CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	208,147/ Original-1 (SDN-1)
Drug Name:	Amphetamine ER oral suspension
Indication:	ADHD
Applicant:	Tris Pharmaceuticals
Date(s):	December 19, 2014 (December 18, 2014)
Review Priority:	Standard
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Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The sponsor submitted a new drug application seeking approval to market Amphetamine ER oral suspension (TRI102) for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 to 12 years. In this application, the sponsor included a clinical study (Study TRI102-ADD-001) to support their efficacy claim of the new treatment: a phase 3, dose-optimized, randomized, double-blind, placebo-controlled, multicenter, laboratory classroom study. It was conducted at five US study sites based on one hundred randomized patients of Sites 1, 2, 4, and 5.This study did not generate efficacy data of Site 3, as the number of enrolled patients of Site 3 was only 4[1].

The SKAMP-Combined score is used as a measure to evaluate both primary and key secondary efficacy. The pre-specified efficacy endpoints were based on an improvement from pre-dose baseline to the respective time point of the double-blind day. The primary efficacy endpoint was the 4 hours post-dosing time point. The two key secondary efficacy objectives were to evaluate the onset and duration, respectively. The sponsor planned to assess efficacy at all post-dosing assessment hours: 1, 2, 4, 6, 8, 10, 12 and 13. The sponsor defined the key secondary efficacy for the onset time of clinical effect as the earliest efficacious time point among the post-dosing hours. The key secondary efficacy for duration of clinical effect was defined as the duration between the onset time point and the last efficacious time point up to which all the previous time points from the onset time point were efficacious.

Using a pre-specified multiple testing procedure that controls the study-wise type I error rate, the sponsor concludes that the primary and key secondary efficacy (onset time and duration) objectives were achieved. In the clinical study report (CSR), the sponsor stated that:

> *The primary efficacy analysis, change from pre-dose in the model-adjusted average of SKAMP-Combined scores at 4 hours post-dose in the ITT Population, showed a statistically significant treatment effect (p <0.0001). The key secondary efficacy analyses, the onset and duration of efficacy (clinical effect) of TRI102 vs. placebo using the change from pre-dose in SKAMP-Combined scores in the ITT Population, were also statistically significant for all time points analyzed (1, 2, 6, 8, 10, 12, and 13 hours post-dose during the laboratory school day [Visit 8]); therefore, the onset of TRI102 clinical efficacy was determined to be 1 hour post dose, and the duration of clinical efficacy was determined to be 12 hours*[2].

The statistical reviewers find that the sponsor's efficacy analyses for the primary and key secondary efficacy objectives are replicable. However, it should be noted that there were issues about the sponsor's study conduct and efficacy analysis method.

Patients of Sites 1, 2, and 5 were mistakenly randomized according to the *a priori* randomization schedules intended for Sites 2, 5, and 1, respectively. The treatment packages of these sites were delivered to the wrong sites. That is, patients of these sites were not given the

[1] See Section 3.2.3 of this review for more details.
[2] Section 11.2.7 (page 72 of the CSR)

treatment kit (the new drug or placebo) in accordance to the planned randomization schedule. As a consequence, about 20% of patients were randomized to an arm that they were not planned to be randomized to. The sponsor mentions this discrepancy in the CSR, but did not consult with the FDA to discuss this issue at any pre-NDA stage. The reviewers requested that the sponsor provide a justification for using the mistakenly randomized patients for the efficacy evaluation. Given the documentation the sponsor provided, the reviewers do not conclude that the actual randomization was problematic to the extent that the study conclusion has to be questioned. Furthermore, the reviewers confirmed the efficacy result remains the same if efficacy analysis is conducted for the original randomization plan. Thus the reviewers conceded the incorrect randomization of about 20 % of the randomized patients does not affect the efficacy conclusion.

Secondly, the reviewers object to the sponsor's primary analysis method for their efficacy claims, specifically the use of subject as random effect and uncorrelated within-subject errors in an application of the MMRM approach. This specification leads to a model equivalent to an MMRM model (with no random subject effect) when the within-subject covariance is assumed to be *compound symmetry*. In the MMRM model for the primary analysis, an unstructured covariance is typically used unless a parsimonious covariance structure is justified. The reviewers performed the primary and key secondary efficacy analyses (Table 6 and Table 7), using an unstructured covariance in their MMRM application, without a random subject effect. The reviewers found there were only small differences in efficacy estimates from the sponsor's analysis, such that the sponsor's overall conclusions on the three efficacy endpoints would not need to be altered.

