CLINICAL STUDY PROTOCOL

Title: A single-dose, open-label pharmacokinetic study of DYANAVEL XR (amphetamine) extended-release oral suspension, in children aged 4 to 5 years with ADHD

Protocol Number:	TRI102-PPK-300 (2970-1)
Investigational Drug:	DYANAVEL® XR
Version:	v. 1.0 (April 2018)
Sponsor:	Tris Pharma, Inc. 2033 US 130 Monmouth Junction, NJ 08852
Authorized Signatory:	Barry Herman, MD, MMM Chief Medical Officer Tris Pharma, Inc.
Primary Study Contact:	Antonio Pardo, MD Associate Director, Clinical Affairs & Pharmacovigilance Tris Pharma, Inc.
Protocol Amendments:	N/A

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

SPONSOR'S SIGNATURE

Approved by:

Barry K. Herman, MD, M.M.M.

Digitally signed by Barry K. Herman, MD, M.M.M.
Date: 2018.05.07 17:16:46 -04'00'

Barry Herman, MD, MMM
Chief Medical Officer
Tris Pharma, Inc.

Date

INVESTIGATOR'S SIGNATURE

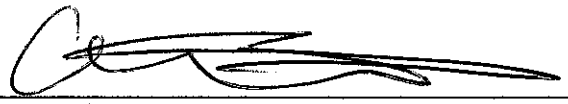
I have read this protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

ANDREW J. CUTLER, MD

Printed Name of Investigator

P.I., MERIDIEN RESEARCH

Title of Investigator



Signature of Investigator

07/MAY/2018

Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	Antonio Pardo, MD	Tris Pharma, Inc. 2033 US 130, Suite D Monmouth Junction, NJ 08552 (732) 823-4755 (office) (917) 514-9058
Chief Medical Officer	Barry Herman, MD, MMM	Tris Pharma, Inc. 2033 US 130, Suite D Monmouth Junction, NJ 08552 (732) 823-4720 (office) (609) 865-6816
Please include and Safety@trispharma.com on all your correspondence		

SYNOPSIS

Study Number:	TRI102-PPK-300 (2970-1)
Title	A single-dose, open-label pharmacokinetic study of DYANAVEL XR (amphetamine) extended-release oral suspension, in children aged 4 to 5 years with ADHD
Study Center(s)	Meridian Research, Inc. 2300 Maitland Center Parkway Maitland, FL 32751
Clinical Phase	1
Indication	ADHD (Attention-deficit/hyperactivity disorder)
Sample Size	4 – 6 subjects
Treatment Duration	Screening can occur up to 6 weeks prior to dosing. A single dose of study medication will be administered on Day 1 and the final study procedures will take place on Day 2.
Objectives	The objective of this study is to evaluate the plasma amphetamine concentration/time profile of DYANAVEL XR in preschool children with ADHD following a single 1 mL (2.5 mg) dose of DYANAVEL XR.
Methodology	This is a Phase 1, open-label study in children with ADHD to investigate the pharmacokinetic profile of DYANAVEL XR over a 28 hour period following the administration of a single dose of 1 mL (2.5 mg) of DYANAVEL XR in children with ADHD. Up to 4 - 6 subjects are planned for enrollment, aged 4 to 5 years of age at the time of signing of the Informed Consent. Subjects will be screened for participation in the study within 6 weeks prior to study drug administration. Medical history, physical examination including height and weight, baseline laboratory testing, 12-lead electrocardiogram (ECG), vital sign measurements, a diagnostic assessment using the K-SADS-PL to confirm ADHD diagnostic criteria are met and informed consent will be completed during the screening visit. Subjects will be confined from the day of dosing to at least approximately 13 hours after dosing. Each subject will receive a dose of 1 mL (2.5 mg) of DYANAVEL XR, administered by the site study staff at Time 0 (Day 1). For pharmacokinetic analyses of d- and l-amphetamine, 9 blood samples will be collected in total from each subject. Samples will be collected at pre-dose Day 1 (Time 0 to -2 hrs.), and at 1, 3, 4, 6, 8, 10, 12 and 28 hours after dose administration. Time after dosing will begin when DYANAVEL XR is administered to the subject. The subjects may then be released to their parents/ guardians with instructions to return to the study center for the final 28 hour (+/- 2 hours) sample; or they may remain at the study site for the duration of the

