CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205831Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Submission Type	NDA
Application Number(s)	0205831
Submit Date(s)	06/18/2014
Received Date(s)	06/18/2014
PDUFA Goal Date	04/18/2015
Division / Office	Division of Psychiatry Products Office of New Drugs 1
Reviewer Name(s)	Cara Alfaro, Pharm.D.
Review Completion Date	03/17/2015
Established Name	Methylphenidate hydrochloride
Proposed Trade Name	Aptensio XR
Therapeutic Class	CNS stimulant
Applicant	Rhodes Pharmaceuticals L.P.

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 7

1.1 Recommendation on Regulatory Action 7
1.2 Risk Benefit Assessment 7
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 7
1.4 Recommendations for Postmarket Requirements and Commitments 7

2 INTRODUCTION AND REGULATORY BACKGROUND 8

2.1 Product Information 8
2.2 Currently Available Treatments for Proposed Indications 8
2.3 Availability of Proposed Active Ingredient in the United States 8
2.4 Important Safety Issues with Consideration to Related Drugs 8
2.5 Summary of Presubmission Regulatory Activity Related to Submission 9
2.6 Other Relevant Background Information 9

3 ETHICS AND GOOD CLINICAL PRACTICES 10

3.1 Submission Quality and Integrity 10
3.2 Compliance with Good Clinical Practices 10
3.3 Financial Disclosures 10

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 11

4.1 Chemistry Manufacturing and Controls 11
4.2 Clinical Microbiology 11
4.3 Preclinical Pharmacology/Toxicology 11
4.4 Clinical Pharmacology 11

5 SOURCES OF CLINICAL DATA 12

5.1 Tables of Studies/Clinical Trials 12
5.2 Review Strategy 14
5.3 Discussion of Individual Studies/Clinical Trials 14

6 REVIEW OF EFFICACY 15

6.1 Indication – Treatment of Attention Deficit Hyperactivity Disorder (ADHD) 16
6.1.1 Methods/Study Design/Analysis Plan 16
6.1.2 Results 19
6.1.3 Other Endpoints 26
6.1.4 Subpopulations 26
6.1.5 Analysis of Clinical Information Relevant to Dosing Recommendations 26
6.1.6 Discussion of Persistence of Efficacy and/or Tolerance Effects 27
6.1.7 Additional Efficacy Issues/Analyses 27
6.2 Indication – Treatment of Attention Deficit Hyperactivity Disorder (ADHD) 27
6.2.1 Methods/Study Design/Analysis Plan 28

6.2.2 Results 30
6.2.3 Other Endpoints 36
6.2.4 Subpopulations 36
6.2.5 Analysis of Clinical Information Relevant to Dosing Recommendations 37
6.2.6 Discussion of Persistence of Efficacy and/or Tolerance Effects 39
6.2.7 Additional Efficacy Issues/Analyses 39

7 REVIEW OF SAFETY 40

7.1 Methods 41
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 41
7.1.2 Categorization of Adverse Events 41
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 41
7.2 Adequacy of Safety Assessments 42
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 42
7.2.2 Explorations for Dose Response 43
7.2.3 Special Animal and/or In Vitro Testing 43
7.2.4 Routine Clinical Testing 43
7.2.5 Metabolic, Clearance, and Interaction Workup 43
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 43
7.3 Major Safety Results 44
7.3.1 Deaths 44
7.3.2 Nonfatal Serious Adverse Events 44
7.3.3 Dropouts and/or Discontinuations 45
7.3.4 Significant Adverse Events 45
7.3.5 Submission Specific Primary Safety Concerns 45
7.4 Supportive Safety Results 46
7.4.1 Common Adverse Events 46
7.4.2 Laboratory Findings 47
7.4.3 Vital Signs/Physical Examination 48
7.4.4 Electrocardiograms (ECGs) 49
7.4.5 Special Safety Studies/Clinical Trials 51
7.4.6 Immunogenicity 52
7.4.7 Suicidal Thoughts and Behaviors 52
7.5 Other Safety Explorations 53
7.5.1 Dose Dependency for Adverse Events 53
7.5.2 Time Dependency for Adverse Events 53
7.5.3 Drug-Demographic Interactions 54
7.5.4 Drug-Disease Interactions 54
7.5.5 Drug-Drug Interactions 54
7.6 Additional Safety Evaluations 54
7.6.1 Human Carcinogenicity 54
7.6.2 Human Reproduction and Pregnancy Data 54

7.6.3 Pediatrics 55
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 56
7.7 Additional Submissions / Safety Issues 56

8 POSTMARKET EXPERIENCE 56

9 APPENDICES 57

9.1 Literature Review/References 57
9.2 Labeling Recommendations 57
9.3 Advisory Committee Meeting 57
9.4 Inclusion and Exclusion Criteria for RP-BP-EF001 and RP-BP-EF002 58
9.5 Schedule of Events for RP-BP-EF001 60
9.4 Schedule of Events for RP-BP-EF002 62

Tables

Table 1 Pivotal Clinical Trials for Efficacy……12
Table 2 Pivotal Clinical Trials for Pharmacokinetics……13
Table 3 Supportive Clinical Trials…… 13
Table 4 Subject Demographics [RP-BP-EF001]…… 20
Table 5 Baseline Disease Characteristics [RP-BP-EF001]…… 21
Table 6 LS Mean SKAMP Total Score Averaged Over all Postdose Timepoints [RP-BP-EF001]……23
Table 7 LS Mean SKAMP Total Scores at Each Timepoint [RP-BP-EF001]…… 24
Table 8 LS Mean ADHD-RS-IV Total and Subscale Scores [RP-BP-EF001]….. 26
Table 9 Subject Demographics [RP-BP-EF002]…… 31
Table 10 Baseline Disease Characteristics [RP-BP-EF002]…… 32
Table 11 Subject Disposition [RP-BP-EF002]…….. 32
Table 12 ADHD-RS-IV Total Score Mean Change from Baseline [RP-BP-EF002]……34
Table 13 ADHD-RS-IV Subscale Scores, Mean Change from Baseline [RP-BP-EF002]……35
Table 14 LS Mean CGI-I Score [BP-EF-002]…… 36
Table 15 ADHD-RS-IV Total Score, Gender Subgroups…… 37
Table 16 Methylphenidate ER Exposure…….. 42
Table 17 Extent of Methylphenidate ER Exposure by Days…….. 43
Table 18 Serious Adverse Events [RP-BP-EF002]…… 45
Table 19 Adverse Events in ≥ 2 Subjects in Double-Blind Phase [RP-BP-EF002]…….. 46
Table 20 Vital Signs: Mean Change from Baseline [RP-BP-EF001]……48
Table 21 Vital Signs: Mean Change from Baseline [RP-BP-EF002]……49
Table 22 ECG Parameters: Mean Change from Baseline [RP-BP-EF001]…… 50
Table 23 ECG Parameters: Mean Change from Baseline [RP-BP-EF002]…… 50
Table 24 Subjects with QTc ≥ 450 msec [RP-BP-EF002]…… 51

Figures

Figure 1 Mean SKAMP Total Scores at Each Timpoint [RP-BP-EF001]……24

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval for this 505(b)(2) NDA application for Aptensio XR for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (b) (4) (6 to (b) (4)). The sponsor submitted two pivotal clinical trials that supported the efficacy and safety of Aptensio XR administered in doses up to 60 mg/day in children (b) (4) with ADHD. (b) (4)

1.2 Risk Benefit Assessment

Methylphenidate ER was shown to be effective for the treatment of ADHD in children and adolescents 6 to (b) (4) . The adverse event profile of methylphenidate ER is similar to other methylphenidate products with no new safety findings noted.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a Postmarket Risk Evaluation and Mitigation Strategy at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on discussions between DPP and PeRC, a pharmacokinetic and an efficacy and safety study should be conducted in children 4 to less than 6 years of age with ADHD. Additionally, a long-term safety study should be conducted to evaluate longer term safety of this product in this age cohort.

There is increasing evidence that ADHD medications are used in a substantial number of 4 and 5 year olds. DPP believes that it is important to study these younger children because we know the drugs are being prescribed to them.

2 Introduction and Regulatory Background

2.1 Product Information

The Sponsor has developed methylphenidate hydrochloride extended-release (ER) capsule formulation intended as a single daily dose for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This extended-release formulation provides a biphasic plasma profile, similar to other extended-release methylphenidate products. This NDA was submitted as a 505(b)(2) with the Reference Listed Drug designated as Ritalin and Ritalin SR. Under the trade name Biphentin, methylphenidate ER capsules were approved by Health Canada in March 2006.

The ratio of immediate release methylphenidate to controlled release methylphenidate in the methylphenidate hydrochloride ER capsules is 40%/60%. Methylphenidate ER capsules are a single, multilayer controlled-release beads comprising approximately 40% immediate release and 60% controlled release layers of methylphenidate which are filled into capsules. The controlled-release layers are comprised of a (b) (4) coating that provide controlled release of the drug substance.

The Sponsor is proposing (b) (4) capsule strengths: 10, 15, 20, 30, 40, 50, 60 (b) (4)

2.2 Currently Available Treatments for Proposed Indications

There are currently a number of available treatments for ADHD. These include methylphenidate immediate release and extended-release dosage formulations (Ritalin, Ritalin SR, Ritalin LA, Concerta, Metadate CD, and various generics), methylphenidate transdermal patch (Daytrana), atomoxetine (Strattera), mixed amphetamine salts (Adderall, Adderall XR), dextroamphetamine (Dexedrine), dexmethylphenidate (Focalin, Focalin XR), guanfacine (Tenex), and lisdexamfetamine (Vyvanse).

The ratio of immediate release methylphenidate to controlled release methylphenidate for Concerta is 22%/(b) (4), for Metadate CD is 30%/70% and for Ritalin LA is (b) (4).

2.3 Availability of Proposed Active Ingredient in the United States

Methylphenidate is an approved drug in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

In product labeling for the methylphenidate products, the following adverse events/clinical issues are listed in the Warnings and Precautions section: potential for abuse and dependence, serious cardiovascular reactions (e.g. sudden death, stroke,

MI), blood pressure and heart rate increases, psychiatric adverse reactions (e.g. exacerbation of pre-existing psychosis, induction of a manic episode in patients with bipolar disorder, new psychotic or manic symptoms), suppression of growth, priapism and peripheral vasculopathy (including Raynaud's Phenomenon).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

5/19/2009 - Pre-IND meeting. The sponsor was interested in filing a 505(b)(2) NDA for methylphenidate ER with clinical data that supported the approval of this product by Health Canada (approved 3/2006, trade name Biphentin). The Sponsor had obtained the rights to incorporate all data for the new drug filing in the US as well as access to the data sources. DPP stated that additional pharmacokinetic and efficacy/safety studies would likely be needed. None of the clinical studies that supported approval of Biphentin included an evaluation of dose response and outcome measures were not the standard instruments used in most US studies. Pharmacology reminded the sponsor that if clinical systemic exposures to the parent drug and/or metabolites are significantly higher than those for the approved reference listed drug (RLD) for this 505(b)(2) submission, additional nonclinical studies may be needed.

2/3/2010 - IND 104,624 Submitted.

3/5/2010 - May Proceed Letter sent to sponsor with CMC, OCP and Clinical comments

2/11/2013 - Pre NDA Meeting. Preliminary comments were provided to the sponsor and the meeting was canceled. (b) (4) DPP stated that it was unlikely that the recommended daily dose could exceed 60 mg. The maximum daily dose for methylphenidate products in the US is 60 mg for children, adolescents, and adults (except for Concerta). In the Biphentin Product Monograph, the maximum recommended daily dose for children and adolescents is 60 mg. (b) (4)

(b) (4)

2.6 Other Relevant Background Information

No other relevant background information was identified.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the course of this review, no significant issues or concerns were noted with respect to data quality or integrity.

The Office of Scientific Investigations was consulted to inspect clinical sites for RP-BP-001 and RP-BP-002. The following clinical sites were inspected in October through December 2014: S. Wigal, Ph.D., Irvine CA; A. Childress, M.D., Las Vegas, NV; and G. Gunsten, New Bern, NC. RP-BP-001 was conducted at a single site (Wigal), this site also enrolled subjects into RP-BP-002. The other sites for RP-BP-002 were chosen primarily based on the large numbers of subjects enrolled at those sites.

For all sites, no significant deficiencies were observed and a Form FDA 483 was not issued. The data from the sites appeared reliable as reported in the NDA. The final inspection outcome classification was pending at the time this clinical review was completed.

3.2 Compliance with Good Clinical Practices

The sponsor indicated that the clinical studies were performed in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) Guideline for GCP, Declaration of Helsinki and the United States Code of Federal Regulations (21 CFR 50, 21 CFR 56).

3.3 Financial Disclosures

The sponsor submitted Form FDA 3454 indicating: "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators…whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The sponsor also provided a financial certification statement indicating that "in accordance with 21 CFR 54.4, no financial interests or arrangements existed for any of the clinical investigators, sub-investigators, their spouses, or dependent children at the time the clinical trials were conducted in support of this application".

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review was conducted by R. Kambhampati. Facilities were inspected with no significant deficiencies noted. Refer to CMC review for a comprehensive analysis.

4.2 Clinical Microbiology

No clinical microbiology studies were submitted.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology studies were submitted. In this 505(b)(2) submission, the sponsor relied on data for the reference listed drug, Ritalin and Ritalin SR for preclinical data.

4.4 Clinical Pharmacology

The clinical pharmacology review was conducted by A. Jackson. Refer to the clinical pharmacology review for a comprehensive analysis.

The two pivotal pharmacokinetic studies (RP-BP-PK001, RP-BP-PK002) were conducted with an 80 mg methylphenidate ER capsule and the reference listed drug, Ritalin immediate release (IR), 25 mg TID in healthy adults. A number of supportive pharmacokinetic studies were also included in the submission, most conducted in Canada to support the initial approval of methylphenidate ER (Biphentin) by Health Canada (approved in 2006).

The clinical pharmacology reviewer noted that study RP-BP-PK001 showed that the 80 mg capsule of methylphenidate ER was bioequivalent to Ritalin (IR) under fasting conditions when administered as sprinkles with a teaspoon of applesauce for extent of exposure but not for peak exposure. Study RP-BP-PK002 showed that the relative bioavailability for methylphenidate ER following a single dose and multiple dosing in the fed state were not bioequivalent for Cmax.

(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This submission contains two pivotal efficacy trials, two pivotal pharmacokinetic (bioavailability/bioequivalency) trials and a number of supportive trials. Most of the supportive trials were conducted by Purdue Pharma, the manufacturer of Biphentin which is the methylphenidate multilayer controlled release product approved and marketed in Canada.

