CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	212038
Priority or Standard	Standard
Submit Date(s)	4/27/2018
Received Date(s)	4/27/2018
PDUFA Goal Date	2/27/2019
Division/Office	Division of Psychiatry Products/ ODE1
Reviewer Name(s)	Nancy Dickinson, PharmD.
Review Completion Date	1/29/2019
Established/Proper Name	Methylphenidate HCL
(Proposed) Trade Name	Adhansia XR
Applicant	Purdue Pharma Canada
Dosage Form(s)	Capsule, extended-release
Applicant Proposed Dosing Regimen(s)	25, 35, 45, 55, 70, 85 (b) (4) mg once daily in the morning
Applicant Proposed Indication(s)/Population(s)	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Patients ages 6 and above

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 8
1.4 Recommendations for Postmarket Requirements and Commitments 8

2 INTRODUCTION AND REGULATORY BACKGROUND 9

2.1 Product Information 9
2.2 Table of Currently Available Treatments for Proposed Indication 9
2.3 Availability of Proposed Active Ingredient in the United States 9
2.4 Important Safety Issues with Consideration to Related Drugs 10
2.5 Summary of Presubmission Regulatory Activity 10
2.6 Other Relevant Background Information 11

3 ETHICS AND GOOD CLINICAL PRACTICES 11

3.1 Submission Quality and Integrity 11
3.2 Compliance with Good Clinical Practices 11
3.3 Financial Disclosures 11

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES 12

4.1 Chemistry Manufacturing and Controls (CMC) 12
4.2 Clinical Microbiology 12
4.3 Preclinical Pharmacology-Toxicology 13
4.4 Clinical Pharmacology 13
4.5 Controlled Substances 13
4.6 Pediatric and Maternal Health 13

5 SOURCES OF CLINICAL DATA 13

5.1 Table of Clinical Trials 13
5.2 Review Strategy 16

6 REVIEW OF EFFICACY 16

6.1 Methods Protocol 063-010 (Adults) 18
6.2 Subject Disposition 19
Demographics 20
6.3 Analysis of Primary Endpoint 21
6.4 Analysis of Secondary Endpoints 21
6.5 Other Relevant Endpoints 22
6.6 Subpopulations 22
6.7 Clinical Information Relevant to Dosing Recommendations 22
6.8 Persistence and Durability of Effect; Tolerance 23
6.1.1 Methods Protocol 063-008 (Adults) 23

6.2.1 Subject Disposition....24
Demographics....24
6.3.1 Analysis of Primary Endpoints....25
6.4.1 Analysis of Secondary Endpoints....25
6.1.2 Methods Protocol 063-009 (Adolescents 12 to 17 years)....26
6.2.2 Subject Disposition....27
6.3.2 Analysis of Primary Endpoints....27
6.4.2 Analysis of Secondary Endpoints....28
6.1.3 Methods Protocol 063-015 (Children 6 to 12 years)....29
6.2.3 Subject Disposition....30
6.3.3 Analysis of Primary Endpoints....30
6.4.3 Analysis of Secondary Endpoints....30

7 REVIEW OF SAFETY....31

Safety Summary....31
7.1 Methods....32
7.1.2 Categorization of Adverse Events....32
7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence....32
7.2 Adequacy of Safety Assessments....32
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations....32
7.2.2 Explorations for Dose Response....33
7.2.3 Special Animal and In Vitro Testing....33
7.2.4 Routine Clinical Testing....33
7.2.5 Metabolic, Clearance, and Interaction Workup....33
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class....33
7.3 Major Safety Results....33
7.3.1 Deaths....33
7.3.A. Protocol 063-010 Adults....33
7.3.2 Nonfatal Serious Adverse Events (063-010)....34
7.3.3 Dropouts and Discontinuations (063-010)....34
7.3.4 Significant Adverse Events (063-010)....34
7.4 Supportive Safety Results (063-010)....35
7.4.1 Common Adverse Events (063-010)....35
7.4.2 Laboratory Findings (063-010)....38
7.4.3 Vital Signs (063-010)....38
7.4.4 Electrocardiograms (063-010)....38
7.3.B. Protocol 063-008 Adults....39
7.3.2.1 Nonfatal Serious Adverse Events (063-008)....39
7.3.3.1 Dropouts and Discontinuations (063-008)....39
7.3.4.1 Significant Adverse Events (063-008)....40
7.4.1.B Supportive Safety Results (063-008)....40
7.4.1.1 Common Adverse Events (063-008)....40
7.4.2.1 Laboratory Findings (063-008)....41

7.4.3.1 Vital Signs (063-008) 41
7.4.4.1 Electrocardiograms (063-008) 41
7.3.C. Protocol 063-009 (12 to 17 years) 42
7.3.2.2 Nonfatal Serious Adverse Events (063-009) 42
7.3.3.2 Dropouts and Discontinuations (063-009) 42
7.3.4.2 Significant Adverse Events (063-009) 45
7.4.1.C Supportive Safety Results (063-009) 45
7.4.1.2 Common Adverse Events (063-009) 45
7.4.2.2 Laboratory Findings (063-009) 46
7.4.3.2 Vital Signs (063-009) 46
7.4.4.2 Electrocardiograms (063-009) 46
7.3.D. Protocol 063-015 (6 to 12 years) 47
7.3.2.3 Nonfatal Serious Adverse Events (063-015) 48
7.3.3.3 Dropouts and Discontinuations (063-015) 48
7.4.1.D Supportive Safety Results (063-015) 48
7.4.1.3 Common Adverse Events (063-015) 48
7.4.2.3 Laboratory Findings (063-015) 51
7.4.3.3 Vital Signs (063-015) 51
7.4.4.3 Electrocardiograms (063-015) 51
7.4.5 Special Safety Studies/Clinical Trials 51
7.4.6 Immunogenicity 51
7.5 Other Safety Explorations 52
7.5.A. Protocol 063-012 long-term safety 52
7.5.1 Dose Dependency for Adverse Events 54
7.5.2 Time Dependency for Adverse Events 54
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 and Assessment of Effects on Growth 55
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 55
7.6.5 Submission-Specific Primary Safety Concerns 55
7.7 Additional Safety Issue 55

8 POSTMARKET EXPERIENCE 55

9 APPENDICES 55

9.1 Literature Review/References 55
9.2 Labeling Recommendations 55
9.3 Advisory Committee Meeting 55

Table of Tables

Table 1: Drugs Approved for Attention Deficit Hyperactivity Disorder 9
Table 2: Phase 3 Clinical Trials of PRC-063 15
Table 3: Disposition of All Randomized Subjects 20
Table 4: ADHD-5-RS Total Score and Change from Baseline to Visit 6, Week 5 ... 21
Table 5: Disposition of All Randomized Subjects 24
Table 6: Optimized Dose of PRC-063 (Study 063-008) 25
Table 7: Primary Endpoint PERMP-T Score for PRC-063 vs. Placebo 25
Table 8: Disposition of Randomized Subjects in FA 27
Table 9: Clinician rated ADHD-5-RS Total Scores (all doses combined, Study 063-009) 28
Table 10: Comparison of Efficacy on Doses 25, 45, 70, and 85 mg (Study 063-009) 28
Table 11: Optimized Dose and Number of Subjects (Study 063-015) 30
Table 12: SKAMP-C Scores all PRC-063 vs. Placebo (Study 063-015) 30
Table 13: Reason for Study 063-010 Discontinuation by Dose 34
Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms ... 36
Table 15: Optimized and Mean Doses (Study 063-008) 39
Table 16: Reason for Subject Discontinuation from Study 063-008 40
Table 17: TEAEs Occurring >2% in Study 063-008 by Treatment Arm 41
Table 18: PRC-063 Doses and Reason for Subject Discontinuation (Study 063-009) 43
Table 19: Study 063-009 Dose Titration Schedule 44
Table 20: TEAEs in Patients 12 to 17 years over 2% (Study 063-009) 46
Table 21: Number of Subjects by PRC-063 Dose 47
Table 22: TEAEs Reported during Study 063-015 50
Table 23: Number of Youngest Adolescents by Dose (Study 063-012) 53

Table of Figures

Figure 1: Graph of Clinical Global Impression by PRC-063 dose 22
Figure 2: Study 063-010 Adverse Event by Dose 37
Figure 3: Outcome of TEAEs per Treatment Arm (Study 063-010) 38
Figure 4: Days to Discontinuation any PRC-063 dose in Study 063-009.....44
Figure 5: Dose Distribution in Study 063-015 47
Figure 6: AE Counts by Treatment and Period of Study 063-015 49
Figure 7: Day of Start of AE During Study 063-015 51
Figure 8: Average Weight by Age Group Over Time 53

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The efficacy and safety of PRC-063 (methylphenidate, extended-release) are adequate to recommend approval for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). PRC-063 was evaluated in patients ages 6 years and over in four clinical trials.

The Applicant seeks approval for PRC-063 dosages 25, 35, 45, 55, 70, 85 (b) (4) mg. (b) (4)

Based on the differences in safety and efficacy findings among doses studied in the adult and pediatric populations, I recommend that the prescribing information in the label include the following information:

- Pediatric patients (6 to 17 years) have a target dose of 45 or 55 mg daily and maximum of 85 mg per day.
- Adult patients have a maximum daily dose of 100 mg. Adults taking doses above 85 mg daily had more adverse events.

The agreed-to-language in the label, to convey the mild-to-moderate safety concerns, is:

> Dosages higher than 100 mg daily in adults and 85 mg daily in pediatric patients have not been evaluated in clinical trials and are not recommended. Although efficacy was demonstrated in short-term controlled trials in adults at dosages of 100 mg daily, dosages above 85 mg daily were associated with a disproportionate increase in the incidence of certain adverse reactions. In short-term controlled trials in pediatric patients, efficacy was demonstrated at dosages of 70 mg daily, but dosages 70 mg daily and higher were associated with a disproportionate increase in the incidence of certain adverse reactions.

1.2 Risk-Benefit Assessment

ADHD is a childhood-onset disease with core symptoms of inattentiveness and/or hyperactivity. Psychostimulants or central nervous system (CNS) stimulants, have been the mainstay of pharmacologic therapy for ADHD for a half-century. Methylphenidate, a psychostimulant, was reformulated multiple times since the 1990s to increase the duration of clinical effect to address ADHD symptoms during the school day as well as during evening activities. There are already a number of extended-release, stimulant-based treatments for ADHD available at this time. PRC-063 was developed (b) (4).

Benefit: From the regulatory perspective, there is no reason to not approve PRC-063. Results of Phase 3 trials demonstrated reasonable safety and effectiveness when PRC-063 is dosed so that the benefits outweigh the risks (adverse events).

The risks listed below are generally not worse than with other marketed methylphenidate formulations.

Risk:

- In pediatric patients 12 to 17 years, distressing psychiatric adverse events (i.e., suicidal ideation, delirium) occurred at the highest doses, 70 and 85 mg/day during a fixed-dose study. However, in clinical practice, the dose would be optimized instead of taking a fixed-dose.
- PRC-063 treats ADHD symptomology for 11 to 13 hours based on results of environmental workplace or classroom studies. This duration is no added benefit from the numerous approved methylphenidate extended-release formulations. (Refer to Section 6.4.1 for discussion of PRC-063 meeting statistical significance in adults after the 13-hour timepoint.)
- PRC-063 was studied in the highest dosage strength (85-mg capsule) of methylphenidate to date. There is abuse potential of crushing the time-release beads to immediately obtain the full dose. However, it is unlikely that someone wishing to do this would seek 85 mg of PRC-063 instead of crushing multiple strengths of other methylphenidate products.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing requirement (PMR) is recommended to address the Pediatric Research Equity Act (PREA) requirement to ensure a that Adhansia XR (PRC-063) is evaluated in the pre-school ADHD population because we have evidence that extended-release stimulant formulations are used by patients ages 4- to 5-years-old.

Long-term safety data in pediatric patients (6 to 12 years) was not conducted for this application. I recommend requiring a long-term safety extension study for ages 4 to 12 years.

The agreed-to initial pediatric study plan, dated December 20, 2017, and submitted in the NDA application contains the Applicant's request for partial waiver to conduct studies in a pediatric population 0 to 3 year of age (neonates and young children) because the necessary studies are impossible or highly impractical in that population. I concur.

The agreed-to plan defers the following PREA studies, to be PMRs until Final Study Report submissions in February 2022, and March 2024, respectively.

- The Applicant will conduct a pharmacokinetic (PK) study in pediatric patients (4 to 5 years), then extrapolate efficacy to this younger population.
- A 1-year, open-label, study to assess the long-term safety of PRC-063 in children 4 to 12 years of age will be conducted. (b) (4)

The Pre-NDA meeting minutes dated December 26, 2017, state "The Division requested that the Sponsor perform z-score analyses for weight and height, adjusted for age and sex, for patients in the deferred 12-month safety study in children up to and including age 12 years. The Sponsor agreed to do so."

