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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 202100 / O-1 (SDN 001 in DARRTS)

Drug Name: NWP06 (Methylphenidate HCl) extended-release powder for oral suspension 25 mg/5 mL

Indication(s): ADHD in pediatric subjects of 6-12 years of age

Applicant: NextWave Pharmaceuticals

Date(s): Date of Initial Submission: July 29, 2010

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Biometrics Division: Division of Biometrics I

Statistical Reviewers: Andrejus Parfionovas, Ph.D., Yeh-Fong Chen, Ph.D.

Concurring Reviewers: Peiling Yang, Ph.D., HM James Hung, Ph.D.

Medical Division: Division of Psychiatry Products

Clinical Team: Mark Ritter, M.D., HFD-130
Robert Levin, M.D., HFD-130

Project Manager: ShinYe Chang, Pharm. D., HFD-130

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1. EXECUTIVE SUMMARY

The sponsor submitted one trial, NWP06-ADD-100, to demonstrate the efficacy of Methylphenidate HCl Extended-Release Power for Oral Suspension for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older.

Study NWP06-ADD-100 was a Phase 3, randomized, double-blind, placebo-controlled, crossover, multicenter, laboratory classroom study. It was conducted in 45 pediatric patients (ages 6 to 12 years) with ADHD.

The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dose. Treatment comparisons for this endpoint were assessed using a analysis of variance (ANOVA) model. The key secondary efficacy parameters were the onset and duration of clinical effect as determined by SKAMP-Combined scores at each post-dose time point by using a closed testing procedure.

Since the sponsor's analysis results showed statistically significant differences between the drug and placebo from 0.75 hours to 12 hours, the sponsor concluded that the primary efficacy endpoint assessed at 4 hours was met, the onset of efficacy was determined to be 0.75 hours post-dose and the drug's efficacy was maintained throughout the entire study period.

After evaluating the sponsor's analysis results that showed significant findings at all time points, the statistical reviewers found that Data in Study NWP06-ADD-100 showed a statistically significant treatment-by-period interaction. So, the interpretability or validity of the trial results based on the combined period data becomes questionable. Technically speaking, in this case, if one still considers using this trial to support the drug's efficacy, only the first period of data can be used.

Based on the first period of data, the statistical reviewers found that the differences between the drug and placebo were still statistically significant at all time points. However, one concern is that if we treat this study as a parallel study instead of the cross-over study that the sponsor originally planned, the size of this study appears to be small (only total 44 patients). To evaluate the robustness of the efficacy findings, we have also performed the permutation test. Our permutation test results showed that the differences between the drug and placebo are also statistically significant at all time points based on the first period data.

2. INTRODUCTION

2.1 Overview

The sponsor submitted one trial, NWP06-ADD-100, to demonstrate the efficacy of Methylphenidate HCl Extended-Release Power for Oral Suspension for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 years and older.

According to the sponsor, Methylphenidate has been a well-established therapeutic agent for the treatment of ADHD since 1955. Many studies have been performed with methylphenidate and these studies have provided consistent information with regard to its use. The pharmacokinetics (PK) of methylphenidate have been reported to be consistent across age groups and genders.

NWP06 is a new, liquid-based extended-release formulation of methylphenidate hydrochloride and the sponsor's motivation is to provide a pediatric-friendly formulation of methylphenidate with a fast onset and extended duration of effect. Even though their primary clinical objective of the development program was to demonstrate an efficacy and safety profile that was comparable to other marketed ER methylphenidate formulations, their overall goal was to create a stimulant medication that would facilitate treatment of those challenged with solid oral dosage forms of medication for any reason.

Study NWP06-ADD-100 was a Phase 3, randomized, double-blind, placebo-controlled, crossover, multicenter, laboratory classroom study. It was conducted in 45 pediatric patients (ages 6 to 12 years) with ADHD.

The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dose. Treatment comparisons for this endpoint were assessed using analysis of variance (ANOVA) model. The key secondary efficacy parameters were the onset and duration of clinical effect as determined by SKAMP-Combined scores at each post-dose time point by using a closed testing procedure. Since the sponsor's analysis results showed statistically significant differences between the drug and placebo from 0.75 hours to 12 hours, the sponsor concluded that the primary efficacy endpoint assessed at 4 hours was met, the onset of efficacy was determined to be 0.75 hours post-dose and efficacy was maintained throughout the entire period.

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):