The two pivotal trials for safety and efficacy are:
RP-BP-EF001 "A randomized, double-blind study of the time course of response to [Biphentin] methylphenidate hydrochloride extended-release capsules as compared to placebo in children 6 to 12 years with Attention Deficit Hyperactivity Disorder (ADHD) in an analog classroom setting" (note, the approved trade name is Aptensio XR and not Biphentin)

RP-BP-EF002 "A randomized, parallel, double-blind efficacy and safety study of [Biphentin] methylphenidate hydrochloride extended release capsules compared to placebo in children and adolescents 6 to 18 years with Attention Deficit Hyperactivity Disorder" (note, the approved trade name is Aptensio XR and not Biphentin)

Table 1. Pivotal Clinical Trials for Efficacy

Clinical Trial	Subjects	Design*	Treatment Groups, Sample Size	Duration
RP-BP-EF001 1 Center, US	Children with ADHD (6 to 12 years)	Open-label titration followed by R, DB, PC crossover trial	Open label MPH ER titration: n = 26 DB phase MPH ER/placebo: n = 22	Titration – up to 4 weeks DB – 1 week Safety follow-up: 30 days Open label extension: up to 21 months
RP-BP-EF002 16 Centers in US	Children and Adolescents with ADHD (6 to 17 years)	R, DB, PC, parallel group	DB phase: n = 221 MPH ER 10 mg/d MPH ER 15 mg/d MPH ER 20 mg/d MPH ER 40 mg/d Placebo	DB phase: 1 week OL titration/follow-up: 11 week Open label extension: up to 21 months

*R = randomized, DB = double-blind, PC = placebo-controlled,

Table 2. Pivotal Clinical Trials for Pharmacokinetics

Clinical Trial	Subjects	Design*	Treatment Groups, Sample Size	Duration
RP-BP-PK001 1 Center in US	Healthy adults	Single dose PK, crossover bioavailability study	Single 80 mg dose MPH ER capsule, single 80 mg dose MPH ER capsule dosed as sprinkles, Ritalin IR 25 mg TID N = 26	1-day x 3 treatments
RP-BP-PK002 1 Center in US	Healthy adults	Steady-state PK, crossover bioavailability study	MPH ER 80 mg Ritalin IR 25 mg TID N = 26	4-day treatment period each

*R = randomized, DB = double-blind, PC = placebo-controlled,

Table 3. Supportive Clinical Trials (Efficacy and Pharmacokinetics)

Clinical Trial	Subjects	Design*	Treatment Groups, Sample Size	Duration
022-004 Multicenter, Canada	Children and Adolescents with ADHD (6 to 17 years)	R, DB, cross-over	Open label MPH ER titration DB phase MPH ER/ Ritalin IR BID N = 90	Titration up to 3 weeks DB: 2 weeks each
022-005 1 Center, Canada	Children and Adolescents with ADHD (6 to 15 years)	R, DB, PC, cross-over	MPH ER weight based Ritalin IR weight based Placebo N = 18	DB: 1 week each
022-008 Multicenter in Canada	Adults with ADHD	R, DB, PC crossover	MPH ER weight based Placebo N = 50	Titration 3 weeks DB: 2 weeks each
022-001 1 Center, Canada	Healthy adults	Single dose PK, fed and fasted	4-way crossover MPH ER 20 mg Ritalin IR 20 mg N = 12	1-day x 4 treatments
022-006 1 Center, Canada	Healthy adults	Single dose PK, fed and fasted	4-way crossover MPH ER 20 mg Ritalin IR 20 mg N = 24	1-day x 4 treatments

Table 3 (cont.) Supportive Clinical Trials (Efficacy and Pharmacokinetics)

Clinical Trial	Subjects	Design*	Treatment Groups, Sample Size	Duration
022-010 1 Center, Canada	Healthy adults	Single dose PK	R, 2-way crossover 2 different production batches MPH ER 20 mg N = 24	1-day x 2 treatments
022-011 1 Center, Canada	Children (6-12 years) with ADHD	Single dose PK	R, 2-way crossover MPH ER Ritalin IR N = 18	1-day x 2 treatments
022-013 1 Center, Canada	Healthy adults	Single dose PK	R, 2-way crossover MPH ER 20 mg Concerta 18 mg N = 24	1-day x 2 treatments

*R = randomized, DB = double-blind, PC = placebo-controlled,

5.2 Review Strategy

Material reviewed included the clinical study reports for the pivotal safety/efficacy studies, RP-BP-EF001 and RP-BP-EF002, case report forms, data listings and clinical trial datasets (JMP). The pivotal PK trials (RP-BP-PK001, RP-BP-PK002) and supportive studies (both PK and safety/efficacy) were reviewed for serious adverse events and discontinuations due to adverse events. The sponsor submitted clinical study reports for the supportive studies but did not perform any data analyses. The supportive studies were conducted by Purdue Pharma in Canada to support approval of methylphenidate ER (Biphentin) by Health Canada (approved 2006).

5.3 Discussion of Individual Studies/Clinical Trials

Two pivotal trials were submitted to support the safety and efficacy of methylphenidate ER for the treatment of ADHD in children and adolescents. These studies are described in detail in Section 6 of the review. The following is a brief description:

RP-BP-EF001 was a double-blind, randomized, placebo-controlled, cross-over study in 26 children (6 to 12 years of age) with ADHD. The double-blind phase included 1 week of treatment with methylphenidate ER and 1 week treatment with placebo (cross-over). The primary endpoint was the average of the SKAMP Total Score (timepoints up to 12 hours post-dose) comparing methylphenidate ER and placebo.

RP-BP-EF002 was a double-blind, randomized, placebo-controlled, parallel group, fixed-dose study in 221 children and adolescents (6 to 17 years of age) with ADHD. Subjects were randomized to methylphenidate ER 10 mg, 15 mg, 20 mg, 40 mg or

placebo administered for one week. The primary endpoint was the mean change from baseline in ADHD-RS-IV total score, methylphenidate ER vs. placebo (and comparisons of each methylphenidate dose to placebo).

6 Review of Efficacy

The sponsor submitted two clinical trials to support the efficacy and safety of methylphenidate ER for the treatment of ADHD in children and adolescents, 6 to 17 years of age. Study RP-BP-EF001 was a randomized, double-blind, cross-over study in 26 children (6 to 12 years) with ADHD. In this clinical trial, subjects received methylphenidate ER open-label for 2-4 weeks to determine the "optimal" dose. A two-week double-blind phase followed in which subjects received one week of methylphenidate ER (the dose from the open-label phase) or placebo and then received the opposite treatment for another week. At the end of each week of treatment, the SKAMP rating scale was administered at multiple timepoints (up to 12 hours postdose) in an analog classroom setting. Statistically significant differences favoring methylphenidate ER were demonstrated for the primary efficacy endpoint, the SKAMP Total score averaged over all postdose timepoints ($p = 0.0001$). Statistically significant differences favoring methylphenidate ER were demonstrated for the key secondary endpoint, duration of efficacy as measured by the SKAMP Total scores at each timepoint.

Study RP-BP-EF002 was a randomized, double-blind, fixed-dose, parallel study in 230 children and adolescents (6 to 17 years) with ADHD. Subjects were randomized to one of 4 fixed doses of methylphenidate ER (10, 15, 20 or 40 mg/day) or placebo for one week. Statistically significant differences favoring methylphenidate ER were demonstrated on the primary efficacy endpoint, mean change from baseline on the ADHD-RS-IV Total score ($p = 0.0046$). Each methylphenidate ER dose was compared to placebo on the primary efficacy endpoint. Statistically significant differences favoring methylphenidate ER were demonstrated for the 20 mg dose ($p = 0.0145$) and 40 mg dose ($p = 0.0011$) only. This study also included an 11-week open-label phase in which subjects could receive methylphenidate ER up to 60 mg/day.

These two clinical trials support the efficacy of methylphenidate ER in the treatment of ADHD in children and adolescents, 6 to 17 years of age.

6.1 Indication – Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Clinical trial RP-BP-EF001 "A randomized, double-blind study of the time course of response to [(b) (4) Aptensio XR] methylphenidate hydrochloride extended-release capsules as compared to placebo in children 6 to 12 years with Attention Deficit Hyperactivity Disorder in an analog classroom setting"

This was a single site study conducted at the Child Development Center at the University of California at Irvine. Principal investigator was Sharon B. Wigal, Ph.D.

6.1.1 Methods/Study Design/Analysis Plan

Primary Objective
To assess the time of onset and time course of efficacy over 12 hours of methylphenidate ER compared to placebo in a laboratory school setting as measured by the Swanson, Kotkin, Agler, M-Flynn, Pelham Rating Scale (SKAMP) rating scale.

Primary Efficacy Endpoint: The average of the SKAMP Total Score (timepoints: 1, 2, 3, 4.5, 6, 7.5, 9, 10.5, 12 hours) during the double-blind phase comparing methylphenidate ER and placebo.

Key Secondary Endpoint*: The duration of efficacy between methylphenidate ER and placebo using the SKAMP total score at each postdose timepoint

*For this reviewer, there was some confusion regarding what the agreed key secondary endpoint was for this study (this reviewer was not assigned to the IND when these discussions/amendments would have occurred). In some versions of the protocol and even in the introduction in the current clinical study report, the key secondary endpoint is noted as the onset and time course of the efficacy of methylphenidate ER compared to placebo in the laboratory setting as measured by the age-adjusted math test, the Permanent Product Measure of Performance (PERMP). In other places, it is noted as the duration of efficacy between methylphenidate ER and placebo using the SKAMP total score at each postdose timepoint. A discussion regarding the definition of duration of effect occurred during the preNDA meeting with comments about testing sequence of timepoints and the SKAMP-Total score. Therefore, it appears that there was discussed with DPP. The statistician (J. Zhong) confirmed that the Statistical Analysis Plan stated that the key secondary endpoint evaluated duration of efficacy using the SKAMP, not the PERMP.

Other Secondary Objectives
To evaluate the efficacy (ADHD Rating Scale – 4th Edition, PERMP), safety, tolerability, and quality of life in subjects receiving methylphenidate ER compared to placebo.

Methods/Study Design

This was a randomized, double-blind, placebo-controlled, crossover outpatient study conducted at a single site in a laboratory school setting in children (6 to 12 years of age) with ADHD. The study included 5 phases: a Screening/Washout phase, an Open-Label Dose Optimization phase, a Double-Blind phase, a Safety Follow-Up phase and an open-label extension phase (the sponsor referred to this last phase as the Compassionate-Use phase)

Screening/Washout Phase: Screening assessments, minimum 48 hour washout of prior stimulant medications (Visit 1). Parents received medication washout instructions by telephone.

Open-Label Dose Optimization Phase: After baseline assessments (Visit 2), subjects were given methylphenidate ER 15 mg and instructed to take the first dose the following morning. Subjects continued morning dosing with "incremental" adjustments approximately every 7 days until an optimal, individualized dose was achieved (15, 20, 30, or 40 mg/day) – optimization was to be completed in a 2 to 4 week period (Visits 3, 4, 5). Subjects were evaluated at each visit (adverse events, ADHD-RS-IV, Clinical Global Impression-Improvement [CGI-I]). Subjects weighing ≤ 25 kg could not receive the highest dose (40 mg) of methylphenidate ER.

Double-Blind Phase: Subjects were assigned to 1 of 2 treatment sequence groups – methylphenidate ER:placebo or placebo: methylphenidate ER. The double-blind phase comprised a practice classroom session (Visit 6) and 2 double-blind periods (Visit 7, Visit 8). During Visit 6 (Saturday), subjects attended a half-day practice laboratory school day to familiarize themselves with other study participants and study staff and to participate in an abbreviated study day schedule with classroom procedures. Subjects received their "optimized" dose of methylphenidate ER or placebo with the first dose to be taken the following morning. Subjects continued daily morning dosing of methylphenidate ER or placebo and returned to the classroom the following Saturday (Visit 7) after receiving 7 daily doses of methylphenidate ER or placebo. Efficacy assessments were conducted at Visit 7. At the end of Visit 7, subjects were dispensed the alternate double-blind treatment (placebo or methylphenidate ER) with dosing to begin the following morning. The second classroom day was one week later (Visit 8) after receiving 7 daily doses of placebo or methylphenidate ER. For Visits 7and 8, subjects arrived at the classroom in the morning and study staff administered the double-blind study medication approximately 1.5 hours after arrival. Breakfast was provided after dosing.

Safety Follow-Up Phase: Approximately 30 days after the subject's last dose of study medication (Visit 8), study staff followed up with subjects by telephone (adverse events, concomitant medications).

Open-Label Extension Phase: At the clinician's discretion, subjects who had received clinical benefit from methylphenidate ER could receive open-label methylphenidate ER for up to 21 months following the end of the study (Visit 8). Study visits occurred every 1 to 2 months for 15 months and every 3 months thereafter.

Inclusion/exclusion criteria
Key inclusion and exclusion criteria are summarized in this section. A complete list of criteria are in Appendix 9.4.
Included in this study were generally healthy male or female subjects; 6 to 12 years of age with a DSM-IV-TR diagnosis of ADHD(supported by K-SADS-PL) including subtypes inattentive, hyperactive-impulsive or a combination; ADHD-RS-IV total or subscale scores $\geq$ 90th percentile relative to the general population of children by age and gender. Subjects must be in need of pharmacological treatment for ADHD. If subjects were currently receiving medications for ADHD, they still had symptoms of being "inadequately managed" (including lack of efficacy or tolerability). Females of child-bearing potential must have a negative serum pregnancy test and, if sexually active, be using an acceptable form of birth control (including abstinence). Subject's parent or legally authorized representative must have provided informed consent with assent obtained from the participating subject.

Excluded were subjects with an estimated full scale intellectual level < 80; other concurrent DSM-IV-TR Axis I diagnoses including severe anxiety disorder, conduct disorder, psychotic disorders, pervasive developmental disorder, obsessive-compulsive disorder, major depressive disorder, bipolar disorder, chronic tic disorder and personal or family history of Tourette's syndrome; chronic medical illnesses; clinically significant ECG or laboratory abnormalities; history of hypersensitivity to methylphenidate; well controlled on current treatment for ADHD or unable to take oral capsules.

Concomitant medications
Prohibited concomitant medications included any psychotropic medication including, but not limited to any stimulant, atomoxetine, SSRIs, clonidine, MAOIs, mood stabilizers, antipsychotics and sedative hypnotics. Sedative hypnotics were only allowed if the dose was stable prior to and during the clinical trial.

Assessments
For a complete list of assessments/procedures and frequency, refer to the Schedule of Events in Appendix 9.5.

Efficacy assessments included the following rating scales: SKAMP, Permanent Product Measure of Performance (PERMP) Math Test, ADHD-RS-IV, CGI-S, CGI-I, Pediatric

Quality of Life (PedsQL), Child Sleep Habits Questionnaire (CSHQ) parent and self-report, Weiss Functional Impairment Rating Scale (WFIRS) and the Daily Parental Rating of Evening and Morning Behavior (DPREMB-R).

Safety assessments included physical examination, ECG, vital signs (sitting), adverse events, routine laboratory tests. The C-SSRS was included for monitoring suicidal thoughts and behaviors.

Analysis Plan

Refer to the Biometrics review (J. Zhong) for a more comprehensive description of the statistical analysis plan for this study. A brief review of the statistical approach for the primary efficacy analysis only is included here.

This summary is taken from the CSR and was not independently evaluated by this reviewer (e.g. assumptions in sample size calculations, etc.).
The primary efficacy endpoint was the mean of the double-blind post-dose SKAMP Total score – mean total score over timepoints 1, 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours. The mean of the SKAMP Total scores for methylphenidate ER and placebo were to be compared using a mixed effects ANCOVA using the Evaluable population (see Results subsection in this section of the review). The model contained fixed class effects for treatment sequence and period; a random class effect for subject within sequence; and a covariate term, the SKAMP baseline Total score for the corresponding subject/treatment/period. An addendum to the Statistical Analysis Plan confirmed the sequential order of testing (as discussed in the preNDA meeting) and agreement to conduct a repeated measures analysis of SKAMP as part of the sensitivity analysis for the key secondary endpoint.