	study. Safety assessments will include monitoring of AEs and concomitant medications throughout the study and collection of vital signs prior to medication administration and 4 hours post dosing.
Inclusion Criteria:	Subjects must meet all of the following criteria to be considered eligible to participate in the study: 1. Male or female aged 4 to 5 years at the time at the time of enrollment into this study 2. Body weight ≥ 28 lb. at screening visit 3. Diagnosed with ADHD by a psychiatrist, psychologist, developmental pediatrician, pediatrician, or an experienced licensed allied health professional approved by the Sponsor by using the DSM-5 criteria and supported by a structured Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) interview, administered at the Screening Visit 4. Provide written informed consent (parent/guardian) prior to participation in the study
Exclusion Criteria:	Subjects who meet any of the following criteria will be excluded from participating in the study: 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. History of chronic medical illnesses including seizure disorder (excluding a history of febrile seizures), moderate to severe hypertension, untreated thyroid disease, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy and 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 ≥ 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 dosing: • 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 dosing: • 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 dosing 8. Planned use of prohibited drugs or agents from the Screening visit through the end of the study. Medications used to support sleep may be acceptable

	with the written approval of the Sponsor or Medical Monitor 9. Abnormal clinically significant laboratory test values at screening that, in the opinion of the Sponsor or Medical Monitor would preclude study participation 10. Known history of allergy/hypersensitivity to amphetamine or any of the components of DYANAVEL XR, heparin flush and topical anesthetics 11. Parent or guardian's inability or unwillingness to follow directions of the Investigator or study research staff 12. Any uncontrolled medical condition that in the opinion of the Sponsor or Medical Monitor would preclude study participation 13. History of significant illness requiring hospitalization, or surgery requiring anesthetics within 30 days of dosing.
Assessments:	• K-SADS-PL • Adverse Events • Electrocardiogram • Safety Labs • Physical Exam • Vital Signs • Medical History • Concomitant Medications
Criteria for evaluation:	Pharmacokinetics: The pharmacokinetic parameters for the concentrations of d- and l-amphetamine in plasma will be determined for each subject receiving study medication.
Statistical methods:	Sample size determination: The sample size for this study was powered per FDA instruction. 4 - 6 subjects aged 4 to 5 years will provide adequate power for a pharmacokinetic analysis. Study populations: Adverse events will be reported for all subjects once enrolled. Total and treatment-emergent adverse events will be reported. All subjects with sufficient plasma concentration data for estimating pharmacokinetic parameters will be included in the pharmacokinetic analyses. Pharmacokinetic analysis: Pharmacokinetic parameters will be summarized and no formal comparisons will be made. Pharmacokinetic plasma samples: All PK Plasma samples will be sent frozen to the analytical lab after the end of the study. Safety analysis: MedDRA, current version will be used to classify all AEs with respect to system organ class and preferred term.
Safety:	Adverse Event (AE) collection

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from Time 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from Time 0 to last sampling time (t) with a quantifiable plasma drug concentration
AUC_{0-12}	Area under the concentration-time curve from Time 0 to 12 hours after dosing
CFR	(United States) Code of Federal Regulations
ºC	degrees Centigrade
C_{max}	Peak (maximum) observed plasma drug concentration
CRF	case report form
D	Day
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition
ECG	Electrocardiogram
ER	extended release
ºF	degrees Fahrenheit
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
H	Hour
HCl	Hydrochloride
HR	Heart Rate
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
K-SADS-PL	Kiddie-SADS Present and Lifetime Version
kg	Kilogram
L	Liter
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
PK	Pharmacokinetic

Abbreviation	Definition
SAE	serious adverse event
$t_{½}$	terminal-phase elimination half-life
t_{max}	time to peak (maximum) observed plasma drug concentration
US	United States
USP	United States Pharmacopeia
WBC	white blood cell

1.0 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 that contains 2.5 mg/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 3.2:1 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 frequency and severity of adverse event.

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 (± 2.01 h) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 (± 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 information[1].

The present study will fulfill a part of the Phase 4 Commitments Tris Pharma has made to conduct the following FDA required post-marketing studies in children aged 4-5 years with ADHD:

2970-1 A single-dose, open-label pharmacokinetic study of DYANAVEL XR (amphetamine) extended-release oral suspension, in children aged 4 to 5 years with ADHD

2970-2 A randomized, double-blind, placebo-controlled, flexible-dose titration study of DYANAVEL XR (amphetamine) extended-release oral suspension in children aged 4 to 5 years diagnosed with ADHD.

2970-3 A one year Pediatric Open-Label Safety Study of patients aged 4 to 5 years diagnosed with ADHD treated with DYANAVEL XR (amphetamine) Extended-Release oral suspension.

2.0 STUDY OBJECTIVE

The objective of this study is to evaluate the plasma amphetamine concentration/time profile of DYANAVEL XR in children aged 4 to 5 years with ADHD following a single 2.5 mg dose of DYANAVEL XR.

These data will guide appropriate dosing in planned safety and efficacy studies with DYANAVEL XR in a preschool population with ADHD.

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open-label, single-dose study in 4 -6 pediatric subjects with ADHD and who are otherwise healthy. Subjects will receive a single 1 mL dose of DYANAVEL XR (amphetamine) Extended-Release oral suspension 2.5 mg/mL.

