CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208147Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #208147

Sponsor:	Tris Pharma, Inc.
Drug:	Amphetamine ER Oral Suspension
Indications:	Attention Deficit Hyperactivity Disorder
Material Submitted:	New Drug Application
Correspondence Date:	12/18/2014
Date Received:	12/19/2014
PDUFA Goal Date:	10/19/2015

I. Introduction and Regulatory Background

Tris Pharma submitted a 505(b)(2) application for amphetamine ER oral suspension (referred to as TRI102 during development; trade name Dyanavel), an extended-release liquid formulation of mixed amphetamine salts, referencing immediate-release Adderall (NDA 011522). The sponsor describes amphetamine ER oral suspension (eq. 2.5 mg amphetamine base per mL) as a once-daily, extended-release formulation of amphetamine, and is seeking an indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older.

The sponsor states that the product utilizes an ion-exchange resin, sodium polystyrene sulfonate, which complexes with amphetamine. A portion of the amphetamine-resin complexes is further coated with a flexible, semi-permeable coating material that provides for the gradual, extended release of amphetamine over several hours. The final suspension is prepared by (b) (4)

The sponsor's first interaction with the Agency related to this product was a request for a pre-IND meeting, dated November 8, 2012. The sponsor submitted a background package for the pre-IND meeting on December 20, 2012, and received preliminary comments from FDA on January 17, 2013. At that time, the sponsor intended to (b) (4) , and ultimately to pursue an NDA via the 505(b)(2) pathway. The sponsor cancelled the face-to-face meeting after receiving FDA's preliminary comments.

In the time between the pre-IND meeting request and the IND submission, the sponsor conducted two pilot bioavailability studies with different formulations of the extended-release amphetamine oral suspension. One of these studies demonstrated bioequivalence between an (b) (4) formulation and Adderall XR 30mg.

On December 2, 2013, the sponsor submitted two protocols to open IND 116,985—protocols SD-2014-3401, a relative bioavailability study, and TRI102-ADD-001, a

clinical efficacy trial. The sponsor initially proposed to evaluate amphetamine ER oral suspension for the treatment of ADHD (b) (4) under this IND.

The sponsor outlined the rationale for developing this product, noting that the drug product is intended to provide convenience to patients who prefer oral dosage forms but have difficulty swallowing solids. There are currently no available long-acting liquid amphetamine products. Because children are often unable to swallow pills, and because children comprise a large subset of the ADHD patient population, the sponsor noted that this product would fill an unmet need.

With the initial IND submission, the sponsor noted a change in the development plan. (b) (4), the sponsor proposed to rely upon FDA's general findings of safety and efficacy for an immediate release formulation of Adderall. The sponsor noted that Adderall tablets (Teva Womens NDA 011522) have been discontinued, and proposed to use the RLD dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablet (ANDA 040422, Teva/Barr Laboratories, Inc.). The sponsor also proposed to use a different formulation of the extended release suspension (20mg/8ml). The RLD's highest strength is slightly lower so, in the pharmacokinetic study, the sponsor planned to match the strength of the reference product and administer to patients 7.5 mL of amphetamine ER oral suspension, therefore administering 18.8 mg of amphetamine base. The sponsor still stated an intent to develop this product with an aim toward filing a 505(b)(2) NDA.

In these two studies, TRI102 was provided as an oral suspension containing 20mg of amphetamine base per 8ml, with an amphetamine base consisting of (b) (4)

In the May Proceed later dated January 9, 2014, the following clinical comment was conveyed to the sponsor:

> We note that the development plan outlined in this submission is markedly different from that proposed in your pre-IND meeting request. As a result, many of the comments we provided at that time no longer apply. We wish to remind you that the protocols included in this submission have been reviewed for safety only.

The sponsor submitted a Statistical Analysis Plan for TRI102-ADD-001 on April 24, 2014, with an amendment on Jun 2, 2014. This plan was reviewed by Andrejus Parfionovas, Ph.D., and comments were sent to the sponsor requesting clarification of the protocol version being used and the trial status. Dr. Parfionovas's final review dated September 2, 2014, describes the sponsor's response to that request, and notes that database lock would be occurring in early September.

The sponsor submitted a pre-NDA meeting request on September 4, 2014. The meeting occurred on November 16, 2014, and minutes were sent to the sponsor on November 19, 2014. During the pre-NDA meeting, FDA informed the sponsor that a pediatric PK study

would be required so that there would be some basis for interpolating efficacy in adolescents. The sponsor had PK data in adults and clinical data in children ages 6 to 12 years; in the absence of PK data in children, there would be no basis for interpolation of efficacy in adolescents. The sponsor agreed to conduct the required study and submitted a protocol for our review on December 6, 2014. The Office of Clinical Pharmacology (OCP) team provided comments on the protocol on December 18, 2014, and the sponsor submitted an amended protocol addressing OCP's concerns on March 6, 2015.

