CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207960Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207960
Priority or Standard	Standard 505(b)(2)
Submit Date(s)	02/04/2015
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Division / Office	DPP/OND
Reviewer Name(s)	Christina P. Burkhart, M.D.
Review Completion Date	10/21/2015
Established Name	Methylphenidate Extended-Release Tablet
(Proposed) Trade Name	QuilliChew ER
Therapeutic Class	Stimulant
Applicant	Pfizer Inc.
Formulation(s)	Chewable Tablet
Dosing Regimen	20 to 60 mg orally once daily
Indication(s)	ADHD
Intended Population(s)	Patients aged 6 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At this time, negotiations are ongoing with the Applicant for agreement on proprietary and established names for methylphenidate hydrochloride extended-release chewable tablet (methylphenidate HCl ERCT[1]) for the treatment of ADHD. In addition, internal discussions are ongoing about dose strengths with respect to compliance with USP guidances and salt policy. Pending successful resolution of these negotiations, this reviewer would recommend approval of NDA 207960. The NDA for this chewable extended-release methylphenidate product follows a 505(b)(2) regulatory pathway. NDA 207960 relies upon the FDA's general findings of safety and efficacy of the Listed Drug (LD), Methylin® chewable tablets (immediate-release [IR], NDA 21,475) and on two clinical studies conducted using the final formulation of methylphenidate HCl ERCT. These two studies consisted of a Phase 1 relative bioavailability (BA) study (Study B7491004) in healthy adults that demonstrated bioequivalence (BE) between methylphenidate HCl ERCT and the LD and a Phase 3 laboratory classroom study (Study B7491005) in pediatric patients (6 to 12 years old) with ADHD that demonstrated the safety and efficacy of this new chewable formulation of methylphenidate. In addition, this NDA cross-references data generated from studies of the methylphenidate HCl ER powder for oral suspension (Quillivant XR®) to further support safety and efficacy.

1.2 Risk Benefit Assessment

Methylphenidate has been a mainstay of treatment for ADHD for many years and has a well-known, acceptable safety profile. The safety findings in the pivotal Phase 3 laboratory classroom study (Study B7491005) were consistent with the known safety profile of methylphenidate. The benefits of chewable tablets include palatability, drug product stability, precise dosing, portability, and ease of delivery. Chewable tablets provide a useful alternative to traditional pediatric drug formulations and offer significant advantages in children and adults who have difficulty in swallowing pills.

[1] Methylphenidate ERCT will be used as the established name throughout this review. This is the established name proposed by the Applicant. The Agency sent an e-mail (9/14/2015) to the Applicant recommending that the established name be "methylphenidate extended release tablets" with dosage strength in terms of methylphenidate free base.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will be adequate to manage the risk-benefit profile of methylphenidate HCl ERCT in the treatment of ADHD.

1.4 Recommendations for Postmarket Requirements and Commitments

Deferred pediatric studies under PREA for the treatment of ADHD in pediatric patients ages 4 to less than 6 years old will be required.

2 Introduction and Regulatory Background

2.1 Product Information

Methylphenidate has been a well-established therapeutic agent for the treatment of ADHD since the approval of Ritalin in 1955. Since the approval of this first IR formulation, multiple formulations of both IR and ER methylphenidate have been approved. Methylphenidate HCl ERCT is a new formulation of methylphenidate for the indication of treatment of ADHD. Methylphenidate HCl ERCT (NWP09) is a once-daily chewable tablet formulation of methylphenidate developed using proprietary extended-release technology. According to the Applicant, the rationale for the development of this formulation was that chewable tablets could offer an additional ER formulation option for patients who cannot or will not swallow tablets or capsules, such as pediatric patients.

2.2 Tables of Currently Available Treatments for ADHD

Psychostimulants are the most commonly used class of medication used to treat ADHD. They include methylphenidate, dexmethylphenidate, mixed amphetamine salts, and lisdexamfetamine. The nonstimulant medications atomoxetine, clonidine, and guanfacine are also approved for treatment of ADHD.

The table below details some of the currently available treatments for ADHD:

Table 1: Medications Used in the Treatment of ADHD

Drug	Short-acting	Intermediate-acting	Extended Release
Methylphenidate	Ritalin Metadate Methylin	Ritalin SR Metadate ER Methylin ER	Concerta Metadate CD Ritalin LA
Dexmethylphenidate	Focalin	--	Focalin XR
Amphetamine	Dexedrine Dextrostat	Adderall Dexedrine spansule	Adderall XR
Lisdexamfetamine	--	--	Vyvanse
Atomoxetine (SNRI)	--	--	Strattera
Guanfacine	--	--	Intuniv
Clonidine	--	--	Kapvay

2.3 Availability of Proposed Active Ingredient in the United States

Methylphenidate is widely available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Oral formulations of methylphenidate and other stimulants have been associated with the potential for abuse and dependence; serious cardiovascular events including sudden death, stroke, and myocardial infarction; blood pressure and heart rate increases; psychiatric adverse reactions including psychotic or manic symptoms; priapism; peripheral vasculopathy including Raynaud's Phenomenon; and long-term suppression of growth in pediatric patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The methylphenidate HCl ERCT clinical development program is comprised of 4 clinical trials:

- Two Phase 1 pilot relative BA studies were conducted, Studies B7491002 and B7491003, which used prototype chewable tablet formulations to support formulation development activities and the administration of the tablet by chewing or swallowing whole.
- A single Phase 1 pivotal relative BA study in healthy adults, Study B7491004, which was conducted to evaluate BE between methylphenidate HCl ERCT and the LD Methylin® chewable tablets (IR, NDA 21,475), and to support the registration of the final formulation of methylphenidate HCl ERCT. Study B7491004 was also designed to assess the effect of food on the relative BA of methylphenidate HCl ERCT formulation.

- A pivotal Phase 3 laboratory classroom study, Study B7491005, which was conducted in pediatric patients with ADHD, ages 6 to 12 years, to demonstrate the safety and efficacy of this new formulation.

The development of this new formulation of methylphenidate HCl ERCT was conducted under IND 111020. Studies B7491002, B7491003 and B7491004 were sponsored by Tris Pharma (NextWave's development and manufacturing partner). Study B7491005, was sponsored by NextWave Pharmaceuticals, a subsidiary of Pfizer. The Applicant has obtained permission from Tris Pharma to include data from Tris-sponsored studies in this application. Tris Pharma holds the Drug Master File (DMF 025909).

Pre-IND meetings were held between FDA and representatives of Next Wave Pharmaceuticals and Tris Pharma, on April 01, 2011 and April 04, 2012. These meetings provided general advice on the CMC, non-clinical, and clinical development plans for the new formulation of methylphenidate HCl ERCT. The 505(b)(2) regulatory filing pathway using Methylin® chewable tablets (IR) as the LD was also confirmed. There was considerable discussion regarding the efficacy endpoint structure for the Phase 3 trial. The 2012 meeting entailed several topics including Agency advice that the Sponsor's use of the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores over the course of the full laboratory day as the primary variable was not objectionable but the Agency's review of the study results would include examination of the score at each time point to insure that efficacy was not driven by robust findings at only one or two time points. Also, the Agency stated that this variable alone would not support an onset or duration claim, and advice on the data needed to support such claims was conveyed to the Sponsor (i.e., sequential testing at multiple time points in a pre-specified order).

IND 111,020 was submitted by NextWave on May 02, 2012. This submission described Clinical Pharmacology and Safety results of the pilot BA (B7491002 and B7491003) and the Phase 3 Quillivant XR® (ER powder for oral suspension; NWP06-ADHD-100) studies and included the protocols for both the Phase 1 pivotal relative BA study (B7491004) and the Phase 3 pivotal laboratory classroom safety and efficacy study (B7491005).

A 'Study May Proceed' letter was provided on June 11, 2012 which included comments on the Statistical Analysis Plan and CMC comments regarding levels of degradation impurities and labeling of drug strength per USP guidance.

Representatives of the Sponsor and Tris Pharma met with FDA on October 02, 2014 for a pre-NDA Type B meeting. The purpose of the meeting was to discuss and reach agreement on the structure, content, and format for the NDA and the preliminary draft labeling. The key topics discussed at the meeting were the Agency's indication that a deferred pediatric assessment in children ages 4 to 5 years would likely be required, the support necessary to gain FDA concurrence that no PK study in pediatric patients using

methylphenidate HCl ERCT would be required, and support for potential label statements regarding the effect of concurrent alcohol use and chewed versus swallowed whole tablet administration. A proposal to (b) (4) was discussed. The Agency agreed to discuss this matter internally to determine the feasibility of the proposal to (b) (4). Timing for submission and agreement of the Pediatric Study Plan was also discussed. Agreement was reached to include in vitro data from the alcohol effect study in the DMF and a statement that advises 'do not use with alcohol', similar to that included in labels of currently marketed products would be proposed in the label for methylphenidate HCl ERCT. The Agency also agreed to review the submitted data that supports the proposal to include a statement that the tablet (b) (4) in the label.

2.6 Other Relevant Background Information

Pediatric Study Plan

The Applicant submitted the iPSP with the NDA in February 2015. The Applicant consulted with experts in pediatric ADHD clinical trials to help refine the original proposed study design and then submitted a revised initial Pediatric Study Plan (iPSP) on 24 April 2015.

The Applicant requested a deferral for the required pediatric assessment in children 4 and 5 years of age. As discussed at the pre-NDA meeting, the Applicant proposed (b) (4)

The Applicant also requested a partial waiver for children less than 4 years of age for the following reasons:

- There are no validated diagnostic criteria and assessment measures for diagnosing ADHD in children less than 4 years of age.
- Assessment measures for determining treatment effect in children less than 4 years old are not well defined.
- Non-medication interventions are preferred treatment for behavioral disorders such as ADHD in very young children (eg, <4 years of age).

Therefore, the Applicant requested a partial waiver for children less than 4 years of age because Methylphenidate HCl ERCT does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients <4 years of age and is not likely to be used in a substantial number of pediatric patients <4 years of age.

The Applicant also provided an acceptable rationale for extrapolation from available data in pediatric patients 6 to 12 years of age and healthy adults for the pediatric population 13 to 17 years of age.

In a 15 June 2015 e-mail to the Division, the Applicant requested preliminary feedback on the iPSP. The Division supplied this feedback in a 17 July 2015 e-mail to the Applicant. The Division communicated the following points to the Applicant:

- (b) (4)
- We do not agree with your study design. (b) (4) . We recommended a double-blind, placebo controlled pivotal trial of at least 6 weeks duration. This trial should include a placebo-controlled dose-optimization phase and placebo-controlled dose-maintenance phase in order to obtain adequate safety and efficacy data. We also request that you conduct an open-label long-term extension study in order to provide additional safety data for this age group.
- Primary Endpoint and Inclusion Criteria Based on Total Score (b) (4) : We recognize the difficulty in the diagnosis of ADHD in this population. However, the indication that you are seeking is the treatment of ADHD. Therefore, the primary endpoint should be the change from baseline in the Total Score of the clinician-administered Preschool ADHD-IV RS (b) (4) . We also recommend that the inclusion criterion for the Preschool ADHD-RS score at screening or baseline be based on the Total Score (b) (4) . Accordingly, your sample size calculation and statistical plan may need to be adjusted due the diagnostic uncertainty at this age range.
- In addition to the assessments/exclusion criteria that you have proposed, the protocol should also include the following: Specific assessments for sleep and for growth (e.g., height using stadiometer), discontinuation criteria based on increased HR and BP using pediatric normative data, and an exclusion criterion of ≤ 5th percentile for height or weight.

The Applicant submitted (9/11/2015) a revised PSP incorporating these recommendations. The Division discussed the revised PSP with PeRC on October 21, 2015. In general, PeRC was in agreement with the requested waiver in children < 4 years of age and deferral of studies in children 4 to < 6 years of age. We are currently in discussions about a PMR for a PK study in children 4 to < 6 years of age.

Proprietary Name Review
The Applicant initially proposed the proprietary name, (b) (4). The Agency reviewed the proposed proprietary name and found it unacceptable for the following reasons which were communicated to the Applicant (6/11/2015):

We have concerns that your proposed name could lead to errors given the similarity it has to Quillivant XR (methylphenidate oral suspension). (b) (4) *n your proposed proprietary name for the chewable tablets would mislead healthcare providers and patients to mistakenly believe that the two products have no clinically meaningful differences in onset and duration of clinical effect. Such misunderstanding is likely to lead to some cases of indiscriminant switching between these two products, which could meaningfully impact patients.*

On 17 July 2015, the Applicant submitted a request for a proprietary name review for the trade name QuilliChew (b) (4). The Division met with DMEPA on 18 August 2015 to discuss the proposed trade name. There was discussion that QuilliChew might be too similar to the original proposal for (b) (4) and might be unacceptable for similar reasons (i.e., lack of bioequivalence). Dr. David Claffey (CMC lead) also noted that current USP guidelines recommend that term chewable tablets should only be used in the established name for formulations that must be chewed, not for formulations that could be chewed or swallowed with similar pharmacokinetics. On 9 October 2015, the sponsor submitted an amendment requesting a review of the revised proposed proprietary name, Quillichew ER. On 15 October 2015, the Division of Medication Error Prevention and Risk Management (DMEPA) sent a letter to the Applicant stating that the proposed proprietary name, QuilliChew ER was conditionally acceptable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No problems with data quality or integrity were identified. The submission was organized and electronic navigation was not difficult.

3.2 Compliance with Good Clinical Practices

The Applicant states that Study B7491004 and Study B7491005 were conducted in compliance with the International Conference of Harmonisation Guidelines for Good

Clinical Practice and other applicable regulatory requirements. In addition, the Applicant certified that they did not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

The Division requested an OSI Consult for routine inspections of the following clinical sites:

Table 2: Sites Requested for OSI Clinical Inspection

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
03 Andrew J. Cutler, M.D. Florida Clinical Research Center, LLC 8043 Cooper Creek Blvd., Suite 107 Bradenton, FL 34201 941-747-7900 FAX: (941) 747-7992 e-mail: info@FLCRC.com	B7491005	14	ADHD
04 Matthew N. Brams, M.D. Bayou City Research, Ltd. 550 Westcott, Suite 200 Houston, Texas 77007 (832) 251-7000 FAX: (832) 251-7011	B7491005	14	ADHD
07 John M. Giblin, M.D. Clinical Study Centers, LLC 11215 Hermitage Road, Suites 200 and 201 Little Rock, AR 72211 Telephone: (501) 312-1318 FAX: (501) 312-1427 e-mail: GIBLINMD@CLINSTUDY.COM	B7491005	13	ADHD

The results of the inspections are as follows:

Site	Inspection Results
03 Andrew J. Cutler, M.D. Florida Clinical Research Center, LLC 8043 Cooper Creek Blvd., Suite 107 Bradenton, FL 34201	NAI
04 Matthew N. Brams, M.D. Bayou City Research, Ltd. 550 Westcott, Suite 200 Houston, Texas 77007	Pending
07 John M. Giblin, M.D. Clinical Study Centers, LLC 11215 Hermitage Road, Suites 200 and 201 Little Rock, AR 72211	Cancelled: Contact info was invalid. Sponsor provided additional contact info from the Arkansas State Medical Board. OSI was unable to contact this investigator.

3.3 Financial Disclosures

See Appendix 9.5

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Reviews are pending at this time. I am not aware of significant issues at this time.

4.3 Preclinical Pharmacology/Toxicology

Reviews are pending at this time. I am not aware of significant issues at this time.

