



CLINICAL STUDY PROTOCOL

Title: Dyanavel[®] XR Extended-Release Oral Suspension in the Treatment of Children with ADHD: A Laboratory School Study.

Protocol Number:	TRI102-ADD-300
Investigational Drug:	Dyanavel [®] XR
Version:	v. 2.0 (02 February 2017)
IND Applicant/Sponsor:	Tris Pharma, Inc. 2033 Route 130 Monmouth Junction, NJ 08852
Authorized Signatory:	Sally A. Berry, MD, PhD Chief Medical Officer Tris Pharma, Inc.
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Protocol Amendments:	N/A

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

Confidentiality Statement

The confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

INVESTIGATOR'S SIGNATURE

I have read protocol TRI102-ADD-300 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Title of Investigator

Signature of Investigator

Date

SPONSOR'S SIGNATURE

Approved by:

Sally A. Berry, MD, PhD
Chief Medical Officer
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Date

PROCEDURES IN CASE OF EMERGENCY

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SYNOPSIS

Title:	Dyanavel® XR Extended-Release Oral Suspension in the Treatment of Children with ADHD: A Laboratory School Study
Study number	TRI102-ADD-300 Version: 2.0 (02 February, 2017)
Study Center(s)	1 site
Clinical Phase	III - IV
Indication	ADHD (Attention-deficit/hyperactivity disorder)
Objectives	<p>Primary Efficacy Objective: To demonstrate that Dyanavel® XR extended-release oral suspension has an onset of action of 30 minutes post-dose as determined by change from pre-dose in SKAMP-Combined scores at 30 minutes post-dose during the laboratory school days (Visits 3 and 4), relative to placebo.</p> <p>Safety Objective: To assess the safety and tolerability of Dyanavel XR in pediatric subjects with ADHD.</p>
Study Design	Double-blind, Two Treatment, Two Sequence
Sample Size/ Study Population	Up to 18 males or females aged 6 to 12 with ADHD 1 cohort
Treatment Duration	<ul style="list-style-type: none"> • Screening • Baseline (Visit 1) • Practice Classroom (Visit 2) • Double blind Classroom (Visit 3) • Double blind Classroom (Visit 4)
Test Product Dose / Route / Regimen	<p>Open label Dyanavel XR: Dyanavel XR as determined by the study doctor, up to 8 mL (20mg)/ day</p> <p>Double-Blinded Classroom: One dose of Dyanavel XR 6 mL (15mg), 7mL (17.5 mg) or 8 mL (20mg) One dose of Dyanavel XR Placebo 6 mL, 7mL or 8 mL</p>
Pharmacokinetics	NA
Methodology	<p><u>Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Males or females aged 6 to 12 years at the time of screening, inclusive 2. Diagnosed with ADHD by a psychiatrist within 6 months of study enrolment or newly diagnosed with ADHD using the DSM-5 criteria for ADHD 3. An ADHD-RS-5 score at Screening ≥ 90th percentile for sex and age in at least one of the following categories: <ol style="list-style-type: none"> a) Hyperactive-impulsive subscale,

	<p>b) Inattentive subscale, or c) Total score.</p> <p>Subjects who do not meet this criteria at screening can have ADHD-RS-5 repeated at baseline, after washout of stimulant medication for a minimum of 24 hours prior to baseline.</p> <p>4. In the clinical judgment of the Investigator, the subject must be in need of pharmacological treatment for ADHD.</p> <p>5. Females of childbearing potential must be non-lactating and must have a negative serum pregnancy test at screening</p> <p>6. Provide written informed consent (parent/guardian) and assent (child aged 10 – 12 years only) prior to participation in the study</p>
	<p><u>Exclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Diagnosed with any DSM-5 active disorder (other than ADHD) with the exception of specific phobias, learning disorders, motor skills disorders, communication disorders, oppositional defiant disorder, elimination disorders, and sleep disorders 2. Known history of chronic medical illnesses including severe hypertension, untreated thyroid disease, peripheral vasculopathy, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, known family history of sudden death 3. Known history or presence of significant renal or hepatic disease, as indicated by clinical laboratory assessment (liver function test results \geq two times the upper limit of normal, blood urea nitrogen, or creatinine). 4. Clinically significant abnormal ECG or cardiac findings on physical examination (including the presence of a pathologic murmur) 5. Use of the following medications within 30 days of Baseline Visit: <ul style="list-style-type: none"> • MAOI - monoamine oxidase inhibitors (e.g., Selegiline, isocarboxazid, phenelzine, tranyleypromine) • Tricyclic Antidepressants (e.g. Desipramine, protriptyline) 6. Use of the following medications within 3 days of Baseline Visit <ul style="list-style-type: none"> • Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid) • Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) 7. Use of atomoxetine within 14 days of Baseline Visit 8. Planned use of prohibited drugs or agents from the Screening visit through the end of the study 9. Abnormal clinically significantly laboratory test value at screening that, in the opinion of the Investigator, would preclude study participation 10. Known history of allergy/hypersensitivity to amphetamine or any of the components of Dyanavel XR, or topical anaesthetics 11. Known history of lack of response to amphetamine 12. Parent or guardian's inability or unwillingness to follow directions of the Investigator or study research staff. 13. Any uncontrolled medical condition that in the opinion of the Investigator would preclude study participation

	14. History of significant illness requiring hospitalization, or surgery requiring anaesthetics within 30 days of Baseline Visit
Assessments	<ul style="list-style-type: none"> • SKAMP Assessments • PERMP • Columbia Suicide Severity Rating Scale (C-SSRS) • ADHD-Rating Scale-5 (ADHD-RS-5) • Adverse Events • Electrocardiogram • Safety Labs • Physical Exam • Vital Signs • Medical History • Concomitant Medications
Statistical Analysis	<p><u>Primary Efficacy Endpoint</u></p> <p>The primary efficacy endpoint is the change from pre-dose in model-adjusted SKAMP-Combined scores at 30 minutes post-dose measured during the laboratory school days (Visit 3 and 4). The difference between Dyanavel XR and placebo will be assessed at the $\alpha = 0.05$ level of significance.</p> <p><u>Secondary Efficacy Endpoints</u></p> <p>Efficacy will also be assessed by the following measures during the laboratory school day (Visits 3 and 4):</p> <p>Change from pre-dose in SKAMP scores at 3 hours post-dose</p> <p>Change from pre-dose in PERMP scores at 30 minutes and 3 hours post-dose</p> <p><u>Safety Endpoints</u></p> <p>Safety will be monitored by adverse events (AEs) assessed at each visit. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at Screening, Baseline and all subsequent visits to assess emergent suicidal thoughts or behaviors. Medical history will capture all medical conditions at Screening. Physical examinations, vital signs, height and/or weight assessments, 12-lead electrocardiogram (ECG), and clinical laboratory tests will be conducted at Screening.</p>

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LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ADHD	Attention-deficit hyperactivity disorder
ADHD-RS-5	ADHD-Rating Scale-5
AE	Adverse event
AR	Adverse reaction
CFR	Code of Federal Regulations
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram/electrocardiography
CRF	Case Report Form
ER	Extended Release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
ITT	Intent to Treat
PERMP	Permanent Product Measure of Performance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale
SOP	Standard Operating Procedure
UAR	Unanticipated Adverse Reaction
WASI	Wechsler Abbreviated Scale of Intelligence

1. INTRODUCTION

Amphetamine has been a well-established therapeutic agent for the treatment of Attention Hyperactivity Disorder (ADHD) for decades. Since the original amphetamine approval, various dosage forms have been approved for use:

- immediate release (IR) dosage forms, oral solution and tablets.
- extended release (ER) dosage forms, capsules, and tablets with various release technologies

Dyanavel XR is an extended-release oral suspension (EROS) that contains 2.5mg/mL amphetamine base. Drug-resin complexation is formed with the amphetamine and Sodium Polystyrene Sulfonate USP, an ion exchange resin. The extended release feature of the product is achieved by coating some drug/resin complexes with an extended-release coating. Dyanavel XR contains approximately a 3:1 ratio of d-amphetamine compared to l-amphetamine.

