CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207960Orig1s000

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 #:	207, 960
Drug Name:	Methylphenidate HCl Extended-Release Chewable Tablets
Indication(s):	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Pfizer
Dates:	Submission receipt date: February 04, 2015
	PDUFA date: December 04, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewers:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatric Products
Clinical Reviewer:	Christina Burkhart, M.D.
Project Manager:	Hiren Patel

Keywords:

NDA review, clinical studies,

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The sponsor submitted New Drug Application (NDA) 205-422 for methylphenidate hydrochloride (HCl) Extended-Release Chewable Tablets (ERCT) in treatment of pediatric patients with attention deficit hyperactivity disorder (ADHD). The reference listed drug for this application is the orally administered METHYLIN® (methylphenidate HCl) 10 mg Chewable Tablets (NDA 21475, Sponsor: Mallinckrodt).

The efficacy of methylphenidate HCl ERCT, also referred to as NWP09, is supported by one pivotal, dose-optimized, randomized, double-blind, placebo-controlled, laboratory classroom efficacy study (Study B7491005) conducted in the United States.

Based on the pre-specified primary statistical analysis, 20-60 mg optimized dose of NWP09 demonstrated efficacy (compared to placebo) as measured by the model adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9). The onset of efficacy was seen beginning 2 hours post-dose time point, and the efficacy was maintained through the 8 hour post-dose time point. The result at 0.75 hour post dose reached nominal statistical significance, but was not statistically significant after adjusting for multiplicity.

2. INTRODUCTION

2.1 Overview

The sponsor submitted New Drug Application (NDA) 205-422 for methylphenidate hydrochloride (HCl) Extended-Release Chewable Tablets, also referred to as NWP09, in treatment of pediatric patients with attention deficit hyperactivity disorder (ADHD). The reference listed drug for this application is the orally administered METHYLIN® (methylphenidate HCl) 10 mg Chewable Tablets (NDA 21475, Sponsor: Mallinckrodt).

2.2 Data Sources

The clinical study report and data sets were submitted electronically. The network path for the submission is: \\CDSESUB1\evsprod\NDA207960\0000. Primary analysis data sets are located at \\CDSESUB1\evsprod\NDA207960\0000\m5\datasets\b7491005 .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data acceptable for the reviewer's analyses.

3.2 Evaluation of Efficacy

The sponsor conducted one pivotal efficacy and safety study (Study B7491005) conducted in pediatric patients with ADHD.

3.2.1 Study Design and Endpoints

Study B7491005 was dose-optimized, randomized, double-blind, placebo-controlled, laboratory classroom study in pediatric patients with ADHD. The study enrolled patients in 6 sites in the United States.

Enrollment criteria

Positive confirmation of ADHD diagnosis by K-SADS questionnaire at Screening; Investigator administered CGI-S score ≥3 at Screening; ADHD-RS score at Screening or Baseline ≥90th percentile for gender and age in at least 1 of the following categories: hyperactive-impulsive subscale, inattentive subscale, or total score

Table 1. Schedule of Visits

Visit	Visit 1	Visit 2	Visits 3-7	Visit 8	Visit 9	Visit 10

				(classroom)	(classroom)	
Phase	Screening	Baseline	Open-Label	Open-Label	Double-Blind	Follow up
Day(s)	-42 to -1	1	8, 15, 22, 29, 36	43	7day post Visit 8	7-14d post Visit 9

Open-Label Dose Optimization Period
During the 6-week Open-label Period, the investigator was allowed to titrate the dose of NWP09 up or down to achieve the optimal dose for efficacy and tolerability. Titration from initial dose of 20mg was performed at weekly intervals in increments of 10-20 mg/day until the optimal dose or a maximum dose of 60 mg/day was reached. Subjects unable to tolerate a minimum dose of 20 mg/day or unable to achieve a stable dose (no change between Visits 7 and 8) during the Open-label Period were discontinued from the study.

Randomization
Subjects who achieved a stable dose of NWP09 and successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8 were randomized in a 1:1 ratio to take double-blind study drug (NWP09 or placebo) orally once daily for 1 week. Randomization followed a fixed schedule using a permuted block design stratified by clinical site. Any subjects who did not complete the 4-hour post-dose laboratory session during Visit 8 were to have been withdrawn and not allowed to receive any double-blind study drug.

Double-blind Phase
During the last week of study drug treatment, the study staff, subjects, and parents/guardians were blinded to treatment assignment (NWP09 or placebo).