2 INTRODUCTION

2.1 Overview

The sponsor submitted an efficacy study, TRI102-ADD-001, to demonstrate the efficacy of Amphetamine oral suspension Extended-Release (TRI102) for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 to 12 years.

Study TRI102-ADD-001 was a dose-optimized, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of dose-optimized TRI102. Informed consent and assent were obtained prior to performing any assessments. After screening and baseline evaluations were completed, eligible subjects enrolled in the study to take open-label TRI102 orally once daily for 5 weeks during the Dose Optimization Period, before being randomized to TRI102 or Placebo for the 1-week double-blind period. The efficacy assessment was planned to be conducted at post-dose hours of 1 through 13 for the Visit 8 day of the double-blind period.

Approximately 108 subjects were to be enrolled. One hundred patients were randomized to either the new drug or placebo, and ninety-nine subjects were included in the sponsor's efficacy evaluations. One patient was removed from the analysis set because this patient

discontinued. Five US study sites participated in the study, but the efficacy evaluation was performed on patients of Sites 1, 2, 4, and 5, since the number of enrolled patients of Site 3 was only four.

For primary and key secondary efficacy objectives, subjects were evaluated for ADHD symptoms in a laboratory classroom setting utilizing the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale.

2.2 Data Sources

The sponsor's submitted data and program listings are available in the following directory of the CDER' electronic document room (EDR):
\\Cdsesub1\evsprod\NDA208147\0000\m5\datasets\tri102-add-001\
An additional submission of data in raw/legacy format is located at:
\\Cdsesub1\evsprod\NDA208147\0005\m5\datasets\tri102-add-001\

With the originally submitted materials, the reviewers were unable to understand how patient ID was generated and matched to randomization ID and to the actually delivered treatment kit (See Section 3.1.2 of this review for more details). The sponsor submitted the requested documents at the following directory: \\Cdsesub1\evsprod\NDA208147\0014.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 Raw data (CRF data) and Analysis datasets for Efficacy evaluations

In a pre-NDA meeting held on November 6, 2014, the FDA requested information with the following comments[3]:

> *In your future NDA submission, please include the following information for the efficacy trial TR1102-ADD-001:*
> - *all raw as well as derived variables in .xpt format,*
> - *the SAS programs that produced all efficacy results,*
> - *the SAS programs by means of which the derived variables were produced from the raw variables, and*
> - *a full list of all relevant communications (e.g., IND/serial numbers and submission dates for all amendments).*

In the initial submission (Original-1; SDN-1; eCTD Number 0000), the sponsor did not include raw data and SAS programs they used to derive analysis variables from raw data variables. In responding to the reviewers' request communicated to the sponsor at the time of the filing review, the sponsor submitted the raw data and SAS programs in eCTD Number 0005 (SDN-6).

[3] DARRTS: Reference ID 3653843

The reviewers verified that the variables of an analysis dataset used for efficacy evaluation match those of raw data with no discrepancies[4].

3.1.2 Discrepancies between the original randomization schedule and the actual treatment assignments

The sponsor included a documentation of the planned randomization schedule and actual treatment assignments in the original NDA submission. This document and the CSR (Section 9.9) indicated that at three of the five study sites, treatment assignments were differently performed with regards to the planned randomization schedule. Twenty-one subjects of these three sites, that is, about 20% of the analysis set, were not given the treatment that was originally planned to be given. Patients of Sites 1, 2, and 5 were randomized according to the *a priori* randomization schedules intended for Sites 2, 5, and 1, respectively. Thus, the sponsor's efficacy analyses were based on "patients as treated". However, in the CSR, the primary and key secondary efficacy results are labeled as "ITT analysis". Moreover, the analysis dataset had the same treatment assignment records in both variables of planned treatment and actually administered treatment.

With the originally submitted materials, the reviewers were unable to understand how patient ID was generated and matched to randomization ID and to the actually delivered treatment kit. The reviewers requested that the sponsor provide (1) a documented verification on the matching of the four items for each patient: randomization ID, planned treatment assignment, patient ID and actually delivered treatment kit, and (2) a justification for use of the efficacy results in the label description of efficacy of the new treatment. The sponsor believes that the randomization is maintained in the efficacy data.

3.2 Evaluation of Efficacy

Study Objectives

The objective of the study was to establish an optimal dose of TRI102 that would result in a significant reduction in signs and symptoms of ADHD compared to placebo treatment in pediatric patients' ages 6-12 years with ADHD.