During the pre-NDA meeting, FDA also noted concerns regard the sponsor's proposed indications. The sponsor intended to seek indications (b) (4) Further, we informed the sponsor that we would not grant an indication for (b) (4)

II. Materials Reviewed

Submission Date	Materials
12/19/2014	2013-3144 Legacy study report 2013-3198 Legacy study report 2014-3401 Study report TRI102-ADD-101 Study report JMP Datasets Case Report Forms Debarment Certification Financial Disclosure Certification Patent Certification Draft labeling Draft carton labeling
2/27/15	Revised Debarment Certification
3/23/15	Patent Amendment
5/8/15	TRI102-PPK-200 Study report Revised draft labeling
8/28/15	Response to labeling request

III. Other Discipline Reviews

a. Product Quality: The Quality Assessment is dated August 18, 2015, with an addendum dated October 16, 2015. The review team for this application included Drug Substance, Drug Product, Process, Microbiology, Facility, and Biopharmaceutics reviewers, as well as a Project/Business Process Manager and Application Technical Lead. The Quality team recommends approval with a post-marketing commitment to develop more discriminatory single-medium dissolution methods for both the drug product and for the extended-release (b) (4)

Of note, the fact that the product releases up to 65% of the drug at 15 minutes caused the review team to carry out a more in-depth examination of the data supporting the proposed extended-release claim. In response to telephone conferences between Tris and FDA on August 3 and 6, 2015, the sponsor provided additional justification for the extended-release claim. The biopharm team found that the totality of the available data supported the extended-release claim.

The product was found to dose dump at 40% alcohol levels – this information will be included in the labeling.

b. Nonclinical Pharmacology/Toxicology: No new non-clinical information was submitted with this application. Ikram Elayan, Ph.D., reviewed the application from a pharmacology/toxicology perspective; her review was filed on September 25, 2015. She notes that the sponsor included safety data for the qualification of one inactive ingredient in their submission; sodium polystyrene sulfonate USP ([redacted] (b) (4) resin) which is present at a concentration of [redacted] (b) (4) mg/ml, well below levels in other approved products.

c. Clinical Pharmacology: The PK studies were reviewed by Kofi Kumi, Ph.D, in his review dated September 21, 2015. He determined that an adequate link has been established between the amphetamine ER oral suspension and amphetamine IR tablets through a relative bioavailability study, and that the pharmacokinetic profile of amphetamine following the administration of amphetamine ER oral suspension supports once-daily dosing. He also noted that, between the amphetamine ER oral suspension and amphetamine IR tablets, total exposure (AUC0-∞), AUC(0-t) and Cmax of both d- and l-amphetamine were equivalent; however, partial(p) AUC(0-4) and pAUC(0-5) of both d- and l-amphetamine were not equivalent. Partial AUC(5-t) of amphetamine was equivalent.

d. Controlled Substances Staff: In their review dated August 21, 2015, Edward Hawkins, Ph.D., and James Hunter, BPharm., MPH, provided labeling recommendations. In addition, they note that the sponsor's claim that the formulation [redacted] (b) (4) was unfounded. They also recommended that the sponsor should update the NDA to include an overview of the abuse potential of the formulation, including a rationale and proposal for scheduling under the CSA, and a literature review on the abuse potential of amphetamine.

An Information Request from CSS to the sponsor dated September 24, 2015, included the following:

> This product is appropriately listed in Schedule II under the CSA, as stated in your proposed label. However, as stated in the Pre-NDA meeting minutes dated November 19, 2014, for IND 116985, you should provide a rationale and proposal for scheduling, as outlined in 21 CFR

314.50(d)(5)(vii). You should submit this information as an amendment to the NDA in Module 1.11.4, Multiple Module Information Amendment, along with your rationale and summary of the abuse potential of the product. We request your amendment by c.o.b. Oct. 1, 2015, and we may, after reviewing your amendment, propose further revision of Section 9 of the labeling currently under consideration.

The sponsor replied, noting that amphetamine is a non-new molecular entity which is already a schedule II compound, and that extended-release formulations of amphetamine have a long history of being in Schedule II. They further state that they assume the Amphetamine ER Oral suspension has similar abuse liability as other extended release amphetamine products.

After reviewer the sponsor's response, CSS determined that the Schedule II classification is appropriate and that no additional abuse liability studies would be required.

e. Pediatric and Maternal Health: In response to an Information Request dated August 06, 2015, to resubmit labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR), the sponsor submitted a literature review on the use of amphetamine in pregnancy and lactationMiriam Dinatale, D.O., reviewed the sponsor's submission and concluded that the review of published literature revealed no new data with amphetamine use in pregnant or lactating women; they recommended revisions to sections 8.1, 8.2, and 17 of the product label for compliance with PLLR.