Study Endpoints
The *primary efficacy endpoint* was average of SKAMP-Combined scores over all post-dose time points. The sponsor also pre-specified *two key-secondary efficacy endpoints*: the onset time of efficacy and the duration of efficacy.

3.2.2 Statistical Methodologies

The primary efficacy analysis was performed on the ITT population. The ITT population included all randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable.

The primary null hypothesis was that the model-adjusted average of SKAMP-Combined scores over all post-dose time points on the test classroom day was the same for NWP09 and placebo.

Primary Analysis Model
The primary efficacy analysis used mixed model repeated measures (MMRM) analysis with treatment, study center, time point, and time point-by-treatment interaction as fixed effect, and subject's intercept as a random effect. Subject's random intercept corresponds to compound symmetry variance–covariance structure.

Multiple Testing

If the primary efficacy endpoint are statistically significant ($p < 0.05$), the key secondary outcomes of onset and duration of efficacy of NWP09 versus placebo using the SKAMP-Combined scores are tested using a fixed-sequence testing procedure. The fixed-sequence testing procedure is conducted in the following order: 4, 8, 2, 10, 12, 13, and 0.75 hours post-dose.

- The onset time of efficacy action is claimed at the first post-dose time point within the fixed sequence at which the difference between the 2 treatments is statistically significant ($p < 0.05$).
- The duration of efficacy is the difference between the onset time and the latest consecutive time point at which the difference between the 2 treatments was still statistically significant ($p < 0.05$).

Missing Individual Items in the SKAMP Scale

Missing or invalid data for individual questions will be handled as follows:

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

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Study NWP09-ADHD-300 was conducted at 6 sites in the United States. Of the 86 randomized subjects, 42 to treatment with NWP09 and 44 to treatment with placebo, 85 subjects completed the study. One subject randomized to placebo was lost to follow-up. Subject disposition is summarized by treatment group in Table 1.

Table 2. Subject Disposition: Number of Patients by Treatment Group

Subjects, N (%)	Placebo	NWP09
Randomized	44 (100%)	42 (100%)
Completed	43 (97.7%)	42 (100%)
Discontinued	1 (2.3%)	0 (0%)

N=number of patients; percentages are relative to the number of randomized patients;
Source: Clinical Study Report NWP09-ADHD-300 Figure 10-1 (pg. 38)

Demographic and Baseline Characteristics

The demographic and baseline characteristics of the analysis population (ITT) are summarized in Table 2. A majority of the patients were male (>62%) and white (>57%). Compared with the placebo group, the NWP09 group had a larger proportion of males (71.4% versus 53.5%) and whites (64.3% versus 51.2%). The overall mean age was approximately 9.6 years, ranging from

6 to 12 years, and majority of subjects were 8 to 10 years old. Compared with the placebo group, the NWP09 group had a smaller proportion of 8-10 year olds (40.5% versus 65.1%)

Table 3. Demographic and Baseline Characteristics (ITT Population)

Subjects	**Placebo** N=43 (100%)	**NWP09** N=42 (100%)	**Total** N=85 (100%)
Gender			
Male	23 (53.5%)	30 (71.4%)	53 (62.4%)
Female	20 (46.5%)	12 (28.6%)	32 (37.6%)
Race			
White	22 (51.2%)	27 (64.3%)	49 (57.6%)
Black	18 (41.9%)	12 (28.6%)	30 (35.3%)
Other	3 (6.9%)	3 (7.1%)	6 (7.0 %)
Age (years): Mean (SD)	9.3 (1.62)	9.9 (1.71)	9.6 (1.69)
Age Group			
6-7 years	8 (18.6%)	5 (11.9%)	13 (15.3%)
8-10 years	28 (65.1%)	17 (40.5%)	45 (52.9%)
11-12 years	7 (16.3%)	20 (47.6%)	27 (31.8%)

N=number of patients; Percentages are relative to the number of ITT patients; SD=Standard Deviation
Source: Clinical Study Report NWP09-ADHD-300 Table 11-2 (pg. 45)

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Primary Efficacy Measure: SKAMP-Combined Score

Primary Endpoint

The primary efficacy endpoint, *the model-adjusted average* of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9), was analyzed by an MMRM model. The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower (i.e., improved) in NWP09 treatment arm compared with placebo arm. The LS mean SKAMP-Combined score was 12.1 in subjects receiving NWP09 compared with 19.1 in subjects receiving placebo (LS mean treatment difference = -7.0; p <0.001).