The efficacy of Dyanavel XR in the treatment of ADHD in children ages 6-12 has been established in a Phase 3 placebo-controlled laboratory classroom study: TRI102-ADD-001. ADHD symptoms in children on an individually optimized dose of amphetamine (range 10-20 mg/day) were significantly lower compared to symptoms experienced by children treated with placebo. Symptom control was demonstrated 1 hour after dosing and efficacy was observed through 13 hours beyond dosing. The effect size in this study was in line with effect sizes demonstrated for other psychostimulants tested in a similar study design. The adverse events in this study were expected for amphetamine treatment with respect for type of adverse event, frequency and severity.

Study TRI102-PPK-200 was conducted in children ages 6 to 12 years old with ADHD to evaluate the single-dose (10 mg) pharmacokinetics of orally administered Dyanavel XR. Following a single 10 mg oral dose of Dyanavel XR in 12 pediatric subjects under fasting conditions, d-amphetamine and l-amphetamine peak plasma concentrations occurred at a median time of 3.9 and 4.5 hours after dosing, respectively. The mean plasma terminal elimination half-life of d-amphetamine was 10.43 (\pm 2.01 h) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 (\pm 3.15 h) hours.

Study 2014-3401 was conducted in 29 healthy adult subjects in a crossover study under fasting conditions, following a single, 18.8 mg oral dose of DYANAVEL XR. d-amphetamine and l-amphetamine, the median (range) time to peak plasma concentrations (T_{max}) were 4.0 (2 – 7) hours after dosing and peak concentration (C_{max}) were 102% and 106%, respectively of the C_{max} of immediate-release (IR) mixed amphetamine salts tablets. The relative bioavailability of DYANAVEL XR compared to an equal dose of mixed amphetamine salts IR tablets is 106% of d-amphetamine and 111% for l-amphetamine.

See the Dyanavel XR Package Insert for further information¹.

2. OBJECTIVES

2.1. Efficacy Objective

To demonstrate that Dyanavel XR has an onset of action as early as 30 minutes post-dose as determined by change from pre-dose in SKAMP-Combined scores at 30 minutes post-dose during the laboratory school days (Visits 3 & 4), relative to placebo.

2.2. Safety Objective

To assess the safety and tolerability of Dyanavel XR in pediatric subjects with ADHD.

3. STUDY DESIGN

3.1. Design

This is a randomized, double-blind, two treatment, two sequence, placebo-controlled crossover study to assess the efficacy and safety of dose Dyanavel XR in reducing signs and symptoms of ADHD compared with placebo in pediatric subjects ages 6 to 12 years with ADHD as early as 30 minutes post-dose. Up to 18 pediatric subjects with ADHD are planned to be enrolled at one investigational site in the United States.

After Screening and Baseline evaluations are complete, eligible subjects will enroll in the study to take open-label Dyanavel XR orally once daily in the morning beginning the day after the baseline visit.

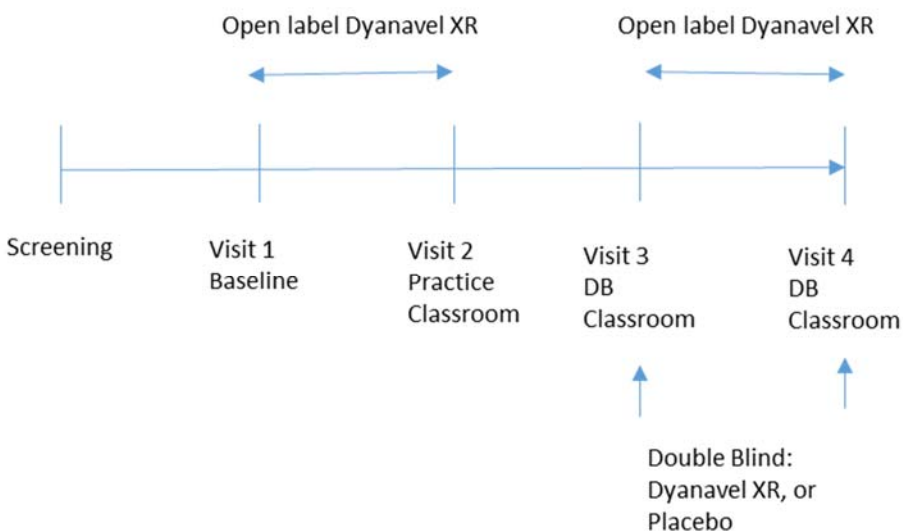
Subjects will be randomized at Visit 2 to sequence to take double-blind study drug (Dyanavel XR 15 mg, 17.5 mg or 20 mg or placebo) orally once during visits 3 and 4 (Double Blind Classroom Visits).

During visits 3 and 4, subjects will be evaluated for ADHD symptoms in a laboratory classroom setting utilizing the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessments. An abbreviated practice laboratory session to acclimate site staff and subjects to the timing and procedures of the analog classroom specific to this protocol will occur during Visit 2. Subjects will received open label Dyanavel XR (15 mg, 17.5 mg or 20 mg) at the study site during the practice laboratory session at Visit 2.

Safety parameters will be evaluated throughout the study.

A schematic of the overall study design is included below. The full schedule of events is found in [Appendix A](#).

Table 1: Study Design



3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from pre-dose in model-adjusted SKAMP-Combined scores at 30 minutes post-dose measured during the laboratory school days (Visit 3 and 4). The difference between Dyanavel XR and placebo will be assessed at the $\alpha = 0.05$ level of significance.

