STATISTICAL ANALYSIS PLAN

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

Study No. TRI102-ADD-300

Authorization Signatures

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1 MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Significant Changes from Previous Authorized Version
Version 1.0 (Final)	13MAR2017	Not applicable – First version

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Commonly used abbreviations such as units (ml, mmHg, h) and abbreviations used for electrocardiogram assessments are not included in this list.

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-5	ADHD-Rating Scale-5
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CBC	Complete Blood Count
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EROS	Extended-Release Oral Suspension
ITT	Intent-to-Treat
IQ	Intelligence Quotient
LS Mean	Least-Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean Square Error
PCS	Potentially Clinically Significant
PERMP	Permanent Product Measure of Performance
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SKAMP	Swanson, Kotin, Agler, M-Flynn, and Pelham rating scale
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
USA	United States of America
WASI	Wechsler Abbreviated Scale of Intelligence
WHO-DD	World Health Organization - Drug Dictionary

3 INTRODUCTION

Amphetamine has been a well-established therapeutic agent for the treatment of Attention-Deficit/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 has been established for pediatric subjects aged 6 to 12 years old in a Phase 3 placebo-controlled laboratory classroom study TRI102-ADD-001. The ADHD symptoms were significantly lower in children on an individually optimized dose of amphetamine (range 10-20 mg/day), and the symptom control was demonstrated 1 hour after dosing with efficacy observed through 13 hours beyond dosing. The single-dose pharmacokinetics of orally administered Dyanavel XR were evaluated in Study TRI102-PPK-200 in pediatric subjects aged 6 to 12 years old with ADHD (10 mg oral dose) and in Study 2014-3401 in healthy adult subjects (18.8 mg oral dose).

This statistical analysis plan (SAP) provides detailed descriptions of the statistical analysis needed for a study manuscript. The information and methodology described and to be presented in the tables in this SAP is intended to be sufficient to produce a manuscript appropriate for submission to a peer-reviewed medical journal and for the purpose of a producing an abbreviated clinical study report.

4 STUDY OBJECTIVES

The efficacy objective is 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 Swanson, Kotin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores at 30 minutes post-dose during the laboratory school days (Visits 3 and 4), relative to placebo.

The safety objective is to assess the safety and tolerability of Dyanavel XR in pediatric subjects with ADHD.

5 STUDY DESIGN

5.1 General Description

This randomized, double-blind, two treatment, two sequence, placebo-controlled crossover study assesses the efficacy and safety of Dyanavel XR in reducing signs and symptoms of ADHD compared with placebo in pediatric subjects aged 6 to 12 years with ADHD utilizing a laboratory classroom design. Safety parameters will be evaluated throughout the study.

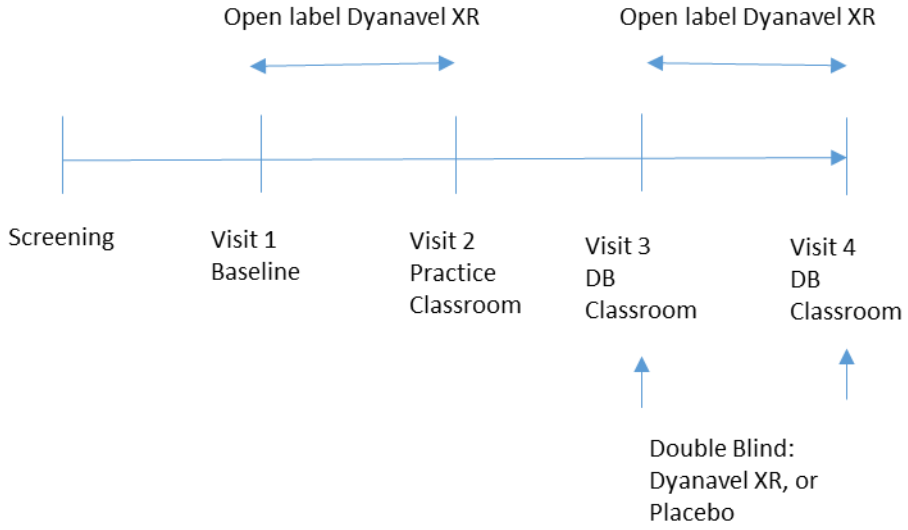
5.2 Discussion of Study Design

This study will be conducted at one investigational site in the United States with approximately 18 pediatric subjects enrolled. The study duration is 6-8 weeks consisting of the following visits:

- **Screening**: Up to 4 weeks to determine eligibility.
- **Baseline (Visit 1)**: Once the subject is determined to be initially eligible at Screening, the Baseline evaluations will be performed. If the subject continues to meet eligibility criteria, the subject will be enrolled and take open-label Dyanavel XR orally once daily in the morning beginning the day after the Baseline Visit. The dose may be increased as tolerated as often as daily up to a maximum dose of 20 mg daily or until an optimal dose reached.
- **Practice classroom (Visit 2)**: Visit 2 will occur on the same day for all subjects. The date of the visit will be determined to permit the last enrolled subject to have at least 3 days of exposure to Dyanavel XR prior to Visit 2. The maximum length of exposure to Dyanavel XR prior to Visit 2 shall be limited to 5 weeks. All subjects will be administered 15 mg, 17.5 mg or 20 mg of open-label Dyanavel XR by the study staff at the Practice classroom (Visit 2). The subjects will be randomized at Visit 2 to double-blind treatment sequence to be administered at Visits 3 and 4. The sequences are Dyanavel XR (Visit 3) followed by Placebo (Visit 4), or, Placebo (Visit 3) followed by Dyanavel XR (Visit 4).
- **Double blind classroom (Visits 3 and 4)**: Visit 3 will be scheduled the day following Visit 2. Visit 4 will be scheduled the weekend following Visit 3. The subjects will take double-blinded drugs (15 mg, 17.5 mg or 20 mg of Dyanavel XR or Placebo) in the randomized treatment sequence. The efficacy assessments for ADHD symptoms will be measured by SKAMP and Permanent Product Measurement of Performance (PERMP) at pre-dose and at 30 minutes and 3 hours post-dose. The open-label Dyanavel XR will be dispensed to subjects between Visits 3 and 4 which may be adjusted as often as daily up to a maximum of 20 mg daily.

A schematic of the overall study design is shown in Figure 5.2-1.

FIGURE 5.2-1: STUDY DESIGN



5.3 Method of Assigning Subjects to Treatment Groups

Approximately 18 pediatric subjects (male or female) with a diagnosis of ADHD per DSM-5 criteria will

be enrolled. Subjects must be aged 6-12 years at the time of screening, inclusive.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria at Screening and Baseline (Visit 1), sign the assent form (subjects aged 10 to 12 years only) and whose parent/guardian sign the informed consent form will be enrolled to take open-label Dyanavel XR.

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.

5.4 Treatment

Open-label Dyanavel XR will be dispensed to enrolled subjects. Subjects who are stimulant naive will take Dyanavel XR beginning at 2 mL daily. Subjects who have a history of stimulant treatment may be initiated on Dyanavel XR at whole mL doses between 2 and 6 mL per day, inclusive, as selected by the investigator. The previous stimulant medication must be discontinued prior to starting study medication.

The dose of study medication 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.

Following randomization, during Visits 3 and 4, 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.

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.

5.5 Blinding

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. 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. Dyanavel XR and Placebo will be supplied as a liquid suspension in identical bottles and will be similar in physical characteristics (color, smell, and appearance), thereby enabling double-blind conditions.

5.6 Determination of Sample Size

The primary efficacy outcome is change from pre-dose in the model-adjusted SKAMP-Combined score at 30 minutes 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 completing the double-blind treatment, this study will have greater than 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 time point and reducing that by 20%. The power calculations are based on an assumed 15% dropout rate.

