Clinical Pharmacology Review

NDA:	202100
Proposed Brand Name:	To be determined
Generic Name:	Methylphenidate HCl
Dosage Form:	Extended-Release Powder for Oral Suspension
Dosage Strength:	25 mg/5 mL
Indication:	Attention Deficit Hyperactive Disorder (ADHD)
Sponsor:	NextWave Pharmaceuticals Inc.
Submission type:	505(b)(2)
Submission date:	July 29, 2010
OCP Reviewers:	Huixia Zhang, PhD, Jogarao Gobburu, PhD, Hui Zheng, PhD, Yaning Wang, PhD

OCP Optional Inter-Division Briefing was held on February 14, 2011.

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1. EXECUTIVE SUMMARY

(b) (4) Methylphenidate Extended-Release Powder for oral suspension, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (b) (4), (b) (4) is a new (b) (4) extended-release (b) (4) formulation (b) (4) of methylphenidate (MPH) HCl. This formulation is intended to be used by patients with ADHD (b) (4)

Pharmacokinetics of NWP06 was characterized in children and adolescent with ADHD, (b) (4) Food and alcohol do not meaningfully interfere with NWP06's PK. The efficacy of NWP06 in ADHD children (6 to 12 years of age) was demonstrated in a double-blind, placebo-controlled laboratory classroom study (NWP06-ADD-100). (b) (4)

1.1 Recommendation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1.3 Summary of Clinical Pharmacology Findings

In the current submission, the Sponsor has submitted the results from (b) (4), one single-dose pharmacokinetic study in children and adolescent patients with ADHD (NWP06-PPK-101), and one efficacy and safety Phase III trial in 45 6-12 year-old patients (NWP06-ADD-100) to support their application.

- NWP06 is efficacious in the treatment of children ages 6-12 years old with ADHD.
- Similar PK parameters were obtained for children and adolescents with ADHD.
- NWP06 and Methylin Oral Solution have different shapes of the concentration-time curves (see Figure 1). Owing to the complex drug release characteristics to match the q6h reference PK profile, conventional BE metrics are not appropriate for NWP06. The test-reference ratio for AUC is 0.95 (90% CI: 0.92-0.99), and C_{max} is 0.69 (90% CI: 0.64 - 0.75). (b) (4)
- Food increased NWP06's AUC by 20%, C_{max} by 28% and shortened Tmax (4 hrs vs 5 hrs-fasted). NWP06 can be administered with or without food.

2. QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Is there evidence of effectiveness for NWP06 in children aged 6-12 years (b) (4)?

Yes. The efficacy of NWP06 in ADHD children (6 to 12 years of age) was demonstrated in study NWP06-ADD-100.

Study NWP06-ADD-100 was a randomized, double-blind, placebo-controlled, crossover, multicenter, laboratory classroom study. In the open-label dose optimization phase (4 to 6 weeks), the initial methylphenidate dose for all subjects was 20 mg once daily in the morning. The dose was titrated weekly in increments of 10 or 20 mg until an optimal dose or maximum dose (60 mg/day) was reached. After 4 to 6 weeks of dose-optimization, subjects were randomized to one of two double-blind treatment sequences. Subjects were treated with active methylphenidate (with the optimal dose that was established in the open-label, optimization phase) for one week, followed by placebo for one week or vice versa.

The primary efficacy endpoint in this study was the SKAMP-Combined score at 4 hours post-dose, and this endpoint was met. SKAMP combined scores were also obtained for time points of 0.75, 4, 8, 10, and 12 hrs post-dose as secondary end points. The onset of efficacy was determined to be 0.75 hours post-dose, and efficacy was maintained throughout the 12-hour period.

2.1.2 Are sponsor's claim about onset of effect by 45 min and sustained effect through 12 hr justified?

Yes.