IV. Financial Disclosures

On December 16, 2014, W. Scott Groner, Director of Regulatory Affairs for Tris Pharma, Inc., certified that Tris had not entered into any financial arrangement with the principal or sub-investigators whereby the value of the compensation could have been affected by the outcome of the study. Also, he certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the sponsor did not disclose any such interests. He further certified that none of these investigators was the recipient of significant payments of other sorts.

V. Review of Clinical Studies

The clinical development program consisted of five studies: two pilot bioavailability studies (2013-3144 and 2013-3198) which did *not* use the to-be-marketed formulation, an additional bioavailability study (2014-3401) using the to-be-marketed formulation, a Phase 3 efficacy study (TRI102-ADD-001), and a pediatric PK study (TRI102-PPK-200/2015-3778). See Table 1, below.

Comparative bioavailability data from study 2014-3401 and PK data from TRI102-PPK-200 were reviewed in detail by the OCP review team and will not further discussed in this review; however, important clinical safety data from these trials and related labeling are discussed below.

Table 1: Studies Conducted in Support of NDA 208147

Type of study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Health Subjects of Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pilot BA	2013-3144	Module 5.3.1.1	Compare rate of absorption and oral BA of test ER oral suspension to ER tablet	Single-Dose, Open-Label, Randomized, Two-Period Crossover	Test: ER Oral Susp. 12 mL once at 0 hour (18.8 mg amphetamine base per 12 mL) Reference: Adderall XR, 1 tablet once at 0 hour (18.8 mg amphetamine base per tablet)	14 enrolled; 14 completed	Healthy Subjects	9 days	Complete; abbreviated
Pilot BA	2013-3198	Module 5.3.1.1	Compare rate of absorption and oral BA of test ER oral suspension to ER tablet	Single-Dose, Open-Label, Randomized, Two-Period Crossover	Test: ER Oral Susp. 12 mL once at 0 hour (18.8 mg amphetamine base per 12 mL) Reference: Adderall XR, 1 tablet once at 0 hour (18.8 mg amphetamine base per tablet)	14 enrolled; 13 completed	Healthy Subjects	9 days	Complete; abbreviated
BA	2014-3401	Module 5.3.1.2	Compare BA of test under fasted and fed conditions Evaluate relative BA of test to reference	Single-Dose, Three-Period, Open-Label, Three-Way Crossover	Test: ER Oral Susp., 7.5 mL at 0 hour (18.8 mg amphetamine base per 7.5 mL) Reference: Adderall, one 15 mg tablet at 0 and 4 hours post dosing (9.4 mg amphetamine base per 1 tablet; total dose = 18.8 mg amphetamine base)	30 enrolled; 29 completed	Healthy subjects	17 days	Complete; full
Efficacy, Phase 3	TRI102-ADD-001	Module 5.3.5.1	To evaluate the effect of TRI102 vs placebo on the signs and symptoms of ADHD in children	Randomized, Double Blind, Placebo controlled	Test: ER Oral Susp, 2.5 to 20 mg daily oral doses of TRI102 (2.5 mg per mL)	108 enrolled; 99 completed	Children with ADHD, 6 to 12 years old	Multiple dose 7 weeks	Complete; full
BA	TRI102-PPK-200/ 2015-3778	Module 5.3.1.2	Evaluation of the Single Dose Pharmacokinetics of TRI102 in Children with ADHD	Single-Dose, One-Period, Open-Label	Test: ER Oral Susp, 4 mL at 0 hour (2.5 mg per mL)	12 enrolled; 12 completed	Children with ADHD, 6 to 12 years old	One dose	Complete; full

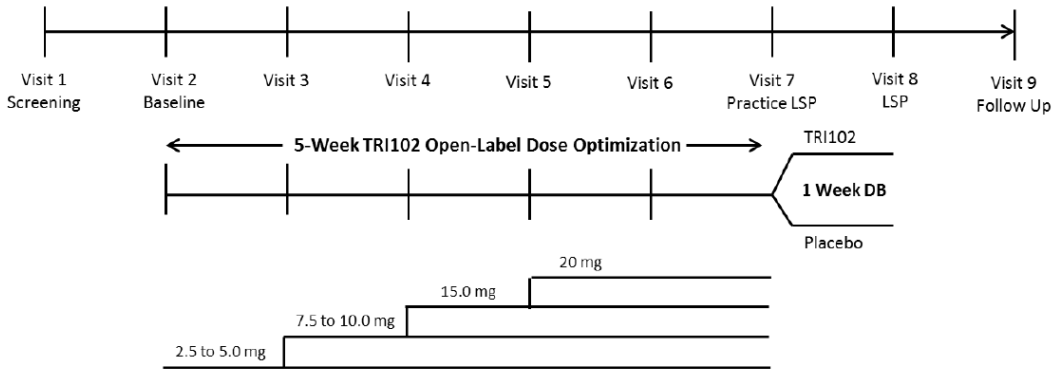
(source: NDA submission, Module 5.2, Table of Studies)

TRI102-ADD-001

Study Design

TRI102-ADD-001, *Amphetamine Extended-Release Oral Suspension in the Treatment of Children with ADHD: A Laboratory School Study*, was a dose-optimized, randomized, double-blind, placebo-controlled study in pediatric subjects with ADHD. See Figure 1, below, for a study design schematic and dosing schedule.