Table 4. Analysis of the Primary Endpoint: Average of post-dose SKAMP-Combined Scores (Visit 9, ITT Population)

SKAMP-Combined Score	**Placebo** N=43	**NWP09** N=42	**Treat. Difference: NWP09 – Placebo**
Pre-Dose (Baseline) Mean (SD)	13. 8 (10.0)	17. 5 (11.6)	
Average Post-Dose LS Mean (SE)	19.1 (1.4)	12.1 (1.4)	-7.0 (2.0)
95% Confidence Interval	(16.4, 21.8)	(9.3, 14,9)	(-10.9, -3.1)
p-value			<0.001

N=number of Patients; SE=Standard Error; SD=Standard Deviation
Source: Clinical Study Report NWP09-ADHD-300 Table 11-3 (pg. 47)
Results confirmed by the reviewer

Key Secondary Endpoints

The key secondary efficacy variables were the onset of efficacy (onset of clinical effect) and the duration of efficacy of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9).

For the comparison of NWP09 and placebo at the post-dose time points, the fixed-sequence testing procedure was conducted at 5% significance level (two-sided) in the following order: 4, 8, 2, 10, 12, 13, and 0.75 hours post-dose. The results are displayed in Table 5. Based on the pre-specified hierarchical multiple testing approach, the onset of efficacy was determined to be 2 hours post-dose and efficacy was maintained through the 8-hour time point.

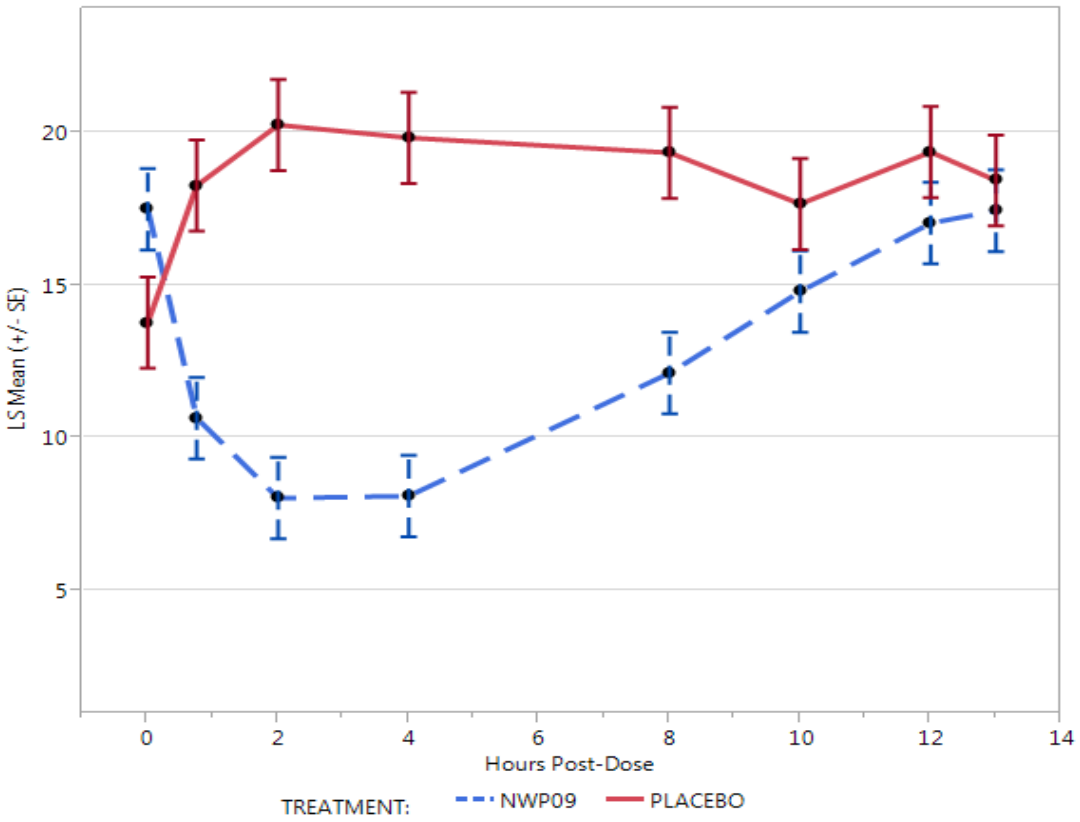
Table 5. LS Mean SKAMP-Combined Scores by post-dose time points (Visit 9, ITT Population)