1) Time course of concentrations:

The mean concentrations in the first 45 min for both products are similar. Methylin Oral Solution exhibited higher concentrations beyond 5 hrs compared to NWP06. Mean d-MPH plasma concentration-time profiles were compiled from different studies, after oral administration of NWP06 60 mg, Methylin Oral Solution 2x30 mg (NDA202100) and Concerta 54 mg (NDA21121). As shown in Figure 1, different shapes of curves were observed for those products. Concerta has two absorption peaks, Methylin Oral Solution also has two peaks due to q6h administration, while NWP06 only has one peak. Although the concentrations beyond 5 hr for NWP06 and Concerta are similar, Methylin Oral Solution exhibited higher concentrations till 12 hr.

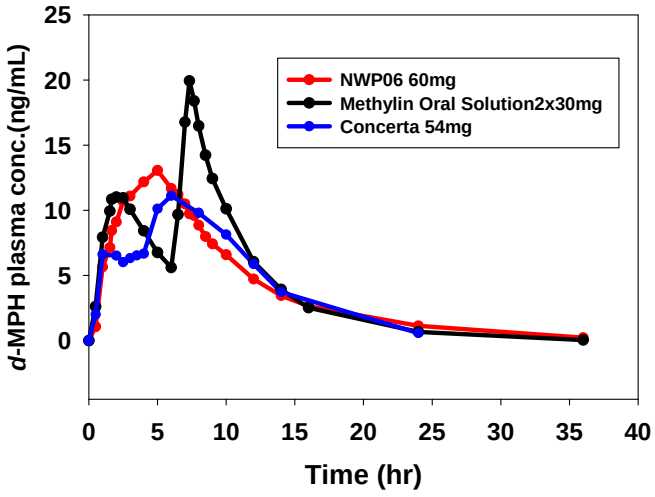


Figure 1. Plasma concentration time profiles of d-MPH after oral administration of NWP06 (60 mg), Methylin Oral Solution q6hr (2x30 mg), and Concerta (54 mg). Total MPH was measured for Concerta (*l*-MPH concentration is 1/40 of *d*-MPH in the circulation). Concerta information source: \\Cdsesub1\evsprod\NDA021121\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\02-160

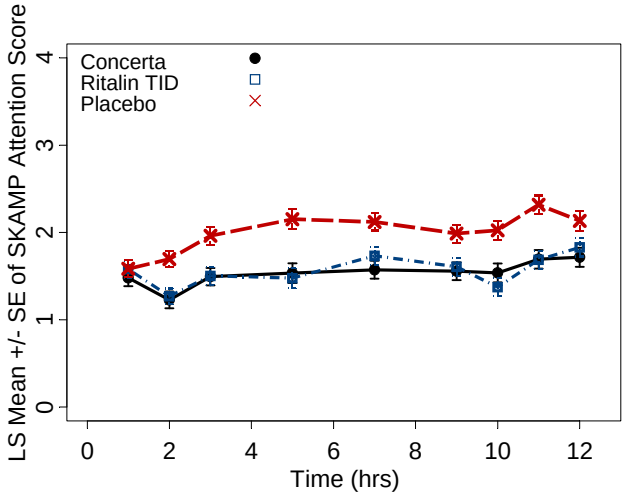
Overall AUC for NWP06 and Methylin Oral Solution are similar. Comparison of partial AUCs of NWP06 and Methylin Oral Solution indicates that at the earlier (0-2 hr) and late phases (6-8, 8-12 hr) of the curves, NWP06 has 30-40% lower AUC compared to Methylin Oral Solution (Table 1).