Sample size calculations were based on the primary efficacy endpoint of the average SKAMP Total scores across the classroom day timepoints in the double-blind phase. The sponsor assumed a treatment difference of 1.0 between methylphenidate ER and placebo and a standard deviation of the treatment difference of 1.6. It was calculated that if 12 subjects in each treatment sequence completed the double-blind crossover treatment period, the study should have 80% power to detect a treatment difference at a 2-sided significance level of 0.05. A target of 27 randomized subjects was estimated to be required, based on a potential dropout rate of 10%.

6.1.2 Results

Thirty-two subjects were screened and 26 of those entered the Open-Label Dose Optimization Phase. Four subjects discontinued during the Open-Label Phase (difficulty swallowing capsules, adverse event of sleep latency, lack of efficacy, noncompliance with blood draw). Twenty-two subjects entered and completed the Double-Blind Phase of the study.

Safety Population (N = 26) was defined as subjects who completed Visit 2 of the study and had taken at least one dose of study drug.

ITT Population (N = 22) was defined as subjects who took at least one dose of double-blind medication.

Evaluable Population (N = 20) was defined as subjects who completed SKAMP assessments for all the study timepoints on study days 35 and 42 and who received the scheduled treatment in both periods during the double-blind phase (see Protocol Violations).

Demographics

Demographics are provided in Table 4. Since this is a cross-over study, each subject served as their own control and the study was not imbalanced between treatments. The demographics were fairly representative of ADHD patients in the general community.

Table 4. Subject Demographics [RP-BP-EF-001]

	Safety Population N = 26
Age (years)	
Mean (SD)	8.7 ± 1.89
Median	9
Minimum	6
Maximum	12
Gender, n (%)	
Male	14 (54%)
Female	12 (46%)
Race, n (%)	
White	21 (81%)
Black/African American	3 (12%)
Asian	1 (4%)
Other	1 (4%)
Ethnic group, n (%)	
Hispanic or Latino	6 (23%)
Not Hispanic or Latino	20 (77%)
Weight (kg)	
Mean (SD)	33.7 ± 12.01
Median	31.6
Minimum	19.8
Maximum	70.8
Height (cm)	
Mean (SD)	135.9 ± 12.76
Median	136
Minimum	114.0
Maximum	159.5

Source: Tables 11-2 and 14.1.3 in CSR

Baseline Disease Characteristics

Since this is a cross-over study, each subject served as their own control and the study was not imbalanced between treatments with regard to baseline disease characteristics. The majority of subjects were diagnosed with the ADHD subtype combined or predominantly inattentive. Eleven subjects had received outpatient treatment for their psychiatric diagnosis. No subjects had previous psychiatric hospitalization and no subjects had received antipsychotics, antidepressants, sedatives or lithium. Six (23.1%) subjects had previously received stimulants and one had previously received atomoxetine.

Table 5. Baseline Disease Characteristics [RP-BP-EF001]

	Safety Population N = 26
ADHD Subtype, n (%)	
Combined	11 (42.3%)
Predominantly Hyperactive/Impulsive	3 (11.5%)
Predominantly Inattentive	12 (46.2%)
Concurrent Diagnoses, n (%)	
Oppositional defiant disorder	5 (19.2%)
Enuresis	2 (7.7%)
Chronic motor or vocal tic disorder	1 (3.8%)
Transient tic disorder	1 (3.8%)
Generalized anxiety disorder	1 (3.8%)
Baseline CGI-S, Mean (SD)	4.73 ± 0.45
Baseline ADHD-RS-IV, Mean (SD)	
Total Score	40.85 (6.35)
Inattention Score	22.46 (3.48)
Hyperactivity Score	18.38 (5.71)

Source: Tables 14.1.5.1, 14.1.6, 11-3

Subject Disposition

Thirty-two subjects were screened and 26 of those entered the Open-Label Dose Optimization Phase. Four subjects discontinued during the Open-Label Phase (difficulty swallowing capsules, adverse event of sleep latency, lack of efficacy, noncompliance with blood draw). Twenty-two subjects entered and completed the Double-Blind Phase of the study.

Concomitant Medication Use

No subjects used prohibited medications prior to or during the study. Two subjects were using stimulants at screening (mixed amphetamine salts [Adderall XR], lisdexamfetamine [Vyvanse]) that required a washout. Several subjects used concomitant medications permitted by protocol including acetaminophen and short courses of prescription/non-prescription medication for acute illnesses.

Protocol Violations

The Sponsor defined an Evaluable Population for the efficacy analyses. The Evaluable Population (N = 20) was the ITT Population (N =22) with the exclusion of two subjects. Subject 1-01-01-401 was excluded since he received placebo drug in both periods due to a packaging error. Subject 1-01-28-422 was excluded since he was absent from the Period 2 lab school session due to illness and no SKAMP assessments were performed.

Distribution of Drug Dose

For this study, subjects were titrated to an "optimal dose" during the open-label dose optimization phase which was continued in the double-blind cross-over phase. The most commonly used doses of methylphenidate ER were 30 mg (n = 11, 50%) and 20 mg (n = 9, 41%) [ITT Population]. One subject received 40 mg methylphenidate ER and 1 subject received 15 mg methylphenidate ER. Dose distribution was similar for the Evaluable Population, though no subjects received 15 mg methylphenidate ER.

Analysis of Primary Endpoint(s)

The primary efficacy analysis population was the ITT Population per protocol. In the CSR, the primary analysis population was defined as the Evaluable Population (analyses were performed on all populations). In the original protocol, the Evaluable Population was defined to include all subjects in the ITT population who have completed SKAMP assessments for all study time points on both study days. This definition was revised after the blind was broken (see Protocol Violations) and is now defined as subjects who completed SKAMP assessments for all the study time points on study days 35 and 42 *and* who received the scheduled treatment in both periods during the double-blind phase

The primary efficacy endpoint was the mean postdose SKAMP total score during each treatment in the double-blind phase. SKAMP assessments were completed at the following timepoints postdose: 1, 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours. For each subject/treatment/time point, SKAMP scores were calculated as the mean of items 1-13. Then for each subjects/treatment, the mean of these SKAMP total scores over postdose time points (hours 1 to 12) was calculated. ANCOVA was used for the primary analysis

with terms for treatment, period, sequence, subject within sequence and covariate). The covariate was the SKAMP total score at time 0.

The Sponsor also evaluated the data for 4 different ITT population variations as sensitivity analyses due to the issues identified in Protocol Violations. For ITT data sets version 1 and 2, Subject 1-01-01-401 are included as recorded and the assigned treatments are used (placebo Period 1, methylphenidate ER Period 2). For ITT data sets version 3 and 5, Subject 1-01-01-401 data are included and the actual treatments are used (placebo in both Periods).
Subject 1-01-28-422 received placebo in Period 1 and methylphenidate ER in Period 2 and had SKAMP data for Period 1, but not for Period 2. For ITT version 1 and 3, Period 1 data for this subject was duplicated for Period 2. For ITT data sets version 2 and 4, only Period 1 data were included in the data sets with this subject missing data in Period 2.

Regardless of the analysis population, the results were statistically significant favoring methylphenidate ER over placebo. The covariate was significant indicating that the predose score helps predict the postdose score. SKAMP total scores were not different for subjects who received treatment in sequence 1 (placebo then methylphenidate ER) compared to sequence 2 (methylphenidate ER then placebo).

Table 6. LS Mean SKAMP Total Score Averaged Over all Postdose Timepoints [RP-BP-EF001]

	LS Mean		P-Values			
	Placebo	Methylphenidate ER	Treatment	Covariate	Sequence	Period
Evaluable Population (N = 20)	2.18	1.32	0.0001	0.0003	0.5279	0.0714
ITT Version 1 (N = 22)	2.05	1.32	0.0005	0.0006	0.8824	0.2570
ITT Version 2 (N = 22)	2.06	1.33	0.0011	0.0005	0.8524	0.3168
ITT Version 3 (N = 22)	2.05	1.28	0.0002	0.0006	0.9955	0.1664
ITT Version 4	2.05	1.29	0.0004	0.0008	0.9966	0.1912

Source: Table 11-5 from CSR

Analysis of Key Secondary Endpoints(s)

The key secondary endpoint was the duration of efficacy between methylphenidate ER and placebo during the double-blind phase using the SKAMP total score at each postdose timepoint. The “time of onset of efficacy” was defined as the timepoint when the difference on the SKAMP total score between methylphenidate ER and placebo first

became statistically significant. The "last time of efficacy" was defined as the last timepoint when the difference on the SKAMP total score between methylphenidate ER and placebo was statistically significant and all previous timepoints after onset were also statistically significant. The duration of efficacy was defined as the length of time after the time of onset when the difference between methylphenidate ER and placebo continued to be statistically significant (Evaluable Population).
Statistically significant differences were noted favoring methylphenidate ER compared to placebo for all timepoints (1 through 12 hours postdose). There were some statistically significant differences for a few timepoints for sequence (hour 3) and period (hours 2, 6 and 12); however, the majority of the timepoints for sequence and period were not statistically significant.

Table 7. LS Mean SKAMP Total Scores at Each Timepoint (Evaluable Population) [RP-BP-EF001]

	LS Mean		P-Values			
	Placebo	Methylphenidate ER	Treatment	Covariate	Sequence	Period
Hour						
1	1.41	0.76	0.0031	0.0005	0.8267	0.9069
2	1.90	1.01	0.0010	0.0014	0.9002	0.0356
3	2.25	1.29	0.0001	0.0026	0.0397	0.7808
4.5	2.29	1.33	0.0020	< 0.0001	0.5980	0.1303
6	2.32	1.43	0.0021	0.0008	0.6386	0.0415
7.5	2.38	1.25	0.0010	0.0027	0.3266	0.0877
9	2.35	1.66	0.0261	0.0055	0.3966	0.1160
10.5	2.21	1.48	0.0235	0.0326	0.6984	0.4557
12	2.60	1.56	< 0.0001	0.0020	0.7352	0.0412

These data are also graphically displayed in the following Sponsor's Figure:

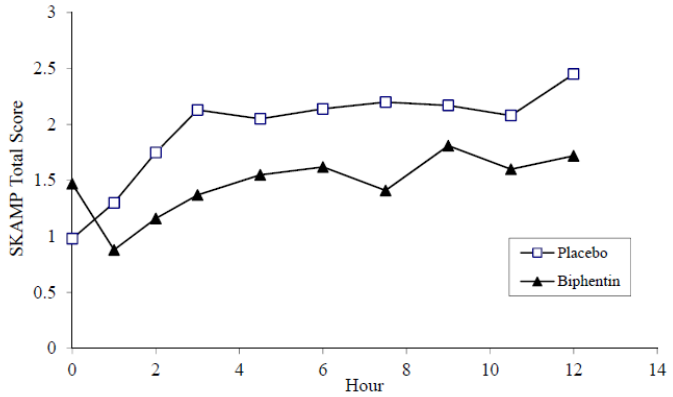


Figure 1. Sponsor's Figure. Mean SKAMP Total Scores at Each Timepoint (Evaluable Population) [RP-BP-EF001]

At hour 0 (predose), the SKAMP total score was statistically significantly higher (indicating worse symptoms) for methylphenidate ER compared to placebo (LS Means 1.52 vs. 0.99, p = 0.0071). At hour 0, the sequence effect was not statistically significant but the period effect was (p = 0.0378).

The Sponsor also performed the time course analysis on the ITT Populations (Versions 1-4). The results of these analyses are similar to those for the Evaluable Population. ITT Population Versions 1 and 2, all timepoints were statistically significant for treatment. ITT Population Versions 2 and 4, all timepoints were statistically significant for treatment with the exception of hour 9.

By request of the Division, the Sponsor was asked to perform a sensitivity analysis using a repeated measures ANCOVA analyzing all postdose treatment times in a single analysis. For all timepoints, SKAMP total scores were statistically significantly lower for methylphenidate compared to placebo (data not shown).
Analysis of Secondary Endpoints(s)

The SKAMP Attention score and SKAMP Deportment scores were secondary endpoints. Scores were averaged over all postdose timepoints for the Evaluable Population. The SKAMP Attention scores were statistically significant favoring methylphenidate ER compared to placebo (LS means 1.05 vs. 1.81, p = 0.0001). The SKAMP Deportment scores were statistically significant favoring methylphenidate ER compared to placebo (LS means 0.78 vs. 1.64, p = 0.0008). Analyses performed on the ITT Populations were similar.

The analyses for the SKAMP Attention scores time course were similar to that obtained for the SKAMP total score time course with statistically significant findings for all timepoints favoring methylphenidate ER compared to placebo. The analyses for the SKAMP Deportment scores time course were statistically significant findings for all timepoints with the exception of hour 10.5 and favored methylphenidate ER compared to placebo.

PERMP math tests were completed at the same timepoints as the SKAMP. Two PERMP scores were calculated – the number of math problems attempted and the number of math problems answered correctly in a 10-minute session. The difficult level of the PERMP was determined at screening based on results of an 8-minute timed math test. PERMP scores were averaged over all postdose timepoints. Statistically significant differences were found for the number of math problems attempted (LS means 113.7 vs. 83.1, p = 0.0054) and correct (109.1 vs. 73.2, p = 0.0006) favoring methylphenidate ER compared to placebo. For evaluation of the PERMP timecourse, the number of correct math problems was statistically significant for all timepoints, with the exception of hour 10.5, favoring methylphenidate ER compared to placebo. For evaluation of the PERMP timecourse, the number of math problems attempted was

statistically significant for most timepoints favoring methylphenidate ER compared to placebo.

The ADHD-RS-IV scale was completed 3 hours postdose during the double-blind period. The LS mean ADHD-RS-IV total score, Inattention score and Hyperactivity-Impulsivity scores were statistically significant favoring methylphenidate ER.

Table 8. ADHD-RS-IV Total, Inattention and Hyperactivity-Impulsivity Scores (Evaluable Population) [RP-BP-EF001]

	LS Mean		P-Values		
	Placebo	Methylphenidate ER	Treatment	Sequence	Period
Total Score	17.64	10.27	0.0019	0.1239	0.1335
Inattention Score	8.42	4.20	0.0003	0.0128	0.0280
Hyperactivity-Impulsivity Score	9.22	6.08	0.0391	0.5745	0.5038

Source: Table 11-33 CSR

No statistically significant differences were found between treatment groups for the Pediatric Quality of Life (PedsQL) scores. For the Child Sleep Habits Questionnaire (CSHQ) parent ratings, the only significant treatment difference was for Sleep Onset Delay with higher scores (worsening delay) for methylphenidate ER compared to placebo (p = 0.0046). No treatment differences were noted for the CSHQ self-report. No treatment differences were noted for the Weiss Functional Impairment Rating Scale or the Daily Parental Rating of Evening and Morning Behavior.

6.1.3 Other Endpoints

No other significant endpoints were explored.