<\\Cdseub1\evsprod\NDA202100\0000\m5\datasets\nwp06-add-100\analysis>

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Description

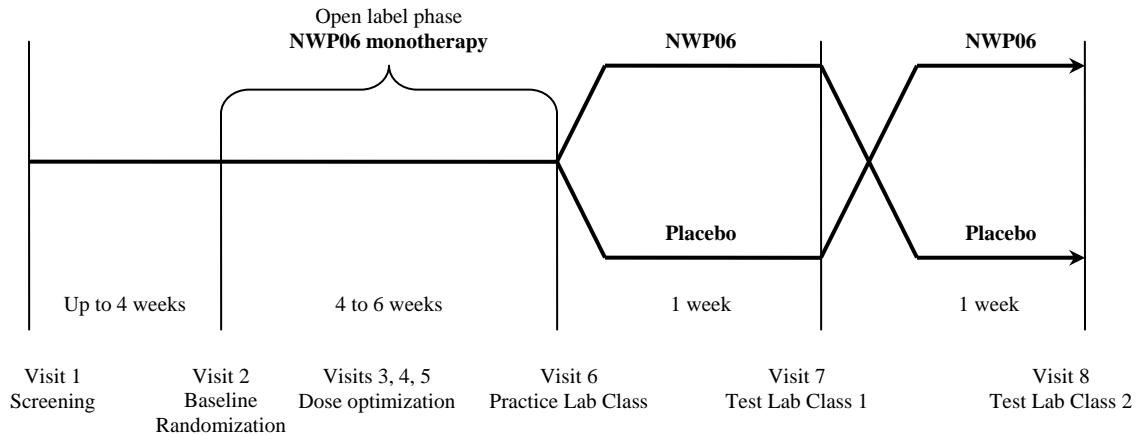
Study Objectives

The objective of the study was to establish that an optimal dose of NWP06 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.

Study Design

This was a randomized, double-blind, placebo-controlled, crossover design, multi-center study investigating the safety and efficacy of NWP06 in the treatment of ADHD in children from 6 to 12 years of age. Study visits were conducted at screening (Visit 1), baseline (Visit 2), Weeks 1 to 3 (Visits 3 to 5; dose optimization), Week 4 (Visit 6; practice laboratory classroom session), and Weeks 5 and 6 (Visits 7 and 8; laboratory classroom sessions). The study design is shown schematically in Figure 1.

Figure 1. Study design.



Source: drawn by the reviewer Dr. Andrejus Parfionovas.

The study consisted of:

- Screening (Visit 1): A 4-week (maximum) screening period,
- Baseline (Visit 2): Visit 2 was designated baseline. If a subject met all entry criteria for the study at Visit 2, he/she was enrolled and received open-label (OL) study medication at this visit. Subjects began study medication at home the morning following Visit 2,
- Open-label Phase (Visits 3 to 6): There were 4 to 6 weeks of OL treatment with NWP06 for dose optimization. Study medication adjustments in approximately weekly intervals (Visits 3, 4, and 5) in 10- or 20-mg increments were allowed. A practice laboratory classroom day was held during Visit 6,
- Double-blind Crossover Phase (Visits 7 and 8): Two weeks DB treatment (1 week of NWP06 with no dose adjustments and 1 week of placebo). Study medication dosages were to remain stable during DB treatment. The first test laboratory classroom day occurred 7 days after the practice session (Visit 7). The second test laboratory classroom day occurred 7 days after the first test session (Visit 8).

The intent-to-treat (ITT) analysis set consisted of all randomized subjects who took at least one dose of study medication and had at least one post-baseline efficacy assessment. The ITT Population was considered as the primary population. Note that because of early drop-out there were 5 patients who were in the ITT population (subject id: 01-006, 01-015, 02-006, 02-011, 02-016) but did not have any record of SKAMP score during Visits 7 and 8.

The Clinically Evaluable population was defined as all ITT subjects who fulfill all of the following:

- Received full prescribed dose of double-blind study medication at both test laboratory classroom sessions.
- Completion of full laboratory classroom tests on both test classroom sessions.
- Subject did not miss more than 4 consecutive days of therapy during the treatment phase.
- No use of disallowed medication during the last two weeks of experimental treatment. Any psychotropic medication including, but not limited to, the following examples are prohibited:
 - o Any stimulant (e.g., methylphenidate, amphetamine, Ritalin, Ritalin SR, Metadate ER, Concerta,
 - o dextromethylphenidate, Focalin, dextroamphetamine, Dexedrine, Adderall).
 - o Atomoxetine (Strattera) SSRIs (e.g., fluoxetine, paroxetine).
 - o Tricyclic antidepressants.
 - o Clonidine MAOIs (monoamine oxidase inhibitors).
 - o Mood stabilizers (e.g., lithium, valproate, quetiapine).
 - o Antipsychotics (e.g., risperidone, olanzapine).
 - o Anticonvulsants.
 - o Sedative hypnotics (unless stable dose before and during the clinical study).
 - o Coumarin anticoagulants.
 - o Anticonvulsants.
 - o Halogenated anaesthetics.
 - o Phenylbutazone.

Regarding the sample size, according to the sponsor, assuming an effect size of 0.50 at 4 hours post-dose between NPW06 and placebo, with approximately 34 subjects completing the DB crossover treatment, this study had 80% power at the level of 0.05 (two-sided) using a paired t-test. Based on a potential drop-out rate of 15%, this study was planned to randomize approximately 40 subjects.

Study Endpoints

The primary efficacy outcome was the SKAMP-Combined score (a 13-item independent observer rating of subject impairment of classroom observed behaviors) at 4 hours post-dose. Key secondary efficacy outcomes as determined by SKAMP-Combined scores at pre-dose and each post-dose (0.75, 2, 4, 8, 10 and 12 hours) time point and each laboratory classroom day (Visits 7 and 8) included:

- Onset of clinical effect;
- Duration of clinical effect.

Other secondary efficacy outcomes, which were measured at pre-dose and each post-dose (0.75, 2, 4, 8, 10 and 12 hours) time point during each test laboratory classroom day, included:

- SKAMP-Attention scores;
- SKAMP-Department scores;
- SKAMP-Quality of Work scores;
- SKAMP-Compliance scores;
- Written math test (PERMP) scores.

