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 - ADDENDUM

NDA/BLA #: NDA 205831

Drug Name: (b) (4) TM(Methylphenidate Hydrochloride Extended-Release Capsules) 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)

Indication(s): Attention Deficit Hyperactivity Disorder

Applicant: Rhodes Pharmaceuticals LP

Date(s): Submission data: June 18, 2014
PDUFA due date: April 18, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics I

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Project Manager: ShinYe Chang, Pharm. D.

Keywords: Clinical Study; NDA Review; ADHD.

Statistical Review Addendum

This addendum corrects the Table 3 in the statistical NDA review of NDA 205831. This table comes from the sponsor's clinical study report (CSR). We noted the errors in the table and asked the sponsor to submit a corrected version. The sponsor could not submit it in time. The corrected table is attached below.

Table 1: Demographics for Trial RP-BP-EF002

Demographic Characteristic	10 mg Biphentin (N=49)	15 mg Biphentin (N=44)	20 mg Biphentin (N=45)	40 mg Biphentin (N=45)	Placebo (N=47)	All (N=230)
Mean±SD Age (yrs)	10.5±2.89	10.2±3.08	11.1±3.51	11.2±2.49	10.9±3.05	10.8±3.02
Age Group, No. (%)						
6-8 yrs	13 (26.5)	17 (38.6)	13 (28.9)	6 (13.3)	11 (23.4)	60 (26.1)
9-11 yrs	16 (32.7)	11 (25.0)	12 (26.7)	17 (37.8)	20 (42.6)	76 (33.0)
12-14 yrs	15 (30.6)	12 (27.3)	9 (20.0)	19 (42.2)	8 (17.0)	63 (27.4)
15-18 yrs	5 (10.2)	4 (9.1)	11 (24.4)	3 (6.7)	8 (17.0)	31 (13.5)
Sex, No. (%)						
Male	30 (61.2)	30 (68.2)	31 (68.9)	33 (73.3)	30 (63.8)	154 (67.0)
Female	19 (38.8)	14 (31.8)	14 (31.1)	12 (26.7)	17 (36.2)	76 (33.0)
Race, No. (%)						
White	34 (69.4)	26 (59.1)	33 (73.3)	32 (71.1)	33 (70.2)	158 (68.7)
Black	13 (26.5)	11 (25.0)	9 (20.0)	11 (24.4)	9 (19.1)	53 (23.0)
Asian	0	2 (4.5)	0	0	1 (2.1)	3 (1.3)
American Indian or Alaska Native	0	0	0	1 (2.2)	1 (2.1)	2 (0.9)
Native Hawaiian or Other Pacific Islander	0	2 (4.5)	0	0	0	2 (0.9)
Other	2 (4.1)	3 (6.8)	3 (6.7)	1 (2.2)	3 (6.4)	12 (5.2)
Ethnicity, No. (%)						
Hispanic or Latino	4 (8.2)	8 (18.2)	7 (15.6)	4 (8.9)	3 (6.4)	26 (11.3)
Not Hispanic or Latino	45 (91.8)	36 (81.8)	38 (84.4)	41 (91.1)	44 (93.6)	204 (88.7)
Weight (kg)						
Mean±SD	43.83±19.5	44.59±21.7	45.75±20.6	48.84±18.7	40.46±14.4	44.64±19.1
Min, Max	20.5, 102.5	16.8, 125.5	18.5, 95.5	27.0, 114.5	21.6, 81.8	16.8, 125.5

Source: Sponsor's Table 11-2 in CSR.

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/s/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205831
Drug Name:	(b) (4) TM(Methylphenidate Hydrochloride Extended-Release Capsules) 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)
Indication(s):	Attention Deficit Hyperactivity Disorder
Applicant:	Rhodes Pharmaceuticals LP
Date(s):	Submission data: June 18, 2014 PDUFA due date: April 18, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jinglin Zhong, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. HM James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Cara Alfaro, M.D. Lucas Kempf, M.D.
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1 EXECUTIVE SUMMARY

This review describes statistical findings about the sponsor's study reports RP-BP-EF001 and RP-BP-EF002 supporting the request for approval of (b) (4) for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).

This review confirms sponsor's finding from RP-BP-EF001 that optimized-dose Biphentin (15 mg, 20 mg, 30 mg, or 40 mg) was statistically better than placebo as measured by Swanson, Kotkin, Agler, M-Flynn, Pelham Rating Scale (SKAMP) total scores in treating children with ADHD in laboratory school setting. The onset of the efficacy of Biphentin started at Hour 1 and continued through Hour 12. This review also confirms sponsor's finding from RP-BP-EF002 that Biphentin 20 mg and 40 mg were statistically better than placebo as measured by ADHD Rating Scale Fourth Version (ADHD-RS-IV) in treatment of ADHD in children and adolescents ages 6 to 18 years.

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2 INTRODUCTION

2.1 Overview

Rhodes Pharmaceuticals has developed a methylphenidate product, (b) (4) Methylphenidate Hydrochloride Extended-Release (ER) Capsules, which is intended to provide a stimulant for treatment of ADHD. These ER capsules are to be taken orally once daily in the morning.

This NDA submission includes two pivotal safety and efficacy studies in ADHD patients 6 years old and older.

Table 1: List of all studies included in analysis

Protocol Number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
RP-BP-EF001	Phase 3, double-blind, crossover, laboratory school setting, conducted at a single center in US	6 weeks total, 2 - 4 weeks open label dose optimization, 2 weeks double-blind randomized phase	30 days	Biphentin/ Placebo, 11 Placebo / Biphentin, 11	Children 6-12 years with ADHD
RP-BP-EF002	Phase 3, double-blind, parallel, 4 doses vs placebo, conducted at 16 sites in US	12 weeks total, 1 week double-blind phase, 11 week open-label phase	30 days	10 mg 49 15 mg 44 20 mg 45 40 mg 45 Placebo 47	Children and adolescents 6-18 years with ADHD

2.2 Data Sources

Electronic datasets and study reports are located at:

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\\cdsesub1\evsprod\NDA205831\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality is fine. The FDA statistical reviewer can reproduce the primary analysis dataset from the original data source. Final statistical analysis plans (SAP) were submitted prior to unblinding. For Trial RP-BP-EF001, when the SAP was written, it was presumed that all subjects in the ITT population would have completed the SKAMP questionnaire at all scheduled timepoints in the Double-Blind phase, i.e., it was presumed that the ITT population and the

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evaluable population both consisted of 22 subjects. However, after the blind was broken it was discovered that the evaluable population consisted of only 20 subjects, as one subject received placebo in both double-blind periods due to a packaging error, and one subject completed SKAMP at all timepoints in Period 1 (randomized to placebo) but did not complete SKAMP at any timepoint in Period 2 (randomized to Biphentin). Therefore, the ITT analysis listed in the statistical analysis plan had to be revised. The sponsor submitted both sets of analysis results based on the planned ITT and revised ITT.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Trial RP-BP-EF001

This was a randomized, double-blind, placebo-controlled, crossover design study comparing Biphentin to placebo in a laboratory school setting. The broad objective was to evaluate the time of onset, duration of efficacy, tolerability and safety of Biphentin (15, 20, 30, or 40 mg) in a double-blind manner in children ages 6 to 12 years diagnosed with ADHD. Doses for each child were optimized via titration in an open manner during a 2 - 4 weeks period prior to the double-blind assessment. At the beginning of the 2-week double-blind phase, patients were randomized in a ratio of 1:1 to their optimized Biphentin dose or placebo for a week then switch to the alternate treatment for a week without a washout period between treatments. At the end of each week double-blind treatment, subjects underwent specific assessments of attention and behavior and objective, individualized math tests at specific timepoints to evaluate the onset and duration effects of Biphentin.

The primary efficacy endpoint was the average of the on-treatment SKAMP Total Score (timepoints: 1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours) across a treatment assessment day during the Double-Blind phase. Biphentin was compared to placebo.