Figure 1: TRI102-ADD-001 Study Design and Dosing Schedule



DB = double-blind; LSP = laboratory school protocol study day
The dosing paradigm is presented as maximum daily dose within the given weekly intervals; not all subjects needed to be titrated to the highest dose of 20 mg/day.
Visit 7 (LSP 1) was an abbreviated practice laboratory school day with a shorter duration than the laboratory school day on Visit 8 (LSP 2).
(source: TRI102-ADD-102 Clinical Study Report, Figure 1, page 20)

The diagnosis of ADHD was established by using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) questionnaire at Screening. At Screening, subjects were also required to have an investigator-administered CGI-S score ≥3 and an ADHD Rating Scale (ADHD-RS) score ≥90th percentile for sex and age in at least one of the following categories:

i. Hyperactive-impulsive subscale
ii. Inattentive subscale
iii. Total score

Any patient receiving ADHD medication at screening were required to show signs of being inadequately managed on their current dose of stimulant treatment based on duration of action, safety, or tolerability. Female patients of childbearing potential were required to have a negative serum pregnancy test at screening.

Subjects were excluded if they had any non-ADHD psychiatric illness, clinically significant cognitive impairment, history of chronic medical illness, hepatitis B or C, HIV, and any recent (within 30 days) use of non-stimulant ADHD medications. Additional exclusion criteria relate to health status, laboratory assessments, and concomitant medications.

After Screening (Week -4 to -1, Study Visit 1) and Baseline (Week 1, Visit 2) evaluations were completed, eligible patients took open-label TRI102 orally once daily and underwent dose optimization activities for five weeks. A dose of either 2.5mg/day or 5mg/day of TRI102 (based on Investigator's discretion) was initiated at the start of the open-label Dose Optimization Period (Weeks 3-5, Visits 3-6). Investigators could dose titrate in 2.5- or 5-mg/day increments during the first 2 weeks of the open-label period and 5- to 10-mg/day weekly increments for the rest of the Dose Optimization Period until an optimal dose or the maximum dose of 20 mg/day was reached. Dose titrations occured at the Investigator's discretion at each visit during the open-label period to achieve

efficacy and tolerability based on assessments of the patient's ADHD signs and symptoms and observations of drug-induced side effects.

Patients who achieved a stable dose on TRI102 for at least one week prior to the end of the open-label period were eligible for continued participation in the study and were then randomized to take double-blind study drug (TRI102 or placebo) orally once daily for one week. Subjects were eligible for randomization at Study Visit 7 if they met the following criteria:

- Stable dose of open-label TRI102 (defined as no change in dose between Study Visits 6 and 7)
- Optimal dose of TRI102 at Study Visit 7 in the judgment of the Investigator
- No change in medical condition that precludes administration of blinded study drug
- Complete the pre-dose and post-dose laboratory classroom assessments during Visit 7

The Randomized, Double-blind, Placebo-controlled Treatment Period encompassed Week 6, Visits 7-8. Study Visit 7 was an abbreviated practice analog school day lasting approximately 6 hours. Efficacy assessments occurred during the practice laboratory school day. Assessments for ADHD symptoms and behaviors were measured by SKAMP and PERMP in an abbreviated analog classroom at each clinical site. Pre-dose assessments were performed prior to the morning study drug dose on the day of the visit. After the pre-dose classroom assessments were completed, patients received their final dose of open-label study drug in the clinic and then completed the post-dose assessments. Two blood draws were included for each patient, one pre-dose and one 4.5 hours ± 30 minutes post-dose, for PK analyses. Following the post-dose PK blood draw, patients were randomized in a 1:1 ratio (TRI102 or placebo) at the optimized dose orally once daily at home until the following visit (Visit 8).

At the end of the double-blind Treatment Period, ADHD symptoms were evaluated in a laboratory classroom setting utilizing Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessments. A complete laboratory school day was performed at Study Visit 8, lasting approximately 14 hours. This visit included the last double-blind dose and the pre- and post-dose assessments. Visit 8 efficacy assessments include a laboratory school session at which ADHD symptoms and behaviors were measured by SKAMP and PERMP in a laboratory classroom setting. The final study visit assessments were also performed at this visit.

An in-person follow-up visit (Visit 9) occurred 7-14 days after Visit 8.