2 Introduction and Regulatory Background

2.1 Product Information

PRC-063, tradename, Adhansia XR, contains methylphenidate, a known psychostimulant for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The proposed doses are 25, 35, 45, 55, 70, 85, (b) (4) mg given orally, once daily in the morning.

NDA 212038 was submitted as a 505(b)(2) with the Reference Listed Drug (RLD) designated as Ritalin. This extended-release (ER) formulation is composed of a single, multilayered bead which provides a plasma profile similar to Ritalin immediate-release (IR) three times daily or Concerta, an approved extended-release methylphenidate, taken once daily. PRC-063 capsules contain multilayered beads that are composed of an IR layer comprising 20% of the methylphenidate dose and a controlled-release layer that comprises 80% of the dose. (b) (4)

2.2 Table of Currently Available Treatments for Proposed Indication

All of the drug products listed in Table 1 are approved for ADHD in children over 6 years old, adolescents, and adults. Various extended-release formulations exist for the stimulants.

Table 1: Drugs Approved for Attention Deficit Hyperactivity Disorder

Stimulants	Non-stimulant
Drug name	Drug name
amphetamine	atomoxetine
mixed salts of a single-entity amphetamine	clonidine
dextroamphetamine	guanfacine
dexmethylphenidate	
lisdexamfetamine	
methylphenidate	

[Source: Reviewer created]

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 events (e.g., sudden death, stroke, myocardial infarction), blood pressure and heart rate increases, psychiatric adverse reactions including induction of manic episode or psychosis, priapism, peripheral vasculopathy, and long-term growth suppression.

2.5 Summary of Presubmission Regulatory Activity

Regulatory History of IND
2013; PIND 118297- Rhodes Pharmaceuticals requested a Pre-IND meeting with the Division of Psychiatry (DPP) initially in 2013. They planned to develop an extended-release methylphenidate to provide efficacy (b) (4) in adolescents and adults. DPP issued a Written Response on June 14, 2013, saying that children (6 to 12 years) should be studied because ADHD is a childhood disorder. DPP gave advice about how to design the Phase 3 trials.

January 23, 2014; IND 11827 opened with four Phase 3 protocols for studies 063-008, -009, -010, and 063-012.

June 19, 2014; Rhodes Pharmaceuticals transfers sponsor obligations to partner with Purdue Pharma Canada.

December 30, 2016; End of Phase 2 meeting minutes include technical information about how to submit the application. DPP advises that Study 063-015 be fixed dose and that children 6 to 11 years be included in the long-term safety study (063-012). Further, the Sponsor planned to request a pediatric study waiver for 0 to (b) (4) years of age. (Notably, the Sponsor did not take DPP advice on evaluating PRC-063 in children.)

May 1, 2017; Written Response issued on Sponsor's Initial Pediatric Study Plan (iPSP). DPP discussed the iPSP twice with the internal Pediatric Review Committee (PeRC), on May 5, 2017, and January 5, 2018 to discuss multiple versions of the iPSP.

December 20, 2017; DPP issues iPSP Agreement letter for Sponsor's November 17, 2017, version of the iPSP. Refer to section 1.4 of this review.

December 26, 2107; Pre-NDA meeting minutes discuss the results of pediatric studies 063-015 and 063-017. Study 063-017 was a PK study. DPP agreed that the overall PRC-063 program and safety database appear acceptable for NDA filing.

Regulatory History of Proprietary Name
April 22, 2016; Proprietary name, (b) (4) denied by Division of Medication Error Prevention and Analysis (DMEPA) on grounds of evoking the word (b) (4)

May 8, 2017; Rhodes submits a request for proprietary name review for Adhansia. DMEPA grants the proprietary name on November 3, 2017.

Regulatory History of NDA
April 27, 2018; NDA 21038 was submitted. The application was filed on July 10, 2018.

December 12, 2018; Purdue Pharma Canada submitted a Change of IND and NDA Sponsor letters. The U.S. agent for IND 118297 is changed to (b) (4). Purdue Pharma Canada changes the ownership of NDA 21038 to Purdue Pharma, L.P., Stamford, Connecticut.

2.6 Other Relevant Background Information

PRC-063 was marketed in Canada in December 2017 with the tradename Foquest.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules appear complete. The submission was reasonably well organized and paginated to allow for an acceptable review. Subject unique identifiers are not duplicated in the patient data, consistent with data integrity.

3.2 Compliance with Good Clinical Practices

The Applicant attests that the studies were conducted in accordance with standard operating practices of Purdue Pharma Canada, which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

(1) Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”) and all of its Amendments to this date concerning medical research in humans.
(2) ICH Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use (Note for Guidance on Good Clinical Practice, 2002).

3.3 Financial Disclosures

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: 53

Number of investigators who are Applicant employees (including both full-time and part-time employees): __0_____

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): __0____

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _0__

Significant payments of other sorts: _0__

Proprietary interest in the product tested held by investigator: _0__

Significant equity interest held by investigator in sponsor of covered study: __0_

Is an attachment provided with details of the disclosable financial interests/ arrangements: Yes ☐ No ☐ N/A ☒

Is a description of the steps taken to minimize potential bias provided: Yes ☐ No ☐ N/A ☒

Number of investigators with certification of due diligence (FDA 3454, box 3) _0___

Is an attachment provided with the reason: Yes ☐ No ☐ N/A ☒

4 Significant Issues from Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

No clinically relevant CMC issues were identified regarding approvability of the application. However, the CMC reviewer learned from the Applicant that if the capsule is sprinkled on food and the beads are chewed instead of swallowed whole, a large proportion of the methylphenidate will be immediately released. This could represent a safety issue in children. Thus, the labeling, including the Medication Guide, will caution caregivers and patients that patients are not to chew the beads when PRC-063 is sprinkled on applesauce or yogurt.

The Office of Scientific Investigations (OSI) identified no issues after inspection of the site of trial 063-018, a bioequivalence study of Canadian PRC-063 compared to the to-be-marketed U.S. drug product.

4.2 Clinical Microbiology

No clinical microbiology studies were submitted.

4.3 Preclinical Pharmacology-Toxicology

No preclinical studies were submitted. The Applicant relies on data from the RLD, Ritalin IR, for this 505(b)(2) application. The Pharmacology/Toxicology will update the nonclinical section of the label to match the recommended dose of 85 (b) (4) mg.

4.4 Clinical Pharmacology

No clinically relevant clinical pharmacology issues were identified. The clinical pharmacology review was conducted by Dr. K. Kumi. Refer to that review for a comprehensive analysis of the pharmacokinetics of PRC-063.

4.5 Controlled Substances

Methylphenidate is a Schedule II medication known to have abuse potential. The Applicant conducted an *in vivo* study to evaluate the dose dumping. The study results indicate that dose dumping did not occur when PRC-063 was co-administered with 40% alcohol based on PK analysis. (b) (4) which will be labeled. PRC-063 does not appear to contain a greater risk of abuse than other approved methylphenidate products.

4.6 Pediatric and Maternal Health

The Division of Pediatric and Maternal Health was consulted for the labeling. They issued an inquiry to the Applicant dated July 31, 2018, about literature review of methylphenidate use in pregnancy and lactation. Purdue Pharma Canada responded on August 31, 2018. No outstanding issues are identified after discussion of the treatment emergent adverse events in the youngest patients receiving the highest dose (i.e., 12 to 13 years at 85 mg) during a 6-month long-term safety in pediatric patients (12 to 17 years). (Study 063-012)

5 Sources of Clinical Data

5.1 Table of Clinical Trials

The NDA 212083 submission contains five efficacy clinical trials and one long-term safety study.

The two trials for safety and efficacy in adults are a 4-week randomized, placebo-controlled, double blind study (063-010) and a 7-week open-label, dose-optimization phase followed by a 1-week double-blind, placebo-controlled phase (063-008). One 4-week, randomized, placebo-controlled, double-blind trial (063-009) was conducted in pediatric patients aged 12 to 17 years. The 4-week efficacy studies, 063-009 and 063-010, were extended into a 6-month open-label safety study (063-012).

Younger pediatric patients, aged 6 to 12 years, were studied in a 7-week trial consisting of 6-week open-label, dose-optimization phase, followed by 1-week, placebo-controlled, double-blind phase (063-015).

(b) (4)

Table 2 describes the aforementioned trials.

Table 2: Phase 3 Clinical Trials of PRC-063

Study Identifier	Study Design and Type of Control	Dosage Regimen; Route of Administration	Number of Subjects	Patient Population	Duration of Treatment
063-008	Randomized, placebo-controlled	Capsule, 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, 100 mg; QD; oral	59	Adults with ADHD (18 to 58 yrs)	Up to 7 weeks dose-optimize; 1-week DB
063-009	Randomized, placebo-controlled	Capsule, 25 mg, 45 mg, 70 mg, 85 mg; QD; oral	354	Adolescents with ADHD (12 to 17 yrs)	4 weeks
063-010	Randomized placebo-controlled	Capsule, 25 mg, 45 mg, 70 mg, 100 mg; QD; oral	375	Adults with ADHD (18 to 72 yrs)	4 weeks
063-012	Open-label, long-term safety	Capsule, 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, 100 mg; QD; oral	360	Adults and Adolescents with ADHD	6 months
[redacted]					(b) (4)
063-015	Randomized, parallel group	Capsule, 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, QD; oral	156	Children with ADHD (6 to 12 yrs)	Up to 6 weeks dose-optimize; 1-week DB

[Source: Reviewer created]

5.2 Review Strategy

Four trials were reviewed for an efficacy determination. Efficacy was evaluated in adults with two trials, Studies 063-008 and 063-010. Efficacy was evaluated in pediatric patients (6 to 17 years) with two trials, Studies 063-009 and 063-015.

Safety data was evaluated in the trials using the review tools JMP 13.0 and JMP Clinical 6.0 versions. Safety was reviewed from the efficacy trials that had placebo arms (i.e., (b) (4)), a 6-month, long-term, open-label safety study in adolescents and adults, and the Integrated Summary of Safety (ISS).

(b) (4)

6 Review of Efficacy

Efficacy Summary

Purdue Pharma Canada submitted four clinical trials for review in this 505(b)(2) application. There are two 4-week placebo-controlled studies (063-010 and -009) and two trials conducted in environmental settings to assess daily duration of efficacy (063-008 and -015). The Studies' designs were adequate, reviewed in the IND stage of development, and mimic other clinical trials described in approved psychostimulant labels with the indication for treatment of ADHD.

The doses of 25, 35, 45, 55, 70, 85, and 100 mg daily were evaluated. The mean doses from the dose-optimization trials were 82 mg/day in adults and 48 mg/day in pediatric patients (6 to 12 years).

Overall, considering the known efficacy of the drug product from a half-century of clinical experience, PRC-063 (methylphenidate, extended-release) demonstrated evidence of clinical efficacy.
I was surprised that not every dose or timepoint was statistically significant in the Applicant's and FDA efficacy analysis in three of the four trials.

The Applicant presented efficacy data in the NDA by combining all doses of PRC-063 vs. placebo, which did reach statistical significance. Not all the methylphenidate doses were efficacious in secondary analyses. The Applicant's stated explanation for why not all doses were efficacious was that a fixed-dose study forces titration to an assigned dose and, unlike in clinical practice, the approach may result in patients being under-treated or over-treated with methylphenidate, since they may exhibit lower efficacy or higher adverse events compared to an optimized dose. They also stated that Study 063-010 and -009 were not powered to demonstrated efficacy of each dose (25, 45, 70, 85 in adolescents, and 100 mg in adults) compared to placebo.

We, the Biostatistical Review Team and I, disagree because it appears that the Applicant did not conduct efficacy analyses as originally agreed. During the course of drug development, the Applicant submitted multiple versions of the Statistical Analysis Plan (SAP) for the 4-week trials, 063-010 and -009, even after the data was unblinded. FDA had given advice when earlier versions of the SAPs were submitted and during meetings. Refer to the Biostatistician Secondary Memo for details on the chronology of how the statistical analysis changed over time.

of the Agency biostatisticians on the review team for this application attempted to duplicate the efficacy results for the four clinical trials. The statistically significant results are:

- Study 063-010, Adults: The 45 (b) (4) mg doses were significant over placebo. The 25 and 70 mg were not.
- Study 063-009, Adolescents 12 to 17 years: The 45 and 70 mg doses were significant over placebo. The 25 and 85 mg were not.
- Study 063-008, Adults, environment study: The primary endpoint showed that PRC-063 was significant over placebo of all timepoint scores combined. At individual timepoints, the 14-hour post-dose time point failed, but the 11- hour and 16-hour efficacy assessments were significant. (b) (4).
- Study 063-015, Children 6 to 12 years, environment sudy: The primary endpoint showed that PRC-063 was significant over placebo of all timepoint scores combined. At individual timepoints, up to 13 hours, PRC-063 was significant compared to placebo.

Regarding the dose optimization study designs of 063-008 and -015, they are more likely than a fixed-dose design to find patients a beneficial dose that minimizes AEs and maximizes efficacy. However, with this open-label, dose-optimization period, patients that cannot tolerate the drug would drop out by the time they reach the placebo-controlled period. This disallows the clinician to get a fuller picture of the AEs during the double-blind, randomized period.