3.2.2. Secondary Endpoint

Efficacy will also be assessed by the following measures during the laboratory school day (Visits 3 and 4):

- Change from pre-dose in SKAMP scores at 3 hours post-dose
- Change from pre-dose in PERMP scores at 30 minutes and 3 hours post-dose
- Subscales of these measures will also be assessed

3.2.3. Safety Endpoint

Safety will be monitored by adverse events (AEs) assessed at each visit. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at Screening, Baseline and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors. Medical history will capture all medical conditions at Visit 1 (Screening Visit). Physical examinations, vital signs, height and/or weight assessments, 12-lead electrocardiogram (ECG), and clinical laboratory tests will be conducted at Screening, or at the discretion of the Principal Investigator.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion Criteria

All subjects must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Males or females aged 6 to 12 years at the time of screening, inclusive
2. Diagnosed with ADHD by a psychiatrist, psychologist, developmental pediatrician, pediatrician, or an experienced licensed allied health professional approved by the Sponsor within 6 months of study enrolment or newly diagnosed with ADHD using the DSM-5 criteria for ADHD
3. An ADHD-RS-5 score at Screening \geq 90th percentile for sex and age in at least one of the following categories:
 - a) Hyperactive-impulsive subscale,
 - b) Inattentive subscale, or
 - c) Total score.

Subjects who do not meet this criteria at screening can have ADHD-RS-5 repeated at baseline, after washout of stimulant medication for a minimum of 24 hours prior to baseline.

4. In the clinical judgment of the Investigator, the subject must be in need of pharmacological treatment for ADHD.
5. Females of childbearing potential must be non-lactating and must have a negative serum pregnancy test at screening
6. Provide written informed consent (parent/guardian) and assent (child aged 10 -12 years only) prior to participation in the study

4.2. Exclusion Criteria

The presence of any of the following exclusion criteria precludes a subject from study enrollment:

1. Diagnosed with any DSM-5 active disorder (other than ADHD) with the exception of specific phobias, learning disorders, motor skills disorders, communication disorders, oppositional defiant disorder, elimination disorders, and sleep disorders
2. Known history of chronic medical illnesses including severe hypertension, untreated thyroid disease, peripheral vasculopathy, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, known family history of sudden death
3. Known history or presence of significant renal or hepatic disease, as indicated by clinical laboratory assessment (liver function test results \geq two times the upper limit of normal, blood urea nitrogen, or creatinine).
4. Clinically significant abnormal ECG or cardiac findings on physical examination (including the presence of a pathologic murmur)

5. Use of the following medications within 30 days of Baseline Visit:
 - MAOI - monoamine oxidase inhibitors (e.g., Selegiline, isocarboxazid, phenelzine, tranylcypromine)
 - Tricyclic Antidepressants (e.g. Desipramine, protriptyline)
6. Use of the following medications within 3 days of Baseline Visit
 - Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)
 - Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)
7. Use of atomoxetine within 14 days of Baseline Visit
8. Planned use of prohibited drugs or agents from the Screening visit through the end of the study
9. Abnormal clinically significant laboratory test value at screening that, in the opinion of the Investigator, would preclude study participation
10. Known history of allergy/hypersensitivity to amphetamine or any of the components of Dyanavel XR, or topical anesthetics
11. Known history of lack of response to amphetamine
12. Parent or guardian's inability or unwillingness to follow directions of the Investigator or study research staff.
13. Any uncontrolled medical condition that in the opinion of the Investigator would preclude study participation
14. History of significant illness requiring hospitalization, or surgery requiring anesthetics within 30 days of Baseline Visit

4.3. Subject Withdrawal Criteria

Within the provisions of informed consent/assent and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete the study. The following are possible reasons to terminate the participation of any subject from the study:

- Signs and symptoms of intolerance to the study medication.
- A treatment-related, serious adverse event (SAE) is observed.
- The subject or parent/guardian is grossly non-compliant, as determined by the Investigator.
- Continued participation, in the opinion of the Investigator, is no longer in the best interest of the subject.
- The subject or parent/guardian wishes to withdraw for any reason.

- Unblinding of the Investigator, site personnel performing assessments, or subject/parent to a subject's treatment assignment during the double-blind Randomization Treatment Period of the study.

Subjects will be encouraged to adhere to the protocol and complete all required assessments for the study. A subject may also be discontinued from the study for any of the following medical and/or administrative reasons:

- Pregnancy
- At the discretion of the Investigator at any time
- At the subject's request
- Occurrence of a treatment-emergent AE or considerable worsening of an AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the Investigator or the Sponsor. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.

Any enrolled subjects desiring to discontinue prior to study completion should be encouraged to continue in the study and adhere to the protocol and subsequent regularly scheduled safety and effectiveness evaluations. Subjects who are discontinued outside of any scheduled visit will be encouraged to complete the final study visit at the time of withdrawal. Subjects who are discontinued during a scheduled visit will be encouraged to complete all assessments for both that study visit and the final study visit at the time of withdrawal. A subject who withdraws following study drug administration will not be replaced.

4.4. Study Stopping Rules

This study may be discontinued at any time if, in the opinion of the Principal Investigator or the Sponsor, continuation of the study represents a significant medical risk to participating subjects.

5. STUDY SCHEDULE AND PROCEDURES

5.1. Study Schedule

The study schedule table can be found in [Appendix A](#).

5.2. Efficacy and Safety Assessments

5.2.1. Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP)

The SKAMP scale will be administered pre-dose, at 30 minutes and 3 hours post-dose during classroom sessions (visits 2, 3 and 4). Training on the SKAMP scale will be required for those who have not received training in the 12 months prior to performing this study assessment. Designated, qualified individuals from the study research team will perform the assessment.

5.2.2. Permanent Product Measurement of Performance (PERMP)

The PERMP scales will be administered pre-dose, at 30 minutes and 3 hours post-dose during classroom sessions (visits 2, 3 and 4). Training on the PERMP will be required for those who have not received training in the 12 months prior to performing this study assessment. Designated, qualified individual from the study research team will perform the assessment.

A placement math test will be administered at Baseline (Visit 1), or at Screening to determine the appropriate level of math test difficulty.

5.2.3. ADHD-Rating Scale-5 (ADHD-RS-5)

The ADHD-RS-5 will be used to determine study eligibility. An ADHD-RS-5 assessment will be done at Screening and/or Baseline (Visit1). The Investigator or other designated, qualified individual from the study research team will perform the assessment.

5.3. Study Visits and Procedures

All study visit assessments will be collected on paper case report forms (CRFs).

Safety will be monitored by observation of and direct inquiry regarding AEs at each post-dose visit. Subjects may experience AEs that necessitate an unscheduled visit. Situations may also arise wherein the Investigator asks a subject to report for an unscheduled visit following the report of an AE or SAE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of subjects during the study. CRFs should be completed for each unscheduled visit. Refer to Section 9.4 for information on AE collection, recording, and reporting.

In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at Screening, and all subsequent visits to assess emergent suicidal thoughts or behaviors. The C-SSRS is a brief, Investigator-administered questionnaire that provides for the identification, quantification, and standardized assessment of the occurrences and severity of suicidal ideation and behavior. The baseline version of the C-SSRS will be administered to all subjects at Screening. The “Since Last Visit” version

will be used at all subsequent study visits (and Early Termination, if applicable). The Investigator or other designated, qualified individuals from the study research team will perform the assessment.

Medical history will capture all medical conditions at Screening. Physical examinations, height and body weight assessments, 12-lead ECG, and clinical laboratory tests will be conducted at Screening. Blood pressure and pulse will be assessed at all study visits and will be taken using automated machines programmed to take 3 consecutive readings (at least 2 minutes apart); manual blood pressure readings will be taken if necessary. Subjects should be comfortably seated for at least a few minutes prior to blood pressure readings. Respiratory rate and temperature will be measured at Screening only.

