CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Laboratory Classroom Study to Evaluate the Safety and Efficacy of d-Amphetamine Transdermal Drug Delivery System (d-ATS) Compared to Placebo in Children and Adolescents with ADHD

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1 SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Laboratory Classroom Study to Evaluate the Safety and Efficacy of d-Amphetamine Transdermal Drug Delivery System (d-ATS) Compared to Placebo in Children and Adolescents with ADHD
Protocol Number:	N25-006
Investigators:	4-5
Study Sites:	4-5
Phase of Development:	Phase II
Objectives: **Primary Objective:**	• To assess efficacy of d-ATS compared to placebo, as measured by SKAMP total score • To assess the safety of d-ATS
Secondary Objectives	• To assess onset of efficacy of d-ATS compared to placebo as measured by the SKAMP total score • To assess duration of efficacy of d-ATS compared to placebo as measured by the SKAMP total score • Additional efficacy assessments include the Permanent Product Measure of Performance (PERMP), the ADHD-RS-IV, Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S) and the Clinical Global Impression (CGI) scale. • To assess the skin irritation, discomfort, adhesion and adhesive residue of d-ATS
Study Design:	This is a randomized, double-blind, multi-center, dose-optimization, crossover, placebo controlled, laboratory classroom study to evaluate the safety and efficacy of d-ATS (5 mg/ 4.76 cm^2, 10 mg/ 9.52 cm^2, 15 mg/14.29 cm^2 and 20 mg/ 19.05 cm^2) in children and adolescents 6 to 17 years of age with ADHD. The study will consist of a four-week screening period, a 72 hour wash-out period (if applicable), a five-week open-label, step-wise dose optimization period and two-week double blind randomized crossover treatment period with weekly classroom assessments and a safety follow-up by telephone 7 days after last dose of study drug. Subjects will be required to visit the clinic at screening (Visit -1), baseline (Visit 0), Dose Optimization Period (Visits 1 through 5, corresponding to Weeks 1 through 5), and Double-Blind Treatment Period (Visits 6 and 7), which are

	analog classroom sessions in the laboratory school setting). Visit 7 will also serve as the End of Study Visit. Following Screening Period and Washout Period (if applicable), eligible subjects will enter the open-label Dose-Optimization Period, during which they will begin receiving d-ATS followed by evaluation for efficacy and tolerability of that dosage approximately 4 days later. Dosage will be initiated at 5 mg/ 4.76 cm^2 d-ATS and adjusted to the next available dose at weekly intervals, until optimal dose is reached. Optimal dose will be defined as the dose that will produce a reduction in ADHD RS-IV score ≥ 30% and CGI-Improvement (CGI-I) score of 1 or 2 and has tolerable side effects. Tolerability will be determined by the investigator, based on review of AEs and clinical judgment. Once reached, the optimal dose will be maintained for the remainder of the Dose-Optimization Period. Subjects will be discontinued if they are unable to tolerate d-ATS or cannot reach their optimal dose by Week 5. If the subject has reached their optimal dose, then at the discretion of a medically qualified investigator, one dose reduction per participant may occur during the dose optimization period for safety reasons. However if the current dose is intolerable and the subject has never reached their optimal dose, the subject would be discontinued from the study. A dose increase may occur at visit 4 if no prior dose has met criteria for optimal response and the current dose is well tolerated as deemed by a medically qualified investigator. The dose used during the week 5 visit will be the dose that the subject is randomized to during the Double-Blind Treatment Period. During Visit 5 (Day 35), subjects will attend a half-day practice laboratory school with analog classroom sessions to become familiar with classroom schedules and procedures. Three SKAMP assessments will be performed, and 3 practice PERMP tests will be given during the practice session. Practice laboratory classroom periods will be 30 minutes in length to allow sufficient time for SKAMP and PERMP ratings and transition times. Following dose optimization, subjects will enter the two-week double-blind treatment period. Subjects will be randomized to receive daily d-ATS treatment (at the optimized dose) for one week followed by daily placebo patches (identical in appearance to d-ATS) for one week, or vice versa. During the Double-Blind Period, for the first six days of each week study drug will be administered by the subject/parent/caregiver. On the last day of each week (analog classroom days) the patches will be applied in the clinic by study staff at

	the start of the laboratory classroom assessment. Patches will be worn for 9 hours every day. After 9 hours the patch will be removed. Every day a new patch will be applied. On Day 42 (Visit 6) and Day 49 (Visit 7) of the Double-Blind Period, subjects will return to the clinic for patch application, dermal evaluations, ECG monitoring, vital sign assessments and laboratory classroom assessments. Laboratory classroom rating periods will be 30 minutes in length to allow sufficient time for SKAMP and PERMP ratings and transition times. Subjects will be discharged from the clinic after all the assessments have been completed. A follow-up telephone call will be made approximately 7 days (Day 56, Visit 8) after the subject's last dose of study drug to collect information on any ongoing or new AEs, serious AEs, and concomitant medications. Total study duration will be approximately 56 days (excluding the screening period).
Selection of Subjects:	Inclusion Criteria: • Gender: Male or female; • Age: Between 6 and 17 years of age, inclusive; • Race: All eligible; • Females of child-bearing potential who agree to practice a clinically accepted method of contraception during the study and for at least one month prior to study dosing and one month following completion of the study. Acceptable contraceptive methods include abstinence, oral contraception, surgical sterilization (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), intrauterine device [IUD], or diaphragm in addition to spermicidal foam and condom on male partner, or systemic contraception [e.g. Norplant System]; • Must meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition – Text Revision (DSM-IV-TR) criteria for a primary diagnosis of ADHD combined, predominately hyperactive impulsive type, or predominately inattentive type; • The screening and baseline visit ADHD-RS-IV total score must be at 90% or greater relative to the general population of children by age and gender. • Must be able to wear a patch for 9 hours. For children and if applicable for adolescents, parent or caregiver must be present to apply and remove the patches and maintain the used and unused patches in a secure controlled area of the home;

	• Must be functioning at an age appropriate level intellectually as determined by an intelligence quotient (IQ) of ≥ 80 on the Wechsler Abbreviated Scale of Intelligence II™ (WASI II™), vocabulary and matrix reasoning components; • Must have, the ability to complete PERMP assessment; • Have parental consent (signed ICF) and written or verbal assent from the subject; • Subject and parent(s)/caregiver are willing and able to comply with all the protocol requirements and parent(s) or caregiver must be able to provide transportation for the subject to and from the analog classroom sessions. Exclusion Criteria: • Has blood pressure outside the 95th percentile for age and gender; • Has a pulse of less than 50 (age 6-17), or greater than 120 (age 6-12), or greater than 125 (age 13- 17); • Is a known non-responder to amphetamine treatment; • Has a documented allergy, intolerance, or hypersensitivity to amphetamine; • Is currently taking an ADHD medication that is providing symptom control with no residual impairment at home or school and has acceptable tolerability and adherence. • Has a recent history (within the past 6 months) of suspected substance abuse or dependence disorder (including nicotine); • Has a history of seizures during the last 2 years (exclusive of infantile febrile seizures), a tic disorder (exclusive of transient tic disorder), a current diagnosis and or a family history of Tourette's Disorder. Mild medication induced tics are not exclusionary; • Has any psychiatric disorder that could interfere with study participation or the safety of the subject or other participants, such as conduct disorder (CD) or oppositional defiant disorder (ODD) with a history of prominent aggressive outbursts. Children meeting CD or ODD but without prominent aggression will be allowed to enroll at the discretion of the investigator. • Has Autism or Asperger's Disorder. • Has a family history (first degree relatives) of sudden cardiac death. • Has current controlled (requiring medication) or uncontrolled comorbid psychiatric conditions such as, post traumatic stress disorder, psychosis, bipolar illness, severe obsessive compulsive disorder, severe depressive or severe anxiety disorder, considered a suicide risk, has previously

	attempted suicide, has recent (last 6 months) suicidal ideation or any lifetime self harm event; • Has a history of abnormal thyroid function; • Has BMI for age greater than 95th percentile per CDC BMI-for-gender specific charts; • Has a known history of symptomatic cardiovascular disease, advance arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug; • Has any skin abnormality present at the potential application site that is likely to be aggravated by the study drug (i.e., infection, rash, atrophy, excessive fragility or dryness, any cut or abrasion, or tattoo); • Has a history of hypersensitivity, allergy to topical medication, preparation, or adhesive dressings; • Has concurrent chronic or significant acute illnesses (such as severe allergic rhinitis or an infectious process requiring antibiotics, unless expected to resolve or has resolved by Day 0) disability or any unstable medical condition that in the investigator's opinion would lead to difficulty complying with the protocol requirements; • Has used any investigational drug within 30 days of the screening visit; • Has a history of physical, sexual, or emotional abuse in the last year; • Has a medical history of Hepatitis A, B,C or HIV; • Has positive urine drug screen for drugs of abuse.
Planned Sample Size:	Sufficient number of subjects will be screened such that at least 90 subjects (6 to 17 years of age) are randomized into the study and at least 74 subjects complete the study. Completers will be defined as subjects who have received both treatments during the double-blind treatment period and have completed both 12-hour classroom sessions during the double-blind treatment period.
Investigational Therapy:	d-Amphetamine Transdermal Drug Delivery System (d-ATS) 9-hour patch (5 mg d-amphetamine /4.76 cm^2 patch). d-Amphetamine Transdermal Drug Delivery System (d-ATS) 9-hour patch (10 mg d-amphetamine /9.52 cm^2 patch). d-Amphetamine Transdermal Drug Delivery System (d-ATS) 9-hour patch (15 mg d-amphetamine /14.29 cm^2 patch). d-Amphetamine Transdermal Drug Delivery System (d-ATS) 9-hour patch

	(20 mg d-amphetamine /19.05 cm^2 patch).
Reference Therapy:	Placebo
Treatment Duration:	5 weeks of dose titration period and 2 weeks of double blind treatment period
Efficacy Assessments	ADHD-RS-IV at Visit 0 (baseline; Day 0), Visit 1 (Day 7), Visit 2 (Day 14), Visit 3 (Day 21), Visit 4 (Day 28), Visit 5 (Day 35), Visit 6 (Day 42) and Visit 7 (Day 49). SKAMP and PERMP will be collected as follows: • Visit -1 (Screening): Level finding math test and 1 PERMP at demonstrated level. • Visit 0 (baseline; Day 0): Two practice PERMPs at demonstrated level • Visit 1(Day 7), Visit 2 (Day 14), Visit 3 (Day 21) and Visit 4 (Day 28): One practice PERMP at demonstrated level • Visit 5 (Day 35): Half day practice classroom;(SKAMP and PERMP pre-dose and 1 and 2 hours post dose) • Visit 6 (Day 42) and Visit 7 (Day 49): PERMP and SKAMP within 30 minutes prior to dosing and at 1, 2, 3, 4.5 (4½), 6, 7, 9, 10, and 12 hours following administration of study drug. • Conners' Parent Rating Scale-Revised Short Form will be completed by parent/caregiver on the day before a clinic visit: on Day 6, Day 13, Day 20, Day 27, Day 34, Day 41, and Day 48. • Clinical Global Impression: CGI-S will be collected on Day 0 (pre-dose). CGI-I will be collected on Visit 1(Day 7), Visit 2 (Day 14), Visit 3 (Day 21), Visit 4 (Day 28), Visit 5 (Day 35), Visit 6 (Day 42) and Visit 7 (Day 49).
Safety Assessments ECG	ECG assessments will be performed as follows: • Visit -1 (Screening) • Visit 0 (baseline; Day 0) • Visit 5 (Day 35), Visit 6 (Day 42), and Visit 7 (Day 49) or early termination (prior to discharge).
Vital Signs	Vital sign assessments will be performed at: • Visit -1 (Screening) • Visit 0 (baseline; Day 0) • Visit 1(Day 7), Visit 2 (Day 14), Visit 3 (Day 21), Visit 4 (Day 28), and Visit 5 (Day 35)

	• Visit 6 (Day 42) and Visit 7 (Day 49): 30 minutes pre-dose and 4 hours and 12 hours post dose or early termination.
Suicidality	C-SSRS will be administered as follows: • Visit 0 (baseline; Day 0) • Visit 1(Day 7, Visit 2 (Day 14, Visit 3 (Day 21, Visit 4 (Day 28, Visit 5 (Day 35, Visit 6 (Day 42, and Visit 7 (Day 49) or early termination: prior to discharge.
Laboratory Evaluations	Blood and urine samples for clinical laboratory evaluations will be collected at: • Visit -1 (Screening) • Prior to discharge on Visit 7 (Day 49) or early termination
Dermal Evaluations	Dermal evaluations will be completed at home and during the clinic visits as follows: • Application site will be evaluated by Parents/Caregivers/Subjects for local skin irritation, discomfort, adhesion, and adhesive residue daily. • Adhesion and discomfort will be evaluated by site personnel at 1 and 2 hours after d-ATS patch application on Visit 5 (Day 35) and at 1, 2, 4, 8, and 9 (prior to removal) hours after d-ATS patch application on Visit 6 (Day 42) and Visit 7 (Day 49). • For discomfort scores greater than 0, discomfort will also be evaluated at 1 and 2 hours hours after d-ATS patch application on Visit 5 (Day 35) and at 1, 2, 4, 8, and 9 hours on) Visit 6 (Day 42), and Visit 7 (Day 49) using the 10-point Wong-Baker Faces or Visual Analog Scale (age dependent). A ± 15 minute window is permissible. • Site personnel will evaluate skin irritation 24 hours after removal of the previous day's patch on Visit 6 (Day 42) and Visit 7 (Day 49). • Site personnel will evaluate skin irritation prior to patch application and at 30 minutes, 1 and 3 hours after patch removal on Visit 6 (Day 42) and Visit 7 (Day 49). • Immediately following the removal of the patch on Day Visit 6 (Day 42) and Visit 7 (Day 49) or early termination the amount of adhesive remaining at the application site will be examined and graded.
Outcome Measures:	**Primary Efficacy Measure:** The primary efficacy measure is the mean SKAMP total score. Multiple SKAMP