3.2.1 Study Design and Endpoints

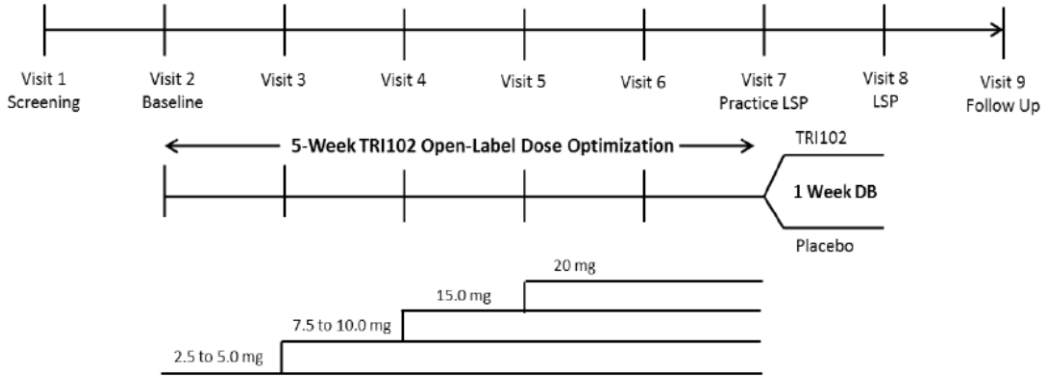
Study Design

Study TRI102-ADD-001 was a dose-optimized, randomized, double-blind, placebo-controlled, multi-site study to investigate the efficacy and safety of dose-optimized TRI102 in reducing signs and symptoms of ADHD compared with placebo in pediatric subjects ages 6 to 12 years with ADHD. This study was conducted at 5 investigational sites in the United States. Study visits were conducted at screening (Visit 1), baseline (Week 1; Visit 2), Weeks 2 to 6 (Visits 2 to 7; dose optimization), Week 6 (Visit 7; practice laboratory classroom session), and Weeks 6 and 7

[4] The only difference was due to missing items of one subject. This subject had two missing item scores at Hour 8, and the sponsor imputed these two scores according to the pre-specified algorithm.

(Visits 7 and 8; laboratory classroom sessions). The last visit of the double-blind period, Visit 8, was the study endpoint for efficacy evaluation. The study design is shown schematically in Figure 1.

Figure 1: Study design scheme



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: Figure 1 of Clinical Study Report (Page 20)]

The study consisted of:

- Screening (Visit 1): A 4-week (maximum) screening period;
- Baseline (Visit 2): Visit 2 was designated baseline. Eligible subjects for the study at Visit 2 would be enrolled and receive open-label (OL) TRI102 orally once daily for 5 weeks. Subjects began study medication at home in the morning following visit 2.
- Open-label Phase (Weeks 2-5, Visits 3 to 6): There were 5 weeks of OL treatment with TRI102 for dose optimization. Investigators could dose-titrate in 2.5- or 5- mg/day increments in the first 2 weeks and further adjustments in approximately weekly intervals (Visits 3, 4, 5, and 6) in 5- or 10-mg increments were allowed. A practice laboratory classroom day was held during Visit 7.
- Randomized, Double-blind, Placebo-controlled Treatment Period (Week 6, Visits 7-8): For each randomized subject a complete laboratory school day would be performed at Study Visit 8 and took approximately 14 hours. At Visit 7, efficacy assessments (SKAMP and PERMP scores) would be taken at practice laboratory school day which took roughly 6 hours. Visit 8 was when the last double-blind dose, pre- and post-dose assessments (SKAMP and PERMP) were administered.
- Follow-up Contact (Weeks 8-9): measurements were taken 7 to 14 days after Visit 8.

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. This subject population may be more appropriately labeled as Modified ITT (mITT) population. The sponsor's ITT Population was considered as the primary population.

The Clinically Evaluable population 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 1 subject and all primary efficacy analysis is performed on the ITT population.

Study Endpoints (Primary and Key secondary efficacy)

The endpoint of the efficacy assessment was Visit 8 (Complete Laboratory School Day). The sponsor defined the efficacy endpoints, in the final version of the protocol, as follows:

The primary efficacy outcome was a change from pre-dose (time immediately before study drug administration at Visit 8) in the SKAMP-Combined score[5] (a 13-item independent observer rating of subject impairment of classroom observed behaviors) at 4 hours post-dose.

Key secondary efficacy parameters were onset of clinical effect and duration of clinical effect[6]. The change scores from pre-dose SKAMP-Combined scores at post-dose time points (1, 2, 4, 6, 8, 10, 12 and 13 hours) during a laboratory school day (Visits 8) were used to evaluate the key secondary efficacy (onset time and duration). Specifically, as seen in the CSR, onset and duration are defined as follows:

- Onset of clinical effect, defined as the earliest post-dose time point at which the difference between the 2 treatments is statistically significant.