4.4 Clinical Pharmacology

Reviews are pending at this time. I am not aware of significant issues at this time.

4.4.1 Mechanism of Action

The mode of therapeutic action in humans is not completely understood, although the drug is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

4.4.3 Pharmacokinetics

The following is a brief synopsis of the results of the Phase 1 Bioavailability Study (Study B7491004) comparing methylphenidate HCl ERCT and the LD, Methylin. Please see the review by Dr. Huixia Zhang (OCP) for a detailed review of this study. A brief summary of the safety findings will also be discussed in Section 7.7 of this NDA review.

Title: "A Three-Way Crossover Relative Bioavailability Study Comparing Methylphenidate HCl Extended-Release Chewable Tablets and METHYLIN Chewable Tablets under Fasting Conditions and Determining the Effect of Food on 40 mg Methylphenidate ER Chewable Tablets"

Objective:
To evaluate the relative bioavailability after a single dose in healthy subjects between:

- methylphenidate HCl extended release 40 mg chewable tablets from Tris Pharma, Inc., USA and Methylin™ 10 mg chewable tablets (immediate release) from Mallinckrodt, Inc., USA administered under fasting conditions and
- methylphenidate HCl extended release 40 mg chewable tablets from Tris Pharma, Inc., USA administered under fasting and fed conditions

Methodology:

- Open-label, single- and multi-dose, randomized, 3-period, 3-sequence, 3-treatment, crossover study, designed to evaluate the relative bioavailability of two formulations of methylphenidate HCl extended release chewable tablets, administered to healthy male and female subjects under fasting and fed conditions.
- Subjects were randomly assigned to one of the three dosing sequences ABC, BCA, and CAB.
- Concentrations of total (racemic) methylphenidate were measured from samples collected over a 24-hour interval after dosing in each period.

Subjects:
31 subjects are included in the PK analysis and the statistical analyses
Inclusion Criteria

- Non-smoking, males and females
- 18 to 55 years of age

- BMI from 18.0 to 30.0 kg/m^2
- Weight ≥ 50 kg
- Healthy based on a medical history, ECG, laboratory evaluation, physical examination, and vital signs measurements
- Willing to remain abstinent or use effective contraception

Exclusion Criteria

- Known history or presence of any clinically significant medical condition
- Known history or presence of Tourette's syndrome or tics
- Known history or presence of coronary insufficiency, myocardial infarction, cardiac arrhythmias (sinus bradycardia of ≥ 50 bpm is allowed), heart failure, coronary heart disease, cerebrovascular disease, chronic renal failure, disorders of cerebral or peripheral perfusion or polyneuropathy
- Known history or presence of galactose or fructose intolerance, sucrose-isomaltase insufficiency, Lapp lactase insufficiency, galactosemia, or glucose-galactose malabsorption syndrome
- History of treatment of marked depression, anxiety, tension or agitation
- + test for urine drugs of abuse
- Use of tobacco or nicotine-containing products within 6 months prior to drug administration
- Use of any drugs known to induce or inhibit CYP enzyme drug metabolism or use of any monoamine oxidase inhibitor (MAOI)

Drug Product:
Test Product: Methylphenidate HCl Extended Release 40 mg chewable tablets
Reference Product: Methylin™ 10 mg chewable tablets (immediate release)

Treatments:
Treatment A: test product (1 tablet, 40 mg) administered under fasting conditions
Treatment B: test product (1 tablet, 40 mg) administered under fed conditions
Treatment C: reference product 2 equal doses of 20 mg (2 x 10 mg/tablet), 6 hours apart, first dose administered under fasting conditions

PK Assessments:
The following pharmacokinetic parameters were estimated using a non-compartmental approach: C_{max}, AUC^{t}, AUC_{inf}, $AUC_{0-0.5}$, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, T_{max}, K_{el}, and T_{half}

Results:

Demographic and Baseline Data

Table 3: Study -1004 Demographics

		Safety Dataset N = 33	PK Dataset N = 31
Age (years)	Mean ± SD	32 ± 10	32 ± 10
	Median	30	30
	Range	18 - 51	18 - 51
Weight (kg)	Mean ± SD	72.0 ± 10.8	72.6 ± 10.9
	Median	70.6	71.0
	Range	50.0 - 98.8	50.0 - 98.8
BMI (kg/m²)	Mean ± SD	24.8 ± 2.6	25.0 ± 2.6
	Median	25.3	25.3
	Range	20.5 - 30.0	20.5 - 30.0
Age Group (%)	<18	0 (0%)	0 (0%)
	18 - 40	23 (69.7%)	22 (71.0%)
	41 - 64	10 (30.3%)	9 (29.0%)
	65 - 75	0 (0%)	0 (0%)
	>75	0 (0%)	0 (0%)
Gender (%)	Female	17 (51.5%)	16 (51.6%)
	Male	16 (48.5%)	15 (48.4%)
Race (%)	Asian	1 (3.0%)	1 (3.2%)
	Black	11 (33.3%)	11 (35.5%)
	Hispanic	10 (30.3%)	10 (32.3%)
	White	11 (33.3%)	9 (29.0%)

Study report, p. 29-30

Disposition of Subjects

Table 4: Study -1004 Disposition of Subjects

		Sequence			
		ABC	BCA	CAB	Total
Period 1	Dosed	11	11	11	33
	Dismissed	0	0	1	1
	Withdrew	0	0	0	0
Period 2	Dosed	11	11	10	32
	Dismissed	1	0	0	1
	Withdrew	1	0	0	1
Period 3	Dosed	9	11	10	30
	Dismissed	1	0	0	1
	Withdrew	0	0	0	0
Total	Dosed	11	11	11	33
	Dismissed	2	0	1	3
	Withdrew	1	0	0	1
	Completed	8	11	10	29

Study report, p. 27

Protocol Deviations

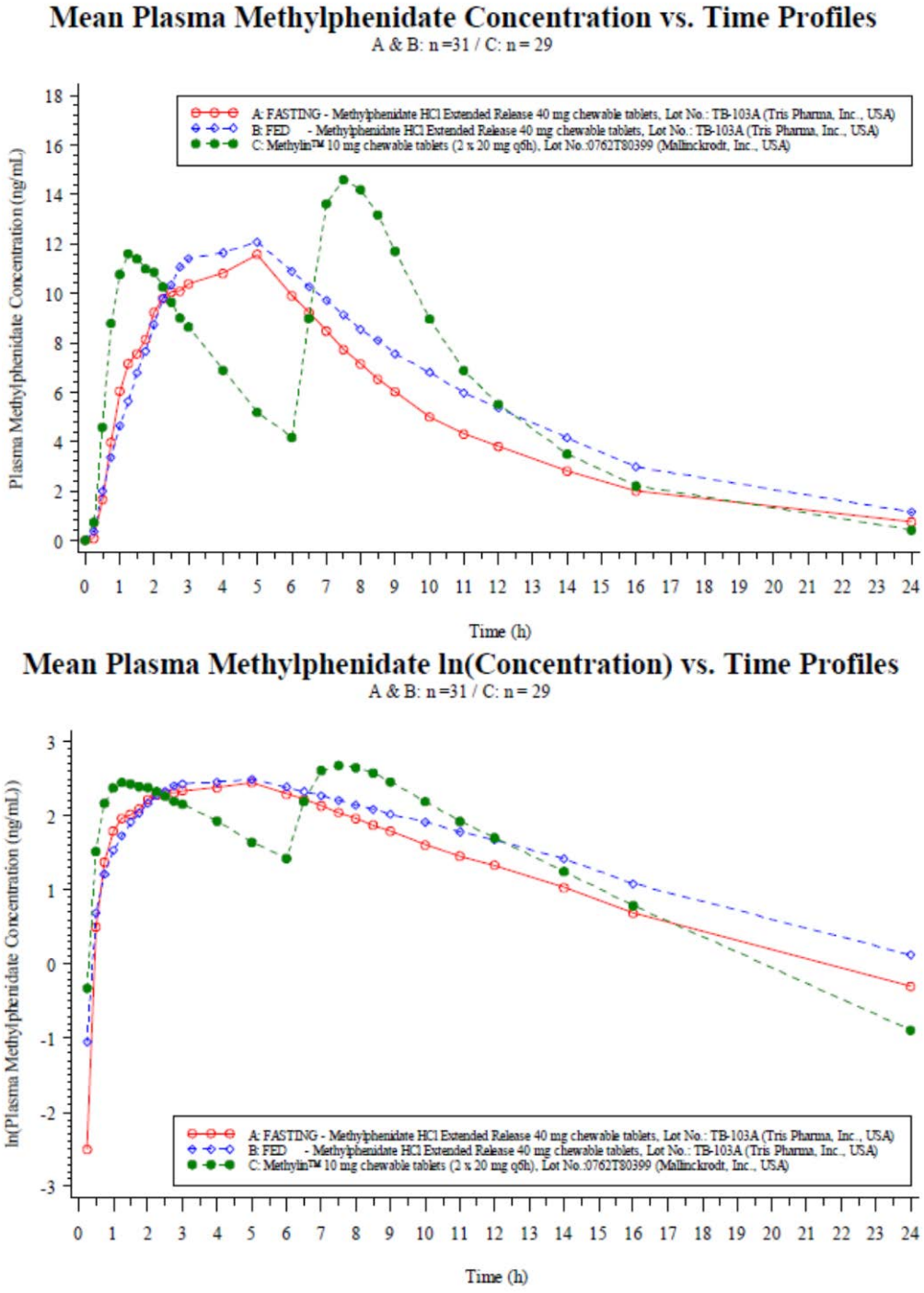
There were no major protocol deviations. One protocol deviation occurred in 5 subjects. These subjects (#10, 16, 18, 22 and 24) required extra water (25 to 100 mL) to consume the study drug during administration.

PK Results

The test product had equivalent total exposure and peak absorption characteristics when administered under fasting and fed conditions. There was no significant food effect on the test product.

Methylphenidate HCl 40 mg ER chewable tablets produced a mean peak concentration 20% lower than b.i.d. administration of 20 mg of the Methylin™ 10 mg (immediate release) product. AUC_{0-t} and AUC_{0-inf} (indicative of the extent of absorption) of Methylphenidate HCl 40 mg ER chewable tablets and Methylin™ (immediate release) tablets, administered under fasted conditions, met the standard 80.00-125.00% bioequivalence acceptance criteria.

Figure 1: Study -1004 Methylphenidate Concentration vs. Time Profiles



Study -1004 Synopsis, p. 6

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This NDA requests approval of methylphenidate HCl ERCT for the treatment of ADHD following the 505(b)(2) regulatory pathway and relies upon the FDA's general findings of safety and efficacy of the LD, Methylin® chewable tablets (NDA 21,475) and on two clinical studies conducted using the final formulation of methylphenidate HCl ERCT: a Phase 1 relative bioavailability study (Study B7491004) in healthy adults to evaluate bioequivalence between methylphenidate HCl ERCT and the LD and a Phase 3 laboratory classroom study (Study B7491005) in pediatric patients (6 to 12 years old) with ADHD to demonstrate the safety and efficacy of this new formulation of methylphenidate HCl ERCT.

Table 5: Overview of Pivotal Studies for NDA 207960

Study Number	Design
B7491004	A single-dose, 3-way cross-over relative BA study conducted in 33 healthy adult subjects to evaluate the relative BA of the intended commercial formulation of methylphenidate HCl ERCT (fasted) versus Methylin® Chewable Tablets (IR; fasted) and to assess the effect of food on the methylphenidate HCl ERCT formulation when administered with food
B7491005	A multicenter, dose-optimized, double-blind, randomized, placebo-controlled Phase 3 study to evaluate the efficacy of methylphenidate HCl ERCT in pediatric patients with attention deficit hyperactivity disorder (ADHD) in a laboratory classroom. This study enrolled 90 subjects (aged 6-12 years) with ADHD into an open-label dose optimization period, followed by a randomized parallel group, double-blind treatment period. Efficacy was measured using the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP) combined score pre-dose and 0.75, 2, 4, 8, 10, 12 and 13 hours post-dose.

Source: Clinical Overview, p. 9

5.2 Review Strategy

I reviewed the following: Clinical Study Reports (-1004 and -1005), synopses of the abbreviated study reports for 2 pilot studies (C11-0082 and C11-1200), JMP datasets for AEs, the FDA Correspondence document, financial disclosure documents, the Pediatric Plan, Proprietary Name documents, the Summary of Clinical Efficacy, and the Summary of Clinical Safety.

I also reviewed Dr. Kordzakhia's draft statistical review. Finalized reviews from the other disciplines are pending at this time.

5.3 Discussion of Individual Studies/Clinical Trials

As stated previously, this NDA submission relies on the data from 2 studies:

- Study B7491004: a Phase 1 relative bioavailability study in healthy adults to evaluate bioequivalence between methylphenidate HCl ERCT and the LD
- Study B7491005: a Phase 3 laboratory classroom study in pediatric patients (6 to 12 years old) with ADHD to demonstrate the safety and efficacy of this new formulation of methylphenidate HCl ERCT

I also reviewed the synopses of the abbreviated study reports for C11-0082 and C11-1200. The following summarizes the results of these studies:

Study C11-0082 was a three-way pilot relative bioavailability study comparing methylphenidate 40 mg ER chewable tablets (chewed and swallowed whole) versus 25 mg/5 ml ER suspension under fasted conditions. In this pilot study, the ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed PK parameters AUC_{0-t}, AUC_{0-inf} and C_{max} for methylphenidate were within the usual 80.00-125.00% acceptance range indicating that the relative bioavailability of methylphenidate in the tablet formulation either chewed or swallowed whole was comparable to the oral suspension. However, the comparison of treatment arms for partial AUC_{0-4} was slightly less than the lower acceptance limit of 80.00%. Early exposure to methylphenidate (AUC_{0-4}) was slightly lower from the tablet (either chewed or swallowed whole) compared to exposure from the suspension formulation.

Study C11-1200 was a relative bioavailability study of two formulations of methylphenidate 40 mg ER chewable tablets versus methylphenidate 25 mg/5 ml ER oral suspension under fasted conditions. In this pilot study, both test formulations met the standard criteria for bioequivalence when compared to the reference formulation with respect to the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and C_{max}. However, the test/reference ratios for partial AUC_{0-4} were not within the 80.00 to 125.00% parameter.

The results of Study -1004 are briefly reviewed in Section 4.4.3 (PK results) and Section 7.7 (safety results). The results of Study -1005 are reviewed in Section 6 (efficacy) and Section 7 (safety). The pilot studies described above (C11-0082 and C11-1200) are not addressed further in this NDA review.

6 Review of Efficacy for Study B7491005

Study B7491005 was a pivotal Phase 3 laboratory classroom study which was conducted in pediatric patients with ADHD, ages 6 to 12 years, to demonstrate the safety and efficacy of methylphenidate extended-release chewable tablets. The primary efficacy outcome, the model-adjusted average of all post-dose SKAMP-Combined scores measured at Visit 9, was significantly lower for subjects randomized to NWP09

treatment than for subjects randomized to placebo. SKAMP-Combined scores were nominally statistically significantly lower for NWP09-treated subjects at 0.75, 2, 4, and 8 hours post-dose at Visit 9. However, the model-adjusted statistical evaluation showed statistically significant results at 2, 4, and 8 hours post-dose. Therefore, in this study the onset of efficacy for NWP09 was determined to be 2 hours post-dose, and efficacy was maintained through the 8-hour time point.