	assessments will be completed at the end of individual classroom sessions across the day by observers who rated each subject on 13 items, using a 7-point impairment scale (0 = normal, 6 = maximal impairment). **Secondary Efficacy Measures:** The PERMP, a 5-page math test consisting of 80 problems per page (total of 400 problems), will be used in this study to evaluate effortful performance in the classroom as a measure of efficacy.. The ADHD-RS-IV is a clinician-rated scale that reflects current symptoms of ADHD based on DSM-IV-TR criteria; it is a global assessment that measures the severity of symptoms from visit to visit, but is not utilized to assess symptoms of ADHD over the course of the day. The CPRS-R:S is a standard instrument for the assessment of ADHD in children and adolescents. It evaluates problem behaviors as reported by the parent or alternative caregivers. The CGI provides a global evaluation of baseline severity and improvement over time. **Safety:** Safety will be assessed by evaluating adverse events including suicidality [assessed using Columbia Suicide Severity Rating Scale (C-SSRS)], concomitant medications, clinical laboratory tests, vital signs, physical examinations and ECGs.
Statistical Methods and Planned Analyses:	**Sample Size Calculations:** Assuming a standard deviation (SD) of [redacted] and based on an average difference in total SKAMP scores between Placebo and d-ATS of [redacted], 74 subjects would need to complete the study to detect a true difference of [redacted] in mean total SKAMP scores between placebo and d-ATS at 80% power when testing at a significance level of $\alpha = 0.05$ (2-sided). Assuming a dropout rate of 20%, 90 subjects will be randomized and it is expected that 74 subjects will complete the study.
Efficacy Analyses:	The primary population for efficacy assessments will be the Full Analysis Set (FAS) population which includes all consented and randomized subjects who have taken at least one dose of study medication. Sensitivity analyses will be conducted with the Completers population.
Safety Analyses:	Safety data for the Dose Optimization Period will be analyzed using combined

	data from all subjects in the safety population (defined as all subjects who entered the Dose Optimization Period and who have received at least one dose of the open-label treatment and have at least one post-dose safety assessment). Safety data from the Double Blind Period will be analyzed using data from each treatment group where applicable in the randomized population (defined as all randomized subjects who received at least 1 dose of study medication during the Double Blind Period and have at least one post-dose safety assessment). Summary tables of treatment-emergent Adverse Events (TEAEs) including suicidality will be summarized using frequency and percentages. Clinical laboratory data will be summarized descriptively. Additionally, shift tables will be provided of pre-versus post-baseline reference range shifts (with classes for below 'Low', within 'Normal', and above 'High' reference ranges). Actual values and the change from baseline at each time point for vital signs and ECG parameters will be listed and summarized. The presence and severity of discomfort at patch site, skin irritation at the patch site, patch adhesion characteristics and adhesive residue will be tabulated.

2 LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
d-ATS	d-Amphetamine Transdermal System
BMI	Body Mass Index
BP	Blood pressure
CFR	Code of Federal Regulations
cm^2	Centimeter(s) squared
CD	Conduct Disorder
CPRS-R:S	Conners Parent Rating Scale Revised Short Form
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
d-AMP	Dextroamphetamine; d-amphetamine
d/l-AMP	Dextroamphetamine and Levoamphetamine; d/l-amphetamine
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorder*, Fourth Edition, Text Revision
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
EOS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus Antibodies
hr, h	Hour
HR	Heart rate
HIPAA	Health Insurance Portability Accountability Act
IND	Investigational New Drug application
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Independent Review Board
IVRS	Interactive Voice Response System
mg	Milligram
min	Minute
MITT	Modifies Intent To Treat
MMRM	Mixed Model Repeated Measures
NDA	New Drug Application
ODD	Oppositional Defiant Disorder
PERMP	Permanent Product Measure of Performance
PP	Per Protocol
RR	Respiration rate

SP	Safety Population
SAE	Serious Adverse Event
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham Scale
TEAE	Treatment Emergent Adverse Event
WASI	Weschler Abbreviated Intelligence Test

3 INTRODUCTION

The American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR) defines Attention Deficit Hyperactivity Disorder (ADHD) as a psychiatric disorder characterized by developmentally inappropriate degrees of inattention and/or hyperactivity-impulsivity. Confirmation of the diagnosis requires some hyperactivity-impulsivity or inattentive symptoms to be present prior to the age of 7 years. In addition, the symptoms must cause impairment in at least two environments (e.g., at home and at school or work). The symptoms must also be shown to be interfering with age appropriate social, academic or occupational functioning that cannot be accounted for by another psychiatric disorder.[1]

ADHD is the most common developmental disorder of childhood. ADHD prevalence estimates gathered by systematic review vary widely from 2% - 18%.[2] DSM-IV-TR estimates the disorder is prevalent in 3% - 7% of school-age children[1]. An analysis of data from the National Survey of Children's Health performed by the Centers for Disease Control estimates that about 7.8% of children aged 4-17 have been diagnosed with the disorder in the United States as of 2003.[1, 3] Supporting this prevalence estimate is a population-based birth cohort study that calculated the incidence of ADHD diagnosis to be 7.4%.[1, 3] The uncertain number of undiagnosed children combined with the estimated number of those already diagnosed support prevalence estimates above 7% in children.

Stimulant medications have been used to treat ADHD in children since 1937.[4] Amphetamine is known to be one of the most potent sympathomimetic amines for stimulating the central nervous system (CNS).[5] Its proposed mechanism of action is via the release of biogenic amines from storage sites in presynaptic nerve terminals. The release of norepinephrine from central noradrenergic neurons is postulated to mediate its alerting effect, its anorectic effect, and at least part of its locomotor-stimulating effect. The release of dopamine from dopaminergic nerve terminals is postulated to mediate other components of its locomotor-stimulating activity as well as the induction of stereotyped behavior. Amphetamines are also thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron. The CNS effects of amphetamines, including the paradoxical effects on hyperactivity, have led to their use as treatment for ADHD and for narcolepsy.

The Noven d-Amphetamine Transdermal System (d-ATS) is designed to be an alternative to current oral formulations of amphetamine and as a means of providing sustained levels of d-amphetamine (d-AMP) while the patch is worn. The d-ATS formulation contains [redacted] delivering d-AMP upon application to intact skin. The formulation contains [redacted] and is intended to provide therapeutic d-AMP levels similar to approved oral d-amphetamine and d/l-amphetamine formulations marketed in the U.S. Advantages of the patch formulation include the following: may be used to treat children who have difficulty swallowing oral formulations; fewer gastro-intestinal side effects; treatment duration can be customized by altering the patch wear time, which gives parents and physicians much more control and flexibility in using the medication.

Previously, three studies have been performed to characterize the pharmacokinetics of d-ATS.[6,7,8] In the most recent study [redacted]

Additional information on d-ATS is provided in the Investigator's Brochure.[9]

4 STUDY OBJECTIVES

Primary:

- To assess efficacy of d-ATS compared to placebo as measured by the SKAMP total score.
- To assess the safety of d-ATS

Secondary:

- To assess onset of efficacy of d-ATS compared to placebo as measured by the SKAMP total score
- To assess duration of efficacy of d-ATS compared to placebo as measured by the SKAMP total score
- Additional efficacy assessments include the Permanent Product Measure of Performance (PERMP), the ADHD-RS-IV, Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S) and the Clinical Global Impression (CGI) scale.
- To assess the skin irritation, discomfort, adhesion and adhesive residue of d-ATS

5 INVESTIGATION PLAN

5.1 Study Design

This is a randomized, double-blind, cross-over, placebo controlled study to evaluate the safety and efficacy of d-ATS (5 mg/ 4.76 cm^2, 10 mg/ 9.52 cm^2, 15 mg/14.29 cm^2 and 20 mg/19.05 cm^2) in children and adolescents 6 to 17 years of age with ADHD.

The study will consist of a four-week screening period, a one-week wash-out period (if applicable), a five-week open-label, step-wise dose optimization period and two-week double blind randomized crossover treatment period with weekly classroom assessments and a safety follow-up by telephone 7 - 10 days after last dose of study drug.

Screening Period (Visit -1): Screening procedures may be performed within four weeks prior to the Dose Optimization Period of the study.

Washout Period: Eligible subjects will undergo a 72 hour wash-out period if applicable.

Baseline Visit (Day 0, Visit 0): Eligible subjects will return to the clinic on Day 0 for baseline assessments. Subjects who continue to meet the eligibility criteria will be entered into the open-label Dose Optimization period.

Dose-Optimization Period [Day 1 to Day 35; Visit 1 (Day 7 ±3 days**), Visit 2 (Day 14** ±3 days**), Visit 3 (Day 21** ±3 days**), Visit 4 (Day 28** ±3 days**) and Visit 5 (Day 35** ±2 days**)]:** Following Screening Period and Washout Period (if applicable), eligible subjects will enter the open-label Dose-Optimization Period, during which they will begin receiving d-ATS followed by evaluation for efficacy and tolerability of that dosage approximately 7 days later. Dosage will

be initiated at 5 mg/ 4.76 cm^2 d-ATS and adjusted to the next available dose at weekly intervals, until optimal dose is reached. Optimal dose will be defined as the dose that will produce a reduction in ADHD RS-IV score ≥ 30% and CGI-Improvement (CGI-I) score of 1 or 2 and has tolerable side effects.

Tolerability will be determined by the investigator, based on review of AEs and clinical judgment. Once reached, the optimal dose will be maintained for the remainder of the Dose-Optimization Period. Investigator can increase the current dose to provide additional symptom control. One dose reduction will be permitted if the subject experiences unacceptable tolerability of the current dose.

Subjects will be discontinued if they are unable to tolerate d-ATS or cannot reach their optimal dose by Week 5. If the subject has reached their optimal dose, then at the discretion of a medically qualified investigator, one dose reduction per participant may occur during the dose optimization period for safety reasons. However if the current dose is intolerable and the subject has never reached their optimal dose, the subject would be discontinued from the study. A dose increase may occur at visit 4 if no prior dose has met criteria for optimal response and the current dose is well tolerated as deemed by a medically qualified investigator. The dose used during the week 5 visit will be the dose that the subject is randomized to during the Double-Blind Treatment Period.

During Visit 5 (Day 35 ± 2 days), subjects will attend a half-day practice laboratory school with analog classroom sessions to become familiar with classroom schedules and procedures. Three SKAMP assessments will be performed, and 3 practice PERMP tests will be given during the practice session.

Subjects will return to the clinic for evaluations and dose adjustments on Visit 1 (Day 7 ± 3days), Visit 2 (Day 14 ± 3days), Visit 3 (Day 21± 3days), Visit 4 (Day 28 ± 3days) and for evaluations (no further dose adjustments) and randomization on Visit 5 (Day 35) ± 2days (see schematic below). Site personnel will contact subjects by telephone on Day 4, Day 11, Day 18, Day 25 and Day 32 or midway between visits. Subjects/parents/caregivers will be instructed to complete a daily dosing diary and a daily dermal diary. All end of study procedures will be completed for subjects who are early discontinuations from the study.

Visit/Week	d-ATS	Evaluations
Visit 0/Week 1	5 mg d-AMP/ 4.76 cm^2 patch (4-10doses)	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs and PERMP

Amendment 4: Version 5.0 May-08-2013
Amendment 3: Version 4.0 December-11-2012
Amendment 2: Version 3.0 October-31-2012
Amendment 1: Version 2.0 August-02-2012
Final Protocol May-25-2012

Visit 1/Week 2	10 mg d-AMP /9.52 cm^2 patch (4- 10 doses)	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs and PERMP
Visit 2/Week 3	15 mg d-AMP /14.29 cm^2 patch (4- 10 doses) unless already achieved optimal dose	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs and PERMP
Visit 3/Week 4	20 mg d-AMP /19.05 cm^2 patch (4- 10 doses) unless already achieved optimal dose	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs and PERMP
Visit 4/Week 5	Optimal dose (4- 10 doses)	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs and PERMP
Visit 5	Randomization to double blind treatment	ADHD RS-IV, CGI-Improvement (CGI-I) and AEs SKAMP and PERMP

Double-Blind Treatment Period [Day 36 to Day 49; Visit 6 (Day 42) and Visit 7 (Day 49)]: Subjects who have reached an optimal dose will be randomized at Visit 5 to receive double-blind treatment. Administration of study medication will begin on Day 36 and continue up to Day 49 (end of Week 7). During Week 6 subjects will receive study patches in accordance with the randomization schedule and during Week 7 subjects will cross-over to receive the other study treatment per the randomization schedule. Subjects/parents/caregivers will be instructed to apply study patches to the hip once daily in the morning at approximately 8:00 am. Patches will be removed after 9 hours. Each day a new patch will be applied to the opposite hip. Subjects will be instructed to continue completing the daily dosing diary and the daily dermal diary. Subjects will return to the clinic for evaluations and analog classroom sessions in the laboratory classroom setting on Visit 6 (Day 42) and Visit 7 (Day 49). Site personnel will contact subjects by telephone on Day 39 and Day 46. All end of study procedures will be completed for subjects who are early discontinuations from the study.

Follow-Up: A safety follow-up by telephone 7- 10 days (Visit 8, Day 56 + 3 days) after last dose of study drug.

Sample Size: Sufficient number of subjects with ADHD will be screened to randomize approximately 90 subjects. Assuming a 20% dropout rate, it is expected that 74 subjects will complete the study. The Full Analysis Set population (FAS) will be used as the primary population for analysis of efficacy endpoints and is defined as subjects who have taken at least one dose of study medication.

Study Duration: The duration of the study will be approximately 56 days for each individual subject (not including screening and washout).

Study Population: The study population will consist of children and adolescents 6 to 17 of age, who have been diagnosed with ADHD.

5.2 Subject Selection Criteria

5.2.1 Inclusion Criteria

1. Gender: Male or female;
2. Age: Between 6 and 17 years of age, inclusive;
3. Race: All eligible;
4. Females of child-bearing potential who agree to practice a clinically accepted method of contraception during the study and for at least one month prior to study dosing and one month following completion of the study. Acceptable contraceptive methods include abstinence, oral contraception, surgical sterilization (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), intrauterine device [IUD], or diaphragm in addition to spermicidal foam and condom on male partner, or systemic contraception [e.g. Norplant System];
5. Must meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition – Text Revision (DSM-IV-TR) criteria for a primary diagnosis of ADHD combined, hyperactive impulsive subtype, or predominately inattentive subtype;
6. The screening and baseline visit ADHD-RS-IV total score must be at 90% or greater relative to the general population of children by age and gender.
7. Must be able to wear a patch for 9 hours. For children and if applicable for adolescents, parent or caregiver must be present to apply and remove the patches and maintain the used and unused patches in a secure controlled area of the home;
8. Must be functioning at an age appropriate level intellectually as determined by an intelligence quotient (IQ) of $\geq$ 80 on the Wechsler Abbreviated Scale of Intelligence II™ (WASI II™), vocabulary and matrix reasoning components;
9. Must have the ability to complete PERMP assessment;

10. Have parental consent (signed ICF) and written or verbal assent from the subject;
11. Subject and parent(s)/ caregiver are willing and able to comply with all the protocol requirements and parent(s) or caregiver must be able to provide transportation for the subject to and from the analog classroom sessions.

