CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-977

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-977 (N000)
Drug Name:	Lisdexamfetamine Caps
Indication:	ADHD in Pediatric Population (Ages 6-12)
Applicant:	New River Pharmaceuticals, Inc
Dates:	Date of Document: 12/06/2005
	PDUFA Due Date: 10/06/2006
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Drug Products, HFD-130
Clinical Team:	Clinical Reviewer: Michelle Chuen, M.D.
	Clinical Team Leader: Ni Aye Khin, M.D.
Project Manager:	Susan Player

Table of Contents

1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted one crossover study (Study 201) and one parallel study (Study 301) with three doses of NRP104 (30, 50, and 70 mg/day) to demonstrate the efficacy for treating children patients with Attention Deficit/Hyperactivity Disorder (ADHD). After evaluation, it was determined that the data from both studies supported the efficacy of NRP104. [redacted]

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Two efficacy studies were submitted in this application to support the efficacy for NRP104 (30, 50, and 70 mg/day) as a treatment for children's ADHD. Study 201 was a crossover study and Study 301 was a parallel-study. The primary endpoint for Study 201 was the SKAMP-DS scores and for Study 301 was the ADHD Rating Scale. Based on the analysis results, the sponsor claimed that daily dose of NRP104 30 mg to 70 mg appears to be an efficacious treatment for childhood ADHD [redacted]

1.3 STATISTICAL ISSUES AND FINDINGS

Both efficacy studies (Studies 201 and 301) were determined to be positive studies with respect to primary endpoints. In addition to the overall efficacy claim, the sponsor [redacted]

2. INTRODUCTION

2.1 OVERVIEW

The sponsor submitted this application with three doses of NRP104, a prodrug of d-amphetamine to seek the approval for being a treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in children patients aged 6 to 12 years old. The efficacy claim for NRP104 was based on two randomized, double-blind, controlled studies, named Studies 201 and 301.

Study 201 was a randomized, double-blind, placebo and active-controlled, phase 2, crossover trial with 3 treatments [NRP104 (30, 50, and 70 mg/day), Adderall XR® (10, 20, and 30 mg/day), and placebo] and 3 treatment periods of 1 week. The primary endpoint was the average of the SKAMP-DS (the Swanson, Kotkin, Alger, M. Flynn, and Pelham rating scales for deportment) scores across a treatment assessment day during the randomized treatment period.

Study 301 was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial with 4 treatment groups [NRP104 (30, 50, and 70 mg/day) and placebo group] for 4 weeks. The primary endpoint was the ADHD Rating Scale (ADHD-RS) assessed on the last treatment visit post randomization.

Table 2.1 summarizes the sponsor's efficacy analysis results for the primary endpoint for both studies. Based on the results, the sponsor claimed that all three doses (30, 50 and 70 mg) of NRP104 were demonstrated to show efficacy comparable with that of the currently marketed product Adderall XR® and may have substantially reduced diversion and abuse liability.

Table 2.1 Summary of Sponsor's Analysis Results for Primary Endpoints (SKAMP-DS and ADHD-RS, respectively) for Studies 201 and 301

Study 201		**NRP204**	**Adderall XR®**		**Placebo**
N (ITT=50)		50	50		50
Mean (SD)		0.8 (0.7)	0.8 (0.8)		1.7 (1.2)
LS Mean (SE)		0.8 (0.1)	0.8 (0.1)		1.7 (0.1)
Difference in LS Mean (vs. Placebo)		-0.9**	-0.9**		
Study 301		**Placebo**	**NRP104 30 mg**	**NRP104 50 mg**	**NRP104 70 mg**
Baseline: Total Score	N	72	69	71	73
	Mean (SD)	42.4 (7.13)	43.2 (6.68)	43.3 (6.74)	45.1 (6.82)
Endpoint: Change from Baseline	N	72	69	71	73
	LS Mean (SE)	-6.2 (1.56)	-21.8 (1.60)	-23.4 (1.56)	-26.7 (1.54)
Placebo-Adjusted Difference	LS Mean		-15.58****	-17.21****	-20.49****

****P<0.0001

2.2 DATA SOURCES

This NDA was submitted by paper copies. Only data sets and some data definitions files were submitted electronically. The data sets for this NDA submission were stored in the center's electronic document room (EDR) by the following directory: \\CDSESUB1\N21977\N_000\2005-12-06.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 Description of Study NRP104.201

This study was entitled "A Phase 2, Randomized, Double-Blind, Placebo- and Active-Controlled, 3-Treatment, 3-Period, Crossover Study with One Week Per Treatment and Once-a-Day Dosing of Either NRP104, Adderall XR®, or Placebo in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD)." There were four study sites in USA participating in the conduct of the study.

3.1.1.1 Study Objectives

Primary Objective

The primary objective of this study was to assess, in a controlled environment, the efficacy and safety of NRP104 and Adderall XR®, compared to placebo in treatment of children (aged 6-12) with ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision criteria (DSM-IV-TR). The therapeutic responses were determined using the SKAMP and PERMP measured throughout a treatment assessment day.

Secondary Objectives

The secondary objectives were:

- To assess the duration of therapeutic responses to NRP104 and Adderall XR® compared to placebo. The duration of therapeutic responses were determined using SKAMP and PERMP measured at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post morning dose.

- To evaluate the efficacy of NRP104 and Adderall XR® compared to placebo, based on the Clinical Global Impression (CGI).

- To evaluate the safety of NRP104 based on occurrence of treatment-emergent adverse events and specific evaluation of blood pressure, and heart rate.

- To evaluate PK profile and PK/PD relationship of NRP104 after multiple doses.

3.1.1.2 Study Design

This was a Phase II, randomized, multi-center, double-blind, 3-treatment and 3-period crossover study conducted in a school laboratory environment to evaluate efficacy and safety of NRP104 (30 mg, 50 mg, or 70 mg) and Adderall XR® (10 mg, 20 mg, or 30 mg) compared with placebo in treatment of children with ADHD. The school laboratory environment included an analog classroom and lasted for a 13-hour school day. The complete study consisted of three periods and one final study visit. The three periods were one week of screen period, three weeks of dose titration period and three weeks of double blind crossover period.

In the dose titration period, eligible subjects who met inclusion/exclusion criteria received Adderall XR® for the treatment of ADHD in an open-label fashion. Subjects started the dose titration with 10 mg per day of Adderall XR® for the first week. At the next two weekly visits (Visit 3, Visit 4), based on the CGI, interview with the parents, and safety data, the investigator evaluated the subject's therapeutic responses and tolerability to treatment, and decided whether the current Adderall XR® dose should be increased or should be remain the same for the second week of titration, or should be increased, decreased or should remain the same for the third week. The investigator made the final selection of Adderall XR® dose at the end of the third titration week (Visit 5), and this selected dose was considered as the optimal daily dose and would be used in the subsequent double-blind phase.