The key secondary endpoints included onset and duration of efficacy between Biphentin and placebo during the Double-Blind phase using the SKAMP Total Score at each post dose timepoint (1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0 hours). (b) (4) [redacted].

Reviewer's note: In an email from FDA to the sponsor dated 25 May 2012, FDA advised the sponsor that "To support any claim, you need to show persistent efficacy for a meaningful period, i.e., the effect needs to onset at some reasonable time after dosing and the duration needs to be at least 8 hours. No time points within the time course are allowed to lose statistical significance."

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Trial RP-BP-EF002

This was a parallel, randomized, double-blind, multicenter, placebo-controlled, forced dose, phase 3 study to evaluate the safety and efficacy of Biphentin in the treatment of ADHD in pediatric and adolescent patients aged 6 to 18 years. Subjects were randomized in a ratio of 1:1:1:1:1 to receive 10, 15, 20, or 40 mg Biphentin or placebo for 1 week. Subjects weighing 25 kg or less were not assigned to the 40 mg dose. Randomization was not stratified by weight. One person not associated with the study performed this screen at randomization for clinical supply assignment. Following the 1-week Double-Blind phase, doses were optimized via titration in an open-label manner and subjects continued receiving Biphentin for 11 weeks.

The primary efficacy endpoint was the change from baseline to the end of Week 1 in the clinician-rated ADHD-RS-IV Total score. There were no key secondary endpoints.

3.2.2 Statistical Methodologies

Trial RP-BP-EF001

The primary endpoint, the mean of the on-treatment SKAMP Total scores for Biphentin and placebo, were compared using a mixed-effects analysis of covariance (ANCOVA) using the evaluable population, with no imputation of missing values. The SAP assumed that a subject might have missing values for some items in the SKAMP questionnaire at some timepoints. In order to evaluate the effect of these missing items scores, the SAP stated that the primary analysis would be repeated with the ITT population and that a missing value for a particular SKAMP item at a particular time would be replaced by the value at the most recent post dose timepoint for which the item was not missing.

The key secondary endpoints included the onset and duration of efficacy between Biphentin and placebo during the Double-Blind phase using the SKAMP Total score at each post dose timepoint (1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0 hours). At each post dose timepoint, the SKAMP Total Score was compared between Biphentin and placebo using a mixed-effects ANCOVA using the evaluable population. The order of testing the timepoints was 3, 4.5, 6, 7.5, 2, 1, 9, 10.5, and 12 hr. The same sensitivity analysis for the Primary Analysis was also performed for the key Secondary endpoints. In addition, at the request of the FDA, the time course of SKAMP Total Score was analyzed with a repeated measures analysis of covariance. All post dose timepoints (Hour 1 to Hour 12) were included in a single repeated measures mixed effects analysis of covariance. The model contained fixed class effects for treatment, sequence, period, and timepoint; a random class effect for subject within sequence; and a covariate term, the SKAMP baseline Total Score from the corresponding subject/treatment/period. The repeated measures analysis was conducted for the evaluable population and for the ITT population.

When the SAP was written, it was presumed that all subjects in the ITT population would have completed the SKAMP questionnaire at all scheduled timepoints in the Double-Blind phase, i.e., it was presumed that the ITT population and the evaluable population both consisted of 22 subjects. However, after the blind was broken it was discovered that the evaluable population

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consisted of only 20 subjects, as one subject (1-01-01-401) received placebo in both double-blind periods due to a packaging error, and one subject (1-01-28-422) completed SKAMP at all timepoints in Period 1 (randomized to placebo) but did not complete SKAMP at any timepoint in Period 2 (randomized to Biphentin) due to illness. Therefore, the ITT analysis listed in the statistical analysis plan had to be revised.

Two methods were used for the ITT analyses for Subject 1-01-28-422 who did not complete a SKAMP at any timepoint at Visit 8. One method is that Visit 8 will be missing (no imputation). The second method is that the data at each timepoint at Visit 8 will be taken as equal to the data at the same timepoint at Visit 7 from the same subject. This subject was randomized to receive placebo in Period 1 and Biphentin in Period 2.

Two methods were used for Subject 1-01-01-401, who received placebo in both periods due to a packaging error. One method is to assign this subject to the planned treatments for the analyses (placebo at Visit 7 and Biphentin at Visit 8). The second method is to assign this subject to the actual treatment (placebo) for both Visits 7 and 8.

Each of the two methods for Subject 1-01-28-422 was used with each of the two methods for Subject 1-01-01-401. All four combinations ITT populations were analyzed.

Trial RP-BP-EF002

The primary endpoint is the change from baseline (Visit 2) to the end of Week 1 (Visit 3) in the Clinician-rated ADHD-RS-IV total score, comparing the 5 treatment groups (placebo, 10, 15, 20, and 40 mg/day Biphentin).

The primary analysis was the overall test for whether all treatments had the same mean. The key secondary analysis was an analysis comparing each Biphentin dose level to placebo. For both analyses, the ITT population (patients who receive at least 1 dose of study drug and have at least 1 ADHD-RS-IV assessment after administration of the study drug) was used. The ITT population is called efficacy population in sponsor's Clinical Study Report (CSR). The sensitivity analysis was performed repeating the primary analysis and the key secondary analysis using the safety population (randomized patients known to have taken at least one dose of study drug), with missing values imputed using the LOCF algorithm. The safety population is called ITT population in sponsor's CSR. For sites with less than 10 subjects, pseudo site 88 was used as planned in SAP.

Reviewer's Note: In an FDA advice letter dated 26 September 2012, FDA advised "Your primary analysis is on testing the overall treatment effect, and key secondary analyses are on individual doses compared with placebo. We remind you that a statistically significant finding from your primary analysis alone would not be sufficient to support an efficacy claim. You would need to demonstrate statistically significant findings from your key secondary analyses to pinpoint the effective dose(s)." The sponsor wrote in their response stamped on 9 October 2012 "We agree and acknowledge this comment."

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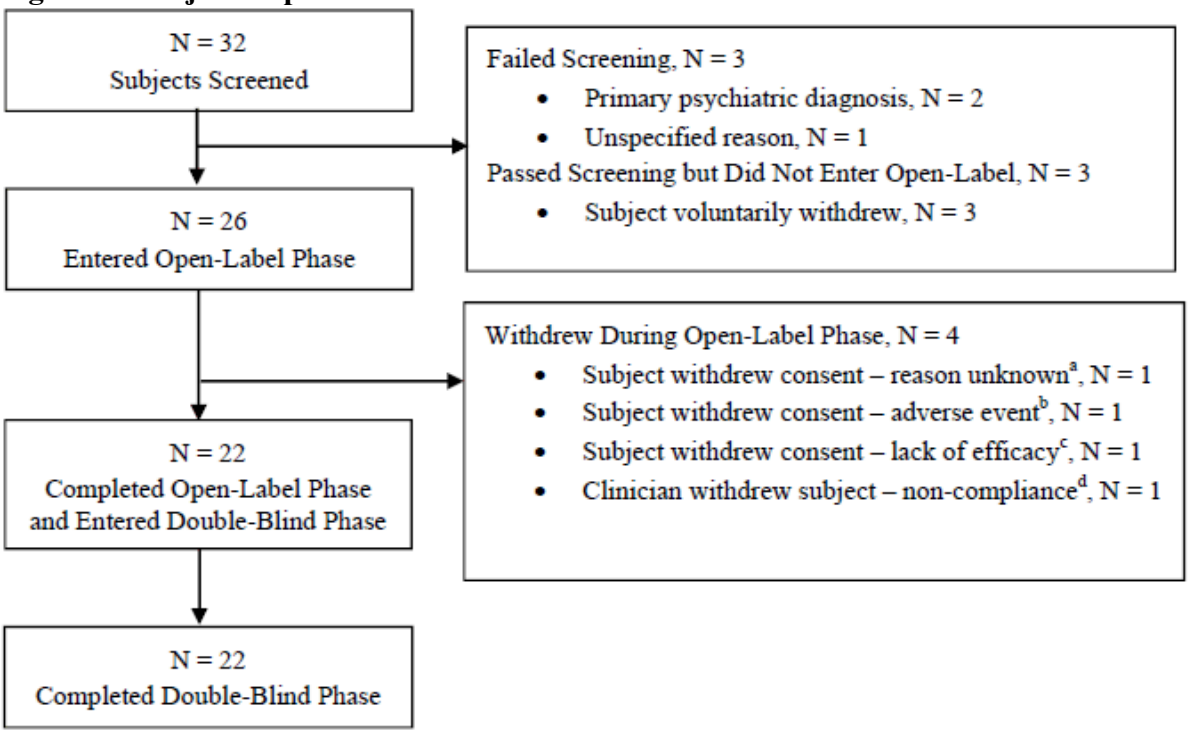
The change from Visit 2 (baseline) to Visit 3 was calculated as Visit 2 minus Visit 3 instead of Visit 3 minus Visit 2. The reason for this change was that, for all scales, a small number indicates fewer symptoms than a large number. Therefore, if there was improvement from Visit 2 to Visit 3, the value of Visit 2 minus Visit 3 was positive. This change did not affect the calculated p-values.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Trial RP-BP-EF001