5.2.2 Exclusion Criteria

1.1 Has blood pressure outside the 95th percentile for age and gender;

1.2 Has a pulse of less than 50 (age 6-17), or greater than 120 (age 6-12), or greater than 125 (age 13-17);

2. Is a known non-responder to amphetamine treatment;
3. Has a documented allergy, intolerance or hypersensitivity to amphetamine;
4. Is currently taking an ADHD medication that is providing symptom control with no residual impairment at home or school and has acceptable tolerability and adherence
5. Has a recent history (within the past 6 months) of suspected substance abuse or dependence disorder (including nicotine);
6. Has a history of seizures during the last 2 years (exclusive of infantile febrile seizures), a tic disorder (exclusive of transient tic disorder), a current diagnosis and or a family history of Tourette's Disorder. Mild medication induced tics are not exclusionary;
7. Has any psychiatric disorder that could interfere with study participation or the safety of the subject or other participants, such as conduct disorder (CD) or oppositional defiant disorder (ODD) with a history of prominent aggressive outbursts. Children meeting CD or ODD but without prominent aggression will be allowed to enroll at the discretion of the investigator;
8. Has Autism or Asperger's Disorder;
9. Has a family history (first degree relatives) of sudden cardiac death;
10. Has current controlled (requiring medication) or uncontrolled comorbid psychiatric conditions such as, post traumatic stress disorder, psychosis, bipolar illness, severe obsessive compulsive disorder, severe depressive or

severe anxiety disorder, considered a suicide risk, has recent (last 6 months) suicidal ideation or any lifetime self harm event.;

11. Has a history of abnormal thyroid function;
12. Has a BMI for age greater than 95th percentile per CDC BMI-for gender specific charts;
13. Has a known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug;
14. Has any skin abnormality present at the potential application site (i.e., infection, rash, atrophy, excessive fragility or dryness, any cut or abrasion, or tattoo);
15. Has a history of hypersensitivity, allergy to topical medication, preparation, or adhesive dressings;
16. Has concurrent chronic or significant acute illnesses (such as severe allergic rhinitis or an infectious process requiring antibiotics, unless expected to resolve or has resolved by Day 0) disability or any unstable medical condition that in the Investigator's opinion would lead to difficulty complying with the protocol requirements;
17. Has used any investigational drug within 30 days of the screening visit;
18. Has a history of physical, sexual, or emotional abuse in the last year;
19. Has a medical history of Hepatitis A, B, C or HIV;
20. Has positive urine drug screen for drugs of abuse.

5.2.3 Subject Withdrawal

Participation in the study is strictly voluntary. Subjects/parents/caregivers have the right to withdraw from the study at any time and for any reason. A subject's participation will be terminated:

- At their own or their parent(s)/legal guardian's request

- If, in the Investigator's or Parent(s)/Caregiver's or Sponsor's opinion, continuation in the study would be detrimental to the subject's well-being
- The subject experiences an AE that is intolerable as defined by the Investigator and/or the subject and/or the parent(s)/caregiver
- If the subject is not able to comply with the study requirements
- If the Sponsor terminates the study
- If FDA or other regulatory authority terminates all study activities

5.3 Study Plan and Procedures by Study Visits

Please refer to APPENDIX 1: Time and Event Schedule.

5.3.1 Screening Period (Visit -1, Day -28 to Day -4)

During the screening period, subjects will be seen in the clinic and the study will be described to them. Parents/legal guardian/caregiver will be asked to sign the informed consent and each subject to provide written or verbal assent. After obtaining informed consent, subjects will be screened for participation in the study. Screening procedures may be performed within 4 weeks prior to the start of the dose optimization period of the study. Procedures to be performed at Screening:

1. Obtain a signed consent and verbal or written assent. No screening procedures may be initiated prior to obtaining parent/legal guardian/caregiver signature on the informed consent form and subject's assent.
2. Confirm inclusion/exclusion criteria.
3. Assign subject number, sequentially.
4. Document medical history.
5. Perform a physical examination, including vital signs (sitting BP, HR, RR, oral body temperature), body weight, and height;
6. Calculate BMI
7. Collect blood and urine for clinical laboratory assessments

- Complete Blood Count (including differential and platelet count)
- Blood Chemistry
- Urine drug screen (for drugs of abuse) and cotinine (for nicotine).
- Urine pregnancy test on all females of child-bearing potential.

8. Perform a 12-lead electrocardiogram (ECG).
9. Obtain ADHD-RS-IV score.
10. Perform the Mini-kid 6.0
11. Perform the Weschler Abbreviated Intelligence Test.
12. Perform one level finding math test and one PERMP at demonstrated level.
13. Record all medications taken within 30 days prior to Screening.
14. Record adverse events.

5.3.2 Washout Period (Day -3 to Day -1)

After receipt of all the test results and confirmation that a subject is eligible to participate in the study, eligible subjects who are currently taking any medication for ADHD will begin a washout period of three days prior to the Baseline visit (Day 0).

5.3.3 Baseline (Visit 0, Day 0)

Subjects who continue to meet the eligibility criteria will report to the clinic on Day 0 (Visit 0) and the following procedures will be performed:

1. Record any AEs or concomitant therapy since previous visit.
2. Obtain ADHD-RS-IV score and confirm eligibility.
3. Obtain weight and vital signs.
4. Perform urine pregnancy testing on all female subjects of child-bearing potential.
5. C-SSRS (Children's Baseline version) will be administered by a trained staff member.
6. Perform CGI-S.
7. Perform a 12-lead electrocardiogram (ECG).

8. Perform two PERMPs at demonstrated level.
9. Demonstrate patch application and provide instructions on correct application to parent/caregiver/subject.
10. Contact IVRS/IWRS to obtain study medication pack number, and dispense study medication.
11. Parents/caregivers/subjects will be instructed to apply patches once daily in the morning beginning the next day and to comply with the study drug dosing regimen.
12. Parents/caregivers/subjects will be instructed to complete their daily dosing diary and daily dermal evaluation diary
13. Parents/caregivers will be instructed on completion of the CPRS-R:S and instructed on which days to complete the assessment.
14. Parents/caregivers/subjects will be informed as to the time and date of next study visit and the importance of having the subject keep that visit.
15. Parents/caregivers/subjects will be instructed to save all unused and used patches and bring them to their clinic visits. Parents/caregivers/subjects will be instructed to save all the used patches in the supplied container.
16. Parents/caregivers/subjects will be instructed to call the site personnel to report any AEs and concomitant therapy.
17. Dismiss from clinic.

5.3.4 Dose Optimization Period (Week 1, Week 2, Week 3, Week 4 and Week 5)

Day 1-6, Day 8-13, Day 15-20, Day 22-27 and Day 29-34 – Home Days (actual days may vary due to permissible window around Day 7, Day 14, Day 21, Day 28, and Day 35). Procedures to be performed:

1. Parent/caregiver/subject will visually inspect the application site for irritation before application and complete the daily dermal evaluation diary as instructed.
2. Parent/caregiver/subject will apply the patch in the morning daily and remove the patch daily as instructed.

3. Parents/caregivers/subjects will complete the daily dosing diary and daily dermal evaluation diary.
4. Parents/caregivers will complete the CPRS-R:S on the day prior to clinical visit: Day 6, Day 13, Day 20, Day 27 and Day 34.
5. Parent/caregiver/subject will call the site to report any AEs or concomitant therapy.

5.3.4.1 Day 4, Day 11, Day 18, Day 25 and Day 32– Telephone Contact

Site personnel will contact subject or parent or caregiver by telephone on Day 4, Day 11, Day 18 Day 25 and Day 32 (Due to the 3 day window around clinic days, the day of the actual telephone call may vary. The call should occur approximately mid-way between clinic visits). During the telephone call the following procedures are to be performed:

1. Review concomitant therapy and adverse events, if any. Record new information.
2. Remind the subject and parent/caregiver that per protocol subjects should not receive medications or therapy to treat ADHD other than the study medication.
3. Remind parents/caregiver/subject to be compliant with patch application and removal and to comply with the study drug dosing regimen.
4. Subjects/parents/caregivers will be reminded to continue completing the daily dosing diary and daily dermal evaluation diary.
5. Subjects/parents/caregivers will be reminded to complete the CPRS-R:S.
6. Subjects will be informed as to the time and date of next study visit and the importance of having the subject keep that visit.
7. Subjects/parents/caregiver will be instructed to save all unused and used patches and bring them to their clinic visits.
8. Subjects/parents/caregiver will be instructed to call the site personnel to report any AEs and concomitant therapy.

5.3.4.2 Visit 1 (Day 7), Visit 2 (Day 14), Visit 3 (Day 21), Visit 4 (Day 28) and Visit 5 (Day 35) – Clinic Days

Subjects will return to the clinic for evaluations on Day 7 ±3 days, Day 14 ±3 days and Day 21 ±3 days, Day 28 ±3 days and Day 35 ±2 days. There must be at least 4 days in between clinic visits). The following evaluations will be performed during each clinic visit:

1. Record any AEs or concomitant therapy since previous visit.

2. Perform drug accountability and collect all used and unused patches.
3. Review the daily dosing and irritation diaries for compliance.
4. Obtain vital signs (sitting BP, HR, RR, oral body temperature).
5. Record weight.
6. Perform a 12-lead electrocardiogram (ECG) on Day 35.
7. Perform urine pregnancy testing on all female subjects of child-bearing potential.
8. Obtain ADHD-RS-IV score (home version).
9. Perform 1 PERMP (for practice on days 7, 14, 21, and 28) at demonstrated level.
10. Half-day classroom with SKAMP and PERMP (Visit 5, Day 35) pre-dose and 1 and 2 hours post-dose (SKAMP and PERMP rating periods will be 20 minutes in duration).
11. Patch application in clinic (Day 35 only) by subject/parent/caregiver/site personnel
12. Adhesion and discomfort will be evaluated by site personnel after d-ATS patch application at 1 hour and 2 hours/ immediately prior to leaving the clinic on Visit 5 (Day 35).
13. For discomfort scores greater than 0, discomfort will also be evaluated at 1 and 2 hours after d-ATS patch application on Visit 5 (Day 35) using the10-point Wong-Baker Faces or Visual Analog Scale (age dependent). A ± 15 minute window is permissible.
14. Site personnel will evaluate skin irritation of the previous day's patch near subject dismissal on Visit 5 (approximately 19 hours after removal of the patch).
15. Administration of the C-SSRS (Children's Since Last Visit version) by a trained staff member.
16. Perform CGI-I.
17. Based on the ADHD-RS-IV score, CGI-I score and side effect profile, adjust the subject's dose to the next available dose (except Visit 4, which can only be a dose reduction and Visit 5 (randomization at optimal dose)
18. If the subject is unable to reach optimal dose, discontinue the subject in IVRS/IWRS and proceed to or schedule the early termination visit.
19. Contact IVRS/IWRS to obtain study medication pack number and dispense study medication on Day 7, Day 14, and Day 21, and 28.

20. On Day 28, after receiving the pack number from IVRS/IWRS, prior to dispensing, remove one pouch from the medication pack, fill in applicable subject information on the label, and retain the pouch for application in the clinic on Day 35.
21. On Day 35, contact IVRS/IWRS to randomize the subject in the system. After receiving the pack number, prior to dispensing, remove one pouch from the medication pack, fill in applicable subject information on the label, and retain the pouch for application in the clinic on Day 42.
22. Dismiss from clinic.

5.3.5 Double Blind Treatment Period (Week 6 and Week 7)

Following dose optimization, subjects will enter the two-week double-blind treatment period. Subjects will be randomized to receive daily d-ATS or placebo at the optimized dose. During the two-week double blind cross-over treatment period each subject will receive treatment per the randomization schedule as follows:

Optimal d-ATS dose during Dose Optimization Period (Day 1 to Day 35)	Cross-Over, Double-Blind Treatment Period	
	Week 6	Week 7
d-ATS (5 mg/ 4.76 cm^2)	d-ATS (5 mg/ 4.76 cm^2) or Placebo	d-ATS (5 mg/ 4.76 cm^2) or Placebo
d-ATS (10 mg/ 9.52 cm^2)	d-ATS (10 mg/ 9.52 cm^2) or Placebo	d-ATS (10 mg/ 9.52 cm^2) or Placebo
d-ATS (15 mg/ 14.29cm^2)	d-ATS (15 mg/ 14.29cm^2) or Placebo	d-ATS (15 mg/ 14.29 cm^2) or Placebo
d-ATS (20 mg/ 19.05 cm^2)	d-ATS (20 mg/ 19.05 cm^2) or Placebo	d-ATS (20 mg/ 19.05 cm^2) or Placebo

During the Double-Blind Period, for the first week subjects will take study drug as per randomization schedule and for the next week they will be crossed over to the other study drug per randomization schedule. During the Double-Blind Period study drug will be administered by the subject/parent/caregiver, however on the last day of each week (analog classroom days Day 42 and Day 49) the study drug will be administered in the clinic by subject/parent/caregiver/site personnel at the start of the laboratory classroom assessment.

Patches will be worn for 9 hours every day. After 9 hours the patch will be removed. Every day a new patch will be applied.

5.3.5.1 Day 36-41 and Day 43-48 – Home Days

Procedures to be performed:

1. Parent/caregiver/subject will visually inspect the application site for irritation before application and complete the daily irritation diary as instructed.
2. Parent/caregiver/subject will apply the patch in the morning daily and remove the patch daily as instructed.
3. Parent/caregiver/subject will examine and grade for adhesive residue immediately following patch removal according to the scale presented in section 6.15.4, Table 5.
4. Parents/caregivers/subjects will complete the daily dosing diary and daily dermal evaluation diary.
5. Parents/caregivers will complete the CPRS-R:S on Day 41 and Day 48
6. Parent/caregiver/subject will call the site to report any concomitant medications or AEs.

