an unblinded staff member (e.g., coordinator or pharmacist). Identity of treatment arm must not be disclosed to the site's blinded study staff or the Sponsor (or designee). An unblinded Clinical Research Associate (CRA) will monitor the SM records.

9.5.10. Concomitant Medications

For subjects who receive SM, concomitant medications and therapies that are ongoing as of the date of informed consent will be recorded on the Concomitant Medication CRF. The Investigator will record all concomitant medications, including over-the-counter medications, on the Concomitant Medication CRF. The Investigator will record the AE for which the concomitant medication was administered on the AE CRF.

9.5.11. Treatment Compliance

Records of SM and doses administered will be kept during the study by unblinded site staff. The unblinded CRA will review SM accountability during investigational site visits and at the completion of the study.

9.5.10. Change of Study Medication Dose

Subjects will be assigned to 1 of 2 treatment groups. All subjects will titrate to the maintenance dose of SM and will remain on SM for 6 weeks during the Maintenance Period. Down titration to the starting dose is allowed for subjects who cannot tolerate the maintenance dose, at the discretion of the Investigator in consultation with the Medical Monitor. Subjects who cannot tolerate study drug after dose-reduction should be removed from the study.

9.6. 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 or CRO's qualified compliance auditing team, which is an independent function from the study conduct team.

9.6.1. Data Collection

The Investigator (or designee) will enter the information required by the protocol into the CRF in accordance with the CRF Completion Instructions that are provided with the CRF. The CRA will visit each investigational site as frequently as documented in the monitoring plan to review the CRF for completeness and accuracy against the source documents. The CRA will highlight any discrepancies found in the documentation of study conduct and ensure that appropriate site personnel address the discrepancies. Procedures for data collection and correction will be discussed at the site initiation visit, routine monitoring visits, and will be included in the completion instructions.

9.6.2. Clinical Data Management

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

9.6.3. Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail. A quality assurance audit will be performed prior to database lock.

9.6.4. Bioanalytical Data Management and Quality Control

PK samples and requisition forms will be shipped by the Investigator to the central laboratory, and instructions will be detailed in the central laboratory manual. Analysis will be performed by means of a validated chromatographic method. Details on the analytical methodology, the method validation, and the analytical within-study quality control procedures will be included in the clinical study report for this protocol.

9.7. Statistical Methods

9.7.1. Statistical and Analytical Plans

Tabular summaries of the data collected during the study will be presented to provide a general description of the subjects studied and an overview of the safety, efficacy, and PK results. Data from all investigational sites will be combined in the computation of these summaries, and summaries will be presented by treatment group.

As down titration from 300mg to 150mg is allowed for subjects who cannot tolerate the maintenance dose, those subjects will be treated as part of the 300mg arm while analyzing the data.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, and minimum and maximum values). Categorical (nominal) variables will be summarized using frequency tables (number and percentage of subjects in each category).

In addition to tabular summaries, subject data listings, as specified in Sections 16.2 and 16.4 of ICH E3, will be provided. Additional subject data listings to be provided for this study are listed under the relevant subsections below.

The full data analyses will be performed by the CRO after the study is completed and the database is locked. Statistical programming and analyses will be performed using SAS® and/or other validated statistical software as required.

The statistical analyses described in this section will be described in more detail in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

9.7.1.1. Analysis Populations

The safety population consists of all randomized subjects who take at least one dose of SM.

The intent-to-treat (ITT) population consists of all randomized subjects who took at least one dose of SM (i.e., the safety population), had baseline efficacy assessment, and had at least one post-baseline efficacy assessment.

The ITT population is the population for the efficacy analysis. Subjects will be analyzed according to treatment assigned.

The restricted ITT population consists of all ITT population subjects with at least 1 efficacy assessment after three weeks of treatment.

The PK population consists of all Safety population subjects with an evaluable PK profile.

9.7.1.1.1. Demographic/Baseline Analyses

Demographic/baseline variables include age, sex, ethnicity, race, baseline height, baseline weight, and medical history. Tabular summaries of the demographic/baseline variables will be presented for the safety, ITT, and restricted ITT populations, except for medical history, which will be summarized for the safety population only.