6.1 Indication

ADHD

6.1.1 Methods

Title: "A Multicenter, Dose-optimized, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of NWP09 in Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom"

Study Centers: 6 sites in the United States (Las Vegas, NV; Irvine, CA; Bradenton, FL; Houston, TX; Lubbock, TX; Little Rock, AR)

Objectives:
Primary
- To assess the efficacy of NWP09 in pediatric patients with ADHD

Secondary
- To assess the safety and tolerability of NWP09 in pediatric patients with ADHD

Design:
This was a dose-optimized, randomized, double-blind, placebo-controlled laboratory classroom study in 90 pediatric patients with ADHD.

Six-Week Open-label Dose Optimization Period
Eligible subjects took open-label NWP09 orally once daily for 6 weeks, beginning with a dose of 20 mg/day. During the 6-week Open-label Dose Optimization Period, the investigator was allowed to titrate the dose of NWP09 up or down to achieve the optimal dose for efficacy and tolerability. This dose was based on investigator clinical judgment of the dose that adequately reduced signs and symptoms of ADHD in the subject with the fewest side effects. Titration was performed at weekly intervals in increments of 10-20 mg/day until the optimal dose[2] or a maximum dose of 60 mg/day was reached. Subjects unable to tolerate a minimum dose of 20 mg/day or unable to achieve a stable dose during the Open-label Dose Optimization Period were discontinued from the study.

[2] The range of effective doses cannot be predicted by the patient's age, body mass, level of hyperactivity, or measurements of plasma drug concentrations for methylphenidate products.

One-Week Double-Blind Treatment Period (Placebo-Controlled Laboratory Classroom)
After completing the Open-label Dose Optimization Period, subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessment in a laboratory classroom setting at multiple time points (abbreviated laboratory classroom day or Visit 8). The SKAMP scale and PERMP were assessed before administration of open-label NWP09 and 0.75, 2, and 4 hours post-dose.

Subjects who achieved a stable dose of NWP09 and successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8 were randomized[3] to take double-blind study drug (NWP09 or placebo; 1:1) orally once daily for 1 week. At the end of the 1-week Double-blind Treatment Period, subjects were evaluated for ADHD symptoms and signs using the SKAMP and PERMP assessment in a laboratory classroom setting at multiple time points throughout the day (complete laboratory classroom day, or Visit 9). During the laboratory classroom day at Visit 9, the SKAMP scale and PERMP were assessed before administration of double-blind study drug and 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose.

Seven to 14 days after the complete laboratory classroom day, subjects were contacted by phone or in person to assess any adverse events (AEs) and concomitant medications.

Swanson, Kotin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale
The SKAMP is a 13-item independent-observer rating of subject impairment of classroom-observed behaviors. Each item is rated on a 7-point impairment scale, with 0 being normal and 6 being maximal impairment. Items are specific to place (classroom setting) and time (during a typical classroom period), and the scale can be used to assess multiple ratings taken within a day. The investigator or other designated, qualified individuals from the study research team performed the assessments. The following composite scores were assessed:

- SKAMP-Combined scores (items 1-13)
- SKAMP-Attention subscale scores (items 1-4)
- SKAMP-Deportment subscale scores (items 5-8)

Permanent Product Measurement of Performance
The PERMP is a 10-minute written test performed as seat work in the classroom. Subjects are given 5 pages of 80 mathematics problems and instructed to work at their desks and to complete as many problems as possible in 10 minutes. The number of problems answered correctly and the number attempted are used to measure a subject's performance. Different versions of the PERMP were used among the study subjects to adjust for ability as determined by the mathematics pretest done at Screening or Baseline. Different versions were also used across classroom cycles to

[3] Randomization followed a fixed schedule using a permuted block design stratified by clinical site.

prevent a subject from taking the same test more than once during a day. A stopwatch was used to time the test. The investigator or other designated, qualified individuals from the study research team performed the assessments. The following PERMP scores were assessed:

- Number of mathematics problems attempted
- Number of mathematics problems correct

Test Product:

Six-week Open-label Dose Optimization Period (Visits 3, 4, 5, 6, 7, and 8)

- NWP09 20-60 mg/day taken orally once daily in the morning before 10:00 am with or without food. The starting dose of 20 mg/day could be titrated up or down by the investigator at weekly intervals in 10-20 mg/day increments at scheduled study Visits 3, 4, 5, 6, and/or 7 until a stable dose was achieved that was optimal for efficacy and tolerability based on physician clinical judgment. The investigator could down-titrate at any time during the Open-label Dose Optimization Period to ensure subject safety.
- 20 mg, 30 mg, and 40 mg chewable tablets were available
- Subjects were instructed to chew the tablet(s) thoroughly and swallow.
- Study drug was always to be administered to the subject by the parent/caregiver or another responsible adult (subjects were never to self-administer study drug regardless of age).

One-week Double-blind Treatment Period

- Optimal dose of NWP09 from the Open-label Dose Optimization Period (20-60 mg/day) taken orally once daily in the morning before 10:00 am or placebo
- Placebo tablets were identical to NWP09 in formulation, taste, and appearance

Subjects:

Inclusion Criteria

- Males or females, aged 6 to 12 years of age
- Diagnosis of ADHD using the Schedule for Affective Disorders and Schizophrenia (K-SADS), Clinical Global Impression of Severity (CGI-S; score ≥3), and Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS; ≥90th percentile for gender and age in at least 1 of the following categories: hyperactive-impulsive (b) (4) or total score)
- Need for pharmacologic treatment for their condition (use of non-investigational stimulant medication for control of ADHD was allowed until 24 hours prior to Baseline)

Exclusion Criteria

- Pregnant or breast-feeding
- Current primary psychiatric diagnosis of severe anxiety disorder, conduct disorder, psychotic disorders, pervasive developmental disorder, eating disorder, obsessive-compulsive disorder, major depressive disorder, bipolar disorder,

substance use disorder, chronic tic disorder, or personal or family history of Tourette's syndrome (DSM-IV-TR; K-SADS)
- Clinically significant cognitive impairment or IQ < 80
- History of chronic medical illnesses including seizure disorder, severe hypertension, untreated thyroid disease, glaucoma, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, or coronary artery disease. If the subject had an immediate family history of sudden cardiac death, review and approval by the medical monitor was required.
- Clinically significant abnormal ECG or abnormal cardiac finding on physical examination
- Use of any psychotropic medication within 30 days prior to Baseline visit (exception: sedative hypnotics prescribed as sleep aids at a stable dose at bedtime only for at least 30 days prior to Baseline were allowed)
- Abnormal clinically significant laboratory test
- + for drugs of abuse; +HIV; active hepatitis B or C

Randomization Criteria

Study subjects who enrolled into the Open-label Dose Optimization Period were evaluated for randomization eligibility at Visit 8. To be randomized to the Double-blind Treatment Period, subjects were required to meet all the following criteria:

- Stable dose of open-label NWP09 (defined as no change in dose between Visits 7 and 8).
- Optimal dose of NWP09 at Visit 8 in the judgment of the investigator.
- No change in medical condition that precluded administration of blinded study drug.
- Completion of the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8; however, subjects who did not complete the 4-hour classroom session at Visit 8 were withdrawn from the study and not allowed to receive double-blind study drug.

Efficacy Criteria for Evaluation:

Primary Efficacy Variable

- Model-adjusted average of all post-dose SKAMP-Combined scores measured on the classroom study day (Visit 9)

Key Secondary Efficacy Variables

- Onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9)

Other Secondary Efficacy Variables

- SKAMP-Attention and SKAMP-Deportment subscale scores at Visit 9
- PERMP scores at Visit 9
- CGI-S
- Clinical Global Impression of Improvement (CGI-I)
- ADHD-RS

- Conners' Parent Rating Scale (CPRS) (Visits 1 and 2); CPRS was used to measure features associated with ADHD and compare scores during the Open-label Dose Optimization Period

Safety Criteria for Evaluation:
(Please see Section 9.4 Schedule of Events for specific timing of safety assessments)

- AEs
- Blood and urine clinical laboratory tests (hematology, serum chemistry, serum and urine pregnancy, screening for drugs of abuse)
- Vital signs (VS), physical exam (PE)
- 12-lead electrocardiogram (ECG)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methods (abstracted from Applicant's Synopsis):
Intent-to-treat population (ITT): all randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable. The ITT population formed the basis for the primary and secondary efficacy analyses.
Clinically evaluable population: ITT subjects who received the full prescribed dose of double-blind study drug at the test laboratory classroom day (Visit 9), completed all laboratory classroom tests, did not miss more than 2 days of therapy during the Double-blind Treatment Period, and did not use prohibited medication during the Double-blind Treatment Period.

Enrolled safety population: all enrolled subjects who received at least 1 dose of open-label study drug and had at least 1 post-Baseline safety assessment.

Randomized safety population: all randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline safety assessment.

Primary Efficacy Analysis
The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9). The primary analysis used the ITT population and a mixed-model, repeated-measures analysis with subject's intercept as a random effect and the following variables as fixed effects:

- Treatment (class effect: NWP09 and placebo)
- Study center (class effect)
- Time point (class effect: 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose)
- Time point-by-treatment interaction

The average treatment difference over all post-dose time points was estimated using least–squares (LS) means from the mixed-effects, repeated-measures model. The treatment comparison was conducted as a 2-sided test at the 5% level of significance.

The standard error and 95% confidence interval (CI) for the treatment difference was provided.

Key Secondary Efficacy Analyses

Key secondary efficacy variables were the onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9). Analyses of the key secondary efficacy variables were performed on the ITT population and repeated on the clinically evaluable population. If the primary efficacy endpoint was statistically significant ($p < 0.05$), the key secondary outcomes of onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores would be tested using a fixed-sequence testing procedure. These analyses used the same mixed-model, repeated-measures method as for the primary efficacy variable.

The fixed-sequence testing procedure was conducted in the following order: 4, 8, 2, 10, 12, 13, and 0.75 hours post-dose. An assessment of treatment difference was tested at a time point only if all previously tested time points had demonstrated a statistically significant treatment difference ($p < 0.05$). The procedure was conducted as follows:

- The onset time of efficacy action was claimed at the first post-dose time point within the fixed sequence at which the difference between the 2 treatments was statistically significant ($p < 0.05$).
- The duration of efficacy was the difference between the onset time and the latest consecutive time point at which the difference between the 2 treatments was still statistically significant ($p < 0.05$).

Other Secondary Efficacy Analyses

Other secondary efficacy variables included:

- SKAMP-Attention and SKAMP-Deportment scores at Visit 9
- PERMP scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose at Visit 9

Secondary efficacy analyses included a repeat of the primary analysis on the clinically evaluable population and mixed-model, repeated-measures analyses of SKAMP-Attention, SKAMP-Deportment, and PERMP scores for the ITT and clinically evaluable populations. The latter analyses used the same mixed-model, repeated-measures method as for the primary analysis. The LS means and associated standard error bars were plotted over time by treatment group.

Other efficacy analyses included summaries of CGI-S, CGI-I, ADHD-RS, and CPRS rating scales by time point using descriptive statistics that included the change in CGI-S (i.e., CGI-I), ADHD-RS, and CPRS rating scores from Baseline. The proportion of responders (subjects with a change from Baseline in the ADHD-RS of 50% or greater) was also presented.

Sensitivity Analysis

At the request of the FDA, an ad hoc sensitivity analysis of the primary efficacy variable was added after database lock and unblinding of the data. As requested, the primary efficacy variable was also analyzed via a repeated-measures analysis, with treatment (NWP09/placebo), study center, time point, and time point-by-treatment interaction as fixed effects using an unstructured within-subject covariance matrix.

Treatment Compliance

Compliance rates were calculated by dividing the number of doses taken by the number of doses that should have been taken during the treatment periods (open-label or double-blind). Compliance rates were summarized by treatment group. Compliance was further summarized by treatment group according to the categories of <80%, 80% to 100%, and >100%.

Protocol Amendments

The original protocol, Version 1 dated 15 March 2012, was amended twice during the study. Version 1 of the protocol was submitted to the FDA and central IRB for review and comment, but was not implemented by the study sites. Version 2 of the protocol, dated 30 April 2012, incorporated changes recommended by the FDA and other changes to improve study design and feasibility, and was implemented by the study sites. Substantive changes in Version 2 included the following:

- Primary efficacy variable was changed to the average of all post-dose SKAMP-Combined scores measured during the Visit 9 classroom study day.
- Screening period was extended to up to 6 weeks (previously 4 weeks) to allow adequate time for pre-study activities.
- Exclusion criteria were modified to identify more clearly the pre-existing psychiatric medical conditions excluded from the study.
- Prohibited medications were clarified in the exclusion criteria and prohibited concomitant medications sections.
- Urine pregnancy testing in females of childbearing potential was added at the Baseline Visit and Visit 9.
- Follow-up contact with subjects to collect AE information was added 7-14 days after Visit 9.

Version 3 of the protocol, issued 18 July 2012, included the following substantive changes:

- Exclusion criterion 15 was added, which was the inability to perform at the basic level of a standardized mathematics test.
- Statistical analysis section was revised to clarify duration of efficacy and provide additional details on handling missing data.
- Assessment of concomitant medications was added at Visit 10.
- Inorganic phosphate was deleted from the serum chemistry panel.

6.1.2 Demographics

The mean age of subjects in Study -1005 was 9.6 years (ITT population). A majority of subjects (52.9%) were 8 to 10 years old, male (62.4%), white (57.6%), non-Hispanic/Latino (84.7%), and had combined type ADHD (72.9%). Most subjects (82.2%) did not have any other comorbid psychiatric diagnoses, but of those that did, the most common was oppositional defiant disorder (7.8% of the enrolled safety population). Demographic characteristics were similar between the NWP09 and placebo groups for age, ethnicity, and ADHD type. The groups differed on the distribution of sex, age categories, and race:

Table 6: Study -1005 Demographic and Other Baseline Characteristics

	Placebo N = 43 n (%)	NWP09 N = 42 n (%)
Gender – n (%)		
Male	23 (53.5)	30 (71.4)
Female	20 (46.5)	12 (28.6)
Age (years)		
n	43	42
Mean (SD)	9.3 (1.62)	9.9 (1.71)
Median (min, max)	10.0 (6, 12)	10.0 (7, 12)
Age categories – n (%)		
6-7 years	8 (18.6)	5 (11.9)
8-10 years	28 (65.1)	17 (40.5)
11-12 years	7 (16.3)	20 (47.6)
Race – n (%)		
White	22 (51.2)	27 (64.3)
Black/African American	18 (41.9)	12 (28.6)
Asian	1 (2.3)	0
Native Hawaiian/Pacific Islander	0	0
American Indian/Alaska Native	0	0
Other	2 (4.7)	3 (7.1)
Ethnicity – n (%)		
Hispanic/Latino	6 (14.0)	7 (16.7)
Non-Hispanic/Latino	37 (86.0)	35 (83.3)
Missing	0	0
ADHD type – n (%)		
Inattentive	11 (25.6)	12 (28.6)
Hyperactive/impulsive	0	0
Combined	32 (74.4)	30 (71.4)
Not otherwise specified	0	0
Missing	0	0

Study report, p. 45

Reviewer comment: It is possible that these differences in demographic characteristics may have had some impact on the efficacy analysis. However, in his draft statistical review, Dr. Kordzakhia states that subgroup analyses of the gender, racial, and age subgroups did not reveal any major inconsistency of the treatment effect among the subgroups.