Based on the optimal Adderall XR® dose obtained for the subject at the end of the third titration week, the exact daily dose of the three treatments each randomized subject received over the course of the 3-week double-blind period was determined using the following conversion table:

Table 3.1.1 Treatment Dose to Receive in Double-Blind Period Instruction

Optimal Adderall XR® Dose Obtained in Dose Titration Period	**Treatment Dose to Receive in Double-Blind Crossover Period**
Adderall XR® 10 mg/day	NRP104 30 mg/day or Adderall XR® 10 mg/day (1×10 mg) or Placebo
Adderall XR® 20 mg/day	NRP104 50 mg/day or Adderall XR® 20 mg/day (2×10 mg) or Placebo
Adderall XR® 30 mg/day	NRP104 70 mg/day or Adderall XR® 30 mg/day (3×10 mg) or Placebo

During each double-blind week, subjects took the treatment dose each morning at home for the first 6 days, and the Day 7 dose of the treatment was administered at the laboratory school visit. Subjects returned on Day 7 of each double-blind week for a laboratory school assessment.

During each laboratory school assessment day (including the practice visit), classroom sessions were arranged at approximately 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post morning dose, and each classroom session lasted for about 30 minutes. Efficacy measures of the SKAMP and PERMP were collected during each of the 8 sessions. In addition, during the double-blind period, the CGI was assessed at the laboratory school visit for that treatment week.

At the end of the 7th day of the first and second double-blind weeks (i.e., Visits 6 and 7), subjects received blinded treatment supplies for the next week.

For the final study visit, all subjects who received study medication including the open label Adderall XR® were seen for a final study visit (or end of study visit) for safety evaluation. The final study visit occurred within three (3) days following the last laboratory school visit or at the time of early study withdrawal.

3.1.1.3 Efficacy Measures and Statistical Analyses

Primary Efficacy Measure

The primary efficacy measure used in this study was the SKAMP Deportment Rating Scale (SKAMP-DS).

Secondary Efficacy Measures

Secondary efficacy measures in this study included SKAMP-AS, PERMP and CGI.

Primary Efficacy Analysis

The primary efficacy analysis was conducted on the primary efficacy endpoint (i.e., the average of SKAMP-DS across the treatment assessment day), using a mixed-effects model of analysis of variance (ANOVA) for the ITT population. The ITT population was defined as all of the randomized subjects who had at least one SKAMP-DS treatment average score post randomization.

The mixed-effects ANOVA model utilized SAS PROC MIXED to perform this analysis and defined treatment (3 levels) and period (3 levels) as fixed effects, and subject-within-site as random effect. The 3 treatment levels were NRP104 (30 mg, 50 mg, and 70 mg combined), Adderall XR® (10 mg, 20 mg, and 30 mg combined), and placebo. The variance components covariance structure was used for this model as planned in the SAP, and the SAS Type III estimation was reported.

Given a significant overall treatment effect ($p<0.05$), pair-wise comparisons of least-square means between individual treatments were further conducted using a t-test. The primary efficacy pair-wise comparison in this study was NRP104 (30 mg, 50 mg, and 70 mg combined) vs. placebo, and the significance level for this comparison was set at 0.05. Comparisons between Adderall XR® (10 mg, 20 mg, and 30 mg combined) vs. placebo and between NRP104 vs. Adderall XR® were reported for reference.

To check if the assumptions of the ANOVA model were met, residuals were examined through histograms, normal plots, Shapiro-Wilk's test, and plots of residuals versus fitted values. If there was strong evidence that the assumptions were not satisfied, the nonparametric Wilcoxon Signed Rank test was to be utilized to perform the pairwise comparisons as indicated above.

To check if there was a strong evidence of carryover effects, the 1st order carryover effect was included in the ANOVA model described above and tested at the significance level of 0.05. If the 1st order carryover effect was found to be significant, the results from both analytical models (i.e., with and without the 1st order carryover effect) were to be evaluated for consistency. Should evidences of inconsistency be found for the treatment effect between the two analytical models, a simple 1-way ANOVA was to be utilized to assess the differences among the three treatments, respectively, for each individual randomized period.

Secondary Efficacy Analysis

The same ANOVA model and analytical approach described above was used to evaluate, respectively, the SKAMP-AS, PERMP-AS, and PERMP-CS averages across the treatment assessment day as well as the CGI-I, for the ITT population and PP population, respectively. In this review, however, only sponsor's analysis results for the ITT population were reported.

3.1.2 Efficacy Results for Study NRP104.201

3.1.2.1 Patient Populations and Baseline Demographic Characteristics

Table 3.1.2.1 summarizes overall subject disposition for this study. A total of 4 investigators enrolled a total of 52 subjects in this study. All of these subjects received the open-label titration treatment and were randomized to double-blind treatment. Of these, 2 subjects terminated the study within the first double-blind treatment week after randomization. Table 3.1.2.2 summarizes patients' demographics and baseline characteristics for the safety and ITT populations. Thirty-six percent of subjects in the safety population were female, and 64% were male. Caucasian and African American counted 56% and 23%, and the rest were 15% for Hispanic, 6% for Native Hawaiian/Pacific Islanders and other races. The ages of study participants ranged between 6 and 12 years with a mean age of 9.1 years (s.d.=1.7). Of the 52 subjects, 30 (or 58%) aged 6-9 years and 22 (or 42%) aged 10-12 years. Subjects weighed between 37 and 150 pounds with the mean of 73 pounds, and their heights ranged from 43.5 to

63 inches with the mean of 53.0 inches. Since this was a crossover design, no inferential statistical analyses were conducted on demographic data.