9.7.1.1.2. Study Medication

Tabular summaries of the treatment percent compliance rate and duration of treatment exposure to SM will be presented for the safety population. The number and percentage of subjects maintained on the target dose versus those reduced in dose during the Maintenance Period will be provided.

Analysis of treatment compliance and exposure will be performed separately for the Baseline and Randomization Period, Dose Treatment Period, and combined Baseline and Randomization and Dose Treatment Periods.

9.7.1.1.3. Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the WHO 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.

9.7.1.2. Efficacy Analyses

Efficacy analyses will be conducted for the ITT population. Where appropriate, a restricted ITT population may also be used.

Descriptive statistics will be presented for all efficacy variables by visit and treatment group.

All significance tests will be performed at the 0.05 level.

9.7.1.2.1. Primary Efficacy Analysis

The primary efficacy measure is the investigator-rated CAARS Total ADHD Symptom Score which is the sum of the Inattention and Hyperactivity/Impulsivity subscales (18 items measured on 4-point scale: 0, 1, 2, and 3).

The changes from baseline to the endpoint (visit 8) in the investigator-rated CAARS Total ADHD Symptom Scores will be compared between the two treatment groups using the Wilcoxon rank-sum test or the two-sample t-test.

To confirm the results (sensitivity analysis), a mixed model repeated measures (MMRM) analysis will be conducted. MMRM analysis will contain fixed effect terms for treatment,

investigative site, visit, and interaction between treatment and visit. The model will include post-baseline values of the investigator-rated CAARS Total ADHD Symptom Score as the dependent variable with a random patient effect and baseline investigator-rated CAARS Total ADHD Symptom Score as a covariate and will use an unstructured covariance.

9.7.1.2.2. Secondary Efficacy Analyses

The following secondary efficacy analyses will be performed:

1. Initial efficacy of SPN-812V starting dose (150 mg/day) when compared to placebo as measured by changes in the investigator-rated CAARS Total ADHD Symptom Score from baseline at week 1 of treatment with starting dose will be analyzed with Wilcoxon rank-sum test or two-sample t-test
2. Effectiveness of any SPN-812V dose when compared to placebo as determined by the weekly changes in the Clinical Global Impression – Improvement (CGI-I) score from baseline severity for 6-week treatment will be plotted as mean CGI-I change versus visit and analyzed using Wilcoxon rank-sum test or two-sample t-test
3. Clinical utility of SPN-812V study dose (300 mg/day) when compared to placebo as determined by the investigator's assessment of the changes in the Conner's Adult ADHD Rating Scale (CAARS) score from baseline at week 2, 3, 4, 5, and 6 of treatment will be analyzed with Wilcoxon rank-sum test or two-sample t-test
4. Study subject's perception of clinical benefit of SPN-812V study dose (300 mg/day) when compared to placebo as determined by changes in the self-rated Conner's Adult ADHD Rating Scale (CAARS) score from baseline at endpoint after 5-week treatment will be analyzed with Wilcoxon rank-sum test or two-sample t-test

9.7.1.2.3. Subgroup Analyses for Efficacy

Subgroup analyses for efficacy will be performed on categories of the following measures:

- Sex
- Race

for the ITT population for the investigator-rated CAARS Total ADHD Symptom Score. Subgroup analyses will also be carried out for the following subscales

- investigator-rated CAARS inattention subscale score
- investigator-rated CAARS hyperactivity/impulsivity subscale score

that together make up the CAARS Total ADHD Symptom Score

9.7.1.3. Pharmacokinetic Analyses

Population PK data will be pooled across all subjects and analyzed using nonlinear mixed-effects modeling methods. The objective of the population PK analyses is to derive individual-specific estimates of apparent oral clearance (CL/F) but not to fully characterize the PK of this formulation of viloxazine.

9.7.1.4. Safety Analyses

Evaluation of safety will be performed for the safety population. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and physical examination findings.

9.7.1.4.1. 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 presented in the summary tables by preferred term nested within System Organ Class (SOC). Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the subject data listings.

