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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	205,489
Drug Name:	Cotempla XR-ODT (Methylphenidate extended release ODT) 10, 20, and 30 mg tablets
Indication(s):	Attention-Deficit Hyperactivity Disorder (ADHD)
Applicant:	NEOS Therapeutics
Dates:	Submitted: 01/09/2015 PDUFA: 11/09/2015
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. (Team leader) H.M. James Hung, Ph.D. (Division director)
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Keywords: Analysis of covariance, baseline imbalance, randomization

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1 EXECUTIVE SUMMARY

This 505(b)(2) application contains one efficacy trial: Study NT0102.1004. This trial provides strong statistical evidence that Methylphenidate XR-ODT is superior to placebo in the treatment of ADHD in the pediatric population (6-12 years) on the endpoints studied. The sponsor's results for both the primary (Average of SKAMP-Combined Scores over duration of the classroom day) as well as for the key secondary (onset and duration) outcome measure were confirmed by this reviewer. The mean over the seven post-dose measurements of the SKAMP-Combined Score during the full day laboratory classroom session is estimated to be 11 points lower (i.e., better) for the MPH XR-ODT treated group compared to the placebo group. The effect of this extended release product is estimated to last from hour 1 to hour 12, with the difference between the groups being greatest in the first half of the day and narrowing towards the later part of the testing session (Figure 2).

2 INTRODUCTION

Methylphenidate XR-ODT (MPH XR-ODT; proposed trade name Cotempla XR-ODT) is an extended release formulation of methylphenidate hydrochloride (HCl) as orally disintegrating tablet (ODT) for the treatment of ADHD. Neos, the sponsor, is requesting approval for three strengths: 10 mg, 20 mg and 30 mg. These three tablet strengths would allow dosing up to 60 mg by a combination of one or two tablets. METADATE CD (methylphenidate hydrochloride USP) Extended-Release Capsules, UCB Inc., NDA 21,259 is the reference listed drug for this 505(b)(2) New Drug Application. However, the sponsor based its draft labeling text on QUILLIVANT XR, since it is the most recently approved methylphenidate product. The 505(b)(2) approval pathway relies on FDA's previous finding of safety and efficacy of the reference listed drug (in this case: METADATE CD). Neos conducted three Bioavailability/Bioequivalence (BA/BE) studies (NT0102.1001, NT0102.1002, and NT0102.1003) and one efficacy and safety study (NT0102.1004) to provide a scientific bridge between MPH XR-ODT (the new product) and METADATE CD (the reference product). Only Study NT0102.1004 is subject of this review.

2.1 Overview

Study NT0102.1004 (hereafter referred to as Study 1004) is a randomized, multicenter, double-blind, placebo-controlled, parallel group study of MPH XR-ODT (equivalent to 20, 30, 40, or 60 mg of methylphenidate hydrochloride) in children (ages 6-12 years) with attention-deficit hyperactivity disorder (ADHD). MPH XR-ODT is also referred to as NT0102 in this review.

The primary objective of this study was to determine the efficacy, safety, and tolerability of MPH XR-ODT in children with ADHD in a laboratory classroom setting. Efficacy measures include the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) and the Permanent Product Measure of Performance (PERMP). The study was initiated on 07/17/2013 and completed on 05/04/2014. The study report date is 12/03/2014.

Table 1. Study Included in Analysis

Study Number	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
NT0102.1004	*Phase 3 Randomized, multicenter, double-blind, placebo-controlled, parallel group study*	*4-week dose optimization, 1 week dose stabilization, 1 week randomized treatment period*	*Placebo: 39 NT0102: 43*	*Children 6-12 years of age with ADHD*

2.2 Data Sources

Original Submission: \\CDSESUB1\evsprod\NDA205489\0000

Study Report: \\CDSESUB1\evsprod\NDA205489\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-\5351-stud-rep-contr\nt01021004

Response to 1st information request (analysis datasets, SAS code):

\\CDSESUB1\evsprod\NDA205489\0004

\\CDSESUB1\evsprod\NDA205489\0006 (SAS code, datasets)

Response to 2nd information request (randomization):

\\CDSESUB1\evsprod\NDA205489\0005

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The original submission did contain legacy converted SDTM datasets, but no analysis datasets and no SAS programs. Those items were provided by the sponsor per FDA request. This reviewer replicated the sponsor's primary ANCOVA analysis for the SKAMP-Combined scores as well as for the SKAMP components of Attention and Deportment starting with the legacy converted SDTM dataset "QS" (Questionnaire). This reviewer could also replicate the key secondary outcomes of onset and duration of MPH XR-ODT (defined as the first and last time

points, during which active drug consecutively separates from placebo on the SKAMP-Combined scores) based on the same SDTM dataset.

Randomization was stratified by site. Sites 1 and 3 randomized subjects in several "batches" utilizing a new randomization list for each batch (two and three "batches" respectively). For information on randomization and blinding see the appendix to this review and page 23 of the study report.

The sponsor performed audits of the two investigator sites with the highest number of enrolled subjects, Dr. Childress's and Dr. Cutler's sites. The audit reports were not included with the original submission, but were provided per request and did not contain any critical findings. FDA inspections of Dr. Childress's and Dr. Cutler's sites did not uncover any major issues.

The study protocol was amended twice (June, 6 2013 and October, 15 2013). The following Statistics relevant changes were implemented:

- A clarification that the statistical analysis would be conducted by treatment, not by treatment received.
- A modification to the statistical methods stating that only one statistical analysis approach (i.e., ANCOVA) will be used based on feedback from the Food and Drug Administration (FDA).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

All subjects were required to meet the DSM-IV-TR criteria for ADHD and all subtypes of ADHD were allowed in this study. However, the majority of subjects were diagnosed with predominantly hyperactive-impulsive or combined subtypes of ADHD. At screening, children were on a stable dose of 20 mg/day to 60 mg/day of Metadate CD or equivalent dose of another immediate release (IR) or extended release (XR) MPH medication.

There were 5 periods in this study: a screening period (approximately 4 weeks), a washout period (3-7 days), an open-label stepwise dose optimization period (4 weeks), a dose stabilization

period (1 week), and a double-blind parallel group treatment period, culminating in a full-day laboratory classroom assessment (1 week). The overall study schedule is displayed in Table 2.

After the washout period, subjects received the study drug once daily for 4 weeks during the dose optimization period. At the end of each week, subjects were evaluated for safety, tolerability, and efficacy and a decision was made to increase, decrease, or maintain the previous week's dose (note that only 1 dose decrease was permitted during the optimization phase). After completion of the 4-week dose optimization period, the optimized dose of the study drug was selected, and subjects stayed on that dose for one week (dose stabilization period). On the last day of the dose stabilization period, which was also the Laboratory Classroom Practice Day (Visit 7), subjects were randomly assigned (1:1) to one of two treatments for the 1-week, double-blind, parallel-group treatment period: either MPH XR-ODT at the optimized daily dose or the matching placebo treatment. Subjects took their assigned treatment once daily for 1 week leading up to the full length classroom testing day.

Table 2. Study Schedule

Study Periods									
	Screening	**Washout [a]**	**Dose Optimization**	**Dose Stabilization**	**Practice Session**	**Double-Blind Treatment**	**Classroom Session**	**Final Visit**	**Follow-up Call**
Period Duration	Up to 4 weeks	1 week	4 weeks	1 week	1 day	6 days	1 day	1 day	1 day
Study Days	-34 to -7	-6 to -0	1-28	29-34	35	36-41	42	43**	75
Visit(s)*	1		2-5	6	7[b]		8[c]	9	Follow-up

*Note: Visits 3 through 6 include a window of ± 2 days
**Note: Final visit is Day 43 (+2 days)
[a] Washout of at least 3 days (up to 1 week)
[b] Visit 7 is the "practice" classroom testing day.
[c] Visit 8 is the "actual" classroom testing day.
(Source: Study Report p. 17)

Subjects were assessed at baseline (pre-dose), and 1, 3, 5, 7, 10, 12, and 13 hours post-dose on the testing day (Visit 8). The primary efficacy objective was to evaluate the efficacy of MPH XR-ODT compared to placebo as measured by the SKAMP-Combined post-dose score averaged across the test day for active drug versus placebo. The treatment average score is defined as the mean daily average across the 7 post-dose measurements.

The key secondary objectives were the following:

• Evaluation of the onset of effect (defined as the first time point at which MPH XR-ODT separates from placebo on the SKAMP-Combined scores).
• Evaluation of the duration of effect (defined as the last consecutive time point at which MPH XR-ODT separates from placebo on the SKAMP-Combined scores).