3.1.2 Analysis for the Primary Efficacy Endpoint

The primary efficacy analysis was conducted on the ITT population. Treatment comparisons for the SKAMP-Combined score at 4 hours post-dose on the test classroom days were assessed using ANOVA model. The analysis will be repeated on the Clinically Evaluable population. For subjects who started a classroom day (Visit 7 or 8) but did not complete the assessments, their last observation within the same classroom day was carried forward (LOCF) for the primary and key secondary efficacy analyses. Data from one test classroom day was not used to impute values for the other test classroom day.

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

The sequence levels were:

- Placebo/NWP06;
- NWP06/Placebo.

The period levels were:

- First test laboratory classroom day (Visit 7);
- Second test laboratory classroom day (Visit 8).

The treatment levels were:

- NWP06;
- Placebo.

Descriptive statistics of the SKAMP-Combined scores at 4 hours post-dose are presented for each treatment, as well as the paired differences between the treatments (NWP06-Placebo). The point estimate of the least-squares mean (LS Mean) and the corresponding 95% confidence interval of the 4 hours post-dose scores are presented for each treatment group. The point estimate, corresponding 95% confidence interval and p-value for the treatment difference in the LS Means, including the effect size (calculated as the LS Means difference divided by the square root of the mean-squared error [MSE]) is presented. The primary efficacy analysis on the ITT Population was repeated for the following subgroups:

- Site;
- Final dose (20 mg, 30/40 mg, 50/60 mg);
- Gender;
- ADHD type (Inattentive, Hyperactive/Impulsive, Combined, not otherwise specified);
- 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).

3.1.3 Analysis for the Primary Efficacy Endpoint

Primary Analysis for the Key Secondary Endpoints - Onset and Duration of Efficacy

The analysis for the key secondary efficacy endpoints was conducted on the ITT Population, and repeated on the Clinically Evaluable Population. If the primary efficacy endpoint was statistically significant (i.e., $p < 0.05$), the key secondary variables of onset and duration of efficacy (clinical effect) of NWP06 vs. placebo using the SKAMP-Combined scores were tested using a closed testing procedure, based on the same ANOVA model as for the primary efficacy variable. The closed testing procedure starts from the time-point of 0.75 hours post-morning dose, then 2, 4, 8, 10 and 12 hours post-dose.

- The onset time of efficacy action was determined as 0.75 hours post-dose if the difference between the two treatments was statistically significant (i.e., $p \leq 0.05$) at that time point.
- If the difference between the two treatments was statistically significant (i.e., $p \leq 0.05$) at the 0.75 hours post-dose time point, the duration of efficacy was claimed as the last consecutive time point at which the difference was still statistically significant (i.e., $p \leq 0.05$).

For example, if a statistically significant difference in SKAMP-Combined scores for NWP06 vs. placebo was determined at 0.75 hours post-dose and statistical significance was measured at all time-points up to and including 10 hours post-dose, but statistical significance was not reached at 12 hours post-dose, onset of clinical effect and duration of clinical effect would be defined as 0.75 hours post-dose and 10 hours post-dose, respectively.

Analyses for Other Secondary Efficacy Endpoints

Descriptive statistics for the SKAMP subscale scores and PERMP scores were calculated at each time point for the test laboratory classroom days (Visits 7 and 8), and are presented for each treatment as well for the paired differences between the treatments (NWP06-Placebo).

The time points the sponsor analyzed were pre-dose, 0.75, 2, 4, 8, 10 and 12 hours post-dose, as well as the mean of the post-dose measurements, calculated as the average of the 0.75, 2, 4, 8, 10 and 12 hours post-dose SKAMP subscale scores for each subject.

3.1.4 Sponsor's Efficacy Analysis Results

3.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

A total of 45 subjects were enrolled in this study and all 45 were randomized, 23 to the Placebo/NWP06 treatment sequence and 22 to the NWP06/Placebo treatment sequence. All 22 (100.0%) subjects in the NWP06/Placebo treatment sequence completed the study, while 17 (73.9%) subjects in the Placebo/NWP06 treatment sequence completed the study. All 6 subjects who discontinued from the study discontinued during the OL phase. The reasons for discontinuation from the study included withdrawal of assent/consent and AE (2 subjects each), and lack of efficacy and lost to follow-up (1 subject each).

Table 1. Subject Disposition

Subject disposition	Treatment sequence		Total N (%)
	Placebo/NWP06 N (%)	NWP06/Placebo N (%)	
Randomized	23 (100)	22 (100)	45 (100)
Completed	17 (73.9)	22 (100)	39 (86.7)
Discontinued	6 (26.1)	0 (0)	6 (13.3)
Reasons for discontinuation			
Subject withdrew assent/consent	2 (8.7)	0	2 (4.4)
Adverse event	2 (8.7)	0	2 (4.4)
Protocol violation	0 (0.0)	0	0 (0.0)
Investigator decision	0 (0.0)	0	0 (0.0)
Lack of efficacy	1 (4.3)	0	1 (2.2)
Lost of follow-up	1 (4.3)	0	1 (2.2)
Other	0 (0.0)	0	0 (0.0)

Source: Table 10.1 (pg. 59) from Clinical Study Report NWP006-ADD-100.