The disposition of the subjects is summarized in Figure 1. The patient demographics are shown in Table 2 for the safety population and ITT population.

Figure 1: Subject disposition in Trial RP-BP-EF001



Source: Sponsor's Figure 10-1 in CSR.

The most important protocol deviations occurred in Subject 1-01-01-401 and Subject 1-01-28-422, and data from these 2 subjects were excluded from the evaluable population. Subject 1-01-01-401 was assigned placebo at Visit 7 and assigned Biphentin at Visit 8; however the subject mistakenly received placebo during both visits. Subject 1-01-28-422 was absent from the Visit 8 laboratory classroom session due to adverse events including rash and pyrexia that the investigator considered mild in severity and unrelated to study drug. As a result, the subject did not complete the SKAMP, PERMP, and ADHD-RS-IV evaluations at Visit 8.

The primary analysis set was the evaluable population. Twenty subjects comprised the evaluable population, defined as subjects who completed SKAMP assessments for all the study timepoints

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on study days 35 and 42 and who received the scheduled treatment in both periods during the double-blind phase. Twenty-two subjects comprised the ITT population, defined as subjects who took at least one dose of double-blind medication.

Table 2: Demographics for Trial RP-BP-EF001

Demographic Characteristic	Safety Population (N=26)	ITT Population Sequence 2 Biphentin/Placebo (N=11)	ITT Population Sequence 1 Placebo/Biphentin (N=11)	ITT Population (N=22)
Age (yrs),				
Mean±SD	8.7±1.89	8.7±1.95	8.9±1.92	8.8±1.89
Min, Max	6, 12	6, 12	6, 12	6, 12
Sex, No. (%)				
Male	14 (54%)	6 (55%)	6 (55%)	12 (55%)
Female	12 (46%)	5 (45%)	5 (45%)	10 (45%)
Race, No. (%)				
White	21 (81%)	9 (82%)	9 (82%)	18 (82%)
Black	3 (12%)	0 (0%)	2 (18%)	2 (9%)
Asian	1 (4%)	1 (9%)	0 (0%)	1 (5%)
Other	1 (4%)	1 (9%)	0 (0%)	1 (5%)
Ethnicity, No. (%)				
Hispanic or Latino	6 (23%)	2 (18%)	3 (27%)	5 (23%)
Not Hispanic or Latino	20 (77%)	9 (82%)	8 (73%)	17 (77%)
Weight (kg)				
Mean±SD	33.7±12.01	30.7±8.86	37.9±15.12	34.3±12.63
Min, Max	19.8, 70.8	19.8, 48.8	24.4, 70.8	19.8, 70.8
Height (cm)				
Mean±SD	135.9±12.76	133.4±11.20	139.2±13.66	136.3±12.54
Min, Max	114.0, 159.5	117.5, 153.8	121.10, 159.5	117.5, 159.5

Source: Sponsor's Table 11-2 in CSR.

Trial RP-BP-EF002

The disposition of the subjects is summarized in Figure 2. The patient demographics are shown in Table 3 for the safety population. We notice lower percentage of 6 – 8 year old in the 40 mg arm. This is due to the restriction that subjects weighing 25 kg or less were not assigned to the 40 mg dose.

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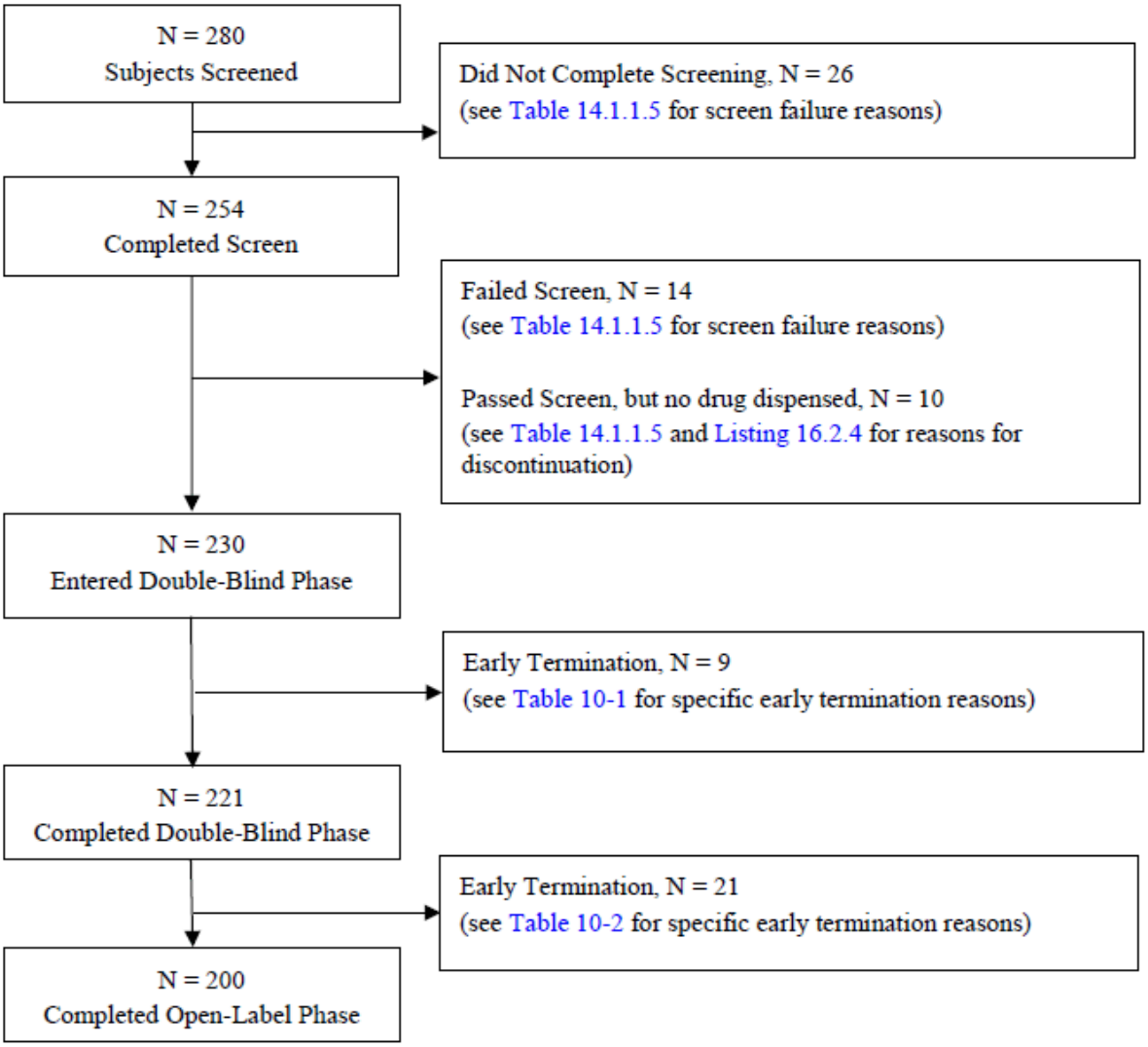
Figure 2: Subject disposition in Trial RP-BP-EF002



Source: Sponsor's Figure 10-1 in CSR.