Data for AEs will be analyzed using the treatment-emergent signs and symptoms (TESS) philosophy. TESS are defined as AEs that:

- emerge during treatment, having been absent at pretreatment, or
- reemerge during treatment, having been present at pretreatment but stopped prior to treatment, or
- worsen in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only treatment-emergent AEs (TEAEs) from the study will be summarized in tables. TEAEs will be summarized by presenting, for each treatment group, the incidence of AEs. The incidence of TEAEs will be based on the numbers and percentages of subjects with TEAEs. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only once in the incidence count for that MedDRA term.

Separate TEAE incidence tables will be presented for the Baseline and Randomization Period, Dose Treatment Period, and combined Baseline and Randomization and Dose Treatment Periods. For the combined Baseline and Randomization and Dose Treatment Periods, the incidence of TEAEs will also be presented by highest severity reported, closest relationship to SM reported, and the dose of SM at first occurrence. For treatment-related TEAEs only, i.e., those TEAEs classified as possibly or definitely related to SM, the incidence rates will also be summarized as described previously for all TEAEs. Listings (and tabular summaries, if warranted) of deaths, other SAEs, and other significant AEs, including AEs resulting in treatment discontinuation, will be provided.

9.7.1.4.2. Laboratory Values

By-visit tabular summaries of the laboratory test results will be presented. For quantitative laboratory tests, both actual values and change from screening values will be summarized.

Laboratory test results will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference ranges provided by the central laboratory. Within treatment comparisons will be based

on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the LNH classification at screening to the LNH classification and the Final Visit.

9.7.1.5. Vital Signs

By-visit tabular summaries of the actual vital sign, height, and weight measurements and the changes from baseline will be presented.

9.7.1.6. ECG Results

By-visit tabular summaries of the quantitative ECG parameters and the overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant) will be presented. For the quantitative ECG parameters, both actual values and change from screening values will be summarized.

9.7.1.7. Other Special Tests

Findings from the physical examinations will be summarized through 2 by 2 shift tables that, for each system or area examined, compare the normal/abnormal finding at screening to the normal/abnormal finding at the Final Visit.

9.7.2. Sample Size and Power Considerations

Approximately 50 subjects (approximately 25 per treatment group) will be randomized in the study. The sample size is not based on any statistical considerations, but it was judged adequate to provide safety, PK, and efficacy information for a proof-of-concept study.

10. PROCEDURES AND INSTRUCTIONS

10.1. Ethics and Good Clinical Practice

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

The protocol, informed consent, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6, Section 3, and any local regulations, i.e. Federal Regulations, Title 21 CFR Part 56. 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 Chairman must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of any SM to the site by the Sponsor (or 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.

Study progress is to be reported to IRB annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB, he/she will forward a copy to the Sponsor at the time of each periodic report. SAEs should be reported to the IRB in accord with local regulatory requirements.

10.2. Subject Information and Informed Consent

As part of administering the informed consent documents, the Investigator (or designee) must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If written consent is not possible, oral consent may be obtained if witnessed by at least one person not involved in the study. The verbal consent will be documented and signed by the Investigator and the witness(s). No subject can enter the study before his/her informed consent has been obtained.

A separate ICF will be given for the optional PK substudy. The above procedures will be followed in obtaining this consent.

10.3. Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. The protocol will be followed as written.

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 IRBs. 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 must be notified promptly and the IRB for the site must be informed promptly.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB detailing such changes.

10.4. Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with ICH E6, Section 4, "Investigator Guideline for Good Clinical Practices".

There are to be no Investigator-initiated deviations from the protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation may be ineligible for analysis and may compromise the study. On occasion, a subject whose medical condition does not exactly conform to the specifications of the protocol but who could potentially benefit from study participation may be considered for enrollment by the Sponsor if the Investigator first reviews the situation with the Medical Monitor. In these cases, the potential subject's participation will be discussed with the Sponsor personnel prior to having the subject sign the informed consent, and the exemption for study enrollment will be sent in writing to the investigational site by the Sponsor. The investigational site will retain a copy of this document. If the Investigator learns at any time after informed consent that a subject does not meet protocol specifications for study participation, he/she will call the Medical Monitor immediately.

Subjects who have not signed an IRB approved ICF cannot receive SM.

The Investigator and research team must comply with ICH E6 principles and all applicable local regulatory laws and regulations.