Table 2. Summary of Patients' Baseline Characteristics

Characteristic	Treatment sequence		Total (N=44)
	Placebo/NWP06 (N =22)	NWP06/Placebo (N=22)	
Age (years)			
Mean (SD)	8.7 (1.81)	9.0 (1.63)	8.8 (1.71)
Min – Max	6 – 12	6 – 12	6 – 12
Age categories n(%)			
6 – 7 years	5 (22.7)	4 (18.2)	9 (20.5)
8 – 10 years	12 (54.5)	13 (59.1)	25 (56.8)
11 –12 years	5 (22.7)	5 (22.7)	10 (22.7)
Gender n (%)			
Male	15 (68.2)	17 (77.3)	32 (72.7)
Female	7 (31.8)	4 (22.7)	12 (27.3)
Race n(%)			
White	18 (81.8)	17 (77.3)	35 (79.5)
Black/African American	1 (4.5)	3 (13.6)	4 (9.1)
Asian	1 (4.5)	2 (9.1)	3 (6.8)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)
Other	2 (9.1)	0 (0)	2 (4.5)
Ethnicity n(%)			
Hispanic/Latino	6 (27.3)	5 (22.7)	11 (25.0)
Non-Hispanic/Latino	16 (72.7)	17 (77.3)	33 (75.0)

ADHD type n (%)			
Inattentive	6 (27.3)	6 (27.3)	12 (27.3)
Hyperactive/Impulsive	1 (4.5)	0 (0)	1 (2.3)
Combined	15 (68.2)	16 (72.7)	31 (70.5)
Not otherwise specified	0 (0.0)	0 (0)	0 (0)
Comorbid psychiatric diagnosis n(%)			
No	16 (72.7)	15 (68.2)	31 (70.5)
Yes	6 (27.3)	7 (31.8)	13 (29.5)
Elimination Disorders	4 (18.2)	0 (0)	4 (9.1)
Oppositional Defiant Disorder	2 (9.1)	6 (27.3)	8 (18.2)
Specific Phobias	0 (0)	2 (9.1)	2 (4.5)

Source: Table 11.2 (pg. 62) from Clinical Study Report NWP06-ADD-100.

3.1.4.2 Sponsor's Results for Primary Endpoint

The sponsor's analysis results for the SKAMP-Combined scores at 4 hours post-dose in the ITT Population are summarized in Table 3.

Table 3. Sponsor's Analysis Results for SKAMP-Combined Scale at 4 Hours Post-Dose.

Time-point	Statistics	Treatment		
		Placebo (N=44)	NWP06 (N=44)	NWP06 - Placebo (N=44)
SKAMP Combined Scale				
4 Hours Post-Dose	N	39	39	39
	Mean (SD)	19.2 (8.38)	7.1 (5.64)	-12.2 (7.19)
	LS Mean (SE)	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)
	95% C.I.	(17.31, 21.86)	(4.85, 9.39)	(-14.75, -10.17)
	P-value			<0.0001
	Effect Size			2.519

Source: Sponsor's Table 11.3 of CSR.

Based on the primary analysis, the sponsor concluded that at 4 hours post-dose, subjects receiving NWP06 had statistically significantly different SKAMP-Combined score (7.12) when compared with subjects receiving placebo (19.58), i.e., patients condition was improved (treatment difference LS mean = -12.46; $p < 0.0001$).

3.1.4.3 Sponsor's Analysis Results for All Time Points

Table 4. Sponsor's Results for All Time Points

	Intent-to-treat population					Clinically evaluable population				
	SKAMP Combined Mean (SE)			effect size	p-value	SKAMP Combined Mean (SE)			effect size	p-value
	Placebo	NWP06	NWP06-Placebo			Placebo	NWP06	NWP06-Placebo		
0.75	16.16 (1.00)	9.84 (1.00)	-6.32 (1.09)	1.32	<.0001	15.71 (0.97)	10.13 (0.97)	-5.58 (0.91)	1.43	<.0001
2	17.28 (1.01)	7.31 (1.01)	-9.98 (1.02)	2.24	<.0001	17.07 (1.02)	7.50 (1.02)	-9.57 (0.98)	2.26	<.0001
4	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	2.52	<.0001	19.55 (1.17)	7.23 (1.17)	-12.32 (1.16)	2.47	<.0001
8	20.41 (1.37)	11.07 (1.37)	-9.33 (1.28)	1.67	<.0001	19.84 (1.34)	10.69 (1.34)	-9.14 (1.31)	1.63	<.0001
10	18.29 (1.37)	14.50 (1.37)	-3.79 (1.11)	0.78	0.0016	18.02 (1.39)	14.19 (1.39)	-3.83 (1.15)	0.78	.0020
12	20.26 (1.58)	15.49 (1.58)	-4.77 (1.40)	0.78	0.0016	20.03 (1.62)	15.31 (1.62)	-4.72 (1.44)	0.76	.0023
post-dose	18.66 (1.02)	10.89 (1.02)	-7.78 (0.74)	2.39	<.0001	18.37 (1.03)	10.84 (1.03)	-7.53 (0.73)	2.39	<.0001

Source: Sponsor's Table 14.2.1.2.1 and Table 14.2.1.2.2 (pp. 133-140) of Clinical Study Report NWP06 ADD-100.