5.3.5.2 Day 39 and Day 46– Telephone Contact

The site personnel will contact subject or parent or caregiver by telephone on Day 39 and Day 46. During the telephone call the following procedures are to be performed:

1. Review concomitant therapy and adverse events, if any. Record new information.
2. Remind the subject and parent/caregiver that per protocol subjects should not receive medications or therapy to treat ADHD other than the study medication.
3. Remind parents/caregiver/subject to be compliant with patch application and removal and to comply with the study drug dosing regimen.
4. Subjects/parents/caregivers will be reminded to continue completing the daily dosing diary and daily dermal evaluation diary.
5. Subjects/parents/caregivers will be reminded to complete the CPRS-R:S.
6. Subjects will be informed as to the time and date of next study visit and the importance of having the subject keep that visit.
7. Subjects/parents/caregiver will be instructed to save all unused study medication and used study medication and bring them to their clinic visits.
8. Subjects will be instructed to call the site personnel to report any AEs and concomitant therapy.

5.3.5.3 Visit 6 (Day 42) and Visit 7 (Day 49, EOS) – Clinic/Classroom Days

Subjects will return to the clinic for evaluations on Day 42 and Day 49. The following evaluations will be performed during each clinic visit:

1. Record any AEs or concomitant therapy since previous visit.
2. Perform drug accountability and collect all used and unused patches
3. Review the daily dosing and daily dermal evaluation diaries for compliance.
4. Obtain vital signs (sitting BP, HR, RR, oral body temperature) within 30 minutes pre-dose and 4 and 12 hours ± 30 min post-dose
5. Record weight (Day 49 only)
6. Collect blood and urine for clinical laboratory assessments (Day 49 only)
7. Perform a complete physical exam (Day 49 only)
8. Perform 12-lead ECG
9. Perform urine pregnancy testing on all female subjects of child-bearing potential.
10. Patch application by subject/parent/caregiver/site personnel.
11. Patch removal at 9 hours by site personnel
12. Evaluate adhesion and discomfort at 1, 2, 4, 8 and 9 (prior to patch removal) hours after d-ATS patch application.
13. For discomfort scores greater than 0, discomfort will also be evaluated at 1, 2, 4, 8 and 9 (prior to removal) hours after d-ATS patch application using the 10-point Wong-Baker Faces or Visual Analog Scale (age dependent). A ± 15 minute window is permissible.
14. Evaluate skin irritation prior to patch application and at 30 minutes, 1 and 3 hours after patch removal.
15. Evaluate skin irritation of the previous day's patch 24 hours after its removal
16. Examine and grade for adhesive residue immediately following patch removal
17. Obtain ADHD-RS-IV (home version) score (may be obtained the same or prior day).

18. Laboratory classroom – perform SKAMP and PERMP: within 30 minutes prior to dosing and at 1, 2, 3, 4.5 (4½), 6, 7, 9, 10, and 12 hours following administration of study drug (SKAMP and PERMP rating periods will be 20 minutes in duration).
19. Perform CGI-I
20. Administration of the C-SSRS (Children's Since Last Visit version) by a trained staff member
21. On Day 42, contact IVRS/IWRS to obtain study medication pack number. After receiving the pack number, prior to dispensing, remove one pouch from the medication pack, fill in applicable subject information on the label, and retain the pouch for application in the clinic on Day 49.
22. Dismiss from clinic
23. On Day 49, contact IVRS/IWRS to complete the subject in the system.

5.3.6 Early Termination

If the subject is discontinued early (prior to Day 49), the following procedures will be performed:

1. Record any AEs or concomitant therapy since previous visit.
2. Perform drug accountability and collect all used and unused patches.
3. Obtain vital signs (sitting BP, HR, RR, oral body temperature).
4. Obtain weight.
5. Collect blood and urine for clinical laboratory assessments
   - Complete Blood Count (including differential and platelet count)
   - Blood Chemistry
   - Urinalysis
6. Perform a 12-lead electrocardiogram (ECG) prior to discharge.
7. Perform complete physical examination
8. Perform urine pregnancy testing on all female subjects of child-bearing potential.

9. Obtain ADHD-RS-IV score.
10. Perform CGI-I.
11. Administration of the C-SSRS (Children's Since Last Visit version) by a trained staff member.
12. Dismiss from clinic.
13. Contact IVRS/IWRS to early discontinue the subject in the system.

5.3.7 ADHD Treatment after Study Completion or Early Withdrawal

At the end of the study or at early withdrawal the investigator (in consultation with the subject/parent/caregiver) may resume the subject's usual ADHD treatment. In the event that the subject experiences intolerable side effects or the subject's ADHD symptoms worsen while in the study, the subject may be discontinued from the study and their usual ADHD treatment may be resumed at the discretion of the investigator (in consultation with the subject/parent/caregiver. The investigator may continue to provide up to 3 months care for behavior and medication management.

5.3.8 Follow-up Telephone Contact (Visit 8, Week 8, Day 56 + 3 days)

A study staff member will call subjects/parent/caregiver 7-10 days after last dose of study drug to inquire about and record any AEs and concomitant therapy since last visit.

6 DESCRIPTION OF ASSESSMENTS

Study procedures are detailed below and summarized in APPENDIX 1.

6.1 SKAMP AND PERMP

The efficacy assessment is the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP) – Teacher Rating Scale (Appendix 5) to evaluate behavioral effects of d-ATS compared to placebo measured at multiple time points throughout the study. The SKAMP scale is a validated rating scale that assesses behavioral symptoms of ADHD in a classroom setting using a 7-point impairment scale (0 = none, 6 = maximal impairment). The SKAMP total score comprises 13 items. The SKAMP was designed for independent observers to rate 13 items representing two factors of classroom behavior: attention and deportment. Each item is rated on a

7-point scale. Items are specific to place (classroom setting) and time (during a typical classroom period) and the scale is used to assess multiple ratings taken within a day. The SKAMP-D subscale evaluates deportment, including interacting with other children, interacting with adults, remaining quiet according to classroom rules, and staying seated according to classroom rules. The SKAMP-A subscale is a measure of attention and evaluates getting started on assignments, sticking with tasks, attending to an activity, and making activity transitions. The SKAMP quality of work subscale includes 3 items: completing assigned work, performing work accurately, and being careful and neat while writing or drawing.

For consistency among clinical sites, SKAMP and PERMP will be measured in three (3) laboratory classroom sessions during the Day 35 (Visit 5, practice) laboratory school study day, and ten (10) laboratory classroom sessions on each of Day 42 (Visit 6) and Day 49 (Visit 7). Additionally, a classroom schedule will be developed for all clinical sites to follow in an effort to standardize timing of activities and transition times to the classroom rating periods. Each approximately 30-minute laboratory classroom session is specified to include a 20-minute rating period with a buffer of up to 10 minutes within the classroom for transitional games surrounding the rating period.

The other efficacy assessment is the Permanent Product Measure of Performance (PERMP) Derived Measures (Appendix 6), an age-adjusted math test to assess the duration of efficacy of ATS compared to placebo administered at multiple time points during the study. The PERMP is a ten-minute written test performed as seatwork in a classroom. Subjects are given five pages of 80 math problems (400 total problems) and are instructed to work at their desks and to complete as many problems as possible in 10 minutes. Performance is measured as the number of problems worked correctly and the number of problems attempted. Different versions will be used among subjects to adjust for ability as determined by the math pre-test at the baseline visit (Day 0). Additionally different versions will be used across classroom cycles so that a subject does not take the same test more than once during the day. A stopwatch should be used to time the test.

6.2 ADHD-RS-IV (Home Version)

The ADHD-RS-IV is a clinician-rated scale that reflects current symptoms of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-

TR) criteria; it is a global assessment that measures the severity of symptoms from visit to visit, but was not used to assess symptoms of ADHD over the course of the day. The ADHD-RS-IV was developed to measure behaviors of children with ADHD and it consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV criteria. Each item is scored from a range of zero (reflecting no symptoms) to three (reflecting severe symptoms) with total scores ranging from 0 to 54. The 18 items may be grouped into two sub-scales: hyperactivity/impulsivity (even number of items numbered 2 through 18) and inattentiveness (odd number of items numbered 1 through 17). Investigators will use the ADHD-RS-IV: Home Version by gender scoring sheet to determine eligibility.

6.3 CGI

Clinical Global Impression (CGI) Scale will also be used to assess efficacy. The CGI permits a global evaluation of the subject's improvement over time. Prior to dosing the investigator will assess the severity of the subject's condition using a CGI-Severity (CGI-S) Scale. During the Dose Optimization Period and the Double Blind Period, the investigator will assess the subject's improvement relative to symptoms prior to dosing, using the CGI-Improvement (CGI-I) Scale. CGI ratings will be completed with respect to ADHD symptoms.

6.4 Conners' Parent Rating Scale Revised Short Form (CPRS-R:S)

The CPRS-R:S is a standard instrument for the assessment of ADHD in children and adolescents. It evaluates problem behaviors as reported by the parent or alternative caregivers. The CPRS-R:S contains 27 items and covers a subset of the subscales and items on the long parent form. Scales include: oppositional, cognitive problems/inattention, hyperactivity, and ADHD index.

6.5 Weschler Abbreviated Scale of Intelligence – Second Edition (WASI II)

The WASI is a general intelligence, or IQ test designed to assess specific and overall cognitive capabilities. The Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI–II), a revision of the WASI, provides a brief, reliable measure of cognitive ability for use in clinical, educational and research settings. The Two-Subtest Form (Vocabulary and Matrix Reasoning) to be employed in this trial, takes about 15 minutes to administer.

6.6 M.I.N.I.-KID/M.I.N.I.-KID-P 6.0

The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I. 6.0), a short, structured diagnostic interview developed in 1990 by psychiatrists and clinicians in the United States and Europe for DSM-IV and ICD-10 psychiatric disorders, will be employed at screening to rule out co-existing exclusionary psychiatric conditions. With an administration time of approximately 15 minutes, the M.I.N.I. 6.0 (10/10/10) is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies. Use of either the child or parent version is at the discretion of the investigator.

6.7 10-Point Pain Scale

A 10 -point pain scale will be employed on laboratory classroom days to evaluate all discomfort scores greater than 0. For subjects 6-11 the Wong-Baker FACES Pain Scale will be used and for subjects 12-17 a Visual Analog Scale (VAS) will be used (See Appendix 6 for examples).

6.8 Medical History and Physical Examination

A complete medical history including a history of ADHD will be collected at the screening visit.

A complete physical examination will be performed by the Investigator or designee. The complete physical examination will include observation and examination of the subject's general appearance, skin, eyes, ears, nose throat, lungs, heart, abdomen, lymph nodes, extremities, nervous system, and musculoskeletal system. Significant findings at Screening, which have a start date before the date of signing of the informed consent, will be recorded as medical history. Any new findings with a start date after the signing of the informed consent or findings showing worsening of a pre-existing condition will be recorded as AEs.

6.9 Vital Signs

Vital sign measurements will consist of oral body temperature, sitting respiratory rate, and sitting systolic and diastolic blood pressure, and sitting pulse[10] after a minimum of 5 minutes rest.

Blood pressure (BP) should be determined by cuff (manual or automated is acceptable; however the same method should be used throughout the study). A BP cuff suitable to the subject's arm should be used for all BP measurements. All BP measurements should be taken from the same arm and whenever possible, performed by the same site personnel throughout the study.

Vital signs will be evaluated to determine whether the values are: 1) Normal; 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Clinically significant values should be recorded as AEs and will be followed to resolution or up to 30 days following patch removal, whichever comes first.

6.10 Height and Weight

Body height and weight will be measured with the subject in ordinary indoor clothing without shoes

6.11 Body Mass Index (BMI)

BMI will be calculated at screening. The CDC growth charts in Appendices 3 and 4 will be used to verify study eligibility.

6.12 Electrocardiogram

A standard 12-lead ECG should be obtained after the subject has been in a supine position for at least 5 minutes. ECGs will be recorded using a standard cardiograph on standard ECG paper.

Any ECG which demonstrates a clinically significant abnormality during the study will be repeated within 24 hours. If the abnormality persists, ECGs will be obtained daily until the changes have resolved or are satisfactorily explained. ECGs will be interpreted by a qualified physician and evaluated to determine whether the ECG findings are: 1) Normal; 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Clinically significant ECG findings should be recorded as AEs and will be followed to resolution or up to 30 days following patch removal, whichever comes first.

6.13 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS facilitates prospective, systematic monitoring for emergence of suicidality within clinical trials and it is a low-burden, clinician-administered tool that covers the wide spectrum of suicidality from ideation to behavior. A training tool will be supplied to the site by the sponsor. The site will document training of selected staff members and file the training certificates in the trial master file.

6.14 Clinical Laboratory Evaluations

A central laboratory will be used to analyze all blood and urine samples with the exception of the urine pregnancy tests. Subjects for whom a urine pregnancy test is required may not begin treatment until results of the test are known. Results of the pregnancy test must be negative for the subject to be eligible for participation in the study. Subjects will not be required to fast prior to collecting blood for laboratory testing. The clinical laboratory assessment will consist of the following:

Hematology: hemoglobin, hematocrit, white blood cell count, red blood cell count, platelet count, basophils, neutrophils, bands, lymphocytes, monocytes, and eosinophils.

Serum Chemistry: total bilirubin, alkaline phosphatase, alanine transaminase, aspartate transaminase, creatine phosphokinase, lactate dehydrogenase, blood urea nitrogen, creatinine, glucose, total protein, albumin, sodium, potassium, chloride, calcium, inorganic phosphorus, and Hemoglobin A_{1c}.

Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, and blood.

Urine drug screen and cotinine (screening only).

The investigator will evaluate all laboratory test values that are outside the normal range and will indicate whether these values are clinically significant or not clinically significant. Clinically significant laboratory values should be recorded as AEs and will be followed to resolution or up to 30 days following patch removal, whichever comes first.

All abnormal laboratory tests considered to be clinically significant by the investigator may be repeated at the investigator's discretion to rule out the possibility of laboratory error.

6.15 Patch Application and Removal

On home days, patches will be applied daily by the subject/parent/caregiver. Demonstration and instructions on patch application will be provided by a study staff member at the Baseline (Day 0) visit. Patches will be applied to the subject's hip and alternated left and right daily. On classroom days (Day 35, Day, 42, and Day 49), the patches will be applied by subject/parent/caregiver/site personnel in the clinic. See Appendix 2 for complete patch

application and removal instructions. Subject/parent/caregiver will be instructed to save the used patches and bring them to the clinic at their next clinic visit. Site staff will collect all used patches.