Table 1. Comparison of PK Parameters of NWP06 and Methylin Oral Solution After 60 mg Oral Administration in Healthy Volunteers Under Fasting Conditions (n=28)		
d-MPH PK parameters	Geometric Mean Ratio (%) (NWP06/Methylin Oral Solution)	90% confidence interval (%)
AUC_{0-2}	70	61-79
AUC_{2-4}	113	106-121
AUC_{0-4}	95	88-104
AUC_{4-8}	108	103-114
AUC_{6-8}	72	67-77
AUC_{8-12}	62	59-66
AUC_{0-inf}	95	92-100
C_{max}	69	64-75
NWP06: 60 mg; Methylin Oral Solution: 2x30 mg, 6 hr apart		

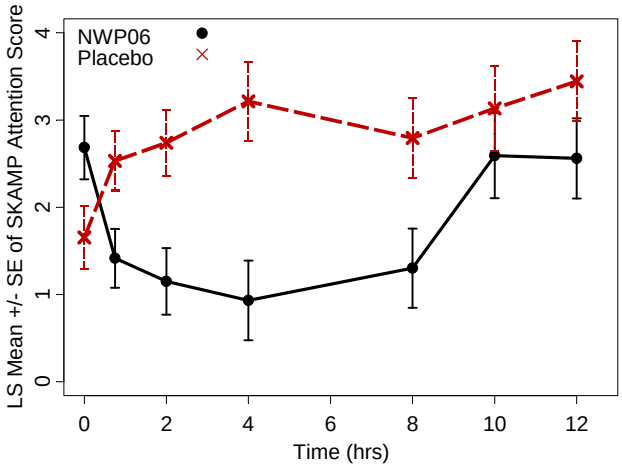
The concentration of d-MPH is higher after NWP06 (60 mg) administration than that after Concerta (54 mg) administration, from about 1 hr to 7-8 hrs after dosing. From 8 hr onward, the concentration-time profiles are almost superimposable. Of note, total MPH concentrations were measured in Concerta study, and *l*-MPH concentration was about 1/40 of d-MPH.

2) Time course of clinical response:
NWP06 exhibited absolute SKAMP scores significantly different from placebo starting from 45 min, and the response sustained up to 12 hr. As Methylin Oral Solution's efficacy was not directly studied, we used Ritalin IR (TID) and Concerta's efficacy results to qualitatively appreciate the time-course of clinical response better (Figure 2). These data suggest that NWP06 is comparable to Concerta and Ritalin IR in terms of effects on SKAMP attention score.

Figure 2: Mean (±SE) SKAMP Attention Scores over Time after Treatment with Concerta (Panel A), Ritalin TID (Panel A) or NWP06 (Panel B).



A: Concerta NDA21121, Study C-98-003 *3 treatment crossover (n=60, age 6-12)*
Dosage: Concerta 18, 36, 54 mg q.d.; Ritalin 5, 10, 15 mg t.i.d.



B: NWP06 NDA202100, Study NWP06-ADD-100
2 treatment crossover (n=45, age 6-12); Dosage: NWP06 20, 30, 40, 50, 60 mg q.d.

(b) (4)

a. Methylphenidate is shown to be efficacious in several clinical trials across a varied range of formulations in patients 6 years and older.
b. Concerta 18 mg was shown to be effective in the treatment of ADHD in children, adolescents and adults. Doses upto 54 mg are approved for children, and upto72 mg for adolescents and adults. 20 mg NWP06 was shown to be efficacious in children.
c. PK of NWP06 in children, adolescents (b) (4) are similar at similar doses.
d. MPH concentrations are directly associated with clinical response (Swanson and Volkow 2003: Neuroscience and Biobehavioral Reviews 26: 615-621). (b) (4)

2.1.4 Is an in vivo alcohol and NWP06 study needed?

An in vitro dissolution study to evaluate the effect of alcohol on the drug release profile showed that high (20%) concentrations of alcohol may have some impact on accelerating the release of methylphenidate from the formulation.

