NWP06, an Extended-Release Oral Suspension of Methylphenidate, Improved Attention-Deficit/Hyperactivity Disorder Symptoms Compared with Placebo in a Laboratory Classroom Study

Sharon B. Wigal, PhD,¹ Ann C. Childress, MD,² Heidi W. Belden, PharmD,³ and Sally A. Berry, MD, PhD³

Abstract

Objective: The purpose of this study was to determine the efficacy of NWP06, a novel extended-release (ER) liquid formulation of methylphenidate (MPH), compared with placebo in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children in a laboratory school.

Methods: A total of 45 subjects ages 6–12 years were enrolled in this dose-optimized, randomized, double-blind, placebo-controlled, crossover laboratory school study. Following open-label dose optimization, subjects received 2 weeks of double-blind treatment (1 week of NWP06 and 1 week of placebo). The treatment sequence (NWP06/placebo or placebo/NWP06) was randomly assigned with the last day of each week-long treatment occurring on the laboratory school test day. Efficacy measures included Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale-Combined and Permanent Product Measure of Performance (PERMP) mathematics tests measured at pre-dose and at 0.75, 2, 4, 8, 10, and 12 hours post-dose on each laboratory classroom day. Safety assessments included physical examination, screening electrocardiogram (ECG), vital signs, clinical laboratory tests, adverse event measures, and assessment of suicidality with the Columbia Suicide Severity Rating Scale.

Results: NWP06 resulted in significant ($p < 0.0001$) improvements in the SKAMP-Combined score at 4 hours post-dose (mean = 7.12) as compared with placebo (mean = 19.58) in the completers ($n = 39$). Significant separation from placebo occurred at each time point tested (0.75, 2, 4, 8, 10, 12 hours), with onset of action of NWP06 at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. Adverse events (AEs) and changes in vital signs following NWP06 treatment were generally mild and consistent with the known safety profile of MPH. The most common AEs in the open-label phase were decreased appetite (55.6%), upper abdominal pain (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%).

Conclusions: NWP06 treatment effectively reduced symptoms of ADHD in children beginning at 45 minutes and continuing for 12 hours post-dose. NWP06 was well tolerated.

Trial registration: ClinicalTrials.gov Identifier: NCT00904670. <http://www.clinicaltrials.gov/ct2/show/NCT00904670>.

Introduction

ONE OF THE MOST COMMON NEUROBEHAVIORAL DISORDERS in children is ADHD. ADHD is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity according to the *Diagnostic and Statistical Manual of Mental Diseases* 4th ed., Text Revision (DSM-IV-TR) (American Psychiatric Association 2000).

Clinical practice guidelines have long supported ADHD treatment in children and adolescents (American Academy of Pediatrics 2001; Pliszka et al. 2007; American Academy of Pediatrics 2011). When medication is necessary, a stimulant, either a methylphenidate (MPH) or amphetamine-based agent, is considered first-line treatment (Pliszka et al. 2007; American Academy of Pediatrics 2011).

¹Department of Pediatrics, University of California, Irvine, Irvine, California.

²Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, Nevada.

³NextWave Pharmaceuticals, Cupertino, California.

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Utility of an extended-release (ER) liquid formulation of MPH in children

Long-acting MPH formulations represent a major advance in the clinical management of ADHD. There are currently no long-acting liquid MPH formulations available, despite the observation in multiple studies that children often have difficulty in swallowing tablets and could benefit from an oral liquid preparation. A common finding is that, although teaching children pill-swallowing techniques can be effective, it is often time consuming and parents are often reluctant to participate. In an observational cohort study assessing pill-swallowing ability, 67/124 (54%) children aged 6–11 years stated they could not swallow a pill, and 20 of these (16%) still could not swallow a pill after receiving scripted swallowing technique instructions (Meltzer et al. 2006). Polaha and colleagues (2008) utilized a parent-completed medication acceptance survey ($n = 304$) to assess children's ability to swallow four different sizes of pills. Parents reported that 33.5% of those children, who had been previously asked to take a pill, had refused to swallow the medication at least once. For large capsules, the proportion of children who reported difficulty approached 75%. In the same survey, parents were asked about their interest in receiving information for teaching their child pill-swallowing techniques and more than half (55.5%) declined receiving such support services (Polaha et al. 2008).