Concomitant Medications

Concomitant medications were defined as all medications being used at the initiation of study drug or started during the Open-label Dose Optimization or Double-blind Treatment Period; they also included medications started after the end of the double-blind period (Visit 9). A total of 65 (72.2%) subjects used at least 1 concomitant medication during the study, with the proportion being larger in the NWP09 group than the placebo group (78.6% versus 68.2%). The most common (≥10% overall) classes of concomitant medications were centrally acting sympathomimetics (55.6%), selective beta-2-adrenoreceptor agonists (14.4%) such as salbutamol, anilides (10.0%) such as paracetamol, and propionic acid derivatives (10.0%) such as ibuprofen. Except for 2 subjects (Subject 07-030 and Subject 03-035), all the subjects who used concomitant centrally acting sympathomimetics did so after the end of the Double-blind Treatment Period (Visit 9).

Subject 07-030 stopped study drug on 26 August 2012 during the Open-label Dose Optimization Period and started taking her pre-study medication methylphenidate on 27 August 2012. She then withdrew consent on 30 August 2012.

Subject 03-035, who received study treatment from 17 August through 06 October 2012, was recorded as taking dexmethylphenidate from January 2012 through 15 August 2012 (15 mg QD) and from March 2012 ongoing (5 mg QD, no end date). The entry of dexmethylphenidate in the CRF was captured twice. Based on confirmation with the parent, the correct entry in the source document and electronic CRF was entry #1. According to the parent, the subject started Focalin (dexmethylphenidate) in January (not March) with a dose of 15 mg (not 5 mg).

6.1.3 Subject Disposition

A total of 101 subjects were screened for the study and 90 subjects were enrolled in the Open-label Dose Optimization Period. Of the 90 subjects, 86 were randomized, 42 to treatment with NWP09 and 44 to treatment with placebo. Eighty-five subjects (94.4% of the enrolled population) completed the study.

Table 7: Study -1005 Subject Disposition

Disposition	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
Enrolled	4 (100)	44 (100)	42 (100)	90 (100)
Randomized	--	44 (100)	42 (100)	86 (95.6)
Completed study	--	43 (97.7)	42 (100)	85 (94.4)
Discontinued study	4 (100)[1]	1 (2.3)	0	5 (5.6)
Reason for discontinuation[2]				
Adverse event(s)	1 (25.0)	0	0	1 (20.0)
Protocol deviation	0	0	0	0
Noncompliance	0	0	0	0
Withdrawal of consent	3 (75.0)	0	0	3 (60.0)
Lost to follow-up	0	1 (100)	0	1 (20.0)
Unable to achieve stable dose	0	0	0	0
Other	0	0	0	0

1 Subject 02-094, Subject 03-079, Subject 07-026, and Subject 07-030.
2 The denominator for reasons for discontinuation was the total number of subjects in that treatment group who discontinued from the study.

Study Report, p.40

Table 8: Study -1005 Reasons for Discontinuation from Study

Subject ID	Treatment	Reason for Discontinuation
02-094	Prior to randomization	Withdrawal of consent: lack of clinical benefit
07-026	Prior to randomization	Withdrawal of consent: inability to attend weekly appointments
07-030	Prior to randomization	Withdrawal of consent: unhappy with treatment and started using her previous ADHD medication; parents disliked the dose changes throughout the study
03-079	Prior to randomization	AE: dysgeusia (bad taste of the medicine itself)
01-020	Placebo	Lost to follow-up after Visit 8

Study Report, p. 39

Protocol Deviations

There were 144 protocol deviations during the study (~58% of subjects). The most common category of protocol deviation overall was dosing error, which included missed dose, late dose, dosing at home on the practice classroom day (Visit 8), incorrect dose, and lost pill.

There were 11 protocol deviations during the Double-blind Treatment Period (between Visits 8 and 9). There were 9 major protocol deviations during the study. Six of these major protocol deviations took place during the Double-blind Treatment Period:

Table 9: Study -1005 Major Protocol Deviations

Subject Number	Treatment Group	Category of Deviation	Description
01-006	NWP09	Dosing error (missed dose)	Between Visits 8 and 9, subject (or parent/guardian) reported 1 missed dose of double-blind study drug.
01-019	NWP09	Dosing error (missed dose)	Between Visits 8 and 9, subject (or parent/guardian) reported 1 missed dose of double-blind study drug.
03-034	NWP09	Dosing error (missed dose)	At Visit 9, subject (or parent/guardian) reported a missed dose.
02-092	NWP09	Prohibited medication/ therapy	Subject took an exclusionary medication, promethazine, in treatment of a viral infection.
01-016	Placebo	Dosing error (missed dose)	Between Visits 8 and 9, subject (or parent/guardian) reported 1 missed dose of double-blind study drug (actual date unknown).
01-018	Placebo	Dosing error (missed dose)	Between Visits 8 and 9, subject (or parent/guardian) reported 1 missed dose of double-blind study drug (actual date unknown).
02-086	Placebo	Dosing error (incorrect dose)	Between Visits 5 and 6, subject received more than prescribed dose of IP from Visit 5 bottle; subject took approximately 2/3 of a pill in AM, and then mother gave subject another pill that evening.
02-088	Placebo	Dosing error (incorrect dose)	Between Visits 3 and 4, subject took 2 extra doses of IP from Visit 3 bottle.
02-089	Placebo	Randomization error	At Visit 8, subject was randomized to blinded IP bottle 431-062, which was dispensed and administered to subject for week leading up to Visit 9. At Visit 9, site inadvertently dosed subject from bottle 431-061, the incorrect treatment arm.

IP = investigational product.

***Note: Subject 02-089 (Placebo group) received active drug at Visit 9.**
Study report, p. 42

Reviewer Comment: These deviations should not have affected the validity of the efficacy conclusions.

6.1.4 Analysis of Primary Endpoint(s)

The following datasets were analyzed:

Table 10: Study -1005 Analysis Populations

Population	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
Enrolled safety	4 (100)	44 (100)	42 (100)	90 (100)
Randomized safety	--	44 (100)	42 (100)	86 (95.6)
Intent-to-treat	--	43 (97.7)	42 (100)	85 (94.4)
Clinically evaluable	--	41 (93.2)	41 (97.6)	82 (91.1)

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Treatment Compliance

During the open-label phase, subjects in the randomized safety population had a mean treatment compliance of 98% and 98.8% of these subjects had a compliance of 80% to 100%. During the double-blind phase, subjects in the randomized safety population had a mean compliance of 99.3% in the placebo treatment group and 99.0% in the NWP09 treatment group.

Primary Efficacy Results

The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9). The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower (i.e., improved) for those receiving NWP09 treatment compared with placebo. The LS mean SKAMP-Combined score was 12.1 in subjects receiving NWP09 compared with 19.1 in subjects receiving placebo (LS mean treatment difference = -7.0; $p < 0.001$). The primary efficacy analysis was performed on the ITT population and is summarized in the table below:

Table 11 : Study -1005 Summary and Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT)

Visit 9 Post-dose Time Point Statistic	Placebo N = 43	NWP09 N = 42	Treatment Difference (NWP09 - placebo)
Average over all post-dose time points			
n	43	42	
Mean (SD)	19.0 (10.59)	12.6 (8.90)	
Median (Q1, Q3)	18.1 (11, 22)	9.9 (6, 15)	
Range (min, max)	(3, 46)	(4, 42)	
LS mean (SE)	19.1 (1.39)	12.1 (1.41)	-7.0 (1.99)
95% CI	(16.4, 21.8)	(9.3, 14.9)	(-10.9, -3.1)
p-value			<0.001

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; Q = quartile; SD = standard deviation; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

Study report, p. 47

Supportive Analyses of the Primary Analysis

As a supportive analysis, the primary analysis was repeated on the clinically evaluable population. The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower for those receiving NWP09 treatment (LS mean = 12.3) than for those receiving placebo treatment (LS mean = 18.1; LS mean treatment difference = -5.8; p = 0.003) in the clinically evaluable population.

At the request of the Agency, the Applicant performed an ad hoc sensitivity analysis of the primary efficacy variable after database lock and unblinding of the data. The primary efficacy variable was analyzed via a repeated-measures analysis, with treatment, study center, time point, and time point-by-treatment interaction as fixed effects using an unstructured within-subject covariance matrix. In the sensitivity analysis, SKAMP-Combined scores were statistically significantly lower for those receiving NWP09 compared with placebo at 0.75, 2, 4, and 8 hours post-dose. The results from the fixed sequence testing procedure using an unstructured within-subject covariance matrix, indicate the treatment difference was no longer statistically significant at 0.75 hour post-dose (p=0.122):

Table 12: Study -1005 Sensitivity Analysis of Primary Efficacy and Key Secondary Efficacy Results (SKAMP-Combined Scores at Visit 9) via an Unstructured Covariance Matrix (ITT)

Visit 9 Post-dose Time Point	Treatment Difference (NWP09 - placebo) LS Mean (SE)	Nominal P-value	Adjusted P-value
Average over all post-dose time points	-7.0 (1.99)	<0.001	
0.75 hours post-dose	-8.2 (2.32)	<0.001	0.122
2 hours post-dose	-12.8 (2.20)	<0.001	<0.001
4 hours post-dose	-12.3 (2.18)	<0.001	<0.001
8 hours post-dose	-7.8 (2.18)	<0.001	<0.001
10 hours post-dose	-3.5 (2.21)	0.122	0.122
12 hours post-dose	-2.9 (2.55)	0.257	0.122
13 hours post-dose	-1.6 (2.33)	0.500	0.122

ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

NOTE: Nominal p-values were generated using a repeated measures analysis, with treatment (NWP09/Placebo), study center, time point, and time point by treatment interaction as main effects using an unstructured within-subject covariance matrix, with SKAMP-Combined score as the dependent variable. Adjusted p-values were generated using a fixed sequence testing procedure from p-values generated from the model.

Study report, p. 49

6.1.5 Analysis of Key Secondary Endpoint(s)

The key secondary efficacy variables were the onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9). The analyses of the key secondary efficacy variables were performed on the ITT population and repeated on the clinically evaluable population.

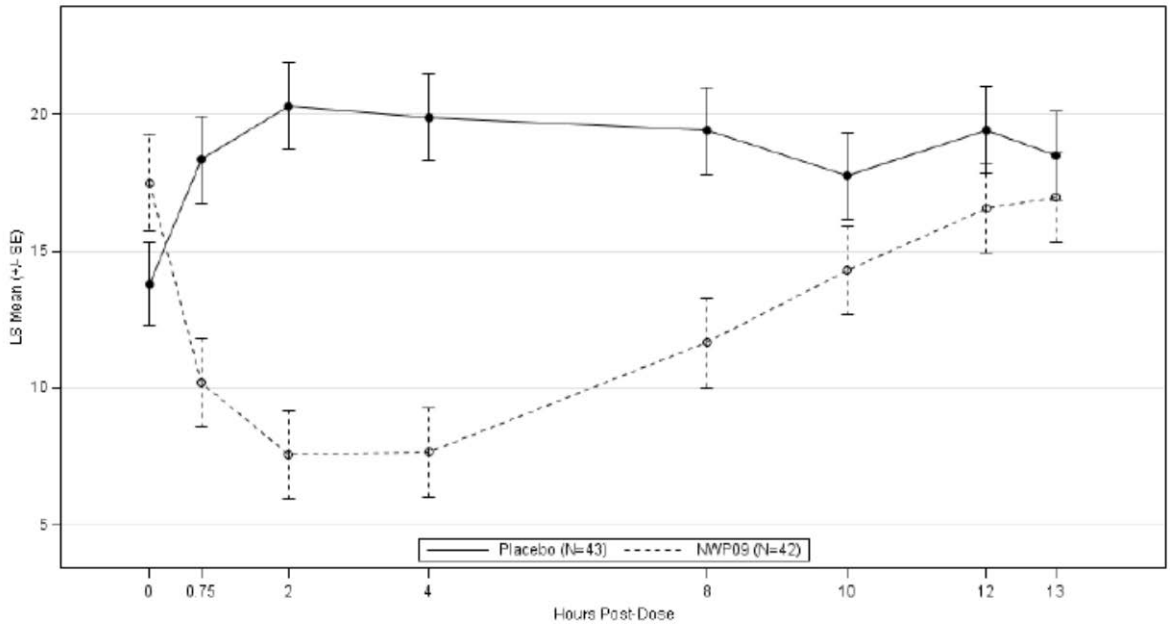
In the ITT population, SKAMP-Combined scores were statistically significantly lower for those receiving NWP09 compared with placebo at 0.75, 2, 4, and 8 hours post-dose. When the p-values were adjusted using a fixed sequence testing procedure, the treatment difference was no longer statistically significant at 0.75 hour post-dose (p = 0.133). Therefore, based on the statistical analysis methodology used in this study, the onset of efficacy was determined to be 2 hours post-dose and efficacy was maintained through the 8-hour time point. The LS mean of the statistically significant treatment difference between NWP09 and placebo ranged from -7.8 at 8 hours post-dose (p <0.001) to -12.8 at 2 hours post-dose (p <0.001). No statistically significant differences were observed after 8 hours post-dose.

Table 13: Study -1005 Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT)

Visit 9 Post-dose Time Point	Treatment Difference (NWP09 – Placebo) LS Mean (SE)	Nominal p-value	Adjusted p-value
Average over all post-dose time-points	-7.0 (1.99)	<0.001	
0.75 hour post-dose	-8.2 (2.28)	<0.001	0.133
2 hours post-dose	-12.8 (2.28)	<0.001	<0.001
4 hours post-dose	-12.3 (2.28)	<0.001	<0.001
8 hours post-dose	-7.8 (2.28)	<0.001	<0.001
10 hours post-dose	-3.4 (2.28)	0.133	0.133
12 hours post-dose	-2.9 (2.28)	0.206	0.133
13 hours post-dose	-1.6 (2.28)	0.496	0.133

ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.
Study report, p. 50

Figure 2: Study -1005 SKAMP-Combined Scores Over Time (LS Mean ± SE) by Treatment Group (ITT)



ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.
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Results for the onset and duration of efficacy based on the SKAMP-Combined score in the clinically evaluable population were similar to those in the ITT population with

statistically significantly lower scores for the NWP09 treatment group than for placebo at 0.75, 2, 4, and 8 hours post-dose

6.1.6 Other Secondary Endpoints

SKAMP-Attention and SKAMP-Deportment Scores

In general, SKAMP subscale scores in the ITT population paralleled the SKAMP-Combined score. For the Attention and Deportment subscales, scores were statistically significantly lower for those receiving NWP09 than for those receiving placebo at 0.75, 2, 4, and 8 hours after dosing during Visit 9.

PERMP Scores

At the 0.75, 2, 4, and 8 hour post-dose time points evaluated during the laboratory classroom day, the number of problems attempted and the number of problems correct on the PERMP were statistically significantly higher for those receiving treatment with NWP09 compared with placebo in the ITT population.

For the number of problems attempted, the LS mean of the treatment difference between NWP09 and placebo ranged from 25.3 at 0.75 hour post-dose ($p = 0.024$) to 36.1 at 2 hours post-dose ($p = 0.001$). For the number of problems correct, the LS mean of the treatment difference between NWP09 and placebo ranged from 22.6 at 0.75 hour post-dose ($p = 0.049$) to 34.4 at 2 hours post-dose ($p = 0.003$). PERMP score results in the clinically evaluable population were similar to those in the ITT population except that significant differences were not observed until 2 hours post-dose for the PERMP score for number of problems correct.