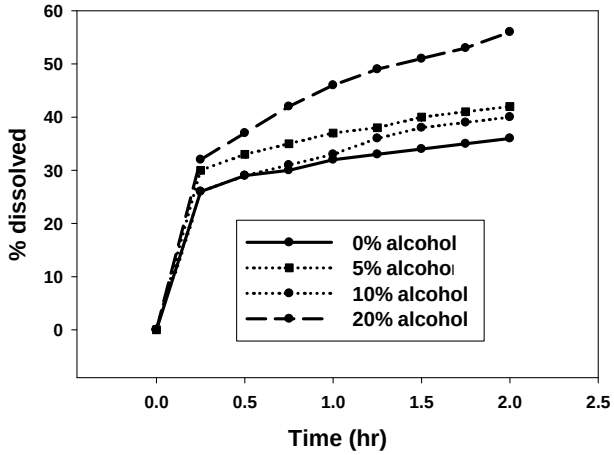


Figure 3: Dissolution profiles of NWP06 in 0.1N HCl with different percentage of alcohol.
Source:\\CDSESUB1\EVSPROD\MF023870

In 0.1 M HCl solution, ~ 36% of the drug powder was dissolved in the medium by 2 hrs; in the presence of 20% of alcohol (v/v), ~ 56% increase in the dissolution of the drug powder was observed. The moderate dose dumping effect with 20% alcohol demonstrates that ~ 60% of the drug powder would be dissolved in 2 hrs.

Clinically, alcohol and medication co-consumption is an unlikely concern for children/adolescents, (b) (4). In the worst case scenario, co-consumption of 20% strength-alcohol might increase the bioavailability and C_{max} by 60%. That means if a patient took 60 mg dose together with a lot of drinking within half an hour, effectively the patient is dosed 96 mg. Doses up to 144 mg were studied for Concerta. No severe adverse events were observed. Therefore, there is no concern about infrequent alcohol consumption, and an in vivo study is not required. However, alcohol is known to impair behavior which might lead to pharmacodynamic interaction with ADHD treatment.

2.1.5 What are the extended release characteristics of NWP06?

NWP06 is a (b) (4) extended release formulation (b) (4) of methylphenidate HCl. Its PK properties are listed in the table below.

Table 2. Pharmacokinetic Parameters (Mean±SD) of d-MPH after oral administration of 60 mg either NWP06 or Methylin IR Oral Solution (30 mg Q6hr) under Fasting Conditions.

PK Parameters	NWP06	Methylin IR Oral Solution
AUC_{0-36}, ng·hr/mL	140±71.4	149 ± 82.6
C_{ave} [a], ng/mL	3.89±2.29	4.14±2.29
C_{max}, ng/mL	13.6±5.79	15.5[b]
C_{24}, ng/mL	1.13±0.81	0.67±0.66
Fluctuation ratio[c]	3.21	3.58
$T_{1/2}$, hr	5.7±0.85	3.74±0.61

[a] C_{ave} is obtained by dividing AUC_{0-36} with 36; [b] C_{max} is the mean of C_{max1} and C_{max2}; [c] fluctuation ratio is obtained following equation $(C_{max}-C_{min})/C_{ave}$ using the mean values.

Because of its half life (~5.7 hr) and once daily dosing regimen, the pharmacokinetic parameters of NWP06 is not expected to change after multiple dosing compared to single dose administration (methylphenidate demonstrates time-independent linear pharmacokinetics). The first dose is almost completed eliminated from the body at the end of 24 hr period, and no significant accumulation of methylphenidate is expected.

2.1.6 Is there any relationship between the final dose and body weight?

Patients in the (b) (4) study received different doses of NWP06 from 20 mg to 60 mg and the patients had different body weight, from 38 lbs up to 137.5 lbs. To determine if there is a need for body weight-based dosing, an analysis was performed between the final dose and patient body weight. As shown in Figure 4, there is no noticeable relationship between the body weight and the final dose. Hence, there is no need for weight based dosing.