Table 3.1.2.1 Subject Disposition for Study 201

	No. of Subjects
Enrolled	52
Titrated in the Open-Label Period	52
Randomized into the Double-Blind Period	52
Completed	50
Discontinued Post Randomization	2
Adverse Events	1
Lost to Follow-up	1
Analysis populations	
Efficacy ITT	50
Efficacy PP	50
Safety	52

Table 3.1.2.2 Demographic and Baseline Characteristics of Safety (or Treated) Population for Study 201

Characteristic	Category/Parameter	Safety Population (N=52)	ITT Population (N=50)
Ethnicity/Race (%)	Caucasian	29 (56%)	27 (54%)
	African American	12 (23%)	12 (24%)
	Hispanic	8 (15%)	8 (16%)
	Others	3 (6%)	3 (6%)
Gender (%)	Male	33 (64%)	31 (62%)
	Female	19 (36%)	19 (38%)
Height (inches)	Mean (SD)	53.0 (4.7)	53.1 (4.8)
Weight (pounds)	Mean (SD)	73.4 (24.9)	73.7 (25.3)
Age (yrs)	Mean (SD)	9.1 (1.7)	9.1 (1.7)
ADHD Type (%)	Combined	52 (100%)	50 (100%)
ADHD onset age (yrs)	Mean (SD)	5.8	5.8
Years of Diagnosis	Mean (SD)	3.3 (2.3)	3.3 (2.3)
CGI Severity (%)	Moderately ill	32 (62%)	30 (60%)
	Markedly ill	11 (21%)	11 (22%)
	Severely ill	9 (17%)	9 (18%)

Source: Table 4 of Sponsor's Clinical Study Report

3.1.2.2 Optimal Adderall XR® Dose

Table 3.1.2.3 summarizes subjects' optimal dose of Adderall XR® achieved at the end of dose titration. Out of 52 subjects titrated, Adderall XR® 30 mg per day was determined as the optimal dose for almost half of them (48%, 25 subjects); Adderall XR® 20 mg per day as the optimal dose for 33% (17 subjects); and, Adderall XR® 10 mg per day as the optimal dose for 19% (10 subjects).

Table 3.1.2.3 Optimal Adderall XR® Daily Dose Achieved at the End of Dose Titration for Study 201

Daily Adderall XR® Dose	Subjects Titrated (N=52)	ITT Population (N=50)
10 mg	10 (19%)	8 (16%)
20 mg	17 (33%)	17 (34%)
30 mg	25 (48%)	25 (50%)

Source: Table 5 of Sponsor's Clinical Study Report

3.1.2.3 Sponsor's Efficacy Results for Primary Endpoint

Table 3.1.2.4 summarizes the ITT subjects' SKAMP Deportment averages and least-square (LS) means across the 8 class sessions of the treatment assessment day. As is shown in the table, both NRP104 and Adderall XR® showed markedly favorable results in terms of controlling ADHD symptoms and behaviors, as compared to placebo. The ANOVA demonstrated that the treatment effect on SKAMP Deportment average across the assessment day was significant, and both pair-wise comparisons of NRP104 vs. placebo and Adderall XR® vs. placebo were also significant ($p<0.0001$).

Table 3.1.2.4 Sponsor's Analysis Results for Primary Efficacy Endpoint, SKAMP Deportment Average for Study 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=50)	50	50	50
Mean (SD)	0.8 (0.7)	0.8 (0.8)	1.7 (1.2)
LS Mean (SE)	0.8 (0.1)	0.8 (0.1)	1.7 (0.1)
Difference in LS Mean (vs. Placebo)	-0.9**	-0.9**	

**P<0.0001. Source: Table 6 of Sponsor's Clinical Study Report

3.1.2.4 Sponsor's Efficacy Results for Secondary Endpoints

The secondary efficacy endpoints included, across the treatment assessment day, the average of SKAMP Inattention, the average of PERMP Attempted, and the average of PERMP Correct, as well as the CGI Improvement. The same analytical approach used for the primary efficacy endpoint was utilized for the secondary efficacy endpoints.

SKAMP Inattention

Table 3.1.2.5 summarizes the sponsor's analysis results for ITT subjects' SKAMP Inattention averages across the 8 class sessions of the treatment assessment day. The LS means were 1.2, 1.2, and 1.8, respectively, for NRP104, Adderall XR®, and placebo. Both NRP104 and Adderall XR® showed markedly favorable results in terms of controlling ADHD symptoms and behaviors, as compared to placebo. The ANOVA demonstrated pair-wise comparisons of NRP104 vs. placebo and Adderall XR® vs. placebo were both significant.

Table 3.1.2.5 Sponsor's Analysis Results for SKAMP Inattention Score for ITT Population for Study 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=50)	50	50	50
Mean (SD)	1.2 (0.7)	1.2 (0.7)	1.8 (0.8)
LS Mean (SE)	1.2 (0.1)	1.2 (0.1)	1.8 (0.1)
Difference in LS Mean (vs. Placebo)	-0.6**	-0.5**	

**P<0.0001. Source: Table 10 of Sponsor's Clinical Study Report

PERMP Attempted

Table 3.1.2.6 summarizes the sponsor's analysis results for ITT subjects' PERMP Attempted average across the 8 class sessions of the treatment assessment day. The LS means were 133.3, 133.6, and 88.2, respectively, for NRP104, Adderall XR®, and placebo. The ANOVA demonstrated that pair-wise comparisons of NRP104 vs. placebo and Adderall XR® vs. placebo were both significant.

Table 3.1.2.6 Sponsor's Analysis Results for PERMP Attempted Score for ITT Population for Study 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=50)	50	50	50
Mean (SD)	132.8 (64.0)	133.6 (55.1)	88.7 (34.9)
LS Mean (SE)	133.3 (7.4)	133.6 (7.4)	88.2 (7.4)
Difference in LS Mean (vs. Placebo)	45.1**	45.5**	

**P<0.0001. Source: Table 11 of Sponsor's Clinical Study Report

PERMP Correct

Table 3.1.2.7 summarizes the sponsor's analysis results for ITT subjects' PERMP Correct averages across the 8 class sessions of the treatment assessment day. The LS means were 129.1, 129.4, and 84.6, respectively, for NRP104, Adderall XR®, and placebo. Both NRP104 and Adderall XR® showed markedly favorable results in terms of controlling ADHD symptoms and behaviors, as compared to placebo. The ANOVA demonstrated that pair-wise comparisons of NRP104 vs. placebo and Adderall XR® vs. placebo were both significant.

Table 3.1.2.7 Sponsor's Analysis Results for PERMP Correct Score for ITT Population for Study 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=50)	50	50	50
Mean (SD)	129.1 (64.0)	129.4 (51.8)	84.6 (36.1)
LS Mean (SE)	129.6 (7.3)	129.4 (7.3)	84.1 (7.3)
Difference in LS Mean (vs. Placebo)	45.5**	45.3**	

**P<0.0001. Source: Table 12 of Sponsor's Clinical Study Report

CGI Improvement

Table 3.1.2.8 summarizes the sponsor's analysis results for ITT subjects' CGI Improvement averages. The LS means were 2.2, 2.3 and 4.2, respectively, for NRP104, Adderall XR®, and placebo. Both NRP104 and Adderall XR® showed markedly improvement from baseline, as compared to placebo. The ANOVA demonstrated that pair-wise comparisons of NRP104 vs. placebo and Adderall XR® vs. placebo were both significant.