5.3.1. Study Periods

Study duration is 6-8 weeks consisting of the following:

- Screening
- Baseline (Visit 1)
- Practice Classroom (Visit 2)
- Double Blind Classroom (Visit 3)
- Double Blind Classroom (Visit 4)

5.3.1.1. Screening

Before any study-specific procedures are performed, the subject and parent/guardian must receive an explanation of all study procedures and must sign and date an Institutional Review Board (IRB) approved written assent and informed consent, respectively. Potential subjects who give their informed consent (parent/guardian) and assent (children aged 10 – 12 years only) will undergo a screening period (up to 4 weeks) to determine eligibility prior to the Baseline Visit.

During the Screening visit, the following activities will be performed:

- Subject assent and parent/guardian informed consent
- Review of inclusion/exclusion criteria
- Review of medical history
- Review of medication history
- Demographics (i.e., sex, age, ethnicity and race)
- C-SSRS
- Physical examination
- Body weight and height
- Blood pressure, pulse, respiratory rate, and temperature
- Resting 12-lead ECG

- Laboratory tests:

Table 2: Laboratory Tests at Screening

Serum chemistry panel:	Hematology CBC:
Alanine aminotransferase Aspartate aminotransferase Blood Urea Nitrogen Creatinine Glucose gamma-glutamyl transpeptidase	WBC - White blood cell count RBC - Red blood cell count Hemoglobin Hematocrit MCV - Mean cell volume MCH - Mean cell hemoglobin MCHC - Mean cell hemoglobin concentration RDW – Red blood cell distribution width Platelet count
	Other:
	Serum pregnancy test (females of child-bearing potential)

- PERMP math pre-test (may be performed at Baseline)
- Establish that DSM-5 diagnostic criteria for ADHD are met as performed by a psychiatrist, psychologist, developmental pediatrician, or pediatrician or permitted licensed allied health professional.
- ADHD-RS-5
- Cognitive functioning assessment by Investigator or WASI

5.3.1.2. Baseline (Visit 1)

Once the subject is determined to be initially eligible at Screening, the Baseline (Visit 1) evaluations will be performed. If the subject continues to meet eligibility criteria at the Baseline Visit, the subject may be enrolled into the study. Subjects will be instructed to take open-label Dyanavel XR orally once daily.

Open-label Dyanavel XR will be dispensed to enrolled subjects. Subjects will be instructed to take open-label Dyanavel XR. Subjects who are stimulant naive will take Dyanavel XR beginning at 2 mL daily in the morning. Subjects who have a history of stimulant treatment may be initiated on open label Dyanavel XR at whole mL doses between 2 and 6mL per day, inclusive, as selected by the investigator based on required doses for adequate symptom control with previous stimulant medication treatment. The dose for all subjects may be increased as tolerated as often as daily up to a maximum dose of 8 mL (20 mg) daily or until an optimal dose is reached as determined by the study doctor. The Investigator may decrease a subject's dose at any time during the open-label period to ensure tolerability. Subjects who find the maximum study dose of 8 mL (20 mg)/day is insufficient to treat their symptoms of ADHD and thus are not adequately controlled will be discontinued from the study.

The parents or guardians of the subjects will be instructed to administer the medication orally to their child once daily prior to 10 am with or without food. Children should not self-administer study medication.

The following assessments will occur at the Baseline Visit:

- Review of inclusion/exclusion criteria
- Blood pressure and pulse
- PERMP placement test (if not performed during Screening)
- Urine pregnancy test (females of child-bearing potential only)
- Follow –up C-SSRS
- ADHD-RS-5 (if subject did not meet ADHD-RS-5 eligibility criteria at screening)
- AE assessment
- Concomitant medications assessment
- Open-label Dyanavel XR dispensing, accountability, and subject/parent/guardian training regarding investigational product

5.3.1.3. Practice Laboratory School Day (Visit 2)

Visit 2 should be scheduled after the last child enrolled in the study has had a minimum of 3 days of open label study medications administered prior to Visit 2. All subjects will have their Baseline visit within 4 weeks of their screening visit. Visit 2 will occur on the same day for all subjects in the cohort and the date of the visit will be determined to permit the last enrolled subject to have 3 days of exposure to open label study medication prior to Visit 2. The maximum length of exposure to study medication prior to Visit 2 shall be limited to 5 weeks.

At Visit 2, efficacy assessments will occur during the practice laboratory school day. Assessments for ADHD symptoms and behaviors will be measured by SKAMP and PERMP in an abbreviated analog classroom. Pre-dose assessments will be performed prior to the morning study drug dose on the day of the visit approximately 30 minutes prior to dosing. After the pre-dose classroom assessments are completed, all subjects will be administered 15 mg, 17.5 mg or 20 mg of open-label Dyanavel XR. The individual dose of study medication will be determined by the Investigator considering symptom control and tolerability.

The following activities will be performed during Study Visit 2:

- Blood pressure and pulse (should be conducted any time after dosing)
- Investigator dose evaluation (should be determined prior to dosing)
- Follow-up C-SSRS
- AE assessment
- Concomitant medications assessment

- Pre-dose:
 - SKAMP (in classroom setting)
 - PERMP (in classroom setting)
- Administer the investigator-assigned open-label dose of Dyanavel XR at study site
- Post-dose:
 - SKAMP (in classroom setting) at 30 minutes and 3 hours post-dose
 - PERMP (in classroom setting) at 30 minutes and 3 hours post-dose

5.3.1.4. Randomized, Double-blind, Placebo-Controlled Treatment Period (Visits 3 and 4)

The subjects will be randomized to the treatment sequence to take double-blind study drug:

- Dyanavel XR 6 mL (15 mg), 7 mL (17.5 mg) or 8 mL (20 mg) at Visit 3, then Placebo 6 mL, 7 mL or 8 mL at Visit 4, or,
- Placebo 6 mL, 7 mL or 8 mL at Visit 3, then Dyanavel XR 6 mL (15 mg), 7 mL (17.5 mg) or 8 mL (20 mg) at Visit 4.

Visit 3 will be scheduled the day following Visit 2. Visit 4 will be scheduled to occur the weekend following Visit 3. After the completion of visit 3, open label study medication will be dispensed to each subject. The study medication may continue to be adjusted as often as daily in increments of 1- 4 mL per day up to a maximum dose of 8 mL (20 mg) per day between visits 3 and 4 as instructed by the investigator considering symptom control and tolerability.

The double blind laboratory school day will be performed at Study Visits 3 and 4 and will take approximately 5 hours.

Pre- and post-dose study visit assessments will also be performed at visits 3 and 4.

The following activities will be performed during Study Visits 3 and 4:

- Blood pressure and pulse (should be conducted any time after dosing)
- Follow-up C-SSRS
- AE assessment
- Concomitant medications assessment
- Pre-dose:
 - SKAMP
 - PERMP
- Administration double-blind study drug at study site
- Post-dose:

- SKAMP at 30 minutes and 3 hours
- PERMP at 30 minutes and 3 hours
- Double-blind study drug accountability and reconciliation

For all activities performed, the results are to be recorded in the CRF.