Study Assessments

The primary efficacy endpoint was the assessment of change from time 0 in model-adjusted SKAMP-Combined scores at 4 hours post-dose measured during the laboratory

school day (Visit 8). The SKAMP is a 13-item independent observer rating of subject impairment in classroom-observed behaviors.

Onset of clinical effect and duration of clinical effect were key secondary measures, determined by change from time 0 in SKAMP-Combined scores at 1, 2, 6, 8, 10, 12, and 13 hours post-dose during the laboratory school day (Visit 8). The fixed-sequence testing procedure was pre-specified in the following order: 4, 6, 8, 2, 10, 12, 13, then 1 hour post-dose. Based on the pre-specified testing procedure, testing for the onset and duration of efficacy (clinical effect) of TRI102 vs. placebo on the SKAMP-Combined scores was not allowed unless the primary efficacy was achieved.

Additional efficacy endpoints include change from time 0 to 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose in SKAMP-Attention and -Deportment scores and PERMP scores, each assessed during the laboratory school day (Visit 8). The Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS), and Conners' Parent Rating Scale (CPRS) were assessed at Visits 3, 4, 5, 6, and 7.

Safety assessments include incidence and severity of adverse events, Columbia Suicide Severity Rating Scale (C-SSRS), physical examinations, vital signs, height and/or weight assessments, 12-lead electrocardiogram (ECG), and clinical laboratory tests. A complete listing of study procedures is provided in Table 2, below.

Table 2: Schedule of Assessments

Study Visit (SV)	1	2	3	4	5	6	7	8	9	Early Termination
Visit Name	SCR WK -4 to -1	BL Wk 1	OL Wk 2	OL Wk 3	OL Wk 4	OL Wk 5	1st LSP Wk 6	2nd LSP Wk 7	FU WK 8 to 9	
Study Day	-28 to - 1	1	8 ±2 days	15 ±2 days	22 ±2 days	29 ±2 days	36 ±2 days	7 days post-SV7	7 to 14 days post-SV8	
Parent/Guardian IC	X									
Pediatric Subject Assent	X									
Eligibility Assessment	X	X					X			
Prev Medications Hx	X									
Medical History	X									
Demographics	X									
DSM-IV Diagnosis	X									
K-SADS	X									
ADHD-RS	X	X	X	X	X	X	X			
CPRS	X	X	X	X	X	X	X			
Cognitive Functioning	X [a]									
CGI-S	X	X	X	X	X	X	X			
CGI-I			X	X	X	X	X			
PK Sampling							X [b]			
Vital Signs	X [c]	X	X	X	X	X	X	X	X	X
12-lead ECG	X								X	X
PERMP Math Pre-test	X [l]	X [l]								
Physical Exam	X								X	X
Height / Weight [d]	X	X							X	X
Hematology CBC	X								X	X
Serum Chemistry	X								X	X
Pregnancy Test [e]	X [f]	X [f]							X [f]	X [f]
Prohibited Drugs Test	X									
C-SSRS [j]		X	X	X	X	X	X	X	X	X
PERMP [g]							X	X		
SKAMP [g]							X	X		
IWRS Entry		X					X			
Dispense OL TRI102		X	X	X	X	X				
Dose Titration Allowed		X	X	X	X	X				
Last OL Dose							X [h]			
DB Randomization							X			
Dispense DB Drug							X	X [k]		
Last DB Dose								X [h]		
Drug Accountability			X	X	X	X	X	X		X
Adverse Events [i]		X	X	X	X	X	X	X	X	X
Concom. Med	X	X	X	X	X	X	X	X	X	X

ADHD = attention deficit hyperactivity disorder; ADHD-RS = ADHD-Rating Scale; CBC = complete blood count; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; Concom. Med. = concomitant medications; CPRS = Conners' Parent Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FU = follow-up; ECG = electrocardiogram; Hx = history; IC = informed consent; IWRS = Interactive Web Response System; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; LD = last dose; LSP = laboratory school protocol study day; OL = open-label; PERMP = Permanent Product Measure of Performance; PK = pharmacokinetic; Prev. = previous; SCR = Screening; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale; SV = Study Visit.

a. When cognitive functioning level was not clear by clinical signs and symptoms, a Wechsler Abbreviated Scale of Intelligence (WASI) was administered to estimate IQ.
b. Pharmacokinetic (PK) sampling occurred pre-dose and 4.5 hours ±30 minutes post-dose on the abbreviated practice laboratory school day (Visit 7).
c. At Screening, vital signs included respiratory rate and temperature.
d. Height measurement was required only at Screening.
e. Females of child bearing potential only.
f. Serum pregnancy tests were performed at Screening; urine dipstick pregnancy tests were performed at Baseline (Visit 2). Pregnancy testing also occurred in the event of a suspected pregnancy.
g. Assessments occurred pre-dose and 1 and 2 hours post-dose at the abbreviated practice laboratory school day (Visit 7); assessments occurred pre-dose and 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose at the complete laboratory school day (Visit 8).
h. Was dosed in clinic.
i. Adverse events were followed until resolution or 30 days after last visit.
j. Different versions of the C-SSRS were used at Baseline and subsequent visits (Since Last Visit).
k. When the drug was dispensed at this visit, it remained at the site and was not sent home with the subject.
l. The PERMP Math Test was performed at Baseline or at Screening (only applicable at Screening for subjects who did not require washout of prior ADHD medications).