- Duration of clinical effect, defined as the difference between the onset time and the latest consecutive time point at which the difference between the 2 treatments is still statistically significant.

The definitions are found in the final version of the statistical analysis plan (Section 7.4.3 (page 29) of the SAP (Version 1.1), which is dated 30 May 2014. As the date of the last subject completed was September 18, 2014, we see that the key secondary efficacy was pre-specified before data unblinding.

Other secondary efficacy measures are listed below. They were measured at pre-dose and each post-dose (1, 2, 4, 6, 8, 10, 12 and 13 hours) time point during the test laboratory classroom day.

- SKAMP-Attention and SKAMP-Deportment scores;

[5] The SKAMP-Combined score is obtained by summing items 1-13, where each item is rated on a 7-point scale (0=normal to 6=maximal impairment).
[6] Page 17 of the study protocol (Version 3.0)

- PERMP scores.
- CGI-S, CGI-I, ADHD-RS, and CPRS scores at Visits 3, 4, 5, 6 and 7. CGI-S, ADHD-RS, and CPRS measurements began at screening (Visit 1); CGI-I began at Visit 3.

Sample size calculation

Assuming an effect size of 0.80 between TRI102 and placebo and approximately 68 subjects randomized to double-blind treatment, this study had 90% power at the level of 0.05 (2-sided) using a 2-sample t-test. To allow for an estimated 15% potential dropout rate during the open label titration period, this study planned to enroll approximately 80 subjects to ensure that at least 68 were randomized. Because subjects needed to be enrolled in cohorts to facilitate classroom visits, approximately 80 to 108 subjects were permitted to be enrolled in the study to accommodate a maximum allowable cohort size of 18 patients at up to 6 sites. The assumed effect size was based on differences measured between active and placebo in previous laboratory school studies conducted with similar drug formulations.

3.2.2 Statistical Methodologies

The following statistical methodologies were pre-specified in the sponsor's statistical analysis plan (SAP Version 1.1, dated 30 May 2014).

Efficacy analysis method (primary and key secondary efficacy)

In accordance with the study protocol, the primary analysis for the primary and key secondary efficacy was planned for the intention to treat (ITT) population. The sponsor's primary analysis method was an MMRM model, as pre-specified to include treatment (TRI102 or placebo), study center, time point and time point by treatment interaction as fixed effects, and subject intercept as random effect with a variance components covariance structure. All observed data was used for the primary analysis. No imputation of missing SKAMP-Combined score was performed in the primary analysis, but two missing item scores of one patient were imputed according to the pre-specified algorithm.

Testing procedure

The fixed-sequence testing procedure was pre-specified in the following order**: 4, 6, 8, 2, 10, 12, 13, then 1 hour** post-dose.

1. Primary efficacy: The null hypothesis was to be rejected if the statistical analysis resulted in a p-value of less than 0.05 for treatment at 4 hours post-dose at Visit 8. Least square (LS) means obtained in the primary analysis were used to conduct a treatment comparison of improvements from baseline in the SKAMP-Combined score at 4 hours post-dose of the Visit 8 day.
2. Key secondary efficacy: 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. The onset

and duration of efficacy was defined as follows:

- The onset time of efficacy action will be claimed at the earliest post-dose time point at which the difference between the two treatments is statistically significant ($p<0.05$).
- The duration of efficacy will be the difference between the onset time and the latest consecutive time point at which the difference between the two treatments is still statistically significant ($p<0.05$).

Reviewer's note: By definition, the duration of efficacy can only be tested when the onset time of efficacy is shown efficacious.

Exploratory Subgroup analysis

The primary efficacy analysis on the ITT Population was planned for the following subgroups as follows:

- Site;
- Age;
- Final optimized dose (10 mg, 15 mg, 20 mg);
- Gender;
- ADHD type (Inattentive, Hyperactive/Impulsive, Combined, not otherwise specified); and
- Baseline ADHD severity (defined as the pre-dose SKAMP- Combined score from the practice lab classroom day, categorized as above or equal to/below the median value for all subjects).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The sponsor reported in the CSR that in a total of 108 subjects who were enrolled in this study, one hundred patients were randomized to either TRI102 (52) or placebo (48). All 48 (100.0%) subjects in the placebo group completed the study, while 51 (98.1%) subjects in the TRI102 treatment group completed the study. One subject in the TRI102 group discontinued due to "other" reason. The sponsor discontinued 4 subjects, as shown in Table 1. According to the sponsor, *Site 3 enrolled only 4 subjects. While not specified in the protocol, ideally 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. (page 69 of CSR)*

