# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**202100Orig1s000**

# STATISTICAL REVIEW(S)

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

# 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 |
| **Review Priority:** | Standard |
| **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. |
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**Keywords:** ADHD, Cross-Over Design, treatment by period interaction, sequence effect

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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):
\\Cdsesub1\evsprod\NDA202100\0000\m5\datasets\nwp06-add-100\analysis

# 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Description

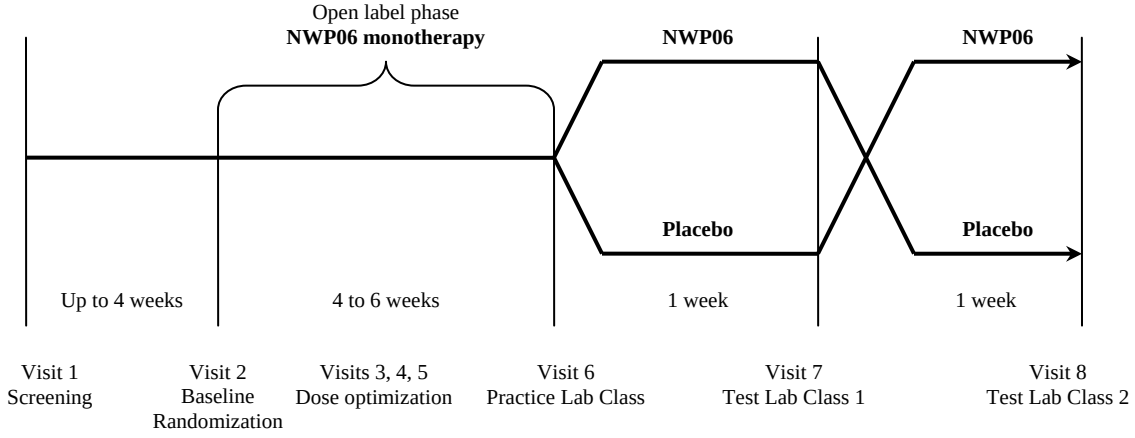
***Study Objectives***

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:
    - Any stimulant (e.g., methylphenidate, amphetamine, Ritalin, Ritalin SR, Metadate ER, Concerta,
    - dextromethylphenidate, Focalin, dextroamphetamine, Dexedrine, Adderall).
    - Atomoxetine (Strattera) SSRIs (e.g., fluoxetine. paroxetine).
    - Tricyclic antidepressants.
    - Clonidine MAOIs (monoamine oxidase inhibitors).
    - Mood stabilizers (e.g., lithium, valproate, quetiapine).
    - Antipsychotics (e.g., risperidone, olanzapine).
    - Anticonvulsants.
    - Sedative hypnotics (unless stable dose before and during the clinical study).
    - Coumarin anticoagulants.
    - Anticonvulsants.
    - Halogenated anaesthetics.
    - 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-Deportment 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., $p\leq0.05$) at that time point.
- If the difference between the two treatments was statistically significant (i.e., $p\leq0.05$) 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., $p\leq0.05$).
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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 Dispostion

| 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 | | NWP06 - Placebo (N=44) |
|---|---|---|---|---|
| | | Placebo (N=44) | NWP06 (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) | | | | | SKAMP Combined Mean (SE) | | | | |
| | Placebo | NWP06 | NWP06-Placebo | effect size | p-value | Placebo | NWP06 | NWP06-Placebo | effect size | p-value |
| 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) | | | | Mean (SD) | | | |
| | Placebo | NWP06 | NWP06-Placebo | p-value | Placebo | NWP06 | NWP06-Placebo | p-value |
| 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) .