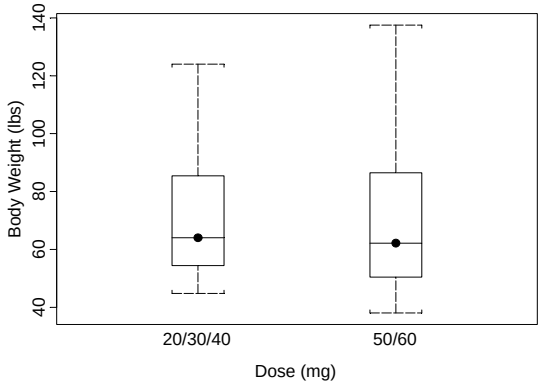


Figure 4: NWP06 Final Dose vs. Body Weight of Subjects

2.2 Standard Questions

2.2.1 Does food affect the bioavailability of NWP06?

High-fat meal increased systemic exposure (AUC_{inf}) of NWP06 by ~ 20%, and C_{max} by ~ 28%. The small increase in exposure is not expected to have a large effect on the efficacy or safety of the product.

Table 3. Pharmacokinetic Parameters of d-Methylphenidate (d-MPH) after oral administration of 60 mg MPH ER oral suspension under Fed or Fasting Conditions

PK Parameters	Fed	Fasting	Ratio of Geometric Means (90% Confidence Interval)
$AUC_{0\text{-}inf}$ [a], ng·hr/mL	163 (49)	144 (51)	119 (115-123)
C_{max} [a], ng/mL	17 (46)	14 (43)	128 (120-136)
T_{max} [b], hr	4 (1-7)	5 (2-6)	
$T_{1/2}$ [a], hr	5 (20)	56(15)	

[a]Arithmetic Mean (%CV), [b]Median (Range)

2.2.2. What are the single dose PK parameters of NWP06 in healthy (b) (4) pediatric patients?

Similar PK parameters were obtained for T_{max} and $T_{1/2,}$ in children and adolescents with ADHD (b) (4) Body-weight corrected clearance values were also similar across the (b) (4) populations. NWP06 exhibited dose-proportional PK between 20 mg – 60 mg.

Table 4. d-MPH PK Parameters (mean ±SD) after 60 mg oral dosing of NWP06 under fed conditions[1]

PK Parameters	Children[2] (n=3)	Adolescent[2] (n=4)	(b) (4)
T_{max} (hr)[3]	4 (4-6)	2 (2-4)	
$T_{1/2}$ (hr)	5±0.1	5±0.2	
C_{max} (ng/mL)	34±14	21±6	
AUC_{inf} (hr*ng/mL)	378±175	178±54	
CL (L/hr/kg)	4±0.7	5±1	

[1]Breakfast was given 30min after drug administration [2] total MPH measured in children and adolescents, l-MPH<2% of d-MPH in circulation [3]data presented as median (range)

SIGNATURES

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Office of Clinical Pharmacology

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Office of Clinical Pharmacology

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Acting Team Leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 202100, DCP1 (Mehta, Uppoor, Gobburu, Zhang)

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3. INDIVIDUAL STUDY REPORTS

(b) (4)