Time Point (post-dose)	**Placebo** N=43	**NWP09** N=42	**Treat. Difference: NWP09 – Placebo**			
	LS Mean (SE)	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI**	**p-value**	**Adjusted p-value**
0.75 hours post-dose	18.3 (1.6)	10.2 (1.6)	-8.2 (2.3)	(-12.7, -3.7)	<0.001	0.496
2 hours post-dose	20.3 (1.6)	7.5 (1.6)	-12.8 (2.3)	(-17.3, -8.3)	<0.001	<0.001
4 hours post-dose	19.9 (1.6)	7.6 (1.6)	-12.3 (2.3)	(-16.8, -7.8)	<0.001	<0.001
8 hours post-dose	19.4 (1.6)	11.6 (1.6)	-7.8 (2.3)	(-12.3, -3.3)	<0.001	<0.001
10 hours post-dose	17.7 (1.6)	14.3 (1.6)	-3.4 (2.3)	(-7.9, 1.1)	0.133	0.133
12 hours post-dose	19.4 (1.6)	16.5 (1.6)	-2.9 (2.3)	(-7.4, 1.6)	0.206	0.206
13 hours post-dose	18.5 (1.6)	16.9 (1.6)	-1.6 (2.3)	(-6.0, 2.9)	0.496	0.496

N=number of Patients; SE=Standard Error; CI=Confidence Interval
Source: Clinical Study Report NWP09-ADHD-300 Table 14.2.6 (pg. 130)
Results confirmed by the reviewer

Figure 1 depicts SKAMP-Combined scores over time by treatment group. Numerically (without multiplicity adjustment), NWP09 separated from Placebo beginning 0.75 hours post-dose and remained superior to Placebo at nominal significance of 5% up to the 8 hours post-dose time point.

Figure 1. SKAMP-Combined Score Over Time (LS Mean $\pm$ SE) by Treatment Group



Source: Reviewer's result

Sensitivity Analysis

After database lock and unblinding of the data, the sponsor performed sensitivity analysis of the primary efficacy findings with respect to the assumption on variance-covariance structure. The primary efficacy variable was reanalyzed via a repeated-measures analysis using an unstructured within-subject covariance matrix. The model included the same fixed effects as the primary efficacy analysis (treatment, study center, time point, and time point-by-treatment interaction) and subject as a random effect. The sensitivity analysis results were similar to those of the primary analysis, and are included in the Appendix A of this review.

Exploratory Analysis of the Imbalance of Baseline and Demographic Characteristics

On face, treatment groups appeared imbalanced with respect to some demographic and baseline characteristics. The differences between the two treatment arms were explored using a permutation test (see Table 6). At two-sided 5% significance level, the proportion of 8-10 years old patients in the placebo arm was significantly higher than the respective proportion in the NWP09 treatment arm. Subgroup analyses of the gender, racial, and age subgroups (including 8-10 years subgroup) presented in Section 4.1 did not reveal any major inconsistency of the treatment effect among the subgroups.

Pre-dose mean SKAMP-Combined score in the placebo arm was 13.8 versus 17.5 in the NWP09 treatment arm. Since higher SKAMP-Combined scores correspond to higher severity of the disease, the observed difference in mean scores at baseline should be conservative.

Table 6. Permutation Test

Subjects	**Placebo** N=43 (100%)	**NWP09** N=42 (100%)	**Permutation Test p-value**
SKAMP- Combined Score at Baseline: Mean (SD)	13.8 (10.0)	17.5 (11.6)	0.1211
Gender			
Male	23 (53.5%)	30 (71.4%)	0.1197
Race			
White	22 (51.2%)	27 (64.3%)	0.2751
Age Group			
8-10 years	28 (65.1%)	17 (40.5%)	0.0299

N=number of patients; Percentages are relative to the number of ITT patients; SD=Standard Deviation
Source: Reviewer's Results

Exploratory Summary by Study Center

This reviewer explored mean differences of average post-dose SKAMP- Combined scores between NWP09 and placebo by study site (using non-model based calculations). Summary is presented in Table 6. The six study sites were similar in size. In all sites, NWP09 had lower mean average scores compared to placebo with differences ranging from -1.6 in Site 01 to -12.0 in Site 03.