Although children's pill-swallowing behavior can be shaped, some children may, for a variety of reasons, be less inclined to adhere to a pill-swallowing regimen. In summary, difficulty in swallowing tablets can impact medication adherence and lead to missed doses or discontinuation of treatment. Some ER stimulants may be sprinkled on food (Adderall XR 2010, Focalin XR 2010), administered transdermally (Daytrana[®] MTS 2010) or dissolved in water (Vyvanse capsules 2010), however each of these methods has its challenges and does not always allow for reliable delivery of a full dose of medication. Therefore, an oral liquid ER formulation of MPH may improve medication compliance while avoiding the challenges of solid ER dosage forms, including compromised medication delivery or dose dumping when such ER medications are chewed (Childress and Berry 2010; Childress et al. 2011).

NWP06 (Quillivant[®] XR, NextWave Pharmaceuticals, Cupertino, CA), (methylphenidate hydrochloride) was developed to meet this need. NWP06 is supplied as a powder that is reconstituted with water by the pharmacist prior to dispensing. The resulting ER methylphenidate oral suspension has a concentration of 25 mg/5 mL (5 mg/mL) and does not require refrigeration. It is composed of cationic polymer matrix particles that bind *d,l*-threo-methylphenidate racemic mixture via an ion exchange mechanism. A proprietary coating of various thicknesses is applied to the particles to confer extended release properties. NWP06 is a blend of uncoated and coated particles that is ~20% immediate release (IR) and 80% ER methylphenidate.

Pharmacokinetics (PK)

Findings from an earlier report on the single dose PK of NWP06 in healthy adults showed similar overall exposure as assessed by area under the plasma concentration time curve (AUC) as two doses of MPH IR oral solution, given 6 hours apart (Childress and Berry 2010). In the first hour post-dose, NWP06 showed rapid increase of plasma concentration of MPH (similar to MPH IR), followed by a prolonged period of extended release, both of which were targeted PK characteristics of NWP06, based on the hypotheses that they would produce rapid onset of clinical effect that would last

throughout the day. In a second report, single dose PK of NWP06 in children and adolescents ($n = 14$) were examined (Childress et al. 2011). Mean values of dose and body weight adjusted maximum plasma concentration (C_{max}) and AUC were similar among all age and dose groups, suggesting dose proportionality and a similar rate and extent of absorption in both age groups. In both studies, NWP06 was well tolerated with an adverse event (AE) profile similar to that of other ER MPH products.

Study objectives

The primary objective of this study was to determine the efficacy of NWP06, a novel liquid formulation of ER MPH, compared with placebo in the treatment of ADHD in children in a laboratory classroom setting. The laboratory classroom study design allowed for the characterization of the onset and duration of effect as well.

Subjects and Methods

Subjects

Males and females between the ages of 6 and 12 years with a diagnosis of ADHD, any type, were eligible for enrollment. Eligibility included a diagnosis of ADHD made by psychiatrist, psychologist, developmental pediatrician, or pediatrician using the DSM-IV. The diagnosis was then confirmed by administering a structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS). Subjects were required to have been in need of pharmacological treatment for ADHD and either experienced suboptimal efficacy, a safety or tolerability issue with their current regimen, or been in need of a long-acting liquid formulation. A score of ≥ 3 on a clinician-administered Clinical Global Impressions-Severity (CGI-S) scale (indicating at least mild severity) and, $\geq$ the 90th percentile normative values for gender and age on the ADHD-Rating Scale (ADHD-RS) (DuPaul et al. 1998) either total score, hyperactive-impulsive subscale, or the inattentive subscale, were also required. Presence of a comorbid DSM-IV Axis I psychiatric diagnosis (active) other than specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders were considered disqualifying. Subjects with significant cognitive impairment (estimated intelligence quotient [IQ] < 80) or presence of chronic illness including seizure disorder, thyroid disease, Tourette's disorder or family history of Tourette's disorder or tics, serious cardiac conditions, cardiomyopathy, serious arrhythmias, structural cardiac disorders, glaucoma, or severe hypertension were also excluded from the study.