Table 3.1.2.8 Sponsor's Analysis Results for CGI Improvement for ITT Population for Study 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=50)	50	50	50
Mean (SD)	2.2 (1.3)	2.3 (1.1)	4.1 (1.5)
LS Mean (SE)	2.2 (0.2)	2.3 (0.2)	4.2 (0.2)
Difference in LS Mean (vs. Placebo)	-2.0**	-1.8**	
No. of Subjects by CGI-I Score			
1 – very much improved	16 (32%)	8 (16%)	1 (2%)
2 – much improved	21 (42%)	28 (56%)	8 (16%)
3 – minimally improved	5 (10%)	6 (12%)	4 (8%)
4-7 (no change or worsening)	8 (16%)	8 (16%)	37 (74%)

**P<0.0001. Source: Table 13 of Sponsor's Clinical Study Report

3.1.2.5 Sponsor's Analysis Results for Duration of Therapeutic Responses

The duration of therapeutic responses was assessed over each assessment session on both the primary efficacy measure and secondary efficacy measures, using the same mixed effects model of analysis of variance (ANOVA) for the ITT population. The ANOVA model included treatment (3 levels) and period (3 levels) as fixed effects, and subject-within-site as random effect. The 3 treatment levels were NRP104 (30 mg, 50 mg, and 70 mg combined), Adderall XR® (10 mg, 20 mg, and 30 mg combined), and placebo. The eight classroom sessions were conducted post the morning dose at 1 hour, 2 hours, 3 hours, 4.5 hours, 6 hours, 8 hours, 10 hours, and 12 hours. Tables 3.1.2.9 show the sponsor's analysis results for primary endpoint SKAMP Deportment. As shown in the tables, both NRP104 and Addreall XR showed significant treatment effects within 2 hours, and the therapeutic effect continued throughout the entire assessment time period (12 hours) for the primary endpoint.

Table 3.1.2.9 Sponsor's Analysis Results for SKAMP Deportment by Sessions for Study 201 (LS Mean and SE)

Session No. – Time Point	NRP104	Adderall XR®	Placebo
Session 1 – 1 Hour Post Dose	1.1 (0.2)	1.2 (0.2)	1.3 (0.2)
Session 2 – 2 Hours Post Dose	0.7 (0.2)**	0.9 (0.2)**	1.5 (0.2)
Session 3 – 3 Hours Post Dose	0.7 (0.2)**	0.6 (0.2)**	1.7 (0.2)
Session 4 – 4.5 Hours Post Dose	0.6 (0.1)**	0.6 (0.1)**	1.9 (0.1)
Session 5 – 6 Hours Post Dose	0.5 (0.2)**	0.6 (0.2)**	1.8 (0.2)
Session 6 – 8 Hours Post Dose	0.7 (0.1)**	0.8 (0.1)**	1.8 (0.1)
Session 7 – 10 Hours Post Dose	0.9 (0.1)**	0.9 (0.1)**	1.5 (0.1)
Session 8 – 12 Hours Post Dose	0.8 (0.1)**	0.9 (0.1)**	1.7 (0.1)

**P<0.0001 (vs. Placebo). Source: Table 14 of Sponsor's Clinical Study Report

3.1.2.6 Statistical Reviewer's Findings and Comments

The sponsor's analysis results for the primary and secondary endpoints were all confirmed by the statistical reviewer. According to the analysis results, Study 201 was a positive study, in which the data supported the efficacy of NRP104 in treatment of children with ADHD in a controlled environment. [redacted]

3.1.3 Description of Study NRP104.301

This study was entitled "A Phase 3, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo Controlled Study of NRP104 in Children Aged 6-12 Years with Attention Deficit Hyperactivity Disorder (ADHD)." There were 40 centers in the USA participating in the conduct of the study.

3.1.3.1 Study Objectives

Primary

The primary objective of this study was to assess the efficacy and safety of NRP104 (administered as a single dose of 30, 50 and 70 mg in the morning) compared to placebo in treatment of children (aged 6-12) with ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision criteria (DSM-IV-TR®).

Secondary

The secondary objectives were:

- To assess duration of therapeutic responses of NRP104 using the efficacy assessments performed in the morning (around 10 am), afternoon (around 2 pm), and evening (around 6 pm), separately.

- To assess global impressions of ADHD severity and improvement from clinician.

- To compare the safety and tolerability of NRP104 to placebo.

3.1.3.2 Study Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of 4-week duration of the efficacy and safety with three daily doses of NRP104 compared to placebo in children (aged 6 to 12 years) with ADHD. The three NRP104 doses were 30 mg/day, 50 mg/day, and 70 mg/day. Following one week washout of previous stimulant treatment (if any), subjects meeting entry criteria were randomly assigned to one of the four treatment arms in 1:1:1:1 ratio to receive a daily morning dose of either active drug or placebo for 4 weeks. Those subjects who were randomized to NRP104 50 mg and 70 mg doses received their assigned doses by a forced dose-escalation. Subjects randomized to the 70 mg dose were titrated to the assigned dose over a 2-week period, i.e., receiving the 30 mg dose in the 1st week, the 50 mg dose in the 2nd week, and the 70 mg dose in the 3rd and 4th week. Subjects randomized to 50 mg were titrated to the assigned dose over a 1 week period., i.e., receiving the 30 mg dose in the 1st week and the 50 mg dose for the rest of the treatment weeks. Subjects randomized to either 30 mg dose or placebo received the assigned treatment dose throughout the 4-week randomized treatment period.
The study consisted of three phases conducted over approximately 6 weeks, including one week to screen subjects, one week to wash out current psychoactive medications, and four weeks for the double-blind treatment. Six (6) visits were scheduled, one to screen candidate subjects (Visit 1: Screening), one to randomize subjects into double-blind treatment (Visit 2: Baseline), and 4 to assess double-blind treatment (Visits 3, 4, 5, and 6). Following the screening visit, eligible subjects were contacted by site personnel via telephone to inform the subject that he or she met all of the entering criteria, and all of the medications for the treatment of ADHD the subject was currently taking, if any, should be stopped. During the Washout period by a phone contact, the visit dates were scheduled for the Baseline visit (Visit 2) to ensure that the washout would have lasted for at least one week, and for the subsequent study visits (Visits 3 to 6). The subsequent visits were scheduled 7 days apart (+/- 2 days) from the Baseline visit and from each other.