5.3.1.5. Early Termination Visit

The following activities may be done for subjects that withdraw prior to completion of Study Visit 4 (i.e., terminate early):

- Blood pressure and pulse
- AE assessment
- Concomitant medications assessment
- Follow-up C-SSRS
- Study drug accountability and reconciliation
- A urine pregnancy test (for females of child-bearing potential only) may be performed in the event of a suspected pregnancy per Investigator's clinical judgment

For all activities performed, the results are to be recorded in the CRF.

6. INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

6.1. Investigational Drug Dose Regimen

Open-label Dyanavel XR will be dispensed to enrolled subjects. Subjects will be instructed to take open-label Dyanavel XR. Subjects who are stimulant naive will take Dyanavel XR beginning at 2 mL daily in the morning. Subjects who have a history of stimulant treatment may be initiated on open label Dyanavel XR at whole mL doses between 2 and 6 mL per day, inclusive, as selected by the investigator based on required doses for adequate symptom control with previous stimulant medication treatment. The dose for all subjects may be increased as tolerated as often as daily up to a maximum dose of 8 mL (20 mg) daily or until an optimal dose is reached as determined by the study doctor. The Investigator may decrease a subject's dose at any time during the open-label period to ensure tolerability. Subjects who find the maximum study dose of 8 mL (20 mg)/day is insufficient to treat their symptoms of ADHD and thus are not adequately controlled will be discontinued from the study.

The parents or guardians of the subjects will be instructed to administer the medication orally to their child once daily prior to 10 am with or without food. Children should not self-administer study medication.

During visits 3 and 4, and following randomization, subjects will receive Dyanavel XR 6 mL (15 mg), 7 mL (17.5 mg) or 8 mL (20 mg) or Placebo 6 mL, 7 mL or 8 mL once. The crossover treatment will be administered at the following double blind classroom session (Visit 4).

6.2. Investigational Drug Packaging and Labeling

Dyanavel XR will be provided during Visit 1 and Visit 3 as a liquid suspension in 4-oz plastic bottles containing 90 mL of oral suspension with an adaptor and an oral syringe to dispense. These bottles will be labeled appropriately and will be used for the open-label Period of the study.

Dyanavel XR and placebo will be provided as a liquid suspension in blinded packaging during the double-blind visits 3 and 4. Double-blinded Dyanavel XR and placebo will have identical physical characteristics.

All investigational products used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of Tris Pharma or those of its designee, Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and applicable regulations.

6.3. Investigational Drug Storage

The study drug should be stored between 15°C to 30°C (59°F to 86°F) at the study center in a secure, locked cabinet or room with limited access. When dispensed, the parent/guardian will be instructed to store the drug at ambient temperature in a cool, dry place and out of reach of children.

6.4. Investigational Drug Dispensing

To allow for flexible dosing options, 4-oz bottles containing 90 mL of Dyanavel XR will be manufactured for this study. An oral syringe will be provided with the investigational product to facilitate accurate dosing of the subjects. Table 3 shows the amphetamine content for relative dosing volumes of Dyanavel XR.

Table 3: Dyanavel XR Content by Volume

Dyanavel XR (Extended-release oral suspension containing 2.5 mg amphetamine base per mL)								
Dosing Volume	1 mL	2 mL	3 mL	4 mL	5 mL	6 mL	7 mL	8 mL
Amphetamine Base Content	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	17.5 mg	20 mg

Beginning at Visit 1, subjects will receive a bottle of investigational product during his/her visit at the site. The Investigator will determine the initial of investigational product and a titration schedule or plan.

6.5. Drug Administration

Study drug will be administered orally, once daily before 10 am with or without food. Subjects will be instructed to take each study drug dose by swallowing. The medication must always be administered to the child by the parent/caregiver or by another responsible adult; the study medication must not be self-administered regardless of the age of the child.

6.6. Investigational Drug Accountability

The Investigator or designee will verify and acknowledge receipt of study drug. All medications must be stored in a secure area under the proper storage requirements with limited access. Medication designated for this clinical study must not be taken by any subjects other than those enrolled in this specific investigation, and may not be utilized for any laboratory or animal research. All study drug dispensed to subjects must be accurately recorded on the Drug Accountability Record maintained at the study center. Subjects should be instructed to return all study drug dispensed to them (including any unused bottles containing study drug and empty containers) at each study visit.

Drug accountability will be performed at each Study Visit starting with Study Visit 1 (Baseline). Subjects will be provided with a new bottle containing 90 mL of study drug at visit 3, and bottles containing study drug should be returned to the site at each subsequent visit. Compliance will be estimated by visual inspection of the remaining bottle volume upon return to the site. By Study Visit 4 (or Early Termination), subjects should return all medication dispensed to them. In the event of a study drug spill during at-home administration, photographic evidence of the spill must be provided by the subject's parental guardian for drug accountability when possible. All medication and empty containers will be retained at the site for Study Monitor and/ or Sponsor verification. All medication should be stored at the study site until further instruction from the Sponsor.

6.7. Investigational Drug Handling and Disposal

All study drug (open –label Dyanavel XR, blinded Dyanavel XR and placebo) will be accounted for on drug inventory records (including records of study drug sent to the Investigator and records generated at the investigational site). The Sponsor and/ or its designate will review inventory forms during the study and at the conclusion of the study. The Investigator will sign the drug inventory record after resolving any questions resulting from the Sponsor and/ or its designate's review. The Investigator must retain a copy of all drug inventory records.

All remaining used and unused study drug must be retained until final instructions are given by the Sponsor.

Tris Pharma will provide detailed drug return instructions to the study site. All post-treatment handling and disposal of study drug will be in accordance with GCP and GMP guidelines and federal and local regulations.

7. SUBJECT COMPLIANCE

7.1. Concomitant Medication and/or Therapy

Concomitant medications information will be collected beginning at Screening and will continue through Study Visit 4 (or Early Termination).

7.2. Prohibited Concomitant Medications and Foods

Psychotropic medications are not allowed during the study except for stimulants (other than study drug), which must be discontinued prior to starting study medication. No anticonvulsant, antidepressant, or antipsychotic medications are permitted during the study. Melatonin is permitted. Prohibited concomitant medications may be resumed 1 day after Study Visit 4.

7.2.1. Prohibited Concomitant Medications

Any stimulant (e.g., methylphenidate, dextromethylphenidate, amphetamine, dextroamphetamine) should be discontinued prior to beginning study medication the day after Visit 1

SSRIs (e.g., fluoxetine, paroxetine)

SNRIs (e.g., Desvenlafaxine, Duloxetine, Venlafaxine)

MAOIs (monoamine oxidase inhibitors)

Mood stabilizers (e.g., lithium, valproate, quetiapine)

Antipsychotics (e.g., risperidone, olanzapine)

Anticonvulsants (e.g., phenobarbital, phenytoin, primidone)

Sedative hypnotics, except melatonin

Anticoagulants

Halogenated anesthetics

Tricyclic antidepressants

Atomoxetine

Guanfacine

Clonidine

CYP2D6 inhibitors (e.g. Paroxetine and fluoxetine, quinidine, ritonavir)

Fentanyl, tramadol, tryptophan, buspirone, St. John's Wort

Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)

Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)

Acetaminophen is permitted for control of fever or pain if needed. Short courses of prescription and nonprescription medications needed for treatment of acute illnesses such as the common cold, viral illnesses, and ear infections are permitted as long as these do not contain medications listed above.