Pharmacokinetics will be assessed over a 28 hour period after the single dose. Subjects may be kept at the study site(s) overnight.

Subjects with ADHD aged of 4 to 5 years will be enrolled at up to 2 study sites. Subjects will be screened for participation in the study within 6 weeks before study drug administration. Medical history, physical examination including height and weight, baseline laboratory testing, 12-lead electrocardiogram (ECG), vital sign measurements, a structured diagnostic interview (K-SADS-PL), and informed consent will be completed during the screening visit.

All subjects currently taking an ADHD medication including all psychostimulants methylphenidate, d-methylphenidate, amphetamines or derivatives of any of these products; must not take these medications for 48 hours prior to dosing with study medication. The ADHD medication can be resumed after the 28 hour sample is taken on Day 2, the final day of the study. The investigator should direct all other approved daily medications (see concomitant medications).

Subjects will be confined at the study center prior to dosing until approximately 13 hours post-dose, or may stay until the 28 hour blood sample per principal investigator discretion.

Serial blood samples will be collected from all subjects at predetermined time points. The pharmacokinetic parameters of interest will include peak (maximum) observed plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve (AUC) from Time 0 to last sampling time (t) with a quantifiable plasma drug concentration (AUC_{0-t}), AUC from Time 0 to infinity ($AUC_{0-\infty}$), and terminal-phase elimination half-life ($t_{½}$).

3.2 Rationale for Study Design and Control Groups

This study will evaluate the pharmacokinetic properties of DYANAVEL XR, administered orally to pediatric subjects aged 4 to 5 years with ADHD. Objective pharmacokinetic measurements will occur over 28 hours post-dose as a primary endpoint; therefore, an open-label, single-dose study design will be used. Due to the pharmacokinetic focus of this study, no placebo control group will be used.

One age group of pediatric subjects will be included in this study. The children will be aged 4 to 5 years on the day of enrollment into this study. Subjects will receive a 1 mL (2.5 mg) dose of DYANAVEL XR.

Dose Rationale: The dose range of the final optimal dose in a recent pivotal Phase 3 study of DYANAVEL XR in the treatment of children aged 6-12 years with ADHD (n=108) (TRI102-ADD-001) was 10 mg/day to 20 mg/day. None of the 108 subjects enrolled in that study discontinued due to an AE. There were no SAEs, deaths or severe AEs reported. Dosing was initiated at 1 to 2 mL (2.5 to 5 mg)/day (investigator's choice) and was titrated in 1 – 4 mL (2.5

to 10 mg) increments every 4 to 7 days until an optimal dose or the maximum dose (20 mg/day) was reached. Subjects had to reach a final optimal dose between 10 to 20 mg/day, inclusive. No subjects discontinued the study due to inability to tolerate a 10 mg dose.

The mean final optimized dose was 15.4 or 0.47 mg/ Kg. According to the CDC Growth Chart[2], the expected weight range with 3rd and 97th percentiles for a pediatric population ages 4 - 6 years is 12 – 24 Kg. Considering the low and high end of the weights for children aged 4 to 5 years, a single dose of 2.5 mg translates to a weight-based dose ranging between 0.21 mg/Kg and 0.11 mg/Kg, less than half of the mean weight-based dose that was well-tolerated in the previous study in children aged 6 to 12 years. Therefore it can be concluded that a single 2.5 mg dose of DYANAVEL XR is expected to be safe and tolerable to pediatric subjects aged 4 to 5 years with ADHD.

Meals: The study will be conducted with meals, snacks and beverages provided ad lib. Rationale: In adult volunteers, DYANAVEL XR had no food effect. Blood draws can be difficult in children, especially when not well-hydrated. Food intake may help reduce emesis (common in children during fasting PK studies) and may reduce vasovagal responses during blood draws.

Timing of PK sample collection: The main goal is to limit samples on the day of dosing to no more than 8 samples (pre-dose plus 7 post-dose samples) in order to collect an adequate amount of data while keeping the study feasible to conduct. The following collection times have been selected to meet goals of adequate data collection and study feasibility: Pre-dose and 1, 3, 4, 6, 8, 10, 12, and 28 hours post-dose.