ADHD stimulants were to be discontinued 1 day before the baseline visit and psychotropic medications (with the exception of sedative hypnotics administered at bedtime for sleep) were not permitted throughout the duration of the trial. Parents or legal guardians agreed at screening that there would be no elective changes in subject's non-ADHD medications for the 10-week duration of the study. Participation in any other investigational medication study within 15 days prior to screening was also not allowed, nor was use of atomoxetine or a monoamine oxidase inhibitor within 30 days of the screening visit. Acetaminophen was allowed for control of fever or pain if needed.

Study design

This double-blind (DB), placebo-controlled, crossover design, laboratory classroom study was designed to evaluate the efficacy

and safety of NWP06 in pediatric patients from 6 to 12 years of age with ADHD.

Newer long-acting MPH formulations have combined IR and ER or sustained release (SR) technologies (Wigal et al. 2006) and have been studied using the laboratory school protocol as a tool to measure efficacy, onset, time response, and duration of effect (Wigal and Wigal 2006). The widely used protocol determines efficacy as measured by subjective assessments of inattention, and hyperactive and impulsive behaviors, for example, the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and objective individualized mathematics tests such as the Permanent Product Measure of Performance (PERMP), spaced throughout the laboratory classroom study days.

The study was conducted at two sites: the Child Development Center at the University of California, Irvine and the Center for Psychiatry and Behavioral Medicine, Inc. in Las Vegas, Nevada. The study was conducted in accordance with Good Clinical Practice guidelines, a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (Mihajlovic-Madzarevic 2010). The study was approved by an institutional review board at each study site. Parents/guardians provided written informed consent for study participation, and all subjects provided assent prior to study-related procedures being conducted. Screening tests were performed to assess for eligibility. If inclusion/exclusion criteria were met, the subject was enrolled at the baseline visit (visit 2). The study design (Fig. 1) included initial open-label (OL) treatment with NWP06 for 4 to 6 weeks until dose optimization. The starting dose of the OL phase was 20 mg for all study participants, which was titrated at weekly intervals at 10–20 mg increments until an optimal dose was achieved or a maximum of 60 mg per day was reached. Medication adjustments were permitted at visits 3, 4, 5, and 6. Subjects were randomly assigned at baseline visit in a 1:1 ratio to either the NWP06/placebo or placebo/NWP06 treatment sequence for the additional 2 week (visits 7 and 8) DB phase of the study. The DB phase consisted of two periods: 1 week of NWP06 treatment (with no dose adjustments) followed by 1 week of placebo, or the opposite sequence. On the last day of each period, subjects were evaluated in

a laboratory classroom setting. The final dose of the first week of DB medication was administered at the school site by study staff on the morning of the first test laboratory classroom day (visit 7). The last dose of the crossover treatment occurred on the morning of the second test laboratory classroom day (visit 8). The crossover design of the study allowed subjects to serve as their own controls. The placebo suspension was designed to be identical in taste and appearance to NWP06.

Outcome measures: efficacy

The laboratory classroom setting allowed for efficacy assessments by trained observers over the course of a typical school day (8 hours) and during the after-school activity period (hours 8–12). Specific assessments designed to evaluate subjective measures such as attention and behavior, as well as objective, individualized mathematics tests throughout the 12-hour test period were employed to measure onset and duration of effect of NWP06.

The primary efficacy outcome was the SKAMP-combined score at 4 hours post-dose. The SKAMP scale is a validated 13 item rating of subjective impairment of classroom observed behaviors, with each item rated on a seven-point scale (0 = normal to 6 = maximal impairment) (Wigal et al. 1998). SKAMP scores were obtained during each laboratory classroom day at pre-dose, and at 0.75, 2, 4, 8, 10, and 12 hours post-dose. The combined scores for SKAMP were obtained by summing the values of items in the assessment. The primary efficacy variable was further analyzed by site (sites 1 and 2), final dose (20 mg, 30–40mg, 50–60mg), age (6–7 years old, 8–10 years old, 11–12 years old), gender, ADHD type (inattentive, hyperactive/impulsive, combined type), and ADHD baseline severity (defined as pre-dose SKAMP from the practice laboratory day, categorized as above or equal to/below the median value for all subjects). The key secondary efficacy outcomes as determined by SKAMP-combined score at the same time points included onset and duration of clinical effect.