All concomitant medications must be recorded on the Concomitant Medication CRF.

7.3. Treatment Compliance

Parent/guardian and subject training at Baseline (Visit 1) and subsequent ongoing retraining regarding proper dosing of study drug will occur to ensure subject compliance. After Visit 1, study staff will assess compliance by inspecting returned study drug bottles at every study visit to confirm that the subject is taking study drug according to the protocol. If the family forgets to bring the bottle to the visit, the visual inspection will occur when the bottle is returned. In the event of a study drug spill during at-home administration, photographic evidence of the spill will be required to demonstrate treatment compliance if possible.

8. RANDOMIZATION AND BLINDING PROCEDURES

Except for Visits 3 and 4, dosing will be conducted in an open-label fashion. The laboratory school days (Visits 3 and 4) and associated classroom testing will be performed in a double-blind manner. All double-blind study medication will be supplied in identical bottles and will be similar in physical characteristics (color, smell, and appearance), thereby enabling double-blind conditions.

Enrollment will occur after all screening procedures have been performed and eligibility for the study is confirmed at the Baseline (Visit 1).

At Visit 2 subjects will be randomized in a 1:1 ratio to treatment sequence: Dyanavel XR followed by Placebo or Placebo followed by Dyanavel XR.

Unblinding should occur only when knowing the treatment assignment has a bearing on the medical treatment or evaluation of a subject. Whenever possible, the need to unblind should be discussed with the Sponsor prior to unblinding.

A subsequent written report, including all pertinent details, must be submitted to the Sponsor within 24 hours of the unblinding. Whenever possible, the blind of the parent/guardian and subject should be maintained.

If an Investigator, site personnel performing assessments, or subject/parent is unblinded, the subject must be withdrawn from the study, and procedures accompanying withdrawal are to be performed.

9. ADVERSE AND SERIOUS ADVERSE EVENTS

This section defines AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, and *ICH Guideline E-6: Guidelines for Good Clinical Practice*.

The Investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational drug. For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

9.1. Definitions of Adverse Events

9.1.1. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

9.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32[a]):

- Death: A death that occurs during the study or that comes to the attention of the Investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life threatening" if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions

that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study drug, the event must be reported to the Sponsor as described in Section 9.5.1.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization is considered serious. Any initial admission (even if less than 24 hours) to a hospital meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the medical floor to the intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same-day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition that did not worsen
- Protocol-specified admission (e.g., for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or procedures should be noted in the baseline documentation for the individual subject.

Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.1.3. Adverse Reaction (AR) and Suspected Adverse Reaction (SAR)

An adverse reaction (AR) means any AE caused by a drug.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than an AR (21 CFR 312.32[a]).

9.1.4. Unanticipated Adverse Reaction (UAR)

The Sponsor is responsible for assessing AEs for expectedness. With regards to reporting to the Health Authority, an AE is considered “unexpected” when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol/package insert/Investigator’s Brochure/prescribing information for Dyanavel XR.

"Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32[a]).

9.2. Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the following criteria:

- Mild; awareness of signs or symptoms but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient.
- Moderate; discomfort enough to interfere with usual daily activities.
- Severe; incapacitating with an inability to perform usual daily activities; signs and symptoms may be of systemic nature or require medical evaluation.

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 9.1.2 serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

9.3. Relationship to Investigational Drug Treatment

An Investigator's causality assessment is the determination of whether a reasonable possibility exists that the investigational drug caused or contributed to an AE. This assessment must be provided for all AEs (serious and non-serious).

The Sponsor's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 4.

Table 4: Attribution of Adverse Events

Not Related	The AE is clearly/most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relation, or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational drug.
Possible Related	An adverse event that has a timely relationship to the administration of the investigational drug/study procedure, follows no known pattern of response, but a potential alternative cause does not exist.
Probably Related	An adverse event that has a timely relationship to the administration of the investigational drug/study procedure and follows a known pattern of response, but for which a potential alternative cause may be present.
Definitely Related:	An adverse event that has a timely relationship to the administration of the investigational drug and follows a known pattern of response for which no alternative cause is present.

9.4. Collecting and Recording Adverse Events

9.4.1. Period of Collection

All AEs will be collected from the completion of informed consent through Visit 4. All AEs and SAEs should be treated as medically appropriate. AEs that occur after at least one dose of study medication has been administered will be considered treatment-emergent AEs.

9.4.2. Methods of Collection

Adverse events may be collected as follows:

- Observing the subject
- Questioning the subject in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the subject or parent/guardian

An abnormal value or result from a clinical or laboratory evaluation (e.g., physical examination, laboratory assessment, or ECG) can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

9.4.3. Recording Method

9.4.3.1. Adverse Events

All AEs occurring during this clinical study will be recorded by the Investigator on the appropriate CRF in precise medical terms, along with the date and time of onset and the date and time of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to the study medication. The severity of the AE and its relationship to the study medication will be assessed by the Investigator.

The Investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication CRF as a concomitant medication administered. The action taken and the outcome must also be recorded. Adverse events will be followed until resolution or stabilization or until 30 days after a participant terminates from the study, whichever comes first. The terms of AE resolution (i.e., not recovered/not resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, fatal, unknown) should also be recorded.

9.4.3.2. Serious Adverse Events

Serious adverse events will be recorded on the AE CRF and on the SAE Report Form Provided by the sponsor as described in Section 9.4.3.1, and health authorities will be notified as outlined in [Section 9.5.2](#).

9.5. Reporting Adverse Events

9.5.1. Reporting SAEs to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the Investigator or designee is responsible for reporting the SAE to the sponsor, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Name of the reporter
- Subject identification
- Study drug
- Serious AE term
- Date of onset
- Relationship to study drug
- Reason why the event is serious

Supplemental CRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study drug administration, and death (as applicable).

Unavailability of certain event details should not delay submission of the known information. As additional details become available, the SAE CRF should be updated and re-submitted. Every time the SAE CRF is submitted, it should be signed by the Investigator or sub-investigator.

The following Sponsor Representative is to be contacted immediately after the occurrence of an SAE:

Antonio Pardo, MD

Manager, Clinical Affairs

Tris Pharma Inc.

Phone: (732) 823-4755

Mobile: (917) 514-9058

Email: apardo@trispharma.com

safety@trispharma.com

9.5.2. Reporting SAEs to Health Authorities

The Sponsor or Sponsor designee will report Investigational New Drug (IND) Safety Reports to the FDA and Investigators in accordance with the FDA regulations detailed in the 21 CFR 312.32.

9.5.3. Reporting SAEs to the Central IRB(s)

It is the responsibility of the Sponsor or Sponsor designee to promptly notify their respective IRB(s) of IND Safety reports or other matters involving risk to subjects as mandated by the IRB(s).