5.7 Changes in the Conduct of the Study or Planned Analyses

There are none at this time.

6 EFFICACY AND SAFETY VARIABLES

6.1 Schedule of Evaluations

A detailed visit schedule is shown in Table 6.1-1.

TABLE 6.1-1: SCHEDULE OF ASSESSMENTS

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				
Previous Medications	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 [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

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.
b. At Screening, vital signs will include respiratory rate and temperature.
c. Height measurement required only at Screening.
d. Females of child bearing potential only.
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.
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 transferase)
g. Assessments will occur pre-dose, 30 minutes and 3 hours post-dose
h. To be dosed in clinic
i. Different versions of the C-SSRS will be used a Baseline and subsequent visits (Since Last Visit)
j. PERMP math pre-test (PERMP placement test may be conducted at screening or baseline)
k. After the completion of visit 3, open label study medication will be dispensed to each subject

6.2 Efficacy Outcome

6.2.1 Primary Efficacy Outcome

The primary efficacy endpoint is the change from pre-dose in model-adjusted SKAMP-Combined scores at 30 minutes post-dose measured during the double-blind laboratory school days (Visits 3 and 4).

The SKAMP scale is a 13-item independent observer rating of subject impairment of classroom observed behaviors. The following SKAMP scores will be assessed at each time point during each of the laboratory school days (Visits 2, 3, 4):

- SKAMP-Combined scores (items 1-13).
- SKAMP-Attention subscale scores (items 1-4).
- SKAMP-Deportment subscale scores (items 5-8).
- SKAMP-Quality of Work subscale scores (items 9-11).
- SKAMP-Compliance subscale scores (items 12-13).

Each item is rated on a 7-point impairment scale (0=normal to 6=maximal impairment). Items are specific to place (classroom setting) and time (during a typical classroom period), and the scale can be used to assess multiple ratings taken within a day. The SKAMP scale is collected during each laboratory classroom day at pre-dose, 30 minutes, and 3 hours post-dose. The combined scores and subscale scores for the SKAMP are obtained by summing the values of corresponding items in the assessment.

Missing or invalid data will be handled in the following manner:

- If 3 or more individual items in the SKAMP have missing or invalid data, the SKAMP-Combined score will be set to missing.
- If 1 or 2 individual items in the SKAMP are missing or invalid, the values for the missing individual items will be imputed using the mean of the non-missing individual items for the particular subject at that visit rounded up to the nearest integer.
- If any item within a SKAMP subscale is missing or invalid, the entire subscale score will be set to missing.

6.2.2 Secondary Efficacy Outcomes

Secondary efficacy endpoints include change from pre-dose in the following measures at 30 minutes and 3 hours post-dose during the double-blind laboratory school day (Visits 3 and 4):

- SKAMP-Combined scores (3 hours post-dose only).
- SKAMP-Attention subscale scores.
- SKAMP-Deportment subscale scores.
- SKAMP-Quality of Work subscale scores.
- SKAMP-Compliance subscale scores.
- PERMP scores.

Refer to Section 6.2.1 for specifications on the SKAMP scale.

PERMP scores will be obtained at pre-dose and each post-dose (30 minutes and 3 hours) time points during each laboratory classroom day (Visits 2, 3, 4). The PERMP is a 10-minute written test performed

as seatwork in the classroom. Subjects are given five pages of 80 math problems, and are instructed to work at their desks and to complete as many problems as possible in 10 minutes. The number of problems correct plus the number of problems attempted will be used to measure a subject's performance. Different versions are used among the subjects to adjust for ability as determined by the math pretest done at the Baseline Visit. In addition, different versions are used across classroom cycles, so that a subject does not take the same test more than once during a day.

Due to the nature of the PERMP, no imputation will be done. If a subject came into the study late and the subject completed the next available scheduled assessment, no imputation will be done for missing classroom assessments.