Safety population (named ITT population in sponsor's CSR) included all 230 randomized who took at least one dose of study drug. The primary analysis set was the ITT population. Two-hundred twenty-one patients comprised the ITT population, defined as randomized patients who receive at least 1 dose of study drug and have at least 1 ADHD-RS-IV assessment after administration of the study drug. Because there is only 1 post treatment assessment on Day 7, the ITT population is equivalent to the efficacy population the sponsor used in CSR, which is defined as patients who completed the ADHD-RS-IV assessments on Day 0 and Day 7. The 9 patients who were randomized but did not complete assessment on Day 7 are:

- Randomized to 10 mg Biphentin
    - 2-11-08-264: Lost to follow-up (Moved and did not return to clinic.)
- Randomized to 15 mg Biphentin
    - 2-03-30-231: Patient non-compliant (Refused to dose after 2 doses at Visit 2.)

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o 2-04-05-252: Patient voluntarily withdrew from the study at Visit 2 (Refused to continue medicinal treatment for ADHD).
o 2-06-17-318: Withdrew due to serious adverse event (adjustment disorders with mixed disturbance of emotion and conduct).
o 2-09-03-141: Lost to follow-up (Moved and did not return to clinic).

- Randomized to 20 mg Biphentin
  o 2-11-06-250: Patient voluntarily withdrew from the study with no reason given
- Randomized to 40 mg Biphentin
  o 2-03-09-131: Withdrew due to adverse event at Visit 2 (insomnia).
  o 2-09-12-228: Withdrew due to adverse Events (nausea, increased heart rate)
- Randomized to Placebo
  o 2-11-09-265: Patient voluntarily withdrew from the study with no reason given

Table 3: Demographics for Trial RP-BP-EF002

Demographic Characteristic	10 mg Biphentin (N=49)	15 mg Biphentin (N=44)	20 mg Biphentin (N=45)	40 mg Biphentin (N=45)	Placebo (N=47)	All (N=230)
Mean±SD Age (yrs)	10.5±2.89	10.2±3.08	11.1±3.51	11.2±2.49	10.9±3.05	10.8±3.02
Age Group, No. (%)						
6-8 yrs	13 (26.5)	17 (38.6)	13 (28.9)	6 (13.3)	11 (23.4)	60 (26.1)
9-11 yrs	16 (32.7)	11 (25.0)	12 (26.7)	17 (37.8)	20 (42.6)	76 (33.0)
12-14 yrs	15 (30.6)	12 (27.3)	9 (20.0)	19 (42.2)	8 (17.0)	63 (27.4)
15-18 yrs	5 (10.2)	4 (9.1)	11 (24.4)	3 (6.7)	8 (17.0)	31 (13.5)
Sex, No. (%)						
Male	30 (61.2)	30 (68.2)	31 (68.9)	33 (73.3)	30 (63.8)	54 (67.0)
Female	19 (38.8)	14 (31.8)	14 (31.1)	12 (26.7)	17 (36.2)	76 (33.0)
Race, No. (%)						
White	34 (69.4)	26 (59.1)	33 (73.3)	32 (71.1)	33 (70.2)	158 (68.7)
Black	13 (26.5)	11 (25.0)	9 (20.0)	11 (24.4)	9 (19.1)	53 (23.0)
Asian	0	2 (4.5)	0	0	1 (2.1)	3 (1.3)
American Indian or Alaska Native	0	0	0	1 (2.2)	1 (2.1)	2 (0.9)
Native Hawaiian or Other Pacific Islander	0	2 (4.5)	0	0	0	2 (0.9)
Other	2 (4.1)	3 (6.8)	3 (6.7)	1 (2.2)	3 (6.4)	12 (5.2)
Ethnicity, No. (%)						
Hispanic or Latino	4 (8.2)	8 (18.2)	7 (15.6)	4 (8.9)	3 (6.4)	26 (11.3)
Not Hispanic or Latino	45 (91.8)	36 (81.8)	38 (84.4)	41 (91.1)	44 (93.6)	204 (88.7)
Weight (kg)						
Mean±SD	43.83±19.5	44.59±21.7	45.75±20.6	48.84±18.7	40.46±14.4	44.64±19.1
Min, Max	20.5, 102.5	16.8, 125.5	18.5, 95.5	27.0, 114.5	21.6, 81.8	16.8, 125.5

Source: Sponsor's Table 11-2 in CSR.

3.2.4 Results and Conclusions

Trial RP-BP-EF001

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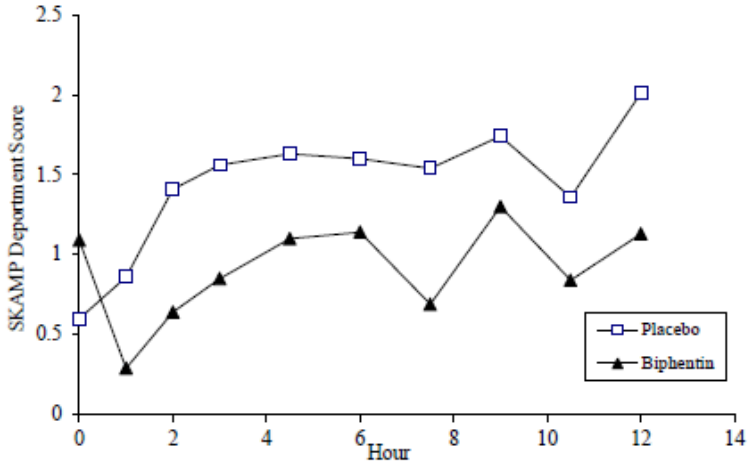
Figure 3 and Table 4 graphically and numerically summarize SKAMP total score. Lower SKAMP total scores indicate improvement. Figure 3 suggests that the largest effect occurred at Hour 1, then deteriorating over time.

Figure 3: Actual mean SKAMP total scores time course (evaluable population, N=20)



Source: Sponsor's Figure 11-2 in CSR.

Table 4: Descriptive statistics for SKAMP average overall post dose timepoints (evaluable population, N = 20)

Statistic	Sequence 1 Biphentin	Sequence 1 Placebo	Sequence 2 Biphentin	Sequence 2 Placebo	All Biphentin	All Placebo
N	9	9	11	11	20	20
Mean	1.64	2.34	1.31	1.77	1.46	2.03
Median	1.45	2.12	1.32	1.54	1.36	1.94
SD	0.64	1.06	0.35	0.74	0.52	0.92
Min	0.62	1.28	0.85	0.64	0.62	0.64
Max	2.71	4.87	1.92	3.06	2.71	4.87
Data Source: Table 14.2.2.1.1						

Source: Sponsor's Table 11-4 in CSR.
Note: Seq 1: Placebo/Biphentin; Seq 2: Biphentin/placebo.

The sponsor's results for the primary endpoints are shown in Table 5. The p-values for the evaluable population and four ITT populations are all less than 0.05. This reviewer repeated the analysis on the raw data and obtained the same results.

The sponsor's results for the key secondary endpoints (evaluable population) are shown in Table 6. The treatment differences are statistically significant at all timepoints. The results from three of the four ITT populations (ITT Versions 1, 2 and 3) are very similar to the results from the evaluable population, showing statistically significant differences at all timepoints. Therefore, those results are not shown in this report. Only the results from the ITT Version 4 (Table 7) are shown here. For this ITT population, Period 2 data from Subject 1-01-12-406, who received placebo during period 2 by mistake, was included and the actual treatment was used. Missing data was assigned to Period 2 Subject 1-01-28-422, who missed the Period 2 assessment due to

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illness. ITT Version 4 is the observed data from the ITT population. All the p-values are statistically significant at all the time points except Hour 9 (p = 0.0709).