Table 1: Subject Disposition

	Not Randomized (N=8) n (%)	**Placebo (N=48) n (%)**	**TRI102 (N=52) n (%)**	**Total (N=108) n (%)**
Randomized	-	48 (100.0)	52 (100.0)	100 (92.6)
Completed	-	48 (100.0)	51 (98.1)	99 (91.7)
Discontinued	8	0 (0.0)	1 (1.9)	9 (8.3)
Reasons for discontinuation				
Adverse event	0	0	0	0
Protocol violation	0	0	0	0

Non-compliance	0	0	0	0
Consent withdrawn	2	0	0	2
Lost to follow-up	1	0	0	1
Study Terminated by Sponsor	4	0	0	4
Physician Decision	0	0	0	0
Pregnancy	0	0	0	0
Death	0	0	0	0
Other	1	0	1	2

N=# of enrolled patients

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

[Source: Table 14.1.1 of Clinical Study Report (page 87)]

Table 2: Demographics

	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: Table 14.1.3 of Clinical Study Report (page 89)]

Mean predose SKAMP Composite score of each treatment group is shown below.

Table 3: Pre-dose SKAMP Composite score by Treatment Group

Treatment Group	**N**	**Mean**	**SD**	**Minimum**	**Maximum**
TRI102	51	17.3	8.88	5	37
PLACEBO	48	15.5	7.35	2	3

N=number of randomized patients; SD=standard deviation

3.2.4 Sponsor's Results and Conclusions

3.2.4.1 Sponsor's results for Primary Efficacy

The reviewer replicated the sponsor's primary efficacy analysis in Table 4. The sponsor reported in the CSR that at 4 hours post-dose (primary efficacy endpoint), the TRI102 group was statistically significantly different (better) in the change score from baseline of the SKAMP-Combined score than the placebo group. The difference in LS mean estimate was -14.8. It is noted that the reviewers do not agree to the sponsor's primary analysis method. The details are given in Section 3.2.5.

Table 4: Sponsor's Primary Efficacy Analysis for SKAMP-Combined Scale 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: Table 14.2.1 of Clinical Study Report (page 133)]

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.

3.2.4.2 Sponsor's results for Key Secondary Efficacy

Statistical reviewers replicated the sponsor's analysis results for all time points: the 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dosing (see Table 4). These results were used to evaluate the primary, key secondary and other secondary efficacy endpoints. It is noted that the reviewers do not agree to the results shown in Table 5.

Following the pre-specified fixed sequence testing procedure, the treatment differences at all-time points in the order of 4, 6, 8, 2, 10, 12, 13, and 1 hour post-dose were found statistically significant. As shown in Table 5, the 1 hour post-dose was the earliest post-dose time point at which the difference between the two treatments is statistically significant (LS mean (SE): -10.2 (1.61), p <0.0001). The sponsor concluded that the 1 hour post-dose is the onset time of clinical effect. The latest consecutive time point at which the difference between the 2 treatments is still statistically significant was the 13 hours post-dose (treatment difference LS mean (SE): -9.2 (1.61), p <0.0001). The sponsor concluded that the duration of clinical efficacy was from the 1 hour post-dose to the 13 hour post-dose.

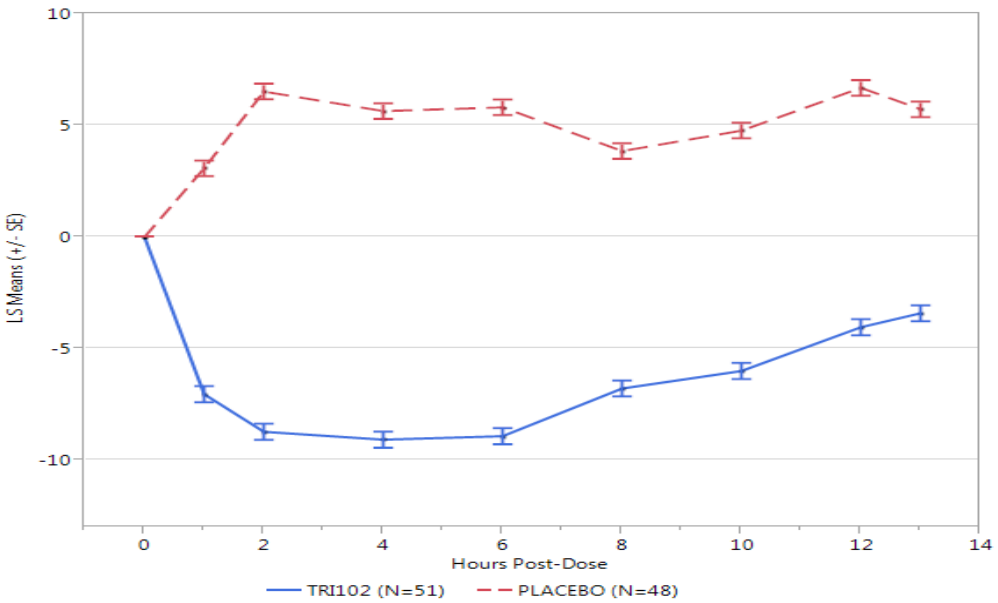
Table 5: Sponsor's Key Secondary Efficacy Analysis for SKAMP-Combined Scale (All time points)