3.2.2 Statistical Methodologies

The primary statistical analyses were conducted on the Full Analysis Set (FAS) defined as all subjects randomized who have at least one post-dose SKAMP-Combined treatment assessment during the classroom testing session at Visit 8.

Primary Efficacy Endpoint

The primary efficacy endpoint was derived from the SKAMP-Combined score (total score of all 13 items). The SKAMP-Combined score is based on a 0 to 78 point scale for which a lower score indicates less symptomatology (i.e., is better). The SKAMP is a rating scale that specifically measures the classroom manifestations of ADHD. The SKAMP ratings were completed for all subjects at baseline (pre-dose) and at 1, 3, 5, 7, 10, 12, and 13 hours post-dose on the classroom testing day (Visit 8). The primary efficacy endpoint was the average of all post-dose SKAMP scores during the 13-hour period.

Null Hypotheses: The post-dose SKAMP-Combined scores averaged over the classroom testing day for MPH XR-ODT and placebo are equal.
Alternative Hypotheses: The post-dose SKAMP-Combined scores averaged over the classroom testing day for MPH XR-ODT and placebo are not equal.

The SKAMP Rating Scale is comprised of two behavioral subscales, “Attention” and “Deportment,” from which sub scores are calculated (see appendix for a brief description of those two subscales). These sub scores were derived from 20 minutes of direct observations of subject behavior, by trained raters, during Visit 7 (practice session: at baseline, and at 1, 3, and 5 hours post-dose) and Visit 8 (pre-dose, and at 1, 3, 5, 7, 10, 12, and 13 hours post-dose). Ratings were based on the frequency and quality of behaviors, as observed by experienced, independent

raters who were trained on SKAMP rating instruments by an instructor not involved in the study [Study Report p. 30].

Key Secondary Efficacy Parameters

Key secondary endpoints were identified in the SAP to include the onset and duration of MPH XR-ODT (defined as the first and last points, respectively, during which active drug consecutively separates from placebo on SKAMP-Combined scores).

A mixed model repeated measures (MMRM) approach was used to assess whether the effect of treatment on the SKAMP-Combined Score post-dose was dependent on the time of assessment post-dose. Terms for treatment, site, pre-dose SKAMP-Combined Score at the classroom testing session, time of assessment post-dose, and treatment-by-time interaction were included in this model as fixed effects and subject was included as a random effect. In addition, this model was used to estimate the differences in the SKAMP-Combined Score between treatments at each post-dose assessment. An unstructured covariance matrix was used to model the covariance of within-subject scores; and the Kenward-Roger approximation to estimate denominator degrees of freedom.

Formal hypothesis testing commenced at the 5-hour time point. Since significance at the 5% level was achieved at this time point, the next time point tested was at 3 hours post-dose. The testing sequence then proceeded as follows: 7, 1, 10, 12, and 13-hour time points. If at any time point significance at the 5% level was not achieved, formal statistical testing had to cease. The onset of effect of MPH XR-ODT and duration of effect of MPH XR-ODT were estimated using the individual p-value for each post-dose assessment.

Other secondary endpoints were the PERMP-Attempted and PERMP-Correct averages of the classroom day. The PERMP consists of 400 math problems and is graded as number of problems “Attempted” and number of problems “Correct”.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Eighty-seven boys and girls, aged 6 to 12 years, diagnosed with any subtype of ADHD and taking a stable dose of 20-60 mg METADATE CD or comparable dose of another MPH IR or

XR medication were enrolled in 4 centers across the US. A majority of subjects had the combined type ADHD (65 subjects [74.7%]), followed by inattentive ADHD (21 subjects [24.1%]), and hyperactive/impulsive ADHD (1 subject [1.1%]).

As shown in Table 3, of the 87 subjects enrolled in the study, the majority (57.5%) were enrolled at Dr. Childress's site, followed by Dr. Cutler's (21.8%), Dr. Marraffino's (12.6%), and Dr. Kollins's (8.0%) sites.

Table 3. Site and ADHD Classification Summaries

Parameter		Not Randomized (N=2) N (%)	Placebo (N=41) N (%)	NT0102 (N=44) N (%)	Overall (N=87) N (%)
Site of Recruitment	Cutler	1 (50.0)	9 (22.0)	9 (20.5)	19 (21.8)
	Childress	1 (50.0)	23 (56.1)	26 (59.1)	50 (57.5)
	Kollins	0 (0.0)	3 (7.3)	4 (9.1)	7 (8.0)
	Marraffino	0 (0.0)	6 (14.6)	5 (11.4)	11 (12.6)
	Total	**2 (100)**	**41 (100)**	**44 (100)**	**87 (100)**
Diagnostic subtype of ADHD K-SADS-PL Subtype	Inattentive	0 (0.0)	10 (24.4)	11 (25.0)	21 (24.1)
	Hyperactive/Impulsive	0 (0.0)	0 (0.0)	1 (2.3)	1 (1.1)
	Combined Type	2 (100)	31 (75.6)	32 (72.7)	65 (74.7)
	Total	**2 (100)**	**41 (100)**	**44 (100)**	**87 (100)**

Abbreviations: ADHD=attention-deficit hyperactivity disorder, K-SADS-PL=Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version, N=number of subjects

(Source: Study Report p. 35)

The disposition of the patients enrolled in the study and the analysis populations are shown in Table 4 and Figure 1. Of the 87 subjects, there were 2 subjects who did not complete dose optimization (Subject 1012 withdrew due to an AE [abdominal pain upper], and Subject 3039 withdrew consent). 85 subjects were randomized and entered dose stabilization (2 subjects did not complete dose stabilization: Subject 1011 withdrew due to an AE [influenza] and Subject 1013 withdrew consent; both were randomized to placebo treatment).

Of the 83 subjects who completed dose stabilization, 1 subject (Subject 1007 randomized to MPH XR-ODT) did not have a baseline SKAMP assessment due to noncompliance with the testing procedures on the classroom testing day and was also positive at Visit 8 for amphetamines.

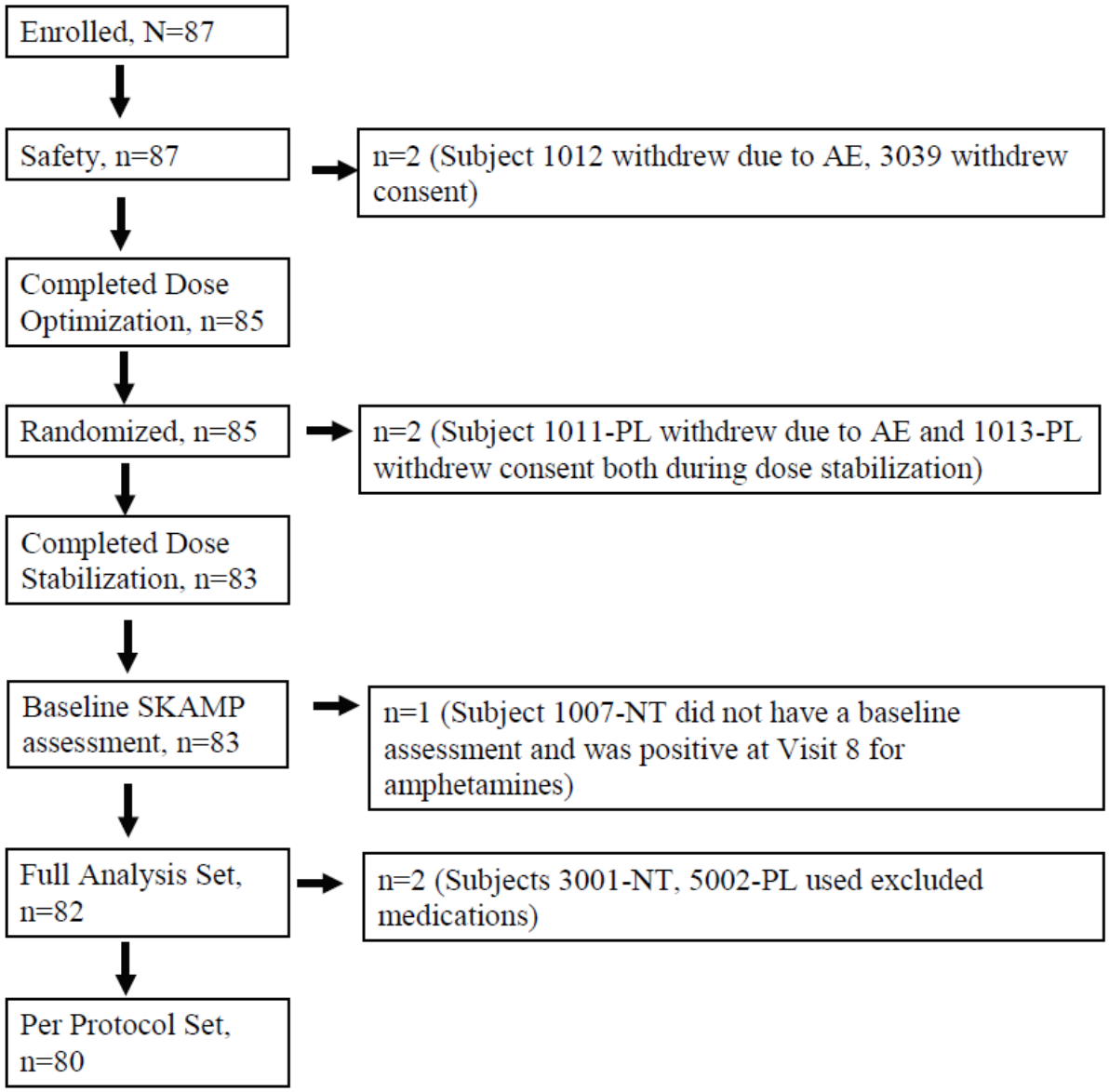
The Full Analysis Set (FAS) is comprised of 82 subjects. The Per Protocol Set (PPS) includes 80 subjects, with 2 subjects from the FAS removed (Subjects 3001 and 5002, randomized to MPH XR-ODT and placebo treatments, respectively, used excluded medications).