Table 5: Primary efficacy endpoint analysis results for Trial RP-BP-EF001

	LS Mean		P-Values[a]			
Total Score	Placebo	Biphentin	Treatment	Covariate	Sequence[b]	Period[c]
Evaluable Population (N = 20)	2.18	1.32	0.0001	0.0003	0.5279	0.0714
ITT Version 1 (N = 22)	2.05	1.32	0.0005	0.0006	0.8824	0.2570
ITT Version 2 (N = 22)	2.06	1.33	0.0011	0.0005	0.8524	0.3168
ITT Version 3 (N = 22)	2.05	1.28	0.0002	0.0006	0.9955	0.1664
ITT Version 4 (N = 22)	2.05	1.29	0.0004	0.0008	0.9966	0.1912

[a] Mixed-effects ANCOVA, fixed terms for treatment, period, sequence; random term for subject within sequence, covariate term is predose value.

[b] Sequence 1 (placebo then Biphentin) vs Sequence 2 (Biphentin then placebo).

[c] Visit 7 (Period 1) vs Visit 8 (Period 2)

Source: Sponsor's Table 11-5 in CSR.

Table 6: SKAMP total scores time course (evaluable population, N = 20)

	LS Mean		P-Value[a]			
Hour	Placebo	Biphentin	Treatment	Covariate	Sequence[b]	Period[c]
1	1.41	0.76	0.0031	0.0005	0.8267	0.9069
2	1.90	1.01	0.0010	0.0014	0.9002	0.0356
3	2.25	1.29	0.0001	0.0026	0.0397	0.7808
4.5	2.29	1.33	0.0020	<0.0001	0.5980	0.1303
6	2.32	1.43	0.0021	0.0008	0.6386	0.0415
7.5	2.38	1.25	0.0010	0.0027	0.3266	0.0877
9	2.35	1.66	0.0261	0.0055	0.3966	0.1160
10.5	2.21	1.48	0.0235	0.0326	0.6984	0.4557
12	2.60	1.56	<0.0001	0.0020	0.7352	0.0412

[a] Mixed effects ANCOVA, fixed terms for treatment, period, sequence; random term for subject within sequence, covariate term is predose value.

[b] Sequence 1 (placebo then Biphentin) vs Sequence 2 (Biphentin then placebo).

[c] Period 1(Visit 7) vs Period 2 (Visit 8)

Source: Sponsor's Table 11-7 in CSR.

Table 7: SKAMP total scores time course (ITT Version 4, N = 22)

	LS Mean		P-Value[a]			
Hour	Placebo	Biphentin	Treatment	Covariate	Sequence[b]	Period[c]
1	1.37	0.75	0.0035	0.0004	0.6566	0.6821
2	1.79	1.01	0.0025	0.0015	0.7499	0.0859
3	2.09	1.28	0.0012	0.0045	0.2154	0.7220
4.5	2.13	1.32	0.0060	<0.0001	0.9993	0.2932
6	2.21	1.41	0.0033	0.0007	0.3613	0.0523
7.5	2.22	1.24	0.0028	0.0027	0.6597	0.1581
9	2.16	1.63	0.0709	0.0086	0.8061	0.2216
10.5	2.08	1.46	0.0397	0.0346	0.9900	0.6289
12	2.48	1.52	0.0003	0.0040	0.4437	0.1978

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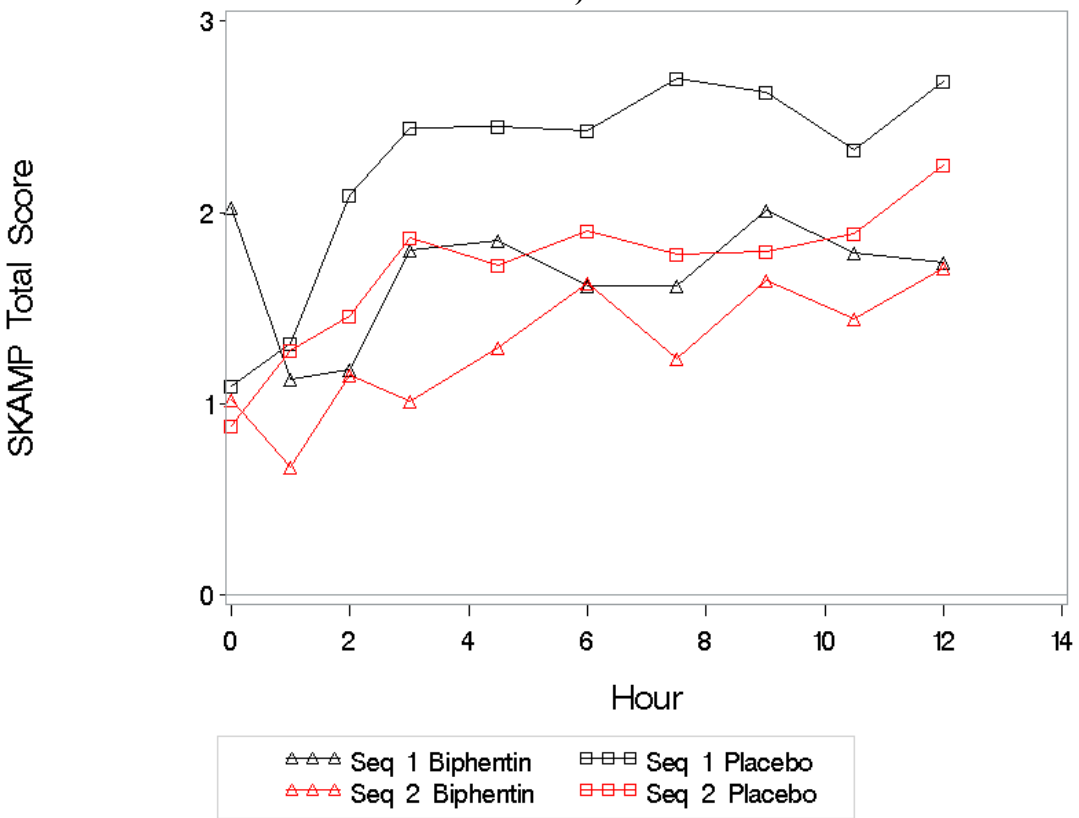
[a] Mixed effects ANCOVA, fixed terms for treatment, period, sequence; random term for subject within sequence, covariate term is predose value.
[b] Sequence 1 (placebo then Biphentin) vs Sequence 2 (Biphentin then placebo).
[c] Period 1 (Visit 7) vs Period 2 (Visit 8)

Source: Sponsor's Table 11-11 in CSR.

To investigate the possible sequence effect, this reviewer plotted the time course of SKAMP total scores by sequence in Figure 4. From Figure 4, we can see that the treatment differences (the distance between the two black lines and the distance between the two red lines) are pretty consistent over the time course for the two sequences. Biphentin are numerically superior to placebo in both treatment sequences, i.e., regardless of whether Biphentin or placebo is taken first.

Figure 4: Actual mean SKAMP total score time course by sequences (evaluable population, N = 20)



Source: This reviewer's figure.
Note: Seq 1: Placebo/Biphentin; Seq 2: Biphentin/placebo.

The sponsor also performed the sensitivity analysis using MMRM method at the request of FDA. The sponsor performed it on the evaluable population and all 4 ITT populations. In this reviewer's view, it seems that only analysis results on evaluable population and ITT Version 4 (Table 8 and Table 9) are relevant. Both analysis results show statistical significance at all timepoints.

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This reviewer repeated the analysis on the raw data and obtained the same results as in Tables 4 to 9.

Table 8: SKAMP total scores time course – repeated measures analysis (evaluable population, N = 20)

Hour	Placebo (LS Mean)	Biphentin (LS Mean)	Pairwise p-Value[a]
1	1.37	0.84	0.0079
2	1.82	1.12	0.0005
3	2.20	1.33	<0.0001
4.5	2.13	1.51	0.0020
6	2.21	1.58	0.0017
7.5	2.27	1.37	<0.0001
9	2.25	1.77	0.0170
10.5	2.16	1.56	0.0027
12	2.25	1.68	<0.0001

Source: Sponsor's Table 11-12 in CSR.