The following PERMP scores will be assessed at each individual time point of each laboratory classroom day (Visits 2, 3, 4):

- Number of math problems attempted.
- Number of math problems correct.

6.3 Baseline Characteristics

6.3.1 Demographic and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be recorded at Screening, and these characteristics will be summarized and presented in a table for the randomized safety study population.

6.4 Safety Variables

6.4.1 Adverse Events

The occurrence of adverse events (AEs) will be assessed at all visits. The C-SSRS will be assessed at each visit.

For the purpose of this study, data related to this will summarized as described in section 8.6.1.

6.4.2 Clinical Laboratory Assessments

Clinical laboratory assessments, including serum chemistry panel, hematology complete blood count (CBC), and a serum pregnancy test (where applicable) will be performed at Screening.

The purpose of these screening laboratories is to assist the physician in determining if potential subjects have medical issues which would preclude their participation in the clinical study.

Subjects may not be eligible for participation in the clinical study if any screening laboratory test is outside of the reference range and is considered clinically significant.

For the purpose of this study, data related to clinical laboratory assessments will be incorporated into the CRFs for each subject, but will not be included in the electronic database and therefore not summarized.

6.4.3 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be collected at Screening in order to exclude subjects with

cardiac abnormalities.

For the purpose of this study, ECG tracing results will be part of the CRF for each subject. The electronic database will include whether each ECG was assessed as normal, abnormal not clinically significant or abnormal clinically significant at screening. This data will not be summarized.

6.4.4 Physical Examinations and Vital Signs

Blood pressure (systolic and diastolic) and pulse rate will be measured at all visits in triplicate.

Respiratory rate and temperature will be measured only in conjunction with the physical examinations at Screening. Focused examinations may be performed if needed at all other visits.

Height and weight will be measured at Screening and Visit 4 (or Early Termination Visit). Body mass index (BMI) will be calculated as Weight (kg) / Height $(m)^2$.

For the purpose of this study, only potentially clinically significant vital sign values will be summarized in a table as described in section 8.6.2. Data related to physical examination will be collected and stored in the electronic database.

6.4.5 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to assess emergent suicidal thoughts or behaviors. The “Baseline” version of the C-SSRS will be administered to all subjects at Screening. The “Since Last Visit” version is to be used at all subsequent visits.

The C-SSRS is a brief clinician-administered questionnaire that provides for the identification, quantification and standardized assessment of the occurrences and severity of suicidal ideation and behavior. The interview includes a few skip out questions so that participants are asked only relevant questions and the typical administration time is a few minutes.

The results of the C-SSRS at each visit will categorize each subject as having suicidal ideation (yes/no) and suicidal behavior (yes/no).

A subject will be defined as having suicidal ideation if they have a ‘Yes’ to any of the following questions:
- Wish to be dead.
- Non-specific active suicidal thoughts.
- Active suicidal ideation with any methods (not plan) without intent to act.
- Active suicidal ideation with some intent to act, without specific plan.
- Active suicidal ideation with specific plan and intent.

A subject will be defined as having suicidal behavior if they have a ‘Yes’ to any of the following questions:
- Actual attempt.
- Interrupted attempt.
- Aborted attempt.
- Preparatory acts or behavior.
- Suicidal behavior.

For the purpose of this study, data related to this will be summarized in a table by each stage of the study and treatment sequence when applicable as described in 8.6.3.

7 STATISTICAL METHODS

7.1 General Methodology

All analyses will be conducted by using SAS® for Windows, Version 9.2 (or higher), SAS Institute, Cary, North Carolina, USA.

Descriptive summary statistics will include:

- Number of observations (n), mean, standard deviation (SD), minimum, median and maximum values for continuous parameters.
- Number of subjects (n) and relative frequencies (%) for categorical parameters.

Hypothesis testing, unless otherwise indicated, will be two-sided and performed at the 5% significance level. All p-values less than or equal to 0.05 will be considered statistically significant.