6.1.4 Subpopulations

The sponsor evaluated the effect of age (6-8 years, 9-12 years) and gender on the primary efficacy endpoint, mean postdose SKAMP total score. No statistically significant differences were found between younger children (6-8 years) and older children (9 to 12 years) [p = 0.9301]. No statistically significant differences were found between male and female subjects (p = 0.2881). It should be kept in mind that the sample sizes for these subgroup analyses were small, though each subject served as their own control in this cross-over study.

6.1.5 Analysis of Clinical Information Relevant to Dosing Recommendations

In this study, methylphenidate ER was dosed in an open-label phase to determine each subject's "optimal" dose prior to the double-blind phase of the study. Dosing was initiated at 15 mg with "incremental" (undefined) adjustments approximately every 7 days. Optimization was to be completed in a 2 to 4 week period.

The sponsor had proposed an initial dose [redacted] (b) (4)

Based on the data from this (small) study, and RP-BP-EF002, proposed initial dosing for this product is 10 mg/day with increases every 7 days (in increments of 10 mg) to a maximum dose of 60 mg/day. This dosing is also consistent with other methylphenidate products.

See Section 6.2.5 for a more comprehensive discussion.

6.1.6 Discussion of Persistence of Efficacy and/or Tolerance Effects

An open-label extension phase (up to 21 months) followed the double-blind phase. Twenty-two subjects completed the double-blind phase and entered the open-label extension. Subjects were monitored through "periodic" follow up visits on a 1 to 2 month frequency and less frequently starting at 15 months (at least quarterly). The ADHD-RS-IV rating scale and CGI were performed at each visit. This extension phase was not designed to evaluate persistence of efficacy and/or tolerance effects. Additionally, with so few subjects continuing into this phase, definitive data to address persistence of efficacy and/or tolerance effects could be generated from this trial.

6.1.7 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

6.2 Indication – Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Clinical trial RP-BP-EF002 "A randomized, parallel, double-blind efficacy and safety study of [redacted] (b) (4) Aptensio XR] methylphenidate hydrochloride extended release capsules compared to placebo in children and adolescents 6 to 18 years with Attention Deficit Hyperactivity Disorder"

This was a multicenter study conducted in 16 sites in the United States.

6.2.1 Methods/Study Design/Analysis Plan

Primary Objective
To assess the efficacy of methylphenidate ER compared to placebo.
Primary Efficacy Endpoint: Mean change from baseline to the end of Week 1 in the clinician-rated ADHD Rating Scale, Version 4 (ADHD-RS-IV) total score.

Secondary Endpoints
Change from baseline in ADHD-RS-IV subscales of Inattention and Hyperactivity-Impulsivity
Clinical Global Impressions Scale – Improvement at the end of Week 1

Methods/Study Design

This was a parallel, randomized, double-blind, placebo-controlled, fixed-dose outpatient study in children and adolescents (6 to 17[1] years) with ADHD. The study included 5 phases: a Screening/Washout phase, a Double-Blind phase, an Open-Label phase, a Safety Follow-Up phase and an open-label extension phase (the sponsor referred to this last phase as the Compassionate Use phase).

Screening/Washout Phase: Screening assessments, minimum 48 hour washout of prior stimulant medications (Visit 1). Parents received medication washout instructions by telephone.

Double-Blind Phase: Following baseline assessments (Visit 2, Day 0), subjects were randomized (1:1:1:1:1) to one of 5 treatment groups: methylphenidate ER, 10, 15, 20 or 40 mg/day or placebo. Subjects weighing $\leq$ 25 kg were not assigned to receive the 40 mg dose of methylphenidate ER. Methylphenidate ER and placebo were administered for one week. Parents were required to administer study drug daily, no later than 10 a.m. Subjects returned to the clinic on Visit 3 (Day 7) for study assessments.

Open-Label Phase: Subjects completing the Double-Blind phase could enter the 11-week Open-Label phase. During this phase, subjects were permitted to receive any of the following daily doses of methylphenidate ER: 10, 15, 20, 30, 40, 50 or 60 mg. The Open-Label phase began at Visit 3 (Day 7) and all subjects were dispensed 10 mg unless the Investigator deemed it necessary to begin at a higher dose based on methylphenidate treatment experience prior to entering the study. Dose was titrated, based on clinical response and tolerance, every 3 to 7 days up to the maximum dose of 60 mg/day. Clinic visits occurred on Days 14, 21, 28, 56, 84 corresponding to Visits

[1] Per inclusion criteria, subjects 6 to 18 years of age (inclusive) could be enrolled into the trial; however, no subjects over 17 years of age were enrolled.

4, 5, 6, 7 and 8. For the open-label phase, there was no restriction on dosing based on weight.

Safety Follow-Up Phase: Approximately 30 days after the subject's last dose of study medication (Visit 8), study staff followed up with subjects by telephone (adverse events, concomitant medications).

Open-Label Extension Phase: At the clinician's discretion, subjects who had received clinical benefit from methylphenidate ER could receive open-label methylphenidate ER for up to 21 months following the end of the Open-Label phase (Visit 8). Study visits occurred every 1 to 2 months for 15 months and every 3 months thereafter.

Inclusion/exclusion criteria

Key inclusion and exclusion criteria are summarized in this section. A complete list of criteria are in Appendix 9.4. The inclusion and exclusion criteria are essentially the same as that for RP-BP-EF001 except the age of the subjects was 6 to 18 years of age (note that the study did not enroll any subjects > 17 years of age).

Concomitant medications

Prohibited concomitant medications included any psychotropic medication including, but not limited to any stimulant, atomoxetine, SSRIs, clonidine, MAOIs, mood stabilizers, antipsychotics and sedative hypnotics. Sedative hypnotics were only allowed if the dose was stable prior to and during the clinical trial.

Assessments

For a complete list of assessments/procedures and frequency, refer to the Schedule of Events in Appendix 9.6.

Efficacy assessments included the following rating scales: ADHD-RS-IV, CGI-S, CGI-I, Pediatric Quality of Life (PedsQL), Child Sleep Habits Questionnaire (CSHQ) parent and self-report, Weiss Functional Impairment Rating Scale (WFIRS) and the Daily Parental Rating of Evening and Morning Behavior (DPREMB-R).

Safety assessments included physical examination, ECG, vital signs (sitting), adverse events and routine laboratory tests. The C-SSRS was included for monitoring suicidal thoughts and behaviors.

Analysis Plan

Refer to the Biometrics review (J. Zhong) for a more comprehensive description of the statistical analysis plan for this study. A brief review of the statistical approach for the primary efficacy analysis only is included here.

This summary is taken from the CSR and was not independently evaluated by this reviewer (e.g. assumptions in sample size calculations, etc.).
The primary efficacy analysis was to analyze the change from baseline to the end of Week 1 in the Clinician-Rated ADHD-Rating Scale IV total score, comparing the 5 treatment groups: placebo, methylphenidate 10 mg, 15 mg, 20 mg and 40 mg/day. The overall test for whether all treatments had the same mean was the primary result. The primary analysis was an ANCOVA with a model which had a class term for treatment and site and a covariate term for baseline ADHD-RS-IV total score.

Sample size calculations were based on the primary efficacy endpoint LS mean change from baseline in ADHD-RS-IV total score. Assuming an effect size of 0.65 between methylphenidate ER and placebo, with approximately 200 subjects (40 per group) completing the double-blind period, this study had 80% power to detect a treatment difference at a 2-sided significance level of 0.05. A target of 225 randomized subjects was estimated to be required, based on a potential dropout rate of 12%.

6.2.2 Results

Two hundred eighty subjects were screened, 230 subjects entered the double-blind phase and 221 subjects completed the double-blind phase.

Safety population (N = 230) was defined as subjects who took at least one dose of study drug.

ITT population (N = 230) is defined differently in the protocol and the CSR. In the protocol, it is defined the same as the Efficacy Population while in the CSR it is defined as the same as the Safety population.

Efficacy Population (N = 221) was defined as subjects who completed the ADHD-RS-IV assessments on Day 0 and Day 7.

Demographics

The mean age of subjects in this clinical trial was 10.8 years and was fairly equally distributed between the 6-8, 9-11 and 12-14 year old groups with fewer subjects in the 15-18 year old age group. There was a majority of male subjects (67%) and Caucasian (69%). These demographics are fairly representative of the larger ADHD population. The mean weight was 44.6 kg, no subjects $\leq$ 25 kg were in the 40 mg methylphenidate ER group as dictated by protocol. Although subjects 18 years of age could be enrolled into the trial, no subjects over 17 years of age were enrolled (Listing 16.2.4 CSR).

Table 9. Sponsor's Table. Subject Demographics (Safety Population) [RP-BP-EF002]

Demographic Characteristic	10 mg Biphentin (N=49)	15 mg Biphentin (N=44)	20 mg Biphentin (N=45)	40 mg Biphentin (N=45)	Placebo (N=47)	All (N=230)
Mean±SD Age (yrs)	10.5±2.89	10.2±3.08	11.1±3.51	11.2±2.49	10.9±3.05	10.8±3.02
Age Group, No. (%)						
6-8 yrs	13 (26.5)	17 (38.6)	13 (28.9)	6 (13.3)	11 (23.4)	60 (26.1)
9-11 yrs	16 (32.7)	11 (25.0)	12 (26.7)	17 (37.8)	20 (42.6)	76 (33.0)
12-14 yrs	15 (30.6)	12 (27.3)	9 (20.0)	19 (42.2)	8 (17.0)	63 (27.4)
15-18 yrs	5 (10.2)	4 (9.1)	11 (24.4)	3 (6.7)	8 (17.0)	31 (13.5)
Sex, No. (%)						
Male	30 (61.2)	30 (68.2)	31 (68.9)	33 (73.3)	30 (63.8)	54 (67.0)
Female	19 (38.8)	14 (31.8)	14 (31.1)	12 (26.7)	17 (36.2)	76 (33.0)
Race, No. (%)						
White	34 (69.4)	26 (59.1)	33 (73.3)	32 (71.1)	33 (70.2)	158 (68.7)
Black	13 (26.5)	11 (25.0)	9 (20.0)	11 (24.4)	9 (19.1)	53 (23.0)
Asian	0	2 (4.5)	0	0	1 (2.1)	3 (1.3)
American Indian or Alaska Native	0	0	0	1 (2.2)	1 (2.1)	2 (0.9)
Native Hawaiian or Other Pacific Islander	0	2 (4.5)	0	0	0	2 (0.9)
Other	2 (4.1)	3 (6.8)	3 (6.7)	1 (2.2)	3 (6.4)	12 (5.2)
Ethnicity, No. (%)						
Hispanic or Latino	4 (8.2)	8 (18.2)	7 (15.6)	4 (8.9)	3 (6.4)	26 (11.3)
Not Hispanic or Latino	45 (91.8)	36 (81.8)	38 (84.4)	41 (91.1)	44 (93.6)	204 (88.7)
Weight (kg)						
Mean±SD	43.83±19.5	44.59±21.7	45.75±20.6	48.84±18.7	40.46±14.4	44.64±19.1
Min, Max	20.5, 102.5	16.8, 125.5	18.5, 95.5	27.0, 114.5	21.6, 81.8	16.8, 125.5

Source: Table 11-2 CSR

Baseline Disease Characteristics

The majority of subjects had the diagnosis of either ADHD combined subtype of inattentive subtype. Concurrent diagnoses were few, the most common being oppositional defiant disorder which a common concurrent diagnosis in patients with ADHD. Statistically significant differences were noted for the baseline CGI-S between the methylphenidate ER 15 mg group and placebo (ANOVA, Dunnett adjusted pairwise p = 0.0351). Baseline ADHD-RS-IV total scores, the primary endpoint, were not statistically significantly different between groups.

Table 10. Baseline Disease Characteristics

	MPH ER 10 mg N = 49	MPH ER 15 mg N = 44	MPH ER 20 mg N = 45	MPH ER 40 mg N = 45	Placebo N = 47
ADHD Subtype, n (%)					
Combined	30 (61.2)	28 (63.6)	27 (60.0)	26 (57.8)	29 (61.7)
Hyperactive/Impulsive	1 (2)	0	2 (4.4)	2 (4.4)	1 (2.1)
Inattentive	16 (32.7)	15 (34.1)	16 (35.6)	15 (33.3)	13 (27.7)
Not reported	2 (4.1)	1 (2.3)	0	2 (4.4)	4 (8.5)
Concurrent Diagnoses					
Adjustment Disorder	0	1 (2.3)	0	0	0
Conduct Disorder	0	1 (2.3)	0	0	0
Encopresis	1 (2.0)	0	0	0	1 (2.1)
Enuresis	5 (10.2)	4 (9.1)	0	1 (2.2)	1 (2.1)
Oppositional Defiant Disorder	4 (8.2)	5 (11.4)	2 (4.4)	4 (8.9)	4 (8.5)
Simple Phobia	0	1 (2.3)	0	1 (2.2)	0
Social Phobia	0	0	1 (2.2)	0	0
Baseline CGI-S, Mean (SD)	4.48 (0.65)	4.70 (0.65)	4.59 (0.62)	4.47 (0.63)	4.35 (0.64)
Baseline ADHD-RS-IV, Mean (SD)					
Total Score	37.6 (8.32)	38.0 (8.64)	36.2 (8.46)	35.6 (9.16)	33.4 (11.01)
Inattention Score	21.2 (4.09)	21.1 (4.15)	21.1 (4.45)	20.1 (4.78)	18.8 (5.30)
Hyperactivity Score	16.5 (6.14)	16.8 (6.55)	15.1 (7.30)	15.5 (6.43)	14.6 (7.75)

Source: Tables 11-3, 11-5, 14.1.7,

Subject Disposition

Two hundred fifty four (254) subjects were screened and 230 entered the double-blind phase. Most subjects (96%) completed the one week double-blind phase.

Table 11. Subject Disposition in Double-Blind Phase [RP-BP-EF002]

	MPH ER 10 mg	MPH ER 15 mg	MPH ER 20 mg	MPH ER 40 mg	Placebo
Entered DB Phase	49	44	45	45	47
Completed DB Phase	48 (98%)	40 (90.9%)	44 (97.8%)	43 (95.6%)	46 (97.9%)
Discontinued DB Phase	1 (2%)	4 (9.1%)	1 (2.2%)	2 (4.4%)	1 (2.1%)
Adverse Events	0	1	0	2	0
Lack of Efficacy	0	0	0	0	0
Protocol Violation	0	0	0	0	0
Non Compliance	0	1	0	0	0
Withdrew Consent	0	1	1	0	1
Lost to Follow-up	1	1	0	0	0

Source Tables 14.1.1.2

Concomitant Medication Use

Medications that were prohibited during the study included any psychotropic medication except sedative hypnotics (if stable dose prior to and during trial). The sponsor stated that none of the patients in the study were documented to have used prohibited medications during the study. Seventy-five patients (~30%) were using a psychotropic medication at screening and required a washout. The majority of the psychotropic medications used prior to the study were stimulants. The frequency of stimulant use prior to the study was similar between treatment groups (~9%). Few subjects were receiving other psychotropic medications prior to the study (risperidone, escitalopram, guanfacine, clonidine, aripiprazole, and bupropion).

Protocol Violations

The most common protocol violations were missed assessments, assessments performed out of the study window and missed doses of study drug. During the one-week double-blind phase, 11 patients (< 5%) missed at least 1 dose of study drug (n/group: 3- 10 mg, 2-20 mg, 2-15 mg, 3-40 mg, 1-placebo). Three of these 11 patients missed 2 doses (groups: 20 mg, 40 mg, placebo). Since patients in all groups missed doses, it is unlikely this would have impacted the overall study results.
In error, one patient received placebo the first week of the open-label phase rather than methylphenidate ER 10 mg.

Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the change in the ADHD-RS-IV Total Score from baseline (Visit 2) to the end of the Double-Blind phase (Visit 3). The primary analysis was the ANCOVA with terms for subject, treatment, and site and with the subject's baseline ADHD-RS-IV total score as a covariate. Overall, there was a treatment difference for mean change in ADHD-RS-IV favoring methylphenidate ER compared to placebo.

Table 12. ADHD-RS-IV Total Score Mean Change from Baseline (Efficacy Population) [RP-BP-EF002]

	Placebo N = 46	MPH ER 10 mg N = 48	MPH ER 15 mg N = 40	MPH ER 20 mg N = 44	MPH ER 40 mg N = 43	P-value Treatments
Mean Decrease from BL (SD)	5.1 (10.3)	9.3 (8.9)	11.2 (12.1)	12.3 (9.8)	13.2 (10.3)	
LS Mean Decrease	5.4	9.1	10.3	11.4	13.0	0.0046
LS Mean Diff from PC		3.7	4.9	6.0	7.5	
95% CI for Diff from PC		-1.3, 8.6	-0.4, 10.1	0.9, 11.0	2.5, 12.5	
P-value vs. PC		0.2083	0.0769	0.0145	0.0011	

Source: Tables 11-6, 14.2.1.1.3

This analysis indicated that the baseline covariate had a significant contribution to the model ($p < 0.0001$) and there was a significant difference among study sites ($p = 0.0018$). The mean decreases (averaged over all treatments) in ADHD-RS-IV ranged from 0.7 (Site 18) to 18.2 (Site 9). The 3 largest sites (Sites 1, 3, 16) had mean decreases (averaged over all treatments) ranging from 7.9 to 12.9.

The Sponsor also performed this analysis with the ITT Population and found similar results as that noted for the Efficacy Population (data not presented).

Analysis of Key Secondary Endpoint(s)

The Key Secondary Endpoint was the change from baseline (Visit 2) to the end of the Double-Blind phase (Visit 3) in ADHD-RS-IV Total Score comparing each methylphenidate ER dose to placebo for the Efficacy Population. The pairwise difference between each methylphenidate ER dose and placebo using Dunnett multiple comparison adjustment was calculated using the same ANCOVA used for the primary analysis. The pairwise difference from placebo was statistically significant for methylphenidate ER 20 mg ($p = 0.0145$) and 40 mg ($p = 0.0011$) doses (see Table 12). Similar results were obtained for the ITT Population. The mean and LS mean decrease from baseline in ADHD-RS-IV Total score did appear to follow a linear pattern related to dose – as the dose increased, the ADHD-RS-IV Total score decreased.

Analysis of Secondary Endpoint(s)

Mean Change in ADHD-RS-IV Subscale Scores
Statistically significant differences favoring methylphenidate ER were found for the the ADHD-RS-IV Hyperactivity-Impulsivity and Inattention Subscale scores. For the Hyperactivity-Impulsivity subscale, only the methylphenidate ER 40 mg dose was different from placebo. For the Inattention subscale, the methylphenidate 20 and 40 mg doses were different from placebo.

Table 13. ADHD-RS-IV Subscale Scores, Mean Change from Baseline (Efficacy Population) [RP-BP-EF002]

	Placebo N = 46	MPH ER 10 mg N = 48	MPH ER 15 mg N = 40	MPH ER 20 mg N = 44	MPH ER 40 mg N = 43	P-value Treatments
Hyperactivity-Impulsivity Subscale						
LS Mean Decrease	2.3	3.7	4.6	4.7	5.6	0.0240
LS Mean Diff from PC		1.5	2.4	2.4	3.4	
P-value vs. PC		0.4302	0.1034	0.0840	0.0061	
Inattention Subscale						
LS Mean Decrease	3.1	5.4	5.7	6.8	7.3	0.0080
LS Mean Diff from PC		2.3	2.5	3.6	4.2	
P-value vs. PC		0.1825	0.1453	0.0118	0.0026	

Source: Tables 11-11, 11-12 from CSR

Similar to the primary analysis, these analyses indicated that the baseline covariate had a significant contribution to the model ($p < 0.0001$ for Hyperactivity-Impulsivity, $p = 0.0028$ for Inattention) and there was a significant difference among study sites ($p = 0.0054$ for Hyperactivity-Impulsivity, $p = 0.0028$ for Inattention).

Clinical Global Impression – Improvement (CGI-I) Score
The CGI-I scores at the end of the Double-Blind phase were compared. For this scale, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Overall, CGI-I was statistically significant favoring methylphenidate ER compared to placebo. The pairwise difference from placebo was statistically significant for the 20 mg and 40 mg doses. Similar to the other analyses, there was a significant difference among sites ($p = 0.0004$), but not baseline CGI-Severity scores ($p = 0.1122$).

Table 14. LS Mean CGI-I Score at End of Double-Blind Phase (Efficacy Population) [RP-BP-EF002]

	Placebo N = 46	MPH ER 10 mg N = 48	MPH ER 15 mg N = 40	MPH ER 20 mg N = 44	MPH ER 40 mg N = 43	P-value Treatments
LS Mean	3.5	3.3	3.2	2.9	2.8	0.0121
LS Mean Diff from PC		-0.2	-0.3	-0.6	-0.8	
P-value vs. PC		0.7391	0.5518	0.0311	0.0072	

6.2.3 Other Endpoints

The sponsor performed some exploratory analyses for the 8-week Open-Label phase of this study. In general, improvement was noted in the ADHD-RS-IV total score, subscale scores and CGI-I throughout the open-label phase. The doses of methylphenidate ER in the Open-Label phase ranged from 10 mg to 60 mg/day; by the end of this phase most subjects were receiving $\geq$ 30 mg/day.

Pediatric Quality of Life (PedsQL) was assessed at baseline (Visit 2), end of Double-Blind phase (Visit 3) and end of the Open-Label phase (Visit 8). The sponsor stated that scoring "was modified from its usual scoring in that the 5-point response scale was inadvertently replaced by a yes/no option". There was no difference on the PedsQL between the methylphenidate ER and placebo groups.

6.2.4 Subpopulations

The sponsor evaluated age, gender and race on the ADHD-RS-IV total score during the double-blind phase. The sponsor used the full model ANCOVA with terms for treatment, site, age group, gender, race, the two-way interactions of site, age group, gender and race with treatment and the covariate baseline ADHD-RS-IV total score.

In the full model, the age (6-8, 9-11, 12-14, 15-17 years) by treatment was not significant ($p = 0.7919$) and the race by treatment was not significant ($p = 0.9757$).

In the full model, the gender by treatment was significant ($p = 0.0238$) indicating that the difference between treatment groups for males was different than the difference between treatment groups for females. The sponsor then evaluated a reduced model that did not include the nonsignificant interactions and the results still found a significant gender by treatment effect ($p = 0.0110$). For females, none of the methylphenidate ER groups were significantly different from placebo (Table 15). For males, all but the methylphenidate ER 10 mg group were significantly different from placebo (Table 15). The sponsor interprets these gender differences on "abnormally" large decreases in ADHD-RS-IV total scores in the placebo group. The sponsor cites 3 female subjects

receiving placebo who had high ADHD-RS-IV total scores at baseline and very low scores at the end of the double-blind phase – decreases of 32, 28 and 29 points.

There were twice as many male as female subjects in the study (147 males, 74 females). When dividing the number of subjects into treatment cells, the females had much fewer subjects per treatment group, it is possible that a few large placebo responses may have impacted this particular subgroup analysis. Clearly, the LS mean decrease in the females in the placebo group (9.8) was much greater than in the males in the placebo group (1.2).

Table 15. ADHD-RS-IV Decrease in Total Score from Baseline to the End of the Double-Blind Phase; LS Means from Reduced Model for Gender and Treatment [RP-BP-EF002]

Gender	Placebo	MPH ER 10 mg	MPH ER 15 mg	MPH ER 20 mg	MPH ER 40 mg
Male					
n	29	29	27	31	31
LS Mean Decrease	1.2	8.6	12.3	10.8	11.2
p-value vs. placebo	-	0.1595	0.0019	0.0070	0.0037
Female					
n	17	19	13	13	12
LS Mean Decrease	9.8	8.1	4.9	10.2	13.4
p-value vs. placebo	-	1.000	0.999	1.000	1.000

Source: Tables 11-32, 14.2.1.5.1 from CSR

6.2.5 Analysis of Clinical Information Relevant to Dosing Recommendations

Methylphenidate ER dosing in RP-BP-EF001: during the open-label dose optimization phase, methylphenidate ER was initiated at 15 mg with “incremental adjustments” approximately every 7 days until an optimal dose was achieved. Subjects ≤ 25 kg could not receive the highest dose (40 mg).

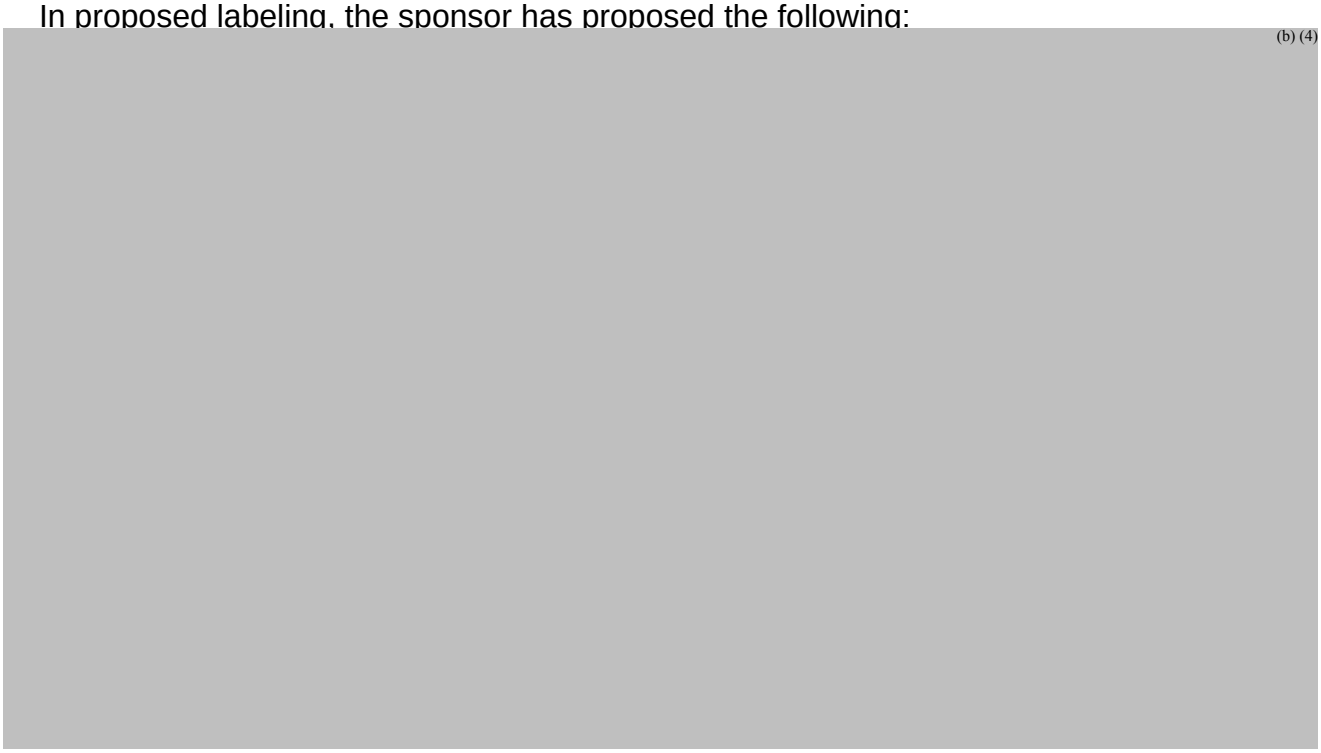
Methylphenidate ER dosing in RP-BP-EF002: during the double-blind phase, all subjects were started at the assigned fixed-dose (10, 15, 20, or 40 mg/day). Subjects ≤ 25 kg could not receive the highest dose (40 mg).
During the 11-week open-label phase that followed, methylphenidate ER was initiated at 10 mg and titrated every 3 to 7 days to a maximum of 60 mg.

In the Biphentin Product Monograph (Canada), the following dosing information is included:
For children > 6 years of age: for patients not currently treated with methylphenidate, Biphentin should be initiated in low doses, as a single daily dose in the morning. Dosage should be individualized on the basis of factors such as age, body weight and individual response. The usual initial dose should be 10-20 mg/day orally.
Patients currently receiving immediate-release formulations of methyphenidate may be converted to the same daily dose of Biphentin, as a single daily dose in the morning.

The total daily dose may be adjusted in weekly increments of 10 mg/day up to a maximum of 60 mg/day.
Dosing information is also provided for adults and is similar to that for children but with a maximum dose of 80 mg/day.

In proposed labeling, the sponsor has proposed the following:

(b) (4)



In general, the approach for dosing methylphenidate products is a conservative initial dose and then increases in dose depending on the clinical response and tolerability of the dose in the individual patient. For this product, dosing should reflect the dosing in the pivotal clinical trials. Though there were some differences between the two trials, a 10 mg starting dose with incremental 10 mg increases every week to an optimum dose is consistent with the protocols and with the dosing recommendations for other methylphenidate products. The maximum dose should be 60 mg/day, which is the highest dose studied in the pivotal trials (open-label extension phases allowed dosing up to 60 mg/day) and is the maximum dose for other methylphenidate products.

6.2.6 Discussion of Persistence of Efficacy and/or Tolerance Effects

Following the 1-week double-blind phase, there was an 11-week open label phase followed by an additional open-label extension phase up to 21 months. Two hundred twenty one subjects completed the double-blind phase, 220 entered the 11-week open-label phase and 200 completed the 11-week open-label phase.

During the 11-week open-label phase (beginning on day 7), ADHD-RS-IV ratings were conducted on study days 14, 21, 28, 56 and 84. The mean ADHD-RS-IV total scores at baseline and day 84 were 36.1 and 13.5, respectively. Mean ADHD-RS-IV total scores showed improvement (decreases) at all visits. The sponsor did not perform any statistical analyses on these data. At the day 56 visit, the most commonly prescribed methylphenidate ER doses were 20 mg (17%), 30 mg (28%), 40 mg (29%) and 50 mg (18%).

6.2.7 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

7 Review of Safety

The focus of the safety review included data from the two pivotal efficacy/safety studies, RP-BP-EF001 and RP-BP-EF002. Serious adverse events and discontinuations due to adverse events were reviewed for the two pivotal PK studies and all supportive studies.

RP-BP-EF001 (n = 26) included an up to 4 week open-label phase prior to the one week double-blind phase. RP-BP-EF002 (n = 230) included a one week double-blind phase followed by an 11-week open label phase. For both trials, subjects had the option to continue receiving open-label methylphenidate ER in an open-label extension phase lasting up to 21 months. During the one week double blind phase of each trial, subjects could receive methylphenidate ER up to 40 mg/day; in the open-label phases subjects could receive methylphenidate ER up to 60 mg/day. The extent of exposure across the two studies was 137.7 patient years.