Population Generalizability

The Phase 3 clinical trials for PRC-063 were conducted in the United States and Canada, therefore, a high degree of generalizability of the trials' results to U.S. ADHD patients is anticipated.

The prevalence of ADHD among adults (18 to 44 years) is 4.4% based on diagnostic interview data from the National Comorbidity Survey Replication (NCS-R), (NIMH ADHD website accessed 1/4/19, https://www.nimh.nih.gov/health/statistics/attention-deficit-hyperactivity-disorder-adhd.shtml). As with pediatric patients, prevalence is higher for males (5.4%) versus females (3.2%). For race and ethnicity, non-Hispanic white patients have a higher prevalence (5.4%) than all other groups.

Age and race of the adult population from the PRC-063 studies is generalizable. The mean age of adults was about 35 years (Study 063-010, 33 ± 10.8 years; Study 063-008, 36 ± 11.9 years). The predominant race of subjects was 85 to 90% white. Unlike ADHD in the general U.S. population, the adult PRC-063 studies enrolled about 55% females.

The pediatric subject (6 to 17 years) population of the PRC-063 trials is generalizable to the U.S. ADHD population. The majority of subjects had "combined" subtype of ADHD, meaning inattentive and hyperactivity. There were about approximately twice as many males as females and the predominant race was about 60% white. African-American was the second most predominant race in the pediatric studies.

6.1 Methods Protocol 063-010 (Adults)

The objective of Study 063-010, a randomized, double-blind, placebo-controlled, parallel-arm, multi-center study, was to evaluate the clinical efficacy and safety of PRC-063 at 25, 45, 70, and 100 mg in adults (≥ 18 years) with ADHD. The study was conducted at 34 clinical sites in the United States and Canada.

The primary efficacy measure was the clinician administered adult ADHD Rating Scale (ADHD-5-RS) for dosage strengths of PRC-063 (25, 45, 70, or 100 mg/day) compared to placebo at Visit 6, Week 5. The secondary efficacy measure used a global clinical measure of improvement, the Clinical Global Impression–Improvement (CGI-I). The CGI-I was not pre-specified in the SAP. There were various other secondary endpoints not described in this review because they will not be described in the label and the results did not provide new information about use of methylphenidate for ADHD.

The study was adequately designed with a double-blind treatment period of 4-weeks. After informed consent, subjects were randomized to one of five treatment groups and received PRC-063 or placebo. The study had four phases:

(1) Screening, washout and a 1-week baseline;
(2) Forced-dose titration from starting dose of 25 or 45 mg up to the assigned final dose (25, 45, 70, or 100 mg) over a 2-week period;
(3) Evaluation over a 2-week period at the randomized dose (Visits 5 and 6 at Week 4 and 5, respectively); and
(4) 14-day safety follow-up by phone unless the subject continued to the 6-month safety study (063-012).

Subjects
Study 063-010 randomized 375 male and female patients (18 to 72 years).

Key Inclusion criteria were:

(1) Diagnosis of ADHD inattentive, hyperactive/impulsive or combined, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5);
(2) Non-pregnant or lactating females;
(3) Total score of 24 or greater on the clinician-rated ADHD-5-RS, as assessed at Visit 2, baseline.

Key Exclusion criteria were:

(1) Being diagnosed with or having a history of strokes, epilepsy, migraine headaches (greater than one instance every 2 months), glaucoma, thyrotoxicosis, tachyarrhythmias or severe angina pectoris or serious or unstable medical illness. Subjects with controlled or stable asthma or diabetes were permitted.
(2) Having cardiovascular issues such as elevated blood pressure or electrocardiogram (ECG) abnormalities at screening or any history of cardiovascular diseases.
(3) Having comorbid psychiatric diagnosis or substance abuse problem.

6.2 Subject Disposition

The investigators of Study 063-010 screened 465 subjects. Of these, 90 subjects were screening failures, and 375 subjects were randomized evenly by treatment group into the study. The Full Analysis Set was 368 per our Biostatistical Secondary Review memo. Table 3 lists subjects' disposition. Rates of subject discontinuation were similar between PRC-063 doses combined group (11.1%) and the placebo group (11.5%). Among subjects who received active treatment, the percentage of subjects who prematurely discontinued appears to be dose-related.

Protocol violations were not impactful to the primary analysis and were primarily missed doses or the evaluation visit was outside of the time window.

Table 3: Disposition of All Randomized Subjects

	Treatment Groups				
Category	**Placebo**	**25 mg**	**45 mg**	**70 mg**	**100 mg**
Randomized	78	77	73	73	74
Completed	69 (88.5%)	73 (94.8%)	69 (94.5%)	62 (84.9%)	61 (82.4%)
Discontinued (total)	9 (11.5%)	4 (5.2%)	4 (5.5%)	12 (16.4%)	13 (17.6%)
Reason for discontinuation					
Adverse event	2 (2.6%)	0	1 (1.4%)	2 (2.7%)	5 (6.8%)
Subject's choice	2 (2)	2 (2.6%)	2 (2.7%)	2 (2.7%)	3 (4.1%)
Lost to follow-up	3 (3.8%)	2 (2.6%)	0	5 (6.8%)	4 (5.4%)
Protocol violation	0	0	0	1 (1.4%)	1 (1.4%)
Non-Compliant	1 (1.3%)	0	0	2 (2.7%)	0
Incarceration	0	0	1 (1.4%)	0	0
Subject moved	1 (1.3%)	0	0	0	0

[Source: Reviewer modified Table 5 of Study 063-010 Report Body, Table ST 7-1, and Biostatistician Secondary Review]

Demographics

The mean age of all patients was 36 ± 11.9 years, ranging from 18 to 72 years old. Approximately one-third (35.2%) were between 18 and 29 years of age. Almost half (48.5%) were between 30 and 49 years of age. The smallest age range (15.7%) were older adults between 50 and 69 years and two were ≥70 years of age. The ages in the treatment groups were balanced. The placebo treatment group had a mean age of 37 ± 12.4 years and patients in all PRC-063 treatment groups had a mean age of 36 ± 11.8 years. Subjects in the placebo treatment group were 55.1% female and subjects in all PRC-063 treatment groups were 52.2% female.

As expected in the United States ADHD population, 84.5% of all subjects were white. The second largest racial demographic in Study 063-010 was African-American making up 10.9% of the adult study population. Race and ethnicity were balanced among the placebo, 25, 45, and 100 mg treatment groups. Subjects in the 70 mg PRC-063 group consisted of 93.2% white and only 1.4% African-American. Although unusual, it is doubtful that the imbalance among treatment arms affected efficacy results.

All subtypes of ADHD were evenly distributed among active and placebo groups. Subjects in the placebo treatment group were 28.2% inattentive, 2.6% hyperactive, and 69.2% combined-type. In the PRC-063 group the ADHD subtypes were 24.2% inattentive, 1.0% hyperactive, and 74.7% combined-type. In the placebo arm, 92.3% (72/78) of patients and 93.9% (279/297) of PRC-063 patients were markedly or moderately ill as baseline as assessed from the CGI-Severity scale.

6.3 Analysis of Primary Endpoint

Primary efficacy analyses were conducted on the Full Analysis Population (N=368). The primary endpoint, change from baseline, as measured by the ADHD-5-RS Total Score, met statistical significance for the combined all-PRC-063 subjects group (p=0.0026), the 45-mg group (p=0.0013) (b) (4) compared to placebo. The least squares (LS) Mean Total score for improvement from baseline was 14.49 for all subjects receiving PRC-063 compared to 9.82 for placebo-treated subjects. Although numerically superior, the 25 and 70 mg treatment groups were not statistically improved compared to the placebo treatment group. Refer to Table 4 for ADHD-5-RS scores by treatment arm.

Table 4: ADHD-5-RS Total Score and Change from Baseline to Visit 6, Week 5

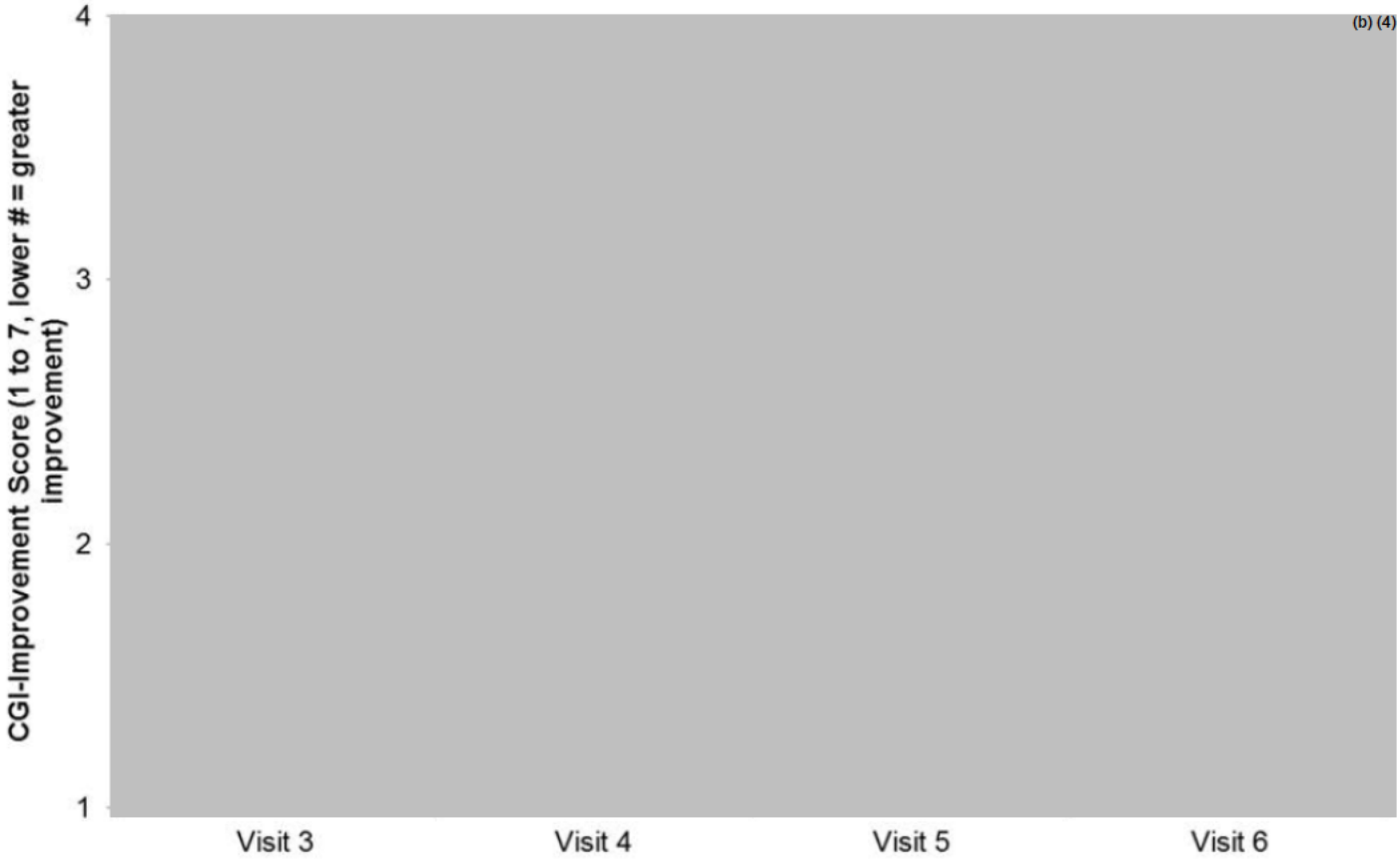
Score	25 mg PRC-063 (N=77) n (%)	45 mg PRC-063 (N=73) n (%)	70 mg PRC-063 (N=73) n (%)	100 mg PRC-063 (N=74) n (%)	All PRC-063 (N=297) n (%)	Placebo (N=78) n (%)
Total Score ADHD-RS-5				(b) (4)		
Baseline						
n	77	73	73		297	78
Mean (SD)	36.1 (8.14)	36.5 (7.19)	35.4 (7.44)		36.3 (7.68)	35.7 (8.42)
Median	39.0	36.0	36.0		37.0	36.5
Min, Max	14, 51	18, 52	15, 51		14, 52	17, 52
Visit 6 Observed Score						
n	73	69	62		265	69
Mean (SD)	24.2 (11.88)	19.9 (12.45)	24.0 (11.25)		21.8 (11.97)	26.1 (11.99)
Median	24.0	18.0	23.5		21.0	25
Min, Max	4, 54	1, 51	3, 49		0, 54	3, 51
p-value	<.0001	<.0001	<.0001		<.0001	<.0001
Visit 6 Change from baseline						
LS Mean	-11.8	-16.7	-11.9		-14.5	-9.8
LS Mean Diff from PBO	-2.0	-6.9	-2.1		-4.7	N/A
95% CI Diff from PBO	(-6.6, 2.6)	(-11.5, -2.2)	(-6.8, 2.7)		(-7.7, -1.6)	N/A
p-value	0.6750	0.0013	0.6720		0.0026	N/A

[Source: reviewer modified Table ST 8-11 in 063-010 Report Body]

6.4 Analysis of Secondary Endpoints

At Visit 6, the mean CGI-Improvement score was superior to placebo by 0.5 for all combined doses of PRC-063 (p=0.0017). At Visit 5, subjects in the 25, 45, 70 (b) (4) mg PRC-063 arms were statistically significantly improved compared to subjects on placebo (p=0.0068, p<0.0001, p=0.0072, (b) (4) respectively). Then, at Visit 6, only subjects in the 45-mg (p=0.0006) (b) (4) treatment groups met significance over placebo. Figure 1 graphically shows that all doses of PRC-063 clinically improved over the duration of the trial.