With the exception of the 0 (pre-dose) and the 28 hour sample, samples will be collected within ± 15 minutes of the scheduled post-dose time. The pre-dose sample may be collected up to 2 hours before dosing. The 28 hour sample may be collected within 2 hours of the scheduled time. Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's case report forms.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Male or female aged 4 to 5 years at the time of enrollment into this study
2. Body weight ≥ 28 lb. at screening visit
3. Diagnosed with ADHD by a psychiatrist, psychologist, developmental pediatrician, pediatrician, or an experienced licensed allied health professional approved by the Sponsor by using the DSM-5 criteria and supported by a structured Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) interview, administered at the Screening Visit (Visit 0)
4. Provide written informed consent (parent/guardian) 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. History of chronic medical illnesses including seizure disorder (excluding a history of febrile seizures), moderate to severe hypertension, untreated thyroid disease, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy and 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 ≥ 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 dosing:
    - 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 dosing
    - 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 dosing.
8. Planned use of prohibited drugs or agents from the Screening visit through the end of the study. Medications used to support sleep may be acceptable with the written approval of the Sponsor or Medical Monitor.
9. Abnormal clinically significant laboratory test value at screening that, in the opinion of the Sponsor or Medical Monitor, would preclude study participation

10. Known history of allergy/hypersensitivity to amphetamine or any of the components of DYANAVEL XR, heparin flush and topical anesthetics
11. Parent or guardian's inability or unwillingness to follow directions of the Investigator or study research staff.
12. Any uncontrolled medical condition that in the opinion of the Investigator would preclude study participation
13. History of significant illness requiring hospitalization, or surgery requiring anesthetics within 30 days of dosing

4.3 Discontinuation of Subjects

4.3.1 Subject Withdrawal Criteria

Within the provisions of informed consent 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 not alleviated by dose reduction.
- 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 parent/guardian wishes to withdraw for any reason.

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:

- At the discretion of the Investigator or Sponsor at any time
- 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 evaluations. Subjects who are discontinued outside of any scheduled visit will be encouraged to complete 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.

5.0 STUDY SCHEDULE AND PROCEDURES

5.1 Study Schedule

Schedules of study procedures for overall study assessments and day-of-dosing assessments are provided in Appendix A: Table 2.

5.1.1 Screening

Before any study-specific procedures are performed, the parent/guardian must receive an explanation of all study procedures and parent/guardian must sign and date an Institutional Review Board (IRB) approved written informed consent. Potential subjects who give their informed consent (parent/guardian) will undergo a Screening period (up to 6 weeks) to determine eligibility. Exceptions for longer screening periods for children requiring specialist consultation in order to qualify may be approved as evidenced by written confirmation from the Sponsor or Medical Monitor.

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

- Parent/ guardian informed consent
- Review of inclusion/exclusion criteria
- Review of medical history
- Review of medication history
- Demographics (i.e., sex, age, race and ethnicity)
- Physical examination
- Body height and weight
- Blood pressure, pulse, respiratory rate, and temperature
- Resting 12-lead ECG
- K-SADS-PL
- AE assessment
- Concomitant medications assessment
- Laboratory Tests:

Table 1: Laboratory Tests

Serum chemistry panel:	Hematology CBC:
Alanine aminotransferase Aspartate aminotransferase Blood Urea Nitrogen Creatinine Glucose Gamma-glutamyl transferase (GGT)	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

A local laboratory will be used to analyze screening laboratory tests. Out-of-range laboratory results may be repeated at the investigator's discretion. If additional screening laboratory tests are required, the sponsor must be contacted for approval.

5.1.2 Day 1 & 2

Subjects will be confined from the day of dosing to at least approximately 13 hours post-dose. Each subject will receive a dose of 1 mL (2.5 mg) of DYANAVEL XR, administered by the site study staff at Time 0 (Day 1). The subjects may then be released to their parents/guardians 13 hours post-dose with instructions to return to the study center for the final 28 hour (± 2 hours) sample; or they may remain at the study site for the duration of the study, at the discretion of the Investigator.

The following assessments will be conducted on the day of admission (Day 1) for all subjects:

- Vital signs taken before dosing and 4 to 6 hours after dosing;
- Body height and weight
- AE assessment
- Concomitant medications assessment
- PK sampling, processing and storage

5.1.3 Pharmacokinetic (PK) Assessments

5.1.3.1 Sample Collection, Processing & Storage

A total of 27 mL (9 × 3 mL samples) will be collected for PK analysis.

A detailed blood sample processing procedure will be provided in Appendix B.

9 blood samples will be collected in total from each subject for PK analysis of d- and l-amphetamine. Samples will be collected at pre-dose and at 1, 3, 4, 6, 8, 10, 12 and 28 hours after dose administration. Time after dosing will begin when DYANAVEL XR is administered to the subject.

With the exception of the 0 (pre-dose) and 28 hour samples, samples will be collected within ± 15 minutes of the scheduled time. The pre-dose sample may be collected up to 2 hours prior to dosing. The 28 hour sample may be collected 26-30 hours post dose. Actual times will be

recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's case report forms.

5.1.3.2 Shipping of Pharmacokinetic Samples

The first set of aliquots will be packed in dry ice and sent to the analytical facility at the completion of the clinical portion of the study. The second set of aliquots will be packed in dry ice and shipped only after written confirmation that the first set has been received, see Appendix B for further details.