10.5. Retention of Records

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location in the original format until at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the SM.

Essential documents include:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable) and enrollment log
- Record of all communications between the Investigator and the IRB
- Copies of CRFs and of documentation of corrections for all subjects
- SM accountability records
- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH E6 Guideline for GCP (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

10.6. Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department may conduct audits of clinical research activities in accordance with the Sponsor's 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 immediately that this request has been made.

10.7. 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. The study is being conducted as part of a multicenter clinical trial. As stipulated in the protocol, data from all such sites shall be pooled and analyzed. 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, at least ninety (90) days prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until any 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).

10.8. Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and 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 be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator.

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 (provided by the Sponsor).

10.9. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. Reimbursement for expenses covering subjects, laboratory tests, and other professional fees will be made. 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. In such an event, final settlement of the grant-in-aid will be adjusted pro rata, and the Investigator will refund the excess of payments made in advance. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

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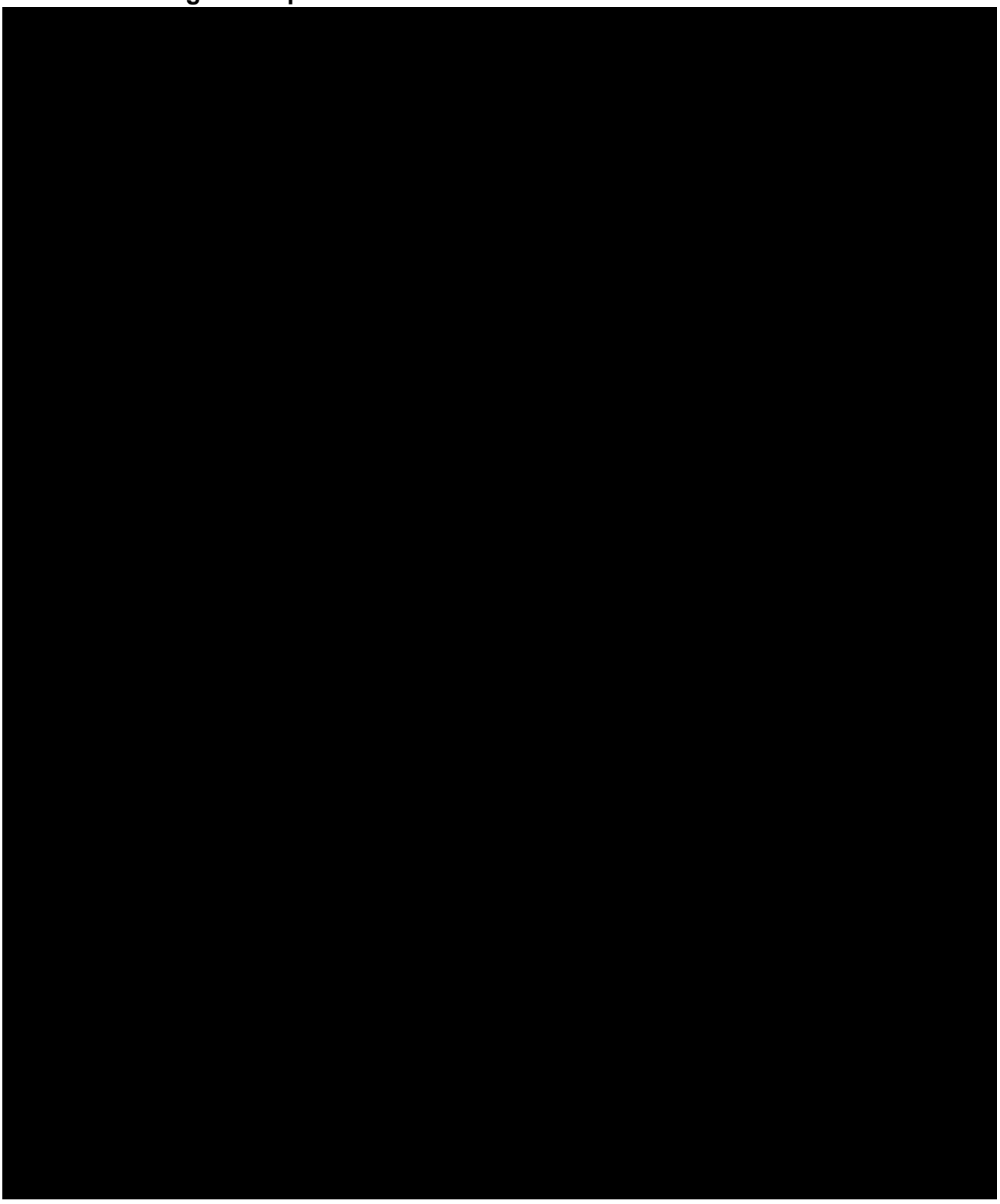
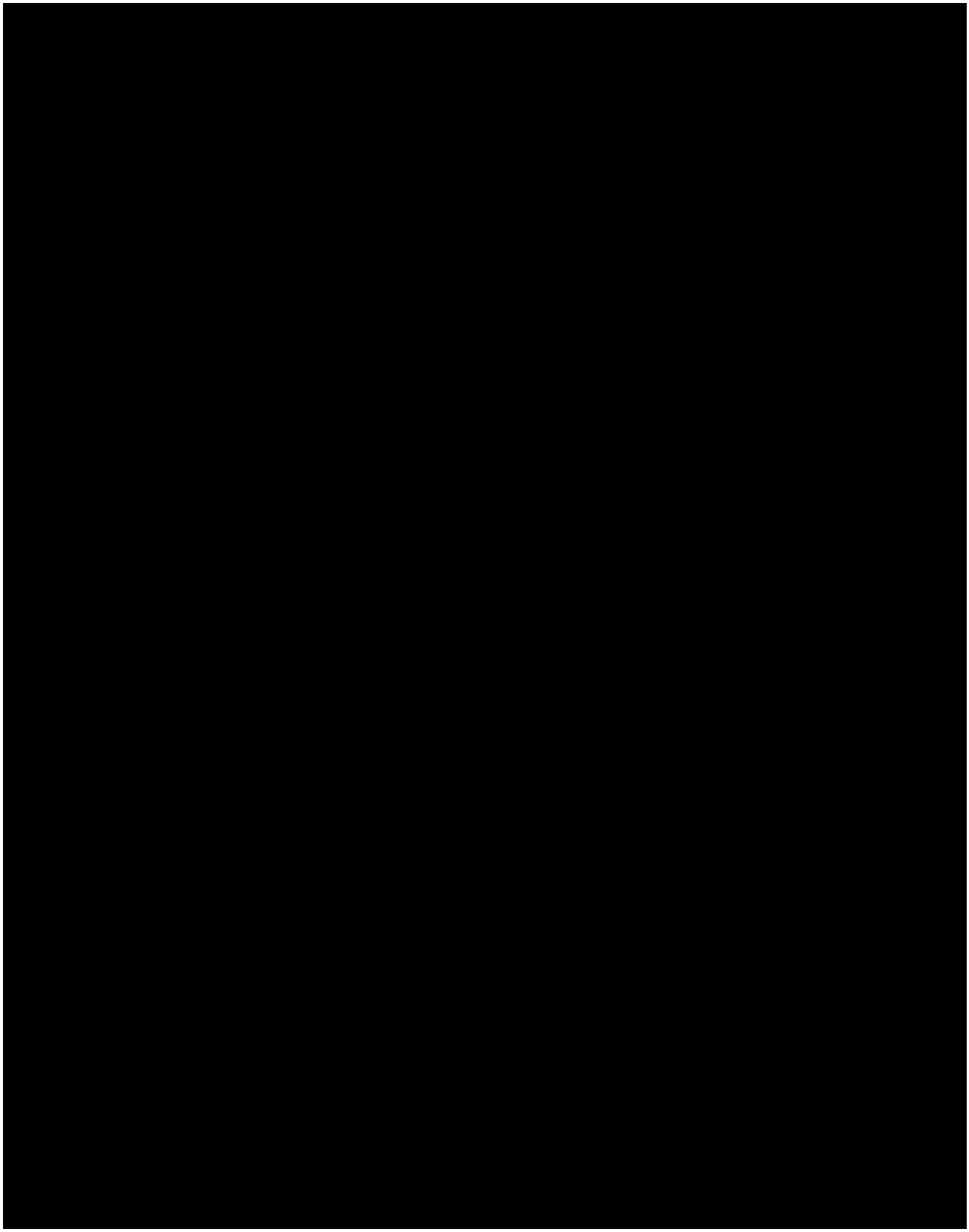
12. APPENDICES