Table 4. Disposition - Enrolled Population

Period	**Parameter**	**Statistic**	**Not Randomized**	**Placebo (N=41)**	**NT0102 (N=44)**	**Overall (N=87)**
Safety Set	Completed Classroom Visit	N (%)	2 (100)	41 (100)	44 (100)	87 (100)
FAS		N (%)	0	39 (95.1)	43 (97.7)	82 (94.3)
PPS		N (%)	0	38 (92.7)	38 (95.5)	80 (92.0)
Screening/Washout	Entered	N (%)	2 (100)	41 (100)	44 (100)	87 (100)
Period	Withdrew	N (%)	0	0	0	2 (2.3)
Dose Optimization	Entered	N (%)	2 (100)	41 (100)	44 (100)	87 (100)
Period	Withdrew	N (%)	2	0	0	2 (2.3)
	Due to Adverse Event	N (%)	1 (50)			
	Due to Consent Withdrawal	N (%)	1 (50)			
Dose Stabilization	Entered	N (%)	0	41 (100)	44 (100)	85 (97.7)
	Withdrew	N (%)	0	0	0	0
Double-Blind Period	Entered	N (%)	0	41 (100)	44 (100)	85 (97.7)
	Withdrew	N (%)	0	2 (4.9)	0	2 (2.3)
	Due to Adverse Event	N (%)	0	1 (2.4)		1 (1.1)
	Due to Consent Withdrawal	N (%)	0	1 (2.4)	0	1 (1.1)

(Source: Study Report p. 69-70)

Figure 1. Study Populations



Abbreviations: AE=adverse event, N or n=number of subjects, NT=NT0102, PL=placebo, V8=Visit 8
(Source: Study Report p. 36)

Overall, there were 54 males (65.9%) enrolled in the study with a slightly higher percentage in the MPH XR-ODT arm (69.8%) compared to the placebo (61.5%) arm. Age, race, ethnicity, height, weight, and body mass index (BMI) were similar in both groups (Table 5).

The mean (standard deviation [SD]) age in years was 9.2 (1.75) across both groups, with a range of 6 to 12 and a median of 9 years in both treatment groups. The majority of the subjects were

White (79.3%), followed by Black or African American (12.2%), Other (4.9%), Asian (2.4%), and Native Hawaiian or Other Pacific Islander (1.2%). There were 34.1% of subjects who were Hispanic or Latino. The average (SD) weight was 36.3 (12.73) kg, with a range from 15.4 to 82.6 kg. Demographic characteristics appear similar for both treatment groups.

Table 5. Demographic and Baseline Characteristics - FAS

Parameter		Placebo Total N=39	NT0102 Total N=43	Total N=82
Sex		**N (%)**	**N (%)**	**N (%)**
	Male	24 (61.5)	30 (69.8)	54 (65.9)
	Female	15 (38.5)	13 (30.2)	28 (34.1)
Age Categories		**N (%)**	**N (%)**	**N (%)**
	6-7 years	6 (15.4)	11 (25.6)	17 (20.7)
	8-10 years	24 (61.5)	19 (44.2)	43 (52.4)
	11-12 years	9 (23.1)	13 (30.2)	22 (26.8)
Age				
	Mean ± SD	9.3 ± 1.64	9.1 ± 1.86	9.2 ± 1.75
	Median (min, max)	9.0 (6, 12)	9.0 (6, 12)	9.0 (6, 12)
Race		**N (%)**	**N (%)**	**N (%)**
	White	31 (79.5)	34 (79.1)	65 (79.3)
	Black or African American	5 (12.8)	5 (11.6)	10 (12.2)
	Asian	1 (2.6)	1 (2.3)	2 (2.4)
	Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (2.3)	1 (1.2)
	Other	2 (5.1)	2 (4.7)	4 (4.9)
Ethnicity		**N (%)**	**N (%)**	**N (%)**
	Hispanic/Latino	13 (33.3)	15 (34.9)	28 (34.1)
	Not Hispanic/Latino	26 (66.7)	28 (65.1)	54 (65.9)
BMI kg/m^2				
	Mean ± SD	18.34 ± 4.184	18.65 ± 3.804	18.50 ± 3.967
	Median (min, max)	17.00 (12.4, 30.4)	17.60 (13.6, 30.5)	17.10 (12.4, 30.5)

Abbreviations: BMI=body mass index, max=maximum, min=minimum, N=number of subjects, SD=standard deviation
(Source: Study Report p. 39)

It is interesting to compare the SKAMP baseline score at Visit 7 (the practice classroom session before one week of DB treatment) with the pre-dose score at Visit 8 (classroom session at the end of one week of DB treatment). Leading up to visit 7 all subjects were taking NT0102 (i.e.,

finishing up one week of dose stabilization after four weeks of dose optimization). Note that the baseline mean scores are fairly similar at visit 7 (Table 6), however at visit 8 (after one week of double-blind treatment with placebo or NT0102) we observe a pre-dose imbalance (with drug treated subject having a worse SKAMP Combined score compared to placebo subjects possibly due to a withdrawal effect 24 hours after last dose received).

Table 6. Pre-dose SKAMP Combined Scores - FAS

SKAMP Scale	**Visit 7 SKAMP Scores Raw Mean (Std)**		**Visit 8 SKAMP Scores Raw Mean (Std)**	
	"Placebo"* (N = 39)	**NT0102 (N = 43)**	**Placebo (N = 39)**	**NT0102 (N= 43)**
Combined	20.4 (9.09)	21.1 (9.56)	19.1 (11.04)	26.8 (11.52)

(Source: Study Report p. 130; Reviewer)

The difference in pre-dose scores at Visit 8 is observed at each site (Table 7).

Table 7. Pre-dose SKAMP Combined Scores by Site – FAS

Site # (Investigator)	**Visit 7 SKAMP Combined Scores Raw Mean (Std)**		**Visit 8 SKAMP Combined Scores Raw Mean (Std)**	
	"Placebo"* (N=39)	**NT0102 (N=43)**	**Placebo (N=39)**	**NT0102 (N=43)**
1 (Cutler)	16.9 (7.38) (7)	15.6 (6.91) (8)	14.7 (5.65) (7)	19.9 (9.57) (8)
3 (Childress)	22.4 (9.26) (23)	21.7 (8.93) (26)	20.8 (12.2) (23)	28.2 (10.66) (26)
5 (Kollins)	19.3 (8.62) (3)	20.5 (7.59) (4)	10.7 (2.08) (3)	18.0 (5.83) (4)
6 (Maraffino)	17.7 (10.50) (6)	27.0 (15.07) (5)	21.7 (11.83) (6)	37.4 (13.07) (5)

(Source: Study report p. 138, Reviewer [V7_Exploration_1004]; "Placebo"* stands for group of subjects that are randomized to NT0102 at Visit 8)

Table 8 provides a breakdown of the optimized dose levels. Each dose level (i.e., 20, 30, 40, and 60 mg) was "optimal" for at least some of the pediatric patients. The 20 mg dose was "optimal" for the fewest number of patients, whereas the proportion of subjects at each of the other three dose levels was higher and fairly similar.