3.1.3.3 Efficacy Measures and Statistical Analyses

<u>Primary Efficacy Measure</u>

The primary efficacy measure of the study was the ADHD-RS, Version IV. The ADHD-RS assessed on the last treatment visit post randomization was defined as the treatment endpoint for primary efficacy evaluation.

<u>Secondary Efficacy Measures</u>

The secondary efficacy measures included Conner's Parent Rating Scale (CPRS) ADHD Index and Clinical Global Impression (CGI-I) Scale.

Primary Efficacy Analysis

The primary efficacy analysis was performed on the change from baseline of the ADHD-RS total score at the treatment endpoint, using a two-way analysis of covariance (ANCOVA) model, for the intention-to-treat (ITT) population. The ITT population included all the randomized and treated subjects who had the baseline assessment and at least 1 post-randomization assessment of the primary efficacy measure. As the treatment endpoint was used for the efficacy analysis, the results obtained were therefore numerically identical to the last observation carried forward (LOCF) approach at the end of the planned treatment period.

The ANCOVA model included treatment (the effect of interest), site, and the corresponding baseline score (the covariate). The site effect was used as a blocking factor in the model to control the potential treatment differences among sites. The null hypothesis stated that there were no differences among the four (4) groups of subjects receiving different doses, including placebo, with the alternative of non-zero differences among them. For the ANCOVA, the type I error rate for rejecting a null hypothesis was controlled at an alpha level of 0.05.

Based on the results from the ANCOVA model, the Dunnett's test for multiple mean comparisons with least-square adjustment, which controls the overall family-wise error rate at the predefined level, was employed to compare the ADHD-RS change from baseline of three (3) active treatment groups to placebo. For the Dunnett's test, the family-wise type I error rate for rejecting a null hypothesis was set at the significance level of 0.05 (2-sided).

Secondary Efficacy Analysis

To assess the duration of therapeutic response, each individual dose was compared with placebo on the CPRS ADHD Index change from baseline score by the same ANCOVA model described for the primary efficacy endpoint at treatment endpoint, separately, for morning (10am), afternoon (2pm), and evening (6pm) responses. For each treatment dose, the duration of drug action was to be claimed at the last time point at which the Dunnett's test revealed a significant difference as compared to placebo, given that the primary efficacy analysis of the ADHD-RS also showed a significant difference between the corresponding treatment dose and placebo.

An ANOVA model with two effects of dose group and (pooled) study site was used to evaluate the CGI-I at treatment endpoint. The Dunnett's test for multiple mean comparisons with least-square adjustment was also employed to compare the CGI-I scores of three (3) active drug groups to placebo. In addition, the CMH test adjusting for (pooled) site was used to examine effects at treatment endpoint for the CGI-I. The test was performed separately for each pair of an active dose vs. placebo. Prior to the analysis, this variable was dichotomized to have two categories, with 'very much improved' and 'much improved' into one category and the remaining levels into the other.

Sensitivity Analysis

Per SAP, a mixed-effects model analysis was performed, as a sensitivity approach, on all of data points for ADHD-RS and CPRS ADHD Index to evaluate the effects of missing data on drug efficacy and the robustness of the results obtained in the primary efficacy analysis.

This sensitivity analysis utilized a mixed-effects model for repeated measures and included all of the scores as observed of Week 1 to Week 4 in the double-blind treatment for the ADHD-RS and CPRS ADHD Index, respectively, at each assessment time point. The model utilized SAS PROC MIXED with treatment (4 levels), week of treatment (4 levels), their interaction, and pooled site as fixed effects, and subject (within pooled site) as random effect, as well as the baseline measure as a covariate. The 4 treatment levels were NRP104 30 mg, 50 mg, and 70 mg as well as placebo. The 4 week-of-treatment levels were Weeks 1, 2, 3, and 4. The covariance structure was based on the variance components. Given a significant overall treatment effect ($p<0.05$), pairwise comparisons of least-square means between each pairs of treatment groups was further conducted at the level of 0.05, using a T-test, at each week of treatment.

3.1.4 Efficacy Results for Study NRP104.301

3.1.4.1 Patient Disposition, Population and Baseline Demographic Characteristics

Table 3.1.4.1 summarizes overall subject disposition, including patients' reasons of discontinuation for this study. A total of 297 subjects were enrolled in this study. Of the 297 subjects, 290 received the randomized and blinded treatment, and 7 discontinued the study prior to being randomized or receiving the randomized treatment. Of those who received the randomized treatment, 230 completed the study and 60 terminated before study completion.

Table 3.1.4.1 Patient Disposition for Study 301

	Total	TPR*	Placebo	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
Randomized	290	0	72	71	74	73
Efficacy ITT	285	-	72	69	71	73
Completed	230	0	54	56	60	60
Discontinued	67	7	18	15	14	13
Primary reason for discontinuation, N (%)						
Adverse Event(s)	21 (7.1)	0	1 (1.4)	6 (8.5)	4 (5.4)	10 (13.7)
Lack of Efficacy	14 (4.7)	0	12 (16.7)	1 (1.4)	0	1 (1.4)
Protocol Violation	3 (1.0)	0	1 (1.4)	0	2 (2.7)	0
Lost to Follow-up	16 (5.4)	5 (71.4)	1 (1.4)	4 (5.6)	4 (5.4)	2 (2.7)
Withdrew Consent	6 (2.0)	1 (14.3)	2 (2.8)	2 (2.8)	1 (1.4)	0
Physician Decision	2 (0.7)	0	0	0	2 (2.7)	0
Ineligible for Randomization	1 (0.3)	1 (14.3)	-	-	-	-
Other	4 (1.3)	0	1 (1.4)	2 (2.8)	1 (1.4)	0

* Terminated prior to receiving randomized treatment

Table 3.1.4.2 summarizes demographics and baseline characteristics of the ITT population. As shown in the table, none of the subjects' demographic and disease characteristics and baseline disease severity were related to the treatment assignment among the ITT population.