6.16 Dermal Evaluations

A trained individual will evaluate the d-ATS application site for adhesion of the patch to the skin and for any discomfort or irritation caused by it. The evaluator will observe the skin directly under the clear d-ATS, without removing the system, and interview the subject. Post-removal, the evaluator will assess the application site and the surrounding area for irritation and adhesive residue. Dermal evaluations must be completed in accordance with the instructions listed below.

In order to ensure reliability between successive ratings, a dedicated evaluator should follow each subject through the completion of the study. If this is not possible, then every effort must be made to limit the number of evaluators to two. ***Signs and/or symptoms of discomfort or irritation related to the patch should NOT be recorded as AEs, unless (i) they occur at a site different from the application site; (ii) if the subject or patch application site is discontinued prematurely from the study due to discomfort or irritation at the patch site; (iii) the symptoms of discomfort or irritation are so severe that in the investigator's judgment it should be recorded as an AE; (iv) the subjects requires a concomitant therapy to treat discomfort or irritation. If discomfort or irritation is recorded as an AE then the AE will be followed to resolution or up to 30 days following patch removal, whichever comes first.***

Spontaneous complaints of irritation or discomfort at the patch application site at times that are unscheduled will be also recorded. Spontaneous reports might include but are not limited to the following: initial complaint irritation or discomfort, exacerbation of an existing irritation or discomfort. The time elapsed between the unscheduled evaluation and d-ATS application must be recorded. At times when the laboratory classroom is scheduled on the same hour as a dermal evaluation, the dermal evaluation may take place up to 10 minutes prior to the start of the classroom.

6.16.1 Adhesion

Adhesion will be evaluated by site personnel on Visit 6 (Day 42) and Visit 7 (Day 49). The 9-hr assessment will be performed immediately prior to patch removal. Findings will be recorded as an estimate of the percentage of the system surface in contact with the skin, according to the scale presented in Table 1.

The system should not be secured with adhesive tape or occlusive dressing of any type. In the unlikely event that a patch should detach completely, the same patch should not be reapplied and a new patch must not be applied. The time and activity at the time of detachment must be documented.

Table 1: Adhesion

Score	Definition
0	≥ 90% adhered (essentially no lift off the skin)
1	≥ 75% to < 90% adhered (some edges only lifting off the skin)
2	≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
3	>0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4	0% adhered – Patch detached (patch completely off the skin)

Additionally, every day at home, prior to patch removal, adhesion will be evaluated by the subject or parent/caregiver. Adhesion will be evaluated according to a Yes/No question. If patch is detached then subject/parent/caregiver will be asked to make a note of the time of detachment and will be asked not reapply the detached patch or apply a new patch Subject/parent/caregiver will be required to answer the following questions:

1. Is the patch fully attached to the skin? Yes/No
2. If 'No', did the patch fall off completely? Yes/No
    a. If 'Yes', then enter time of patch detachment (hh:mm) and activity at the time of detachment.

6.16.2 Discomfort

While assessing discomfort, the evaluator must ask the subject, "Are you experiencing any discomfort related to the patch?" If the answer is "no", the overall level of discomfort will be rated as zero. If the answer is "yes", the evaluator will ask the subject to rate the discomfort as mild, moderate, or severe. If the discomfort is mild, moderate, or severe, the evaluator will probe the subject further, i.e. "Describe your discomfort". The type of discomfort should be specified

and recorded i.e., itching, burning, or other. Any discomfort will be followed to resolution. Discomfort should be recorded and rated according to the scale in Table 2.

Table 2: Experience of Discomfort

Score	Definition
0	No discomfort
1	Mild discomfort
2	Moderate but tolerable discomfort
3	Severe, intolerable discomfort
4	Patch not present

For discomfort scores greater than 0, discomfort will also be evaluated after d-ATS patch application on Day 35, Day 42, and Day 49 using the10-point Wong-Baker Faces or Visual Analog Scale (age dependent). A ± 15 minute window is permissible.

Additionally, every day at home, prior to patch removal, discomfort will be evaluated by the subject/parent/caregiver. Discomfort will be evaluated according to a Yes/No question. Subject will be required to answer the following questions:

1. Are you experiencing any discomfort? Yes/No
2. If 'Yes', then describe your discomfort? Burning, itching or other

NOTE: Signs and/or symptoms of discomfort related to the patch should NOT be recorded as AEs, unless they occur at a site different from the application site or if the subject or patch application site is discontinued prematurely from the study due to discomfort at the patch site or the symptoms of discomfort are so severe that in the investigator's judgment it should be recorded as an AE. If discomfort is recorded as an AE then the AE will be followed to resolution or up to 30 days following patch removal, whichever comes first.

6.16.3 Irritation

The application site will be graded according to the following grading scales. Half grades will not be assigned if reactions fall between the unit grades, rather the more severe of the two grades will be assigned. The examination and readings will be performed by trained evaluators only, except for the home evaluations by parent/caregiver. Findings will be graded and recorded according to the following two scales presented in Table 3 and Table 4.

Table 3: Dermal Response Scale

Score	Skin Appearance
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (i.e., application) site

Table 4: Other Effects

Score (Numeric equivalent)	Observation
N (0)	No other effects
A (0)	Slightly glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

Additionally, every day at home, prior to patch application and 30 minutes after patch removal, irritation will be evaluated by the subject/parent/caregiver by visually inspecting the patch application site. Irritation will be evaluated according to a Yes/No question. Subject will be required to answer the following questions:

1. Do you see any irritation? Yes/No
2. If 'Yes', then describe the irritation? Redness, swelling or other

NOTE: Signs and/or symptoms of skin irritation related to the patch should NOT be recorded as AEs, unless they occur at a site different from the application site or if the subject or patch application site is discontinued prematurely from the study due to irritation at the patch site and/or symptomatic intolerable irritation or the symptoms of irritation are so severe that in the investigator's judgment it should be recorded as an AE. If irritation is recorded as an AE then the AE will be followed to resolution or up to 30 days following patch removal, whichever comes first. In addition, a score of "N" (none) for the Other Effects Scale will be added as an option on the eCRF when no other effects are observed. This must also be noted on a source document.

6.16.4 Adhesive Residue

Immediately following the removal of the patch daily at home by subjects/parents/caregivers and on Visit 6 (Day 42) and Visit 7 (Day 49), the amount of adhesive remaining at the application site will be examined and graded according to the scale presented in Table 5.

If necessary, patch removal may be facilitated by gently applying an oil-based product (i.e., petroleum jelly, olive oil, or mineral oil) to the patch edges, gently working the oil underneath the patch edges. If any adhesive remains on the skin following patch removal, an oil-based product may be applied to patch sites in an effort to gently loosen and remove any residual adhesive that remains following patch removal. In the unlikely event that a patch remains tightly adhered despite these measures, the subject/parent/caregiver should contact the site personnel. Nonmedical adhesive removers and acetone-based products (i.e., nail polish remover) should not be used to remove patches or adhesive.

Table 5: Adhesive Residue

Score	Definition
0	None
1	Light
2	Medium
3	Heavy
4	Patch not present

6.17 Adverse events

Per the International Conference of Harmonization (ICH), an adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing events, which increase in frequency or severity or change in nature during or as a consequence of use of a drug in

clinical trials, will also be considered an AE. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

Any medical condition or clinically significant laboratory abnormality with an onset date before the date of signing of Informed Consent is considered to be pre-existing, and should be documented as Medical History. Any new medical condition or clinically significant laboratory abnormality or an exacerbation of a pre existing condition with an onset date after signing of Informed Consent should be recorded as an AE.

Adverse events will be collected throughout the study beginning from the time the subject signs the consent form and up to 30 days following last patch removal. For all AEs the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Ongoing AEs, at the End of Study or Early Termination, will be followed until the event resolves or stabilizes at a level acceptable to the Investigator or up to 30 days after last patch removal, whichever occurs first. Follow-up beyond 30 days should be discussed with the medical monitor.

6.17.1 Assessment of Adverse Events

All clinical AEs occurring during the clinical study will be assessed by the Investigator and recorded including the date and time of onset and resolution, severity, relationship to study treatment, outcome and action taken with study treatment. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. In such cases, the diagnosis should be documented as the AE and not the individual sign/symptom.

Severity of AEs will be graded on a three point scale: mild, moderate, severe.

- Mild discomfort noticed but no disruption of normal daily activity.
- Moderate discomfort sufficient to reduce or affect daily activity.
- Severe inability to work or perform normal daily activity

Relationship to study treatment should be assessed using the following definitions:

Probable (must have first three): This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered probable, if:

- It follows a reasonable temporal sequence from administration of the drug.
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias.)
- It follows a known pattern of response to the suspected drug.
- It reappears upon rechallenge.

Possible (must have first two): This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when:

- It follows a reasonable temporal sequence from administration of the drug.
- It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known pattern of response to the suspected drug.

Remote (must have first two): In general, this category is applicable to an adverse event which meets the following criteria:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.

- It does not reappear or worsen when the drug is re-administered.

Unrelated: This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under remote, possible, or probable.

6.18 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- Life threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study treatment;
- Other: Important medical events that may not result in death, be immediately life threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are: Intensive treatment in an emergency room or at home for allergic bronchospasm; Blood dyscrasias or convulsions that do not result in hospitalization; Development of drug dependency or drug abuse.

6.18.1 Serious Adverse Event Reporting Requirements

Any clinical adverse event or clinically significant abnormal laboratory test value that is serious and which occurs during the course of the study, regardless of the treatment arm, occurring from the time the subject signs the Informed Consent (start of study screening procedures), must be reported to Noven within one working day of the investigator becoming aware of the event.

Serious Adverse Events with a start date within 30 days of last patch removal MUST be collected and reported.

Suspected Unexpected Serious Adverse Reactions are reported to investigators at each site and associated IRB/IEC when the following conditions occur:

- The event must be a SAE.
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure.

When all subjects at a particular site are off treatment as defined by the protocol:

- only individual reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;
- individual reports considered to be a significant safety issue and/or which result in Sponsor recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all investigators and IRBs/IECs;
- individual reports originating from other trials using the same investigational product will be provided as six monthly reports to investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.

A female subject must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies to Noven within one working day of the investigator becoming aware of the event. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 30 days after the completion of the test "drug" must also be reported to the investigator. Pregnancy occurring in the partner of a male subject participating in the study should be reported to the investigator and the sponsor. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the

pregnancy and follow-up pregnancy reports must be submitted to sponsor within 24 hours. If subject is lost to follow-up then this should be documented in a follow-up report.

This study adheres to the definition and reporting requirements of "ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2."

6.19 Anticipated Adverse Events

Some of the adverse events noted in more than one clinical trial of oral forms of d/l-amphetamine are: headache, decreased appetite, stomach ache, trouble sleeping, nervousness, mood swings, weight loss, dizziness, dry mouth, blurred vision, seizures (mainly in patients with a history of seizures), and slowing of growth in children. It should be assumed that the adverse event profile for the d-ATS should be similar to that found in clinical trials of oral d/l-amphetamine.

7 STUDY TREATMENT

7.1 Investigation Product and Reference Treatment

7.1.1 Investigational Product

d-ATS contains [redacted]. Each patch is designed to release d-amphetamine upon application to intact skin and contains about [redacted].

Each d-ATS patch comprises 3 layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: (1) A translucent flexible film; (2) an adhesive formulation containing amphetamine; and (3) a release liner, which is attached to the adhesive surface and must be removed before the patch can be used. The investigational product will be supplied by Noven. Table 6 identifies the drug product and dosage formulations to be used in this study.

Table 6.

d-Amphetamine Transdermal Drug Delivery System(d-ATS)	5 mg/4.76 cm^2 9-hour patch
d-Amphetamine Transdermal Drug Delivery System(d-ATS)	10 mg/9.52 cm^2 9-hour patch
d-Amphetamine Transdermal Drug Delivery System(d-ATS)	15 mg/14.29 cm^2 9-hour patch
d-Amphetamine Transdermal Drug Delivery System (d-ATS)	20 mg/19.05 cm^2 9-hour patch

7.1.2 Reference Treatment

The reference treatment for use during this study is a placebo patch which will be identical in appearance to d-ATS. The placebo patches will be supplied by Noven.

7.2 Dosage and Administration

Dose-Optimization Period: During the five week dose optimization period subjects will receive d-ATS. Subjects will be instructed to apply one patch daily for 9-hours. Patch will be removed after 9-hours and a new patch will be applied the next day.

Dosing on Visit 1 will begin with the lowest strength of d-ATS. Based upon the ADHD-RS-IV score, CGI-I score and tolerability, subjects will receive the next available dose of d-ATS until optimal dose is achieved.

Double-Blind Treatment Period: Administration of double blind study medication will begin on Day 36 and continue up to Day 49. Subjects/parents/caregiver will be instructed to apply patch once daily in the morning and remove the patch after 9 hours. A new patch will be applied the next day. Subjects must continue to apply the patches up to the day of their clinic visit. Day 42 and Day 49 patches will be applied in the clinic by subject/parent/caregiver/site personnel.

7.3 Randomization and Blinding

Randomization will occur prior to the start of the double-blind study period. Subjects will be randomized to one of the two treatments in a 1:1 ratio. Each eligible subject will be randomized to group assignment by a centralized Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). Randomization will be applied centrally across all sites to ensure even distribution of subjects across each treatment sequence.

For the dose-optimization period, the study staff at the clinical site will dispense open-label study drug to all eligible subjects.

For the double-blind treatment period, the study staff at the clinical site will dispense the double blind study medication according to the randomization code as assigned by the IVRS/IWRS. All personnel, including the investigator, site personnel, sponsor or designee, and the study subject

will be blinded to the medication codes. The medication codes will not be available to the study personnel until completion of the study and final data review (clinical database lock) except in the case of an emergency.

In the case of an emergency, if the investigator deems identification of the study drug necessary for the purpose of providing urgent patient care, and knowledge of the subject's treatment assignment will alter subsequent care, then the investigator is authorized to break the blind at the clinical site. Whenever possible, the medical monitor must be notified prior to unblinding. In the event that this is not possible, the medical monitor must be notified within 24 hours of unblinding.

7.4 Prior and Concomitant Therapy

7.4.1 Rules for Recording Prior and Concomitant Therapies

Concomitant therapy is defined to include all medications, procedures, and therapies that are used to treat the subject during the study. Rules for recording therapies are as follows:

- In the case of an AE, all concomitant therapies used to treat the AE will be recorded.
- All concomitant medications and over-the-counter medications that are ongoing as of the date of the informed consent and taken during the study must be documented.