9.5.4. Reporting Pregnancy

During the study, all subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The Investigator is responsible for reporting all available pregnancy information on the pregnancy CRF within 24 hours of becoming aware of the event, although pregnancy itself is not an SAE. The Investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The subject should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy should be reported as it becomes available.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 9.5.1. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE

report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

10. STATISTICS

10.1. Power and Sample Size Determination

The primary efficacy outcome is change from pre-dose in the model-adjusted SKAMP-Combined score at 30 minutes hours post-dose as measured during the laboratory school days (Visits 3 and 4). Assuming an effect size of 1.00 between Dyanavel XR and placebo and approximately 15 subjects randomized to double-blind treatment, this study will have 90% power at the level of $\alpha = 0.05$ (2-sided) to detect a treatment effect. To allow for an estimated 15% potential drop-out rate, this study plans to enroll approximately 18 subjects.

The assumed effect size is based on differences measured between active and placebo in previous laboratory school studies conducted with similar drug formulations at the earliest measured timepoint and reducing that by 20%.

A detailed statistical analysis plan (SAP) will be written and finalized prior to unblinding of the data.

10.2. Analysis Populations

The analysis populations are defined as follows:

- The enrolled safety population is defined as all enrolled subjects who receive at least 1 dose of open-label study drug treatment.
- The randomized safety population is defined as all randomized subjects who receive at least 1 dose of double-blind study drug treatment.
- The ITT population is defined as randomized subjects who receive at least 1 dose of double-blind study drug treatment and have at least 1 post-dose assessment of the primary efficacy variable at both Visits 3 and 4.
- The clinically evaluable population is defined as all ITT subjects who have no major protocol deviations. This includes any subject who:
 - Received the morning dose of double-blind study medication at Visits 3 and 4
 - Completed all laboratory classroom assessments
 - Did not use prohibited medication during the double-blind Treatment Period.

The primary efficacy analyses will be performed on the ITT population. Secondary efficacy analyses on the ITT and clinically evaluable populations will be supportive of the primary analysis.

The safety analyses will be performed on the enrolled and randomized safety populations.

Deviations from the original statistical plan as planned in this protocol will be reported and justified in the SAP and clinical study report (CSR) as appropriate.

10.3. Efficacy and Safety Analyses

10.3.1. Background and Demographic Characteristics

Baseline demographic variables will be reported.

10.3.2. Efficacy Analyses

10.3.2.1. Primary Efficacy Analysis

The primary efficacy analysis will be performed on the ITT population. The primary efficacy outcome is change from pre-dose in the model-adjusted average of SKAMP-Combined score at 30 minutes post-dose.

The treatment difference will be estimated using least squares means from a mixed-effects repeated-measures model. The treatment comparison will be conducted as a 2-sided test at the 5% level of significance. All available data will be used; there will be no imputation of missing data. Effect size will be calculated.

10.3.3. Safety Analyses

All safety data will be analyzed descriptively by treatment group

The frequency of subjects reporting AEs will be summarized within each system organ class and preferred term during the open-label period, double-blind period.

The C-SSRS analyses will be summarized.

10.4. Concomitant Medications and Concomitant Therapies

Concomitant medications and therapies will be summarized and listed by subject.

10.5. Other Statistical Considerations

10.5.1. Significance Levels

The type I error significance level for each set of study analyses as applicable will be set at $\alpha = 0.05$.

10.5.2. Missing Data

Although the rate of missing data is expected to be low, missing data could occur under either or both of the following scenarios: missing or invalid data for individual questions in the SKAMP and missing SKAMP-Combined scores at individual time points.

In general, missing or invalid data for individual questions will be handled by rules specific to the validated SKAMP questionnaire and will be described in the SAP. No additional imputation for missing or invalid SKAMP responses will be performed.

No imputation of missing SKAMP-Combined scores will be done for the primary efficacy analysis. The mixed-model repeated-measures method used to analyze the primary endpoint has been designed to

utilize all available data and provides valid estimates under the assumption of data which are missing completely at random or missing at random. To evaluate the sensitivity of the primary analysis results to the use or non-use of imputation, analyses using single imputation (last observation carried forward) and multiple imputation methods may be conducted. This decision will be made prior to database unblinding, and the methods will be described in the SAP.

11. DIRECT ACCESS TO PROCEDURAL DOCUMENTS

11.1. Study Monitoring

According to GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the CRFs. The Sponsor is responsible for assigning the study monitor(s) to this study. The study monitors' duties are to aid the Investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the Investigator of the regulatory necessity for trial-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the Investigator all regulations applicable to the clinical evaluation of an investigational drug as documented in ICH guidelines.

It is the study monitors' responsibility to inspect the CRFs throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details may be outlined in the study monitoring plan.

11.2. Source Documents

Tris Pharma requires that the Investigator prepare and maintain adequate and accurate records for each subject treated with the investigational drug. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the Investigator's files with the subject's study records.

No database will be created for this study. The source documents will be considered the study CRFs. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

Adverse events will be coded with the Medical Dictionary for Regulatory Activities . Concomitant medications will be coded using World Health Organization – Drug Reference List.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from Tris Pharma (or a qualified delegate), who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

13. ETHICS

13.1. Ethics Review

This study will be conducted according to GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007). The conduct of the study will be in accordance with the Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (2000).

13.2. Ethics Committees

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. The investigator agrees to allow the IRB or IEC direct access to all relevant documents. The IRB or IEC must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents or data needed for IRB or IEC review and approval of the study. Before investigational products and CRFs can be shipped to the site, the sponsor must receive copies of the IRB or IEC approval, the approved informed consent form, and any other information that the IRB or IEC has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The investigator must promptly forward to the sponsor copies of the IRB or IEC approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB or IEC approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB or IEC approval can be sought.

13.3. General Considerations

The Investigator must conduct the study in accordance with this protocol and ICH GCP guidelines which have their origins in the Declaration of Helsinki. The Investigator and Tris Pharma will sign the protocol and study contract to confirm agreement. The Investigator will not implement any amendment (deviation or changes of the protocol) without agreement by Tris Pharma and the IRB approval/information, except where necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study.

When any new and important information that may be relevant to the subject's consent is obtained, the Investigator and Tris Pharma will consult with each other on how to deal with the information. When Tris Pharma and a responsible Investigator judge it necessary, the Investigator must immediately provide the subjects with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the IRB(s). In this instance, the Investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

13.4. Informed Consent

Subjects aged 10 to 12 years must sign an assent form and parent or legal guardian must sign the informed consent form. The sponsor will provide investigators with a sample informed consent form and assent form for this study. Investigators are encouraged to use the sample form; however, they may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final informed consent form must be accepted by the sponsor and approved by the IRB or IEC. Investigators must provide the sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB or IEC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the informed consent form, the sponsor will provide investigators with a revised informed consent form. The IRB or IEC must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, and possible risks.

Before written informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject (or his or her legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form and the assent form must be signed and dated by the subject (or his or her legally authorized representative) and any other signatories as required by the IRB or IEC.