3.1.4.4 Sponsor's Analysis Results for Other Secondary Endpoints

Table 5. Summary and analysis of PERMP (intent-to-treat population) .

	PERMP # of problems attempted				PERMP # of problems correct			
	Mean (SD)			p-value	Mean (SD)			p-value
	Placebo	NWP06	NWP06-Placebo		Placebo	NWP06	NWP06-Placebo	
0.75	85.5 (51.88)	111.1 (62.40)	25.7 (28.21)	<.0001	80.4 (50.21)	105.2 (60.85)	24.8 (27.70)	<.0001
2	82.4 (50.54)	118.2 (63.87)	35.8 (33.39)	<.0001	77.5 (49.47)	113.1 (62.14)	35.6 (32.68)	<.0001
4	75.5 (48.62)	119.2 (64.31)	43.7 (47.68)	<.0001	70.3 (47.16)	114.3 (62.06)	43.9 (45.75)	<.0001
8	72.1 (52.41)	105.2 (63.94)	33.1 (44.23)	<.0001	67.0 (50.46)	99.9 (60.54)	32.9 (40.30)	<.0001
10	82.7 (57.59)	95.6 (63.64)	12.9 (38.88)	.0155	76.5 (56.05)	91.0 (59.59)	14.6 (34.67)	.0016
12	78.1 (51.83)	94.0 (61.69)	16.8 (45.8)	.0019	72.6 (50.94)	88.6 (57.88)	16.9 (42.11)	.0008
post-dose	79.1 (49.39)	107.2 (60.16)	28.1 (30.53)	<.0001	73.8 (48.13)	102.0 (57.45)	28.2 (28.62)	<.0001

Source: Sponsor's Table 14.2.2.1.1 (pg. 450) of Clinical study Report NWP06-ADD-100.

Table 6. Summary and analysis of PERMP (clinically evaluable population) .

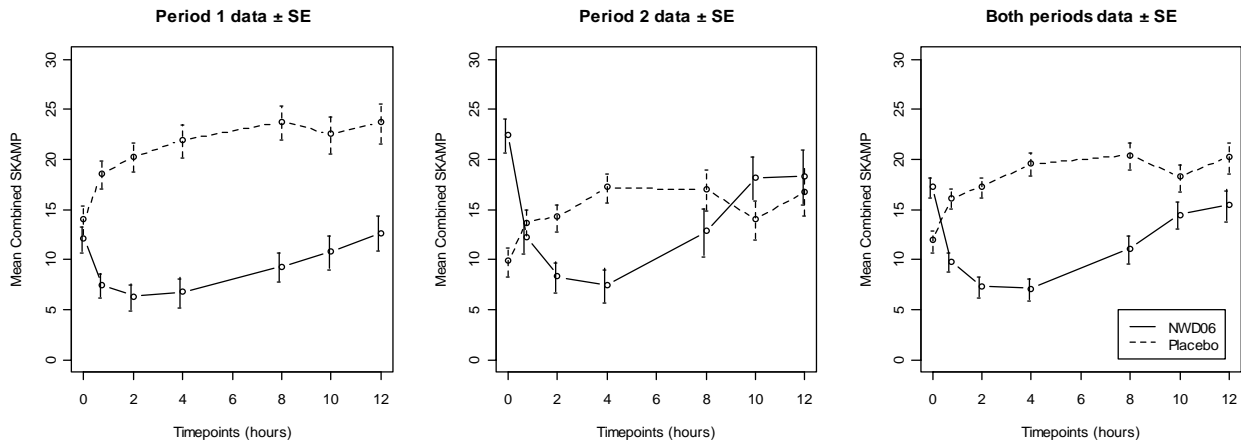
	PERMP # of problems attempted				PERMP # of problems correct			
	Mean (SD)			p-value	Mean (SD)			p-value
	Placebo	NWP06	NWP06-Placebo		Placebo	NWP06	NWP06-Placebo	
0.75	87.3 (51.25)	112.0 (63.00)	24.7 (27.86)	<.0001	82.1 (49.67)	105.9 (61.51)	23.8 (27.31)	<.0001
2	83.2 (50.91)	118.7 (64.63)	35.5 (33.77)	<.0001	78.2 (49.91)	113.5 (62.92)	35.3 (33.06)	<.0001
4	76.8 (48.58)	119.7 (65.10)	42.9 (48.04)	<.0001	71.5 (47.20)	114.6 (62.85)	43.1 (46.06)	<.0001
8	73.6 (52.28)	105.9 (64.66)	32.3 (44.53)	<.0001	68.3 (50.43)	100.4 (61.26)	32.1 (40.51)	<.0001
10	84.3 (57.51)	95.9 (64.46)	11.7 (38.58)	.0258	77.9 (56.07)	91.2 (60.38)	13.3 (34.24)	.0030
12	78.1 (51.83)	94.9 (62.26)	16.8 (45.68)	.0017	72.6 (50.94)	89.4 (58.43)	16.9 (42.11)	.0007
post-dose	80.6 (49.25)	107.9 (60.84)	27.3 (30.54)	<.0001	75.1 (48.10)	102.5 (58.14)	27.4 (28.59)	<.0001

Source: Sponsor’s Table 14.2.2.1.2 (pg. 458) of Clinical study Report NWP06-ADD-100.