Table 14 : Study -1005 Summary and Analysis of Post-dose PERMP Scores at Visit 9 (ITT)

Visit 9 Post-dose Time Point Statistic	Placebo N = 43	NWP09 N = 42	Treatment Difference (NWP09-placebo)
Number of problems attempted			
Average over all post-dose time points			
n	43	42	
Mean (SD)	102.9 (48.99)	125.6 (54.70)	
Median (Q1, Q3)	99.4 (65, 133)	117.7 (80, 162)	
(min, max)	(21, 224)	(45, 312)	
LS mean (SE)	103.5 (7.20)	128.0 (7.30)	24.5 (10.25)
95% CI	(89.4, 117.6)	(113.7, 142.4)	(4.4, 44.7)
p-value			0.017

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; Q = quartile; SD = standard deviation; SE = standard error; PERMP = Permanent Product Measure of Performance.

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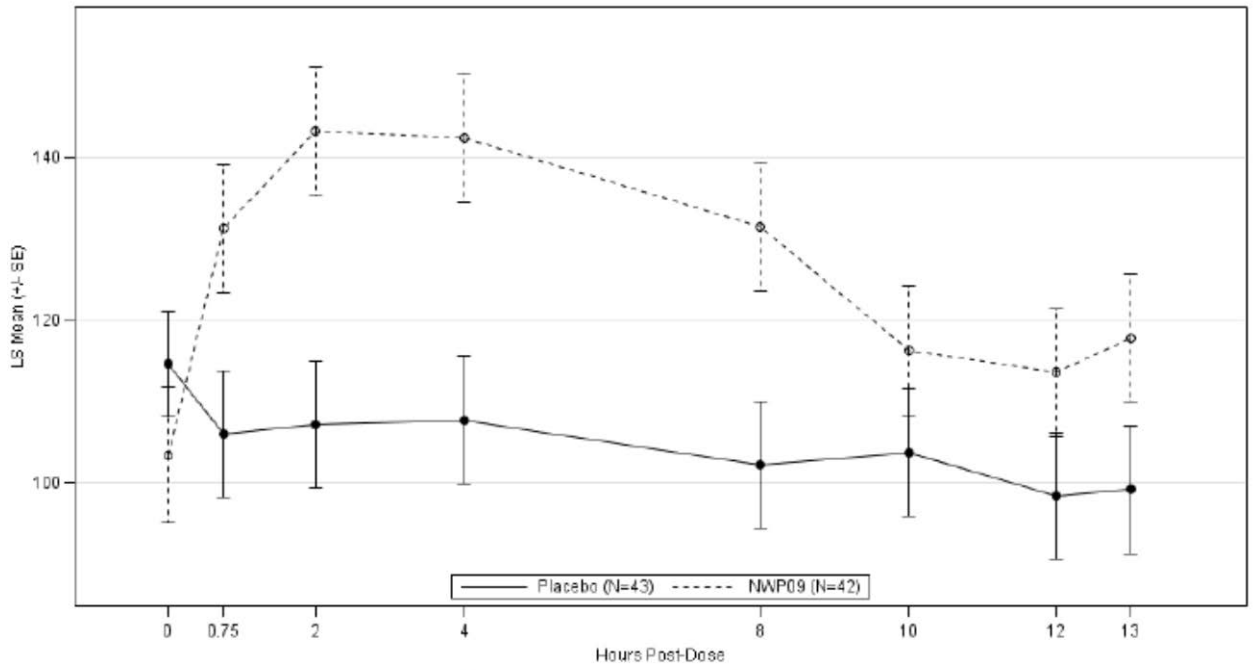
Figure 3: PERMP Number of Problems Attempted Over Time (LS Mean ± SE) by Treatment Group (ITT Population)



ITT = intent-to-treat; LS = least squares; PERMP = Permanent Product Measure of Performance; SE = standard error.

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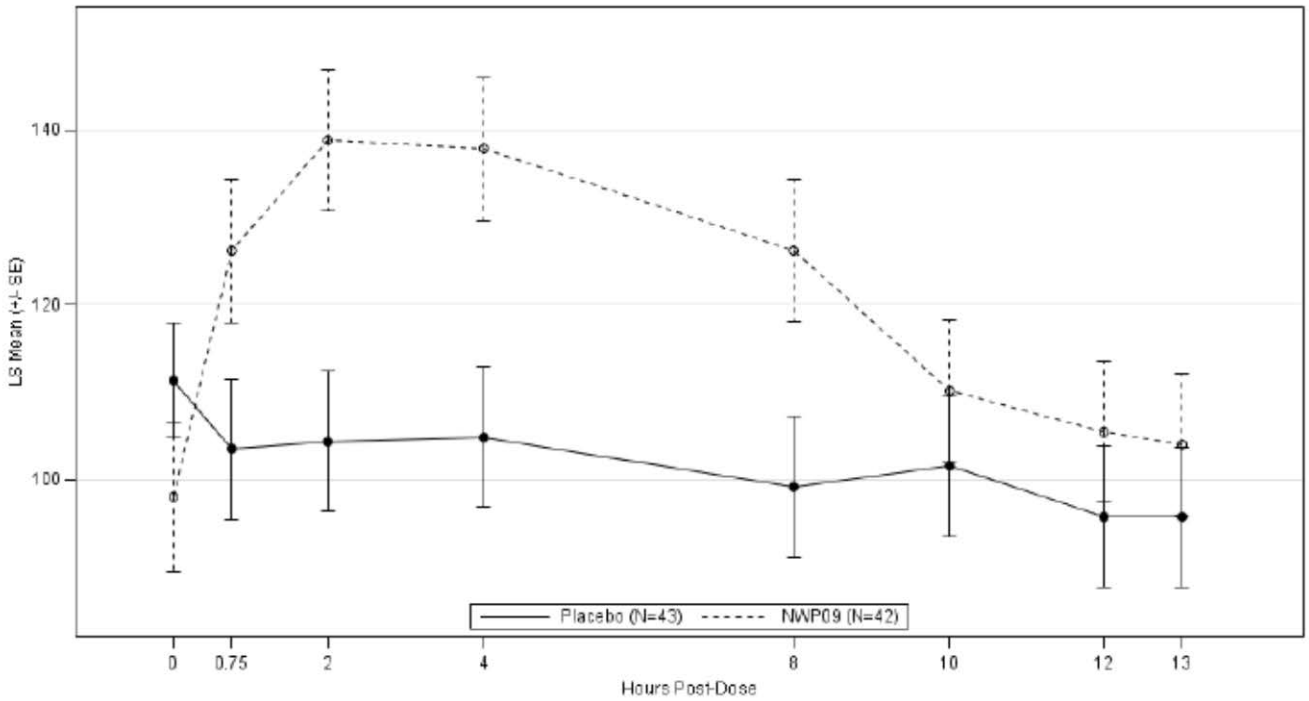
Figure 4: PERMP Number of Problems Correct Over Time (LS Mean ± SE) by Treatment Group (ITT Population)



ITT = intent-to-treat; LS = least squares; PERMP = Permanent Product Measure of Performance; SE = standard error.

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CGI-S and CGI-I

During the Open-Label Period, CGI-S scores decreased from a mean of 4.6 at Baseline (Day 1) to a mean of 2.0 at Visit 8.

During the Open-Label Period, mean CGI-I scores improved from 3.0 (minimally improved) at Visit 3 to 1.3 (much improved to very much improved) at Visit 8.

ADHD-RS

The mean changes from Baseline to Visit 8 were -27.5, -13.7, and -13.8 for the Total score, Hyperactivity/Impulsivity score, and Inattentiveness score, respectively (ITT population). Of the 85 subjects with ADHD-RS data at Visit 8, 74 (87.1%) were considered responders. There was a steady decline in ADHD-RS scores from Visit 3 to Visit 7.

CPRS

There was a decrease in CPRS scores between Baseline and Visit 8 for all of the CPRS scales. The mean changes from Baseline to Visit 8 for the CPRS scales were as follows:

Table 15: Study -1005 Summary of CPRS Scores Change from Baseline to Visit 8 (ITT)

Scale	Mean
Oppositional	-17.5
Cognitive Problems/Inattention	-17.1
Hyperactivity	-24.9
Anxious-Shy	-9.4
Perfectionism	-9.0
Social Problems	-6.6
Psychosomatic	-9.9
ADHD Index	-20.9
Restless-Impulse	-21.4
Emotional Lability	-15.9
Conners' Global Index	-21.5
Inattentive	-20.0
Hyperactive-Impulsive	-23.7
DSM-IV	-23.4

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6.1.7 Subpopulations

The primary, key secondary, and secondary efficacy analyses were repeated for the following subgroups:

- Final dose (20 mg, 30/40 mg, and 50/60 mg)
- Age (6-7 years, 8-10 years, and 11-12 years)
- Gender (male and female)
- Type of ADHD (inattentive, hyperactive/impulsive, combined, and not otherwise specified)
- Clinical site (SKAMP-Combined scores only)
- Race (SKAMP-Combined scores and SKAMP-subscale scores only)

Subgroup analyses of the SKAMP and PERMP indicate there may be variability in the treatment differences observed between NWP09 and placebo in regard to final dose, age, and gender. However, it should be noted that the number of subjects in each subgroup was typically small, and that the study was not powered to detect differences between the subgroups. For this reason, I will describe only the subgroup analysis for the primary efficacy analysis:

SKAMP-Combined Scores by Final Dose

20 mg: No significant treatment difference on average or at any post-dose time point during Visit 9 (placebo n=7; NWP09 n=4)

30/40 mg: Significant treatment difference (LS mean = -7.0, p = 0.034) observed only at 2 hours post-dose (placebo n=17; NWP09 n=19)
50/60 mg: LS mean of the treatment difference between NWP09 (n=19) and placebo (n=19) was significant at 0.75, 2, 4, and 8 hours post-dose and averaged over all post-dose time points (p = 0.003).

SKAMP-Combined Scores by Age Groups
Statistically significantly improvements in SKAMP-Combined scores at Visit 9 with NWP09 compared with placebo were observed for all age groups. The largest treatment difference was observed in 6-7 year-old subjects (placebo n = 8, NWP09 n = 5) at 2 hours post-dose when the LS mean of the treatment difference was -25.9 (p <0.001).

SKAMP-Combined Scores by Gender
For male subjects (placebo n = 23, NWP09 n = 30), the LS mean of the treatment difference averaged over all time points was -12.2 (p <0.001) with significant treatment differences observed at 0.75 hour post-dose (-12.9, p <0.001) lasting through 12 hours post-dose (-7.5, p = 0.012).

For female subjects (placebo n = 20, NWP09 n = 12), the LS mean of the treatment difference averaged over all time points was not significant (-3.3, p = 0.189); however, significant treatment differences were observed at 2 hours post-dose (-6.3, p = 0.040) lasting through 4 hours post-dose (-6.7, p = 0.028).

SKAMP-Combined Scores by ADHD Subtype
There were no subjects in the study with hyperactive/impulsive type ADHD.

SKAMP-Combined scores were statistically significantly lower with NWP09 treatment than with placebo treatment for subjects with both combined (placebo n = 32, NWP09 n = 30) and inattentive (placebo n = 11, NWP09 n = 12) type ADHD. Both types showed significant treatment differences at 0.75 hour post-dose, with effects lasting through 10 hours for inattentive type (-9.0, p = 0.029) and 8 hours for combined type ADHD (-8.0, p = 0.003).

SKAMP-Combined Scores by Site
Statistically significant treatment differences between NWP09 and placebo were observed at all sites except Sites 01 (placebo n= 8, NWP09 n = 9) and Site 02 (placebo n = 6, NWP09 n = 7).

SKAMP-Combined Scores by Race
Statistically significant improvements in SKAMP-Combined scores at Visit 9 with NWP09 treatment compared with placebo treatment were observed for both white (placebo n = 22, NWP09 n = 27) and black/African American (placebo n = 18, NWP09 n = 12) subjects.

For white subjects, the LS mean of the treatment difference averaged over all time points was -8.7 (p = 0.005) with significant treatment differences observed at 0.75 hour post-dose (-7.2, p = 0.035) lasting through 8 hours post-dose (-9.3, p = 0.007). For black/African American subjects, the LS mean of the treatment difference averaged over all time points was -7.0 (p = 0.005) with significant treatment differences observed at 0.75 hour post-dose (-11.4, p <0.001) lasting through 8 hours post-dose (-7.9, p = 0.009).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

During the open-label phase, subjects were titrated up or down by the investigator at weekly intervals in 10-20 mg/day increments at scheduled study visits until a stable dose was achieved that was optimal for efficacy and tolerability based on physician clinical judgment. As detailed in Section 6.1.7, the LS mean of the treatment difference between NWP09 and placebo was significant at 0.75, 2, 4, and 8 hours post-dose and averaged over all post-dose time points (p = 0.003) for the 50/60 mg subgroup only during the double-blind phase. However, as previously stated, the study was not powered to detect differences between the dose subgroups.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This pivotal study was not designed to address persistence of efficacy and/or tolerance effects.

7 Review of Safety

Safety Summary

There were no new or unexpected findings with respect to safety. There were no deaths and no SAEs. There were no discontinuations due to adverse events in the NWP09 group during the double-blind treatment period. Two subjects had nonserious TEAEs (dysgeusia and decreased appetite) that led to discontinuation of study drug during the Open-label Dose Optimization Period. Drug-related common adverse events during the entire study included decreased appetite, upper abdominal pain, mood swings, irritability, insomnia, headache, and vomiting. The NWP09 group showed modest mean increases from Baseline in pulse rate and systolic blood pressure consistent with the known safety profile of methylphenidate.

7.1 Methods

The clinical study report for Study -1005, the raw data sets, the Summary of Clinical Safety, and the case narratives/CRFs of serious adverse events were reviewed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This 505(b)(2) NDA primarily relies upon the FDA's general findings of safety of the LD, Methylin® chewable tablets (NDA 21,475). Two clinical studies conducted using the final formulation of methylphenidate HCl ERCT (B7491004 and B7491005) provide supportive safety data for this new formulation. Study B7491004 was a Phase 1 relative bioavailability study in healthy adults to evaluate bioequivalence between methylphenidate HCl ERCT and the LD. Study B7491005 was a Phase 3 laboratory classroom study in pediatric patients (6 to 12 years old) with ADHD. As only Study B7491005 provided blinded safety data, this NDA review will focus on the safety data from this study.

7.1.2 Categorization of Adverse Events

Study -1005
Adverse events were coded with Medical Dictionary for Regulatory Activities Version 15.0. An AE was considered a treatment-emergent adverse event (TEAE) if it started on or after the date of the first dose of study drug. If a subject terminated early from the study and had an AE after his/her last dosing date, the AE was deemed treatment-emergent if it occurred ≤72 hours after the last dose of study drug and not treatment-emergent if it occurred >72 hours after the last dose. Events were counted only for the treatment period in which they started.

The sponsor's categorization of adverse events was assessed and found to be adequate. Verbatim terms compared well with the preferred terms. Safety signals did not appear to be diminished through splitting.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of safety data was done.

7.2 Adequacy of Safety Assessments

(Please see Section 9.4 Schedule of Events for specific timing of safety assessments) All tests reasonably applicable were conducted to assess safety. As stated previously, this 505(b)(2) application relies primarily on the FDA's finding of safety for the LD.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The mean duration of exposure to any dose of NWP09 during the entire study was 44.5 days. Mean exposure was longer for the 60-mg dose group than the lower dose groups: 22.0 days versus a range of 11.9 to 16.4 days for NWP09 20 mg and NWP09 40 mg,

respectively. The mean daily dose of NWP09 during the entire study was 33.0 mg. This 505(b)(2) NDA primarily relies upon the FDA's general findings of safety of the LD, Methylin® chewable tablets (NDA 21,475).