Table 8. Optimal Doses Used During the Double-Blind Phase

Dose Level	Not Randomized (N=2) N (%)	Placebo (N=41) N (%)	NT0102 (N=44) N (%)	Overall (N=87) N (%)
20 mg	0 (0.0)	5 (12.2)	6 (13.6)	11 (12.6)
30 mg	0 (0.0)	8 (19.5)	13 (29.5)	21 (24.1)
40 mg	0 (0.0)	13 (31.7)	11 (25.0)	24 (27.6)
60 mg	0 (0.0)	15 (36.6)	14 (31.8)	29 (33.3)
Total	0 (0.0)	41 (100)	44 (100)	85 (97.7)

Abbreviations: N=number of subjects
(Source: Study Report p. 42)

Note that the SKAMP pre-dose score at the laboratory classroom day (after one week of double-blind treatment) for the NT0102 group was numerically worse at each optimized dose level compared to placebo (Table 9).

Table 9. Visit 8 Pre-dose SKAMP Scores by Optimized Dose

Group ID	Optimal Dose	N	Mean	Std Dev	Minimum	Maximum
NT0102	**20 mg/day**	6	23.33	14.39	5.00	49.00
	30 mg/day	13	28.08	9.86	10.00	42.00
	40 mg/day	11	26.91	10.63	13.00	46.00
	60 mg/day	13	27.00	13.39	7.00	54.00
Placebo	**20 mg/day**	5	9.20	2.17	8.00	13.00
	30 mg/day	8	21.63	8.05	9.00	31.00
	40 mg/day	11	21.55	10.48	8.00	42.00
	60 mg/day	15	19.20	13.23	4.00	49.00

(Source: Reviewer)

3.2.4 Results and Conclusions

Sponsor's Results

Primary Endpoint

The primary efficacy endpoint is the average of all post-dose SKAMP-Combined scores assessed at 1, 3, 5, 7, 10, 12, and 13 hours post-dose during the classroom testing day on Visit 8.

The primary analysis was carried out on the Full Analysis Set (FAS) population using an Analysis of Covariance (ANCOVA) model with factors for treatment and site and with a covariate for pre-dose SKAMP-Combined Score. A lower SKAMP-Combined score indicates less symptomatology (i.e., is better). The model estimated a treatment effect of -11.0 (95%CI: -13.9, -8.2) at a significance level of p<0.0001.

Table 10 summarizes the differences in least squares means (LS means) between MPH XR-ODT and placebo treatment groups for SKAMP-Combined scores. There was no significant site-level effect for the SKAMP-Combined Score (p-value = 0.1216 [FAS]). Of note, there was a significant difference at pre-dose in the SKAMP-Combined score (p<0.0001 for FAS), as already described in section 3.2.3 of this review.

Table 10. Primary Analysis Results for the SKAMP-Combined Scores Averaged Over the Classroom Testing Day

	SKAMP-Combined (Full Analysis Set) N=82 (Primary Endpoint Analysis)	SKAMP-Combined (Per Protocol Set) N=80 (Primary Endpoint Sensitivity Analysis)	SKAMP-Attention (Full Analysis Set) N=82	SKAMP-Deportment (Full Analysis Set) N=82
LS Mean (95% CI)				
NT0102	14.3 (12.2, 16.4)	14.6 (12.4, 16.7)	7.7 (6.7, 8.7)	6.7 (5.2, 8.1)
Placebo	25.3 (23.0, 27.6)	25.9 (23.5, 28.3)	12.2 (11.1, 13.4)	12.8 (11.3, 14.3)
Difference	-11.04 (-13.9, -8.20)	-11.29 (-14.2, -8.42)	-4.49 (-5.91, -3.08)	-6.13 (-7.97, -4.28)
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Baseline Pre-dose				
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Site Main Effect				
P-value	0.1216	0.1338	0.0098	0.6299

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham
(Source: Study Report p. 44; Results [SKAMP-Combined, SKAMP-Attention, and SKAMP-Deportment] for FAS replicated by reviewer [Primary_Analysis_1004.sas and SKAMP_Deport_Att_1004.sas])

Missing data: Not an issue

The SAP stated that if individual item scores were missing from the questionnaire they were replaced by the adjacent score (estimated by last observation carried forward) for that question and that if more than 20% of the item scores were missing at any time point, the total score was set to missing; *however, there were no missing scores, so these adjustments were not performed*. The SAP also stated that if a subject had more than 2 of the 7 post-dose scores missing, they were omitted from the analysis; *however, no subjects were omitted from the analysis as a result of this missing data criterion* [Study Report p. 42].

Sensitivity Analyses for primary endpoint

1) **Per Protocol Set (PPS)**

   Table 10 above displays the results for the per protocol population. The PPS has two fewer patients compared to the FAS. Hence it is no surprise that the results of this supportive analysis are in line with the analysis results on the FAS.

2) **Non-parametric model**

Normality assumptions for the ANCOVA were tested by an examination of the residual plots and the Shapiro-Wilk test of normality. The results of those explorations were submitted per FDA request. The normality approximation appears adequate (Figure 3 in reviewer's analysis section). A sensitivity analysis was performed on the primary model using a non-parametric model ranking the average post-dose SKAMP-Combined scores. Subjects who withdrew during the double-blind phase due to treatment-related reasons were assigned the worst possible outcome (worst rank), subjects withdrawing due to non-treatment-related reasons were assigned the next worst outcome (second worst rank), subjects without an adequate number of SKAMP scores but completing the classroom visit were assigned the third worst rank, and subjects with SKAMP data were ranked according to their average of all post-dose SKAMP scores (i.e., the highest score was assigned the fourth worst rank and the lowest score was assigned the best rank). These outcome rankings were compared between treatment groups via analysis of covariance of ranked data with factors for treatment group and site and a covariate for pre-dose SKAMP-Combined score (Table 11). The results are in line with the results of the primary analysis.

<u>Reviewer's note:</u> Most of the ranking rules are not relevant given the data (almost no withdrawals). Also, the clinical meaningfulness of bins in 20 point increments is not clear.

Table 11. Sensitivity Analysis for Primary Endpoint

Sensitivity analysis utilizing a non parametric model on the ranked average post-dose SKAMP Combined scores during the 13-hour period of the classroom day
All subjects randomized

	Statistic	Placebo (N=41)	NT0102 (N=44)
Average score <20	N (%)	14 (34.1%)	31 (70.5%)
Average score 20 to <40	N (%)	22 (53.7%)	12 (27.3%)
Average score 40 to <60	N (%)	3 (7.3%)	1 (2.3%)
Average score 60 to 78	N (%)	0 (0.0%)	0 (0.0%)
Subject without an adequate number of SKAMP scores	N (%)	0 (0.0%)	0 (0.0%)
Withdrew due to non-treatment related reasons	N (%)	0 (0.0%)	0 (0.0%)
Withdrew due to treatment-related reasons	N (%)	1 (2.4%)	0 (0.0%)

Source	d.f	Error d.f.	F value	P value
Baseline pre-dose rank main effects	1	77.0	34.58	<0.0001
Site main effects	3	77.0	0.72	0.5450
Treatment main effects	1	77.0	33.25	<0.0001

(Source: Study Report p. 129)

Additional sensitivity analyses were planned using different approaches to adjust for missing data; however, in this study there were no missing data and no further sensitivity analyses were performed.

Key Secondary Efficacy Endpoint Analyses: Onset and Duration of Effect

Onset of efficacy was met at the first post-dose assessment of 1 hour, and duration of efficacy was consecutively observed through Hour 12, but not at Hour 13 (Table 12).