12.1. Conners' Adult ADHD Rating Scale (CAARS)

12.1.1. Investigator-Report



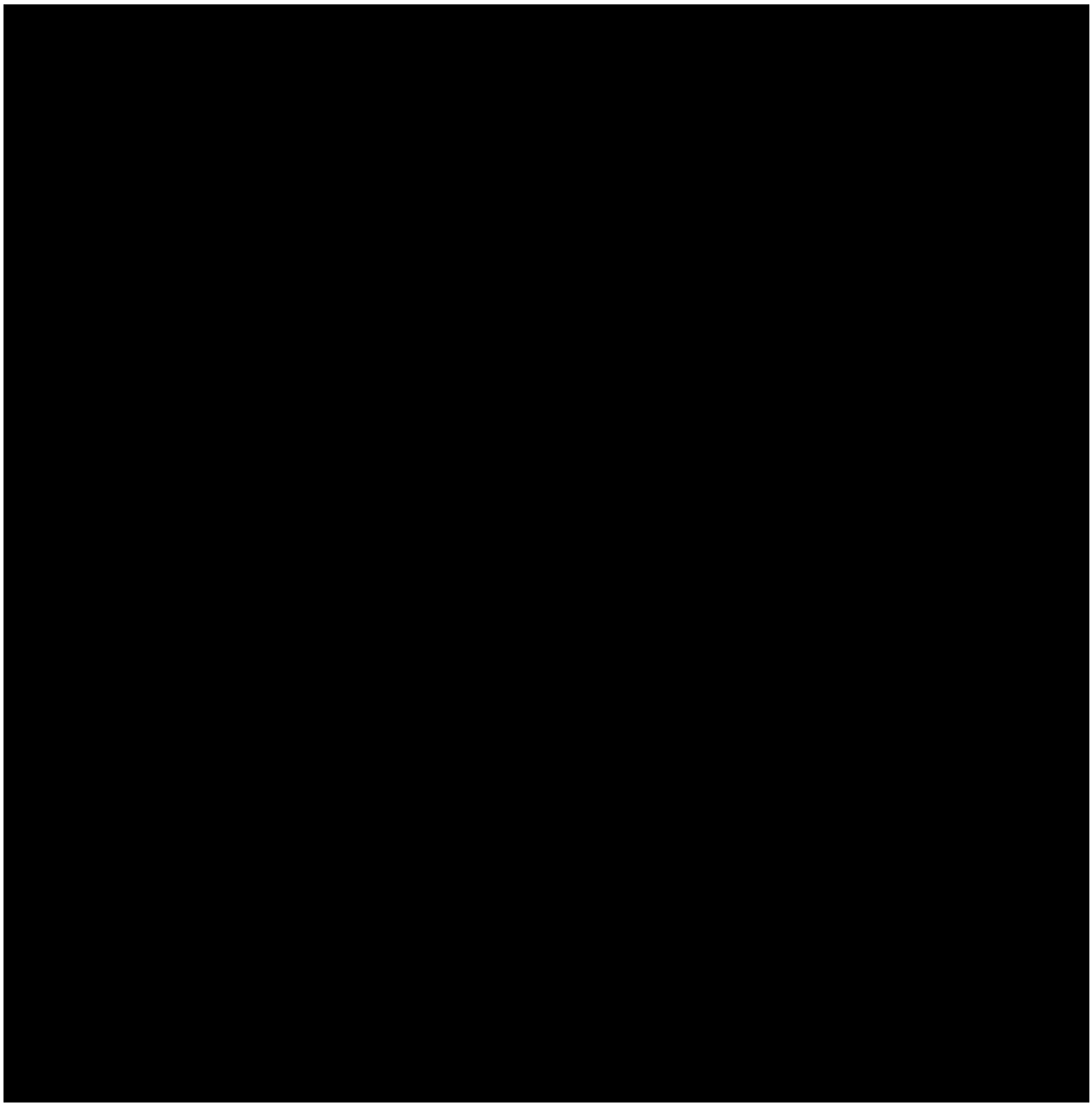