Figure 1: Graph of Clinical Global Impression by PRC-063 dose



[Source: Study 063-010 Report Body Figure 6]

6.5 Other Relevant Endpoints

Not applicable.

6.6 Subpopulations

Not applicable.

6.7 Clinical Information Relevant to Dosing Recommendations

Reviewer's Comment on Study 063-010:
The drug methylphenidate has long-standing clinical efficacy in adults and is dose-related until AEs appear at high doses. However, in Study 063-010 only the 45 (b) (4) mg doses were statistically significant over placebo on the primary endpoint. On the secondary endpoint, the individual doses were not statistically significant at the end of trial, but were at Visit 5, the week prior to Visit 6. The efficacy outcomes of Study 063-010 do not make sense with what is expected from methylphenidate using the familiar study design of a 4-week double-blind trial.

The recommended (b) (4) *45* (b) (4) *mg. I recommend approval of the 25 mg as a starting dose for titration purposes. I also recommend approving the 70 mg dose for ease of titration. Further, the 70 mg dose group numerically had greater change from baseline in the ADHD-RS-5 scale at Visit 6 compared to the placebo subjects' change in score (-11.9, PRC-063 70 mg vs. -9.8 placebo). A possible explanation for its failure to achieve statistical significance could be a flaw in the SAP or shoddy clinical trial data collection. The Biostatistical Reviewer's review describes flaws in the efficacy analysis.*

The Applicant's rationale for certain dose failures to meet the efficacy endpoint was that treatment is randomly assigned in a fixed-dose model, so subjects were not optimized on the dose that may treat their ADHD symptom better. The Report Body also said this study was not designed to properly assess efficacy by dose. Again, our Biostatistical Reviewer and I disagree with Applicant's rationale for the 25-mg and, especially, the 70-mg PRC-063 doses not showing statistical significance.

6.8 Persistence and Durability of Effect; Tolerance

Methylphenidate is a psychostimulant where the durability of effect and characterization about dose tolerance is already known. Not applicable.

6.1.1 Methods Protocol 063-008 (Adults)

The objective of Study 063-008, a randomized, double-blind, crossover, placebo-controlled, optimized-dose study was to assess the clinical efficacy, time of onset, and time course of efficacy over 16 hours of PRC-063 compared to placebo in adults in an adult workplace environment (AWE) setting. The study was conducted at two clinical sites in the United States.

Primary efficacy analysis was defined as the average Permanent Product Measure of Productivity (PERMP) total score. The PERMP is a skill adjusted math test which compares scores from the treatment and placebo groups at timepoints 1, 2, 5, 8, 11, 14 and 16 hours, post-dose. PERMP-T is the combined score obtained by adding PERMP-A (number of math problems attempted) and PERMP-C (number of math problems answered correctly). Secondary outcome measures included the onset and time course of efficacy of PRC-063 compared to placebo as measured by the PERMP-T, PERMP-A and PERMP-C at pre-dose and the aforementioned timepoints, post-dose. Again, there were various other secondary endpoints not described in this review because they will not be described in the label and the results did not provide new information about methylphenidate.

Subjects were titrated to an optimal dose of PRC-063—either 25, 35, 45, 55, 70, 85, or 100 mg—between a 2- and 7-week, open-label treatment period, followed by a 1-week, placebo-controlled, double-blind period prior to the AWE session. The optimized-dose design was employed to increase likelihood that subjects were titrated to a dose of PRC-063 that adequately controlled their ADHD symptoms without unwanted adverse events. The crossover design allowed for within subject analysis, increasing the statistical power of the study and enabling subjects to be their own control. There was a 7-day washout between the active treatment AWE session and placebo AWE session crossover periods.

Study 063-008 randomized 59 male and female patients (18 to 58 years). The subject inclusion and exclusion criteria were the same as Study 063-010.

6.2.1 Subject Disposition

Investigators from Study 063-008 screened 75 subjects. Of these, 16 subjects were screening failures, and 59 subjects were randomized into the study. The majority of discontinuations occurred in patients titrated with PRC-063 in the first period of the crossover study. The 13 discontinued subjects either did not have a first AWE session (n=10) or did not have a crossover (n=3) period. Table 5 lists the reasons for discontinuation.

Table 5: Disposition of All Randomized Subjects

Treatment Sequence Category	PRC-063 to Placebo	Placebo to PRC-063	All Subjects
Randomized	31	28	59
Completed	23 (74.2%)	23 (82.1%)	46 (78.0%)
Discontinued (total)	8 (25.8%)	5 (17.9%)	13 (22.0%)
Titration Phase	5 (16.1%)	1 (3.6%)	6 (10.2%)
AWE session 1	2 (6.5%)	2 (7.1%)	4 (6.8%)
AWE session 2	1 (3.2%)	2 (7.1%)	3 (5.1%)
Reason for discontinuation	5 (16.1%)	2 (7.1%)	7 (11.9%)
Adverse Event			
Subject's choice	2 (6.5%)	3 (10.7%)	5 (8.5%)
Lost to follow-up	0	0	0
Protocol violation	0	0	0
Lack of response to highest dose	1 (3.2%)	0	1 (1.7%)

[Source: Reviewer modified Tables 4 and ST 7-2 of 063-008 Report Body]

Demographics

The demographic data between the PRC-063 and placebo groups was evenly distributed for sex, age, and race. Ninety percent (n=53) subjects were white. More females (n=33, 55.9%) than males (n=26, 44.1%) were randomized. Mean age of all subjects at study entry was 33 ± 10.8 years. Of subjects in the study, 47.5% were between 18 and 29 years of age, 44.1% were between 30 and 49 years of age and 8.5% were between 50 and 69 years of age.

I calculated the mean optimized dose to be 82 mg/day based on number of patients optimized to each dose in Table 6. Our Biostatistics Reviewer calculated the modal optimal dose to be 70 mg/day.

Table 6: Optimized Dose of PRC-063 (Study 063-008)

Optimized Dose	**35 mg**	**45 mg**	**55 mg**	**70 mg**	**85 mg**	**100 mg**	**Total**
Number of Subjects	**0**	**2**	**5**	**15**	**11**	**12**	**45**

[Source: Table ST 7-2 of Applicant's CSR Study 063-008]

6.3.1 Analysis of Primary Endpoints

The Full Analysis (FA) population (N=46) consisted of all randomized subjects who received any amount of study medication and who had a baseline and a complete assessment of PERMP on both AWE sessions (i.e., with both active and placebo treatments) for at least one post-dose time point. Analysis of PERMP total scores were compared at timepoints pre-dose, 1, 2, 5, 8, 11, 14, and 16 hours. In the primary efficacy analysis, a strong period effect was discovered as the average (across treatments) PERMP scores in Period 2 were statistically significantly larger than in Period 1 ($p<0.0001$). The reason may be that patients had already practiced the test during the first period. Per the Biostatistics Review Team, the applicant conducted an ad hoc analysis by including the pre-dose score as a covariate in the MMRM model because of noticeable imbalance in pre-dose scores.

Subjects receiving PRC-063 had statistically significant improvement in attention, based on PERMP-T scores over placebo for all time points combined as shown in Table 7.

Table 7: Primary Endpoint PERMP-T Score for PRC-063 vs. Placebo

	PERMP-total; All time points combined	
	PRC-063	Placebo
n	45	45
Mean (SD)	270.2 (81.46)	256.5 (73.86)
Median	254.1	248.9
Min, Max	130, 470	109, 428
LS Mean	268.7 (11.24)	255.6 (10.87)
LS Mean Diff	13.05 (4.550)	N/A
95% CI for LS Mean Diff	(3.88, 22.23)	N/A
Treatment p-value	0.0064	N/A

[Source: Reviewer created from CSR and confirmed by FDA Statistician]

6.4.1 Analysis of Secondary Endpoints

Secondary analysis included the onset and time course of efficacy of PRC-063 compared with those of placebo as measured by the Total PERMP Score (PERMP-T), Number of Questions Attempted (PERMP-A), and Number of Questions Correct (PERMP-C) at pre-dose and 1, 2, 5, 8, 11, 14, and 16 hours post-dose. The "time of onset of efficacy" was defined as the earliest time point when the difference in the PERMP-T between the active treatment and placebo became statistically significant. The "time course of efficacy" (i.e., duration of efficacy) was defined as the latest time point

when the difference in the PERMP-T between the active treatment and placebo was statistically significant.

PRC-023 demonstrated superiority over placebo at time points 1, 2, 8, 11, and 16 hours post-dose (p-value= 0.0063, 0.0088, 0.0014, 0.0278, and 0.0045, respectively). PRC-063 was not statistically superior to placebo at time points 5 and 14 hours (p-value= 0.0786 and 0.2442). (b) (6) .

Reviewer's Comment on Study 063-008: The Biostatistician and I agree that PRC-063 was not significant at the 14-hour timepoint. Based on the FDA statistical review, a possible reason not all the timepoints through 16 hours post-dose were significant is because the effect of subjects learning the AWE session testing during the first testing period, so at the second crossover period, PRC-063 separated from placebo scores at all timepoints.

During labeling negotiations with the Applicant, we admitted that it did not make sense for the methylphenidate to show efficacy over placebo at 11-hours, not at 14-hours, but then again at 16-hours. We know that the PRC-063 release mechanism wanes over time in a slope and is not jagged.

6.1.2 Methods Protocol 063-009 (Adolescents 12 to 17 years)

Study 063-009 in adolescents was designed like the 4-week double-blind study in adults (063-010). The objective of this randomized, double-blind, placebo-controlled, parallel-arm, multi-center study was to evaluate the clinical efficacy and safety of PRC-063 25, 45, 70, and 85 mg in adolescents (12 to 17 years) with ADHD.

The study was conducted at 42 clinical sites per the subject level dataset. Site 08 was removed from Purdue Pharma Canada's FA population because of multiple major protocol violations. Our biostatistical review team agreed with not including Site 08 in their duplication of the Applicant's statistical analysis of Study 063-009.

The primary measure of efficacy was the clinician administered ADHD Rating Scale (ADHD-5-RS) for each dose of PRC-063 (25, 45, 70 or 85 mg/day) compared to placebo at Visit 6 at Week 5. The key secondary measure of efficacy used a global clinical measure of improvement, the Clinical Global Impression–Improvement (CGI-I). There were various other secondary endpoints not described in this review.

The study was adequately designed with a double-blind treatment period of 4-weeks. After informed consent, subjects were randomized to one of five treatment groups and received PRC-063 or placebo. The study had four phases:

(1) Screening, washout and a 1-week baseline;
(2) Forced-dose titration from starting dose of 25 mg up to the assigned final dose (25, 45, 70 or 85 mg) over a 2-week period;
(3) Evaluation over a 2-week period (Visits 5 and 6 at Weeks 3 and 4, respectively); and
(4) 14-day safety follow-up, unless the subject continued into the 6-month safety study (063-012).

Subjects
Study 063-009 had the same inclusion and exclusion criteria as the adult ADHD trials.

6.2.2 Subject Disposition

Study 063-009 randomized 354 male and female patients (12 to 17years), with the removal of clinical Site 08 (n=13). The FA population was 352. The safety population includes subjects from Site 08.

Subjects had a mean age of 14.2 years, ranging from 2 to 17 years old. The treatment groups had similar mean ages. The majority of subjects were male (67.5%), and this was true in each treatment group as well. Most subjects were white (68.6%), and not Hispanic or Latino (75.7%). Similar distributions of race and ethnicity were seen in the treatment groups. The population demographics of sex and race are as expected in an adolescent U.S. ADHD population.
The percentage of subjects who discontinued was slightly higher among subjects who received active treatment (9.2%) than among subjects who received placebo treatment (7.0%). Among subjects who received active treatment, the highest percentage of subjects who prematurely discontinued was in the highest dose group (12.9%) as shown in Table 8.