(source: TRI102-ADD-102 Clinical Study Report, Table 3, pages 21-22)

Study Results

A total of 108 pediatric patients with ADHD ages 6 to 12 years old enrolled in this study, 100 patients were randomized (52 to TRI102, 48 placebo), and 99 patients (51 TRI102, 48 placebo) completed the study. One patient in the TRI102 group discontinued due to "other" reason. The sponsor discontinued 4 patients from a study site that only enrolled 4 patients total. Although not specified in the protocol, the sponsor noted that a classroom cohort should not have less than 10 subjects. Based on this guidance, the 4 enrolled subjects at Site 3 were discontinued before the double-blind Treatment Period, and accordingly were only included in the Enrolled Safety population and related safety analyses.

The study was conducted at five sites in the United States. The sponsor's efficacy data was reviewed in detail by Semhar Ogbagaber, Ph.D., and Eiji Ishida, M.S., in their review dated September 10, 2015.

The sponsor defines the intent-to-treat (ITT) analysis set as all randomized subjects who took at least one dose of study medication and had at least one post-baseline efficacy assessment. The sponsor also defined a Clinically Evaluable population which was defined as all ITT subjects who had no major protocol deviations and include the following:

- Received the morning dose of double-blind study drug, as determined during the Dose Optimization Period, at the practice laboratory school day;
- Completed all laboratory classroom assessments (Visit 7 and Visit 8);
- Did not miss more than 2 days of therapy during the double-blind Treatment Period; and
- Did not use prohibited medication during the double-blind Treatment Period.

The Clinically Evaluable population differs from the ITT population by only one subject; the primary and key secondary efficacy analyses were performed on the ITT population.

Baseline patient demographics and clinical characteristics are outlined in Table 3, below.

Table 3: Patient Demographics, TRI102-ADD-001

	Placebo (N=48)	TRI102 (N=51)	Total (N=99)
Gender n (%)			
Male	22 (66.7)	36 (70.6)	68 (68.7)
Female	16 (33.3)	15 (29.4)	31 (31.3)
Age (years)			
Mean (SD)	9.6 (1.76)	9.2 (1.95)	9.4 (1.86)
Age Categories n (%)			
6 - 7 Years	8 (16.7)	13 (25.5)	21 (21.2)
8 - 10 years	24 (50.0)	22 (43.1)	46 (46.5)
11 - 21 Years	16 (33.3)	16 (31.4)	32 (32.3)
Race n (%)			
White	28 (58.3)	27 (52.9)	55 (55.6)
Black/African American	15 (31.3)	19 (37.3)	24 (34.3)
Other	5 (10.4)	5 (9.8)	10 (10.1)
Ethnicity n (%)			
Hispanic/Latino	21 (43.8)	18 (35.3)	39 (39.4)
Non-Hispanic/Latino	27 (56.3)	33 (64.7)	60 (60.6)
ADHD Type n (%)			
Predominantly Inattentive	8 (16.7)	12 (23.5)	20 (20.2)
Predominantly Hyperactive-Impulsive	1 (2.1)	0	1 (1.0)
Combined	39 (81.2)	39 (76.5)	78 (78.8)

N=# of randomized patients

Note: At three of the 5 sites, subjects were randomized according to the *a priori* randomization schedules intended for a different site.

(source: Statistical Review; extracted from TRI102-ADD-102 Clinical Study Report, Table 14.1.3, page 89)

The sponsor's results of the primary efficacy analysis are shown in Table 4, below. The statistical reviewer repeated the efficacy analysis using a mixed effect model for repeated measures (MMRM) method with an unstructured covariance matrix. The LS mean estimates and standard error estimates in his analyses were only slightly different from the sponsor's and do not alter the sponsor's conclusion on the primary efficacy of the new treatment.

Table 4: Primary Efficacy Analysis for SKAMP-Combined Score at 4 Hours Post-Dose

Sponsor Analysis results for Primary efficacy endpoint	Statistics	Treatment Group		Treatment difference
		Placebo	TRI102	TRI102-Placebo
Change from Predose in SKAMP-Combined score (4 hours post-dose)	N	48	51	
	Mean (SD)	5.6 (7.85)	-9.1 (7.51)	-14.7 (7.68)
	LS Mean (SE)	6.0 (1.19)	-8.8 (1.14)	-14.8 (1.61)
	95% CI	(3.6, 8.3)	(-11.1, -6.6)	(-17.9, -11.6)
	Unadjusted P-value			<0.0001

N=number of randomized patients; SD=standard deviation; SE=standard error; CI=confidence interval; LS Mean=least square mean

The estimates were based on the sponsor's analysis model, an MMRM with random subject effect.