7.4.2 Ongoing, Prior and Concomitant Therapies

Rules for ongoing prior and concomitant therapies are as follows:

- Prescription medication for stable medical, non-psychiatric illness will be permitted during the study provided the dose has remained stable for 30 days prior to screening.
- Use of an investigational study medication within 30 days prior to screening is not permitted

7.4.3 Prohibited Concomitant Medication

Subjects will not be allowed to take the following medications and therapies during the entire duration of the study:

- Any stimulant other than study drug (e.g. methylphenidate, amphetamine, Ritalin, Ritalin SR, Metadate ER, Concerta, dextromethylphenidate, Focalin, dextroamphetamine, Dexedrine, Adderall
- Atomoxetine (Strattera), SSRIs and SNRIs

- Tricyclic antidepressants
- Clonidine, MAOIs
- Mood Stabilizers (e.g. lithium, valproate, quetiapine)
- Antipsychotics (e.g. risperidone, olanzapine)
- Anticonvulsants
- Sedative hypnotics (unless stable dose at least 30 days prior to screening and during the clinical study)
- Coumarin anticoagulants
- Halogenated anesthetics
- Phenylbutazone
- Alternative therapies to treat ADHD
- Other investigational drugs

7.5 Treatment Compliance

Subjects/parents/caregivers will be instructed to bring used and unused patches to their clinic visits. Site personnel will collect all used and unused patches at each clinic visit and perform drug accountability and clarify any discrepancies with the subject/parent/caregiver during the clinic visit.

7.6 Investigation Product and Reference Treatment Management

7.6.1 Packaging and Labeling

Packaging and labeling will be performed by Noven or designee in conformance with all regulatory requirements.

7.6.2 Drug Accountability

The d-Amphetamine transdermal patch is a Schedule II controlled substance (CII) and the Investigator and/or designee must follow federal, state and local regulations governing the handling and distribution of CII substances. Upon receipt of the study medication, the Investigator, site pharmacist, or study coordinator will inspect and inventory the medication. Under no circumstances will the Investigator allow the study drug to be used other than as

directed by the protocol.

Study treatments will be stored in a room that is monitored for temperature. Study drug should be stored pouched below 77°F (25°C). All study treatments will be kept in a dry, locked, and secured storage facility accessible only to those authorized by the Investigator to dispense the study medication. All storage conditions required for storage of CII substances will be followed. An accurate and timely record of the receipt of all clinical supplies and subsequent return of drug to the Sponsor must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug 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.

Used and unused patches will be retained at the site until the Sponsor requests their return or destruction.

8 STATISTICAL METHODS

The Sponsor or designee will perform data analysis.

8.1 Determination of Sample Size

Assuming a standard deviation (SD) of [redacted] and based on an average difference in total SKAMP scores between Placebo and d-ATS of [redacted], 74 subjects would need to complete the study to detect a true difference of [redacted] in mean total SKAMP scores between placebo and d-ATS at 80% power when testing at a significance level of $\alpha = 0.05$ (2-sided). Assuming a dropout rate of 20%, 90 subjects will be randomized and it is expected that 74 subjects will complete the study. .

8.1.1 Analysis Populations

Three populations will be used in analyzing the data obtained from this protocol:

a) **Full Analysis Set** (FAS): includes all consented and randomized subjects who have taken at least one dose of study medication. The FAS population will be used as the primary population for analysis of efficacy endpoints.

b) **Completers:** The completers population includes all consented and randomized subjects who

- received full prescribed dose of the double-blind study medication at both test laboratory classroom sessions
- completed the full classroom tests on both test classroom sessions
- did not miss more than four consecutive days of therapy during the double blind treatment period
- did not use prohibited concomitant medications during the double blind treatment period

The completers population will be used for supportive analyses of efficacy endpoints.

c) **Safety Population (SP):** The safety population includes all subjects who have taken at least one dose of the study medication and have at least one post dose safety measurement (including dermal assessments). In the unlikely event that errors may have occurred in treatment arm assignments, analyses using the Safety populations will be based on treatment actually received. The SP population will be used for the analysis of dermal evaluations and safety endpoints.

8.1.2 Subject Disposition

There will be a clear accounting of all subjects who have signed the informed consent. The following will be summarized by treatment arm:

- The number of subjects who failed screening
- The number of subjects who are screened
- The number of subjects who are randomized,
- The number of subjects who receive study medication
- The number of subjects who complete the study
- The number of subjects who discontinued the study and reason for discontinuation

The reasons for post randomization study discontinuations will be summarized by treatment arm and will also be provided as a by-subject listing. The number and percentage of randomized subjects in each of the three study populations will be summarized for all subjects combined and for each treatment arm.

8.1.3 Demographic and Baseline Characteristics

8.1.4 *Demographics and baseline characteristic data will be summarized by treatment arm for both the Safety and FAS populations. Demographic and baseline characteristics include, but are not limited to age, age group, gender, race, weight, height, BMI, ADHD subtype, ADHD-RS-IV total (continuous and group) and subscale scores at baseline.* ***Treatment Administration and Compliance***

The duration (days) of study drug dosing will be determined as follows for each subject and summarized by treatment group for both Safety and MITT populations:

Duration of study drug dosing (days) = date of last dose – randomization date

The percent compliance with study medication will be calculated at each visit and for the overall double-blind Treatment Period. Compliance during the double-blind Treatment Period will be used to identify the per protocol population (i.e., those who were at least 80% compliant).

Percent compliance = {[(Total number of patches dispensed) – (Total number of patches returned)]/ number of days in the interval} * 100%

All dosing and compliance data also will be provided as data listings.

8.2 Efficacy Analysis

The primary population for efficacy assessments will be the FAS population. The Completers population will be used to conduct sensitivity analyses. Efficacy summaries will be presented by visit by treatment arm. Variables that are collected in both the Dose-Optimization and double-blind Treatment Periods will be combined on the same table, but no summaries will be presented in the placebo column for the Dose-Optimization Period.

The mean SKAMP total score will be the average of all SKAMP total scores collected over the course of a laboratory assessment day with the exception of the score from the session prior to dosing. For subjects who started a classroom day but did not complete all the assessments, their last observation within the same classroom will be carried forward for the primary and secondary efficacy analyses. Data from one classroom day will not be used to impute values for the other test classroom day.

8.2.1 Primary Efficacy Analysis

A likelihood-based Mixed Model Repeated Measures (MMRM) will be used to assess the primary objective. MMRM is the best method to control type I error rate and minimize bias in the presence of missing data.In the model, the SKAMP total score for each timepoint will be analyzed with the fixed effects of sequence (two levels), period (two levels), treatment (two levels) and time (10 levels, one for each of 30 minutes prior and 1, 2, 3, 4.5, 6, 7, 9, 10, and 12 hours post dosing) while the repeated measures effect of timepoint will be defined for subject and "Variance Components (VC)' covariance structure.

The two treatment levels will be: d-ATS (5, 10, 15, 20 mg doses combined) and placebo. The sequence effect (treatment x period interaction) will be tested at the significance level of 0.10. If significant differences are detected between sequences, data will be reviewed and strength of evidence indicating a crossover effect will be considered. In this case data from Visit 6 only will be presented to aid in assessment of the treatment effect. When only one period of data is used then the efficiencies gained from conducting a crossover trial design may be lost and there is concern associated with treating data as a parallel study due to the sample size being based up on the assumed efficiencies and may no longer be large enough to provide sufficient power. In this case, permutation test will be used to validate the results. Sampling without replacement (i.e. duplicate samples are not allowed) will be performed for 5000 permutations. The average mean treatment difference will be presented along with the associated 95% confidence interval and p-value for the permutation test. This will be compared against a significance level of 0.05.
The primary efficacy analysis on the FAS population will also be conducted for the following subgroups:

- Investigator Site
- Optimized dose
- Gender
- ADHD type (inattentive, hyperactive/impulsive, combined, not otherwise specified)
- Baseline ADHD severity (defined as the pre-dose ADHD rating scale at baseline, Visit 0).
- Age group

8.2.2 Secondary Efficacy Analysis

The onset of efficacy, based on the SKAMP total scores, will be defined as the time of the first assessment time showing statistical significance between d-ATS and placebo. If no significant difference is found at any time point for the onset of efficacy, no onset of efficacy will be deemed to have occurred, and the onset of efficacy will be defined as 'none'. Onset of efficacy as measured by the SKAMP total score will be analyzed using the same MMRM model as for the primary analysis.

To preserve the Type I error rate in analyzing these endpoints of onset and duration of efficacy, a closed test procedure will be used. The closed test principle states that the trial-wise error rate can be controlled by the ordered testing of each hypothesis in the closed family using a suitable α level significance. A condition of the Closed Test procedure is that the order of testing of the endpoints in a family matters. Thus hypotheses in a family must be ordered and the testing of each subsequent hypothesis in the order can only proceed if the testing of the prior hypothesis achieves a significant p-value with Type I error rate of predetermined α level, which will be set at $\alpha = 0.05$ for this study. Testing of the hypotheses in the family proceeds until a hypothesis fails to achieve a significant p-value. If/when a hypothesis in the family fails to achieve significance, then significant p-values cannot be claimed for all subsequent hypotheses in that family, i.e., once one hypothesis fails to achieve significance, testing should cease.

If the primary efficacy endpoint, difference between d-ATS and placebo in mean SKAMP total score for the double-blind phase, is statistically significant (i.e., $p<0.05$), the secondary variables of onset and duration of efficacy will be tested using a closed testing procedure. The closed testing procedure starts from the time-point of 1 hour post-morning dose, then 2, 3, 4.5, 6, 7, 9, 10 and 12 hours post-dose. At each timepoint the order of testing will be onset of efficacy followed by duration of efficacy, before moving to the next timepoint. Duration of efficacy will not be considered until onset of efficacy has been determined.

8.3 Analysis of Dermal Evaluations

8.3.1 Adhesion

The source data are the adhesion scores of the patches. Data from the in-clinic assessments will be summarized for each treatment arm.

- Frequency table showing the number of patches with each adhesion score at each evaluation time point.
- The number of patches that detached will be summarized.
- For detached patches, the duration of patch wear before patch detachment will be summarized (time of patch detachment will be subtracted from time of application).

8.3.2 Irritation

The source data will be the actual irritation scores recorded following visual evaluation of the application sites. If a patch is removed due to irritation, Last Observation carried Forward (LOCF) will be applied for all remaining time points. LOCF is defined as the highest irritation score observed prior to discontinuation of the patch due to irritation.

The letter grades will be converted to numerical equivalents in the following way: N=0, A=0, B=1, C=2, and F, G, and H=3. For each subject, a combined score will be derived by adding the numerical grade and the numerical equivalent of the letter grade at each evaluation time point (e.g., 2C=2+2=4). Analyses for this data will be identified as combined scores.

The following data will be provided for each treatment arm:

- Frequency table with each combined "Dermal Response" and "Other Effect" score using Last Observation Carried Forward for all subjects.
- Frequency table with each combined "Dermal Response" and "Other Effect" score using Last Observation Carried Forward for subjects who discontinued due to irritation.
- Summary of number of patches that were removed due to irritation and number patches that were removed due to irritation split by irritation combined score assessed at 30 minutes after detachment/removal.

8.3.3 Discomfort

The source data will be the discomfort scores of the patches. A summary of Discomfort Scores will present the discomfort scores and a summary of Description of Discomfort with the number

and percent of subjects by each treatment and time point. Summary statistics for values of VAS scores will be presented as continuous variables by treatment arms at each time point and overall. The Wong Baker Faces Scores (WBS) and Visual Analog Scale (VAS) scores will be presented separately and combined, by treatment for each timepoint.

8.3.4 Adhesive Residue

The source data will be the adhesive residue scores of the patches. A summary of Adhesive Residue Scores recorded in clinic will present the adhesive residue scores with the number and percent of subjects by each treatment and time point.

8.4 Safety Analysis

Safety data for the Dose Optimization Period will be analyzed using combined data from all subjects in the safety population.

Safety data from the Double Blind Period will be analyzed using data from each treatment arm where applicable in the safety population.

. No inferential statistics are planned.

8.4.1 Adverse Events

All Treatment Emergent Adverse Events (TEAEs) will be classified by system organ class (SOC) and preferred term using the latest version of MedDRA dictionary. All TEAEs that occur after randomization up to 30 days after last dose of study drug will be summarized. Subjects may have more than one TEAE per system organ class or preferred term.

Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AE, a subject will be counted once if the subject reported one or more events. AEs, TEAEs, SAEs, treatment-related SAEs, and TEAEs leading to premature discontinuation of study drug will be summarized by MedDRA SOC, preferred term, and stratified by intensity.

8.4.2 Clinical Laboratory Test Values

Summary statistics of raw data and change from baseline values to End of Study values for each laboratory parameter will be presented by treatment group and time point. Data will be summarized as

appropriate to the variable type. For change from baseline summaries, patients with an undefined change from baseline, because of missing baseline data, will be excluded. Individual Patient Changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of patients, by treatment group and time point, for shift (change) from baseline, using the normal ranges from the central laboratory.

8.4.3 Vital Signs and ECG

Vital signs, including heart rate, systolic blood pressure and diastolic blood pressure, temperature, and respiratory rate will be summarized. Summary statistics of raw data and change from baseline values for each vital signs parameter will be presented by treatment arm and time point. Data will be summarized as appropriate to the variable type. For change from baseline summaries, patients with an undefined change from baseline, because of missing baseline data, will be excluded. Shift tables will be presented for each vital sign parameter with counts and percentages of subjects, by treatment arm and time point, for shift (change) from baseline, using the normal ranges for vital signs parameters. Vital signs data from unscheduled visits will be listed but will not be included in any summaries.

All quantitative 12-lead ECG interval measurements (QRS, QT, QTc, etc) will be summarized with descriptive statistics by visit, and treatment arm. Summary statistics of raw data and change from baseline values will be presented by treatment arm and time point. Data will be summarized as appropriate to the variable type. For change from baseline summaries, patients with an undefined change from baseline, because of missing baseline data, will be excluded.

ECG assessments at study visits will be evaluated to determine whether the ECG findings are: 1) Normal; 2) Abnormal, Not Clinically Significant and 3) Abnormal, Clinically Significant. Descriptive statistics (numbers and percentages of subjects in each of the three categories) will be presented by treatment arms for each visit. In addition shift tables will be also presented based on the above three categories of ECG interpretations, by treatment arm and time point.