3.1.4.5 Statistical Reviewers’ Findings and Comments

Statistical reviewers confirmed the sponsor’s analysis results for the primary, key secondary and other secondary efficacy endpoints. Although the sponsor’s final results based on the combined two-period data showed statistically significant differences between the study drug and placebo at all time points, we found that the treatment effects were very different between two periods at almost all time points. The following Figure 2 shows patients’ LS mean estimates of SKAMP-combined scores over time for both treatment arms in separate periods (i.e., before and after crossover) and the combined periods (see Figure 3 for easy readability).

Figure 2. LS mean estimates of SKAMP-Combined score over time by treatment group.



Source: produced by Dr. Andrejus Parfionovas *

* First two plots: LS mean estimates of the primary efficacy outcome for each post-dose time point on Visits 7 and 8 respectively. Third plot: LS mean estimates from combined Visit 7 and 8 data.

The visual presentation suggests a treatment \times period interaction (i.e., sequence effect) in the study. As one can observe, even though patients on placebo always showed decreasing response and patients in the drug group always showed increasing response at first and then decreasing response after some time points around 2 or 4 hours for both periods. The response trends in two treatment groups did not cross during the first period but did so twice during the second period. In addition, for the first period, patients in different treatment groups had similar pre-dose values on average but for the second period, patients in the drug group had extremely worse pre-dose values than patients in the placebo group. The significant treatment \times period interaction (i.e., the sequence effect) has been confirmed and shown in the following Table 7.

Table 7. Sponsor Calculated P-values for Sequence, Period and Treatment

Time (h)	p-value		
	Sequence	Period	Treatment
0.75	0.0070	0.9331	<0.0001
2	0.0269	0.0544	<0.0001
4	0.1776	0.0837	<0.0001
8	0.0418	0.2164	<0.0001
10	0.0031	0.6160	0.0016
12	0.0339	0.6512	0.0016
Mean of post-dose	0.0103	0.1284	<0.0001

Source: Sponsor's Table 14.2.1.2.1 pg. 133 of Clinical Study Report NWP06-ADD-100.

When a treatment \times period interaction exists in a two by two cross-over study, using the combined period data to draw inference is problematic. In this case, only the first period data can be used for making inference technically. As a result, we performed the set of analyses for all time points using the first period of data only. That is, in addition to the sponsor planned analysis for the cross-over design, we also performed the simple t-test for the first period. The statistical reviewers' results are shown in Table 8 and Table 9.

Table 8. Statistical Reviewers' Analysis Results for SKAMP Combined Score

Time point (h)	Two periods data (ITT)				First period data (ITT)			
	SKAMP Combined Mean (SE)			p-value	SKAMP Combined Mean (SE)			p-value
	Placebo	NWP06	NWP06-Placebo		Placebo	NWP06	NWP06-Placebo	
Pre-dose	11.9318 (1.0515)	17.2807 (1.0515)	5.3489 (0.8208)	<.0001	14.0000 (1.4430)	12.0909 (1.2685)	-1.9091 (1.9213)	0.3269
0.75	16.1578 (0.9982)	9.8382 (0.9982)	-6.3195 (1.0919)	<.0001	18.5882 (1.4517)	7.5000 (1.2761)	-11.0882 (1.9328)	<.0001
2	17.2834 (1.0059)	7.3061 (1.0059)	-9.9773 (1.0180)	<.0001	20.2941 (1.4889)	6.3182 (1.3088)	-13.9759 (1.9823)	<.0001
4	19.5842 (1.1350)	7.1217 (1.1350)	-12.4626 (1.1298)	<.0001	21.9412 (1.7042)	6.7727 (1.4981)	-15.1684 (2.2690)	<.0001
8	20.4051 (1.3702)	11.0709 (1.3702)	-9.3342 (1.2778)	<.0001	23.7647 (1.6869)	9.3182 (1.4828)	-14.4465 (2.2460)	<.0001
10	18.2874 (1.3694)	14.4973 (1.3694)	-3.7901 (1.1129)	0.0016	22.5294 (1.9343)	10.8182 (1.7004)	-11.7112 (2.5755)	<.0001
12	20.2620 (1.5819)	15.4880 (1.5819)	-4.7741 (1.3992)	0.0016	23.7059 (1.9785)	12.6818 (1.7392)	11.0241 (2.6343)	0.0002

Source: computed by Dr. Andrejus Parfionovas

Consistent with what we observed from Figure 2, the drug showed statistically significant difference from placebo at all time points. However, one should note that these results were obtained based on only a total of 44 patients. To assess the robustness of the efficacy findings based on the t-test, we also performed the permutation test. Our results show that differences between the drug and placebo are statistically significant at all post-dose time points (p-value < 0.0001).

One should also note that among those 44 patients in ITT population, actually there were only 39 patients who contributed data for the SKAMP scores. Based on the sponsor defined ITT population, there were 5 patients who had other type of efficacy measurement before the last two visits when the primary efficacy measurements were assessed. It is interesting to note that all of those 5 patients were randomized to the first sequence, i.e., taking placebo in the first period. However, since all the five patients were discontinued prior the double-blind treatment, excluding them from the analysis is not expected to yield a bias in favor of the drug. We brought this situation to the attention of the medical reviewer, and he expressed no conduct issue about these five patients being removed.