Table 9: SKAMP total scores time course – repeated measures analysis (ITT Version 4, N = 22)

Hour	Placebo (LS Mean)	Biphentin (LS Mean)	Pairwise p-Value[a]
1	1.31	0.75	0.0032
2	1.72	1.04	0.0003
3	2.06	1.24	<0.0001
4.5	1.99	1.42	0.0026
6	2.10	1.50	0.0015
7.5	2.13	1.28	<0.0001
9	2.08	1.68	0.0345
10.5	2.03	1.47	0.0030
12	2.41	1.59	<0.0001

Source: Sponsor's Table 11-16 in CSR.

This reviewer calculated the individual patient difference between Biphentin and placebo. The summary statistics by optimal dose groups are presented in Table 10.

Table 10: Summary statistics of individual treatment difference by optimal dose groups

		Biphentin-placebo	
Optimal Dose	N	Mean	Standard Deviation
20 mg	9	-0.53	0.55
30 mg	10	-0.63	0.73
40 mg	1	-0.41	NA

Source: This reviewer's results.
Note: Standard deviation is not available because N=1.

Trial RP-BP-EF002

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Two hundred thirty subjects were randomized. Nine of them early terminated. These nine subjects have baseline values but no post-baseline scores. A summary table of these nine subjects is presented in Table 11. Their dropout reasons were summarized in Section 3.2.3. The ITT population had 221 subjects.

Table 11: Summary of dropout patients

Subject Identifier	ADHD-RS-IV Baseline	Double Blind Dose (mg/tab)	Age	Sex	Race
2-03-09-131	40	40	9	Male	White
2-03-30-231	45	15	8	Male	Asian
2-04-05-252	16	15	15	Male	Black or African American
2-06-17-318	35	15	14	Female	White
2-09-03-141	53	15	9	Male	White
2-09-12-228	36	40	8	Male	Black or African American
2-11-06-250	49	20	7	Female	Black or African American
2-11-08-264	49	10	6	Male	Black or African American
2-11-09-265	42	Placebo	10	Male	Black or African American

Source: This reviewer.

Figure 5 and Table 12 summarize the primary endpoint, change from baseline to endpoint in ADHD-RS-IV total score, for each treatment arm. The overall test for whether all treatments had the same mean decrease is statistically significant (p = 0.0046). This primary analysis result indicates that there were differences among study treatments for the mean decrease. Then the key secondary analysis was performed. The key secondary analysis was pairwise comparison of each Biphentin dose level to placebo. The pairwise difference from placebo was statistically significant for the 20 mg (ANCOVA, Dunnett adjusted p = 0.0145) and 40 mg (ANCOVA, Dunnett adjusted p = 0.0011). Both primary analysis and the key secondary analysis were repeated on safety population as a sensitivity analysis. The results are very similar to the results from the ITT population. The overall test for treatment difference is statistically significant (p = 0.0078). The pairwise difference from placebo was statistically significant for the 20 mg (ANCOVA, Dunnett adjusted p = 0.0153) and 40 mg (ANCOVA, Dunnett adjusted p = 0.0021).

This reviewer repeated the analyses starting from raw data. The results are very similar. The conclusions are the same. This reviewer's analysis results with unadjusted 95% CI are presented in Table 13.

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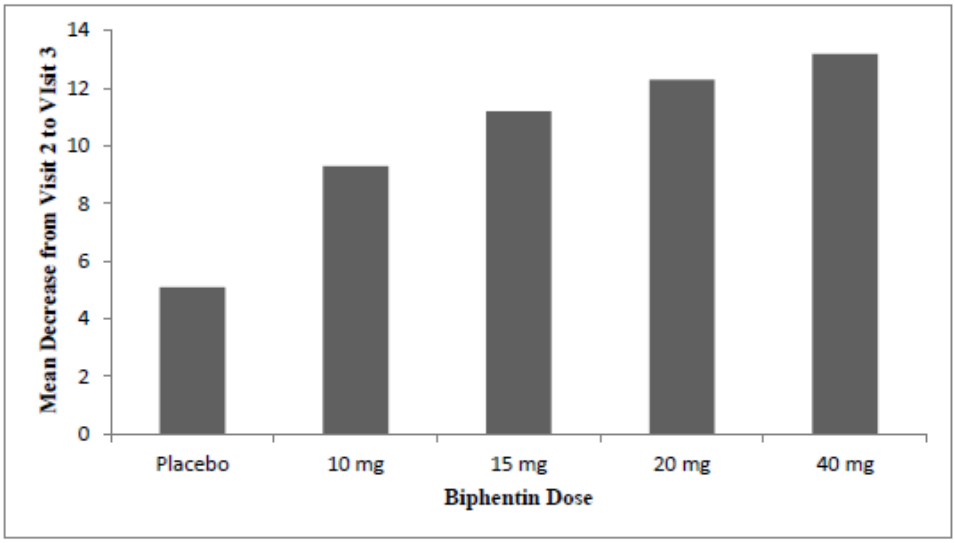
Figure 5: Mean decrease in ADHD-RS-IV total score from baseline to endpoint (ITT population, N=221)



Source: Sponsor's Figure 11-1 in CSR.

Table 12: Descriptive statistics for decrease in ADHD-RS-IV total score from baseline to endpoint (ITT population, N=221)

Statistic	Placebo	10 mg	15 mg	20 mg	40 mg
N	46	48	40	44	43
Mean	5.1	9.3	11.2	12.3	13.2
Median	2.0	8.0	8.0	12.0	13.0
Standard Deviation	10.29	8.86	12.06	9.84	10.29
Min	-22.0	-8.0	-4.0	-5.0	-3.0
Max	32.0	32.0	40.0	45.0	42.0

Source: Sponsor's Table 11-6 in CSR.

Table 13: Decrease from baseline to endpoint in ADHD-RS-IV total score comparing each Biphentin dose level to placebo (ITT population, N=221)

	Placebo	10 mg	15 mg	20 mg	40 mg
LS mean	5.4	9.1	10.3	11.4	13.0
Diff from Placebo		3.7	4.9	6.0	7.4
Unadjusted 95% CI		(-0.31, 7.66)	(0.63, 9.07)	(1.92, 10.02)	(3.38, 11.45)

Source: This reviewer's results.

A summary of the mean ADHD-RS-IV total scores by site is presented in Table 14. There appeared to be some baseline differences among sites in ADHD-RS-IV total score (ANOVA with terms for treatment and site, p = 0.0197).

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Table 14: Mean ADHD-RS-IV total scores by site during the double blind phase (ITT population, N = 221)