Clinic personnel will notify the analytical laboratory prior to each shipment.

Shipments will be accompanied by an inventory list with appropriate documents and delivered to:

Analytical Laboratory
Pharma Medica Research Inc.
6100 Belgrave Road
Mississauga, Ontario, Canada L5R 0B7
Phone: (905) 624-9115 Fax: (905) 624-4433

5.1.3.3 Bioanalytical Methodology

Plasma samples will be assayed for concentrations of d- and l-amphetamine by a validated method.

5.1.4 Study Discontinuation

A subject may be discontinued from the study by the investigator or the sponsor at any time if either determines that it is not in the subject's best interest to continue. The date the subject is withdrawn and the primary reason for discontinuation will be recorded on the subject's case report form (CRF).

5.1.5 Appropriateness of Assessments

The selected pharmacokinetic sampling times and parameters are appropriate to support the objectives of this study. Safety measures used in this study are standard for clinical trials of investigational medications.

5.1.6 Lifestyle Guidelines

Subjects are to continue their usual lifestyle.

5.1.7 Confinement

Eligible subjects will be admitted to the study facility on the day of scheduled dosing and will remain confined for approximately 13 hours after dosing with study medication. The subjects may then be released to their parents/care givers with instructions to return to the study center for the final 28 hour (± 2 hours) sample or they may remain at the study site for the duration of the study. During confinement children will be supervised at all times by study staff. Children will engage in supervised activities appropriate to level of maturity and individual interests such as

crafts, watching videos and playing games. Strenuous exercise and sports will not be permitted during confinement so that catheters will not be displaced.

5.1.8 Diet

While confined, the subjects will be provided meals, snacks and beverages provided ad lib. If necessary to support blood draws, individual subjects may be provided additional amount of food and drink per discretion of the Investigator.

6.0 INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

6.1 Investigational Drug Dose Regimen

Study personnel will administer study medication on Day 1. Each subject will receive a single 1 mL (2.5mg) dose of DYANAVEL XR. Each subject will be observed to be certain the dose is swallowed. Children may drink water after dosing if desired.

6.2 Investigational Drug Packaging and Labeling

DYANAVEL XR will be provided as a liquid suspension in bottles of 464 mL. The same bottle can be used to dose all subjects.

All investigational product 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 for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and applicable regulations. A more detailed description of the investigational product is provided in the Investigator Drug Manual.

6.3 Investigational Drug Storage

The study drug should be protected from high temperature and humidity and stored between 15°C to 30°C (59°F to 86°F) at the study center in a secure, locked cabinet with limited access. Complete details of IP storage and handling will be provided on the Study drug manual compliant with (CFR21 subpart D section 312.61&312.69).

6.4 Investigational Drug Accountability, Handling and Disposal

The study drug (DYANAVEL XR) 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 Study Monitor 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 Study Monitor 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 study monitor.

Tris Pharma will provide detailed drug return instructions to the study sites. All post-treatment handling and disposal of study drug will be in accordance with ICH GCP guidelines.

7.0 SUBJECT COMPLIANCE

7.1 Concomitant Medication and/or Therapy

Concomitant medications information will be collected beginning at Screening and will continue through the end of the study (Day 2).

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 the end of the study (Day 2).

7.3 Prohibited Concomitant Medications

All subjects currently taking an ADHD medication including all psychostimulants methylphenidate, d-methylphenidate, amphetamines or derivatives of any of these products; must not take these medications for 48 hours prior to dosing with study medication. The following medications are prohibited during the study.

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.

Investigators should contact the Medical Monitor for a written Note to File or Memo to File for evidence that the sponsor is aware of a chronic or acute medication and a judgment on whether the subject may continue in the study.

7.4 Treatment Compliance

The study drug will be administered on site by the study personnel.

8.0 RANDOMIZATION AND BLINDING PROCEDURES

Dosing for this study will be conducted in an Open-Label fashion and therefore there are no unblinding procedures. All subjects enrolled in the study will be on DYANAVEL XR.

9.0 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 E6(R2): Good Clinical Practice.*

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

9.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, whether or not the event has a causal relationship with this treatment.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE include the following:

- significant or unexpected worsening or exacerbation of the condition or indication under study, taking into consideration the daily fluctuation of symptoms of ADHD.
- exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding)
- signs, symptoms, or clinical sequelae of a suspected interaction
- signs, symptoms, or clinical sequelae of a suspected overdose of the study medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless non serious or serious sequelae occur).

The following examples are not considered AEs:

- medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- the disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition.

9.2 Definition of a Serious Adverse Event (SAE)

An SAE is defined as any event that meets the following criteria:

- It results in death or is life-threatening (i.e., presents an immediate risk of death from the event as it occurred). (This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle.)
- It results in hospitalization
- It results in prolongation of an existing hospitalization
- It is a congenital anomaly or birth defect
- It requires medical or surgical intervention to prevent any of the above outcomes.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of an SAE.