The duration of exposure to treatment by daily dose during the double-blind period is summarized in the table below:

Table 16: Study -1005 Duration of Exposure to Treatment by Daily Dose during Double-Blind Period (Enrolled Safety Population)

Parameter	NWP09 Dose						All NWP09
	0 (Placebo)	20 mg	30 mg	40 mg	50 mg	60 mg	
n	43	4	4	15	9	10	42
Mean (days)	7.0	7.0	7.0	6.9	6.9	7.0	6.9

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7.2.2 Explorations for Dose Response

This trial was not designed to assess dose response. Subjects were not randomly assigned to a distinct dose. During the 6-week Open-label Dose Optimization Period, the investigator titrated the dose of NWP09 up or down to achieve the optimal dose for efficacy and tolerability. During the Double-Blind Treatment Period, subjects were randomized to their optimized dose or placebo.

7.2.4 Routine Clinical Testing

The routine clinical testing of the subjects appeared to be adequate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pfizer adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

There were no unexpected safety concerns. The safety concerns were similar to what has previously been found in the treatment of children with oral formulations of methylphenidate.

The following tables give an overview of the TEAEs/Deaths/SAEs/Discontinuations during the open-label and double-blind periods:

Table 17: Study -1005 Overview of TEAEs During the Open-Label Dose Optimization Period (Enrolled Safety Population)

Category of Event	Total N = 90 n (%)
TEAEs	213
Subjects with any TEAEs	65 (72.2)
Treatment-related TEAEs[1]	141
Subjects with any treatment-related TEAEs[1]	52 (57.8)
Severe TEAEs	0
Subjects with any severe TEAEs	0
Serious TEAEs	0
Subjects with any serious TEAEs	0
Subjects who died	0
Subjects with TEAEs leading to premature discontinuation of study drug[2]	2 (2.2)

TEAE = treatment-emergent adverse event.

Note: An adverse event was considered treatment-emergent during the open-label period if it started on or after the first dose of open-label study drug, but before the start of the double-blind study drug.

Note: Subjects who experienced 1 or more TEAEs in a category were counted once for that category.

1 Treatment-related TEAEs included those TEAEs with a relationship equal to related or missing.

2 The action taken for the TEAE leading to premature discontinuation in 1 of the 2 subjects (Subject 07-030) was considered an error in the clinical database.

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Table 18: Study -1005 Overview of TEAEs During the Double-Blind Treatment Period (Randomized Safety Population)

Category of Event	Placebo N = 44 n (%)	NWP09 N = 42 n (%)
TEAEs	17	13
Subjects with any TEAEs	13 (29.5)	11 (26.2)
Treatment-related TEAEs[1]	1	2
Subjects with any treatment-related TEAEs[1]	1 (2.3)	2 (4.8)
Severe TEAEs	0	0
Subjects with any severe TEAEs	0	0
Serious TEAEs	0	0
Subjects with any serious TEAEs	0	0
Subjects who died	0	0
Subjects with TEAEs leading to premature discontinuation of study drug	0	0

TEAE = treatment-emergent adverse event.
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7.3.1 Deaths

There were no deaths during Study -1005.

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs during Study -1005.

7.3.3 Dropouts and/or Discontinuations

Two subjects had nonserious TEAEs (dysgeusia and decreased appetite) that led to discontinuation of study drug during the Open-label Dose Optimization Period. The Applicant states that the recorded action for the event of decreased appetite was considered to be an error in the clinical database.

The narratives for these events are as follows:

Subject 03-079*, a 7-year-old white female with combined ADHD, was enrolled in NWP09-ADHD-300 on 09 August 2012 and was first dispensed open-label NWP09 on 16 August 2012. On 17 August 2012 (study Day 1), the subject experienced the nonserious event of dysgeusia (bad taste from medicine), which was graded as moderate. The dysgeusia was considered related to study treatment, and study drug*

was permanently discontinued because of the event on 16 September 2012 (also date of last dose). The event resolved on 17 September 2012, 32 days after onset.

***Subject 07-030**, an 8-year-old white female with combined ADHD, was enrolled in NWP09-ADHD-300 on 24 July 2012 and first dispensed open-label NWP09 on 09 August 2012. The clinical database listed no other medical conditions for the subject. Her prior medications consisted of methylphenidate hydrochloride (2009 through 07 August 2012). On 27 August 2012 (study Day 18), the subject experienced the nonserious event of decreased appetite (loss of appetite), which was graded as mild. The decreased appetite was considered related to study treatment, and the action taken for the event was recorded on the CRF as "discontinued drug." The subject stopped study drug on 26 August 2012 and resumed her pre-study medication (methylphenidate) on 27 August 2012. On 30 August 2012, she withdrew consent for the following reasons: "unhappy with treatment, old medication started, parent disliked changes in doses throughout trial." When the site was asked for clarification about the TEAE and reason for early withdrawal from the study, the site replied "no AE required – lack of efficacy." The site clarified the reason for early withdrawal but did not change the action taken for the TEAE. Thus, the recorded action for the TEAE in the clinical database was considered an error. At the time of last reporting, the event of decreased appetite was ongoing. No other AEs were reported for the subject during the study.*

7.3.4 Significant Adverse Events

There were no severe AEs, or life-threatening AEs reported during any study period of Study -1005.

7.3.5 Submission Specific Primary Safety Concerns

Suicidal Ideation and Behavior (C-SSRS)
No subject reported suicidal ideation or behavior during Study -1005. During Week 4 of the Open-label Dose Optimization Period, 1 subject (Subject 06-036) reported nonsuicidal self-injurious behavior. The Applicant states that in mimicking behavior of other girls at school, the subject used an eraser to excoriate the volar forearm. The subject expressed no wish to die.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common (≥5% overall) TEAEs during the entire study were decreased appetite, upper respiratory tract infection, upper abdominal pain, mood swings, irritability, insomnia, headache, dysgeusia, initial insomnia, and vomiting. Except for upper respiratory tract infection and dysgeusia, these events are consistent with the

known safety profile of methylphenidate. Upper respiratory tract infection is a common pediatric illness and dysgeusia was most likely a subject dislike of the taste of the study drug.[4]

Table 19: Study -1005 Most Common (≥2%) Preferred Terms of TEAEs During the Entire Study

Preferred Term	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
All TEAEs	3 (75.0)	31 (70.5)	33 (78.6)	67 (74.4)
Decreased appetite	1 (25.0)	17 (38.6)	15 (35.7)	33 (36.7)
Upper respiratory tract infection	0	7 (15.9)	7 (16.7)	14 (15.6)
Upper abdominal pain	1 (25.0)	7 (15.9)	5 (11.9)	13 (14.4)
Mood swings	0	4 (9.1)	8 (19.0)	12 (13.3)
Irritability	1 (25.0)	6 (13.6)	5 (11.9)	12 (13.3)
Insomnia	1 (25.0)	7 (15.9)	2 (4.8)	10 (11.1)
Headache	0	6 (13.6)	3 (7.1)	9 (10.0)
Dysgeusia	1 (25.0)	4 (9.1)	3 (7.1)	8 (8.9)
Initial insomnia	0	3 (6.8)	2 (4.8)	5 (5.6)
Vomiting	0	4 (9.1)	1 (2.4)	5 (5.6)
Viral infection	0	1 (2.3)	3 (7.1)	4 (4.4)
Contusion	0	4 (9.1)	0	4 (4.4)
Tic	0	2 (4.5)	1 (2.4)	3 (3.3)
Dry mouth	0	0	3 (7.1)	3 (3.3)
Nausea	0	1 (2.3)	2 (4.8)	3 (3.3)
Gastroenteritis	0	2 (4.5)	1 (2.4)	3 (3.3)
Feeling jittery	0	2 (4.5)	1 (2.4)	3 (3.3)
Excoriation	0	1 (2.3)	2 (4.8)	3 (3.3)
Oropharyngeal pain	0	0	3 (7.1)	3 (3.3)
Middle insomnia	0	1 (2.3)	1 (2.4)	2 (2.2)
Abdominal pain	0	1 (2.3)	1 (2.4)	2 (2.2)
Diarrhea	0	1 (2.3)	1 (2.4)	2 (2.2)
Dizziness	0	0	2 (4.8)	2 (2.2)
Lethargy	0	1 (2.3)	1 (2.4)	2 (2.2)
Fatigue	0	2 (4.5)	0	2 (2.2)
Laceration	0	1 (2.3)	1 (2.4)	2 (2.2)
Wound	0	2 (4.5)	0	2 (2.2)
Nasal congestion	1 (25.0)	0	1 (2.4)	2 (2.2)
Rhinorrhea	0	0	2 (4.8)	2 (2.2)
Tachycardia	0	2 (4.5)	0	2 (2.2)
Tinnitus	0	0	2 (4.8)	2 (2.2)

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[4] All reports of dysgeusia came from a single site (Site 03), with the following verbatim terms: “bad taste” in 4 subjects, “bad taste from medicine” in 3 subjects, and “bad taste from the medicine” in 1 subject.

The treatment-related TEAEs during the Open-Label Phase are detailed in the table below:

Table 20: Study -1005 TEAEs Related to Study Medication During Open-Label Phase (Enrolled Safety)

System Organ Class Preferred Term	Total (N=90) n (%)
Subjects with at least one treatment-related treatment-emergent adverse event	52 (57.8)
METABOLISM AND NUTRITION DISORDERS	33 (36.7)
Decreased appetite	33 (36.7)
PSYCHIATRIC DISORDERS	27 (30.0)
Mood swings	11 (12.2)
Insomnia	10 (11.1)
Initial insomnia	4 (4.4)
Tic	3 (3.3)
Middle insomnia	2 (2.2)
Anger	1 (1.1)
Change in sustained attention	1 (1.1)
Onychophagia	1 (1.1)
GASTROINTESTINAL DISORDERS	18 (20.0)
Abdominal pain upper	10 (11.1)
Dry mouth	3 (3.3)
Abdominal pain	2 (2.2)
Vomiting	2 (2.2)
Diarrhoea	1 (1.1)
Dyspepsia	1 (1.1)
Flatulence	1 (1.1)

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The most common (≥3%) TEAE during the Double-blind Treatment Period in the NWP09 treatment group was upper respiratory tract infection and the frequency was similar to the placebo group.

Table 21: Study -1005: TEAEs During the Double-Blind Treatment Period (Randomized Safety)

System Organ Class Preferred Term	Placebo N = 44 n (%)	NWP09 N = 42 n (%)
All TEAEs	13 (29.5)	11 (26.2)
Infections and infestations	4 (9.1)	3 (7.1)
Upper respiratory tract infection	3 (6.8)	3 (7.1)
Pharyngitis	1 (2.3)	0
Injury, poisoning and procedural complications	5 (11.4)	2 (4.8)
Snake bite	0	1 (2.4)
Subcutaneous hematoma	0	1 (2.4)
Contusion	2 (4.5)	0
Nail injury	1 (2.3)	0
Wound	2 (4.5)	0
Respiratory, thoracic, and mediastinal disorders	0	2 (4.8)
Cough	0	1 (2.4)
Oropharyngeal pain	0	1 (2.4)
Gastrointestinal disorders	1 (2.3)	1 (2.4)
Nausea	0	1 (2.4)
Vomiting	1 (2.3)	0
Investigations	0	1 (2.4)
Weight decreased	0	1 (2.4)
Metabolism and nutrition disorders	1 (2.3)	1 (2.4)
Decreased appetite	0	1 (2.4)
Increased appetite	1 (2.3)	0
Nervous system disorders	1 (2.3)	1 (2.4)
Headache	0	1 (2.4)
Tremor	1 (2.3)	0
Psychiatric disorders	3 (6.8)	1 (2.4)
Aggression	0	1 (2.4)
Emotional poverty	0	1 (2.4)
Anxiety	1 (2.3)	0
Initial insomnia	2 (4.5)	0
General disorders and administration site conditions	1 (2.3)	0
Feeling jittery	1 (2.3)	0
Renal and urinary disorders	1 (2.3)	0
Enuresis	1 (2.3)	0

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The **drug-related TEAEs** during the double-blind period are detailed in the table below:

Table 22: Study -1005 TEAEs Related to Study Medication During Double-Blind Phase (Randomized Safety)

System Organ Class Preferred Term	Placebo (N=44) n (%)	NWP09 (N=42) n (%)
Subjects with at least one treatment-related treatment-emergent adverse event	1 (2.3)	2 (4.8)
INVESTIGATIONS	0	1 (2.4)
Weight decreased	0	1 (2.4)
METABOLISM AND NUTRITION DISORDERS	0	1 (2.4)
Decreased appetite	0	1 (2.4)
RENAL AND URINARY DISORDERS	1 (2.3)	0
Enuresis	1 (2.3)	0

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The possible grades of AE severity were mild, moderate, severe, life-threatening, and fatal. The highest grades of TEAE severity during the entire study were mild and moderate. The table below summarizes the severity of the TEAEs during the Double-blind Treatment Period:

Table 23: Study -1005 Severity of TEAEs During the Double-Blind Treatment Period (Randomized Safety)

Severity Preferred Term (for moderate or greater severity)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)
Mild	12 (27.3)	8 (19.0)
Moderate	1 (2.3)	3 (7.1)
Upper respiratory tract infection (Subject 03-045)		1 (2.4)
Aggression (Subject 02-100)		1 (2.4)
Emotional poverty (Subject 02-100)		1 (2.4)
Decreased appetite (Subject 01-006)		1 (2.4)
Enuresis (Subject 02-089)	1 (2.3)	
Severe	0	0
Life-threatening	0	0
Fatal	0	0

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7.4.2 Laboratory Findings

One subject had 2 clinically significant clinical laboratory results during the study. Subject 02-088, who was randomized to placebo, had an activated partial thromboplastin time of 38.5 seconds and prothrombin time of 12.5 seconds at Visit 1. After medical review of the findings, this subject was allowed to continue.

No other clinical laboratory findings were notable.

7.4.3 Vital Signs

Pulse rate and SBP showed modest mean increases from Baseline during Study -1005 and 41.1% of subjects had PCS increases in DBP from Baseline. These changes are consistent with the known effects of methylphenidate.

Pulse Rate

Baseline mean values for pulse rate were generally similar across the study groups. All groups had small mean increases in pulse rate from Baseline during the open-label phase. However, the largest mean increases in pulse rate from Baseline were at the follow-up Visit 10 (an increase of 11.6 and 11.5 bpm in the NWP09 and placebo groups, respectively). It should be noted that subjects were allowed to resume other medications for ADHD prior to the follow-up Visit 10. Prior to the follow-up Visit 10, the largest mean increases in pulse rate from Baseline in the NWP09 and placebo groups were 6.0 bpm at Week 3 and 6.3 bpm, at Week 4, respectively.