8.4.4 Concomitant Medications

Prior and concomitant therapies will be summarized for the Safety population. All prior and concomitant medications recorded in the eCRF will be coded to generic term and all matching Anatomic Therapeutic Classification (ATC) codes using the current version of WHO Drug. Summaries will be prepared using the coded generic term. All prior and concomitant

medications recorded in the eCRF will be listed.

8.4.5 Physical Examination Findings

There will be no separate physical examination listings since screening physical examination abnormalities were recorded in Medical History table and post-randomization physical examination abnormalities were recorded in AE table.

8.4.6 Columbia Suicide Severity Rating Scale (C-SSRS – Children's Version)

The summary will be presented for each of the subscales (i.e. Suicidal Ideation and Suicidal Behavior.

Suicide Ideation will be summarized for each of the following 5 ideation categories:

1. Wish to be dead
2. Non-specific active thoughts,
3. Active suicidal ideation with any methods (not plan) without intent to act,
4. Active suicidal ideation with some intent to act, without specific plan,
5. Active suicidal ideation with specific plan and intent.

Descriptive summary of the number and percentages of subjects with the responses of "Yes" for each of the five categories will be presented by treatment arms and visit. And the intensity, frequency, duration, controllability, deterrents, and reasons for ideation will all be summarized descriptively by treatment group and visit.

Suicide Ideation will be summarized for each of the following 5 behavior categories:

1. Actual attempt
2. Interrupted intent
3. Aborted attempt
4. Preparatory Acts or Behavior and
5. Suicidal behavior present during assessment period.

Descriptive summary of the number and percentages of subjects with the responses of "Yes" for each of the five categories will be presented by treatment arms and visit. And the intensity,

frequency, duration, controllability, deterrents, and reasons for ideation will all be summarized descriptively by treatment group and visit.

Additionally, the number of subjects who reported at least one occurrence of suicidal ideation **and** at least one occurrence of suicidal behavior and subjects who reported at least one occurrence of suicidal ideation **or** at least one occurrence of suicidal behavior will be summarized by treatment group and visit. For these summaries a subject will only be counted once in each in each sub-category.

9 REGULATORY AND ETHICAL ASPECTS

9.1 Institutional Review Board Requirements

The Investigator must ensure that an appropriately constituted Institutional Review Board (IRB) that complies with the requirements of 21 CFR 56 will be responsible for the clinical study. Prior to initiation of the study, the Investigator must forward copies of the protocol and consent forms to be used for the study to the IRB for its review and approval. A copy of the IRB notification of approval (including a blank copy of the approved consent form) must be forwarded to the Sponsor before any investigational supplies may be shipped to the Investigator.

The Investigator must promptly report all changes in the research activity and all unanticipated problems involving risks to human subjects or others to the IRB. The Investigator will not make any changes in the research without Noven and IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects. For minor changes to previously approved research, it may be possible for the Investigator to obtain an expedited review by the IRB as allowed for under 21 CFR 56.100.

Copies of all correspondence to the Investigator from the IRB indicating its continued approval of this study or withdrawal of such approval must be immediately forwarded to Noven by the Investigator.

9.2 Informed Consent

All subjects/parents/caregivers will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. For each trial subject, written informed consent will be obtained from their parent(s)/legal guardian prior to any protocol-related

activities. As part of administering the informed consent document, the Investigator must explain to each subject/parent/caregiver 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/parent/caregiver 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/parent/caregiver should understand the statement before signing and dating it and will be given a copy of the signed document. For children who are able to provide an assent, assent will be documented in accordance with the policy of the IRB approving the study and local regulations.

An unsigned copy of an IRB and Sponsor (or designee)-approved written informed consent must be prepared in accordance with ICH E 6, Section 3, and all applicable local regulations, i.e. Federal Regulations, Title 21, CFR Part 50, including HIPPAA are provided to the Sponsor (or designee

9.3 Changes to the Protocol and/or Informed Consent

9.3.1 Amendments

Changes in any portion of this protocol that affect subject safety must be documented in the form of an amendment and signed by appropriate Noven representatives, and the Investigator, and be approved by IRB, before the amendment may be implemented.

The IRB chairperson may approve minor changes, or may designate one or more IRB members to approve it. The only circumstance in which the amendment may be initiated without IRB approval is for a change necessary to eliminate an apparent and immediate hazard to the subjects. In that event, the Investigator must notify the IRB in writing within 10 working days after the implementation.

9.3.2 Administrative Changes

Clarification of the study protocol or changes in the methods of statistical analysis may be documented in the form of an administrative change. Administrative changes do not require the Investigator's signature or IRB approval. Administrative changes will be transmitted to the Investigator and be provided to the IRB for completeness.

9.4 Confidentiality

All information provided to the Investigator by Noven including preclinical data, protocols, eCRFs, and verbal and written communications, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. This information may be related in confidence to the IRB. In addition, information about the study or its progress will not be provided to anyone not involved in the study, other than to Noven, its representatives or designees, in confidence to the IRB, except if required by law.

9.5 Subject Confidentiality

Noven affirms and upholds the principle of the subject's right to protection against invasion of privacy. Throughout the study, all data will only be identified by an identification number and subject initials. The data will be blinded correspondingly in all data analysis. However, in compliance with guidelines of the United States Food and Drug Administration (FDA) concerning the acceptance of clinical studies in support of a New Drug Application and in fulfillment of its obligations to the Sponsor to verify compliance with this protocol, the Investigator will permit the Sponsor's monitor or FDA to review that portion of the subject's primary medical records which directly concerns this study (including, but not limited to laboratory test results, reports, ECGs, admission/discharge summaries for hospital admissions occurring during a subject's study participation and autopsy reports for deaths occurring during the study).

9.6 Case Report Forms

The Investigator's responsibilities in regard to the following functions are essential for compliance with this protocol.

All subject's data generated in the study will be recorded on the source documents and subsequently, transcribed to the eCRFs provided by the Sponsor, or a CRO. These forms will be

specifically designed to record the clinical data required by the protocol.

The staff member who obtains data or conducts study-related procedures will record the data on the source document(s) and will initial and date the procedure or group of procedures to provide identification of the staff member. If a person conducts a series of study-related events, the source document(s) will be organized in a design that clearly designates the data obtained and/or procedures conducted by the individual responsible.

Any person who obtains data or conducts study-related procedures or who is an Investigator will sign a study Staff Signature Log clearly indicating his/her name, title or responsibility, date of entry and include his/her signature, and initials. A copy of the Staff Signature Log will be forwarded to Noven for inclusion in the study file. If a correction is necessary to the source documents, the Principal Investigator or an authorized designee will draw a single line through the error and initial and date the correction without obscuring the original entry. If additional data or clarification of an original entry is added to a source document at a time other than when the original entry was made, the additional entry will be initialed and dated by the person making the entry. Only the person who made the original entry may only make corrections. If this is not possible, his/her supervisor may make the correction.

Completed eCRFs will be reviewed by the Investigator who must verify that all entries are accurate and complete. All aspects of the study will be monitored by Noven to assure compliance with Current Good Clinical Practices and other applicable government regulations. Contact with the Investigator will be maintained by a representative of Noven via telephone, and periodic visits to the study site to ensure that the study is conducted according to the protocol, and also, to review eCRFs. The monitor or auditor will have access to all source documentation and necessary records to verify the data recorded on the eCRF.

9.7 Maintenance of Records

Records and documents pertaining to the conduct of the study and distribution of the investigational drug (e.g., eCRFs, consent forms, laboratory test results reports, medication inventory records, and other pertinent information) must be retained by the Investigator for a period of at least 2 years following the date that the NDA or Abbreviated New Drug Application is approved or if no application is filed or approved, until at least 2 years after the investigation is

discontinued and the FDA is so notified. The Sponsor will notify the Investigator of either of these events. The Investigator may be requested by the Sponsor, to maintain the study records for a total of 15 years.

Prior to destroying any record, the Investigator should consult Noven. In addition, Noven should be contacted in the event any study-related documents are inadvertently destroyed or lost.

10 ADMINISTRATIVE ASPECTS

10.1 Initiation of the Study

The Investigator may not administer study treatments to the subjects prior to completion of the study initiation visit, conducted by the Sponsor or representative. This meeting will include a detailed review of the protocol and eCRFs.

10.2 Monitoring Obligations

Noven clinical monitors, or their designees, will conduct site visits to the investigational facilities to monitor the various aspects of the study. The Investigator agrees to allow these monitors and other authorized Noven personnel, including quality assurance monitors, access to the clinical supplies, dispensing and storage area, and to the clinical files of the study subjects, and agrees to assist the Noven personnel in their activities, if requested. Study sites are also subject to inspection by FDA representatives after adequate notice. The Investigator agrees to assist such inspectors in their duties.

Prior to each monitoring visit, the Investigator or designee should record all data generated since the last visit on the eCRFs. The Investigator and his staff will be expected to cooperate with the monitor, and to be available during at least a portion of the monitoring visit to sign eCRFs, answer questions, and to provide any missing information.

10.3 Termination of Study

The Sponsor has the right to terminate this study and remove all study materials from the study site at any time. Examples of where this might occur are the following:

a. It becomes apparent that subject enrollment is unsatisfactory with respect to quality

and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis.

b. The incidence and/or severity of adverse drug events in this or other studies indicate a potential health hazard caused by treatment with the study drug.

10.4 Changes to the Protocol

No deviation will be made from the protocol unless an amendment has been agreed to in writing by the Investigator and Noven and submitted to and approved by the IRB.

10.5 Publication of the Study Results

Matters regarding authorship and the order of authorship on publications reporting the results of single and multiple study findings are covered in a separate agreement.

11 REFERENCES

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7. [redacted] Conducted by Noven. Report on File at Noven Pharmaceuticals, Inc.
8. [redacted] Conducted by Noven. Report on File at Noven Pharmaceuticals, Inc.
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10. Benedetto Vitiello, M.D. Understanding the Risk of Using Medications for ADHD with Respect to Physical Growth and Cardiovascular Function *Child and Adolescent Psychiatric Clinics of North America*, Volume 17, Issue 2, Pages 459-474
11. [redacted]

PENDIX 1: SCHEDULE OF ASSESSMENTS

Screening		Baseline	Assessment Period															
			Dose Optimization Period										Double Blind Treatment Period					
			Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7			
Visit -1		Visit 0		Visit 1±3 days		Visit 2±3 days		Visit 3±3 days		Visit 4±3 days		Visit 5±2days		Visit 6		Visit 7/End of Study	Early Termination	
-28 to -4	-3 to -1	0	1-6	7	8-13	14	15- 20	21	22-27	28	29-34	35	36-41	42	43-48	49		
X		X		X		X		X		X		X		X		X	X	
												X[1]		X		X		
			X (Day 4)		X (Day 11)		X (Day 18)		X (Day 25)		X (Day 32)		X (Day 39)		X (Day 46)			
	X		X		X		X		X		X		X		X			
X																		
X																		
X																		
X																		
X																		
X																X	X	
X																		
X		X		X		X		X		X		X		X		X	X	
X		X		X[2]		X[2]		X[2]		X[2]		X[2]		X[3]		X[3]	X[4]	
X		X										X		X		X	X	

ient 4: Version 5.0 May-08-2013
ient 3: Version 4.0 December-11-2012
ient 2: Version 3.0 October-31-2012
ient 1: Version 2.0 August-02-2012
otocol May-25-2012

Screening		Baseline	Assessment Period															
			Dose Optimization Period										Double Blind Treatment Period					F
			Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7			
Visit -1		Visit 0		Visit 1±3 days		Visit 2±3 days		Visit 3±3 days		Visit 4±3 days		Visit 5±2days		Visit 6		Visit 7/End of Study	Early Termination	
-28 to -4	-3 to -1	0	1-6	7	8-13	14	15- 20	21	22-27	28	29-34	35	36-41	42	43-48	49		
X																X	X	
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X																		
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X																		
		X		X		X		X		X		X		X				
			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
				X		X		X		X		X		X		X	X	
			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
				X		X		X		X		X		X		X		
			X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X		X		

ient 4: Version 5.0 May-08-2013
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Screening		Baseline	Assessment Period															
			Dose Optimization Period										Double Blind Treatment Period					F
			Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7			
Visit -1		Visit 0		Visit 1±3 days		Visit 2±3 days		Visit 3±3 days		Visit 4±3 days		Visit 5±2days		Visit 6		Visit 7/End of Study	Early Termination	
-28 to -4	-3 to -1	0	1-6	7	8-13	14	15- 20	21	22-27	28	29-34	35	36-41	42	43-48	49		
			X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X		X		
			X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X		X		
X		X		X		X		X		X		X		X		X	X	
X																		
X																		
												X		X		X		
												X[1]		X		X		
X		X		X		X		X		X		X[1]		X		X		
		X	X		X		X		X		X		X		X			
		X																
				X		X		X		X		X		X		X	X	
		X		X		X		X		X		X		X		X	X	
		X		X		X		X		X		X		X		X	X	
X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

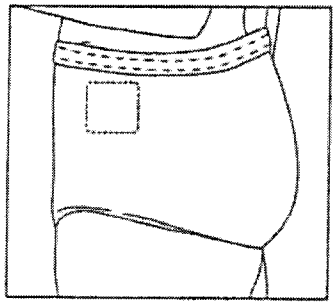
1. Half –day practice classroom

2. *At classroom start*
3. *30 min. pre-dose and 4 and 12 hrs.±30 min. post-dose*
4. *Measured once*
5. *Performed at home by parent/caregiver/patient*

13 APPENDIX 2: PATCH APPLICATION AND REMOVAL PROCEDURES

Application Procedure for the Patch

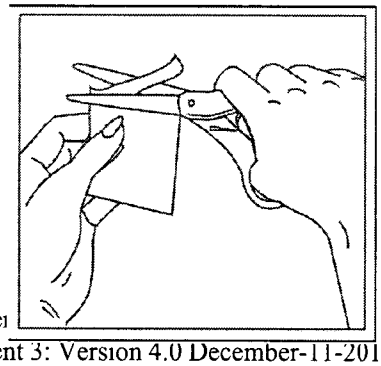
1. Where to Apply the patch
   - Apply patch to the hip area. Avoid the waistline, since clothing may interfere with the adhesion of the patch.
   - When applying patch, alternate application sites each day (between right and left hip) as required by the protocol.