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

13.5. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form

allowing the Investigator to notify the subject's primary health care provider of his/her participation in this study.

13.6. Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR § 50.25(c). The results of and data from this study belong to Tris Pharma. Investigators may not publish on the results from the study (including data specifically from their site) without prior written consent from Tris Pharma.

13.7. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Tris Pharma after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Tris Pharma. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Tris Pharma. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor and the regulatory authorities (e.g., FDA or the IRB[s] if applicable) is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Tris Pharma and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

14. DATA HANDLING AND RECORD KEEPING

14.1. Inspection of Records

Tris Pharma, its designee(s), the IRB(s), or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The Investigator agrees to allow Tris Pharma, its designee(s), the IRB(s), or regulatory authorities to inspect the investigational drug storage area, investigational drug stocks, investigational drug records, subject charts and study source documents, and other records relative to study conduct.

14.2. Retention of Records

The Principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

15. REFERENCES

- 1 DYANAVEL XR [Prescribing Information]. Monmouth Junction, NJ: Tris Pharma Inc.; 2017. Available from: <http://www.dyanavelxr.com/pdfs/pi.pdf>.

APPENDIX A. SCHEDULE OF EVENTS

Procedure	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Early Termination
Parent/Guardian IC	x					
Pediatric Subject Assent	x					
Eligibility Assessment	x	x				
Medical History	x					
Medication History	x					
Physical Examination	x					
Height & Weight ^c	x				x	x
Screening Laboratory ^f	x					
ADHD-RS-5 Score	x	x				
Pregnancy test ^d	x ^e	x				
Cognitive Functioning ^a	x					
Demographics	x					
Vital Signs ^b	x	x	x	x	x	x
12-Lead ECG	x					
PERMP ^g	x ^j	x ^j	x	x	x	
SKAMP ^g			x	x	x	
CSSRS ⁱ	x	x	x	x	x	x
Open Label medication dispensed ^l		x	x	x ^k		
Randomization			x			
Double Blind Medication Administration ^h				x	x	
Drug Accountability		x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x
Adverse Events ⁱ	x	x	x	x	x	x
<p>a. When cognitive functioning level is not clear by clinical signs and symptoms, a Wechsler Abbreviated Scale of Intelligence (WASI) may be administered to estimate IQ.</p> <p>b. At Screening, vital signs will include respiratory rate and temperature. Visits 2, 3 and 4 will include only BP and HR, any time after dose</p> <p>c. Height measurement required only at Screening.</p> <p>d. Females of child bearing potential only.</p> <p>e. Serum pregnancy test will be performed at Screening; Urine dipstick pregnancy test will be performed at Baseline (Visit 2); pregnancy testing will also occur in the event of a suspected pregnancy.</p> <p>f. Laboratory tests will include: hematology (WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHV, RDW, and platelet count) and Chemistry (glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase)</p> <p>g. Assessments will occur pre-dose, 30 minutes and 3 hours post-dose</p> <p>h. To be dosed in clinic</p> <p>i. Different versions of the C-SSRS will be used a Baseline and subsequent visits (Since Last Visit)</p> <p>j. PERMP math pre-test (PERMP placement test may be conducted at screening or baseline)</p> <p>k. After the completion of visit 3, open label study medication will be dispensed to each subject</p>						

APPENDIX B. REVISION HISTORY

The following updates have been applied the present revision (crossed= deleted, bold= added):

The following Inclusion Criteria have been modified:

- #2. Diagnosed with ADHD by a psychiatrist, ~~psychologist, developmental pediatrician, pediatrician, or an experienced licensed allied health professional approved by the Sponsor~~ within 6 months of study enrollment or newly diagnosed with ADHD using the DSM-5 criteria for ADHD
- #4. In the clinical judgment of the Investigator, the subject must be in need of pharmacological treatment for ADHD. ~~Subjects on current treatment with Dyanavel XR may be enrolled provided the ADHD-RS-5 entry criteria are not met while on treatment, but are met after treatment washout.~~
- #6. Provide written informed consent (parent/guardian) and assent (**child aged 10 – 12 years only**) prior to participation in the study

The following Exclusion Criteria have been modified:

- #1 **Diagnosed with any DSM-5 active disorder (other than ADHD) with the exception of specific phobias, learning disorders, motor skills disorders, communication disorders, oppositional defiant disorder, elimination disorders, and sleep disorders** (added)

#5 From: Use of the following medications within 30 days of Baseline Visit:

- MAOI - monoamine oxidase inhibitors (e.g., Selegiline, isocarboxazid, phenelzine, tranylcypromine)
- Tricyclic Antidepressants (e.g. Desipramine, protriptyline)
- Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)
- Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)

To:

5. Use of the following medications within 30 days of Baseline Visit:

- MAOI - monoamine oxidase inhibitors (e.g., Selegiline, isocarboxazid, phenelzine, tranylcypromine)
- Tricyclic Antidepressants (e.g. Desipramine, protriptyline)

6. **Use of the following medications within 3 days of Baseline Visit**

- Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)
- Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)

List or Abbreviations has been updated to correct grammatical errors. Some abbreviations were deleted as they were not applicable to this study

Section 3.1. Design: This section has been updated to give more clarify on the study design

Table 1 has been up dated to reflect the time-frame Open Label Dyanavel will be administrated

Section 3.2.2: Added

- Change from pre-dose in PERMP scores at **30 minutes and 3 hours** post-dose
- **Subscales of these measures will also be assessed**

Section 5 Study Schedule and Procedures: updated to provide more clarify on the study design

5.2. Efficacy: and Safety Assessments: updated for clarity purposes

5.3.1 Study: duration updated to 6-8 weeks

5.3.1.1 Screening: assent required only in children aged 10 – 12 years, no washout needed. The section has been updated accordingly

5.3.1.2 Baseline: This section has been updated to allow the PI to customize titration according to each child's condition

5.3.1.3. Practice Laboratory School Day (Visit 2): This section has been updated to provide more clarity regarding this visit

5.3.1.4 Randomized, Double-blind, Placebo-Controlled Treatment Period (Visits 3 and 4): This section has been updated to provide more clarity regarding this visit

6.4 Investigational Drug Dispensing / Table 3: 5 mL (12.5 mg) was added

7.2.1 Prohibited Concomitant Medications: the following items have been added to be in line with Dyanavel XR Package Insert:

- Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)
- Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)

9 Adverse and Serious Adverse Events:

9.1.4 Unanticipated Adverse Reaction (UAR): Adderall IR was replaced with Dyanavel XR

9.2 Severity of AEs/SAEs: updated to current practice

9.3 Relationship to Investigational Drug Treatment: updated to current practice

9.4.1 Period of Collection - the following has been added: **AEs that occur after at least one dose of study medication has been administered will be considered treatment-emergent AEs.**

10.3.2.1 Primary Efficacy analysis: The primary efficacy outcome is change from pre-dose in the model-adjusted average of SKAMP-Combined score at ~~4 hours~~ 30 minutes post-dose.

Appendix A has been revised to reflect the current study design.

Note: multiple edits have been applied to correct grammatical and typographical errors.