3.2 Evaluation of Safety

The study drug's safety was not evaluated in this review. Please refer to the medical review for the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The current section contains FDA's exploratory analysis results on the primary endpoint for the subgroup populations for the first period data only.

4.1 Gender and Race

Table 9. FDA's Subgroup Analysis Results for the primary endpoint (first period data)

Subgroup	N	SKAMP Combined Score at 4 hours post-dose		Difference (NWP06 - Placebo)	SE of difference	p-value
		NWP06	Placebo			
ITT	44	6.7727	21.9412	-15.1684	2.2690	<.0001
Gender						
Male	32	7.6471	22.7273	-15.0802	2.8089	<.0001
Female	12	3.8000	20.5000	-16.7000	3.9362	0.0022
Race/Ethnicity						
White	35	6.7059	22.8571	-16.1513	2.7134	<.0001
Black	4	9.3333	18.0000	-8.6667	6.6667	0.3232
Asian	3	3.5000	20.0000	-16.5000	0.8660	0.0334
Hispanic	11	5.8000	29.2000	-23.4000	3.4612	0.0001

Source: all subgroup analysis were computed by Dr. Andrejus Parfionovas

4.2 Other Special/Subgroup Populations

Table 10. FDA's Subgroup Analysis Results for the primary endpoint (first period data)

Subgroup	N	SKAMP Combined Score at 4 hours post-dose		Difference (NWP06-Placebo)	SE of difference	p-value
		NWP06	Placebo			
ITT	44	6.7727	21.9412	-15.1684	2.2690	<.0001
ADHD type						
Inattentive	12	8.5000	11.6000	-3.1000	3.8546	0.4420
Combined	31	6.1250	26.1818	-20.0568	2.0418	<.0001
Site						
# 1	28	7.2143	23.1667	-15.9524	2.3357	<.0001
# 2	16	6.0000	19.0000	-13.0000	5.1909	0.0293
Using as a factor	44	6.4423	21.4423	-15.0000	2.2743	<.0001
Final dose in OL period						
20 mg	3	6.0000	27.0000	-21.0000	NA	NA
30 mg	17	7.0000	18.2000	-11.2000	3.5262	0.0073
40 mg	13	9.1667	26.3333	-17.1667	5.0536	0.0068
50 mg	4	4.5000	21.0000	-16.5000	1.8028	0.0117
60 mg	7	3.0000	18.3333	-15.3333	5.3955	0.0468
Baseline ADHD severity						
Equal/below median	20	6.2308	14.4286	-8.1978	2.8216	0.0094
Above median	19	7.5556	27.2000	-19.6444	2.4764	<.0001

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints. After evaluation, the statistical review team found that even though the analysis results based on the combined period data showed statistically significant differences between the drug and placebo at all time points, the treatment-by-period interaction appears to be present. Technically speaking, when the treatment by period interaction exists in a cross-over study, using the combined period data to demonstrate the drug's efficacy is problematic. In this case, only the first period of data can be considered. Thus, the statistical review team also performed the analysis using the first period of data and showed that the differences between the drug and placebo were still statistically significant at all time points. The statistical reviewer also performed the permutation test to evaluate the robustness of the efficacy findings. Our permutation test results also showed that the differences between the drug and placebo are statistically significant at all time points for the period I data.