Table 7. Summary by Study Site: Mean Average of post-dose SKAMP-Combined Scores (Visit 9)

Study Site	**Placebo**		**NWP09**		**Difference of Means: NWP09 – Placebo**
	N	**Mean**	**N**	**Mean**	
01	8	22.4	9	20.7	-1.6
02	6	19.7	7	14.2	-5.4
03	7	21.9	7	9.8	-12.0
04	8	9.8	6	7.2	-2.6
06	7	21.6	7	11.9	-9.7
07	7	19.8	6	8.0	-11.8

N=number of Patients;
Source: Reviewer's Results

Reviewer's Remark: None of the study centers was influential on the primary efficacy outcome in that the removal of either study site from the primary analysis did not affect nominal statistical significance.

Missing Data

The overall observed dropout rate was negligible (1.1%). There was only one randomized patient (in the placebo arm) who did not complete the study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

This section contains reviewer's exploratory subgroup analysis displayed in Table 7. The primary analysis MMRM model was used to investigate gender (Male, Female), racial (White, Black, Other), and Age (6-7 years, 8-10 years, 11-12 years) subgroups. In all considered subgroups, NWP09 arm was numerically better than placebo as measured by the average of all post-dose SKAMP-Combined scores.

Table 8. Subgroup Analysis: Average post-dose SKAMP-Combined Scores (Visit 9)

	Placebo	**NWP09**	**Treatment Difference: NWP09 – Placebo**
Sex: Male, N	N=23	N=30	
LS Mean (SE)	24.0 (1.9)	11.8 (1.7)	-12.2 (2.6)
Sex: Female, N	N=20	N=12	
LS Mean (SE)	13.4 (1.5)	10.1 (1.9)	-3.3 (2.5)
Race: White, N	N=22	N=27	
LS Mean (SE)	20.7 (3.1)	11.9 (2.5)	-8.7 (3.1)
Race: Black, N	N=18	N=12	
LS Mean (SE)	20.2 (1.9)	13.2 (2.1)	-7.0 (2.4)
Race: Other, N	N=3	N=3	
LS Mean (SE)	21.9 (5.1)	19.5 (4.1)	-2.4 (6.5)
Age: 6-7 years, N	N=8	N=5	
LS Mean (SE)	27.0 (4.2)	14.5 (5.1)	-12.5 (6.5)
Age: 8-10 years , N	N=28	N=17	
LS Mean (SE)	17.5 (1.7)	13.5 (2.1)	-4.0 (2.8)
Age: 11-12 years , N	N=7	N=20	
LS Mean (SE)	11.3 (1.9)	14.5 (3.1)	-3.2 (3.7)

N=number of patients; SE=Standard Error
Source: Reviewer's results

4.2 Other Special/Subgroup Populations

Not applicable

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Statistical efficacy analyses (used by sponsor) were pre-specified in the clinical study protocols. Primary efficacy analysis used MMRM with random subject's intercept which assumed parsimonious compound symmetry variance-covariance matrix. The sponsor performed sensitivity repeated measure analysis with unstructured variance–covariance matrix. Results of

the sensitivity analysis were consistent with the primary efficacy findings. Given that assessments of the primary efficacy measure were done on the same day (Visit 9), the assumption of random intercept may not be completely unreasonable because it models the scenario in which, for each subject, the random effect remains the same for all time points throughout the day.

The two treatment groups appeared to have some imbalance with respect to demographic characteristics and SKAMP-Combined score at baseline. Pre-dose mean SKAMP-Combined score in the placebo arm was 13.8 versus 17.5 in the NWP09 treatment arm. Since higher SKAMP-Combined scores correspond to higher severity of the disease, the observed difference in mean scores at baseline should be conservative. Gender, racial, and age subgroup analyses did not reveal any major inconsistencies in treatment effect between the respective subgroups.

The overall observed dropout rate was negligible (1.1%). There was only one randomized patient who did not complete the study.

Overall, this reviewer did not identify serious issues with sponsor's statistical methods.

5.2 Collective Evidence

The primary endpoint, the model adjusted average of all post-dose SKAMP-Combined scores on a classroom test day (Visit 9), was analyzed by the MMRM with random subject's intercept. Optimized dose of NWP09 was statistically superior to Placebo with LS mean treatment difference of -7.0 (p-value<0.001). At individual time points, based on pre-specified fixed-sequence testing procedure, NWP09 was statistically better than placebo at 2, 4, and 8 hours post-dose. The result at 0.75 hour post dose reached nominal statistical significance, but not after adjusting for multiplicity. Results are presented in Table 8.