Table 24: Study -1005 Pulse Rate at Screening and Baseline (Enrolled Safety)

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Pulse Rate (BEATS/MIN)		
Visit 1 (Screening)		
n	44	42
Mean	80.6	78.7
SD	9.10	11.21
Median (Q1,Q3)	81.5 (77,86)	76.5 (72,88)
Range (Min, Max)	(57,97)	(57,98)
Baseline (Day 1)		
n	44	42
Mean	84.1	80.8
SD	10.93	10.80
Median (Q1,Q3)	85.0 (75,91)	80.0 (74,87)
Range (Min, Max)	(65,112)	(56,105)

Study report, p. 907

Table 25: Study -1005 Change from Baseline in Pulse Rate from Baseline to Last Dose Open Label Visit and Last Dose Double-Blind Visit (Enrolled Safety)

The mean change from baseline to Last Dose Double-Blind 2nd Classroom Visit was only 2.5 (SD 10.3) bpm for the NWPO9 group:

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Pulse Rate (BEATS/MIN)		
Last Dose Open Label 1st Classroom Visit (Day 43 +/- 2D)		
n	44	42
Mean	81.2	82.5
SD	10.20	9.63
Median (Q1,Q3)	83.0 (76,88)	82.5 (77,89)
Range (Min, Max)	(53,101)	(63,101)
Change from Baseline to Last Dose Open Label 1st Classroom Visit (Day 43 +/- 2D)		
n	44	42
Mean	-2.9	1.7
SD	11.96	12.00
Median (Q1,Q3)	-4.0 (-10,7)	-1.0 (-7,8)
Range (Min, Max)	(-30,25)	(-16,33)
Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	83.0	83.3
SD	10.50	10.86
Median (Q1,Q3)	81.0 (76,92)	82.0 (76,89)
Range (Min, Max)	(64,103)	(66,126)
Change from Baseline to Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	-1.5	2.5
SD	11.24	10.31
Median (Q1,Q3)	-2.0 (-10,8)	0.0 (-5,8)
Range (Min, Max)	(-26,20)	(-14,37)

Study report, p. 910

Potentially Clinically Significant (PCS) pulse values during the entire study are detailed in the table below:

Table 26 : Study -1005 PCS Pulse Values During Entire Study (Enrolled Safety)

Parameter	Criteria	Placebo (N=44) n (%)	NWP09 (N=42) n (%)	Total (N=90) n (%)
Pulse	Post-baseline value > 110 bpm	4 (9.1)	4 (9.5)	8 (8.9)
	Increase from Baseline >= 25 bpm	7 (15.9)	10 (23.8)	17 (18.9)

Study report, p. 912

Potentially Clinically Significant (PCS) pulse values during the double-blind period are detailed in the table below:

Table 27: Study -1005 PCS Pulse Values During Double-Blind Phase (Randomized Safety)

Parameter	Criteria	Placebo (N=44) n (%)	NWP09 (N=42) n (%)
Pulse	Post-baseline value > 110 bpm	0	1 (2.4)
	Increase from Baseline >= 25 bpm	0	2 (4.8)

Study report, p.913

Systolic Blood Pressure

NWP09 and placebo groups of the enrolled safety population had similar mean values for systolic blood pressure (SBP) at Baseline. During the remainder of the study, most mean changes in SBP from Baseline were increases, with the largest being 7.0 mmHg and 6.5 mmHg in the NWP09 and placebo groups, respectively, at the follow-up visit. Again, it is important to note that subjects were allowed to resume other medications for ADHD prior to the follow-up visit. Prior to the follow-up visit, the largest mean increase in SBP from Baseline in the NWP09 group was 2.5 mmHg at Week 3; in the placebo group, the largest mean increase was 3.4 mmHg at Week 4 and the last open-label dose.

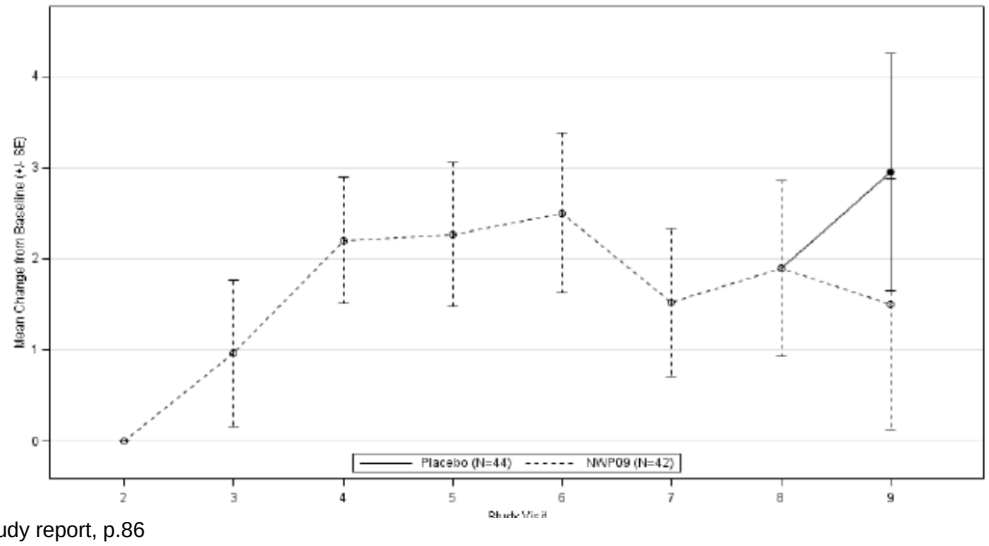
The mean change from baseline to last dose double-blind 2nd Classroom visit in the systolic blood pressure was actually higher in the placebo group than the NWP09 group (3 vs 1.5 mmHg):

Table 28: Study -1005 Change from Baseline to Last Dose Open Label and Double-Blind Visits (Enrolled Safety)

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Systolic Blood Pressure (mmHg)		
Last Dose Open Label 1st Classroom Visit (Day 43 +/- 2D)		
n	44	42
Mean	107.0	104.2
SD	9.46	11.00
Median (Q1,Q3)	107.0 (101,115)	103.0 (96,113)
Range (Min, Max)	(88,128)	(82,125)
Change from Baseline to Last Dose Open Label 1st Classroom Visit (Day 43 +/- 2D)		
n	44	42
Mean	3.4	0.3
SD	9.25	8.51
Median (Q1,Q3)	2.0 (-3,7)	0.0 (-7,6)
Range (Min, Max)	(-13,34)	(-18,17)
Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	106.8	105.4
SD	7.83	8.83
Median (Q1,Q3)	106.0 (102,114)	105.0 (99,112)
Range (Min, Max)	(90,126)	(87,125)
Change from Baseline to Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	3.0	1.5
SD	8.52	8.95
Median (Q1,Q3)	4.0 (-1,8)	1.5 (-4,10)
Range (Min, Max)	(-16,23)	(-23,17)

Study report, p.913

Figure 5: Study -1005 Mean Change in Systolic BP from Baseline by Visit (Randomized Safety)



Study report, p.86

Diastolic Blood Pressure

Baseline mean values for DBP were also similar across the study groups of the enrolled safety population. During the study, the NWP09 and placebo groups had no notable mean changes in DBP from Baseline, except possibly for a mean increase of 5.4 mmHg from Baseline in the NWP09 group at the follow-up visit.[5] At all other time points, mean increases in DBP from Baseline in the NWP09 group did not exceed 2.2 mmHg.

Table 29: Study -1005 Diastolic BP at Baseline (Enrolled Safety)

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Diastolic Blood Pressure (mmHg)		
Visit 1 (Screening)		
n	44	42
Mean	65.0	64.5
SD	6.23	6.03
Median (Q1,Q3)	65.5 (61,69)	65.0 (60,68)
Range (Min, Max)	(53,79)	(49,75)
Baseline (Day 1)		
n	44	42
Mean	63.2	64.1
SD	6.00	6.61
Median (Q1,Q3)	63.0 (60,68)	63.5 (59,69)
Range (Min, Max)	(52,76)	(51,80)

Study report, p. 902

Table 30: Study -1005 Change from Baseline to Last Dose Double-Blind Visit (Enrolled Safety)

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	65.7	65.5
SD	6.16	6.67
Median (Q1,Q3)	66.0 (62,69)	64.0 (61,70)
Range (Min, Max)	(52,76)	(50,80)
Change from Baseline to Last Dose Double Blind 2nd Classroom Visit (7 Days Post Visit 8)		
n	43	42
Mean	2.4	1.3
SD	7.22	7.05
Median (Q1,Q3)	3.0 (-4,8)	2.0 (-3,6)
Range (Min, Max)	(-11,22)	(-12,15)

Study report, p. 902

[5] Again, it is important to note that subjects were allowed to resume other medications for ADHD prior to the follow-up visit.

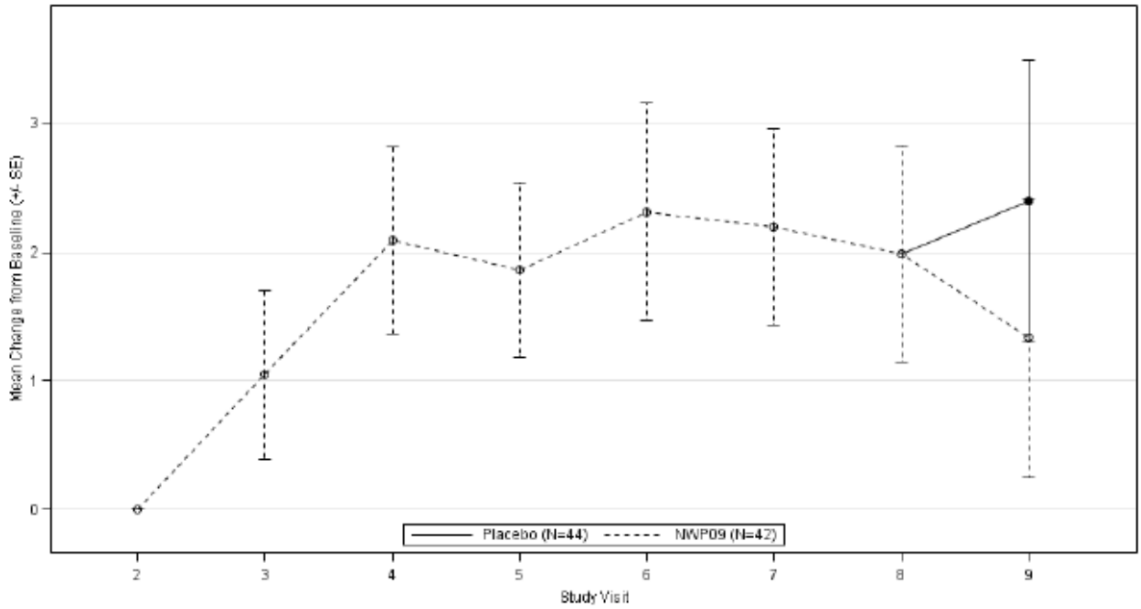
Table 31: Study -1005 Change from Baseline to Follow-Up Visit (Enrolled Safety)[6]

Vital Sign (unit) Visit Statistic	Placebo (N=44)	NWP09 (N=42)
Diastolic Blood Pressure (mmHg)		
Follow-up		
n	6	7
Mean	66.2	70.4
SD	5.95	4.76
Median (Q1,Q3)	66.0 (62,71)	69.0 (69,74)
Range (Min, Max)	(58,74)	(64,79)
Change from Baseline to Follow-up		
n	6	7
Mean	-0.3	5.4
SD	6.38	7.70
Median (Q1,Q3)	-3.0 (-5,5)	10.0 (0,11)
Range (Min, Max)	(-6,10)	(-9,12)

Study report, p. 906

The pattern for mean observed DBP over time was similar to that for mean change in SBP:

Figure 6: Study -1005 Mean Change in Diastolic BP from Baseline by Visit (Randomized Safety)



Study report, p. 88

[6] Again, it is important to note that subjects were allowed to resume other medications for ADHD prior to the follow-up visit.

The following tables detail PCS systolic and diastolic BP values during the entire study and during the double-blind period:

Table 32: Study -1005 PCS Systolic and Diastolic BP Values During Entire Study (Enrolled Safety)

Parameter	Criteria	Placebo (N=44) n (%)	NWP09 (N=42) n (%)	Total (N=90) n (%)
Systolic Blood Pressure	Post-baseline value > 95th percentile	9 (20.5)	8 (19.0)	17 (18.9)
	Increase from Baseline >= 20 mmHg	5 (11.4)	2 (4.8)	7 (7.8)
Diastolic Blood Pressure	Post-baseline value > 95th percentile	5 (11.4)	3 (7.1)	8 (8.9)
	Increase from Baseline >= 10 mmHg	22 (50.0)	15 (35.7)	37 (41.1)

Study report, p. 912

Table 33: Study -1005 PCS Systolic and Diastolic BP Values During Double-Blind Phase (Randomized Safety)

Parameter	Criteria	Placebo (N=44) n (%)	NWP09 (N=42) n (%)
Systolic Blood Pressure	Post-baseline value > 95th percentile	1 (2.3)	2 (4.8)
	Increase from Baseline >= 20 mmHg	1 (2.3)	0
Diastolic Blood Pressure	Post-baseline value > 95th percentile	0	0
	Increase from Baseline >= 10 mmHg	7 (15.9)	6 (14.3)

Study report, p. 913

7.4.4 Electrocardiograms (ECGs)

The NWP09 and placebo groups had similar mean values for all ECG variables. The mean overall Fridericia-corrected QT interval was 405.1 msec, with a range of 370 to 443 msec. Only 2 subjects had abnormal ECG interpretations (not clinically significant). Both were at the Screening visit and in the placebo group.

7.5 Other Safety Explorations

7.5.3 Drug-Demographic Interactions

Mean Final Dose

Mean final doses of NWP09 were similar between males and females. The older age groups had higher mean final doses than the youngest age group. Mean final doses were also higher for white and black/African American subjects than for Asian subjects and subjects whose race was categorized as "other":

Table 34: Study -1005 Final NWP09 Dose by Demographic Characteristics

Parameter-Gender	Male	Female
Mean Final Dose of NWP09	42.7	42.3

Parameter-Age Group	6-7 years	8-10 years	11-12 years
Mean Final Dose of NWP09	35.6 mg	43.6 mg	44.8 mg

Parameter-Race	White	Black/AA	Asian	Other
Mean Final Dose of NWP09	42.1 mg	45 mg	20 mg	36 mg

Study report, p. 69

Mean Systolic BP

Compared with the overall randomized safety population, mean SBPs from Visit 2 through 8 tended to be slightly lower in the age group 6-7 years and slightly higher in the age group 11-12 years than the entire population. Black or African American subjects also tended to have higher mean SBPs from Visit 2 through 8. No notable gender differences were observed.

Mean Diastolic BP

Compared with the overall randomized safety population, mean DBPs from Visit 2 through Visit 8 tended to be slightly lower in the age group 6-7 years. Black or African American subjects had generally higher mean DBPs from Visit 2 through 8 than the entire randomized safety population. No notable gender differences were noted for mean observed DBP.

7.7 Additional Submissions / Safety Issues

Study -1004 (pivotal bioavailability study comparing methylphenidate HCl ERCT and Methylin chewable tablets)

Please note that the design and PK results of Study -1004 have been previously detailed in Section 4.4.3.

Safety Summary:
There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events during the conduct of this study. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Safety Assessments:
An assessment of safety was based primarily on the frequency and severity of AEs. There was no formal evaluation of safety or tolerability. Subjects were under constant supervision while confined in the clinical facility. Subjects were observed and/or questioned at regular intervals throughout the study to monitor adverse events.

Vital signs (blood pressure and pulse rate) were measured prior to drug administration and at 1, 2, 3.5, 6, 8, 12 and 24 hours (±20 minutes) post-dose.

ECGs were recorded prior to drug administration and at 4, 12 and 24 hours (±30 minutes) post-dose.