Site	Visit	Statistic	Placebo	10 mg	15 mg	20 mg	40 mg	All
All	All	N	46	48	40	44	43	221
	Baseline, Visit 2	Mean	33.4	37.6	38.0	36.2	35.6	36.1
	End Double Blind, Visit 3	Mean	28.3	28.3	26.7	23.9	22.3	26.0
	Decrease From Visit 2 to 3	Mean	5.1	9.3	11.2	12.3	13.2	10.1
1	All	N	5	7	5	8	2	27
	Baseline, Visit 2	Mean	26.6	38.4	41.2	32.8	31.5	34.6
	End Double Blind, Visit 3	Mean	23.4	18.7	24.4	23.8	12.5	21.7
	Decrease From Visit 2 to 3	Mean	3.2	19.7	16.8	9.0	19.0	12.9
3	All	N	6	7	12	5	7	37
	Baseline, Visit 2	Mean	36.7	40.0	30.8	36.8	30.4	34.2
	End Double Blind, Visit 3	Mean	31.2	33.1	25.3	23.0	19.6	26.3
	Decrease From Visit 2 to 3	Mean	5.5	6.9	5.6	13.8	10.9	7.9
6	All	N	1	4	2	1	3	11
	Baseline, Visit 2	Mean	30.0	37.0	39.0	29.0	37.0	36.0
	End Double Blind, Visit 3	Mean	16.0	30.8	34.0	13.0	26.7	27.3
	Decrease From Visit 2 to 3	Mean	14.0	6.3	5.0	16.0	10.3	8.7
7	All	N	5	3	2	4	5	19
	Baseline, Visit 2	Mean	28.2	38.0	49.0	30.3	34.2	33.9
	End Double Blind, Visit 3	Mean	20.2	25.7	19.0	22.3	20.6	21.5
	Decrease From Visit 2 to 3	Mean	8.0	12.3	30.0	8.0	13.6	12.5
9	All	N	3	3	5	4	5	20
	Baseline, Visit 2	Mean	40.0	41.3	41.4	38.8	34.8	39.0
	End Double Blind, Visit 3	Mean	21.7	23.7	24.4	18.0	17.4	20.9
	Decrease From Visit 2 to 3	Mean	18.3	17.7	17.0	20.8	17.4	18.2
12	All	N	2	5	2	5	3	17
	Baseline, Visit 2	Mean	41.0	40.4	40.5	40.4	45.0	41.3
	End Double Blind, Visit 3	Mean	30.5	30.4	35.5	28.4	40.7	32.2
	Decrease From Visit 2 to 3	Mean	10.5	10.0	5.0	12.0	4.3	9.1
15	All	N	2	2	1	3	2	10
	Baseline, Visit 2	Mean	44.5	42.5	41.0	40.7	37.5	41.2
	End Double Blind, Visit 3	Mean	37.0	31.0	36.0	24.3	31.0	30.7
	Decrease From Visit 2 to 3	Mean	7.5	11.5	5.0	16.3	6.5	10.5
16	All	N	14	6	4	7	8	39
	Baseline, Visit 2	Mean	32.8	36.0	34.3	38.6	36.4	35.2
	End Double Blind, Visit 3	Mean	28.6	26.8	27.8	28.1	14.3	25.2
	Decrease From Visit 2 to 3	Mean	4.1	9.2	6.5	10.4	22.1	10.0
18	All	N	4	5	2		2	13
	Baseline, Visit 2	Mean	26.3	30.2	42.5		31.5	31.1
	End Double Blind, Visit 3	Mean	31.5	28.6	40.5		22.5	30.4
	Decrease From Visit 2 to 3	Mean	-5.3	1.6	2.0		9.0	0.7
88[a]	All	N	4	6	5	7	6	28
	Baseline, Visit 2	Mean	39.3	36.3	43.0	35.3	38.8	38.2
	End Double Blind, Visit 3	Mean	38.8	34.7	23.4	22.7	31.0	29.5
	Decrease From Visit 2 to 3	Mean	0.5	1.7	19.6	12.6	7.8	8.8

Source: Sponsor's Table 11-7 in CSR.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results.

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4.1 Gender, Race, Age, and Geographic Region

Both studies were conducted in the US. Majority of the subjects in both studies are white (82% for Trial RP-BP-EF001 and 68.7% for Trial RP-BP-EF002). Therefore, subgroup analyses by race and geographic region are not relevant.

Trial RP-BP-EF001

The population of this study is children 6-12 years old. Therefore, subgroup analysis by age group is not relevant.

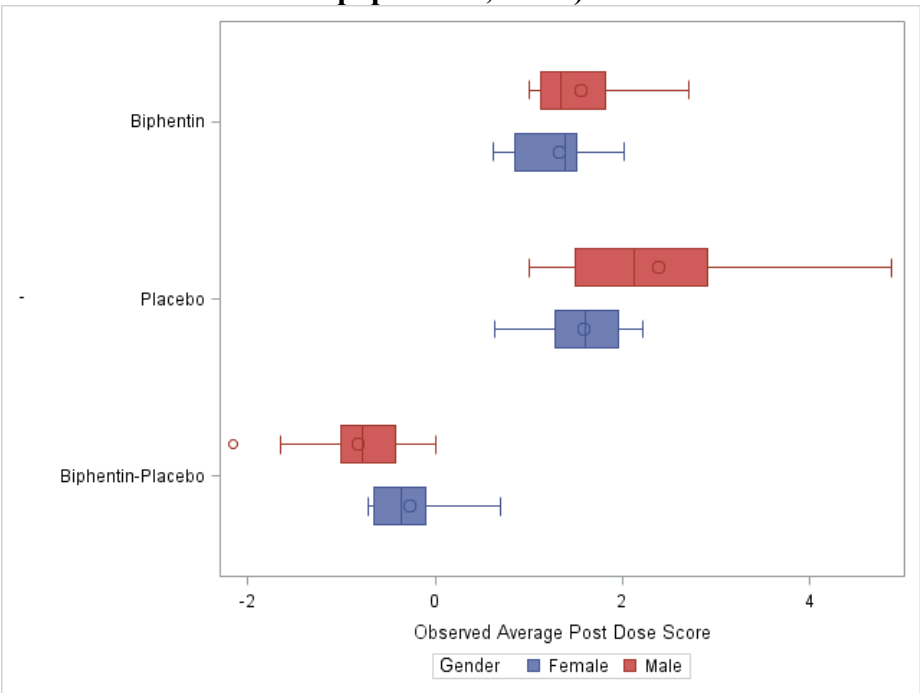
This reviewer plotted and summarized the treatment effects on the primary endpoint for each gender and treatment group.

Table 15: Summary statistics of average SKAMP score by gender and treatment (evaluable population, N=20)

Gender	N	Biphentin Mean (std)	Placebo Mean (std)	Biphentin-Placebo Mean (std)
Female	9	1.33(0.48)	1.59(0.50)	-0.26(0.48)
Male	11	1.56(0.55)	2.39(1.05)	-0.82(0.63)

Source: This reviewer's results.

Figure 6: Box plot of average SKAMP score by gender and treatment (evaluable population, N=20)



Source: This reviewer's results.

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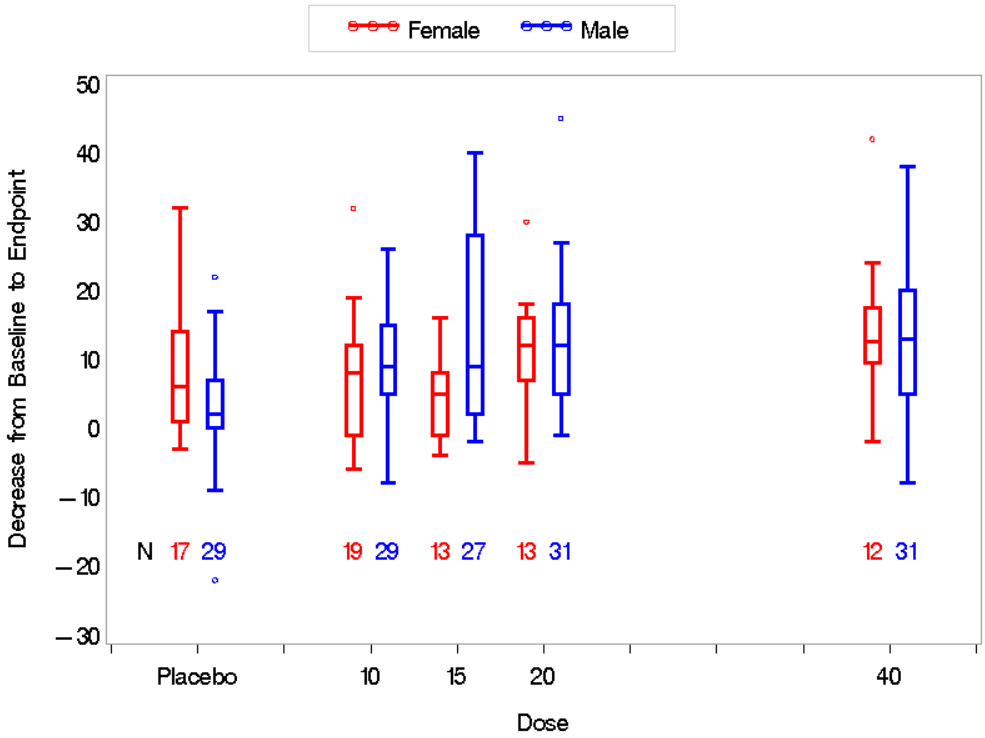
Trial RP-BP-EF002

This reviewer plotted and summarized the changes from baseline in ADHD-RS-IV for each gender and dose group. The female placebo group had a higher median response and more variability than the male placebo group. Female subjects in the 10 mg, 20 mg and 40 mg dose groups had the similar median responses as the male subjects. Female subjects in the 15 mg dose group had less response than the male subjects. In general, there are less female subjects in each dose group. The smaller sample size may contribute to the variability of the means of the female groups.