Table 8: Disposition of Randomized Subjects in FA

	Treatment Groups				
Category	**Placebo**	**25 mg**	**45 mg**	**70 mg**	**85 mg**
Randomized	71	71	69	73	70
Completed	66 (93.0%)	65 (91.5%)	64 (92.8%)	67 (91.8%)	62 (88.6%)
Discontinued (total)	5 (7.0%)	6 (8.5%)	5 (7.2%)	6 (8.2%)	8 (11.4%)
Reason for discontinuation					
Adverse Event	0	2 (2.8%)	3 (4.3%)	2 (2.7%)	3 (4.3%)
Subject's choice	3 (4.2%)	3 (4.2%)	1 (1.4%)	2 (2.7%)	4 (5.7%)
Lost to follow-up	1 (1.4%)	0	0	0	0
Protocol violation	1 (1.4%)	1 (1.4%)	0	1 (1.4%)	0
Physician decision	0	0	1 (1.4%)	1 (1.4%)	2 (2.9%)

[Source: Reviewer modified Tables 5 and ST 7-1 of 063-009 Report Body]

6.3.2 Analysis of Primary Endpoints

Primary efficacy analyses were conducted on the Full Analysis Population (N=354). For the primary efficacy analysis at Visit 6, subjects receiving PRC-063 had statistically significant improvement in ADHD symptoms compared to subjects who received placebo, based on the ADHD-5-RS Total Score. By Visit 6, the total LS mean score improved from baseline by 15.17 for all PRC-063 subjects vs. 10.98 for placebo-treated subjects (p=0.0067) demonstrated in Table 9.

Table 9: Clinician rated ADHD-5-RS Total Scores (all doses combined, Study 063-009)

ADHD-5-RS	Placebo (n=71)			All PRC-063 Treatments (n=283)		
Total Score	Mean (SD)	Median	Min, Max	Mean (SD)	Median	Min, Max
Visit 2 (Baseline)	37.3 (8.40)	36.0	21, 52	37.0 (8.44)	37.0	10, 54
Visit 6	26.2 (13.81)	27.5	0, 52	22.1 (12.19)	20.0	0, 54
Change from baseline	-10.98			-15.17		
	p<0.0001			p<0.0001		
Change from baseline vs. placebo	N/A			p=0.0067		

[Source: Reviewer created from CSR 063-009]

The LS mean differences and p-values of individual doses were inconsistent between the Applicant's statistical analysis and FDA's. Table 10 shows both. Viewing the individual treatment data as analyzed by Purdue Pharma Canada, only the 45 mg and 70 mg PRC-063 treatment groups had significant improvements from baseline at Visit 6 compared to placebo (16.60, p=0.0155 and 15.89, p=0.0401, respectively). By FDA analysis, the 85 mg dose in adolescents was p< 0.05 (p=0.0226) and nominally significant, but statistical significance was not reached after adjusting for multiplicity using the pre-specified procedure (p=0.0692). Based on our analysis, we agree that only the 45 and 70 mg doses of PRC-063 were significant over placebo.

Table 10: Comparison of Efficacy on Doses 25, 45, 70, and 85 mg (Study 063-009)

Analysis	**Change from Baseline (Week 1, Visit 2) in ADHD-5-RS Total Score to Week 5 (Visit 6)**					
		25mg	**45mg**	**70mg**	**85mg**	**All PRC-**
CSR	LS Mean diff	-2.0	-5.6	-4.9	-4.3	-4.2
Analysis:	95% CI	(-6.8, 2.8)	(-10.4, -0.8)	(-9.7, -0.2)	(-9.1, 0.6)	(-7.2, -1.2)
ANCOVA on	**p (adjusted)**	0.7031	**0.0155**	**0.0401**	0.1011	0.0067
Observed	p (unadjusted)	0.3112	0.0043	0.0115	0.0311	0.0067
Case						
SAP 2.0	LS Mean diff	-2.2	-5.4	-5.2	-4.4	-4.3
Analysis:	95% CI	(-5.9, 1.6)	(-9.2, -1.6)	(-9.0, -1.4)	(-8.2, -0.6)	(-7.3, -1.3)
MMRM	p (unadjusted)	0.2562	0.0052	0.0069	0.0226	0.0049

[Source: FDA Biostatistician Secondary Review]

6.4.2 Analysis of Secondary Endpoints

The key secondary measure of efficacy used a global clinical measure of improvement, the Clinical Global Impression –Improvement (CGI-I). However, the CGI-I was not pre-specified in the SAP to be included in labeling if positive. Therefore, I did not focus on this global measure or any of the various secondary scales.

Reviewer's Comment on Study 063-009:
Like the adult study 063-010, the Applicant stated that Study 063-009 was not powered to assess individual dose efficacy. I disagree. The FDA attempt to duplicate the Applicant's efficacy analysis was key in finding the discrepancies in the multiple versions of the SAP and finally, the individual dose findings. Refer to the FDA Statistics Secondary Review for details. I recommend approving the 25 mg for titration purposes. The 45, 70, and 85 mg doses should be approved for efficacy in pediatric patients (12 to 17 years), with the caveat that lower doses may be as effective with less CNS AEs. Refer to Section 7.3.C. in Review of Safety.

6.1.3 Methods Protocol 063-015 (Children 6 to 12 years)

The objective of this randomized, double-blind, crossover, placebo-controlled, optimized-dose study was to assess the clinical efficacy, time of onset and time course of efficacy over 13 hours of PRC-063 25, 45, 55, 70, and 85 mg compared to placebo in pediatric patients (6 to 12 years) diagnosed with ADHD in an analog classroom setting.

Primary efficacy of PRC-063 compared to placebo was measured by the Swanson, Kotkin, Agler, M-Flynn and Pelham-Combined (SKAMP-C) score. The SKAMP is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. The mean SKAMP-C score for each subject was the average of all SKAMP-C scores collected during the full day laboratory classroom, with the exception of the SKAMP-C score prior to dosing.

The key secondary objective was to estimate the time to onset and the duration of efficacy of PRC-063 as measured by the SKAMP-C score assessed during timepoints, through 13-hours in the laboratory classroom. As with the other three Phase 3 PRC-063 trials, there were various other supportive endpoints not described in this review because they will not be described in the label and the results did not provide new information about methylphenidate.

The study design was adequate; it lacked a crossover treatment period, as with the adult workplace environment study (063-008).
The study had the following periods:

1) Screening Period: up to 28 days;
2) 3-day Washout Period: for washout and collection of baseline diary information. Some medications may have required a washout period > 3 days or required a dose taper depending on the product labeling recommendations;
3) Open-label, Dose-optimization Period: up to a 6-week open-label, dose-optimization period during which subjects were titrated from a starting dose of 25 mg up to his/her optimal dose (25, 35, 45, 55, 70, or 85 mg/day);
4) Double-blind Treatment Period: 1-week double-blind period which included 1 full day of evaluations in a laboratory classroom;
5) Safety Follow-up Period: 1-week safety follow-up after the last dose of study medication.

Study 063-015 had the same inclusion and exclusion criteria as above except for age: Males or females ≥ 6 and ≤ 12 years of age. After giving written informed consent and screening,156 subjects were enrolled.

6.2.3 Subject Disposition

As expected in ADHD cases, there are more white males enrolled: 34.6% (n=54) female and 65.4% (n=102) male. The predominant races were either white (87 subjects; 55.8%) or African-American (60 subjects; 38.5%), and not Hispanic or Latino (112 subjects; 71.8%). The median age was 9 years. Overall, the ADHD subtype was predominately "combined" (131 subjects; 84.0%), with a small percentage of subjects who were "inattentive" (25 subjects, 16.0%). There were no subjects of the "hyperactive-impulsive" subtype.

The full analysis population was 147. There were eight discontinuations from the trial in the open-label period of the trial and one removed (total nine) after the classroom laboratory day for not meeting the FA population definition.

As in Table 11, the most patients were optimized to a dose between 45 to 55 mg. The approximate mean dose is 48 mg daily.

Table 11: Optimized Dose and Number of Subjects (Study 063-015)

	Optimal PRC-063 Dose						**Total PRC-**	**Total Placebo**	**Total Subject**
	25 mg	35 mg	45 mg	55 mg	70 mg	85 mg			
N of completers	8	15	20	19	8	4	74	73	147

[Source: FDA Biostatistician Review]

6.3.3 Analysis of Primary Endpoints

Based on the primary analysis results, PRC-063 demonstrated a statistically significant superiority to placebo in reducing the SKAMP-C score averaged across all post-dose hours during the laboratory classroom, as demonstrated in Table 12.

Table 12: SKAMP-C Scores all PRC-063 vs. Placebo (Study 063-015)

Treatment Group	Mean Pre-Dose Score on Classroom Day (SD)	LS Mean (SE) for the Classroom day	Placebo-subtracted Difference (95% CI)
PRC-063 (N=74)	14.4 (10.58)	10.3 (0.74)	-8.6 (-10.6, -6.6)
Placebo (N=73)	11.5 (7.13)	18.9 (0.73)	--

[Source: Table 14.2.1.1.1, Table 2.1.1.4, and FDA Statistician Review]

6.4.3 Analysis of Secondary Endpoints

The secondary efficacy endpoints were onset and duration of clinical effect. The treatment difference SKAMP-Combined scores at post-dose time points (1, 2, 4, 6, 8, 10, 12 and 13 hours) were used to evaluate the key secondary efficacy endpoints. The SKAMP-Combined scores were also statistically significantly lower (improved) at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with PRC-063 compared to placebo.

Reviewer's Comment on Study 063-015:
Based on this clinical trial, the recommended target dose for this young population should be 45 or 55 mg/day. In the 6- to 12-year-old ADHD population, (b) (6)

7 Review of Safety

Safety Summary

I reviewed safety datasets of 4 Phase 3 clinical trials of PRC-063. Of the four placebo-controlled studies, two studies were 4-week fixed-dose (063-010, 063-009) which allows for more meaningful adverse event (AE) comparison to patients in the placebo groups. The other two studies (063-008, 063-015) had an open-label, dose-optimization period lasting several weeks, which allowed time for patients to either drop out because of AEs or time to tolerate the AEs prior to the 1-week crossover double-blind periods. Hence, the former study design is superior for evaluating AEs.

Overall, psychiatric-related adverse events were the primary reason for patients discontinuing from the studies. The number of subjects discontinuing the Phase 3 trials early was predictable and occurred between 2 and 3 weeks.

Adults
Safety in adults was reviewed in 2 controlled trials (Protocols 063-010, 063-008). The safety findings were as expected with a psychostimulant, including from the 6-month safety extension study (063-012). The most common (≥5% and twice the rate of placebo) treatment-emergent adverse events (TEAEs) occurring with PRC-063 in adults were insomnia, dry mouth, decreased appetite, gastroesophageal reflux disease, gastroenteritis, and palpitations. Although more TEAEs were generally reported at the highest dosages, there is an inconsistent dose-response picture. The fixed-dose study leaned towards dose-related TEAEs, but Study 063-008 results did not. I do not have an explanation for the slightly inconsistent pattern of dose-dependent AEs in adults (e.g., diarrhea, feeling jittery) because in clinical practice, a dose-dependent relationship is expected. The mean dose in a small (N=59) dose-optimization study was approximately 82 mg daily.

Pediatric patients
This safety review focused more on the pediatric patient population because ADHD is a common childhood disease and patients (6 to 17 years) are likely to use an extended-release methylphenidate, like PRC-063. The most common (≥5% and twice the rate of placebo) TEAEs occurring with PRC-063 in pediatric patients were decreased appetite, insomnia, weight decreased, and upper abdominal pain. Because of the decreased appetite and weight decreased, I analyzed specific safety data from the 6-month long-term study.

Safety in adolescent patients, ages 12 to 17 years, was analyzed from one fixed-dose study (063-009). In the adolescent study, TEAEs were typically dose-related. The highest doses, 70 and 85 mg, are associated with psychiatric AEs leading to patient drop out for certain patients. Safety in patients ages 6 to 12, children, was analyzed from an acceptably sized trial (N=156, Study 063-015), considering that methylphenidate is a known drug. The optimized mean dose was 48 mg daily.

7.1 Methods

Safety was evaluated in five studies of PRC-063. There were four placebo-controlled studies (063-010, 063-008, 063-009, 063-015) and one open-label 6-month extension study (063-012). Safety results for each controlled study are described in sequence, below, after each study header.

7.1.2 Categorization of Adverse Events

The Applicant categorized adverse events using MedDRA versions as follows:

- 063-010, version 17.0
- 063-008, version 17.0
- 063-009, version 17.0
- 063-015, version 20.0
- 063-012, version 17.0

I analyzed Adverse Events Analysis Datasets (ADAE) by body system, dictionary-derived term category (AEDECOD), and the reported terms for the AE (AETERM). I determined if the AETERMs were appropriately collected in the AEDECOD, combining similar terms together (e.g., insomnia, initial insomnia) for analysis. For the pediatric studies, I investigated age sub-groups for AE comparison.

7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence

I did not pool studies because there were different populations based on age and study design. The ISS pooled all five trials, but that dataset did not confer ease of review due to differences in duration of the placebo-controlled periods.

7.2 Adequacy of Safety Assessments

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

During the drug development, including pharmacokinetic trials, there were 1126 subjects exposed to PRC-063. The greatest number of subjects were exposed to the 45-mg dose level (n=749) and the 25-mg dose level (n=708) because those were the starting doses for titration. The median cumulative duration of exposure was 33.0 days, ranging from 1 to 250 days. There were no subjects who were exposed to PRC-063 for greater than 12 months.