All efficacy comparisons from the mixed-effects repeated-measures model will be based on Type III tests. In the case of substantial non-normality, the normality-based analyses will be carried out on the ranked scores instead of the actual values. The normality assumption will be assessed for the primary efficacy variable using residual plot. When confidence intervals are presented, they will be two-sided with a confidence coefficient of 95%.

Data will be summarized based on the recorded visit; no visit windowing will be conducted.

For summary purposes, Baseline will be defined as the last available non-missing pre-dose observation, which should be Visit 1. When pre-dose observations at Visit 1 are missing, the last available non-missing pre-dose observations at Screening will be designated Baseline. Post-baseline will be defined as post-dose observations.

The treatment periods will defined for the analysis. The open label period will include (1) The time from first dose of open label study medication the start of the double blind study medication at Visit 3, and (2) given Visit 3 happened, the time of first dosing at home after Visit 3 to the start of double blind study medication at Visit 4.

The double blind period will include the time from first dose of double blind medication on Visit 3 until the first home dose of open label medication the next morning, and the time from first dose of double blind medication on Visit 4 until 24 hours later.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher. Medications will be coded using the latest version of World Health Organization - Drug Dictionary (WHO-DD).

7.2 Adjustments for Covariates

No adjustments for covariates will be made.

7.3 Handling of Drop-outs or Missing Data

In general, missing or invalid data of efficacy assessments will be handled by individual scales or subscales on the basis of each individual assessment, and is described in the corresponding sub-section of Section 6.2. No imputation will be carried out on missing combined and subscale scores

between the time points of the classroom days.

Missing end dates for medical history findings and AEs will not be imputed. If end date information is not available, it will be assumed that the finding or event is ongoing.

Missing AE start dates will be imputed based on the following assumptions:

- If only the year is known, the date will be set to 01 January of that year. If the year is the same as the year of the first dose of study medication, the date will be set to the date of the first dose of study medication.
- If the year and month are known the date will be set to first day of the month. If the year and month is the same as the year and month of the first dose of study medication, the date will be set to the date of the first dose of study medication.
- If the start date is completely missing it will be set to the date of the first dose of study medication.

Missing end dates for prior and concomitant medication will be imputed based on the following assumptions:

- If only the year is known, the date will be set to 31 December of that year. If the year is the same as the year of the last visit, the date will be set to the last visit date.
- If the year and month are known the date will be set to the end of that month.
- If the end date is completely missing it will be assumed that the medication is ongoing for the duration of the study, and as such regarded as concomitant.
- If these rules are followed and the completed end date is after the last visit date, the end date will be set to the last visit date.

7.4 Interim Analyses and Data Monitoring

No interim analysis or official data monitoring is planned for this study.

8 STATISTICAL ANALYSIS

8.1 Disposition of Subjects

Subject disposition, including the number and percentage of subjects who were enrolled, randomized, completed the study, and discontinued early during open-label and double-blind periods (including reasons for discontinuations), will be summarized in a table.

8.2 Protocol Deviations

Protocol deviations will be discussed in the abbreviated clinical study report by the sponsor.

8.3 Analysis Populations

A review of subject disposition and relevant data will take place before unblinding to determine the analysis populations.

The database will be hard locked (all user rights revoked) when:

- The SAP is authorized.
- There are no outstanding data issues.
- The authorized analysis populations are imported as SAS® data sets.

8.3.1 Enrolled Safety Population

Enrolled Safety population is defined as all enrolled subjects who receive at least one dose of open-label study medication and have at least one post-dose safety assessment.

8.3.2 Randomized Safety Population

Randomized Safety population is defined as all randomized subjects who receive at least one dose of double-blind study medication.

For the purpose of this study, the safety analyses will be performed on the Enrolled Safety populations.

8.3.3 Intent-to-Treat (ITT) Population

Intent-to-Treat (ITT) population is defined as all randomized subjects who receive at least one dose of double-blind study medication and have at least one post-dose assessment of the primary efficacy variable at both Visits 3 and 4. The ITT population will be considered as the primary population for efficacy analysis.