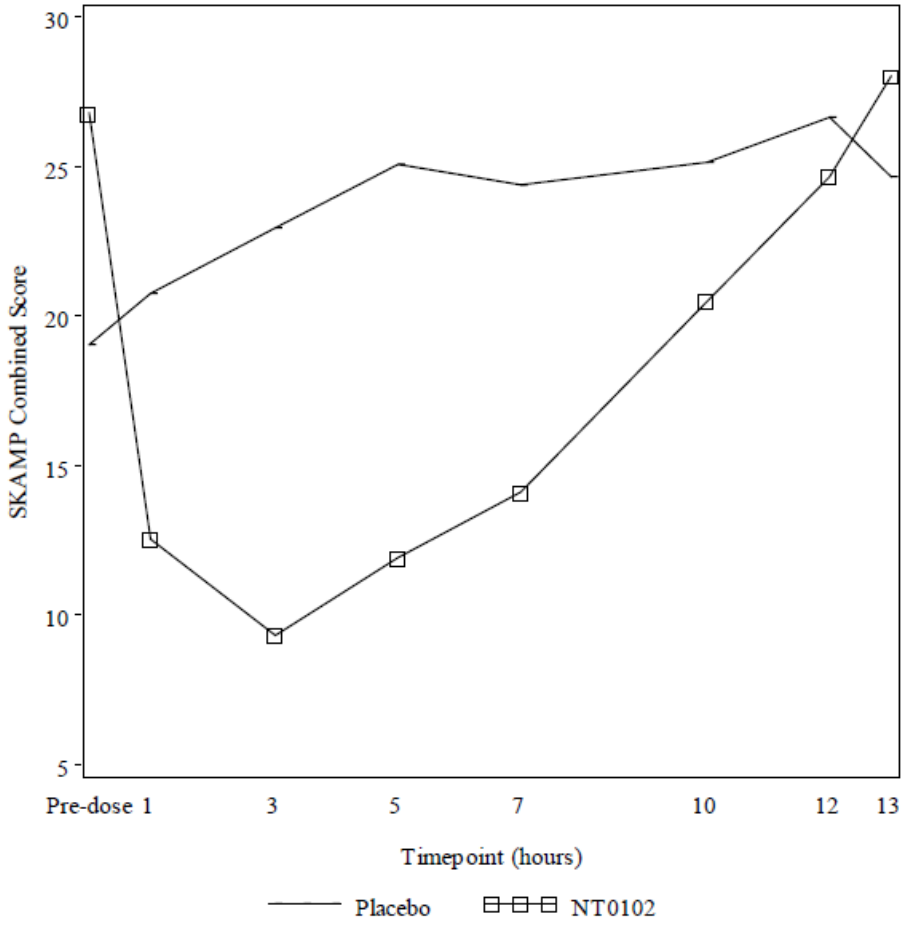
Figure 2 displays summary profiles for the SKAMP-Combined score during the classroom testing day for the FAS [Study Report p. 45].

Table 12. Least Squares Mean SKAMP-Combined Scores at All Time Points - FAS

Time Point (Hour)	Placebo LS Mean (SE)	NT0102 LS Mean (SE)	Difference LS Mean (SE)	95% CI	P Value
1	21.2 (1.19)	10.5 (0.993)	-10.7 (1.44)	(-13.6, -7.86)	<0.0001
3	23.4 (1.43)	7.28 (0.831)	-16.1 (1.55)	(-19.2, -13.0)	<0.0001
5	25.5 (1.52)	9.86 (1.16)	-15.7 (1.82)	(-19.3, -12.1)	<0.0001
7	24.8 (1.51)	12.1 (1.42)	-12.7 (1.99)	(-16.7, -8.77)	<0.0001
10	25.6 (1.80)	18.5 (1.48)	-7.11 (2.25)	(-11.6, -2.61)	0.0024
12	27.1 (1.48)	22.7 (1.42)	-4.46 (1.97)	(-8.37, -0.542)	0.0262
13	25.2 (1.60)	26.0 (1.52)	0.817 (2.13)	(-3.42, 5.06)	0.7022

Abbreviations: CI= confidence interval, LS Mean=least squares mean, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham
(Source: Study Report p. 46; Key secondary results replicated by reviewer [Key_Second_Analysis_1004.sas])

Figure 2. Mean Profiles for SKAMP-Combined Score During the Classroom Testing Day - FAS



(Source: Study Report p. 47)

Note the aforementioned pre-dose mean difference in the SKAMP combined score with the NT0102 subjects scoring worse compared to the placebo subjects (Figure 2). This phenomenon reverses rapidly after drug administration. The sponsor provided similar figures separately for the SKAMP Attention and Deportment results.

Other secondary endpoints: PERMP-A and PERMP-C

Both PERMP endpoints (Attempted and Correct) showed significant treatment effects in the FAS (Table 13) based on the ANCOVA model. The average post-dose scores over the classroom day

by treatment group were compared adjusting for the pre-dose score and site. Of note, as with the SKAMP assessment, there was a significant difference at pre-dose in the PERMP score.

Table 13. PERMP Efficacy Assessments - FAS

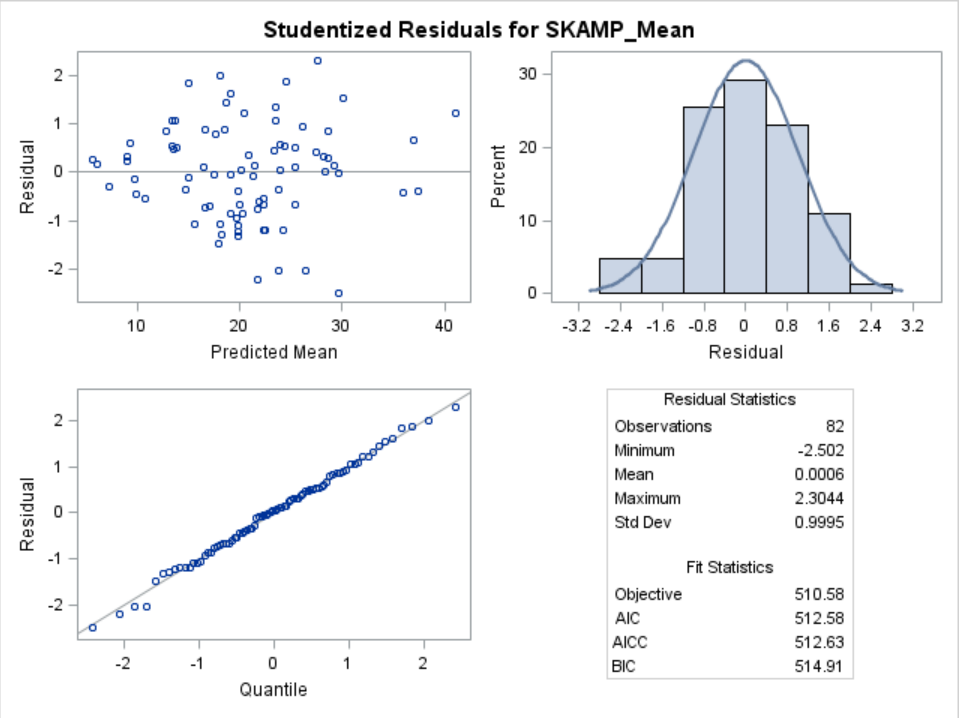
	PERMP-Attempted (Full Analysis Set)	PERMP-Correct (Full Analysis Set)
LS Mean (95% CI)		
NT0102	111 (102, 119)	107 (98.9, 116)
Placebo	79.3 (70.3, 88.2)	75.7 (67.0, 84.4)
Difference	31.4 (20.5, 42.2)	31.7 (21.1, 42.2)
P-value	<0.0001	<0.0001
Baseline Pre-dose		
P-value	<0.0001	<0.0001
Site Main Effect		
P-value	0.8517	0.8949

Abbreviations: CI= confidence interval, LS Mean=least squares mean, PERMP=Permanent Product Measure of Performance
(Source: Study Report p. 54)

Reviewer's analysis

Assessment of normality assumption underlying primary analysis (ANCOVA)

Figure 3. Studentized Residuals for SKAMP-Combined Mean Scores



(Source: Reviewer [Normality_1004])

Table 14. Tests for Normality for SKAMP Mean Residuals

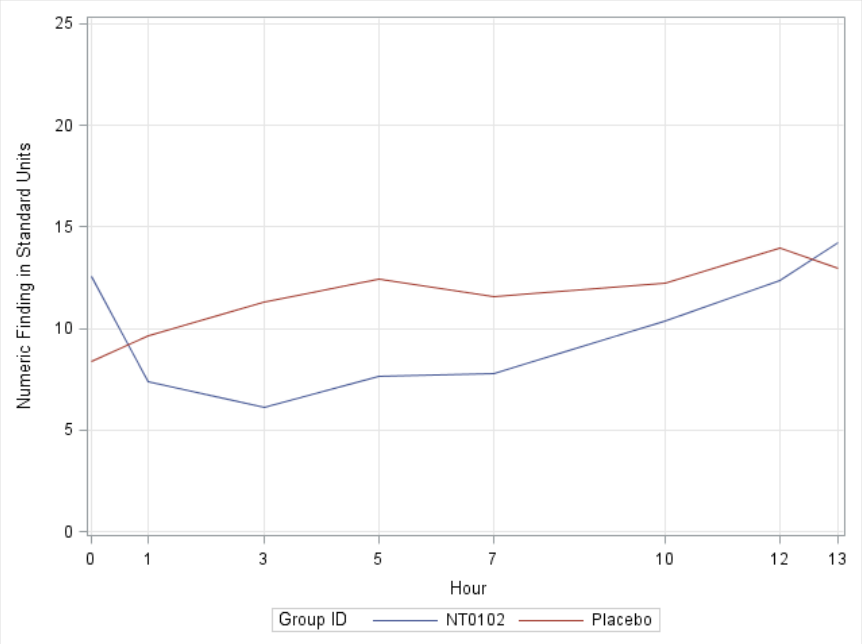
Test		Statistic		p Value
Shapiro-Wilk	**W**	0.993245	**Pr < W**	0.9497
Kolmogorov-Smirnov	**D**	0.046536	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.01806	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.142517	**Pr > A-Sq**	>0.2500

(Source: Reviewer [Normality_1004])

Conclusion: Given the residual diagnostics displayed in Figure 3 and the tests for normality in Table 14 the normality assumption underlying the ANCOVA (primary analysis) appears to hold.