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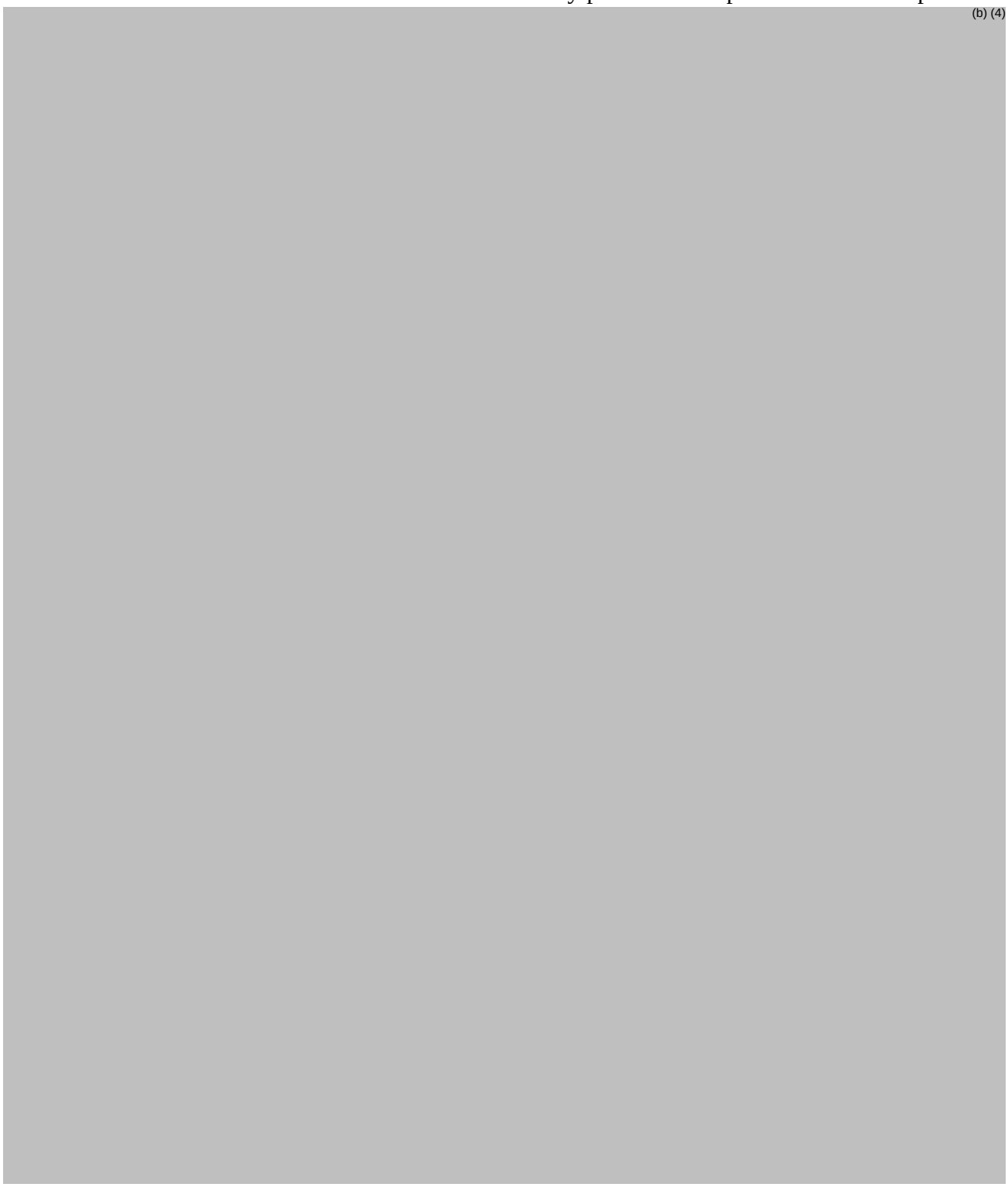
(b) (4)



3.1.2 Single Dose Pharmacokinetics in Children and Adolescents with ADHD

Report # NWP06-PPK-101	**Study Period**: clinical phase start: April 23, 2010; Study treatment date: May 8-9, 2020	EDR Link
Title	Evaluation of the Single Dose Pharmacokinetics of NWP06 in Children and Adolescents with ADHD	