The size of the Phase 3 safety database was adequate to evaluate the safety of PRC-063. There were 925 subjects exposed to PRC-063 in the Phase 3 studies. The highest number of subjects were

exposed to 45 mg (748 subjects; 80.9%), and the lowest number of subjects were exposed to 100 mg (145 subjects; 15.7%).

The doses of PRC-063 ranged from 25 to 100 mg depending on the age group and study design. The available dosage strengths were adequate for the pediatric and adult populations and provided ease of titration (25, 35, 45, 55, 70, 85, and 100 mg). The 100-mg dose was only studied in adult patients, therefore it will not be approved for the pediatric patients. For comparison, the highest approved extended-release methylphenidate for pediatric patients is Concerta 72mg.

Demographics of the populations are discussed in Section 6 of this review.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

The biopharmaceutical studies submitted in the application were for the purpose of bioavailability and bioequivalence. No new information was submitted on metabolic pathways; refer to the RLD.

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

Not applicable. PRC-063 is a 505(b)(2) application for a well-known psychostimulant, methylphenidate, having expected AEs.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in any study of PRC-063.

7.3.A. Protocol 063-010 Adults

I used the Distribution of Adverse Events review from the tool JMP Clinical 6.0 to analyze the safety results of Study 063-010 in adults. I then cross-referenced the study results with the Report Body and JMP 13.0.

The safety dataset consisted of 375 patients. The largest number of subjects was in the 100-mg treatment arm. Although this creates an uneven distribution among treatment groups, the largest number is acceptable in the highest dose group in order to analyze safety.

- Placebo, n=78
- All PRC-063, n=297
- PRC-063 25 mg, n=77
- PRC-063 45 mg, n=73
- PRC-063 70 mg, n=73
- PRC-063 100 mg, n=100

7.3.2 Nonfatal Serious Adverse Events (063-010)

One subject in the PRC-063 45 mg group had uterine cancer, which was not related to treatment.

7.3.3 Dropouts and Discontinuations (063-010)

The treatment-emergent adverse events (TEAEs) leading to study discontinuation were in the psychiatric disorder body system. Eight subjects discontinued the trial in the PRC-063 group and two in the placebo group. Table 13 shows that most patients (7%) who withdrew from the trial were in the 100-mg PRC-063 treatment group, which is indicative of dose-related AEs with methylphenidate.

Table 13: Reason for Study 063-010 Discontinuation by Dose

Treatment group	Number of subjects (%)	TEAE
placebo	2(2.6)	irritability
PRC-063 25 mg	0	N/A
PRC-063 45 mg	1(1.4)	insomnia
PRC-063 70 mg	2(2.7)	anxiety, irritablity
PRC-063 100 mg	5(6.8)	affect lability, anxiety, emotional disorder, insomnia, lip swelling*
* unrelated to PRC-063		

[Source: Reviewer created from Table ST 9-7]

7.3.4 Significant Adverse Events (063-010)

Severe TEAEs occurred in twice as many patients taking PRC-063 (n=12, 4.0%) than in the placebo group (n=2, 2.6%). Based on the mechanism of action of methylphenidate, I concluded that the reported severity, along with the type of TEAEs was dose-related. For example, in the 100-mg PRC-063 group, the reported severe TEAEs were anxiety, emotional disorder, insomnia, mood altered, and psychotic disorder. The patient ((b) (6)) who reported severe mood altered and psychotic disorder

experienced “resolved” symptoms. The patients (n=3) who reported the other severe TEAEs discontinued from Study 063-010.

The patients in the placebo and 45-mg and 70-mg PRC-063 groups each reported two cases of severe TEAEs. In the 25-mg PRC-063 group, four patients reported severe TEAEs, but the adverse events were not attributable to active drug (e.g., cellulitis, muscle strain, nephrolithiasis). The other patient reported severe headache.

7.4 Supportive Safety Results (063-010)

7.4.1 Common Adverse Events (063-010)

As expected, TEAEs were lowest in the placebo group and increased in frequency as the daily dose of PRC-063 was increased. TEAEs were experienced by 44.9% of subjects in the placebo group, 51.9% in the 25-mg group, 65.8% in the 45-mg group, 69.9% in the 70-mg group and 74.3% in the 100-mg group.

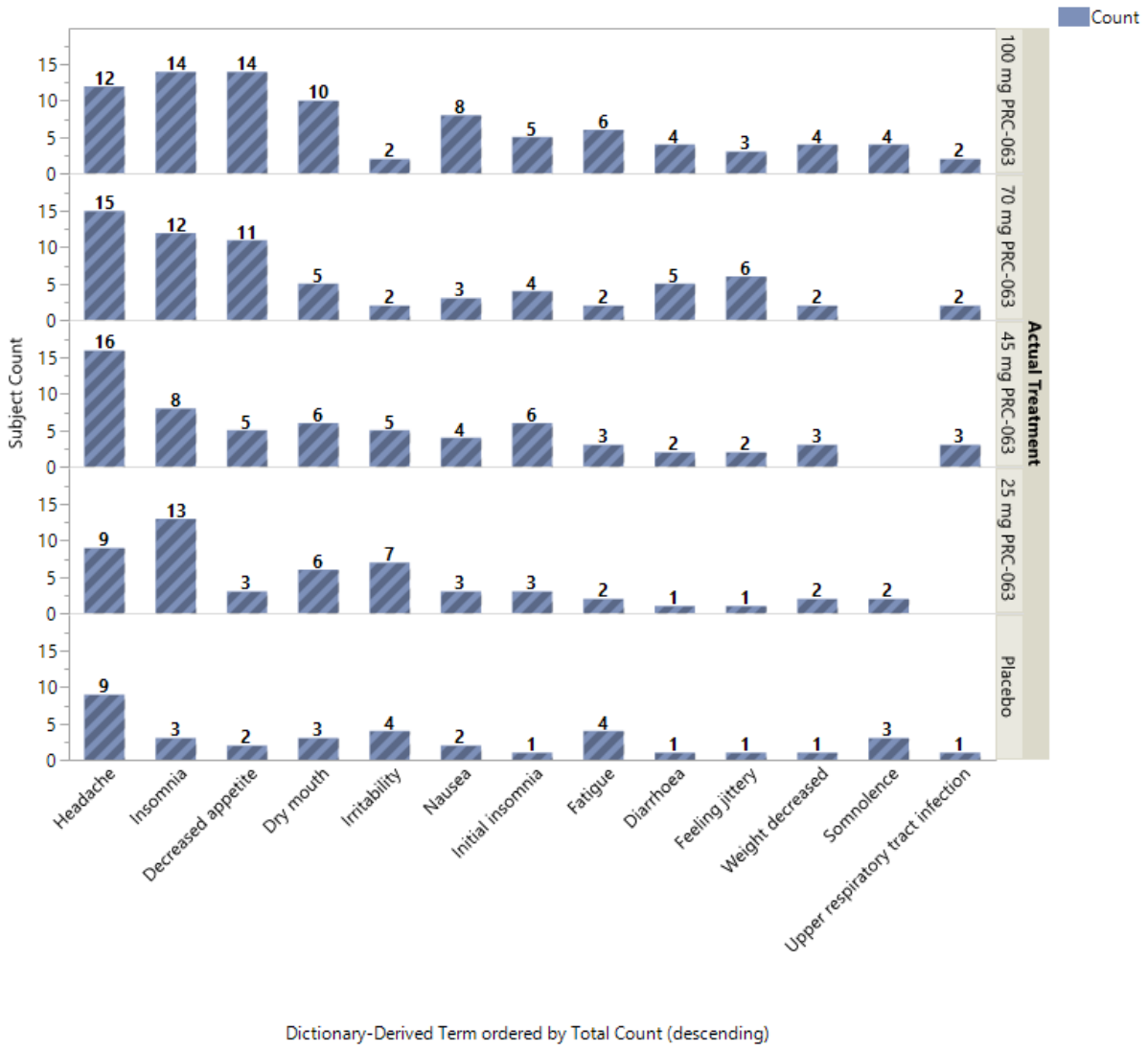
The most frequent treatment-emergent adverse events for subjects on PRC-063 were headache (17.5% of subjects receiving PRC-063 vs. 11.5% of subjects receiving placebo), insomnia/initial insomnia (21.8% vs. 5.1%), decreased appetite (8.8% vs. 2.6%), dry mouth (7.2% vs. 3.8%), nausea (4.8% vs. 2.6%), diarrhea (3.2% vs. 1.3%), feeling jittery (3.2% vs. 1.3%) and weight decreased (2.9% vs. 1.3%). The TEAEs reported ≥2% by dose, presented in Table 14 and graphically depicted in Figure 2, were mostly dose-related. Exceptions were insomnia (which occurred at nearly the same rate between the 25-mg and 100-mg PRC-063 doses), feeling jittery (with the greatest percent (8.2%) in the 70 mg arm), and weight decreased. Although upper respiratory infections occurred collectively more in the PRC-063 arms, I do not believe it is treatment-related based on the mechanism of methylphenidate.

Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms

Study 063-010 N=375	PRC-063 25mg N=77		PRC-063 45mg N=73		PRC-063 70mg N=73		PRC-063 100mg N=100		PRC-063 all doses N=297		Placebo N=78	
Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Insomnia	13	16.9%	8	11.0%	12	16.4%	14	18.9%	47	12.5%	3	3.8%
Initial insomnia	3	3.9%	6	8.2%	4	5.5%	5	6.8%	18	4.8%	1	1.3%
Dry mouth	6	7.8%	6	8.2%	5	6.8%	10	13.5%	27	7.2%	3	3.8%
Nausea	3	3.9%	4	5.5%	3	4.1%	8	10.8%	18	4.8%	2	2.6%
Diarrhea	1	1.3%	2	2.7%	5	6.8%	4	5.4%	12	3.2%	1	1.3%
Decreased appetite	3	3.9%	5	6.8%	11	15.1%	14	18.9%	33	8.8%	2	2.6%
Feeling jittery	1	1.3%	2	2.7%	6	8.2%	3	4.1%	12	3.2%	1	1.3%
Weight decreased	2	2.6%	3	4.1%	2	2.7%	4	5.4%	11	2.9%	1	1.3%
Upper respiratory tract infection	.	.	3	4.1%	2	2.7%	2	2.7%	7	1.9%	1	1.3%

[Source: Reviewer created using JMP Clinical 6.0]

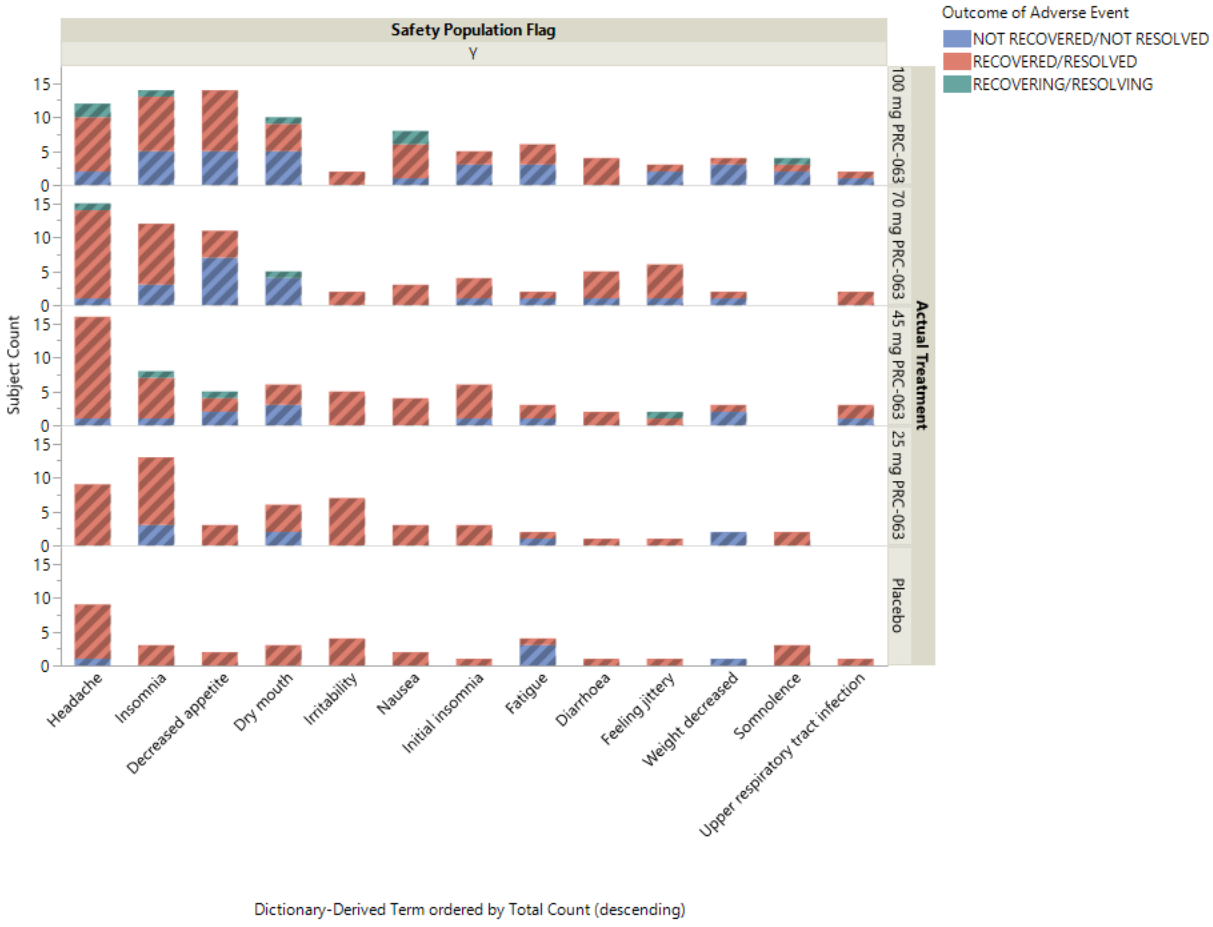
Figure 2: Study 063-010 Adverse Event by Dose



[Source: Reviewer created using JMP Clinical 6.0]

In Study 063-010, the 70-mg and 100-mg PRC-063 treatment arms reported the most “not resolved” TEAEs. No treatment arm had zero “not resolved” TEAEs reported, shown in Figure 3.