Additional secondary efficacy outcomes included the four SKAMP subscales: SKAMP-Attention, SKAMP-Depotment, SKAMP-Quality of Work, and SKAMP-Compliance which were measured at each time point during each of the test laboratory classroom days (visits 7–8). PERMP scores were also obtained at

FIG. 1. NWP06 laboratory classroom trial design. ^a4–6 weeks open-label treatment with NWP06 for dose optimization. Study adjustments in approximately weekly intervals (visits 3, 4, 5) in 10 or 20 mg adjustments allowed. ^bMedication doses remain stable during double-blind phase.

pre-dose and at each post-dose time point. CGI-S and CGI-Improvement (CGI-I) were measured as additional efficacy outcomes to assist in decision making for dose optimization in the OL phase of the study. In addition, the ADHD-RS was utilized to determine eligibility, dose optimization, and response to treatment. Further discussion of the secondary outcome measures will be presented in a separate published report.

Safety

Occurrence of AEs was assessed at each visit, and all directly observed and spontaneously reported AEs were collected throughout the study. Medical history was reviewed at visit 1, and subjects were queried about concomitant medications at all visits throughout the study. Screening ECG and clinical laboratory assessments, including complete blood count, chemistry panel, urine drug screen, and serum pregnancy test, were also performed. Height and weight were measured and body mass index (BMI) calculated throughout the study, and blood pressure and pulse rate were measured at all visits in triplicate. The Columbia Suicide Severity Rating Scale (C-SSRS) was used to assess suicidal thoughts or behaviors at baseline and all subsequent visits.

Statistical analysis

The primary and secondary efficacy analyses were conducted on the intent-to-treat (ITT) population, which consisted of all randomized subjects who took at least one dose of study medication and had at least one post-baseline efficacy assessment available for analysis. Treatment comparisons for the SKAMP-combined score at 4 hours on the test classroom days were assessed using a linear analysis of variance (ANOVA) model with SAS software (SAS Institute, Cary, NC). The point estimate of the least squares mean (LS mean) and corresponding 95% confidence interval of the 4 hours post-dose scores were presented for each treatment group. The *p* value for the treatment difference in the LS means, including effect size, was also presented. The effect size was calculated as the LS mean difference divided by the square root of the mean squared error. The same linear ANOVA model was used to test the key secondary variables of onset and duration (clinical effect) of NWP06 versus placebo as measured by SKAMP-combined scores. In order for this analysis to occur, the primary efficacy endpoint was required to be of statistical significance ($p < 0.05$).

Results

Patient disposition

Forty-five subjects (33 boys and 12 girls) were enrolled in this study and all 45 were randomized, 23 to the placebo/NWP06 treatment sequence and 22 to the NWP06/placebo treatment sequence. Forty-four subjects were in the ITT population, and 39 subjects (87%) completed the study. All 22 (100%) subjects in the NWP06/placebo treatment sequence completed the study, whereas 17 (74%) in the placebo/NWP06 sequence completed the study.

Table 1 shows the demographic and baseline patient characteristics of the ITT population. The majority of the subjects were white (80%), male (73%) and were not of Hispanic/Latino ethnicity (75%). The mean age of subjects was 8.8 ± 1.7 years and showed a normal distribution. All ADHD types (inattentive, hyperactive/impulsive and combined) were represented, and most subjects (71%) were diagnosed with the combined type. Thirty percent of subjects had an allowed comorbid psychiatric diagnosis, the most common being oppositional defiant disorder (18%). Of the 45

TABLE 1. PATIENT DEMOGRAPHICS^a

Characteristic	Total (n = 44) n (%)
Age (years, mean $\pm$ SD)	8.8 $\pm$ 1.71
6–7	9 (20.5)
8–10	25 (56.8)
11–12	10 (22.7)
Gender	
Male	32 (72.7)
Female	12 (27.3)
Race	
White	35 (79.5)
Black/African American	4 (9.1)
Asian	3 (6.8)
Other	2 (4.5)
Ethnicity	
Hispanic/Latino	11 (25.0)
Non-Hispanic/Latino	33 (75.0)
ADHD type	
Inattentive	12 (27.3)
Hyperactive/impulsive	1 (2.3)
Combined	31 (70.5)
Comorbid psychiatric diagnosis	
Yes	13 (29.5)
Elimination disorder	4 (9.1)
Oppositional defiant disorder	8 (18.2)
Specific phobias	2 (4.5)
No	31 (70.5)

^aIntent-to-treat.