Table 9. Primary analysis summary: LS Mean SKAMP-Combined Scores (Visit 9, ITT Population)

Time Point (post-dose)	**Treat. Difference: NWP09 – Placebo**			
	LS Mean (SE)	**95% CI**	**p-value**	**Adjusted p-value**
Average post-dose	-7.0 (2.0)	(-10.9, -3.1)	<0.001	<0.001
0.75 hours post-dose	-8.2 (2.3)	(-12.7, -3.7)	<0.001	0.496
2 hours post-dose	-12.8 (2.3)	(-17.3, -8.3)	<0.001	<0.001
4 hours post-dose	-12.3 (2.3)	(-16.8, -7.8)	<0.001	<0.001
8 hours post-dose	-7.8 (2.3)	(-12.3, -3.3)	<0.001	<0.001
10 hours post-dose	-3.4 (2.3)	(-7.9, 1.1)	0.133	0.133
12 hours post-dose	-2.9 (2.3)	(-7.4, 1.6)	0.206	0.206
13 hours post-dose	-1.6 (2.3)	(-6.0, 2.9)	0.496	0.496

N=number of Patients; SE=Standard Error; CI=confidence interval
Source: Clinical Study Report NWP09-ADHD-300 Table 14.2.6 (pg. 130)
Results confirmed by the reviewer

5.3 Conclusions and Recommendations

Optimized dose of NWP09 (20-60 mg) did demonstrate superiority to placebo in pediatric patient population with ADHD as measured by the model adjusted average of all post-dose SKAMP-Combined scores on a test classroom day. Per the pre-specified testing procedure, the onset of efficacy was seen at 2 hours post-dose, and the efficacy was maintained through 8 hours post-dose time point.

APPENDIX A. Sensitivity Analysis via an Unstructured Covariance Matrix

Table 10. Sensitivity Analysis: LS Mean SKAMP-Combined Scores (Visit 9, ITT Population)

Post-Dose Time-Point	**Placebo** N=43	**NWP09** N=42	**Treat. Difference: NWP09 – Placebo**
	LS Mean (SE)	**LS Mean (SE)**	**LS Mean (SE); p-value**
Average over post-dose time points	19.1 (1.4)	12.1 (1.4)	-7.0 (2,0); p<0.001
0.75 hours post-dose	18.4 (1.6)	10.1 (1.7)	-8.2 (2.3); p<0.001
2 hours post-dose	20.3 (1.5)	7.5 (1.6)	-12.8 (2.2); p<0.001
4 hours post-dose	19.9 (1.5)	7.6 (1.6)	-12.3 (2.2); p<0.001
8 hours post-dose	19.4 (1.5)	11.6 (1.6)	-7.8 (2.2); p<0.001
10 hours post-dose	17.7 (1.6)	14.3 (1.6)	-3.5 (2.2); p=0.122
12 hours post-dose	19.4 (1.8)	16.5 (1.8)	-2.9 (2.6); p=0.257
13 hours post-dose	18.5 (1.6)	16.9 (1.7)	-1.6 (2.3); p=0.500

N=number of Patients; SE=Standard Error; p= nominal p-value
Source: Clinical Study Report NWP09-ADHD-300 Table 14.2.5 (pg. 127) and Reviewer's Results
Sponsor's Results confirmed by the reviewer

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

/s/

GEORGE KORDZAKHIA
11/03/2015

PEILING YANG
11/03/2015

HSIEN MING J HUNG
11/03/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207-960/ SN000 **Applicant: Pfizer** **Stamp Date: 02/04/2015**

Drug Name: Methylphenidate HCl ERCT **NDA/BLA Type: Standard**

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			Per the October 2, 2014 pre-NDA meeting, the ISS and ISE are not required for this NDA
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
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? __Yes_____

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	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			x	No Missing SKAMP-Combined

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				Scores at Individual Time Points

George Kordzakhia 03/23/2015

Reviewing Statistician Date

Peiling Yang 03/23/2015

Supervisor/Team Leader Date

File name: Statistics Filing Checklist for a New NDA 206-302

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

/s/

GEORGE KORDZAKHIA
03/23/2015

PEILING YANG
03/23/2015