8.3.4 Clinically Evaluable population (CE) Population

The clinically evaluable (CE) 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 CE population will be determined by the sponsor prior to unblinding and provided to CRO for statistical analysis of the secondary endpoints.

8.4 Baseline Characteristics

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics including age (both continuous and categorized: 6-7 years,

8-10 years, 11-12 years), gender, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), and ADHD type (inattentive, hyperactive/Impulsive, combined) will be summarized by treatment sequence in tables for the randomized safety population.

8.4.2 Medical History

Medical history findings will be summarized descriptively by system organ class (SOC) and preferred term (PT) on the Enrolled Safety population.

8.4.3 Prior and Concomitant Medication

Prior medications are medications that were taken prior to the first dose of open-label study medication. Concomitant medications are medications that were taken during the treatment period. The double-blind period will include medications that were taken during the day of Visit 3 and the day of Visit 4, whether the start date was before or on that day.

Medications with partial start dates will be imputed as outlined in Section 7.3, and determined as concomitant medications based on the imputed start date. Medications with completely missing start dates (i.e. missing information for medication start day, month, and year) are assumed to be concomitant medications.

The frequency of subjects using prior and concomitant medications at screening, open label and double blind stage of the study will be summarized according to medication name.

8.5 Analysis of Efficacy

8.5.1 Primary Efficacy Analysis

The primary efficacy analysis will be conducted on the ITT population. The primary efficacy outcome is the change from pre-dose in SKAMP-Combined score at 30 minutes post-dose on the double-blind classroom days. Treatment comparisons for the primary efficacy outcome will be assessed using a mixed-effects repeated-measures model. The analysis will be repeated on the Clinically Evaluable population only if it differs from the ITT population.

The mixed-effects repeated-measures model will include sequence (2 levels), period (2 levels), and treatment (2 levels) as fixed effects, and subject within sequence as a repeated effect with a compound symmetry correlation structure. This two-tailed test at the 5% significance level will be carried out with SAS using the MIXED procedure.

The sequence levels are:

- Placebo / Dyanavel XR.
- Dyanavel XR / Placebo.

The period levels are:

- First double-blind classroom day (Visit 3).
- Second double-blind classroom day (Visit 4).

The treatment levels are:

- Dyanavel XR.
- Placebo.

Descriptive statistics of the SKAMP-Combined scores at pre-dose, 30 minutes post-dose, and change from pre-dose to 30 minutes post-dose will be presented in a table for the double blind period by treatment. In addition, the paired differences between the treatments for each subject (Dyanavel XR - Placebo) will be presented for the double blind period. The difference in the change from pre-dose to 30 minutes post-dose within each treatment will be assessed using a one-sample (paired) t-test, and the raw SKAMP-Combined scores at 30 minutes will be also be assessed using a one sample t-test. Furthermore, a graphical representation of the SKAMP-Combined scores will be presented for the double blind phase.

The point estimate of the least-squares mean (LS Mean) and the corresponding 95% confidence interval of the change from pre-dose to 30 minutes post-dose scores will be presented for each treatment group. The point estimate, corresponding 95% confidence interval and p-value for the treatment difference in the LS Means, including the effect size (calculated as the LS Means difference divided by the square root of the mean-squared error (MSE)) will be presented.

8.5.2 Secondary Efficacy Analyses

The secondary efficacy outcome include the following scores:

- Change from pre-dose to 3 hours post-dose for SKAMP-Combined scores
- Difference of PERMP scores (number of math problems attempted and number of math problems correct) between Dyanavel XR and placebo at 30 minutes and 3 hours.
- Change from pre-dose to 30 minutes and 3 hours post-dose for SKAMP subscale scores (Attention, Deportment, Quality of Work and Compliance).

. Each secondary efficacy outcome will be analyzed and presented the same way as the primary outcome variable as described in section 8.5.1.