ADHD, attention-deficit/hyperactivity disorder.

subjects randomized, a total of six subjects (13%) prematurely discontinued the study, and all discontinued during the OL phase. The reasons for discontinuation from the study included withdrawal of assent/consent ($n = 2$), AEs ($n = 2$), lack of efficacy ($n = 1$) and lost to follow-up ($n = 1$).

Efficacy assessments: Primary measure

NWP06 demonstrated significant improvement on the SKAMP-combined scores at 4 hours post-dose compared with placebo (Table 2). The LS mean SKAMP-combined score was 7.12 in subjects receiving NWP06 compared with 19.58 in those receiving placebo. The treatment difference LS mean was -12.46 ($p < 0.0001$) with an effect size of 2.519.

In the subgroup analyses of the primary efficacy variable, the SKAMP-combined scores at 4 hours post-dose by site revealed that both locations had statistically significantly lower (improved) values during NWP06 treatment than with placebo, with an LS mean of the treatment difference of -13.45 ($p < 0.0001$) at site 1 and -10.13 ($p = 0.0003$) at site 2. Subjects with an optimized dose of 30–40 mg showed an LS mean of the treatment difference of -11.33 ($p < 0.0001$) and those in the 50–60 mg group had a treatment difference of -14.70 ($p = 0.0007$) on the SKAMP-combined score. As only two subjects had a final dose of 20 mg, inferential statistics could not be calculated for this group. The mean final (optimal) daily dose of NWP06 was ~ 40 mg.

The largest treatment difference in SKAMP-combined scores at 4 hours post-dose was seen in the 6–7-year-old age group (-15.67 , $p = 0.0030$). Significant treatment differences also occurred in both the 8–10-year-old (-13.73 , $p < 0.0001$) and the 11–12-year-old age

TABLE 2. SUMMARY OF SKAMP-COMBINED SCALE AT 4 HOURS POST-DOSE (ITT POPULATION)

Scale Time point	Statistic	Treatment		Treatment difference NWP06-placebo (n=44)
		Placebo (n=44)	NWP06 (n=44)	
SKAMP-Combined Scale				
4 hours post-dose	<i>n</i>	39	39	39
	Mean (SD)	19.3 (8.38)	7.1 (5.64)	−12.2 (7.19)
	Median	19	6	−10.0
	Min, Max	4, 40	0, 30	−25, 0
	LS mean (SE)	19.58 (1.14)	7.12 (1.14)	−12.46 (1.13)
	95% CI	(17.31, 21.86)	(4.85, 9.39)	(−14.75, −10.17)
	<i>p</i> -value			<0.0001
	Effect size			2.519

The SKAMP-Combined Scale score was obtained by summing items 1–13, where each item was rated on a 7-point scale (0=normal to 6=maximal impairment). Treatment comparison for observed scores were assessed using linear models with sequence (placebo/NWP06, NWP06/placebo), period (visit 7, visit 8), and treatment (NWP06, placebo) as fixed effects, and subject within sequence as a repeated effect with a compound symmetry correlation structure. The effect size was calculated as the LS means difference divided by the square root of the mean squared error. A negative point difference indicates a positive effect of NWP06 over placebo. The intent-to-treat (ITT) population was defined as all subjects who took at least one dose of study medication and had at least one post-baseline efficacy assessment. Subjects who did not complete laboratory classroom testing were not included in the ITT population for the primary efficacy analysis.

CI, confidence interval; SD, standard deviation; SE, standard error; LS mean, least squares mean; SKAMP, Swanson, Kotkin, Agler, M-Flynn and Pelham.

groups ($-6.75, p=0.0050$). Significant separation was also observed in both genders. The LS mean of the treatment difference between NWP06 and placebo was -11.24 ($p<0.0001$) for male and -15.48 ($p=0.0002$) in female subjects. Subanalysis of ADHD type at 4 hours post-dose revealed statistically significant differences from placebo in both the combined type and inattentive type ADHD. There was only one subject with the hyperactive/impulsive type ADHD, and, therefore, no calculations of inferential statistics could be made. Baseline ADHD severity (below and above the median) demonstrated that subjects in both groups had statistically significant separation from placebo when treated with NWP06. SKAMP-combined scores at 4 hours post-dose were -9.13 ($p<0.0001$) for the below-median severity group and -15.45 ($p<0.0001$) for subjects with baseline scores above the median.