12.1.2. Self-Report

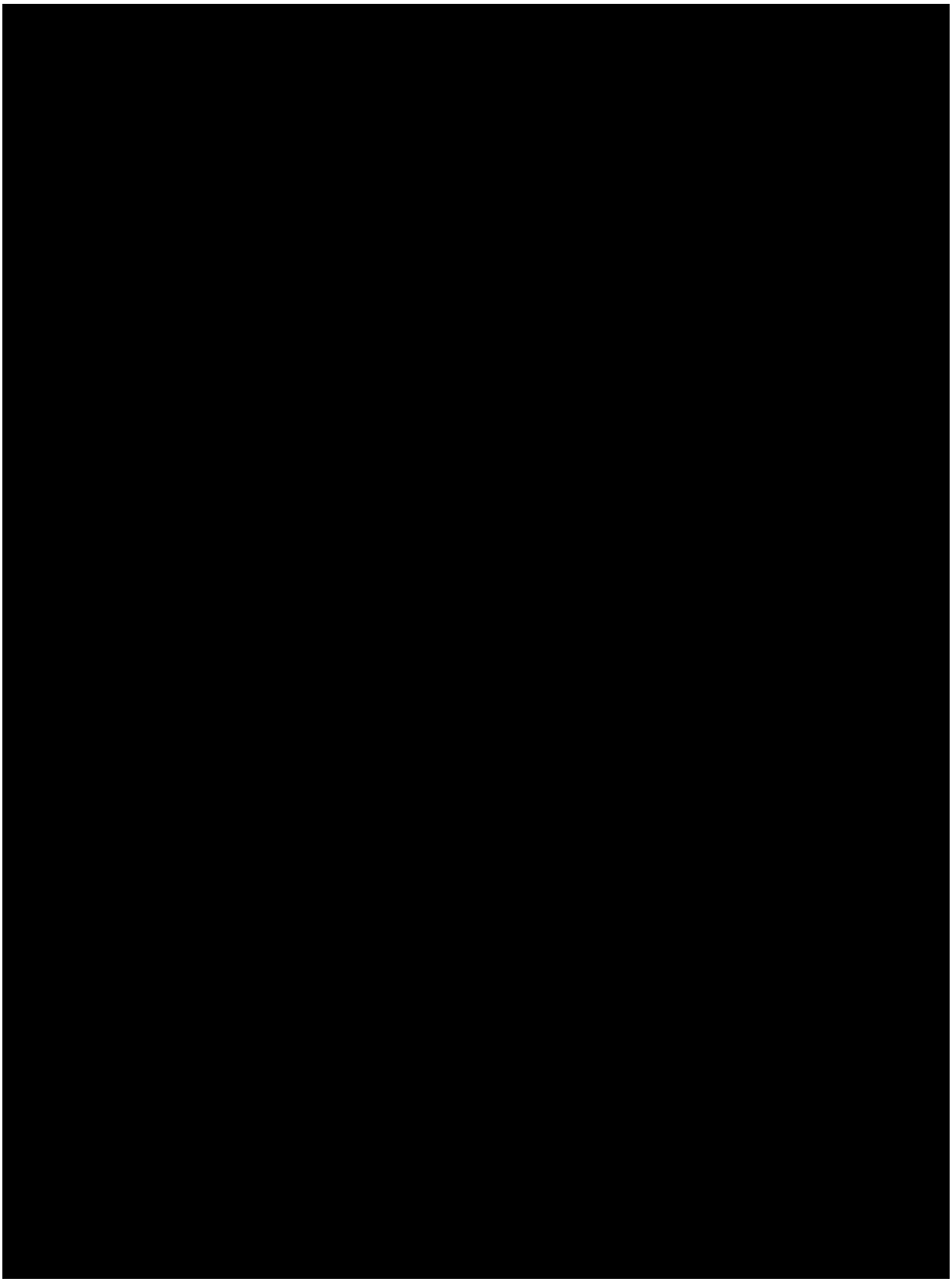


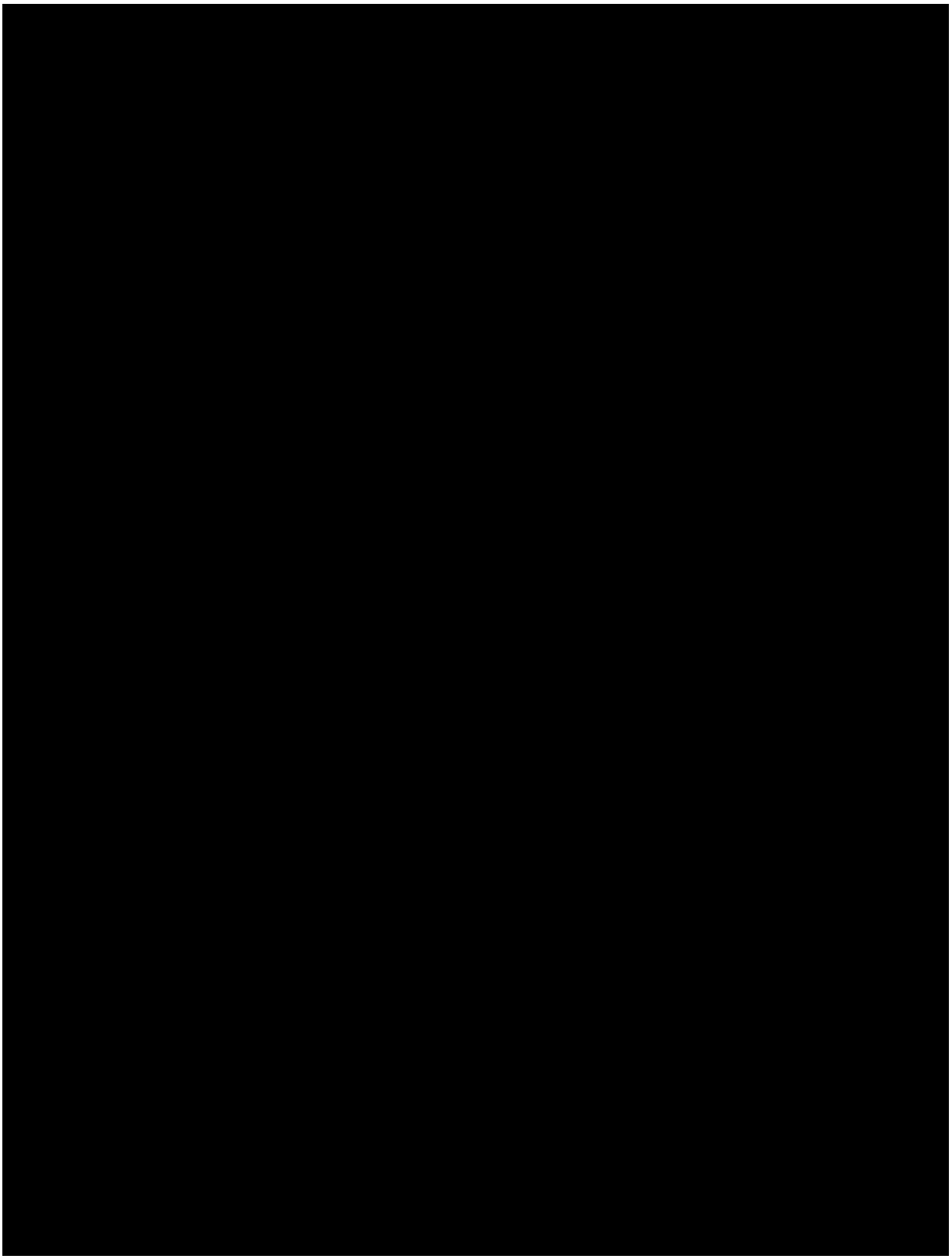
12.2. Clinical Global Impression (CGI) Scale

12.3. Columbia-Suicide Severity Rating Scales (C-SSRS)

12.3.1. Baseline







12.3.2. Since Last Visit