<table>
<tr><td colspan="5">Study Design: phase 1, open label, children (6-12 years-old) and adolescents (13-17years-old) ADHD patients</td></tr>
<tr><td>Number of Subjects/ dose group: 7</td><td>Drug</td><td>Methylphenidate extended release powder for oral suspension</td><td>Placebo</td><td>NA</td></tr>
<tr><td colspan="5">Dose: 20 mg; 60 mg</td></tr>
<tr><td colspan="5">PK Sampling Times: pre-dose (up to 2 hours before dosing) and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose on Day 1 (within ±15 minutes of the scheduled time), and 24 hours post-dose on Day 2 (within 24-28 hours post-dose)</td></tr>
<tr><td colspan="5">Analytical Method:
<table>
<tr><td>Type</td><td>LC/MS/MS (AP LC/MS/MS 070.100)</td><td>Range</td><td>0.1-40 ng/mL</td></tr>
<tr><td colspan="2">The performance of the analytical method is acceptable.</td><td colspan="2">☑ Yes ☐ No</td></tr>
</table></td></tr>
<tr><td colspan="5">Study Population :
<table>
<tr><td>Randomized/Completed/ Discontinued Due to AE</td><td>14/14/0</td></tr>
<tr><td>Age [Median (range)]</td><td>6-17</td></tr>
<tr><td>Male/Female</td><td>11/3</td></tr>
<tr><td>Race (Caucasian/Black/Asian/other)</td><td>10/40/0/0</td></tr>
</table></td></tr>
<tr><td colspan="5">Results</td></tr>
</table>

- Table 1. Pharmacokinetics Parameters (Mean (%CV)) Per Dose Group in Children and Adolescents with ADHD

PK Parameters	20 mg NWP06		60 mg NWP06	
	6-12 years (n=4)	13-17 years (n=3)	6-12 years (n=4)	13-17 years (n=3)
C_{max} (ng/ml)	11.5 (2.2)	9.2 (0.6)	34.4 (14)	21.1 (5.9)
T_{max} (hr)	3.0 (2.0-4.1)	2.0 (2.0-4.0)	4.1 (4.0-6.0)	2.0 (2.0-4.0)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	101 (4.2)	82.4 (4.8)	378 (175)	178 (54.2)
$T_{1/2}$ (hr)	5.3 (0.7)	5.2 (0.2)	5.2 (0.1)	5.0 (0.2)
Cl/F (L/hr/Kg)	5.0 (1.1)	5.1 (0.6)	4.3 (0.7)	5.1 (1.4)

Figure 1. Arithmetic Mean (±SD) Plasma Methylphenidate Concentration-Time Profiles following a Single Oral 20-mg or 60-mg Dose of NWP06 given to Children and Adolescents with ADHD (linear and semi-logarithmic scale).

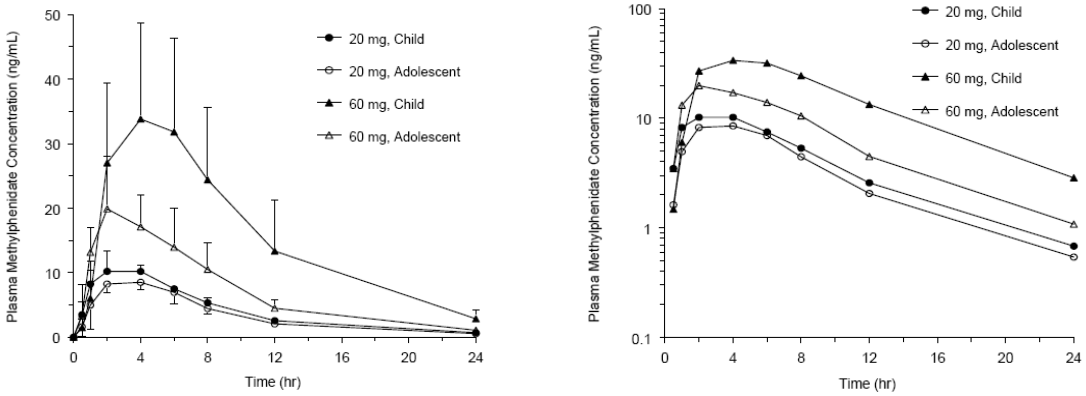


Table 2. Mean (SD) Dose- and Weight-Corrected Plasma Methylphenidate Pharmacokinetic Parameters in Children and Adolescents with ADHD following a Single Oral 20-mg or 60-mg of NWP06.