Efficacy assessments: Secondary measures

Figure 2 displays the SKAMP-combined scores over the course of the laboratory classroom day. Significant separation from placebo occurred at each time point tested (0.75, 2, 4, 8, 10, and 12 hours) throughout the laboratory classroom days, with onset of action of NWP06 at 45 minutes post-dose and duration of efficacy to the last time point measured at 12 hours post-dose. In addition, mean SKAMP-combined scores remained below the pre-dose value at each post-dose time point in the group treated with NWP06. Conversely, SKAMP-combined scores in the placebo group were above pre-dose values at each post-dose time point.

Results for other secondary efficacy parameters will be presented in a later published report.

FIG. 2. Laboratory classroom Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP)-combined scores

TABLE 3. POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGN VALUES (SAFETY POPULATION)

Vital sign	PCS criteria	Statistic	Treatment Sequence		Total (n = 45)
			Placebo/NWP06 (n = 23)	NWP06/placebo (n = 22)	
Mean systolic blood pressure	Any post-baseline value >95th percentile	n (%)	0 (0.0)	1 (4.5)	1 (2.2)
	Any increase from baseline $\geq$ 20 mm Hg	n (%)	2 (8.7)	0 (0.0)	2 (4.4)
Mean diastolic blood pressure	Any post-baseline value >95th Percentile	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Any increase from baseline $\geq$ 20 mm Hg	n (%)	10 (43.5)	11 (50.0)	21 (46.7)
Mean pulse	Any post-baseline value >110 bpm	n (%)	5 (21.7)	4 (18.2)	9 (20.0)
	Any increase from baseline >25 bpm	n (%)	4 (17.4)	6 (27.3)	10 (22.2)
Weight	Any decrease from baseline $\geq$ 5%	n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline was defined as the last available non-missing pre-dose observation at visit 2 (or at visit 1 if missing at visit 2). The 95th percentile for the systolic and diastolic blood pressure measurements was calculated based on each subject's age, sex, and height percentile. Safety population was defined as all randomized patients who received at least one dose of study medication and underwent at least one post-baseline safety assessment. PCS, potentially clinically significant.

Safety assessment

The mean length of exposure to study medication was 41 days; 28.8 days in the OL phase and 13.8 days in the DB portion of the study. The mean daily dose of NWP06 during the study was 32.8 mg. Overall, 42 subjects (93.3%) experienced a treatment-emergent adverse event (TEAE). There were three (6.7%) subjects with severe TEAEs (affect lability, aggression, and initial insomnia) and 2 (4.4%) subjects had TEAEs (affect lability and aggression) that led to discontinuation from study. There were no deaths or serious adverse events (SAEs) during the study. The most common TEAEs reported during the open-label phase were decreased appetite (55.6%), abdominal pain upper (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%). These events were not unexpected, based on the known AE profile of MPH.

Other AEs reported in $\geq$ 5% of the subjects during the OL phase included: vomiting, diarrhea, logorrhea, aggression, dizziness, irritability, fatigue, upper respiratory tract infection, cough, and flushing.

During the DB phase, 11 (24.4%) subjects had a TEAE while receiving NWP06 and 5 (11.1%) subjects had a TEAE while receiving placebo. There were no severe TEAEs, SAEs, deaths, or AEs leading to premature withdrawal of study medication during the DB phase. In general, TEAEs were reported with a lower incidence in the DB phase than during the OL phase. Affect lability in the DB phase was the only TEAE reported in $\geq$ 5% of subjects receiving NWP06, and the incidence of affect lability was higher during treatment with NWP06 (8.9%) than during treatment with placebo (2.2%). No severe TEAEs were reported during the DB phase.

Mean changes in vital signs were small in magnitude, consistent with the known effects of MPH, and not considered clinically significant. The mean change (increase) in blood pressure from baseline to visit 6 (end of the OL phase) was 3.5 mm Hg and 3 mm Hg for systolic and diastolic blood pressure, respectively. Throughout the study, mean increases in pulse of $\sim$ 7–9 bpm were observed, with a mean change during the OL phase of 9.2 bpm. There were no subjects with decreases in weight $\geq$ 5% throughout the study, and the mean change in BMI from baseline to week 6 was a gain of 0.13 kg/m². No incidences of treatment-emergent suicidal ideation or behavior occurred. Table 3 displays the mean incidence of potentially clinically significant vital sign values occurring during the study.