9.2.1 Serious Adverse Events That Occur Before Administration of Study Medication

Before administration of study medication, only SAEs assessed by the investigator as related to study participation (e.g., related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the sponsor.

9.2.2 Serious Adverse Events That Occur After Study Completion

If an investigator becomes aware of an SAE or death that occurs in a subject within 30 days after the subject receives study medication, and that investigator considers the event to be related to the study medication, the investigator is obligated to report the SAE to the sponsor.

9.3 Collecting, Recording and Evaluating Adverse Events and Serious Adverse Events

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE. AEs will be collected from the point the Informed Consent is signed through EOT or Early Termination Visit.

Both total and treatment-emergent AEs will be reported. Treatment-emergent AEs are defined as those that occur after dosing of study medication until EOT or Early Termination Visit.

9.3.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded on the CRF should be assigned to one of the following categories:

- **Mild**: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe**: an event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. *Severity* is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as *serious,* which is based on the subject's or event's outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section **Error! Reference source not found.**).

9.3.2 Assessment of Causality

The investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. The investigator will assess the relationship to the study medication by using the following criteria:

- **Definitely Related**: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely
- **Probably Related**: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive
- **Possibly Related**: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause; dechallenge is positive
- **Not Related**: The subject did not receive the study drug **OR** the AE has no temporal relationship to study drug **OR** the AE has a much more likely alternate etiology **OR** the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always makes an assessment of causality for every event before transmitting the SAE reporting form and AE CRF page(s) to the sponsor. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The

investigator may change his or her opinion of causality in light of follow-up information and amend the SAE reporting form and AE CRF page(s) accordingly.

9.3.3 Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event by using the following terms:

- **Resolved**: The event resolved or the subject recovered without sequelae. An event (either serious or non serious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequelae), an appendectomy (a scar is not a sequelae), a postoperative wound infection, or an upper respiratory tract infection
- **Resolved with sequelae**: The event has at least 1 secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function
- **Not resolved**: At the end of the study, a non serious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea
- **Unknown**: The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown
- Death

9.4 Follow-up of Adverse Events and Serious Adverse Events

Non-serious AEs will not be followed after the last scheduled study visit.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. The investigator will make a reasonable attempt to obtain follow-up information and provide it to the sponsor. This includes results of any additional laboratory tests or investigations or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally completed SAE reporting form and CRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form and CRF pages should be resubmitted to the sponsor within the time frames outlined in Section 9.5. Investigators with subjects with unresolved SAEs at the time that the electronic database is to be closed will be informed and instructed how to make subsequent updates on the SAE to the sponsor. The database will be locked and the data analyzed if unresolved SAEs remain. SAE updates will be reported to the sponsor, to Regulatory Authorities and IRBs within the timelines required by applicable regulations. All updates will also be filed in the Trial Master File retained by the sponsor.

9.5 Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor within 24 hours, including weekends and Holidays.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE, WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY E-MAIL TO THE FOLLOWING SPONSOR CONTACT:

Antonio Pardo, MD
2030 US 130 South, Suite D
Monmouth Junction, NJ 08852
Telephone: 917-514-9058
E-mail: apardo@trispharma.com
Safety@trispharma.com

In the initial e-mail, the investigator must provide to the sponsor the following CRF pages, completed to the greatest extent possible:

- AE record
- medical history
- prior and concomitant medications.

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances, and in the absence of e-mail capacity, notification by telephone is acceptable, with a copy of the SAE reporting form and CRF pages sent by overnight mail. Initial notification via telephone does not replace the need for the investigator to complete the SAE reporting form and CRF pages within the time frames outlined.

If the investigator does not have all information regarding an SAE, he or she must not wait to receive additional information before notifying the sponsor of the event. The form must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the sponsor by using the same procedure and timelines as for an initial report.

9.6 Regulatory Reporting Requirements for Serious Adverse Events

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5, "Prompt Reporting of Serious Adverse Events to the Sponsor."

The investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB. The sponsor is responsible for reporting to Regulatory Authorities.

10.0 STATISTICAL METHODOLOGY

10.1 Determination of Sample Size

The sample size for this study was powered per FDA instruction to meet the FDA PK quality metric. Four to six subjects will provide adequate power for a pharmacokinetic analysis.

The PK of d- and l-amphetamines are characterized well both in adults and children (Study 2014-3401, Adderall IR). The predictions of PK in children based on the PK model developed using Study 2014-3401 match reasonably with those of the observed PK in children administered other approved amphetamine products. This implies body size is the primary source of differences between adults and children. Given the richness of the prior information and the good predictive capacity of the PK model developed, this study design will ensure an informative study in children aged 4 to 5 years.