PK parameters	20 mg NWP06		60 mg NWP06	
	6-12 years (n=4)	13-17 years (n=3)	6-12 years (n=4)	13-17 years (n=3)
C_{max}/D (ng/mL/mg)	0.7 (0.1)	0.5 (0.03)	0.7 (0.3)	0.4 (0.1)
$AUC_{0\text{-}inf}$ /D (hr*ng/mL/mg)	5.8 (0.2)	4.8 (0.3)	7.3 (3.4)	3.4 (1.1)
Cl/F (L/hr/Kg)	5.0 (1.2)	5.1 (0.6)	4.3 (0.7)	5.1 (1.4)

Figure 2. Plasma Methylphenidate CL/F (L/hr/kg) versus Age following A Single Oral 20-mg or 60-mg Dose of NWP06 in Children and Adolescents with ADHD.

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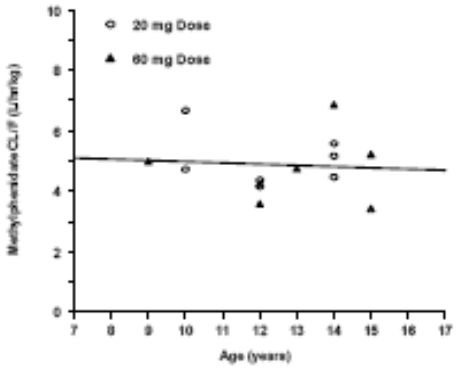

A poor linear correlation was apparent between body weight-adjusted clearance and age (r=0.078), suggesting that when corrected for body weight, methylphenidate oral clearance does not vary with age.

- Was the pharmacokinetics dose proportional? ☑Yes ☐ No

- The pharmacokinetics is best described by:
  ☑Mono-exponential decay, ☐ Bi-exponential decay, ☐ Tri-Exponential Decay
- Was there a lag time in absorption? ☐ Yes ☑ No

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- What is the maximum tolerated dose?
  60mg/day was the highest dose studied in the clinical trial.
- What are the safety profiles of the highest dose?

NWP06 after a single oral dose of 20 or 60 mg was well tolerated. Only a single occurrence of vomiting (mild) was considered possibly related to study medication. No treatment-emergent suicidal thoughts or behaviors were reported.

Comments

The pharmacokinetics of methylphenidate is dose-proportional in the dose range of 20-60 mg in children and adolescents with ADHD. Similar PK parameters were obtained for children and adolescents.

4. NDA FILING FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**202100**	**Brand Name**	**TBD**
OCP Division (I, II, III)	**DCP I**	**Generic Name**	**Methylphenidate extended-release powder for oral suspension**
Medical Division	**Psychiatry Drug Products**	**Drug Class**	**Stimulant**

OCP Reviewer	**Huixia Zhang**	**Indication(s)**	**Attention Deficit Hyperactivity Disorder**
OCP Team Leader	**Raman Baweja**	**Dosage Form**	**Extended-release powder for oral suspension**
		Dosing Regimen	**QD**
Date of Submission	**07/29/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**4/25/2011**	**Sponsor**	**NextWave Pharmaceuticals, Inc.**
PDUFA Due Date	**5/30/2011**	**Priority Classification**	**Standard 10 months**
Division Due Date	**5/2/2011**		

Clin. Pharm. and Biopharm. Information

(b) (4) for methylphenidate extended-release powder for oral suspension for the treatment of ADHD (b) (4).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies		**3**		
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-		**1**		
single dose:		1		
multiple dose:				
Patients-				
single dose:		1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1		
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:		**1**		
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:		1		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		1		
Bioequivalence studies -				
traditional design; single / multi dose:		1		
replicate design; single / multi dose:				
Food-drug interaction studies:		**1**		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is there any exposure-response relationship between plasma concentrations and SKAMP scores?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Huixia Zhang 08/17/2010**	
Secondary reviewer Signature and Date	**Raman Baweja 08/18/2010**	

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/s/

HUIXIA ZHANG
03/21/2011

YANING WANG
03/21/2011

JOGARAO V GOBBURU
03/21/2011