Discussion

The results of this randomized, DB, placebo-controlled, cross-over design, multicenter trial demonstrate the efficacy of NWP06, a liquid ER MPH formulation, in 6–12-year-old children diagnosed with ADHD. Significant separation from placebo at the first post-dose time point measured demonstrated an onset of effect of NWP06 of 45 minutes, and the duration of effect was maintained throughout the entire 12-hour period (last time point measured). The primary efficacy variable, the SKAMP-combined score at 4 hours post-dose, was statistically significantly lower with NWP06 treatment compared with placebo treatment, and the large effect size observed (2.5) is in line with effect sizes observed for other stimulants in the treatment of ADHD (Faraone and Buitelaar 2010). The laboratory school setting provided structure and a controlled environment that allowed for the simultaneous administration of DB study medication while providing the rigorous measurement of time-course effects. Results of the subgroup analyses of SKAMP-combined scores at 4 hours post-dose support the efficacy of NWP06 regardless of final dose, age, gender, ADHD type, or ADHD severity.

Other available long-acting oral stimulants have demonstrated a range in both onset and duration of effect as measured in laboratory classroom studies (McCracken et al. 2003; Swanson et al. 2004; Silva et al. 2006; Biederman et al. 2007; Brams et al. 2008; Silva et al. 2008; Wigal et al. 2009, 2011; Armstrong et al. 2012). Differences in protocol design among trials, as well as the first and last time points measured in the studies, make direct comparison of onset and duration of effect between products difficult. Such pertinent variations in trial design that complicate product comparisons include different efficacy parameters preselected to determine onset and duration of effect; and characteristics of patient population including age, severity of illness at baseline, selection criteria for responder status, enrichment for hyperactive/impulsive type ADHD, and dosing scheme.

Overall, NWP06 was safe and well tolerated during the study with AEs consistent with known effects of MPH. The most common TEAEs reported during the OL phase were decreased appetite, upper abdominal pain, affect lability, initial insomnia, insomnia, and headache. TEAEs were reported with a lower incidence in the DB phase than during the OL phase. Affect lability was the only TEAE reported in $\geq$ 5% of subjects receiving NWP06 during the DB phase. There were three subjects with severe TEAEs (affect lability, aggression, and initial insomnia) during the OL phase, and no severe

TEAEs were reported during the DB phase. There were no deaths or SAEs during the study. There were two subjects who withdrew from the study during the OL phase because of TEAEs (affect lability and aggression). There were no subjects with any occurrences of suicidal ideation or behavior during the study, a finding in line with practice guidelines that state that, with the possible exception of atomoxetine, there is no evidence that medications used to treat ADHD increase suicide or suicidal ideation (Pliszka et al. 2007). Mean changes in systolic blood pressure, diastolic blood pressure, height, weight, and BMI were small in magnitude, consistent with the known effects of MPH, and not clinically meaningful. There were mean increases in pulse of ~7–9 bpm observed.

The strengths of this study include using clinically relevant doses of NWP06 based on dose-optimization procedures. The mean daily dose of NWP06 in this study was 32.8 mg and the mean final (optimal) dose was ~40 mg. The OL dosing was titrated based on subject response on the clinician-administered ADHD-RS and CGI-I, and treatment tolerability, a practice similar to dosage titration performed in clinical practice. Although not studied in this trial, a long-acting liquid MPH formulation such as NWP06 may offer a flexible treatment option during dose initiation and titration, when frequent dosage modification is often required.

This study of NWP06 allowed inclusion of patients who were either treatment naïve or had previously been treated with stimulants, and patients with all three types of ADHD (inattentive, hyperactive/impulsive, or the combined type) were included. Many existing studies of ADHD limit inclusion to the hyperactive/impulsive or combined subtypes of the disorder and/or to known treatment responders. Our population more closely reflects a real-world population and provides a more rigorous test of the study drug.