Although preschool-aged children will be enrolled in this study, the key demographic driving the differences between children and adults is body size, not age.

The estimated between-subject variability for DYANAVEL XR in adults is about 20% (for Clearance and Volume, the primary parameters of interest). Hence a sample size of 4-6 subjects should allow precise estimate of the mean Clearance and Volume.

10.2 Study Endpoints

10.2.1 Pharmacokinetic Endpoints

The pharmacokinetic parameters for the concentrations of d- and l-amphetamine in plasma will include C_{max}, $t_{max,}$ AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$. Mean, geometric mean, standard deviation, and percentage coefficient of variation will be calculated for the pharmacokinetic data, within the context of limited samples which can be collected from a pediatric population.

10.2.2 Safety Endpoints

Safety endpoints will include the following:

All AEs; treatment-emergent AEs

10.3 General Considerations for Statistical Analysis

10.3.1 Analysis Populations

All treated subjects will be included in the analysis for safety and tolerability assessments. All subjects with sufficient plasma concentration data for estimating pharmacokinetic parameters will be included in the pharmacokinetic analyses.

10.3.2 Test Hypothesis and P Value Justification

No formal statistical tests are planned.

10.3.3 Procedures for Handling Missing Data

In general, no imputation will be done for missing data. However, AEs with missing severity assessments will be assigned as "severe," and AEs with missing relationship assessments will be assigned as "related" for the purpose of analysis.

10.3.4 Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures will be the last measurements taken before the subject receives the study medication. Because this study requires a single dose of formulation, all measures taken after the subject has received the study medication will be considered *on-treatment* and *end-of-treatment measures*. The height and weight collected on the day of dosing will be used for all calculations.

10.4 Study Population Summaries

Population summaries will be provided for the pharmacokinetic population included in this study.

10.4.1 Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, subjects who discontinued from the study and reason for discontinuation). Identification numbers for discontinued subjects will also be included in the tables.

Disposition in terms of number of subjects excluded from each analysis population (safety and pharmacokinetic) will also be provided.

10.4.2 Demographics

The demographic summary will include descriptive statistics for age, sex, race, weight, and height.

10.4.3 Protocol Violations

All protocol violations and deviations will be tabulated.

10.4.4 Treatment Compliance

No formal summary of treatment compliance will be produced.

10.4.5 Prior and Concomitant Medications

All concomitant medications will be tabulated.

10.4.6 Efficacy Analysis

No efficacy assessment is planned for this study.

10.5 Safety and Tolerability Evaluations

Analyses will be provided.

10.5.1 Extent of Exposure

No formal extent-of-exposure analysis will be produced.

10.5.2 Adverse Events

MedDRA will be used to classify all AEs with respect to system organ class and preferred term. The dictionary version will be recorded in the clinical study report.

10.5.3 Clinical Laboratory Tests

Screening laboratory values will be preserved in source documentation.

10.5.4 Vital Sign Measurements

Vital sign values will be contained in the data listings.

10.5.5 Electrocardiograms

No formal analysis of abnormal ECG findings will be produced.

10.5.6 Subgroup Analyses

All analyses will be provided for the overall group.

10.5.7 Summaries of Pharmacokinetic Endpoints

All pharmacokinetic parameters for the concentrations of d- and l-amphetamine in plasma (including C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$) will be estimated for each treated subject.

10.5.8 Interim Analyses

No interim analysis is planned for this study.

11.0 DIRECT ACCESS TO PROCEDURAL DOCUMENTS

11.1 Study Monitoring

According to ICH 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 eCRF. Tris Pharma and its designated CRO are responsible for assigning the study monitor(s) to this study. The study monitors' duties are to aid the Investigator and its designated CRO 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 eCRFs 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 will 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.

Data will be captured electronically. Study site personnel will record eCRF data from source documents. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

11.3 Data Collection Management

This study will use electronic data collection techniques to collect data directly from the investigational site using eCRFs. The data will be stored centrally in a fully validated clinical database compliant with FDA regulations on electronic data integrity. The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

At intervals throughout the study and upon completion, data will be exported from the database into SAS datasets.

Data management will be coordinated by the data managers of Tris or its designate in accordance with their SOPs for data management and a formal study data management plan. The data managers will provide a quality control statement following database lock.

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

12.0 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.

13.0 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 for Harmonization (ICH) Guidance for Industry, E6(R2) GCP; 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' parent or legal guardian must sign the informed consent form. The sponsor will provide investigators with a sample informed consent 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' parents/guardians 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 parent/guardian 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 must be signed and dated by the subject's parent/guardian 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 parent/guardian 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 file.

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 parent/guardian 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.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Inspection of Records

Tris Pharma, their 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, their 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.