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: Table 14.2.1 on Page 133 of Clinical Study Report]

The sponsor provided in the CSR a figure of plots of LS mean estimates in change score from predose obtained from their primary analysis. The reviewers reproduced the figure below. The observed efficacy estimates (LS mean estimates) show a trend that the TRI102 group was continually less and less efficacious after 6 hours till the end of the double-blind hours; the deteriorating trend was less apparent over time in the placebo group. Despite the observed declining effect of the new treatment towards the last hour (Hour 13), the key secondary efficacy analysis showed statistical significance at all time points. The magnitude of the observed improvement with TRI102 at the end of double-blind hours seems clinically relevant. The mean pre-scores for placebo and TRI102 were 15.5 and 17.3, respectively.

Figure 2: Change From Pre-dose in SKAMP-Combined Score Over Time by Treatment



N=# of randomized patients who completed; LS Mean=least squares mean; SE=standard error
The estimates were based on the sponsor's analysis model, an MMRM with random subject effect.
[Source: Reproduced Sponsor's figure (Figure 2: Change From Pre-dose SKAMP-Combined scores Over Time Treatment Group (page 54 of the CSR))]

3.2.4.3 Sponsor's results for Other Secondary Efficacy Endpoints

The efficacy results of the PERMP scores (the number of problems correct and the number of problems attempted) and the SKAMP subscale scores (Attention and Deportment) supported the primary and key secondary efficacy conclusions[7]. It is noted that each of the SKAMP subscale scores appear to have mimicked the time profile of the SKAMP Combined score.

3.2.4.4 Sponsor's Efficacy Conclusions

The sponsor stated in the CSR:

> *The primary efficacy analysis, change from pre-dose in the model-adjusted average of SKAMP-Combined scores at 4 hours post-dose in the ITT Population, showed a statistically significant treatment effect (p <0.0001). The key secondary efficacy analyses, the onset and duration of efficacy (clinical effect) of TRI102 vs. placebo using the change from pre-dose in SKAMP-Combined scores in the ITT Population, were also statistically significant for all time points analyzed (1, 2, 6, 8, 10, 12, and 13 hours post-dose during the laboratory school day [Visit 8]); therefore, the onset of TRI102 clinical efficacy was determined to be 1 hour post dose, and the duration of clinical efficacy was determined to be 12 hours*[8].

[7] Sections 11.2.1.2.3.1 and 11.2.1.2.3.2 (pages 56 and 58 of the CSR)
[8] Section 11.2.7 (page 72 of the CSR)

3.2.5 FDAs' Efficacy Evaluations

The reviewers do not agree to the analysis model that the sponsor used in the efficacy analyses, and conducted the primary analysis using the following specifications: The MMRM model contains fixed effects: treatment, study center, time point and treatment-by-time interaction with an unstructured covariance matrix used to formulate the within-subject variations. The MMRM is based on a restricted (residual) maximum likelihood (REML). The REML approach produces unbiased estimates of variance and covariance parameters. The Kenward-Roger approximation is used to estimate denominator degrees of freedom. There is no guarantee that a specification of any covariance structure is true. We recommend that an unstructured covariance be used for the MMRM-based primary analysis. As shown below, the estimated variance-covariance matrix obtained using an unstructured covariance structure appears to be very different from that of Compound Symmetry as was specified by the sponsor. This estimated variance-covariance matrix has heterogeneous variances over data points (hours) and the estimated covariance is far from uniform.