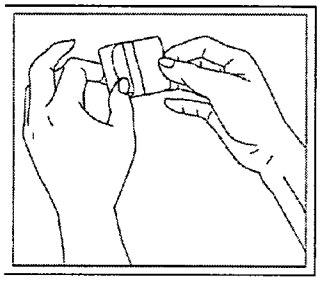
2. Skin Condition

   Ensure the skin is:
   - Clean (freshly washed), dry, and cool.
   - Free of any powder, oil, or lotion.
   - Free of cuts and/or irritation (rashes or other skin problems).
   - If there are any signs of irritation or itching at the intended application site (pictured above), apply the patch to a non-irritated area as close as possible to that area.

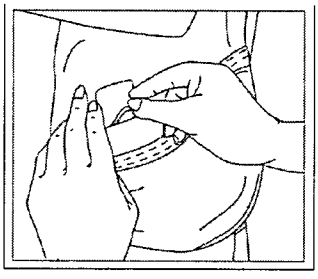
3. How to Apply the patch.
   - Each patch is individually sealed in a protective pouch. DO NOT DISCARD THE POUCH.
   - Carefully cut the pouch open with scissors, being careful not to cut the patch.
   - Remove the patch from the pouch.



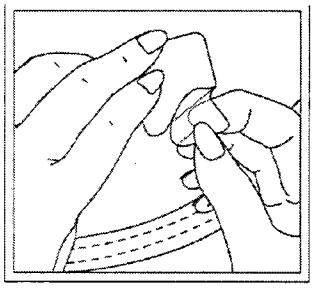
- Apply the patch immediately after removing from pouch.
- Holding the patch with the rigid protective liner facing you, remove half of the liner, which covers the sticky surface of the patch.
- Avoid touching the sticky side of the patch with your fingers.



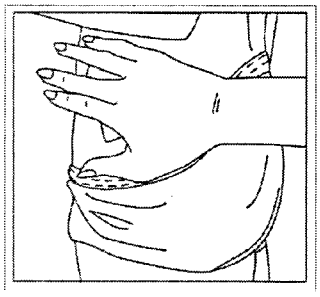
- Using the other half of the protective liner as the handle, apply the sticky side of the patch to the selected area of the hip.
- Press the sticky side of the patch firmly into place.
- Smooth it down.



- While still holding the sticky side down, fold back the other half of the patch.
- Grasp an edge of the remaining protective liner and gently pull it off.
- DO NOT DISCARD THE LINER.
- SAVE THE LINER IN THE EMPTY POUCH.



- Avoid touching the sticky side of the patch with your fingers.



- Press the entire patch firmly into place with the palm of your hand over the patch, for approximately 30 seconds, making sure that the entire patch is in contact with the skin.
- Make sure the patch is firmly stuck to the skin.
- Go over the edges and the center of the patch with your fingers to assure good contact around the d-ATS.

Please note:

- Contact with water while bathing, swimming, or showering should not affect the patch.
- If immediately prior to application the system wrinkles or folds, a new patch may be applied and the old one marked "failed during application" will be saved.
- In the unlikely event that the patch falls off (adhesion score of 4), the same patch should not be reapplied and a new patch should not be applied.

Patches should not be secured with adhesive tape or occlusive dressing of any type.

B. Patch Removal Procedures

The patch should be removed by lifting an edge and peeling the system away from the skin. Care should be taken to avoid mechanical trauma especially if the patch appears to be firmly attached.

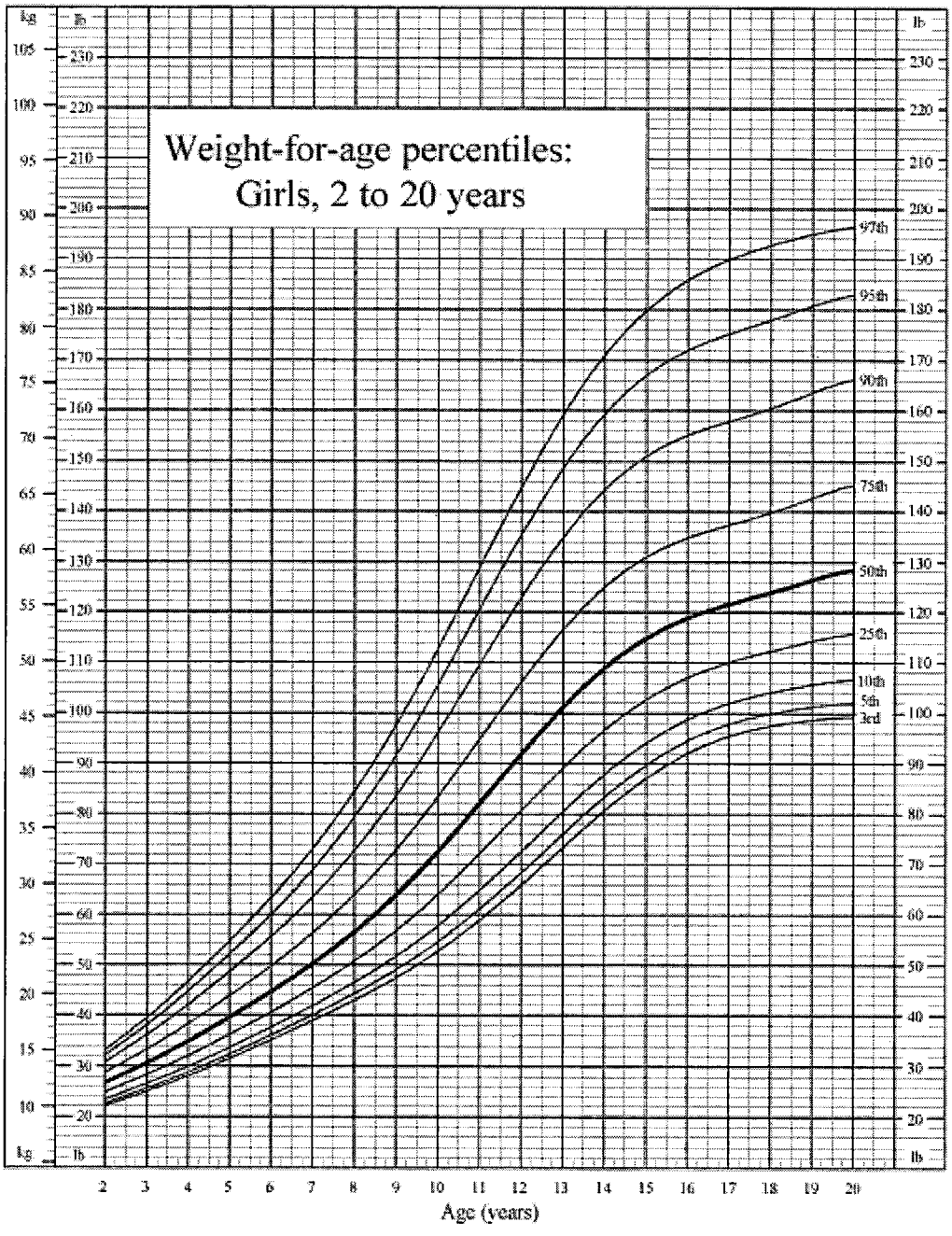
If necessary, patch removal may be facilitated by gently applying an oil-based product (i.e., petroleum jelly, olive oil, or mineral oil) to the patch edges, gently working the oil underneath the patch edges. If any adhesive remains on the skin following patch removal, an oil-based product may be applied to patch sites in an effort to gently loosen and remove any residual adhesive that remains following patch removal.

In the unlikely event that a patch remains tightly adhered despite these measures, the subject/parent/caregiver should contact the site personnel. Nonmedical adhesive removers and acetone-based products (i.e., nail polish remover) should not be used to remove patches or adhesive.

The used patches should be collected and stored until Sponsor requests their return or destruction.

APPENDIX 3: CDC GROWTH CHART (GIRLS)

CDC Growth Charts: United States

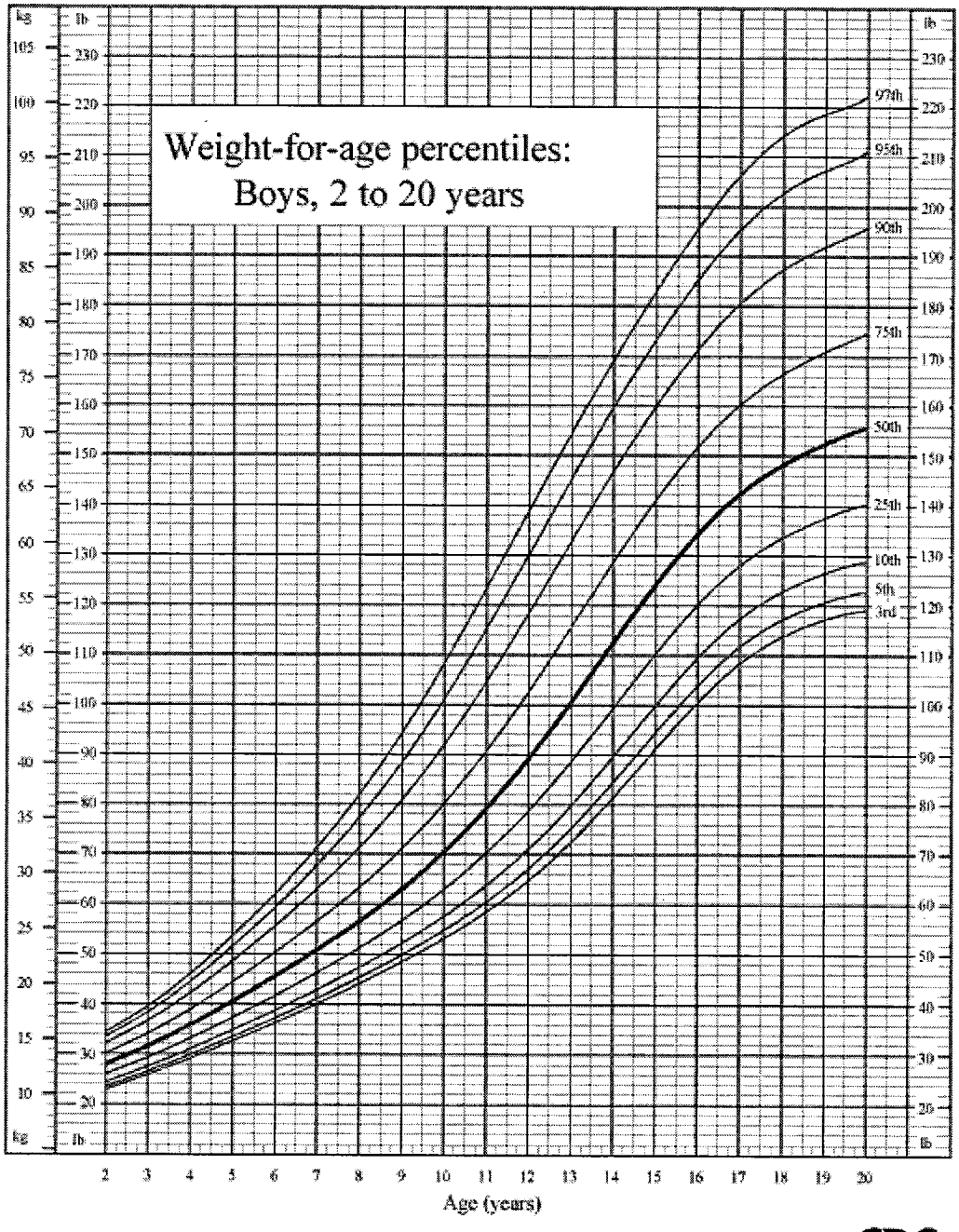


SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

CDC

14 APPENDIX 4: CDC GROWTH CHART (BOYS)

CDC Growth Charts: United States



SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

CDC

Amendment 4: Version 5.0 May-08-2013
Amendment 3: Version 4.0 December-11-2012
Amendment 2: Version 3.0 October-31-2012
Amendment 1: Version 2.0 August-02-2012
Final Protocol May-25-2012

15 APPENDIX 5: SWANSON, KOTKIN, ALGER, M-FLYNN, AND PELHAM (SKAMP) DEPORTMENT AND ATTENTION RATING SCALE

	LEVEL OF IMPAIRMENT						
	Normal No Impairment	Slight Impairment	Mild Impairment	Moderate Impairment	Severe Impairment	Very Severe Impairment	Maximal Impairment
CLASSROOM BEHAVIOR:							
1. Getting started on assignments for classroom periods	⓪	①	②	③	④	⑤	⑥
2. Sticking with tasks or activities for the allotted time	⓪	①	②	③	④	⑤	⑥
3. Attending to an activity or a discussion of the class	⓪	①	②	③	④	⑤	⑥
4. Stopping and making transition to the next period	⓪	①	②	③	④	⑤	⑥
5. Interacting with other subjects	⓪	①	②	③	④	⑤	⑥
6. Interacting with teacher or aide	⓪	①	②	③	④	⑤	⑥
7. Remaining quiet according to classroom rules	⓪	①	②	③	④	⑤	⑥
8. Staying seated according to classroom rules	⓪	①	②	③	④	⑤	⑥
WRITTEN WORK:							
9. Completing assigned work	⓪	①	②	③	④	⑤	⑥
10. Performing work accurately	⓪	①	②	③	④	⑤	⑥
11. Being careful and neat while writing or drawing	⓪	①	②	③	④	⑤	⑥
GENERAL:							
12. Complying with teacher's usual requests or directions	⓪	①	②	③	④	⑤	⑥
13. Following the rules established for the classroom	⓪	①	②	③	④	⑤	⑥

Comments: _____

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RATER'S INITIALS: _____

Amendment 4: Version 5.0 May-08-2013
Amendment 3: Version 4.0 December-11-2012
Amendment 2: Version 3.0 October-31-2012
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16 APPENDIX 6: PERMANENT PRODUCT MEASURE OF PERFORMANCE (PERMP) MATH TEST (SAMPLE)

Easy test (2 digit without renaming):

66	35	85	86	52
+23	-24	+12	-45	+33
29	85	69	93	32
-25	-62	+20	-42	+54

Moderate Test (2 digit with renaming):

56	78	29	30	41
+27	-59	+34	-22	-18
91	45	27	83	66
-58	+19	+37	-69	+24

Difficult Test (3 digit with renaming):

452	259	402	847	742
- 384	+ 493	- 139	+ 132	+ 236
529	263	572	425	652
+ 459	+ 492	- 399	+ 554	- 338

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Amendment 3: Version 4.0 December-11-2012
Amendment 2: Version 3.0 October-31-2012
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17 APPENDIX 6: 10-POINT PAIN SCALE