15.0 REFERENCES

[1] DYANAVEL XR [Prescribing Information]. Monmouth Junction, NJ: Tris Pharma Inc.; 2017.

[2] Centers for Disease Control and Prevention. Clinical Growth Charts. Available at: http://www.cdc.gov/growthcharts/clinical_charts.htm

[3] American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

16.0 APPENDICES

APPENDIX A - Schedule of Study Procedures

Table 2: Study Procedures

Procedure	Screening Visit (Within 6 Weeks of Day 1)	Procedures To Be Performed									
		Day 1									Day 2
		0h	1h	3h	4h	6h	8h	10h	12h	13h [b]	28h
Informed Consent	X										
Physical Examination	X										
Clinical Laboratory	X										
K-SADS-PL	X										
Demographics/ Medical History	X										
Vital Signs	X[a]	X[a]			X[a]						
Height/Weight	X	X									
12-Lead ECG	X										
PK Blood Samples		X	X	X	X	X	X	X	X		X
Study Drug Admin.		X									
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

[a] At Screening, vital signs will include BP , HR respiratory rate and temperature. On study Vital signs will include only BP and HR (average of triplicate measurements)
[b] Send home per Investigator discretion.

APPENDIX B: PK SAMPLES PROCESSING AND HANDLING

Sample Collection

The actual date and clock time of each sample collection will be recorded. Samples will be collected in pre-chilled, labeled 3 mL blood collection tubes containing K_2EDTA as the anticoagulant.

Blood will be collected by direct venipuncture or from an indwelling cannula, which will be placed in a vein of the subject.

The samples will be maintained in an ice bath for no more than 3 hours. If needed, the samples can be maintained in refrigerator conditions (5±3Cº) for up to 8 hours throughout sample collection and until further processing.

Sample Processing and Storage

Within 8 hours of collection, the blood samples will be centrifuged at room temperature for 10 minutes at 3000 rpm. Samples that are interrupted during centrifugation, disturbed during the separation process will be re-spun under the same conditions in an attempt to separated and obtain the maximum amount of plasma from each sample.

Following centrifugation, the plasma will be divided in 2 approximately equal aliquots, placed in labeled polypropylene tubes, and kept in an ice bath until storage at −25±10°C.

Within 60 minutes of centrifugation, the aliquot tubes should be stored at −25±10°C.

No more than 8 hours should elapse between blood draw and centrifugation and no more than 60 minutes should elapse after samples centrifugation and the freezing of the plasma samples.

Sample Shipment

Packing & Bundling

1. PMRI will provide the clinic site with the Blood Collection Tubes, Aliquot Tubes and labels to be used for this study
2. The labels will contain the following information:
   - Study #
   - Subject #
   - Sampling Time point
   - Aliquot #
3. Pack the samples in Ziploc bags as follows:
   a. Bundle all the samples for an individual subject – for a single aliquot –together with an elastic band in a small Ziploc bag
   b. Label the bag with the study # and subject #
   c. Put all bags in a larger Ziploc bag and label the bag noting the study # and subject numbers

Example: 2015-3778, Subjects 01, 02 and 03

Never combine both aliquots in a single bag.

4. The samples will be shipped within a week of sample processing; the storage conditions must be maintained until sample shipment (−25±10°C.)

Documentation

1. With each shipment, include an *Inventory (Bundling) Checklist* and a *PK Sample Shipment Memo*.
2. Detail all samples included along with totals per subject/patient and the total number of samples in the shipment on the *Inventory (Bundling) Checklist*.
3. Complete the *PK Sample Shipment Memo* including the following information:
   a. Missing samples: any discrepancies from the number of samples outlined in the protocol.
   b. Any sample processing or storage temperature deviations from the protocol. Detail the extent and duration that the samples were outside the required temperature range
   c. Provide information on concomitant medications if applicable

Shipping

1. The PK sample shipment will be set up by PMRI
2. Notify the PMRI analytical laboratory by email to pm@pharmamedica.com or fax prior to shipment. Include the courier tracking number in the notification.
3. Ship only the 1st aliquot of the samples in the 1st shipment.
4. Wait until you have received written confirmation from the PMRI lab that the first set has been received, before planning to hip Aliquot 2
5. Pack the aliquots in sufficient dry ice to keep the samples frozen for at least 72 hours and include a data logger. The courier will provide the data logger with their temperature probe service.

[ALL SHIPMENTS TO PMRI WILL B E MADE ON MONDAY OR TUES DAY ONLY, FOR ARRIVAL ON TUESDAY OR WEDNESDAY, RESPECTIVELY]

Shipping Address:
Analytical Laboratory
Pharma Medica Research Inc.
6100 Belgrave Road
Mississauga, Ontario, Canada
L5R 0B7
Phone (905) 624-9115
Fax (905) 624-4433