Figure 3: Outcome of TEAEs per Treatment Arm (Study 063-010)



[Source: Reviewer created using JMP Clinical 6.0]

7.4.2 Laboratory Findings (063-010)

No safety issued identified.

7.4.3 Vital Signs (063-010)

Increased blood pressure was reported in four patients in Study 063-010. No dose correlation can be made with blood pressure and treatment group.

7.4.4 Electrocardiograms (063-010)

In the placebo group, one patient had a repolarization abnormality. This finding is not clinically meaningful for PRC-063.

7.3.B. Protocol 063-008 Adults

I analyzed TEAEs that occurred during the crossover, 1-week randomized withdrawal period of Study 063-008 using JMP Clinical 6.0 and cross-referenced with JMP 13.0. No unexpected TEAEs related to methylphenidate were reported during the 7-week open-label dose-optimization period of the trial and are not discussed in this review. Additionally, the design of Study 063-008 lends subjects to incur less TEAEs over time due to tolerance.

The safety dataset consisted of the 59 patients randomized to PRC-063 or placebo. The treatment groups were balanced with 28 in placebo group and 31 in the PRC-063 group because subjects were their own controls and compared two crossover periods.

As listed in Table 15, most patients were optimized to PRC-063 at 70 mg daily. The approximate mean was 82 mg daily.

Table 15: Optimized and Mean Doses (Study 063-008)

PRC-063 Dose after optimization	Number of Subjects N=59
35 mg	1
45 mg	4
55 mg	7
70 mg	19
85 mg	14
100 mg	14
Mean Dose	approximately 82 mg

[Source: Reviewer created.]

7.3.2.1 Nonfatal Serious Adverse Events (063-008)

No deaths or serious adverse events were reported during Study 063-008.

7.3.3.1 Dropouts and Discontinuations (063-008)

During the randomized period of Study 063-008, more subjects discontinued the study in the PRC-063 group (5, 16.1%) compared to the placebo group (2, 7.1%). The TEAEs leading to discontinuing the study are in Table 16. The nausea, elevated blood pressure, and hypomania appear attributable to PRC-063.

Table 16: Reason for Subject Discontinuation from Study 063-008

Subject ID	Dose PRC-063	TEAE leading to D/C
(b) (6)	70	nausea, moderate severity
	35	viral infection
	85	bronchitis
	55	viral gastroenteritis
	45	elevated BP, mild
	85	weight loss on Day 60, stomach flu Days 53 to 58
	70	hypomania

[Source: Reviewer created from ADAE and ADSL datasets using JMP 13.0]

7.3.4.1 Significant Adverse Events (063-008)

Subject (b) (6) had a case of severe insomnia on Day 73 but did not withdraw from the trial; likely because the safety analysis period ended the next day. The investigator labeled the insomnia as not applicable to drug and the subject was labeled "recovered." It is unlikely that the patient would develop insomnia at the end of a methylphenidate trial due to a drug-effect, so I agree with the investigator.

7.4.1.B Supportive Safety Results (063-008)

7.4.1.1 Common Adverse Events (063-008)

Reviewer's Comment: Near the end of the review cycle, during labeling negotiations, we ultimately decided to remove the results of this study because it was a crossover study and when subjects are their own control during a double-blind period, the results are difficult to interpret and apply to the general population. During labeling, the table of adverse events occurring during the double-blind phase was displayed two different ways. The first was a comparison of adverse events occurring in the first cross-over period (PRC-063-to-Placebo) to the second (Placebo-to-PRC-063), as below. The second version of the table planned to compare the percentage of adverse events reported while subjects took PRC-063 or placebo. (That table is not in this review, but the raw data I generated was provided to the Applicant.)

The most frequently reported TEAEs over 2% and greater than placebo were libido decreased, gastroesophageal reflux disease, gastroenteritis, abdominal pain, postural dizziness, tremor, and palpitations (as listed in Table 17). The likely TEAEs related to PRC-063 are libido decreased, abdominal pain, postural dizziness, tremor, and palpitations. Total insomnia (including initial insomnia, middle insomnia, terminal insomnia, and delayed sleep phase) occurred at 15.1% in both treatment groups. Withdrawal effects may explain why the placebo group experienced insomnia at the same rate as the PRC-063 treatment group.

Table 17: TEAEs Occurring >2% in Study 063-008 by Treatment Arm

Study 063-008 Crossover		PRC-063 Any dose		Placebo		
N=59		N=31		N=28		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Psychiatric disorders	Initial insomnia	10	40.0%	7	26.9%	17
	Insomnia	7	28.0%	8	30.8%	15
	Middle insomnia	5	20.0%	7	26.9%	12
	Terminal insomnia	.	.	1	3.8%	1
	Delayed sleep phase	1	4.0%	.	.	1
	insomnia*	23	15.1%	23	15.1%	46
	Libido decreased	1	4.0%	.	.	1
Gastrointestinal disorders	Gastrooesophageal reflux disease	2	8.0%	.	.	2
	Gastroenteritis	2	8.0%	.	.	2
	Abdominal pain	1	4.0%	.	.	1
Nervous system disorders	Dizziness postural	1	4.0%	.	.	1
	Tremor	1	4.0%	.	.	1
Cardiac disorders	Palpitations	2	8.0%	.	.	2

* insomnia, initial insomnia, terminal insomnia, middle insomnia, delayed sleep phase

7.4.2.1 Laboratory Findings (063-008)

No safety issued identified.

7.4.3.1 Vital Signs (063-008)

The mean change in systolic blood pressure (SBP) was 3.3 mmHG. However, no dose correlation can be made with blood pressure and treatment group.

7.4.4.1 Electrocardiograms (063-008)

No clinically significant abnormalities occurred.

7.3.C. Protocol 063-009 (12 to 17 years)

I used the Distribution of Adverse Events review from the tool JMP Clinical 6.0 to analyze the safety results of Study 063-009 in pediatric patients (12 to 17 years). I then cross-referenced the study results with the Report Body and JMP 13.0.

The safety dataset consisted of 367 patients. The highest dose studied in pediatric patients (12 to 17 years) was 85 mg PRC-063. The treatment groups were evenly balanced by number of subjects, sex (with each group including roughly twice as many males as females), and by race (where approximately 55% of patients in each group were white). The distribution of randomized patients represents the incidence of ADHD in the United States.

- Placebo, n=74
- All PRC-063, n=293
- PRC-063 25 mg, n=73
- PRC-063 45 mg, n=72
- PRC-063 70 mg, n=76
- PRC-063 85 mg, n=72

7.3.2.2 Nonfatal Serious Adverse Events (063-009)

No deaths nor serious adverse events occurred during Study 063-009.

7.3.3.2 Dropouts and Discontinuations (063-009)

There were 10 patients (3.4%) who terminated the study early due to TEAEs. Each PRC-063 treatment group (25, 45, 70, and 85 mg) had patients discontinue the study prematurely, whereas no one in the placebo group dropped out from TEAEs. Refer to the shaded boxes in Table 18 for the number of dropouts in each PRC-063 arm. There appears to be no correlation with dose and rate of discontinuations.

The reasons for patient withdrawal from the trial are listed in Table 18. There were three cases of irritability leading to discontinuation in the PRC-063 groups, with two in the 85-mg treatment group.

Table 18: PRC-063 Doses and Reason for Subject Discontinuation (Study 063-009)

Count Total % Col % Row %	# in Arm	#D/C	Total of Safety Pop.	Subject ID	Reason
25 mg PRC-063	71	2	73	(b) (6)	dizziness
	19.4	0.5	19.9		dysphoria
	19.9	20.0			
	97.3	2.7			
45 mg PRC-063	69	3	72		irritiability
	18.8	0.8	19.6		anxiety
	19.3	30.0			headaches
	95.8	4.2			
70 mg PRC-063	74	2	76		depressed mood
	20.2	0.5	20.7		suicidal ideation
	20.7	20.0			
	97.4	2.6			
85 mg PRC-063	69	3	72		irritiability
	18.8	0.8	19.6		delirium
	19.3	30.0			irritiability
	95.8	4.2			
Placebo	74	0	74		
	20.2	0.0	20.2		
	20.7	0.0			
	100.0	0.0			
Total	357	10	367		
	97.3	2.7			

[Source of Table 13: Reviewer created using JMP Clinical 6.0 and supporting tables]

The patients in Table 18 who discontinued Study 063-009 in the 70- and 85-mg groups experienced psychiatric TEAEs that were likely PRC-063-related. The more distressing ones are described below.

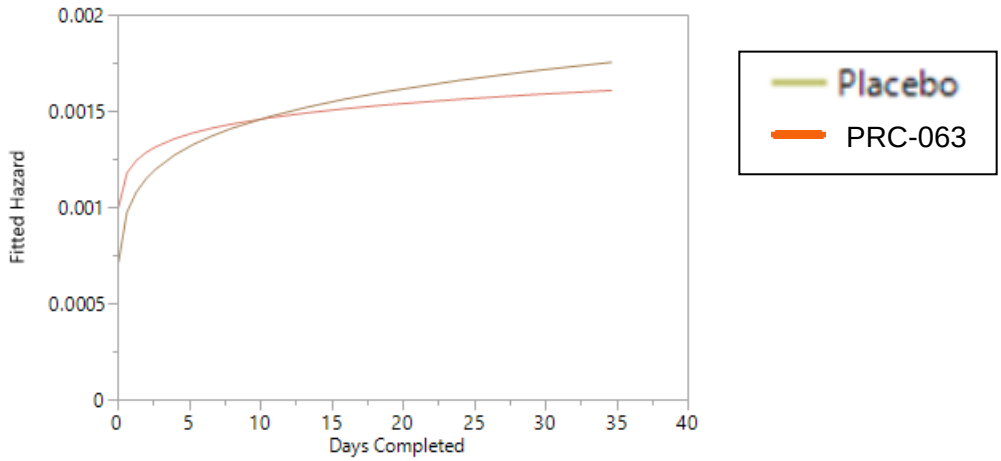
Subject ID (b) (6) (PRC-063 70 mg) withdrew from the study on 21-days post-Visit 1. At the time of the study, he was 14 years-old. The investigator gave the reason of depressed mood. However, the case report form for this subject indicates a myriad of other psychiatric- or nervous system-related events that started on the same day. They were “severe” thirst, lethargy, irritable mood, blunted “zombie affect”, slurred speech, indecision, and confusion. The subject recovered after withdrawing PRC-063.

At the time of the study, Subject ID (b) (6) (PRC-063 70 mg) was a 17-year-old male without previous psychiatric history or concomitant medications, per the case report form. After 19-days post Visit 1, he experienced “moderate” suicidal ideation and PRC-063 was discontinued.

Subject (b) (6) (PRC-063 85 mg) withdrew from the study on 16-days post-Visit 1. At the time of the study, he was 14 years-old. On Day 16, the investigator observed moderate restlessness. Then on Day 18, moderate delirium was reported. On Day 19, the investigator discontinued the PRC-063 and started risperidone 0.5 mg twice daily. The patient had two unscheduled visits for vital signs on Days 20 and 23. The restlessness and delirium resolved on Day 22. No other concomitant medications were listed in the case report form.

Figure 4 illustrates the time to discontinuation during Study 063-009. Subjects in the PRC-063 treatment groups start dropping out 10 days after the study starts.

Figure 4: Days to Discontinuation any PRC-063 dose in Study 063-009



[Source: Reviewer created using JMP Clinical 6.0]

During the review cycle, I asked the Applicant to describe the PRC-063 titration schedule to the randomized fixed dose to assess if the titration schedule was too quick and was responsible for study discontinuations. The titration schedule in Table 19 was fitting with clinical usage and not overly quick.