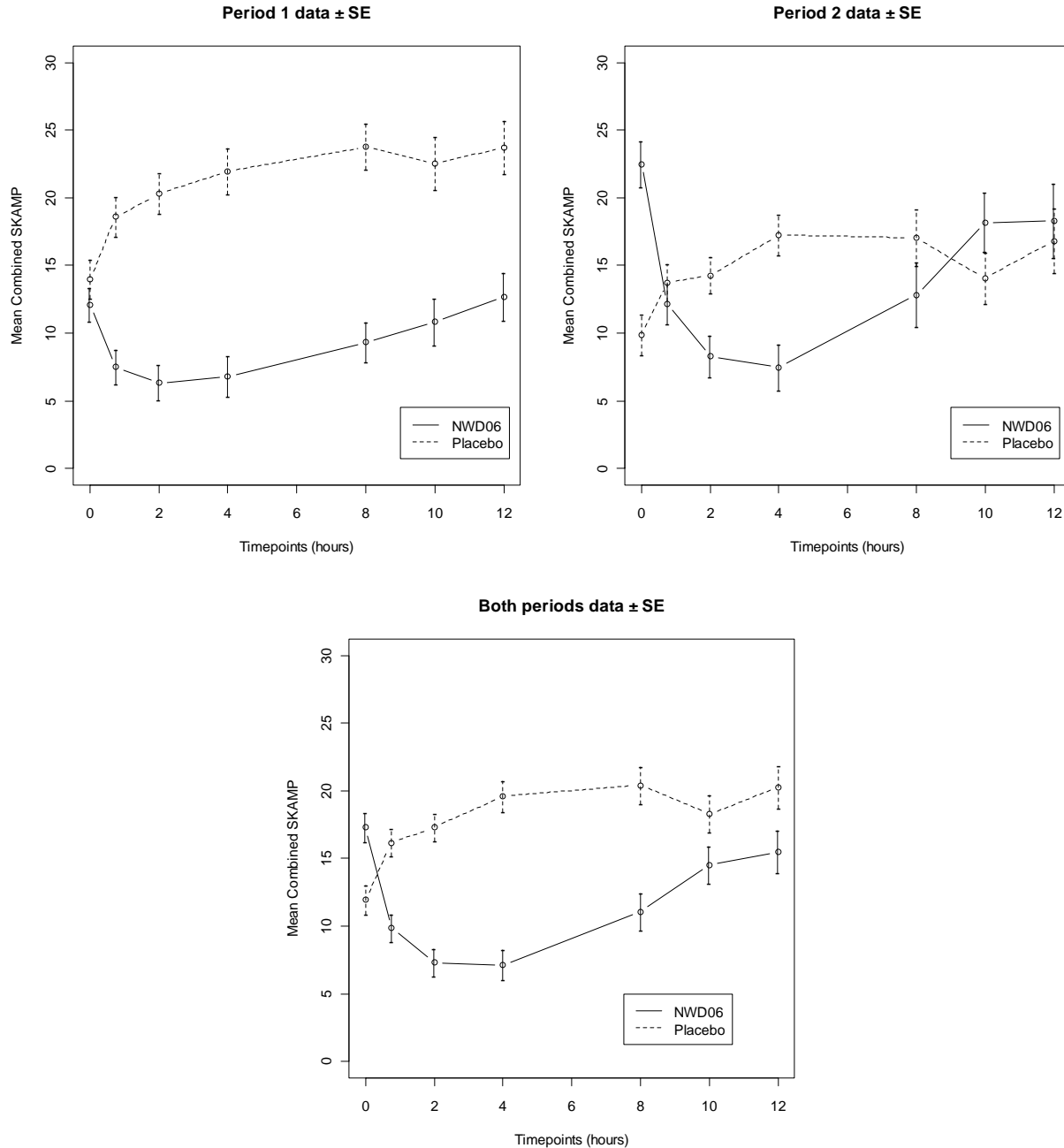
5.2 Conclusions and Recommendations

Based on the first period of data in the cross-over Study NWP06-ADD-100, the efficacy of NWP06 (Methylphenidate HCl) extended-release powder for oral suspension 25 mg/5 mL in treating ADHD pediatric subjects of 6-12 years of age from Hour 0.75 to the overall study period was demonstrated.

cc: NDA 202100
HFD-130/Dr. Laughren
HFD-130/Dr. Mathis
HFD-130/Dr. Ritter
HFD-130/Ms. Chang
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

6. APPENDIX

Figure 3. LS mean estimates of SKAMP-Combined score over time by treatment group (high resolution).



Source: produced by Dr. Andrejus Parfionovas. The graphs repeat Figure 2 in high resolution. First two plots: LS mean estimates of the primary efficacy outcome for each post-dose time point on Visits 7 and 8 respectively. Third plot: LS mean estimates from combined Visit 7 and 8 data. See Appendix Table 11 for values.

Table 11. FDA's Analysis Results for the SKAMP-Combined Score with 95% C.I.

		Primary Efficacy Assessment Time (hrs)						
		Pre-dose	0.75	2	4	8	10	12
Period 1 LS mean lower 95% C.I. upper 95% C.I.	NWP06	12.0909	7.5000	6.3182	6.7727	9.3182	10.8182	12.6818
		9.5207	4.9143	3.6663	3.7373	6.3137	7.3729	9.1578
		14.6612	10.0857	8.9700	9.8081	12.3227	14.2635	16.2058
	Placebo	14.0000	18.5882	20.2941	21.9412	23.7647	22.5294	23.7059
		11.0761	15.6468	17.2774	18.4881	20.3468	18.6101	19.6970
		16.9239	21.5297	23.3108	25.3942	27.1826	26.4488	27.7148
Period 2 LS mean lower 95% C.I. upper 95% C.I.	NWP06	22.4706	12.1765	8.2941	7.4706	12.8235	18.1765	18.2941
		19.0156	9.0445	5.1883	4.0144	8.0171	13.7740	12.7905
		25.9255	15.3084	11.3999	10.9267	17.6299	22.5789	23.7978
	Placebo	9.8636	13.7273	14.2727	17.2273	17.0455	14.0455	16.8182
		6.8266	10.9742	11.5426	14.1891	12.8204	10.1755	11.9802
		12.9007	16.4804	17.0029	20.2654	21.2705	17.9154	21.6562
Both LS mean lower 95% C.I. upper 95% C.I.	NWP06	17.2807	9.8382	7.3061	7.1217	11.0709	14.4973	15.4880
		15.1501	7.8157	5.2680	4.8219	8.2946	11.7227	12.2828
		19.4114	11.8608	9.3443	9.4214	13.8471	17.2720	18.6932
	Placebo	11.9318	16.1578	17.2834	19.5842	20.4051	18.2874	20.2620
		9.8012	14.1352	15.2453	17.2844	17.6288	15.5128	17.0568
		14.0624	18.1803	19.3216	21.8840	23.1814	21.0621	23.4672

Source: computed by Dr. Andrejus Parfionovas

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/s/

ANDREJUS PARFIONOVAS
04/20/2011

YEH FONG CHEN
04/20/2011

PEILING YANG
04/20/2011
I concur.

HSIEN MING J J HUNG
04/20/2011