No deaths occurred in any of the pivotal or supportive studies. Four serious adverse events (SAE) were reported for RP-BP-EF002, three of these occurred during open-label administration of methylphenidate ER. These SAEs were likely not related to methylphenidate ER (adjustment disorder with mixed disturbance of emotion and conduct, injury-induced migraine headache, appendicitis and conversion disorder). Sixteen subjects discontinued studies RP-BP-EF001 and RP-BP-EF002 due to adverse events, the majority of these (13/16) discontinuations occurred during open-label administration of methylphenidate ER. Adverse events included insomnia, increased heart rate, nausea, decreased appetite, aggression, headache, mood swings, fatigue, upper abdominal pain, irritability, tearfulness, social avoidant behavior, agitation, affect lability and abdominal discomfort.

Common adverse events noted in these trials were consistent with the known adverse event profile for methylphenidate products and included upper abdominal pain, nausea, vomiting, decreased appetite, dizziness, and insomnia. There was not a consistent pattern of adverse events and dose observed in the fixed-dose trial (RP-BP-EF002).

There were no notable findings for laboratory assessments (chemistry/hematology). Vital signs were assessed during the one week double-blind phase of RP-BP-EF002. The methylphenidate ER groups revealed a small mean increase in systolic blood pressure up to 1.83 mmHg (0.91 mmHg in placebo group) and diastolic blood pressure up to 2.23 mmHg (0.48 mmHg in placebo group). Mean increases in pulse were also noted, up to 2.9 bpm (-0.30 in placebo group). Mean weight decreases were noted for most methylphenidate ER groups, up to 1.05 lb weight loss (0.40 weight gain in placebo group). There did appear to be a trend for changes in vital signs and methylphenidate ER dose (the highest dose [40 mg] had the greatest mean changes for DBP, pulse and weight decrease). These changes in vital sign parameters are known effects of methylphenidate products.

ECG parameters were evaluated and small and inconsistent findings were noted for mean changes. Approximately 11 subjects who had QTc < 450 at baseline/screening were noted to have QTc ≥ 450 during the double-blind or open-label phases of study RP-BP-EF002. All of these were QTcB corrections, no subjects had QTcF ≥ 450. There is some confounding of QTcB corrections with changes in heart rate, though many of these subjects had a heart rate < 100 bpm.

In general, this reviewer did not note any new and significant safety findings for this methylphenidate ER product that were different from the known safety profile of other methylphenidate products and included in currently approved product labeling for these products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This submission included results from two pivotal efficacy and safety studies, RP-BP-EF001 and RP-BP-EF002, as well as two pivotal pharmacokinetic studies and a number of supportive clinical trials (see Tables 1, 2 and 3). All of the safety data from the two pivotal efficacy and safety studies were reviewed. For the pivotal pharmacokinetic studies and the supportive studies, only serious adverse events were reviewed.

7.1.2 Categorization of Adverse Events

MedDRA (version not specified) was the coding dictionary used in studies RP-BP-EF001 and RP-BP-EF002. A review of the JMP adverse event database for these studies did not note significant discrepancies in the coding of verbatim terms to preferred terms. Examples of coding that were questionable (in the absence of other information) included “cracking knuckles” coded to Obsessive-Compulsive Disorder (n = 1).

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

The adverse event data for the two pivotal efficacy trials was not pooled since they had very different study designs. RP-BP-EF001 was a flexible-dose, cross-over study and RP-BP-EF002 was a fixed-dose, parallel group study.

7.2 Adequacy of Safety Assessments

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

From the pivotal ADHD efficacy trials, RP-BP-EF001 and RP-BP-EF002, a total of 256 unique subjects received at least one dose of methylphenidate ER. Doses ranged from 10 mg to 60 mg/day. By protocol design, no subjects weighing ≤ 25 kg could receive ≥ 40 mg/day during the dose optimization or double-blind phases of the pivotal trials, though they could receive a higher dose in the open-label extension phases. The extent of exposure across these two studies is 137.7 patient years.

Table 16. Methylphenidate ER Exposure – Number of Patients (Total Number of Dosing Days) [RP-BP-EF001, RP-BP-EF002]

	Methyphenidate ER									
	10 mg	15 mg	20 mg	30 mg	35 mg	40 mg	45 mg	50 mg	60 mg	All Doses
Double-Blind Phase										
RP-EF-001	0	0	9 (67)	11 (77)	0	1 (7)	0	0	0	21 (151)
RP-EF-002	48 (353)	42 (317)	45 (320)	0	0	44 (305)	0	0	0	
Open-Label Phase*										
RP-EF-001	0	26 (247)	25 (351)	16 (225)	0	4 (25)	0	0	0	26 (848)
RP-EF-002	184 (1548)	66 (777)	180 (3406)	156 (3838)	0	107 (3132)	0	58 (1654)	24 (764)	220 (15119)
Open-Label Extension*										
RP-EF-001	0	1 (14)	11 (1663)	16 (1901)	0	4 (495)	0	0	0	22 (4073)
RP-EF-002	2 (75)	2 (291)	30 (3559)	53 (7214)	1 (250)	55 (6383)	1 (92)	49 (5781)	37 (5120)	154 (28765)

*The Open-Label phase was an 11-week phase following the Double-Blind phase; the Open-Label Extension phase was an up to 21month phase following the Open-Label phase.
Subjects may appear in more than one column due to titration or dose changes
Source: Table 1, Summary-Clin-Safety

Table 17. Extent of Methylphenidate ER Exposure by Days
(Double-Blind, Open-Label and Open Label Extension Phases Combined)

Number of Days	RP-BP-EF001 Number of Subjects	RP-BP-EF002 Number of Subjects
1-30	4	16
31-60	1	12
61-120	5	63
121-180	2	26
181-270	6	30
271-360	5	61
361-451	3	18

Source: Table 2, Summary-Clin-Safety

7.2.2 Explorations for Dose Response

The dose response of methylphenidate ER in children with ADHD was explored in study RP-BP-EF002. Subjects received methylphenidate ER 10 mg/day, 15 mg/day, 20 mg/day, 40 mg/day or placebo. The mean and LS mean decrease from baseline in ADHD-RS-IV Total score did appear to follow a linear pattern related to dose – as the dose increased, the ADHD-RS-IV Total score decreased. However, statistically significant differences favoring methylphenidate ER were demonstrated for the two highest doses (20 and 40 mg/day) only.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing in this submission.

7.2.4 Routine Clinical Testing

Routine clinical testing was included in the protocol as discussed in section 6.1.1. In general, it appears that clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal studies of drug metabolism or interactions were submitted with this NDA.

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

The adverse event profile for methylphenidate ER was evaluated for adverse events known to occur with other methylphenidate products (e.g. insomnia, tachycardia, nausea, upper abdominal pain, etc.).

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in in the two pivotal efficacy/safety trials (RP-BP-EF001, RP-BP-EF-002), the two pivotal PK studies (RP-BP-PK001, RP-BP-PK002) or any of the supportive studies.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events occurred in any of the supportive trials or in the two pivotal PK studies.
No serious adverse events were reported for study RP-BP-EF001. Four SAEs occurred in RP-BP-EF002, one during the double-blind phase and three during open-label phases. Investigators did not consider these SAEs related to methylphenidate ER. The 14 YOF with adjustment disorder with mixed disturbance of emotion and conduct had a history of adjustment disorder with mixed mood and conduct, oppositional defiant disorder since the age of 12. The 17 YOF with injury-induced migraine headache experienced a closed head injury (described as mild) approximately 1 month after beginning methylphenidate ER (patient struck head on wooden shelf upon standing). The patient was hospitalized for ~5 days for injury-induced migraine headaches, she was withdrawn from the study and no further information is available. The 9 YOM who experienced appendicitis had been receiving methylphenidate ER for approximately 9 months prior to the event. The event resolved (appendectomy) and the patient continued in the study. The 11 YOM with conversion disorder reported having developed “numbness and paralysis of feet and falling” after being involved in a fight with a classmate. He was hospitalized for 2 days, MRI, MRA and CT of the head were all negative, EEG was also negative. At the time of the event, he had been receiving methylphenidate ER for ~17 months, he had been receiving 60 mg during the open label extension phase. The event is noted as having resolved, no further details were available.

Table 18. Serious Adverse Events [RP-BP-EF002]

Subject ID	Age/Sex	Study Phase*	Study Dose	Adverse Event	Severity	Action/Outcome
20617318	14 F	DB	15 mg	Adjustment disorder with mixed disturbance of emotion and conduct	Moderate	Study discontinuation; resolved
21813342	17 F	OL	30 mg	Injury-induced migraine headache	Moderate	Study discontinuation, ongoing
20908175	9 M	OL extension	40 mg	Appendicitis	Extreme	None, resolved
20408297	11 M	OL extension	60 mg	Conversion disorder	Marked	None, resolved

*DB: double blind, OL: 11-week open-label phase, OL extension: up to 21 month open-label phase
Source: Table 12-8 CSR RP-BP-EF002

7.3.3 Dropouts and/or Discontinuations

RP-BP-EF001
One subject (10 YOWM) withdrew from the study due to the adverse event "prolonged sleep latency" occurring during the open-label dose optimization phase.

RP-BP-EF002
Fifteen subjects withdrew from the study due to adverse events: 3 during the double-blind phase (n = 1 - 15 mg, n = 2 - 40 mg); 10 during the 11-week open-label phase and 2 during the 21-month open-label extension phase. Most of these subjects had more than one adverse event. The mean age for subjects discontinuing due to adverse events was 11.5 years (range 6 to 17 years) and the range of methylphenidate ER doses was 10 – 50 mg/day. The majority of the adverse events were consistent with the known adverse event profile of methylphenidate and included insomnia (n = 6), increased heart rate (n = 1), nausea (n = 1), decreased appetite (n = 2). Other adverse events included adjustment disorder (as in Table 18), aggression, headache, mood swings, fatigue, upper abdominal pain, irritability, tearfulness, social avoidant behavior, agitation, affect lability, head injury (as in Table 18), and abdominal discomfort.

7.3.4 Significant Adverse Events

This reviewer did not identify other significant adverse events occurring in these clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Double-Blind Phase

Adverse events occurring in ≥ 2 subjects in RP-BP-EF001 (cross-over study) in the methyphenidate ER group (N = 21) include headache [n = 3 (14.3%)], abdominal pain [n = 2 (9.5%)], and pyrexia [n = 2 (9.5%)]. No adverse events occurring in > 2 subjects were reported in the placebo group (N = 22).

Adverse events occurring in ≥ 2 subjects in RP-BP-EF002 (fixed-dose study) are in Table 19. In general, the adverse events noted are consistent with the known adverse event profile for methylphenidate. For study RP-BP-EF002, no adverse events appeared to be dose-related.

Table 19. Adverse Events in ≥ 2 Subjects in Any Methylphenidate ER Group (Double-Blind Phase) [RP-BP-EF002]

SOC/Preferred Term	MPH ER 10 mg (N = 49)	MPH ER 15 mg (N = 44)	MPH ER 20 mg (N = 45)	MPH ER 40 mg (N = 45)	MPH ER All Doses (N = 183)	Placebo (N = 47)
Cardiac Disorders						
Tachycardia	0	1 (2.3%)	0	0	1 (0.5%)	0
GI Disorders						
Abdominal pain upper	4 (8.2%)	4 (9.1%)	6 (13.3%)	1 (2.2%)	15 (8.2%)	0
Nausea	3 (6.1%)	0	2 (4.4%)	2 (4.4%)	7 (3.8%)	1 (2.1%)
Vomiting	3 (6.1%)	2 (4.5%)	1 (2.2%)	1 (2.2%)	7 (3.8%)	0
General Disorders						
Fatigue	2 (4.1%)	0	0	1 (2.2%)	3 (1.6%)	1 (2.1%)
Metabolism/Nutrition DO						
Decreased appetite	1 (2.0%)	2 (4.5%)	4 (8.9%)	2 (4.4%)	9 (4.9%)	0
Nervous System Disorders						
Dizziness	0	4 (9.1%)	0	0	4 (2.2%)	1 (2.1%)
Headache	6 (12.2%)	3 (6.8%)	6 (13.3%)	5 (11.1%)	20 (10.9%)	4 (8.5%)
Insomnia	5 (10.2%)	2 (4.5%)	6 (13.3%)	5 (11.1%)	18 (9.8%)	1 (2.1%)

Source: 12-2 from CSR

Open-Label Phases

The common adverse events in the open-label phases are noted below. These adverse events are consistent with the known adverse event profile for methylphenidate products.

Open-Label Dose Optimization phase of RP-BP-EF001 (N = 26)
The most common adverse events (> 2 subjects) included insomnia (30.8%), decreased appetite (23.1%), headache (23.1%), irritability (19.2%), cough (15.4%), pyrexia (15.4%), abdominal pain (11.5%), nasal congestion (11.5%), rhinorrhea (11.5%) and vomiting (11.5%).

Open Label Phase (11-week) phase of RP-BP-EF002 (N = 221)
The most common adverse events (≥ 5% of subjects) included decreased appetite (19.0%), headache (17.6%), insomnia (11.8%), upper abdominal pain (10.9%), upper respiratory tract infection (6.3%), irritability (5.4%) and fatigue (5.0%). Insomnia was categorized twice, as 11.8% under Nervous System Disorders and as 3.2% under Psychiatric Disorders. Other adverse events of interest that occurred in < 5% of subjects included affect lability (4.5%), vomiting (3.6%), nausea (2.7%), tachycardia (0.9%), tic (0.9%) and self-injurious behavior (0.5%).

Open Label Extension (up to 21 months) phase of RP-BP-EF001 (N = 22) and RP-BP-EF002 (N = 173)
The most common adverse events (> 2 subjects) for RP-BP-EF001 included insomnia (22.7%), decreased appetite (13.6%), headache (13.6%), viral infection (13.5%),
The most common adverse events (> 5% of subjects) for RP-BP-EF002 included headache (6.9%) and upper respiratory tract infection (6.9%).

7.4.2 Laboratory Findings

RP-BP-EF001 – clinical laboratory tests were collected at screening and visit 8 (end of double blind phase). Ten subjects had an abnormal chemistry result following a normal result at screening and 3 subjects had an abnormal hematology result following a normal result at screening, none were considered clinically significant.

RP-BP-EF002 – clinical laboratory tests were collected at screening, visit 3 (end of double-blind phase) and visit 8 for all subject. Fasting was not a requirement.

The sponsor included the laboratory findings as listings in the CSR (listing of patients with abnormal results by analyte and by patient, and shift results) as well as datasets in the submission. The sponsor did not provide an analysis of mean changes over time or potentially clinically significant (PCS) changes.

For the chemistry analytes, the majority of abnormal values were just below the lower limit of normal and were not clinically significant (e.g. low creatinine, BUN, LDH, protein). Subjects were not required be in a fasted state which likely affected some of the analytes such as glucose and some lipids; however, only a few subjects had elevated glucose (up to 169 mg/dL [normal range 60-115 mg/dL]) and triglycerides (up to 462 mg/dL [normal range 10-210 mg/dL]). Elevations in creatine kinase occurred in several subjects, most of these were also elevated at screening. For those subject with

elevations in CK (normal range 45-235 U/L), most were in the range of 250 – 350 U/L. A small number of subjects with normal screening CK had significant elevations at the end of the double-blind phase (e.g. 703, 798 and 1085 U/L); all received Methylphenidate ER during the double-blind phase. There were no comments regarding changes in physical activity or other variables that might influence CK. No adverse events consistent with elevated CK were reported in the clinical trial (rhabdomyolysis, muscle weakness, muscle aches, etc).