Table 3.1.4.2 Demographic and Baseline Characteristics of the ITT Population for Study 301

Characteristics	Treatment Group			
	Placebo N=72	NRP104 30 mg N=69	NRP104 50 mg N=71	NRP104 70 mg N=73
Sex				
Male	50 (69.4%)	51 (73.9%)	44 (62.0%)	52 (71.2%)
Female	22 (30.6%)	18 (26.1%)	27 (38.0%)	21 (28.8%)
Ethnicity/Race				
Caucasian	43 (59.7%)	35 (50.7%)	33 (46.5%)	41 (56.2%)
Black	16 (22.2%)	18 (26.1%)	18 (25.4%)	17 (23.3%)
Hispanic	9 (12.5%)	10 (14.5%)	17 (23.9%)	12 (16.4%)
Others	4 (5.6%)	6 (8.6%)	3 (4.2%)	3 (4.1%)
Age (yr) mean	9.4 ± 1.7	9.0 ± 1.9	8.9 ± 1.8	8.7 ± 1.8
Age Group (yr)				
06-09	35 (48.6%)	43 (62.3%)	46 (64.8%)	48 (65.8%)
10-12	37 (51.4%)	26 (37.7%)	25 (35.2%)	25 (34.2%)
Height (in) mean	55.0 ± 3.9	54.4 ± 4.8	53.7 ± 4.1	53.7 ± 4.1
Weight (lb) mean	82.6 ± 22.8	80.8 ± 27.3	80.7 ± 25.8	79.0 ± 23.7
Diagnosis:				
Combined	69 (95.8%)	65 (94.2%)	68 (95.8%)	71 (97.3%)
Hyperactive	3 (4.2%)	4 (5.8%)	3 (4.2%)	2 (2.7%)
ADHD Onset Age (yr)	7.6 ± 2.2	7.0 ± 2.2	6.9 ± 2.2	7.0 ± 2.2
Duration of Disease (yr)	1.8 ± 2.4	2.0 ± 2.5	2.1 ± 2.3	1.8 ± 2.5
CGI Severity at Baseline				
Mildly – 3	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Moderately – 4	27 (37.5%)	25 (36.2%)	24 (33.8%)	25 (34.2%)
Markedly – 5	33 (45.8%)	35 (50.7%)	34 (47.9%)	32 (43.8%)
Severely – 6	11 (15.3%)	9 (13.0%)	9 (12.7%)	16 (21.9%)
Extremely – 7	1 (1.4%)	0 (0.0%)	3 (4.2%)	0 (0.0%)

Source: Table 4 of Sponsor's Clinical Study Report

3.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

Table 3.1.4.3 summarizes subjects' ADHD-RS total score at baseline and its change from baseline at endpoint for the ITT population. As shown in the table, there were no differences in ADHD-RS total score among treatment groups at baseline. All groups, including the placebo group, showed improvement in the ADHD-RS total score from baseline to endpoint. While the ADHD-RS total score reduction was 6.2 in the placebo-treated subjects, the improvement in the active treatment groups was approximately 4 to 5 times compared to placebo, with the greatest improvement seen in the 70 mg group.

Table 3.1.4.3 Sponsor's Analysis Results for ADHD-RS Score in the ITT Population for Study 301

		Placebo	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
Baseline: Total Score	N	72	69	71	73
	Mean (SD)	42.4 (7.13)	43.2 (6.68)	43.3 (6.74)	45.1 (6.82)
Endpoint: Change from Baseline	N	72	69	71	73
	LS Mean (SE)	-6.2 (1.56)	-21.8 (1.60)	-23.4 (1.56)	-26.7 (1.54)
Comparison: Placebo-Adjusted Difference	LS Mean P-Value*	0	-15.58 <0.0001	-17.21 <0.0001	-20.49 <0.0001

* Dunnett's test was used for the construction of p-values
Source: Table 5 of Sponsor's Clinical Study Report

3.1.4.3 Sponsor's Efficacy Results for Secondary Endpoints

Secondary efficacy endpoints included the CPRS ADHD Index assessed in the morning (10 am), afternoon (2 pm), and evening (6 pm), respectively, and the CGI Improvement (CGI-I). The same analytical approach used for the primary efficacy endpoint was utilized for the secondary efficacy endpoints. The model included treatment, site (pooled), and for CPRS, the baseline score (the covariate).

CPRS ADHD Index

Table 3.1.4.4 summarizes the morning (10 am), afternoon (2 pm), and evening (6 pm) scores of the CPRS ADHD Index at baseline and their changes from baseline at endpoint for the ITT population. There were no differences in the CPRS ADHD Index among the treatment groups at baseline for either the morning, afternoon, or evening. All groups, including the placebo group, showed improvement at each of the 3 assessment time points from baseline to endpoint. For all three time points in the morning, afternoon or evening, the active treatment groups showed statistically significantly differences in comparison with placebo.

Table 3.1.4.4 CPRS ADHD Index at Baseline and Change from Baseline at Endpoint in Each of the Assessed Time Points for the ITT Population for Study 301

		Placebo	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
In the Morning (10 am):					
Baseline: Total Score	N	72	69	69	71
	Mean (SD)	25.7 (7.70)	25.0 (7.92)	25.3 (8.02)	27.5 (7.47)
Endpoint: Change from Baseline	N	72	67	68	70
	LS Mean (SE)	-2.6 (1.07)	-11.2 (1.13)	-13.8 (1.10)	-15.0 (1.08)
Comparison: Placebo-Adjusted Difference	LS Mean P-Value*	0	-8.55 <0.0001	-11.18 <0.0001	-12.36 <0.0001

		Placebo	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
In the Afternoon (2 pm):					
Baseline: Total Score	N	72	69	68	72
	Mean (SD)	25.6 (7.32)	25.6 (7.76)	25.7 (8.41)	28.2 (6.56)
Endpoint: Change from Baseline	N	72	67	66	71
	LS Mean (SE)	-2.3 (1.10)	-11.1 (1.16)	-14.7 (1.15)	-15.2 (1.11)
Comparison: Placebo-Adjusted Difference	LS Mean P-Value*	0	-8.84 <0.0001	-12.46 <0.0001	-12.90 <0.0001
In the Evening (6 pm):					
Baseline: Total Score	N	72	69	70	70
	Mean (SD)	25.7 (8.03)	25.9 (8.13)	25.5 (9.02)	28.3 (6.81)
Endpoint: Change from Baseline	N	72	67	69	69
	LS Mean (SE)	-1.8 (1.07)	-10.7 (1.13)	-13.0 (1.10)	-14.6 (1.10)
Comparison: Placebo-Adjusted Difference	LS Mean P-Value*	0	-8.90 <0.0001	-11.17 <0.0001	-12.79 <0.0001

* Dunnett's test was used for the construction of CIs and p values.
Source: Table 9 of Sponsor's Clinical Study Report

CGI Improvement (CGI-I)

Table 3.1.4.5 summarizes the CGI severity at baseline and the CGI improvement at treatment endpoint, as well as the number (%) of subjects in each of the dichotomized categories (improved vs. not improved) at treatment endpoint for the ITT population.