The estimated variance-covariance matrix for the repeated measures is as follows:

	Hour 1	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12	Hour 13
Hour 1	47.0139	37.3232	36.3251	28.5545	35.1246	34.5760	33.3014	20.0750
Hour 2	37.3232	59.2282	41.3438	37.4906	36.7816	39.1217	43.6861	33.4296
Hour 4	36.3251	41.3438	60.3551	46.7785	39.9790	44.6038	46.1558	33.3430
Hour 6	28.5545	37.4906	46.7785	58.3710	39.7527	46.5259	42.7271	36.3540
Hour 8	35.1246	36.7816	39.9790	39.7527	61.7524	46.0893	48.9548	44.0511
Hour 10	34.5760	39.1217	44.6038	46.5259	46.0893	69.2952	55.4518	48.1982
Hour 12	33.3014	43.6861	46.1558	42.7271	48.9548	55.4518	77.9341	53.0148
Hour 13	20.0750	33.4296	33.3430	36.3540	44.0511	48.1982	53.0148	76.0319

Table 6 shows the reviewers' efficacy analysis results of an application of an MMRM method with an unstructured covariance matrix. The LS mean estimates and standard error estimates are only slightly different from the sponsor's (Table 4). The reviewers' results do not alter the sponsor's conclusion on the primary efficacy of the new treatment.

Table 6: FDA's Primary Efficacy Analysis for SKAMP-Combined Scale at 4 Hours post-dose

Primary efficacy: FDA Analysis results		**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)	6.1 (1.16)	-8.7 (1.11)	-14.8 (1.56)
	95% CI	(3.8, 8.4)	(-10.9, -6.5)	(-17.9, -11.6)
	Unadjusted P-value			<0.0001

N=# of randomized patients who completed**;** SD=standard deviation; SE=standard error; CI=confidence interval

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

Table 7: FDA's Key Secondary Efficacy Analysis for SKAMP-Combined Scale (All time points)

Time (post-dose hours)	**FDA Reviewers' Efficacy analysis results:** 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	3.6 (1.03)	-6.7 (0.99)	-10.2 (1.38)	<.0001
2	7.0 (1.15)	-8.3 (1.10)	-15.3 (1.55)	<.0001
4	6.1 (1.16)	-8.7 (1.11)	-14.8 (1.56)	<.0001
6	6.3 (1.14)	-8.5 (1.09)	-14.8 (1.54)	<.0001
8	4.3 (1.17)	-6.4 (1.12)	-10.7 (1.58)	<.0001
10	5.2 (1.24)	-5.6 (1.19)	-10.9 (1.68)	<.0001
12	7.2 (1.31)	-3.7 (1.26)	-10.8 (1.78)	<.0001
13	6.2 (1.29)	-3.0 (1.24)	-9.2 (1.75)	<.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, with an unstructured covariance.
Note: At three of the 5 sites, subjects were randomized according to the a priori randomization schedules intended for a different site. There was only 1 subject who dropped out.

3.3 Evaluation of Safety

Safety evaluation was not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed their model-based exploratory subgroup analyses to assess the consistency of the treatment effect with the overall population analysis. The subgroups are based on baseline patient characteristics. The sponsor concluded in the CSR[9] that almost all of the SKAMP Combined score subgroup analyses were consistent with the overall ITT Population analysis. A few exceptions were observed, but the reviewers do not think these exceptions indicate something substantial.

Because of the exploratory nature of the subgroup analyses, in this section, the reviewers provide sample means of change scores from predose to the primary efficacy endpoint (Hour 4) in SKAMP Combined score for each treatment arm, and sample means and standard deviations of the treatment difference from placebo of the change scores from predose to the primary efficacy endpoint (Hour 4) in SKAMP Combined score. The same statistics are included for all

[9] Section 11.2.1.1 (page 52 of the CSR)

randomized patients. The subgroup effects examined here are gender, age group, race, ADHD type, and site as in the CSR. For other subgroup analysis results, the readers are referred to the study report.

It is noted that in all subgroups listed above, efficacy results at other time points look similar to those at Hour 4 time point.

In short, the reviewers think there is no substantial evidence suggesting any meaningful differences in the subgroups.

4.1 Gender, Race and Age group

Mean differences from placebo in SKAMP Combined score for Gender, Race and Age group are shown in Table 8. The trends appear consistent in great favor of TRI102 across subgroups.