For the hematology indices, the majority of abnormal values were not clinically significant (e.g. hematocrit just above ULN). The majority of subjects did not have shifts from normal to low or high values for hematology indices.

7.4.3 Vital Signs/Physical Examination

RP-BP-EF001, vital signs were collected at each visit. Small mean increases were noted for systolic blood pressure and diastolic blood pressure. Interestingly, the mean change in pulse decreased and the mean change in weight increased – while the reverse is usually reported with stimulant therapy.

Table 20. Vital Signs: Mean Change from Baseline to End of Double-Blind Phase [RP-EF-001]

	Mean Change from Baseline
SBP (mmHg)	
Baseline (SD)	103.3 (6.5)
End of DB Phase	105.2 (9.9)
Change	1.88 (10.3)
DBP (mmHg)	
Baseline	60.5 (4.9)
End of DB Phase	64.5 (8.5)
Change	4.04 (8.8)
Pulse (bpm)	
Baseline	84.7 (11.4)
End of DB Phase	82.7 (11.5)
Change	-1.92 (13.1)
Weight (lb)	
Baseline	33.7 (12.1)
End of DB Phase	34.0 (12.4)
Change	0.26 (1.26)

Source: Tables 14.3.5 and 14.3.7 in CSR

For RP-BP-EF-002, vital signs were collected at each visit. Based on mean changes from baseline, there were small increases noted in systolic blood pressure, diastolic blood pressure and pulse. There did appear to be a trend for changes in vital signs and methylphenidate ER dose (the highest dose [40 mg] had the greatest mean changes for DBP, pulse and weight decrease). The methylphenidate ER 10 mg group was similar to placebo for mean change in systolic blood pressure and diastolic blood pressure. The sponsor did not perform a separate analysis evaluating the change in vital signs in the

Reference ID: 3717614

two potential cohorts in the study, younger children (6-12 years) and adolescents (13 – 17 years).

Adverse events resulting from vital sign abnormalities included “heart rate increased” occurring in 3 subjects receiving 30, 40 and 60 mg methylphenidate ER during the open-label phase. Two of these events were considered mild and one was moderate and led to discontinuation from the study. The subject who discontinued the study was an 8 YOM who had a heart rate of 82 bpm at screening, 101 bpm at baseline and 95 bpm at study termination. “Blood pressure increased” was noted in 3 subjects receiving 40 mg (n = 2) and 60 mg methylphenidate ER. All blood pressure increases were noted as mild and resolved, in two subjects the dose of study drug was reduced.

Table 21. Vital Signs: Mean Change from Baseline to End of Double-Blind Phase [RP-EF-002]

	MPH ER 10 mg (N = 49)	MPH ER 15 mg (N = 44)	MPH ER 20 mg (N = 45)	MPH ER 40 mg (N = 45)	Placebo (N = 47)
SBP (mmHg)					
Baseline (SD)	103.9 (12.3)	105.1 (11.3)	105.9 (13.7)	107.5 (12.5)	102.9 (12.6)
End of DB Phase	104.4 (12.1)	107.0 (10.8)	106.6 (14.2)	109.2 (11.8)	103.8 (11.2)
Change	0.60	1.83	0.63	1.67	0.91
DBP (mmHg)					
Baseline	65.4 (10.0)	64.6 (9.3)	65.3 (11.5)	65.6 (11.3)	62.4 (8.7)
End of DB Phase	65.8 (9.5)	65.3 (8.4)	65.7 (10.9)	67.8 (10.0)	62.9 (8.6)
Change	0.45	0.65	0.40	2.23	0.48
Pulse (bpm)					
Baseline	78.9 (10.2)	81.0 (12.3)	77.7 (12.5)	80.2 (11.1)	78.5 (14.3)
End of DB Phase	80.8 (12.9)	83.2 (12.5)	79.3 (12.1)	83.0 (12.1)	78.2 (13.2)
Change	1.92	2.15	1.52	2.86	-0.30
Weight (lb)*					
Baseline	97.0 (43.4)	99.32 (49.0)	102.0 (46.4)	111.0 (41.0)	89.8 (32.0)
End of DB Phase	96.6 (53.6)	99.42 (49.6)	101.4 (46.5)	109.9 (40.7)	90.2 (31.6)
Change	-0.40	0.10	-0.59	-1.05	0.40

Source: Table 14.3.5-2 from CSR
*Note that subjects ≤ 25 kg could not receive the 40 mg dose, therefore the weight for this treatment group will be higher than the others.

Weight was assessed at visits during the 11-week open-label extension phase. Mean weight change from baseline (lb) for visits 4, 5, 6, 7 and 8 were -0.07 (n = 216), -0.34 (n = 211), -0.53 (n = 208), -0.60 (n = 196), and -0.28 (n = 194).

7.4.4 Electrocardiograms (ECGs)

For RP-BP-EF001, ECGs were obtained at screening, baseline and end of the double-blind phase. The sponsor included a table for “ECG results over time” which is assumed to reflect ECGs when subjects were receiving methylphenidate ER – though this is not explicitly stated.

Table 22. ECG Parameters: Mean Change from Baseline to End of Double-Blind Phase [RP-BP-EF001]

ECG Parameter	Change from Baseline to End of DB Phase
PR (msec)	0.08
QRS (msec)	4.16
QT (msec)	-4.68
QTcB (msec)	12.92
QTcF (msec)	6.4
RR (msec)	-61.24
Heart rate (bpm)	7.48

Source: Table 12-9 of CSR

For RP-BP-EF002, ECGs were obtained at screening, baseline, end of the double-blind phase and end of the 11-week open-label phase.

The mean changes in QTcB and QTcF were small and variable between the methylphenidate ER groups and similar to placebo. The mean change in heart rate was similar to that obtained for vital signs, but was highest in the lowest methylphenidate ER group.

Table 23. ECG Parameters: Mean Change* from Baseline to End of Double-Blind Phase [RP-BP-EF002]

	Mean Change from Baseline				
ECG Parameter	MPH ER 10 mg (N = 49)	MPH ER 15 mg (N = 44)	MPH ER 20 mg (N = 450	MPH ER 40 mg (N = 45)	Placebo
PR (msec)	-0.1	-1.7	0.1	-0.2	0.1
QRS (msec)	-1.3	-1	-0.2	-1.6	0.3
QT (msec)	-4.5	-4.3	0.4	-9.7	0.9
QTcB (msec)	3.2	-1	0.3	0	1.6
QTcF (msec)	0.5	-2.2	0.2	-3.5	1.3
RR (msec)	-32	-15.4	1.6	-45.6	-2.4
Heart Rate (bpm)	3.1	1.7	-2	-3	0.2

Source: 12-13 from CSR
*Calculated from means obtained at baseline and end of double-blind period (not from raw data)

The sponsor provided a table with ECG mean changes that included minimum and maximum values (Table 12-13 in CSR). In reviewing this table, it was noted that the maximum values for QTcB and QTcF were $\geq$ 450 msec. Upon review of the JMP datasets, it was noted that a number of these higher QTc occurred during the screening and/or baseline phases of the study. The subjects who had a QTc < 450 at screening/baseline but had a QTc $\geq$ 450 during the double-blind phase or open-label phase are noted in Table 24. Of these 11 subjects, 9 had QTc $\geq$ 450 during the open-label phase. All of the QTc $\geq$ 450 were QTcB corrections and no subjects had QTcF $\geq$ 450. Though QTcB, can be inaccurate in cases of heart rate < 60 or > 100, only about half of these subjects had a heart rate > 100. A few of the cases do show an increasing QTc with increasing methylphenidate ER dose, though heart rate is also increasing with increasing dose and likely contributes to this finding (though this trend is also noted with QTcF, but to a lesser extent). Current product labeling for methylphenidate products do

include warnings regarding serious cardiac events such as sudden death, though product labeling does not include any data regarding QT prolongation as an adverse effect.

Table 24. Subjects* with QTc ≥ 450 msec in Double-Blind or Open-Label Phases [RP-BP-EF-002]

Subject No.	ECG Parameter	Baseline (Visit 2)	Double-Blind Phase (Visit 3)	Open-Label Phase (Visit 8)	Study Drug in DB Phase	MPH ER Dose at Visit 8
2-01-33-323	HR QTcB QTcF	59 404 404	52 425 435	79 *460* 439	Placebo	MPH ER 40 mg
2-03-05-104	HR QTcB QTcF	96 434 401	100 *455* 418	105 *456* 416	MPH ER 10 mg	MPH ER 30 mg
2-03-08-114	HR QTcB QTcF	74 424 410	102 434 397	103 *458* 419	MPH ER 10 mg	MPH ER 60 mg
2-03-12-132	HR QTcB QTcF	63 411 407	71 432 419	96 *472* 437	MPH ER 40 mg	MPH ER 40 mg
2-03-22-190	HR QTcB QTcF	77 446 427	87 433 407	102 *469* 429	MPH ER 15 mg	MPH ER 50 mg
2-03-26-201	HR QTcB QTcF	76 422 406	60 405 403	99 *459* 422	MPH ER 20 mg	MPH ER 30 mg
2-06-08-209	HR QTcB QTcF	86 433 407	87 421 395	109 *454* 410	MPH ER 15 mg	MPH ER 30 mg
2-07-20-345	HR QTcB QTcF	73 443 429	75 *452* 436	76 431 415	MPH ER 40 mg	MPH ER 50 mg
2-09-18-266	HR QTcB QTcF	88 434 407	107 *452* 410	71 390 378	MPH ER 10 mg	MPH ER 40 mg
2-11-01-144	HR QTcB QTcF	63 414 410	66 444 437	71 *454* 441	Placebo	MPH ER 20 mg
2-12-06-129	HR QTcB QTcF	98 432 398	85 437 412	87 *453* 425	MPH ER 10 mg	Unknown**

Source: JMP Datasets for ECG data
*Screening/baseline QTc < 450 msec
**Methylphenidate ER dose at Visit 8 obtained from JMP Dataset EXCM (Drug Dispensing), no notation at Visit 8 for this subject

No clinically significant abnormal ECGs were noted during the double-blind phase that were not present at either screening or baseline.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

No immunogenicity studies were conducted.

7.4.7 Suicidal Thoughts and Behaviors

The Columbia Suicide Severity Rating Scale (C-SSRS) was included as an instrument to monitor suicidal thoughts and behaviors in studies RP-BP-EF001 and RP-BP-EF002. The sponsor described the ratings findings and provided patient listings and the JMP dataset for C-SSRS ratings.

RP-BP-EF001 – At baseline, 4 patients provided an affirmative answer for at least one question concerning suicidal ideation. None of the patients had previous suicide attempts or non-suicidal self-injurious behavior. None of the patients indicated suicidal ideation since the last visit and none of the patients had actual attempts or non-suicidal injurious behavior since the last visit.

RP-BP-EF002 – At baseline, 11 patients provided an affirmative answer for at least one question concerning suicidal ideation. One patient reported a previous suicide attempt and non-suicidal self-injurious behavior in their lifetime – suicide attempt occurred ~4 years prior.

Four patients indicated suicidal ideation since the last visit – all instances occurred during open-label administration of methylphenidate ER. A 10 YOM (2-03-16-168) answered “yes” about wishing to be dead at Visit 4 with a comment in the JMP dataset “admitted just mad about not getting game”. This patient did not endorse this item at subsequent visits (5, 6 and 14). A 7 YOM (2-04-01-215) answered “yes” that he wished he was dead at Visit 7, but not at subsequent visits (8 and 15). A 10 YOM (2-12-17-309) reported wishing to be dead and having non-specific active suicidal thoughts during the second to last visit in the 21-month open-label extension phase, but not at the last visit that occurred 2 months later. A 9 YOF (2-04-09-339) reported wishing to be dead at visit 15 in the 21-month open-label extension phase, but not at any of the other visits either before or after visit 15 (16, 17 and 18 occurring 2, 4 and 6 months after visit 15). No patients in the study had actual attempts or non-suicidal injurious behavior since the last visit.

A review of the adverse events in the JMP database noted 4 patients with adverse events coded to preferred terms “self-injurious behavior”, “self-injurious ideation” or “intentional self-injury”. The verbatim terms for these adverse events were:

1. “threaten to harm himself at school. I will get a knife out of my…” [truncated in JMP] for a 7 YOM patient (2-16-14-159) with early termination at visit 14. This adverse event was coded to self-injurious ideation. This reviewer was not able to find any C-SSRS ratings in patient listings or JMP for this patient

after the screening ratings. Upon query, the sponsor indicated that this subject experienced self-injurious ideation at the end of the washout phase and did not continue in the study. No study drug was dispensed to this subject.

2. "self deprecation" coded to self-injurious behavior for a 7 YOM patient (2-18-11-333) at visit 7. Per JMP and patient listings, no C-SSRS items were endorsed at visits 3, 4, 5, 6, 7 or 8.

3. "Zyrtec overdose" coded to self-injurious behavior for a 17 YOM patient (2-06-13-226) at visit 15. Per JMP and patient listings, no C-SSRS items were endorsed at visits 3, 4, 5, 6, 7, 8, 16 or 17.

4. "skin clipping – both hands secondary to anxiety" coded to intentional self-injury for an 8 YOF patient (2-06-19-328) at visit 8. Per JMP and patient listings, no C-SSRS items were endorsed at visits 3, 4, 5, 6, 7 or 8.

CRFs for these subjects were not submitted by the sponsor as they did not meet criteria for submission (serious adverse event, discontinuation due to adverse event). The first case occurred in a subject after the washout phase, no study drug was administered. For the other cases, subjects were receiving open-label methylphenidate ER at the visit when the adverse event was captured. The second and fourth cases do not indicate symptoms consistent with suicidal thoughts or behaviors and no items on the C-SSRS were endorsed by these subjects. No further information is available for the third case, though the subject did continue in the study after this adverse event occurred.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study RP-BP-EF002 was a fixed-dose study evaluating the efficacy and safety of Methyphenidate ER 10, 15, 20 and 40 mg compared to placebo. In evaluating the common adverse events occurring in this study, there was no pattern of dose dependency (see Table 19).

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not studied in this submission.

7.5.3 Drug-Demographic Interactions

The Sponsor provided a tabulation of numbers of adverse events by gender, age and race without statistical analyses. In general, Study RP-EF-001 is too small for any meaningful interpretation regarding subgroup analyses.

Gender: For study RP-EF-002, though the numbers of females and males per dose group are small (e.g. n < 34 males, n < 20 females), there is a trend for females to report more adverse events compared to males in the 10, 15 and 20 mg groups, but not the 40 mg group. For the open-label extension phases, males and females reported similar rates of adverse events.

Race: For study RP-EF-002, approximately 70% of subjects were white. A greater frequency of adverse events occurred in the white compared to the nonwhite subgroup in the 10, 15 and 20 mg groups, but not the 40 mg group.