Table 3.1.4.5 CGI Severity at Baseline and Improvement at Endpoint for the ITT population for Study 301

		Placebo	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
Baseline: CGI Severity	N	72	69	71	73
	Mean (SD)	4.8 (0.74)	4.8 (0.67)	4.9 (0.82)	4.9 (0.74)
Endpoint: CGI Improvement	N	72	69	71	73
	LS Mean (SE)	3.7 (0.14)	2.3 (0.14)	2.1 (0.14)	1.9 (0.14)
Comparison: Placebo-adjusted difference	LS Mean P-Value*	0	-1.43 <0.0001	-1.55 <0.0001	-1.78 <0.0001
Endpoint: CGI-I Improved	N (%) P-Value**	13 (18%)	48 (70%) <0.0001	50 (70%) <0.0001	56 (77%) <0.0001

*Dunnett's test was used for the construction of p values
**CMH test adjusting site (pooled) for each of the active treatment groups vs. placebo

As shown in the table, there were no differences in CGI severity at baseline among the treatment groups. For the CGI improvement, Dunnett's test determined that the differences in CGI-I score were lower for each NRP104 group relative to placebo, and statistically significant. The investigators rated on the CGI-I, respectively, 70%, 70%, and 77% of subjects on NRP104 30 mg, 50 mg, and 70 mg, respectively, as either 'very much improved' or 'much improved', as compared to 18% of subjects on placebo. The differences in proportion of subjects improved between an active group and placebo were highly significant for all NRP104 groups.

3.1.4.4 Sponsor's Sensitivity Analysis Results

Mixed-Effects Model Sensitivity Analysis for ADHD-RS

Table 3.1.4.6 summarizes the sponsor's mixed-effects model analysis results at Week 3 and Week 4. As shown in the table, the sponsor concluded that comparisons among active doses showed consistent and favorable efficacy for high doses as compared to a lower dose, and the difference between the highest (70 mg) and lowest (30 mg) doses was approximately 5 unit points, which was not only statistically significant, but also clinical meaningful.

Table 3.1.4.6 Sponsor's Mixed-Effects Model Analysis Results for ADHD-RS for Study 301 (Between-Group Differences in LS Mean)

Treatment Week	Actual Dose	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
Week 3	Placebo	-14.4 ***	-15.8***	-18.9***
	NRP 104 30 mg		-1.4	-4.5*
	NRP 104 50 mg			-3.0
Week 4	Placebo	-15.5***	-18.1***	-20.4***
	NRP104 30 mg		-2.7	-5.0
	NRP104 50 mg			-2.3

*P<0.05, ***p<0.0001
Source: Table 13 of Sponsor's Clinical Study Report

Mixed-Effects Model Sensitivity Analysis for CPRS ADHD Index

Table 3.1.4.7 summarizes the sponsor's mixed-effects model analysis results at Week 3 and Week 4. As shown in the table, the sponsor concluded that comparisons among active doses showed consistent and favorable efficacy for high doses, as compared to a lower dose, and the difference between the highest and lowest doses were approximately 4 to 5 unit points in all of the 3 time points, which were statistically significant ($p<0.05$) and clinically meaningful.

Table 3.1.4.7 Sponsor's Mixed-Effects Model Analysis Results for ADHD-RS for Study 301 (Between-Group Differences in LS Mean)

Treatment Week	Actual Dose	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
Morning (10 am) Assessment				
Week 3	Placebo	-6.5***	-8.1***	-10.9***
	NRP 104 30 mg		-1.6	-4.3**
	NRP 104 50 mg			-2.8
Week 4	Placebo	-8.1***	-11.1***	-12.1***
	NRP104 30 mg		-2.9	-3.9**
	NRP104 50 mg			-1.0
Afternoon (2 pm) Assessment				
Week 3	Placebo	-6.9***	-10.0***	-11.4***
	NRP 104 30 mg		-3.0	-4.5**
	NRP 104 50 mg			-1.5
Week 4	Placebo	-8.8***	-12.9***	-13.1***
	NRP104 30 mg		-4.1*	-4.3**
	NRP104 50 mg			-0.2
Evening (6 pm) Assessment				
Week 3	Placebo	-6.8***	-8.5***	-11.5***
	NRP 104 30 mg		-1.7	-4.7**
	NRP 104 50 mg			-3.0
Week 4	Placebo	-8.6***	-11.3***	-12.6***
	NRP104 30 mg		-2.7	-4.0*
	NRP104 50 mg			-1.3

*P<0.05, **P<0.01,***p<0.0001
Source: Table 14 of Sponsor's Clinical Study Report

3.1.4.5 Statistical Reviewer's Findings and Comments

This reviewer confirmed all of the sponsor's analysis results reported in this review for this study. In summary, Study 301 was determined as a positive study, where data collected for the primary endpoint (ADHD-RS score) and secondary endpoints (CPRS ADHD Index and CGI-I improvement) supported the efficacy of all three doses of NRP 104. [redacted]

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Since Study 201 was a small study, the sponsor only performed the subgroup analyses with respect to demographic characteristics on the primary endpoint for Study 301. The primary endpoint, ADHD-RS score, was analyzed by gender (boys and girls), age (6-9 years and 10-12 years of age), and ethnicity/race (Caucasian and non-Caucasian). Tables 4.1 to 4.3 show the sponsor's demographic subgroup analysis results. This reviewer confirmed the sponsor's analysis results shown in this section.

Table 4.1 Sponsor's Analysis Results for ADHD-RS Score at Baseline and Change from Baseline to Endpoint for Gender Subgroups for Study 301

Characteristic	Statistics	Placebo	NRP 104 30 mg	NRP 104 50 mg	NRP 104 70 mg
Boys					
Baseline Score	N	50	51	44	52
	Mean (SD)	43.6 (7.27)	43.8 (6.64)	43.3 (6.50)	45.2 (6.78)
Change from Baseline	LS Mean (SE)	-5.9 (1.88)	-23.8 (1.88)	-24.8 (2.01)	-27.6 (1.81)
Comparison with Placebo*	LS Mean		-17.9	-18.89	-21.67
	P-Value		<0.0001	<0.0001	<0.0001
Girls					
Baseline Score	N	22	18	27	21
	Mean (SD)	39.7 (6.11)	41.3 (6.64)	43.2 (7.23)	44.8 (7.10)
Change from Baseline	LS Mean (SE)	-8.1 (3.14)	-19.0 (3.33)	-18.8 (2.88)	-24.8 (3.27)
Comparison with Placebo*	LS Mean		-10.85	-10.68	-16.67
	P-Value		0.0537	0.0345	0.0035

*Dunnett's test was used for the construction of CIs and p values.
Source: Table 2.7.3-17 of Vol3, Mod 2

According to the sponsor, there were no differences in ADHD-RS among the treatment groups at baseline for boys (p-value = 0.4755), but there were differences among the treatment groups for girls (p-value = 0.0451). All treatment groups, including placebo, showed improvement from baseline to endpoint for boys and girls. For both genders, the score reduction in the 50, and 70 mg groups was observed to be statistically significantly larger than in the placebo group at the significance level of 0.05. However, for the 30 mg group only boys' results showed statistically significantly better than placebo at the significance level of 0.05. The large p-value for girl's results could be due to small sample size, so lack of sufficient power for the comparison.