(source: Statistical Review; extracted from TRI102-ADD-102 Clinical Study Report, Table 14.2.1, page 133)

Results of the key secondary efficacy analyses are shown in Table 5, below.

Table 5: Key Secondary Efficacy Analysis for SKAMP-Combined Score, All Time Points

Time (post-dose hours)	Efficacy analysis results from Sponsor' analysis model: Change from Predose in SKAMP-Combined score			
	LS Mean (SE)		Difference in LS Mean (SE)	
	Placebo (n=48)	TRI102 (n=51)	TRI102-Placebo	Unadjusted P-value
1	3.4 (1.19)	-6.8 (1.14)	-10.2 (1.61)	<.0001
2	6.9 (1.19)	-8.5 (1.14)	-15.3 (1.61)	<.0001
4	6.0 (1.19)	-8.8 (1.14)	-14.8 (1.61)	<.0001
6	6.1 (1.19)	-8.7 (1.14)	-14.8 (1.61)	<.0001
8	4.2 (1.19)	-6.5 (1.14)	-10.7 (1.61)	<.0001
10	5.1 (1.19)	-5.7 (1.14)	-10.8 (1.61)	<.0001
12	7.0 (1.19)	-3.8 (1.14)	-10.8 (1.61)	<.0001
13	6.1 (1.19)	-3.1 (1.14)	-9.2 (1.61)	<.0001

N=# of randomized patients who completed; LS Mean=least squares mean; SE=standard error

Treatment comparisons for change from pre-dose scores are assessed using a mixed model repeated measures analysis, with treatment (TRI102/Placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect.

Note: At 3 study sites, subjects were randomized according to the *a priori* randomization schedules intended for a different site. Treatment comparisons for change from pre-dose scores are assessed using a mixed model repeated measures analysis, with treatment (TRI102/Placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect. There was only 1 subject who dropped out and the primary efficacy analysis was not affected significantly.

(source: Statistical Review; extracted from TRI102-ADD-102 Clinical Study Report, Table 14.2.1, page 133)

The sponsor also conducted subgroup analyses for gender, race, age, ADHD subtype, and study site. These results were consistent with the overall study results; however, given the small sample size, one cannot draw any meaningful conclusions about possible subgroup differences from these data.

VI. Review of Safety Data

Given the extensive safety experience to date with amphetamine; the relatively brief duration of the bioavailability, PK, and clinical studies; and the subject samples for these

studies (the bioavailability study was conducted in healthy adult volunteers), the conducted studies are not capable of producing meaningful new safety data that could be extrapolated to the clinical use of Dyanavel. There were no deaths, non-fatal serious adverse events, and no adverse events that led to premature discontinuation from the study in any of the studies listed in Table 1. There were no new, unlabeled safety signals identified in the AE reports, physical exam, vital signs, ECGs, or other safety measures. During both the open-label and double-blind Treatment Periods, no subjects reported any occurrences or types of suicidal ideations or behaviors on the C-SSRS.

TRI102-ADD-001

Adverse events were classified using Version 16.1 of the MedDRA coding dictionary.

During the open-label Treatment Period, 64 subjects (59.8%) reported at least one treatment-emergent adverse event (TEAE), most of which were classified as "mild" in intensity. The most frequently occurring TEAEs by system organ class (SOC) term were psychiatric disorders (33 subjects [30.8%]); metabolism and nutrition disorders (28 [26.2%]); gastrointestinal disorders (21 [19.6%]); injury, poisoning, and procedural complications (10 [9.3%]); nervous system disorders (10 [9.3%]); infections and infestations (8 [7.5%]); general disorders and administration site conditions (6 [5.6%]); and respiratory, thoracic, and mediastinal disorders (6 [5.6%]). All other SOC terms occurred in <5% of subjects.

Fifty-one subjects (47.7%) had at least one treatment-related TEAE. The most frequently occurring treatment-related TEAEs by SOC term were psychiatric disorders (33 subjects [30.8%]), metabolism and nutrition disorders (28 [26.2%]), gastrointestinal disorders (14 [13.1%]), nervous system disorders (9 [8.4%]), and general disorders and administration site conditions (6 [5.6%]). All other SOC terms occurred in <5% of subjects.