8.6 Analysis of Safety

All safety data will be analyzed descriptively by treatment group on the Enrolled and Randomized Safety populations, unless otherwise stated. If the Enrolled and Randomized Safely populations are identical, the data will be presented only once.

8.6.1 Adverse Events

An AE is considered treatment-emergent, if it started on or after the first dose of study medication. If a subject terminates early from the study and has an AE after his/her last dosing date, the AE will not be deemed as treatment-emergent. AEs with partial start dates will be imputed as outlined in Section 7.3, and assigned to the associated treatment phase.

AEs will be presented for (1) the open-label period on the Enrolled Safety population and (2) the double-blind cross-over period on the randomized safety population. The double-blind period will include adverse events that started after Visit 3 or Visit 4 dosing. The frequency of subjects reporting the following AEs will be presented by SOC and PT for the enrolled safety population:

- TEAEs.
- TEAEs by severity.

- SAEs.
- AEs leading to premature discontinuation

8.6.2 Physical Examination and Vital Signs

Physical examination data from the screening visit will be recorded and stored in the electronic database, and will be available should a discussion require this information, but it will not be summarized.

The incidence of sponsor defined potentially clinically significant (PCS) post-treatment vital sign values will be presented by treatment sequence to examine the frequency and percentage of subjects that meet the PCS criteria outlined in Table 8.10-1a.

TABLE 8.10-1A: POTENTIALLY CLINICALLY SIGNIFICANT (PCS) VITAL SIGN VALUES

Parameter	Observed Value	Change from Baseline
Systolic Blood Pressure	> 95th percentile	≥ 20 mmHg increase
Diastolic Blood Pressure	> 95th percentile	≥ 20 mmHg increase
Pulse	> 110 bpm	≥ 25 bpm increase
Weight	N/A	≥ 5% decrease

The systolic and diastolic percentile is determined based on the subjects' age, gender, and height percentile, using the chart created by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents[1], as outlined in Tables 8.10-1b and 8.10-1c.

TABLE 8.10-1B: SYSTOLIC BLOOD PRESSURE NORMATIVE VALUES

		95th Percentile for Systolic Blood Pressure						
		Percentile for Height						
Gender	**Age**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
Male	6	109	110	112	114	115	117	117
	7	110	111	113	115	117	118	119
	8	111	112	114	116	118	119	120
	9	113	114	116	118	119	121	121
	10	115	116	117	119	121	122	123
	11	117	118	119	121	123	124	125
	12	119	120	122	123	125	127	127
Female	6	108	109	110	111	113	114	115
	7	110	111	112	113	115	116	116
	8	112	112	114	115	116	118	118
	9	114	114	115	117	118	119	120
	10	116	116	117	119	120	121	122
	11	118	118	119	121	122	123	124
	12	119	120	121	123	124	125	126

TABLE 8.10-1C: DIASTOLIC BLOOD PRESSURE NORMATIVE VALUES

		95th Percentile for Systolic Blood Pressure						
		Percentile for Height						
Gender	**Age**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
Male	6	72	72	73	74	75	76	76
	7	74	74	75	76	77	78	78
	8	75	76	77	78	79	79	80

	9	76	77	78	79	80	81	81
	10	77	78	79	80	81	81	82
	11	78	78	79	80	81	82	82
	12	78	79	80	81	82	82	83
Female	6	72	72	73	74	74	75	76
	7	73	74	74	75	76	76	77
	8	75	75	75	76	77	78	78
	9	76	76	76	77	78	79	79
	10	77	77	77	78	79	80	80
	11	78	78	78	79	80	81	81
	12	79	79	79	80	81	82	82

8.6.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The frequency of suicidality using the C-SSRS will be summarized by treatment for the Enrolled Safety population, for the following parameters:

- Number of subjects reporting at least one occurrence of suicidal ideation or behavior.

9 REFERENCES

[1] High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555-576.

Version 1 of the TRI102-ADD-300 clinical study protocol dated 30JAN2017.