Limitations

This NWP06 study was a registration trial that was submitted in a New Drug Application (NDA) to gain United States Food and Drug Administration (FDA) approval for use of NWP06 in the treatment of ADHD. Because this study was the first efficacy assessment of this novel formulation, the primary efficacy outcome was set at one particular time point, 4 hours post-dose. Without data to predict the approximate onset and duration of effect at the time of protocol development, the selection of the mean SKAMP-combined score across all post-dose time points as the primary efficacy measure was not possible. A more rigorous test of efficacy is to set the primary efficacy parameter to the LS mean of the average scores from the SKAMP rating scale across a treatment day. This planned analysis was highly significant, but classified as a secondary efficacy outcome per protocol.

During the FDA review process, the FDA statistical reviewer confirmed our per-protocol analysis results as reported in this article. However, the statistical review team found that even though the analysis results based on the combined period data showed statistically significant differences between the drug and placebo at all time points, a treatment-by-period interaction appeared to be present. Therefore, the statistical review team also performed the analysis using the first period of data and showed that the differences between NWP06 and placebo were still statistically significant at all time points. The statistical reviewer also performed a permutation test to evaluate the robustness of the efficacy findings. The permutation test results also showed that the differences between NWP06 and placebo to be statistically significant at all time points for the Period I data (Food and Drug Administration 2011). NWP06 received FDA approval in individuals with ADHD ages 6–65 years on September 27, 2012 based on the Period I data alone

(Quillivant XR 2012). Laboratory classroom studies have traditionally employed a crossover design, which may limit the ability of discerning readers to understand how period effects may have influenced findings in already published laboratory school studies. However, given the treatment-by-period interaction observed in this study, further research is required to understand this issue and to determine if the reliability of findings derived from classroom studies could be enhanced by a parallel design.

Whereas inclusion of some of the most common comorbidities was allowed, exclusion of patients with significant psychiatric and medical comorbidities limited the generalizability of the findings in this study. As is typical in clinical trials on children with ADHD, boys tend to be over-represented compared with girls, which may limit the ability to adequately compare for sex differences.

Although the efficacy of NWP06 was demonstrated from the earliest post-dose time point measured (45 minutes) up to and including the last post-dose time point measured (12 hours), no earlier or later measurements were performed; therefore, it is not known whether onset of action would have been seen at an earlier time point or whether duration of effect would have been seen at a later time point. The study design also did not allow for testing the long-term efficacy and safety effects of treatment with NWP06.

Conclusions

NWP06 resulted in significant ($p < 0.0001$) improvements in the SKAMP-combined score at 4 hours post-dose (mean = 7.12) as compared with placebo (mean = 19.58) in the completers ($n = 39$). Significant separation from placebo occurred at each time point tested (0.75, 2, 4, 8, 10, and 12 hours), with onset of action of NWP06 at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. AEs and changes in vital signs following NWP06 treatment were generally mild, and were consistent with the known safety profile of MPH. The most common AEs in the OL phase were decreased appetite (55.6%), upper abdominal pain (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%). This study shows that NWP06 significantly improved ADHD symptoms in school-aged children and was well tolerated.

Clinical Significance

This study demonstrates the efficacy of the first ER MPH liquid formulation in reducing symptoms of ADHD in school-aged children in a laboratory classroom setting. Significant separation from placebo occurred at each time point tested (0.75, 2, 4, 8, 10, and 12 hours) throughout the laboratory classroom days, with onset of action of NWP06 at 45 minutes post-dose and duration of efficacy to the last time point measured at 12 hours post-dose. In addition, mean SKAMP-combined scores remained below the pre-dose value at each post-dose time point in the group treated with NWP06. Conversely, SKAMP-combined scores in the placebo group were above pre-dose values, indicating impaired attention and behavior, at each post-dose time point. As an FDA-approved treatment for ADHD, NWP06 represents the only long-acting stimulant available in a pediatric-friendly, liquid formulation.

Disclosures

Dr. Wigal has served on the advisory board, consulted to, received research support from, or been on the Speakers Bureau of the following: Addrenex Pharmaceuticals, Eli Lilly and Company, McNeil Consumer & Specialty Pharmaceuticals, Next Wave

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Address correspondence to:
Sally Berry, MD, PhD
Pfizer, Inc.
235 E. 42nd St.
New York, NY 10017

E-mail: sberry1004@hotmail.com