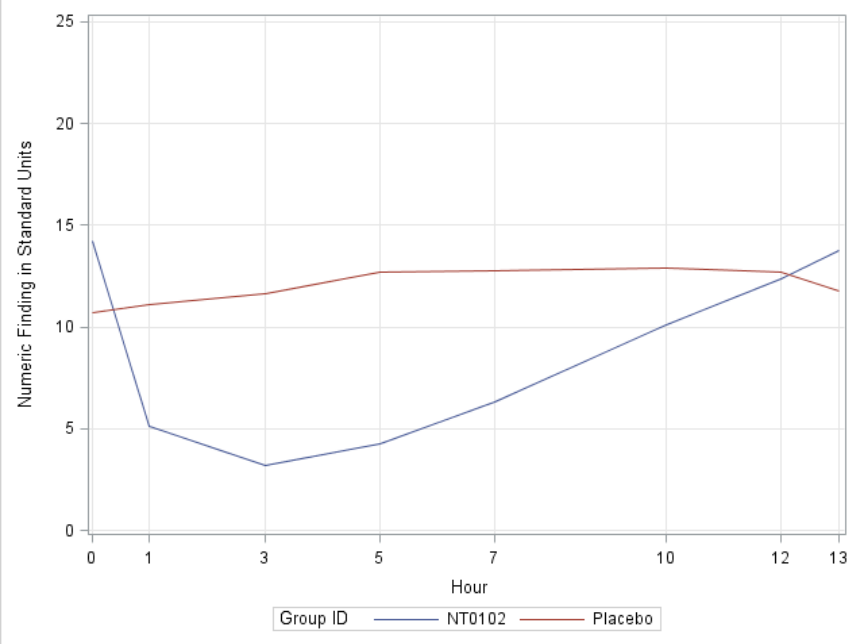
Explore effect on SKAMP deportment vs. attention score

Figure 4. Visit 8 SKAMP-Attention Raw Mean Scores - FAS



(Source: Reviewer [SKAMP_Deport_Att_1004])

Figure 5. Visit 8 SKAMP-Deportment Raw Mean Scores - FAS



(Source: Reviewer [SKAMP_Deport_Att_1004])

Note that a numerically slightly stronger impact on the deportment score compared to the attention score can be observed when comparing Figure 4 and Figure 5.

Efficacy by optimized dose

Table 15. Visit 8 Post-dose SKAMP Raw Mean Scores by Optimized Dose – FAS

Group ID	Optimal Dose	N	Mean	Std Dev	Minimum	Maximum
NT0102	**20 mg/day**	6	17.36	12.67	5.57	38.86
	30 mg/day	13	18.15	6.97	7.29	29.29
	40 mg/day	11	18.30	6.26	9.00	28.71
	60 mg/day	13	15.60	6.54	7.00	28.43
Placebo	**20 mg/day**	5	13.80	2.90	9.86	17.57
	30 mg/day	8	25.43	9.52	10.86	41.14
	40 mg/day	11	24.94	8.09	12.14	35.14
	60 mg/day	15	26.61	10.14	9.43	47.86

(Source: Reviewer [Primary_Analysis_by_optimized_dose_1004.sas])

The SKAMP raw mean scores are fairly similar within treatment group (with the exception of the optimized dose of 20 mg in the placebo group) regardless of optimized dose.

(b) (4)

Section 14 of the proposed label contains (b) (4)

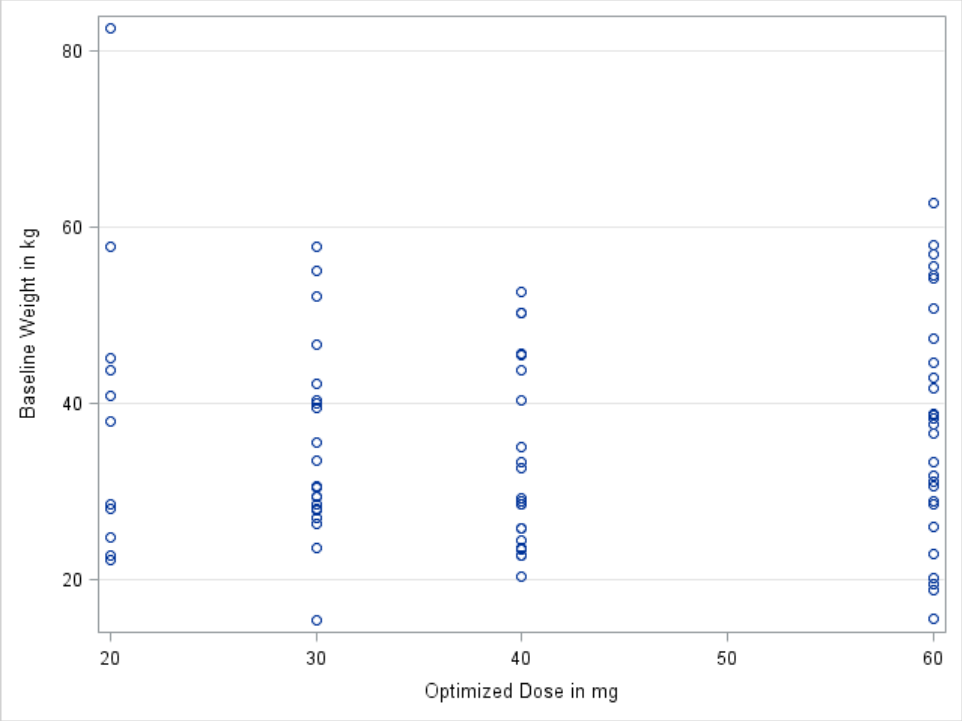
Baseline Weight versus Optimized Dose

Table 16. Baseline (Screening) Weight in kg vs. Optimized Dose - FAS

Opt_dose (mg)	N	Mean	Std Dev	Minimum	Maximum
20	11	39.52	18.13	22.30	82.60
30	21	35.24	10.91	15.40	57.80
40	22	33.36	10.39	20.40	52.60
60	28	38.11	13.31	15.60	62.70

(Source: Reviewer [Primary_Analysis_by_optimized_dose_1004.sas])

Figure 6. Baseline (Screening) Weight in kg vs. Optimized Dose - FAS



(Source: Reviewer [Primary_Analysis_by_optimized_dose_1004.sas])

Given the results displayed in Table 16 and Figure 6 there appears to be no correlation between baseline weight and optimized dose.