During the double-blind Treatment Period, 15 subjects (6 placebo [12.5%], 9 TRI102 [17.3%]) reported at least one TEAE, most of which were classified as "mild" by the investigator. The most frequently occurring TEAE by SOC term was respiratory, thoracic, and mediastinal disorders (3 TRI102 subjects [5.8%]). No AE (preferred term or combined SOC) occurred in more than 2 subjects in either the TRI102 or placebo group, with the exception of respiratory, thoracic and mediastinal disorders (comprised of epistaxis and allergic rhinitis), which occurred in 3 subjects on TRI102 and no subjects on placebo.

The adverse events reported in the double-blind portion of TRI102-ADD-001 are listed in Table 6, below.

Table 6: Summary of Treatment-Emergent Adverse Events During Double Blind Phase—Randomized Safety Population

System Organ Class	Preferred Term	Placebo (N=48) n (%)	TRI102 (N=52) n (%)
Subjects with at least one treatment-emergent adverse event		6 (12.5)	9 (17.3)
Respiratory, thoracic, and mediastinal disorders		0	3 (5.8)
	Epistaxis	0	2 (3.8)
	Rhinitis allergic	0	2 (3.8)
Gastrointestinal disorders		2 (4.2)	2 (3.8)
	Abdominal pain upper	1 (2.1)	2 (3.8)
	Vomiting	1 (2.1)	1 (1.9)
Infections and infestations		2 (4.2)	1 (1.9)
	Gastroenteritis viral	1 (2.1)	1 (1.9)
	Upper respiratory tract infection	1 (2.1)	0
Metabolism and nutrition disorders		0	1 (1.9)
	Decreased appetite	0	1 (1.9)
Musculoskeletal and connective tissue disorders		0	1 (1.9)
	Musculoskeletal pain	0	1 (1.9)
Nervous system disorders		2 (4.2)	1 (1.9)
	Abdominal pain upper	1 (2.1)	1 (1.9)
	Vomiting	1 (2.1)	0
Psychiatric disorders		2 (4.2)	1 (1.9)
	Insomnia	1 (2.1)	1 (1.9)
	Initial insomnia	1 (2.1)	0
General disorders and administration site conditions		1 (2.1)	0
	Malaise	1 (2.1)	0
	Pyrexia	1 (2.1)	0
Injury, poisoning, and procedural complications		1 (2.1)	0
	Arthropod bite	1 (2.1)	0

(source: extracted from TRI102-ADD-102 Clinical Study Report, Table 21, pages 78-79)

VII. Pediatric Plan

This product was developed for use in a pediatric population. On March 26, 2014, the sponsor submitted an initial pediatric study plan (iPSP), outlining a plan to include clinical study data for pediatric patients aged 6 to 12 years in its 505(b)(2) application, and to extrapolate efficacy for pediatric patients aged 6 to 12 years to pediatric patients aged 13 to 17 years. The sponsor also requested a deferral for studies in children ages 4 to 5 years. Following feedback from FDA, the sponsor submitted the Agreed PSP on September 23, 2014.

VIII. OSI Inspection

The Division of Clinical Compliance Evaluation, Office of Scientific Investigations (OSI) was consulted on March 4, 2015, for inspection of Study TRI102-ADD-001. The following clinical sites were inspected:

Name of Clinical Investigator Location	Protocol Study Site Number of Subjects Enrolled (n)	Inspection Date
John Turnbow, M.D. Westex Clinical Investigations 3315 81st Street, Suite A, Lubbock, TX 79423	TRI102-ADD-001 Site #04 N = 34	05/18/2015 to 05/20/2015
Ann Childress, M.D. Center for Psychiatry and Behavioral Medicine, Inc. 7351 Prairie Falcon Road, Suites 150 and 160, Las Vegas, NV 89128	TRI102-ADD-001 Site #02 N = 30	04/10/2015 to 04/13/2015

In her review dated June 1, 2015, Jenn Sellers, M.D., Ph.D. noted that these clinical investigator sites were inspected in support of this NDA and no significant regulatory violations were noted, that the data submitted in support of the requested indication are acceptable, and that the studies appear to have been conducted adequately.

IX. Labeling Review

The sponsor intends to use the currently approved labeling language from Adderall IR tablets, with updates to reflect the Physicians' Labeling Rule (PLR) format, using other recently approved amphetamine products as reference for format only. The Division provided a number of minor editorial comments; more substantive changes are summarized below.

(b) (4)

(b) (4)

X. Conclusions and Recommendations

From a clinical perspective, I recommend approval. In addition to the post-marketing commitment recommended by the Quality team, there will be post-marketing requirements to conduct PK and efficacy studies in pediatric patients ages 4 to 5 years old.

[See appended electronic signature]
Tiffany R Farchione, MD
Medical Officer, DPP

cc: NDA #208147
HFD-130 (Div. File)
HFD-130/Farchione
/Mathis
/Grewal

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIFFANY R FARCHIONE
10/16/2015

MITCHELL V Mathis
10/19/2015