Age: For study RP-EF-002, the numbers of subjects per age cohort (6-8, 9-11, 12-14, 15-18) per dose group were small (the 20 mg and 40 mg had no subjects in the 15-18 year cohort). In the highest dose groups (20 and 40 mg), $\geq$ 50% of subjects in the 6-8 year cohort had adverse events compared to 33-44% in the other age cohorts. In the open-label phases, the percentage of subjects experiencing adverse events was similar between age cohorts.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied in this submission.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were studied in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity study was deemed necessary.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred in this study.

Reference ID: 3717614

7.6.3 Pediatrics

Refer to Section 7.4.3 of the review. A meeting with the Pediatric Review Committee (PeRC) is scheduled for March 11, 2015.

The sponsor submitted an Initial Pediatric Study Plan (iPSP) to IND 104,624 on 4/30/2014. DPP met with PeRC to review this iPSP on 6/18/2014. DPP clarified that ER products for ADHD are currently used off-label in patients 4 to < 6 years of age. PeRC recommended that studies be conducted in this age cohort but that these studies could be deferred because studies in patients > 6 years of age have been initiated. PeRC also recommended that the design of the study in this age cohort should be based on available information at the time of deferral (e.g. extrapolation from older aged patients versus placebo controlled study). Therefore, the iPSP should not include a specific study design.
These recommendations were outlined in a letter to the sponsor (7/24/2014):

1. (b) (4)
   We will grant a waiver in patients ages birth to less than 4 years of age. A deferral would be given for patients 4-(b) (4)years. An assessment would be presented for 6 to less than 18 years of age.
2. We recommend that the Plan for Pediatric Formulation Development section now include a development plan for patients 4 to less than 6 years of age.
3. We recommend that the Clinical Studies section include a plan for studies in patients 4 to less than 6 years of age.
4. We recommend that the Timeline of the Pediatric Plan now include for the types of studies needed in patients 4 to 5 years of age. We recommend 5 years from the date of this letter to commence studies.

The NDA for methylphenidate ER was submitted on 6/18/2014, before an agreed iPSP was in place. Therefore, the PSP timeline process is no longer relevant.

In an email sent to the sponsor 10/16/14, the following comment was included regarding the proposed pediatric plan:

1. (b) (4) PK studies for patients 4-6 years of age. The pharmacodynamic effects are correlated with the PK profile so any changes in profile may alter efficacy. Your product has a complex programmed release; therefore, we feel it is necessary to characterize the shape of the PK profile in the target population prior to initiation of the efficacy study. This information can be used to inform formulation suitability in this age range and design of the efficacy and safety trials (e.g., sampling for efficacy or safety assessment). The design of your PK study must be agreed upon with the Agency prior to initiating the study.
2. You are expected to initiate trials in this population as soon as feasible; you should justify the proposed start date of your pivotal efficacy trial based on the

timeline for your endpoint development plan. We encourage you to work with the Division and with the Agency's Study Endpoints and Labeling Development staff during your endpoint development process.

3. You will need to submit a new pediatric waiver/deferral plan to the NDA for review and provide us with the milestone dates (protocol submission, study completion, and final report submission).

Draft protocols for the PK (b) (4) and efficacy/safety (b) (4) studies for children with ADHD 4 to less than 6 years of age were submitted to IND 104624 on (b) (4).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose or drug abuse were identified in the clinical trials. These studies did not evaluate withdrawal or rebound symptoms.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Methylphenidate ER, under the tradename Biphentin, was approved by Health Canada in 2006. Between September 2008 and July 2012, approximately 101, 060 patient years of treatment occurred (patient use in the interval between product launch and September 2008 was not available to this sponsor). The sponsor reviewed the Annual Summary Safety Reports and identified adverse events that were serious or unlisted in the Biphentin Product Monograph. These adverse events included cardiac disorders (not further described), tachycardia, vision blurred, INR abnormal, WBC decreased, juvenile arthritis, scoliosis, diabetes mellitus, hypoglycemia, memory impairment, serotonin syndrome, aggression, agitation, depressive symptom, completed suicide, paranoia, suicidal ideation, tic, urinary incontinence, pollakiuria, dyspnea, angioedema and rash. Many of these adverse events are in current US product labeling for methylphenidate products (e.g. tachycardia, angioedema, rash).

9 Appendices

9.1 Literature Review/References

The sponsor did not provide a comprehensive review of the literature for methylphenidate. However, they did provide a list of literature citations used to support data presented in the submission relevant to methylphenidate and/or the treatment of ADHD. Methylphenidate ER was approved by Health Canada in 2006 (tradename Biphentin). The sponsor did provide a summary of the data available for Biphentin.

9.2 Labeling Recommendations

There were extensive revisions made to labeling proposed by the sponsor. Many revisions were for consistency with the "gold standard" labeling for methylphenidate (and other stimulant) products, Quillivant XR.

(b) (4) section 12 which includes the PK data from the pivotal PK studies that evaluated Aptensio XR (b) (4) mg compared to Ritalin IR (RLD) 25 mg TID in healthy adults.

(b) (4) include only data from the fixed-dose study (RP-BP-EF002); data from the smaller study could be described in the text.
Other modifications included (b) (4) replacement of the figure for study results with a table in section 14.

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this submission.

9.4 Inclusion and Exclusion Criteria for RP-BP-EF001 and RP-BP-EF002

Inclusion

1. Males and females ages 6 to 12 years (inclusive) [RP-BP-EF001], 6 to 18 years (inclusive) [RP-BP-EF002] at the time of consent.
2. ADHD diagnosis of all subtypes (except Not Otherwise Specified) as defined by the DSM-IV-TR, and supported by the K-SADS-PL. ADHD-RS-IV total or subscale scores > 90th percentile relative to the general population of children by age and gender at screening and baseline.
3. Subject was in need of pharmacological treatment for ADHD
    a. Subjects currently receiving ADHD medication were inadequately managed on their current stimulant dose which might include duration of action, safety or tolerability and meet these criteria at the screening visit (prior to washout).
    b. Subjects taking ADHD medication at screening completed a washout for a period equal to at least 5 half-lives of the given medication before completing baseline assessments (~1 to 2 days depending on the medication). The washout period will be 2 days.
4. Females of child-bearing potential must have a negative pregnancy test at screening and must be sterile, abstinent, or, if sexually active, be practicing an acceptable form of birth control (e.g. prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study.
5. Subject and parent/legally authorized representative are willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dose administration and transportation to and from the clinic.
6. Subject's parent or legally authorized representative must provide signature of informed consent indicating that they understand the purpose of and procedures required for the study, and willingness to participate in the study. There must be documentation of assent by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions. An assent form specifically addressing birth control is required for subjects who have experienced menses.

Exclusion Criteria (screening or baseline)

1. Subject is functioning at an estimated full scale intellectual level below 80 using the 4 subtest form of the WASI.
2. 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, personal or family history of

Tourette's syndrome as defined by the DSM-IV-TR criteria and supported by the K-SADS-PL.

3. Chronic medical illnesses including seizure disorder (excluding a history of febrile seizures), severe hypertension, untreated thyroid disease, known structural cardiac disorders, serious arrhythmias, cardiomyopathy, a known family history of sudden death, or glaucoma.
4. Use of monoamine oxidase inhibitors, or any psychotropic medication that have CNS effects or affect performance that are expected to have impact exceeding 14 days from the screening visit.
5. Planned use of prohibited drugs or agents from the screening visit until the end of the study.
6. Is pregnant or breastfeeding.
7. Has any clinically significant ECG or laboratory abnormalities at screening and/or baseline.
8. Has received an experimental drug or used an experimental medical device within the last 30 days prior to screening.
9. A history of hypersensitivity to methylphenidate.
10. Inability or unwillingness to follow directions and complete study assessments (subjects and parents/caregivers).
11. Is well controlled on his/her current treatment for ADHD.
12. Inability to take oral capsules.

9.5 Schedule of Events for RP-BP-EF001

Sponsor Table

	Screening (Phase 1)	Wash-out Call	Baseline (Phase 2)	Treatment Period-Dose Optimization (Phase 2)			Laboratory School Visits (Phase 3)			30-Day Follow-up Phone Call (Phase 4)
Visit	1	No visit	2	3	4	5	6 Practice	7	8/ET	No visit
Study Day	Up to -28	-7	0	7	14	21	28	35	42	72
Informed Consent/ Assent	X									
K-SADS-PL	X									
WASI	X									
Demographics	X									
Psychiatric History	X									
Medical/Medication history	X									
Physical Exam (height)	X								X	
Study Entry Criteria	X	X	X							
Body Weight	X		X	X	X	X		X	X	
Sitting Vital Signs	X		X	X	X	X	X	X	X	
Urine Drug Test	X								X	
12-Lead ECG	X		X						X	
Hematology	X								X	
Serum Chemistry	X								X	
Urinalysis	X								X	
Pregnancy Test	X		X						X	
Concomitant Medications	Ongoing log									
Adverse Events	X	X	X	X	X	X		X	X	X
CGI-S	X		X							
CGI-I				X	X	X	X			
ADHD-RS-IV[a]	X		X	X	X	X		X	X	
SKAMP							X	X	X	
PERMP Pre-test			X							
PERMP							X	X	X	
C-SSRS (suicidality)			X	X	X	X	X	X	X	
PedsQL - child			X				X	X	X	
CSHQ – Parent and Self-Report			X				X	X	X	
WFIRS - parent			X				X	X	X	
DPREMB-R (morning & evening)							Days 29,39,31,32,33,34;36,37,38,39,40,41			
Dispense open-label study drug			X	X	X	X				
Investigator dose assessment				X	X	X	X			
Randomization							X			

	Screening (Phase 1)	Wash-out Call	Baseline (Phase 2)	Treatment Period-Dose Optimization (Phase 2)			Laboratory School Visits (Phase 3)			30-Day Follow-up Phone Call (Phase 4)
Visit	1	No visit	2	3	4	5	6 Practice	7	8/ET	No visit
Study Day	Up to -28	-7	0	7	14	21	28	35	42	72
Dispense Double-Blind Study Drug							X	X		
Study Drug Compliance				X	X	X	X	X	X	
Study Completion										X

[a] Different raters and time periods were used for the Open-Label Dose Optimization phase and laboratory school visits of the Double-Blind phase, see Section 9.5.1.1.3.

9.6 Schedule of Events for RP-BP-EF002

Sponsor's Table.

	Screening (Phase 1)	Wash-out Call	Baseline & Randomized Fixed-Dose		Open-Label Treatment Period					30 Day Follow up Call	Compas-sionate Use
Visit	1	No visit	2	3	4	5	6	7	8/ET	No Visit	At least every 3 months
Study Day	Up to -28	-2/-3	0	7	14	21	28	56	84	114	--
Study Week	Up to -4	-1	0	1	2	3	4	8	12	17	--
Informed Consent/ Assent	X										
K-SADS-PL	X										
WASI	X										
Demographics	X										
Psychiatric History	X										
Medical/ Medication history	X										
Physical exam (+height)	X								X		
Inclusion/ Exclusion Criteria	X	X									
Body Weight	X		X	X	X	X	X	X	X		X
Sitting Vital Signs	X		X	X	X	X	X	X	X		X
Urine Drug Test	X								X		
12-Lead ECG	X		X	X					X		
Hematology	X			X					X		
Serum Chemistry	X			X					X		
Urinalysis	X			X					X		
Serum Pregnancy Test	X										
Urine Pregnancy Test			X						X		X
Concomitant Medications	Ongoing Log										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
CGI-S			X								
CGI-I				X	X	X	X	X	X		
ADHD-RS-IV	X		X	X	X	X	X	X	X		
C-SSRS	X			X	X	X	X	X	X		
PedsQL – Child			X	X					X		
CSHQ or ASHQ – Parent & Self-Report			X	X					X		
DPRMEB-R			Days								

	Screening (Phase 1)	Wash-out Call	Baseline & Randomized Fixed-Dose		Open-Label Treatment Period					30 Day Follow up Call	Compas-sionate Use
Visit	1	No visit	2	3	4	5	6	7	8/ET	No Visit	At least every 3 months
Study Day	Up to -28	-2/-3	0	7	14	21	28	56	84	114	--
(morning & evening)			1,2,3,4,5,6								
WFIRS - parent			X	X					X		
Randomization			X								
Dispense Double-Blind Study Drug			X								
Dispense Open-label Study Drug				X	X	X	X	X	X optional		
Study Drug Compliance				X	X	X	X	X	X	X	
Study Completion										X	

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

/s/

CARA L ALFARO
03/17/2015

LUCAS P KEMPF
03/20/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205831 **Applicant: Rhodes Pharmaceuticals, LP** **Stamp Date: 06/18/2014**

Drug Name: Methylphenidate hydrochloride extended release capsules **NDA/BLA Type: NDA 505(b)(2)**

On initial overview of the NDA/BLA 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.				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?				
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		The Sponsor included a Summary of Clinical Safety. Supportive studies not analyzed, summarized from publications.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		The Sponsor only included a Summary of Clinical Efficacy. Since one pivotal study is crossover and one is parallel, efficacy would be not be evaluated as an integrated approach.
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).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Ritalin Immediate Release tablets 25 mg
14.	Did the applicant provide a scientific bridge demonstrating	X			

Reference ID: 3608184

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				BA/BE studies
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: RP-BP-EF002 Study Title: A randomized, parallel, double-blind efficacy and safety study of Biphentin* methylphenidate hydrochloride extended release capsules compared to placebo in children and adolescents 6 to 18 years with attention deficit hyperactivity disorder Sample Size: 230 randomized Arms: Methylphenidate 10, 15, 20 or 40 mg/day; placebo Location in submission: Module 5.3.5.1 (b) (4)	X			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: RP-BP-EF001 A randomized, double-blind study of the time course of response to Biphentin* methylphenidate hydrochloride extended-release capsules as compared to placebo in children 6 to 12 years with attention deficit hyperactivity disorder in an analog classroom setting Pivotal Study #2: RP-BP-EF002 A randomized, parallel, double-blind efficacy and safety study of Biphentin* methylphenidate hydrochloride extended release capsules compared to placebo in children and adolescents 6 to 18 years with attention deficit hyperactivity disorder Indication (Sponsor proposed): Treatment of attention deficit hyperactivity disorder in patients 6 years and older (b) (4)	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Labeling has not been extensively reviewed at this time. Proposed indication (age range) not supported by studies.
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			On face appear to conform, will need input from Biometrics. Many changes made to endpoints during course of pivotal trials.
20.	Has the application submitted a rationale for assuming the			X	

Reference ID: 3608184

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data to U.S. population/practice of medicine in the submission?				
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 arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
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			An estimated 101, 203 patient years of exposure in subjects with ADHD in US and Canadian controlled clinical trials, open-label studies and in the Canadian market as an approved drug through July 2012.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
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			
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			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to			X	505(b)(2) – Schedule

[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.

[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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	assess the abuse liability of the product?				C II drug
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			
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

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

Subject 2-18-13-342 experienced the serious adverse event “injury-induced migraine headache”. The narrative states that the subject experienced a head injury, but no other details are provided. Please provide further details regarding the head injury.

Cara Alfaro, Pharm.D.

Clinical Analyst Date

Clinical Team Leader Date

Reference ID: 3608184

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

/s/

CARA L ALFARO
08/11/2014

MARK A RITTER
08/11/2014