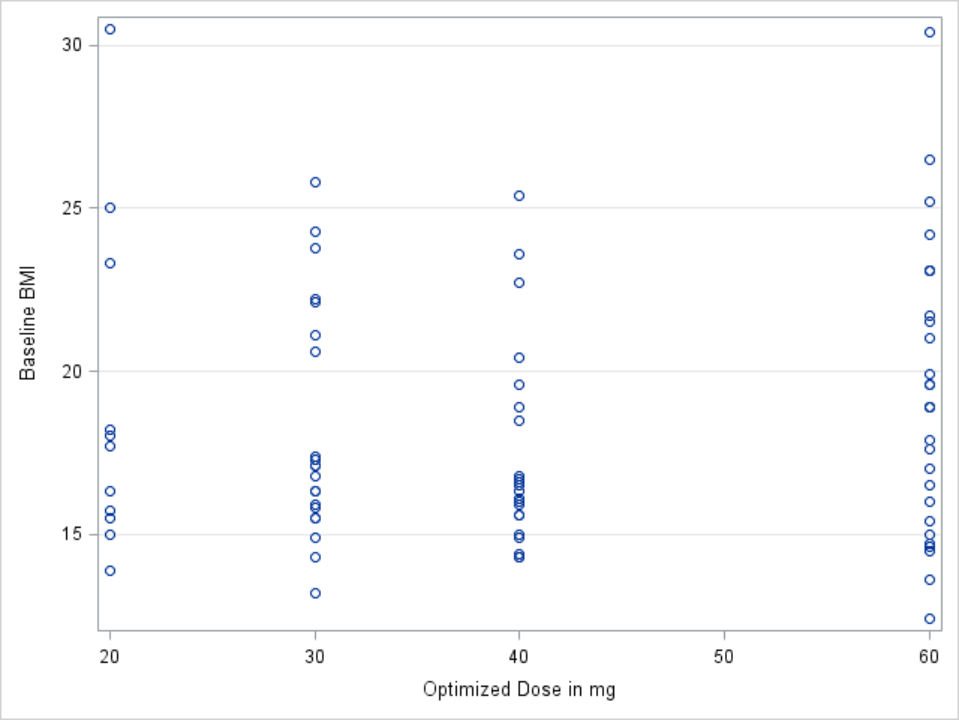
Baseline BMI versus Optimized Dose

Table 17. Baseline (Screening) BMI vs. Optimized Dose - FAS

Opt_dose (mg)	N	Mean	Std Dev	Minimum	Maximum
20	11	19.01	5.12	13.90	30.50
30	21	18.25	3.62	13.20	25.80
40	22	17.46	3.12	14.30	25.40
60	28	19.31	4.31	12.40	30.40

(Source: Reviewer [Primary_Analysis_by_optimized_dose_1004.sas])

Figure 7. Baseline (Screening) BMI vs. Optimized Dose - FAS



(Source: Reviewer [Primary_Analysis_by_optimized_dose_1004.sas])

Again, there seems to be no evidence of a correlation between baseline BMI and optimized dose (Table 17 and Figure 7).

3.3 Evaluation of Safety

The reader is referred to the clinical review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Race

The full analysis set included 65 White, 10 Black or African American and 7 Other patients. Any analysis by such small race subgroups would not produce meaningful results and hence has not been conducted.

A**ge**

The sponsor formed three age subgroups: 6-7 years, 8-10 years, and 11-12 years. Although this classification could be criticized as arbitrary a trend favoring MPH XR-ODT in each of those age subgroups is apparent (Sponsor Table 14.2.1.12).

Gender

The full analysis set included 28 female and 54 male patients. The effect of MPH XR-ODT is trending in the same direction (i.e., improvement for both males and females; Sponsor Table 14.2.1.13).

Region: Patients were enrolled at four sites in the United States.

No firm conclusions can be drawn from those exploratory subgroup analyses due to the limited sample size.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues that impact the overall conclusions were identified.

5.2 Collective Evidence

Patients randomized to MPH XT-ODT in the laboratory classroom study (NT0102.1004), the only efficacy study under this 505(b)(2) application, achieved on average better results on the SKAMP compared to the placebo patients. The primary analysis estimates a difference of -11 points (95% CI: -13.9, -8.2) when averaging the results over the 13 hour classroom session (primary endpoint). This difference is highly statistically significant.

5.3 Conclusions and Recommendations

The statistical results provide adequate evidence to support the claims proposed in the NDA.

5.4 Labeling Recommendations

This reviewer could not confirm the relationship between optimized dose and body weight as implicated (b) (4) from the efficacy data of Study NT0102.1004. There appears to be no relationship in the age segment studied (i.e., 6-12 years; Table 16, Table 17, Figure 6, and Figure 7). After consulting with the ClinPharm team, this reviewer recommends the removal (b) (4)

Other issues pertaining to (b) (4) in the label are the following: (b) (4)

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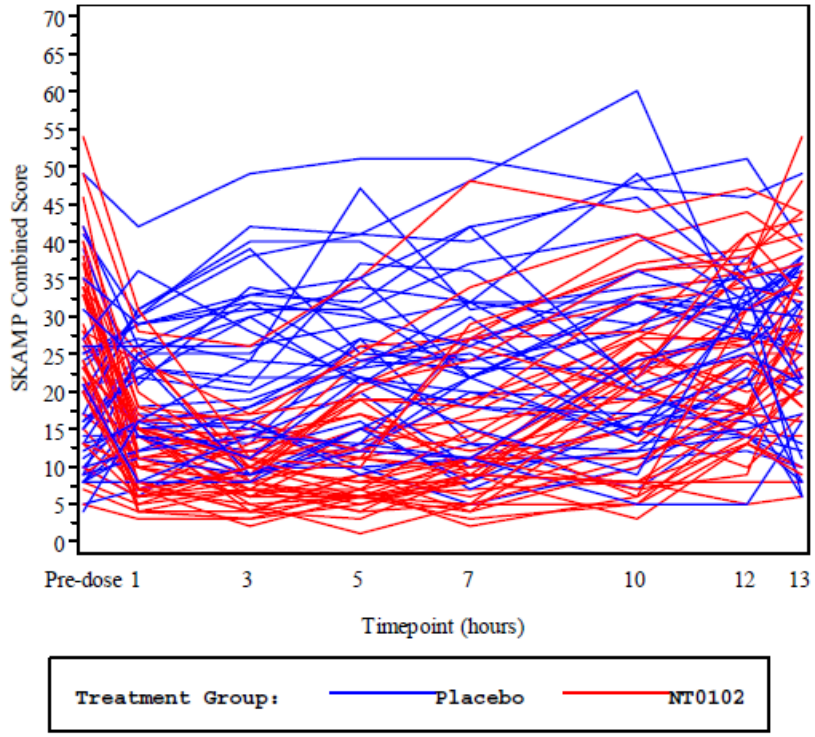
6 APPENDICES

Figure A1. Subject Profiles for SKAMP Combined Score during the Classroom Day - FAS



(Source: Study report Figure 14.2.6 [p. 249])

Description of SKAMP Attention and Deportment Subscales

The items contributing to the **Attention factor/subscale** included the following: difficulty being careful and neat while writing, difficulty in getting started on class assignments, difficulty staying on task for the class period, problems completing assignments, problems performing accurate work, difficulty attending to an activity or discussion in class, and difficulty in stopping. Items contributing to the **Deportment subscale** included the following: problems in interactions with other children in the classroom, problems in interactions with adult staff (teacher, aide, etc.), difficulty remaining quiet according to classroom rules, difficulty staying seated according to classroom rules, and difficulty complying with usual requests or directions from teachers or observers [Study Report p. 31].

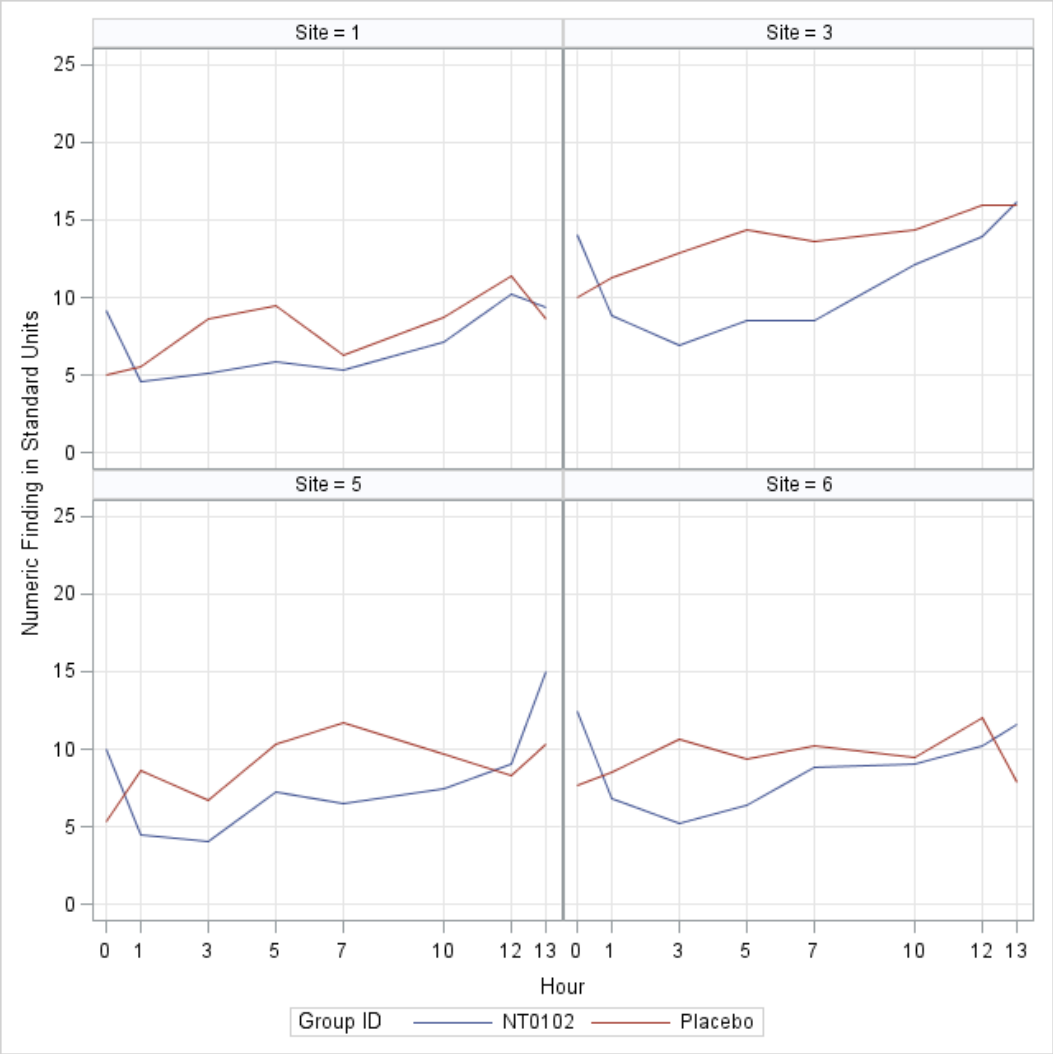
Table A1: Randomization Process for Study NT0102.1004