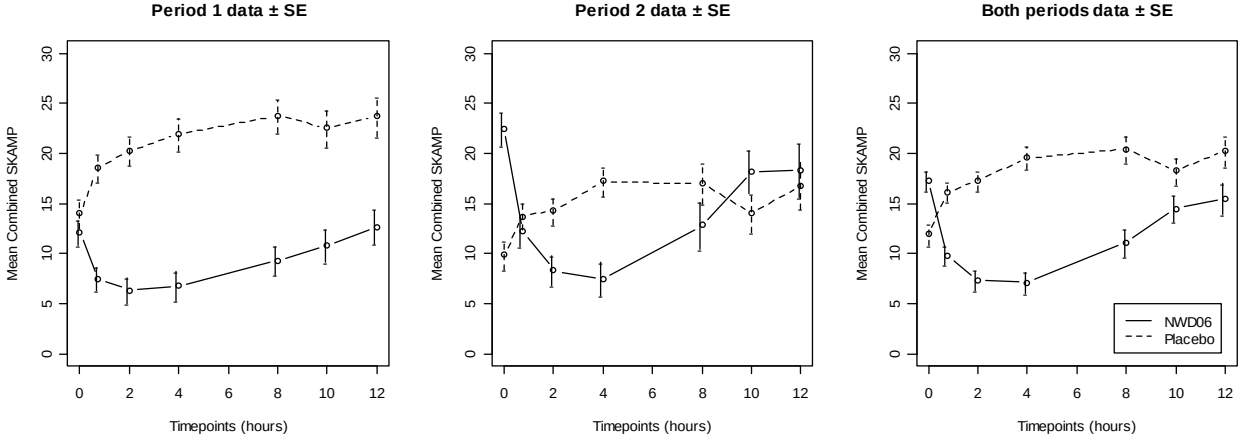
| | PERMP # of problems attempted | | | | PERMP # of problems correct | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | | | p-value | Mean (SD) | | | p-value |
| | Placebo | NWP06 | NWP06-Placebo | | Placebo | NWP06 | NWP06-Placebo | |
| 0.75 | 87.3 (51.25) | 112.0 (63.00) | 24.7 (27.86) | <.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 × 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 × 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 × 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
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HFD-130/Dr. Mathis
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HFD-700/Ms. Patrician
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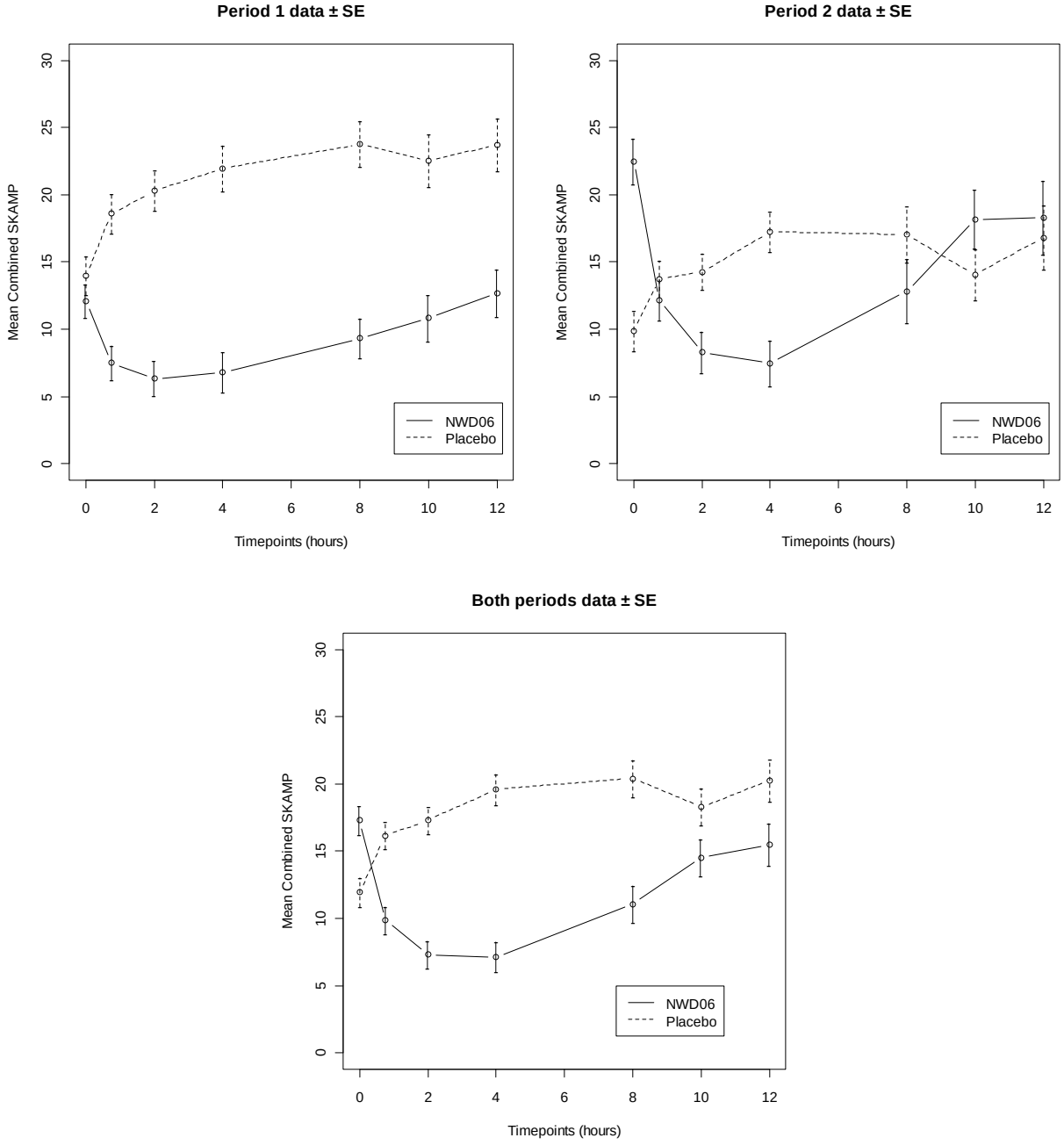
HFD-710/Dr. Hung
HFD-710/Dr. Yang

# 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** | **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 |
| LS mean | | 14.6612 | 10.0857 | 8.9700 | 9.8081 | 12.3227 | 14.2635 | 16.2058 |
| lower 95% C.I. | **Placebo** | 14.0000 | 18.5882 | 20.2941 | 21.9412 | 23.7647 | 22.5294 | 23.7059 |
| upper 95% C.I. | | 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** | **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 |
| LS mean | | 25.9255 | 15.3084 | 11.3999 | 10.9267 | 17.6299 | 22.5789 | 23.7978 |
| lower 95% C.I. | **Placebo** | 9.8636 | 13.7273 | 14.2727 | 17.2273 | 17.0455 | 14.0455 | 16.8182 |
| upper 95% C.I. | | 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** | **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 |
| LS mean | | 19.4114 | 11.8608 | 9.3443 | 9.4214 | 13.8471 | 17.2720 | 18.6932 |
| lower 95% C.I. | **Placebo** | 11.9318 | 16.1578 | 17.2834 | 19.5842 | 20.4051 | 18.2874 | 20.2620 |
| upper 95% C.I. | | 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/

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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

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 202100 **Applicant:** Next Wave Pharmaceuticals **Stamp Date:** July 29, 2010

**Drug Name:** Methylpheniate HCL **NDA/BLA Type:** Regular

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. | × | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | × | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | × | | | |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | × | | | |

**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. | × | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | × | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | × | |
| Appropriate references for novel statistical methodology (if present) are included. | × | | | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | | | × | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | × | | | |

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| | |
|---|---|
| Reviewing Statistician | Date |
| Supervisor/Team Leader | Date |

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