Figure 7: Box plot of decrease from baseline to endpoint in ADHD-RS-IV by gender and dose level (ITT population, N=221)



Source: This reviewer's plot.

Table 16: Summary statistics of decrease from baseline to endpoint in ADHD-RS-IV by gender and dose level (ITT population, N=221)

Double Blind Dose (mg/tab)	DM Subject Sex	N	Baseline Mean(std)	Change Mean(std)
Placebo	Female	17	34.59(10.40)	9.35(11.09)
Placebo	Male	29	32.69(11.47)	2.55(9.07)
10	Female	19	36.63(7.23)	7.74(9.48)
10	Male	29	38.31(9.03)	10.34(8.44)

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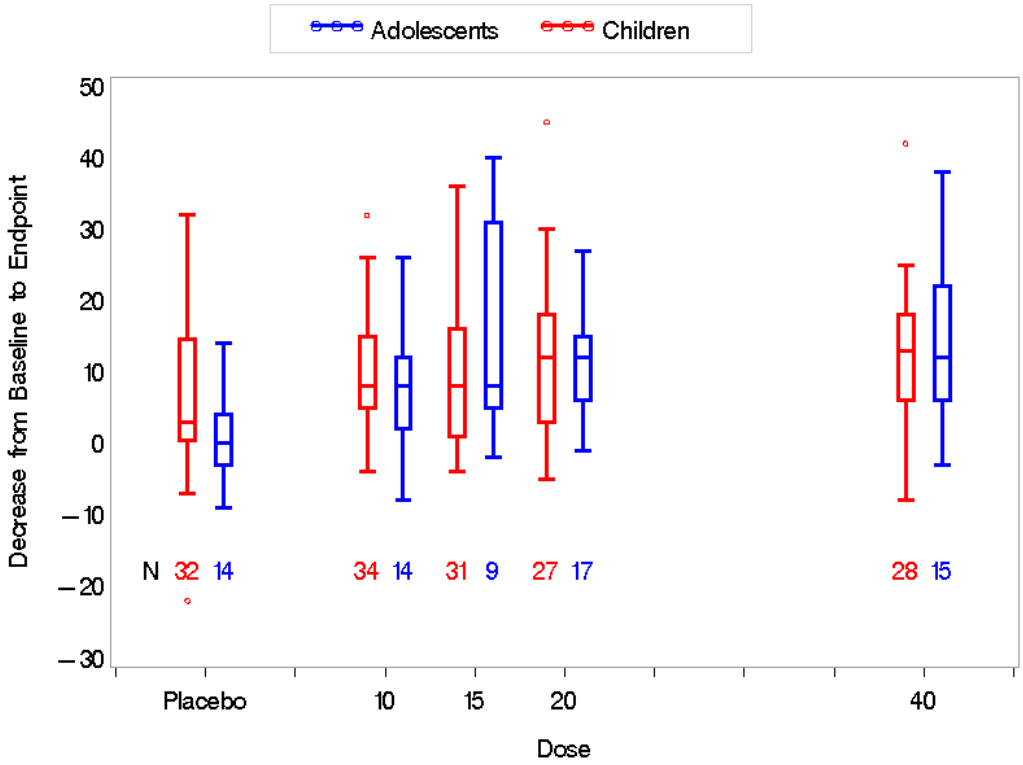
Double Blind Dose (mg/tab)	DM Subject Sex	N	Baseline Mean(std)	Change Mean(std)
15	Female	13	34.31(10.39)	4.54(5.98)
15	Male	27	39.70(7.23)	14.44(12.99)
20	Female	13	35.92(7.42)	11.08(8.88)
20	Male	31	36.29(8.97)	12.84(10.31)
40	Female	12	36.92(9.41)	14.08(11.47)
40	Male	31	34.84(8.96)	12.68(10.32)

Source: This reviewer's results.

This reviewer plotted and summarized the changes from baseline in ADHD-RS-IV by age group and dose group. The two age groups had similar responses across all four drug dose levels except placebo.

Figure 8: Box plot of decrease from baseline to endpoint in ADHD-RS-IV by age group and dose level (ITT population, N=221)



Source: This reviewer's results.

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Table 17: Summary statistics of decrease from baseline to endpoint in ADHD-RS-IV by age group and dose level (ITT population, N=221)

Double Blind Dose (mg/tab)	Age Group	Baseline Mean(std)	Change Mean(std)
Placebo	Adolescents	27.50(12.60)	1.29(5.89)
Placebo	Children	35.97(9.32)	6.72(11.40)
10	Adolescents	36.07(9.96)	7.43(9.44)
10	Children	38.29(7.63)	10.09(8.63)
15	Adolescents	38.78(7.31)	14.56(15.74)
15	Children	37.71(9.08)	10.26(10.90)
20	Adolescents	34.65(7.47)	11.29(7.80)
20	Children	37.15(9.02)	12.96(11.02)
40	Adolescents	35.07(9.43)	14.00(11.66)
40	Children	35.61(8.97)	12.57(10.07)

Source: This reviewer's results.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Trial RP-BP-EF001

There are no statistical issues for this trial.

Trial RP-BP-EF002

There are no statistical issues for this trial.

5.2 Collective Evidence

Trial RP-BP-EF001

The primary efficacy endpoint of this study was met. The mean post dose SKAMP total score was statistically significantly better (lower) for Biphentin than for Placebo (ANCOVA, LS means 1.32 for Biphentin and 2.18 for placebo, p = 0.0001). The key secondary endpoint included the onset and duration of efficacy. The LS mean SKAMP total score were statistically

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significantly better (lower) for Biphentin than placebo at each time point, demonstrating that the onset occurred at Hour 1 and that the effect continued through Hour 12.

Trial RP-BP-EF002

The primary efficacy endpoint of this study was met. The overall test for treatment effect was statistically significant ($p = 0.0046$). The pairwise comparison of each Biphentin dose level vs placebo showed a statistical significance for the 20 mg (ANCOVA, Dunnett adjusted $p = 0.0145$) and 40 mg (ANCOVA, Dunnett adjusted $p = 0.0011$) doses.

5.3 Conclusions and Recommendations

This reviewer concludes, based on statistical evidence in Trial RP-BP-EF001, the onset of the treatment effect of Biphentin started at Hour 1 and lasted through Hour 12. Based on statistical evidence in Trial RP-BP-EF002, Biphentin 20 mg and 40 mg are effective.

5.4 Labeling Recommendations (as applicable)

NA

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

/s/

JINGLIN ZHONG
03/18/2015

PEILING YANG
03/19/2015
I concur.

HSIEN MING J HUNG
03/19/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205831 **Applicant:** RHODES PHARMACEUTICALS LP **Stamp Date: 6/18/2014**

Drug Name: Methylphenidate Hydrochloride Extended-Release Capsules **NDA/BLA Type:NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Refer Safety to clinical team
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Y_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No interim analysis
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				Refer to clinical team
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Jinglin Zhong	8/1/2014
Reviewing Statistician	Date
Peiling Yang	8/1/2014
Supervisor/Team Leader	Date

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/s/

JINGLIN ZHONG
08/01/2014

PEILING YANG
08/01/2014