	Site 1 (Cutler)			Site 3 (Childress)			Site 5 (Kollins)			Site 6 (Marraffino)		
	Rand Date	Rand Schedule	n	Rand Date	Rand Schedule	n	Rand Date	Rand Schedule	n	Rand Date	Rand Schedule	n
Randomization 1st Batch	2013/09/14	Site 01	12	2013/09/07	Site 03	18	2013/11/02	Site 05	7	2013/10/26	Site 02	11
Randomization 2nd Batch	2013/12/07	Site 04	6	2014/02/22	Group 06	18						
Randomization 3rd Batch				2014/04/26	Group 07	13						
N			18			49			7			11

(Source: Reviewer; Rand = Randomization; Randomization Schedule as listed in Appendix 16.1.7 to Study NT0102.1004 Report; Note the initial randomization schedule [Site 01 – Site 05 with 20 randomization numbers each] was created on 06/15/2013, a randomization schedule extension [Group 06 – Group 08 with 20 randomization numbers each] was created 12/12/2013)

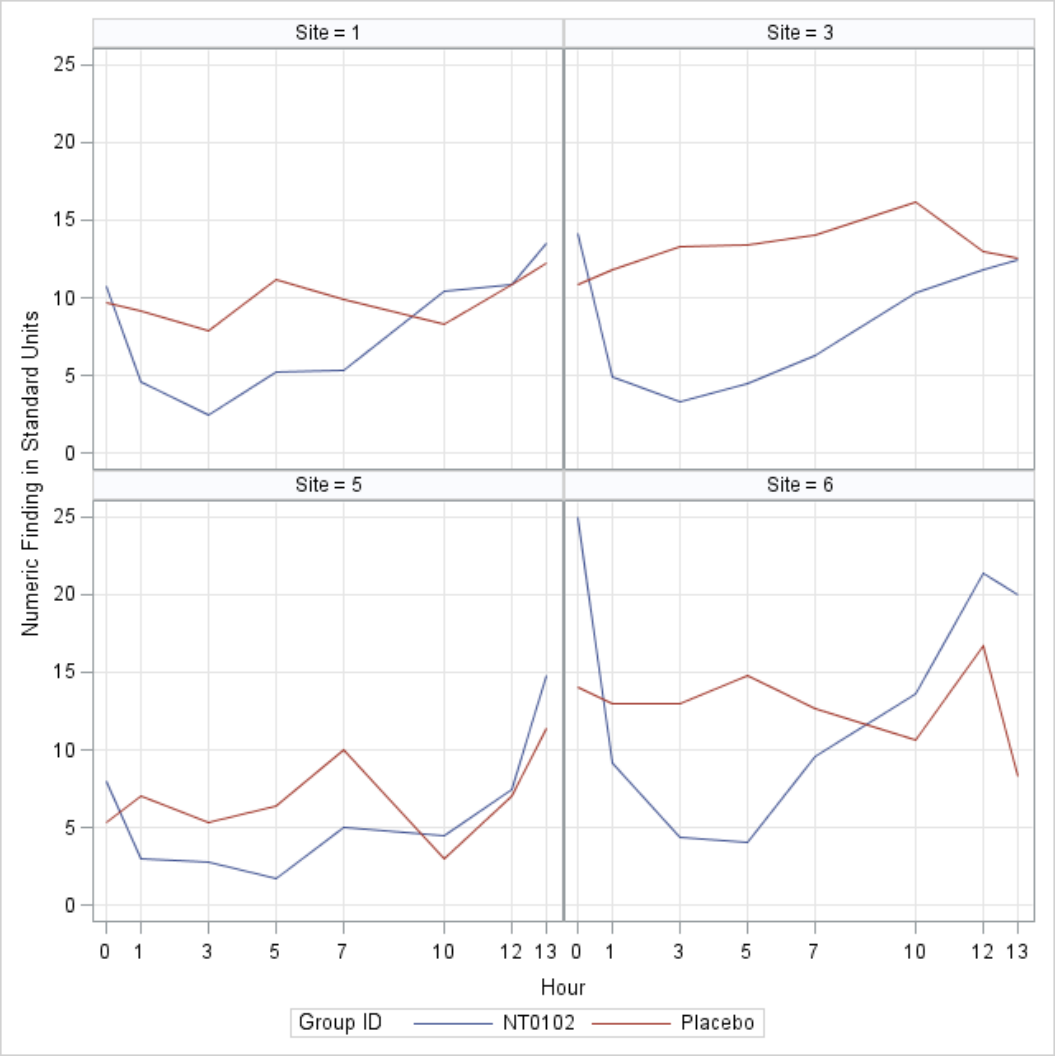
Exploration of Attention versus Comportment scores

Figure A2. Visit 8 SKAMP-Attention Raw Mean Scores by Site



(Source: Reviewer [SKAMP_Deport_Att_1004]; Note that the sample size differed substantially between sites.)

Figure A3. Visit 8 SKAMP-Deportment Raw Mean Scores by Site



(Source: Reviewer [SKAMP_Deport_Att_1004]; Note that the sample size differed substantially between sites.)

Low screen failure rate

The study report contains no information about how many patients were screened to enter the study. This information (A2) was received per FDA request:

Table A2. Number of Screened Subjects and Screen Failures by Site

Investigator	Screened	Screen Failures	Dosed	Completed	Early Term
Cutler (001)	25	6	19	16	3
Childress (003)	51	1	50	49	1
Kollins (005)	7	0	7	7	0
Marraffino (006)	14	3	11	11	0

(Source: Sponsor submission SN05 [Response to 2nd information request])

It is appears somewhat unusual to this reviewer that Site 03 (Childress) screened 51 subjects and only had one screen failure. However, the FDA inspection of clinical site 3 did not reveal anything concerning.

Primary Efficacy at the Site level

Table A3. Post-dose SKAMP Combined Scores by Site, Visit 7 and Visit 8 – FAS

Site # (Investigator)	Visit 7 SKAMP Combined Scores Raw Mean[a] (Std)		Visit 8 SKAMP Combined Scores Raw Mean[b] (Std)	
	"Placebo"* (N=39)	NT0102 (N=43)	Placebo (N=39)	NT0102 (N=43)
1 (Cutler)	8.3 (2.60) (7)	8.0 (3.46) (8)	18.3 (6.92) (7)	14.3 (5.64) (8)
3 (Childress)	11.2 (4.48) (23)	13.5 (5.81) (26)	27.6 (9.86) (23)	18.3 (7.88) (26)
5 (Kollins)	9.1 (3.01) (3)	8.3 (3.30) (4)	16.5 (6.71) (3)	13.3 (4.23) (4)
6 (Maraffino)	6.6 (3.13) (6)	10.6 (5.26) (5)	22.5 (6.19) (6)	20.0 (8.98) (5)

(Source: Study report p. 138, Reviewer [V7_Exploration_1004]; Placebo* equals group of subjects that are randomized to NT0102 at Visit 8; a) average over hours 1, 3, 5, b) average over hours 1, 3, 5, 7, 10, 12 and 13)

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

/s/

THOMAS BIRKNER
10/05/2015

PEILING YANG
10/06/2015
I concur with the review.

HSIEN MING J HUNG
10/14/2015