Table 8: Subgroup Mean Change scores from predose in SKAMP Combined Score (Gender, Race and Age group)

Subgroup	Number of randomized patients	Change scores from Predose in SKAMP Combined score at 4 hours postdose		Difference from Placebo at 4 hours postdose	SD of Difference from Placebo at 4 hours postdose
		TRI102	Placebo		
All randomized patients	99	-9.1	5.6	-14.7	7.7
Gender					
Male	68	-10.2	6.1	-16.3	7.4
Female	31	-6.5	4.7	-11.1	8.1
Race					
White	55	-10.1	5.2	-15.4	7.8
Black	34	-7.8	3.5	-11.3	6.7
Other	7	-8.2	14.4	-22.6	8.1
Age					
6-7 years	21	-9.6	10.6	-20.2	10.5
8-10 years	46	-9.0	5.2	-14.1	7.0
11-12 years	32	-8.8	3.9	-12.7	6.4

SD: Standard Deviation
Note: At three of the 5 sites, subjects were randomized according to the a priori randomization schedules intended for a different site.
[Source: Pages 184, 191, 247, 256, 265 of the CSR]

4.2 Other Special/Subgroup Populations

Mean differences from placebo in SKAMP Combined score for ADHD type are shown in Table 9. The trends also appear consistent in great favor of TRI102 across subgroups. Somewhat large variations in mean differences from placebo are observed among the study sites, but all sites exhibit efficacious results. The reviewers confirmed the primary efficacy conclusion does not change when any single site is taken out from the analysis.

Table 9: Subgroup Mean Change scores from predose in SKAMP Combined Score (ADHD type and Study Site)

Subgroup	Number of randomized patients	Change scores from Predose in SKAMP Combined score at 4 hours postdose		Difference from Placebo at 4 hours postdose	SD of Difference from Placebo at 4 hours postdose
		TRI102	Placebo		
All randomized patients	99	-9.1	5.6	-14.7	7.7
ADHD type					
Inattentive	20	-9.7	3.5	-13.2	6.3
Combined	78	-8.9	6.0	-14.9	8.1
Site					
#1	28	-5.6	3.4	-9.0	6.1
#2	25	-13.0	8.3	-21.3	6.9
#4	34	-10.4	6.4	-16.8	8.8
#5	12	-5.6	3.2	-8.8	7.1

SD: Standard Deviation
Note: At three of the 5 sites, subjects were randomized according to the a priori randomization schedules intended for a different site. Site #3 was not included in the subgroup analysis since it enrolled only 4 subjects out of which 3 were discontinued before the double-blind treatment period.
[Source: Pages 199, 212 220, 227, 234, 241, 142, 149, 156, 164, 171, 178 of the CSR]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Patients of Sites 1, 2, and 5 were mistakenly randomized according to the *a priori* randomization schedules intended for Sites 2, 5, and 1, respectively. The treatment packages of these sites were delivered to the wrong sites. That is, patients of these sites were not given the treatment kit (the new drug or placebo) in accordance to the planned randomization schedule. As a consequence, about 20% of patients were randomized to an arm that they were not planned to be randomized to. The sponsor mentions this discrepancy in the CSR, but did not consult with the FDA to discuss this issue at any pre-NDA stage. The reviewers requested that the sponsor provide a justification for using the mistakenly randomized patients for the efficacy evaluation. Given the documentation the sponsor provided, the reviewers do not conclude that the actual randomization was problematic to the extent that the study conclusion has to be questioned. Furthermore, the reviewers confirmed the efficacy result remains the same if efficacy analysis is conducted for the original randomization plan. Thus the reviewers conceded the incorrect randomization of about 20 % of the randomized patients does not affect the efficacy conclusion.

Secondly, the reviewers consider the sponsor's primary analysis method inappropriate for their efficacy claims, specifically the use of subject as random effect and uncorrelated within-subject errors in an application of the MMRM approach. This specification leads to a model equivalent to an MMRM model (with no random subject effect) when the within-subject covariance is assumed to be *compound symmetry*. In the MMRM model for the primary analysis, an

unstructured covariance is typically used unless a parsimonious covariance structure is justified. The reviewers performed the primary and key secondary efficacy analyses (Table 6 and Table 7), using an unstructured covariance in their MMRM application, without a random subject effect. The reviewers found there were only small differences in efficacy estimates from the sponsor's analysis, such that the sponsor's overall conclusions on the three efficacy endpoints would not need to be altered.

5.2 Conclusions and Recommendations

The statistical results provide adequate evidence to support the claims proposed in the NDA. Using a pre-specified multiple testing procedure that controls the study-wise type I error rate, the sponsor concludes that the primary and key secondary efficacy (onset time and duration) objectives were achieved. The reviewers have no objection to the efficacy conclusion the sponsor has drawn from this single study.

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/s/

SEMHAR B OGBAGABER
09/02/2015

EIJI ISHIDA
09/02/2015

PEILING YANG
09/09/2015
I concur that this study has demonstrated efficacy.

HSIEN MING J HUNG
09/10/2015