Table 4.2 Sponsor's Analysis Results for ADHD-RS Score at Baseline and Change from Baseline to Endpoint for Age Subgroups for Study 301

Characteristic	Statistics	Placebo	NRP 104 30 mg	NRP 104 50 mg	NRP 104 70 mg
Subjects 6-9 years old					
Baseline Score	N	35	43	46	48
	Mean (SD)	42.1 (7.48)	43.6 (6.34)	44.5 (5.97)	45.5 (6.90)
Change from Baseline	LS Mean (SE)	-6.8 (2.40)	-22.4 (2.11)	-23.5 (2.06)	-29.0 (2.01)
Comparison with Placebo*	LS Mean		-15.56	-16.68	-22.15
	P-Value		<0.0001	<0.0001	<0.0001
Subjects 10-12 years old					
Baseline Score	N	37	26	25	25
	Mean (SD)	42.7 (6.87)	42.5 (7.29)	40.9 (7.52)	44.2 (6.74)
Change from Baseline	LS Mean (SE)	-4.5 (2.18)	-21.4 (2.75)	-24.8 (2.82)	-26.0 (2.74)
Comparison with Placebo*	LS Mean		-16.83	-20.29	-21.45
	P-Value		<0.0001	<0.0001	<0.0001

*Dunnett's test was used for the construction of CIs and p values.
Source: Table 2.7.3-18 of Vol3, Mod 2

As shown in Table 4.2, there were no differences in ADHD-RS at baseline among the treatment groups for both age populations. All treatment groups, including placebo, showed improvement from baseline to endpoint in both age populations. For both age populations, the score reduction in the 30-, 50- and 70- groups was statistically significantly larger than in the placebo group at the significance level of 0.05.

Table 4.3 Sponsor's Analysis Results for ADHD-RS Score at Baseline and Change from Baseline to Endpoint for Race Subgroups for Study 301

Characteristic	Statistics	Placebo	NRP 104 30 mg	NRP 104 50 mg	NRP 104 70 mg
Caucasian Subjects					
Baseline Score	N	43	35	33	41
	Mean (SD)	43.0 (7.07)	42.7 (6.82)	43.2 (7.04)	45.2 (6.79)
Change from Baseline	LS Mean (SE)	-4.0 (1.98)	-23.8 (2.32)	-26.1 (2.27)	-26.9 (2.01)
Comparison with Placebo*	LS Mean		-19.79	-22.08	-22.88
	P-Value		<0.0001	<0.0001	<0.0001
Non-Caucasian Subjects					
Baseline Score	N	29	34	38	32
	Mean (SD)	41.6 (7.27)	43.7 (6.59)	43.3 (6.56)	44.9 (6.98)
Change from Baseline	LS Mean (SE)	-10.1 (2.81)	-18.5 (2.51)	-20.2 (2.43)	-25.1 (2.67)
Comparison with Placebo*	LS Mean		-8.41	-10.09	-15.01
	P-Value		0.0754	0.0158	0.0002

*Dunnett's test was used for the construction of CIs and p values.
Source: Table 2.7.3-19 of Vol3, Mod 2

According to the sponsor, there were no differences in ADHD-RS at baseline among the treatment groups for both ethnicity/race populations. All treatment groups, including placebo, showed improvement from baseline to endpoint in both ethnicity/race populations. For the group of Caucasian subjects, the score reduction in the 30-, 50- and 70- mg groups were statistically significantly larger than in the placebo group at the significance level of 0.05. However, for the group of non Caucasian subjects, only the score reduction in the 50- and 70-mg groups were statistically significantly larger than in the placebo group at the significance level of 0.05.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

In Study NRP104.201, the sponsor further assessed dose-response in analysis of the primary efficacy variable (SKAMP Deportment score averaged across the 8 sessions on the treatment assessment day) by optimal dose cohort. This comparison was designed to confirm that subjects who received efficacious treatment for ADHD from 10, 20, or 30 mg of Adderall XR® would be effectively treated by 30, 50, or 70 mg NRP104, respectively. The 3 optimal dose cohorts were again shown in Table 4.2.1 and Table 4.2.2 shows the sponsor's analysis results for three optimal dose cohorts on the primary endpoint. This reviewer confirmed the sponsor's analysis results.

Table 4.2.1 Definition of Three Optimal Dose Cohorts for Study 201

Optimal Dose Cohort A	NRP104 30 mg, Adderall XR® 10 mg, placebo
Optimal Dose Cohort B	NRP104 50 mg, Adderall XR® 20 mg, placebo
Optimal Dose Cohort C	NRP104 70 mg, Adderall XR® 30 mg, placebo

Table 4.2.2 Sponsor's Analysis Results for Three Optimal Dose Cohorts for Study 201

Statistic	Dose Cohort A	Dose Cohort B	Dose Cohort C
N	8	17	25
Difference in LS Mean NRP 104 versus Placebo	-0.4	-1.0	-1.0
P-Value	0.0305	<0.0001	<0.0001

Source: Table 2.7.3-24 of Vol3, Mod 2

As shown in the above table, the 50- and 70-mg optimal dose cohorts showed a numerically greater mean improvement in LS mean score relative to placebo than the 30-mg optimal dose cohort.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Both efficacy studies (Studies 201 and 301) were determined to be positive studies with respect to primary endpoints. [redacted]

5.2 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted one crossover study (Study 201) and one parallel study (Study 301) with three doses of NRP104 (30, 50, and 70 mg/day) to demonstrate the efficacy for treating children patients with Attention Deficit/Hyperactivity Disorder (ADHD). After evaluation, it was determined that the data from both studies supported the efficacy of NRP104. [redacted]

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-977
HFD-130/Dr. Laughren
HFD-130/Dr. Khin
HFD-130/Dr. Chuen
HFD-130/Ms. Player
HFD-130/Mr. Berman
HFD-700/Dr. Nevius
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

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

/s/

Yeh-Fong Chen
7/27/2006 11:43:22 AM
BIOMETRICS

Peiling Yang
7/27/2006 11:54:06 AM
BIOMETRICS

Kooros Mahjoob
7/28/2006 06:04:35 PM
BIOMETRICS