Subjects were questioned for suicide assessment prior to drug administration (between check-in and dosing), at 6 hours post-dose (± 20 minutes), and at the end of the period (± 20 minutes) using the C-SSRS questionnaire.

Screening clinical laboratory tests and a physical examination were performed. In addition, post-clinical laboratory tests for hematology, biochemistry, and urinalysis and a poststudy physical examination (including vital signs measurements), were performed.

Safety Results:
Deaths/SAEs/Significant AEs
There were no deaths, Serious Adverse Events (SAEs), or other significant adverse events during the conduct of the study.

Discontinuations
The following subjects were dismissed or withdrew from the study:

Table 35: Study -1004 Discontinued Subjects

Sbj	Period Discontinued	Action	Reason	Details
10	Period 2	Dismissed	Non Compliant	4-5 drops as the study drug dripped from subject's mouth
18	Period 1	Dismissed	AE	AE (Short PR).
29	Period 3	Dismissed	AE	Subject was dismissed due to AE's (headache (resolved), fluttering sensation in heart (resolved) and hypertension (ongoing)).
33	Period 2	Withdrew	Personal	Personal reasons (family emergency and has to leave town).

Study report, p. 27

The AEs related to study discontinuation occurred with the LD. The following table gives more specifics of these AEs that led to discontinuation:

Table 36: Study -1004 Adverse Events Leading to Study Discontinuation

				MedDRA Coding							
Sbj	Per	Trt-Day	Term	PT	HLGT	Time From Dosing (hrs)	Duration (hrs)	Severity	Action Taken	Relation to Drug	Outcome
18	1	C-1	Short PR	Electrocardiogram PR shortened	Cardiac and vascular investigations (excl enzyme tests)	3.82	357.17	MILD	None	Related	Resolved
	3	C-1	Fluttering sensation in the heart	Cardiac flutter	Cardiac arrhythmias	1.52	4.23	MILD	None	Related	Resolved
29	3	C-1	Headache	Headache	Headaches	3.52	2.23	MILD	None	Related	Resolved
	3	C-1	Hypertension	Hypertension	Vascular hypertensive disorders	5.75	1.38	MILD	None	Related	Resolved

Study report, p. 42

Adverse Events

All adverse events experienced in this study were judged to be mild in severity. The most frequently reported adverse event was hypertension, reported by 12.1% of subjects (2 subjects in the test product fasted group and in 2 subjects in the LD group).

There were 28 AEs considered by the Investigator as having a related relationship to the study drugs. These AEs are summarized in the table below:

Table 37: Study -1004 Incidence of AEs by SOC and PT Judged as Related

System Organ Class Term Preferred Term	Reported Incidence by Treatment Group Trt A N = 32	Trt B N = 32	Trt C N = 31	Total N = 33
Cardiac disorders				
Bradycardia	0 (0%)	0 (0%)	1 (3.2%)	1 (3.0%)
Cardiac flutter	0 (0%)	0 (0%)	1 (3.2%)	1 (3.0%)
Sinus bradycardia	0 (0%)	0 (0%)	1 (3.2%)	1 (3.0%)
Eye disorders				
Vision blurred	0 (0%)	0 (0%)	1 (3.2%)	1 (3.0%)
General disorders and administration site conditions				
Feeling hot	0 (0%)	1 (3.1%)	0 (0%)	1 (3.0%)
Investigations				
Electrocardiogram PR shortened	0 (0%)	0 (0%)	1 (3.2%)	1 (3.0%)
Electrocardiogram QT prolonged	1 (3.1%)	0 (0%)	1 (3.2%)	2 (6.1%)
Metabolism and nutrition disorders				
Decreased appetite	1 (3.1%)	1 (3.1%)	1 (3.2%)	2 (6.1%)
Nervous system disorders				
Dizziness	2 (6.3%)	0 (0%)	1 (3.2%)	3 (9.1%)
Headache	2 (6.3%)	1 (3.1%)	1 (3.2%)	2 (6.1%)
Somnolence	0 (0%)	0 (0%)	2 (6.5%)	2 (6.1%)
Psychiatric disorders				
Hypervigilance	2 (6.3%)	1 (3.1%)	0 (0%)	3 (9.1%)
Vascular disorders				
Hypertension	2 (6.3%)	0 (0%)	2 (6.5%)	4 (12.1%)

Study report, p. 43-44

Reviewer note:
Test Product: Methylphenidate HCl Extended Release 40 mg chewable tablets
Reference Product: Methylin™ 10 mg chewable tablets (immediate release)

Treatments:
Treatment A: test product (1 tablet, 40 mg) administered under fasting conditions
Treatment B: test product (1 tablet, 40 mg) administered under fed conditions
Treatment C: reference product 2 equal doses of 20 mg (2 x 10 mg/tablet), 6 hours apart, first dose administered under fasting conditions

Clinical Laboratory Parameters
All laboratory parameters were evaluated by the study investigator. Clinically significant laboratory results which were repeated were normal or judged to be not clinically significant.

Vital Signs/ECGs
There were no clinically significant vital signs or ECGs that occurred in this study.

Suicidal Ideation or Behavior
All subjects entering the study completed the Columbia Suicide Rating questionnaire and were not considered to have suicidal tendencies. Subjects maintained scores indicating that the study medication had no effect on the suicidal nature of the study subjects.

8 Postmarket Experience

The Applicant states that Methylphenidate ERCT is not approved or marketed anywhere in the world.

9 Appendices

9.1 Literature Review/References

The literature references supplied by the Applicant include general references describing ADHD, the scales used to diagnose ADHD, the classroom trial, the PK of methylphenidate and the treatment of ADHD.

9.2 Labeling Recommendations

Currently, the Division and the Applicant are negotiating language for labeling.

The Applicant has provided a review of Pfizer's pharmacovigilance database and the published literature to support text for Section 8.1 to 8.3 of the USPI in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). The Division of Pediatric and Maternal Health is currently reviewing this submission.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this 505(b)(2) application.

9.4 Study -1005 Schedule of Events

Study Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET
Visit Name	SCR	BL	OL Wk 1	OL Wk 2	OL Wk 3	OL Wk 4	OL Wk 5	OL LD 1stCR	DB LD 2ndCR	FU Contact	
Study Day / Assessment	-42 to -1	1	8 ±2d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	7d post V8	7-14d post V9	
Parent/guardian IC	X										
Subject assent	X										
Eligibility assessment	X	X									
Previous med. history	X	X									
Medical history	X	X									
Demographics	X										
DSM-IV diagnosis	X										
K-SADS	X										
ADHD-RS	X	X	X	X	X	X	X	X			
CPRS	X	X	X	X	X	X	X	X			
Cognitive functioning	X[a]										
CGI-S	X	X	X	X	X	X	X	X			
CGI-I			X	X	X	X	X	X			
Vital signs	X[b]	X	X	X	X	X	X	X	X	X[c]	X[c]
12-lead ECG	X									X[c]	X[c]
Stand. math. pre-test	X										
Physical examination	X									X[c]	X[c]
Height/weight[d]	X	X								X[c]	X[c]
Hematology	X	X[e]								X[c]	X[c]
Serum chemistry	X	X[e]								X[c]	X[c]
Pregnancy[f]	X	X[g]							X[g]	X[c]	X[g]
Drugs of abuse test	X	X[e]									
C-SSRS (BL)		X									
C-SSRS (FU)			X	X	X	X	X	X	X		X
PERMP								X[h]	X[i]		
SKAMP								X[h]	X[i]		
IWRS visit entry		X	X	X	X	X	X	X			X
Dispense OL NWP09		X	X	X	X	X	X				
Dose titration allowed			X	X	X	X	X				
Last OL dose								CR[j]			
Randomization								X			
Dispense DB drug								X			
Last DB dose									CR[h]		
Drug accountability			X	X	X	X	X	X	X		X
Adverse events query		X	X	X	X	X	X	X	X	X	X
Con. med. query		X	X	X	X	X	X	X	X	X	X

ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; BL = Baseline; CGI-I = Clinical Global Impression of Improvement; CGI-S= Clinical Global Impression of Severity; con. = concomitant; CPRS = Conners' Parent Rating Scale; CR = classroom visit; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; ECG = electrocardiogram; FU = follow-up; IC = informed consent; IWRS = interactive web response system; K-SADS = Schedule for Affective Disorders and Schizophrenia for School Age Children; LD = last dose, math. = mathematics; med. = medication; OL = open-label; PERMP = Permanent Product Measure of Performance; SCR = Screening; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale; stand. = standard

a. When cognitive functioning level was not clear by clinical signs and symptoms, a Wechsler Abbreviated Scale of Intelligence could be administered to estimate intelligence quotient.
b. At Screening, vital signs included respiratory rate and temperature.
c. For subjects who terminated early or at Visit 10 (follow-up contact), these activities were optional per investigator judgment.
d. Height measurement was required only at Screening.
e. If the Baseline visit was within 28 days of the Screening visit laboratory tests, laboratory tests were not required at Baseline.
f. Females of childbearing potential only.
g. Urine dipstick pregnancy test was performed at Visit 2 (Baseline) and Visit 9 (last study visit or early termination.
h. Assessments occurred pre-dose and 0.75, 2, and 4 hours post-dose.
i. Assessments occurred pre-dose and 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose.
j. Dosed in clinic.

9.5 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 207960

Submission Date(s): 02/04/2015

Applicant: Pfizer Inc.

Product: Methylphenidate Extended-Release Chewable Tablet

Reviewer: Christina P. Burkhart, M.D.

Date of Review: 08/07/2015

Covered Clinical Study (Name and/or Number): B7491002
B7491003
B7491004
B7491005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 53		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 (speaker honoraria and consulting fees) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ NA	No ☐ (Request explanation from applicant)

All investigators were assessed for equity interest, significant payments of other sorts, other compensation by the sponsor and propriety interest. All significant payments of other sorts were checked via internal Pfizer procedures. One (1) of the 53 investigators listed in the study report had financial information to disclose, which represents 1.9% of the total number of all investigators who participated in the study.

Dr [redacted] (b) (6) was the only investigator with disclosable financial interests/arrangements (as defined in 21 CFR 54.2(a), (b), (c) and (f)). [redacted] (b) (6) received significant payment from the sponsor for consultation/honoraria as detailed below in the sponsor's table:

DISCLOSURE TYPE: SIGNIFICANT PAYMENTS OF OTHER SORTS				
Investigator Name: (b) (6)				
Protocol Number:				
Clinical Investigator or Related Entity	Check Number	Purpose	Payment Date	Amount [USD]
(b) (6)	PAID	HCP CONSULTING (902)	(b) (6)	$1,505.00
	PAID	HCP CONSULTING (902)		$4,300.00
	(b) (6)	HCP CONSULTING (902)		$3,126.00
	PAID	NSB REP SPEAKER HONORARIUM (902)		$2,800.00
	PAID	NSB REP SPEAKER HONORARIUM (902)		$2,800.00
	PAID	HCP CONSULTING (902)		$4,300.00
	PAID	HCP CONSULTING (902)		$3,126.00
	PAID	HCP CONSULTING (902)		$3,126.00
	PAID	HCP CONSULTING (902)		$4,300.00
	PAID	NSB REP SPEAKER HONORARIUM (902)		$2,050.00
Payment exceeds threshold amount of $24,999.00			Total:	$31,433.00

The sponsor states that processes used to minimize the potential for bias included the following:

- Study was conducted at multiple sites.
- Frequent monitoring of investigator trial sites as defined in the clinical monitoring plan
- Validity of the data collected during the study was confirmed by standard monitoring procedures as outlined in the clinical monitoring plan.
- During the course of processing data for this trial, and as defined in the Data Management Plan, cleaning checks (e.g., querying data though electronic edit checks) were utilized to ensure that errors were identified and corrected.
- Appropriate statistical methods were pre-specified and employed with an approved statistical analysis plan.
- The study team remained blinded to randomized treatment assignment until after the database was locked.
- The study report was appropriately reviewed by members of the project team prior to issue and underwent review by Quality Control.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. The disclosed financial interests/arrangements do not affect the approvability of the application.

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

/s/

CHRISTINA P BURKHART
10/21/2015

LUCAS P KEMPF
11/06/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA: NDA 207960 **Applicant:** Pfizer Inc. **Stamp Date:** 2/4/2015

Drug Name: Methylphenidate Hydrochloride Extended-Release Chewable Tablets 20 mg, 30 mg, and 40 mg **NDA Type:** Standard; 505(b)2

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			Labeling is submitted. Draft Container labels are included in Module 1.14.1.1.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	From Pre-NDA meeting minutes: NDA will provide a Summary of Clinical Safety (SCS), Summary of Clinical Efficacy (SCE) and a Clinical Overview (CO) for the pivotal studies with no ISS or ISE.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	See response to #9
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?	x			Methylin Chewable Tablets (NDA 21-475)
14.	Did the applicant provide a scientific bridge demonstrating	x			

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	the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)	BA			Study 1004 was a randomized, three-way crossover, single dose, relative bioavailability study comparing MPH ERCT 40mg under fed and fasted conditions and Methylin IR (2 doses of 20mg 6 hours apart) under fasted conditions in 33 healthy, non-smoking, males and females (ages 18-55). The analysis of PK data included partial AUCs up to 4 hours post-dose.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1**: **Study 1004** was a randomized, three-way crossover, single dose, relative bioavailability study comparing MPH ERCT 40mg under fed and fasted conditions and Methylin IR (2 doses of 20mg 6 hours apart) under fasted conditions in 33 healthy, non-smoking, males and females (ages 18- 55). The analysis of PK data included partial AUCs up to 4 hours post-dose. Indication: BA Study in healthy adults **Pivotal Study #2** **Study 1005**: A Multicenter, Dose-optimized, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of NWP09 in Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom Indication: ADHD	x			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the	x			

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	extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Pivotal efficacy study had only US sites (6). BA study had 1 site in Canada.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	Study 1004: ECGs were recorded prior to drug administration and at 4, 12 and 24 hours (±30 minutes) post-dose. Study 1005: ECGs were only performed at screening in the pivotal efficacy trial. This 505 (b)(2) submission relies on the safety data of the approved RLD.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	The Sponsor intends to request a waiver of the 4-month Safety Update Report, given that the safety profile of methylphenidate has been well-established and there are no ongoing clinical studies with methylphenidate ERCT.
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	505 (b) (2) submission relying on safety data from RLD
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			Study 1005: Version 15.0 of the MedDRA coding dictionary
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Applicant has submitted narratives for adverse dropouts. There were no deaths or SAEs in the pivotal efficacy trial.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Pfizer has requested a **waiver** of the requirement to assess the safety and effectiveness of methylphenidate HCl extended-release chewable tablets in the pediatric population < 4 years and a **deferral** for studies in the pediatric population age group 4 to 5 years.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	As discussed at the 2 October 2014 pre-NDA meeting, a summary of abuse potential is not required for this NDA as it was not required for the Quillivant XR oral suspension NDA approval. The sponsor plans to use labeling, including the use of a Medication Guide, to mitigate abuse and

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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					dependence.
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			Case Report Forms are included in the study report folder for all subjects in study B7491004, including the two that discontinued due to adverse events. Case Report Forms for two subjects that terminated study B7491005 due to adverse events are provided within the study report folder for B7491005.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time

Christina Burkhart, M.D.	3/23/2015
Reviewing Medical Officer	Date
Lucas Kempf, M.D.	
Clinical Team Leader	Date

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

/s/

CHRISTINA P BURKHART
03/23/2015

LUCAS P KEMPF
03/24/2015
I concur