Table 19: Study 063-009 Dose Titration Schedule

063-009	Following a one-week washout/baseline, patients were titrated every 5 to 10 days to a randomized fixed dose according to the scheme below • *25 mg (weeks 2 to 5)* • *45 mg [titrated from 25 mg (week 2) to 45 mg (week 3, week 4 and week 5)]* • *70 mg [titrated from 25 mg (week 2) to 45 mg (week 3) to 70 mg (week 4 and week 5)]* • *85 mg [titrated from 45 mg (week 2) to 70 mg (week 3) to 85 mg (week 4 and week 5)]*

7.3.4.2 Significant Adverse Events (063-009)

Clinically significant TEAEs from Study 063-009 were described in Section 7.3.3.2 Discontinuations.

7.4.1.C Supportive Safety Results (063-009)

7.4.1.2 Common Adverse Events (063-009)

A greater percentage (52.6%) of subjects in the PRC-063 treatment group (all doses combined) had adverse events compared to those treated with placebo (32.4%). As expected with methylphenidate, the most common treatment-related adverse events were psychiatric disorders (22.2% PRC-063 vs. 10.8% placebo), followed by metabolism and nutrition disorders (20.1% vs. 2.7%, respectively) and nervous system disorders (16.0% vs. 13.5%, respectively).

The TEAEs reported ≥2% and greater than placebo are listed in Table 20. Overall, the incidences of metabolism and nutrition disorder TEAEs increase with dose (6.8%, 19.4%, 27.6%, and 26.4% in the 25, 45, 70, and 85 mg dose groups, respectively). Psychiatric disorders represent the combined terms of sleep disorder, initial insomnia, and insomnia. The insomnias are dose-dependent, unsurprisingly (9.6%, 9.7%, 18.4%, and 19.4% for the 25, 45, 70, and 85 mg dose groups, respectively). The incidence of gastrointestinal and nervous system disorder treatment-related AEs did not appear to be dose-related.

Table 20: TEAEs in Patients 12 to 17 years over 2% (Study 063-009)

Study 063-009		25 mg PRC-063		45 mg PRC-063		70 mg PRC-063		85 mg PRC-063		all doses PRC-063		Placebo	
	N=367	N=73		N=72		N=76		N=72		N=293		N=74	
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Psychiatric disorders	Insomnia, initial insomnia, sleep disorder	7	9.6%	7	9.7%	14	18.4%	14	19.4%	42	14.3%	1	1.4%
Nervous system disorders	Dizziness	2	2.7%	2	2.8%	4	5.3%	3	4.2%	11	3.8%	1	1.4%
Metabolism and nutrition disorders	Decreased appetite	5	6.8%	14	19.4%	21	27.6%	19	26.4%	59	20.1%	.	.
Gastrointestinal disorders	Nausea	2	2.7%	4	5.6%	5	6.6%	6	8.3%	17	5.8%	3	4.1%
	Abdominal pain upper	6	8.2%	2	2.8%	5	6.6%	4	5.6%	17	5.8%	2	2.7%
	Dry mouth	1	1.4%	.	.	4	5.3%	3	4.2%	8	2.7%	1	1.4%
	Vomiting	1	1.4%	1	1.4%	2	2.6%	4	5.6%	8	2.7%	.	.
Investigations	Weight decreased	1	1.4%	3	4.2%	9	11.8%	9	12.5%	22	7.5%	.	.

[Source: Reviewer created using JMP Clinical 6.0]

7.4.2.2 Laboratory Findings (063-009)

No safety issues identified.

7.4.3.2 Vital Signs (063-009)

In both the PRC-063 treatment group and the placebo group, 1.4% of subjects had increased blood pressure. No dose-related differences were identified.

7.4.4.2 Electrocardiograms (063-009)

No clinically significant differences between PRC-063 treatment groups and placebo group exist. Additionally, no dose-related abnormalities were identified.

7.3.D. Protocol 063-015 (6 to 12 years)

Like the adult study 063-008, Study 063-015 (6 to 12 years) had a dose optimization period (6-weeks) first followed by a 1-week randomized, double-blind, placebo-controlled phase for evaluating efficacy. To analyze safety, I used the Distribution of Adverse Events review for the controlled period and the Demographic Distribution Report from the tool JMP Clinical 6.0.

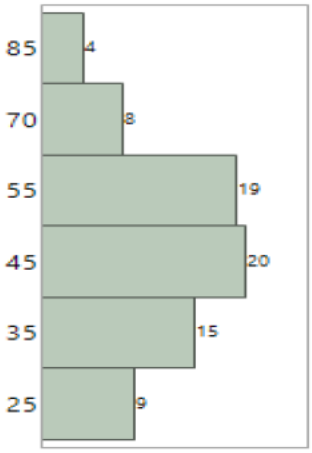
The safety dataset consisted of 156 patients. The pediatric patients were optimized to six different doses. Because this study was not a fixed dose design, there are uneven numbers of subjects taking each dose. The highest dose studied in pediatric patients (6 to 12 years) was 85 mg PRC-063 (n=4). The treatment groups were, overall, balanced by sex with the 25, 35, 45, 55, and 70 mg group including roughly twice as many males as females. The 85-mg PRC-063 group contained two females and two male patients. There were twice as many white patients (n=48) in the study than African-American patients (n=25).

Table 21 and Figure 5 illustrate the number of patients optimized to each available dose strength. The mean was approximately 48 mg daily.

Table 21: Number of Subjects by PRC-063 Dose

- Placebo, n=73
- All PRC-063, n=75
- PRC-063 25 mg, n=9
- PRC-063 45 mg, n=20
- PRC-063 55 mg, n=19
- PRC-063 70 mg, n=8
- PRC-063 85 mg, n=4

Figure 5: Dose Distribution in Study 063-015



[Source: Reviewer created.]

7.3.2.3 Nonfatal Serious Adverse Events (063-015)

No deaths, serious adverse events, nor any TEAEs labeled “severe” occurred during Study 063-015.

7.3.3.3 Dropouts and Discontinuations (063-015)

During the open-label, dose-optimization period (Week 2) of Study 063-015, two subjects, both taking PRC-063 at 35 mg, experienced TEAEs leading to study discontinuation.

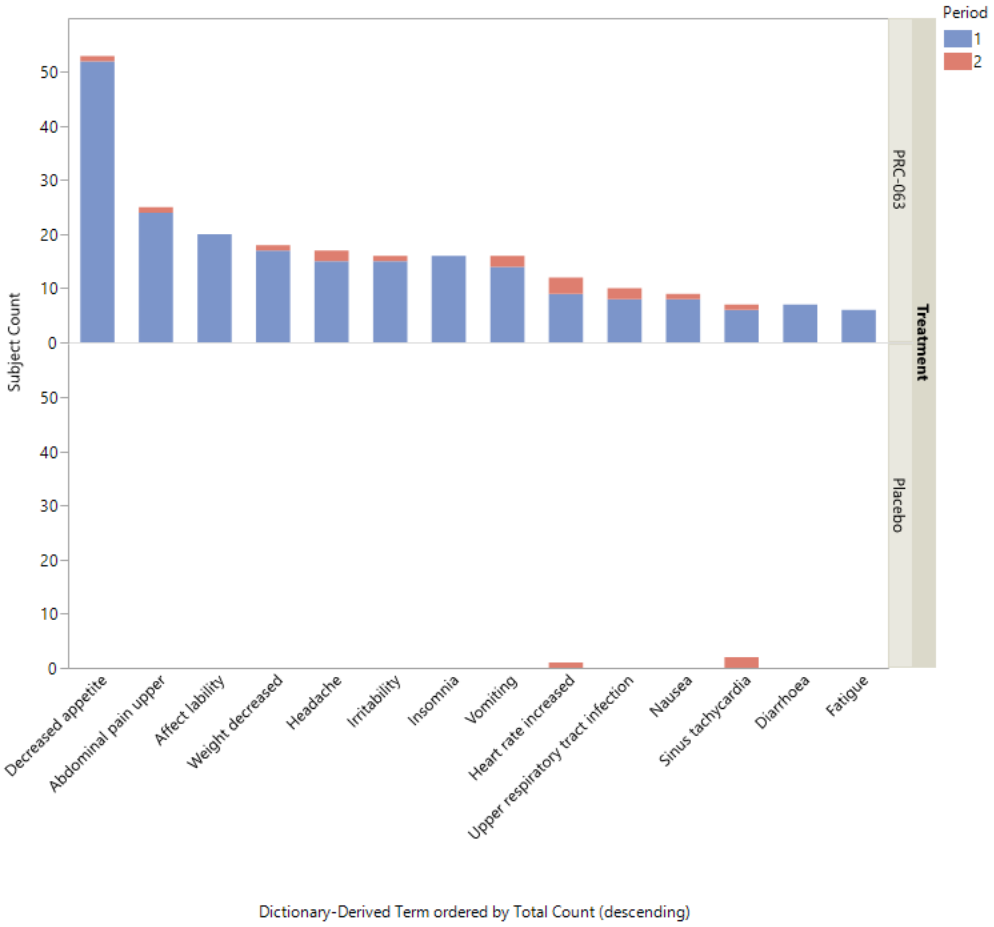
- Subject (b) (6) was a 6-year-old white female who had moderate affect lability and dermatillomania. The events resolved after discontinuing PRC-063.
- Subject (b) (6) was an 11-year-old African-American male who had an ECG abnormality. Per the safety dataset and case report form, the ECG was interpreted as normal at screening. Then, at Baseline (Day -1), the ECG indicated abnormal sinus rhythm with a 1st degree atrioventricular block. The abnormal ECG findings continued on the ECG at Days 7, 14, and 21. The PRC-063 was discontinued on Day 23. The ECG prolongation was asymptomatic but was marked as unresolved.

7.4.1.D Supportive Safety Results (063-015)

7.4.1.3 Common Adverse Events (063-015)

One of the disadvantages of the dose-optimization study design is that subjects either tolerate the active drug or discontinue the study prior to randomization. Figure 6 graphically shows that during the dose-optimization period (Period 1) there were substantially more TEAEs related to PRC-063 than during the double-blind crossover period (Period 2). The TEAEs listed in Table 22 in Period 1 are expected with methylphenidate, but are no greater compared to placebo during the 1-week double-blind period. Therefore, the Adverse Reactions in the label for Study 063-015 may be misleading by only stating the safety results from the controlled period of the trial, so I described the adverse reactions from the dose-optimization phase in the label.

Figure 6: AE Counts by Treatment and Period of Study 063-015



[Source: Reviewer created.]

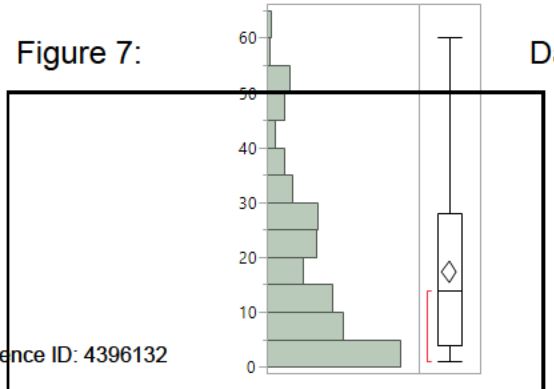
Table 22: TEAEs Reported during Study 063-015

		Treatment					
		PRC-063				Placebo	
		Period				Period	
		1 (Dose optimize)		2 (Crossover)		2	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Gastrointestinal disorders	Abdominal pain upper	24	10.8%	1	0.4%	.	.
	Vomiting	14	6.3%	2	0.9%	.	.
	Nausea	8	3.6%	1	0.4%	.	.
	Diarrhoea	7	3.1%	.	.	.	.
Psychiatric disorders	Affect lability	20	9.0%	.	.	.	.
	Irritability	15	6.7%	1	0.4%	.	.
	Insomnia	16	7.2%	.	.	.	.
Metabolism and nutrition disorders	Decreased appetite	52	23.3%	1	0.4%	.	.
Investigations	Weight decreased	17	7.6%	1	0.4%	.	.
	Heart rate increased	9	4.0%	3	1.3%	1	1.4%
Nervous system disorders	Headache	15	6.7%	2	0.9%	.	.
Infections and infestations	Upper respiratory tract infection	8	3.6%	2	0.9%	.	.
Cardiac disorders	Sinus tachycardia	6	2.7%	1	0.4%	2	2.7%
General disorders and administration site conditions	Fatigue	6	2.7%	.	.	.	.

[Source: Reviewer created]

Figure 7 illustrates that the vast majority of TEAEs occurred in the 5 to 10 days of the study, which is also indicative of the study design.

Figure 7: Day of Start of AE During Study 063-015



Day of Study

Number of Subjects
[Source: Reviewer created]

7.4.2.3 Laboratory Findings (063-015)

No safety issues identified.

7.4.3.3 Vital Signs (063-015)

No safety issues identified.

7.4.4.3 Electrocardiograms (063-015)

No safety issues identified.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

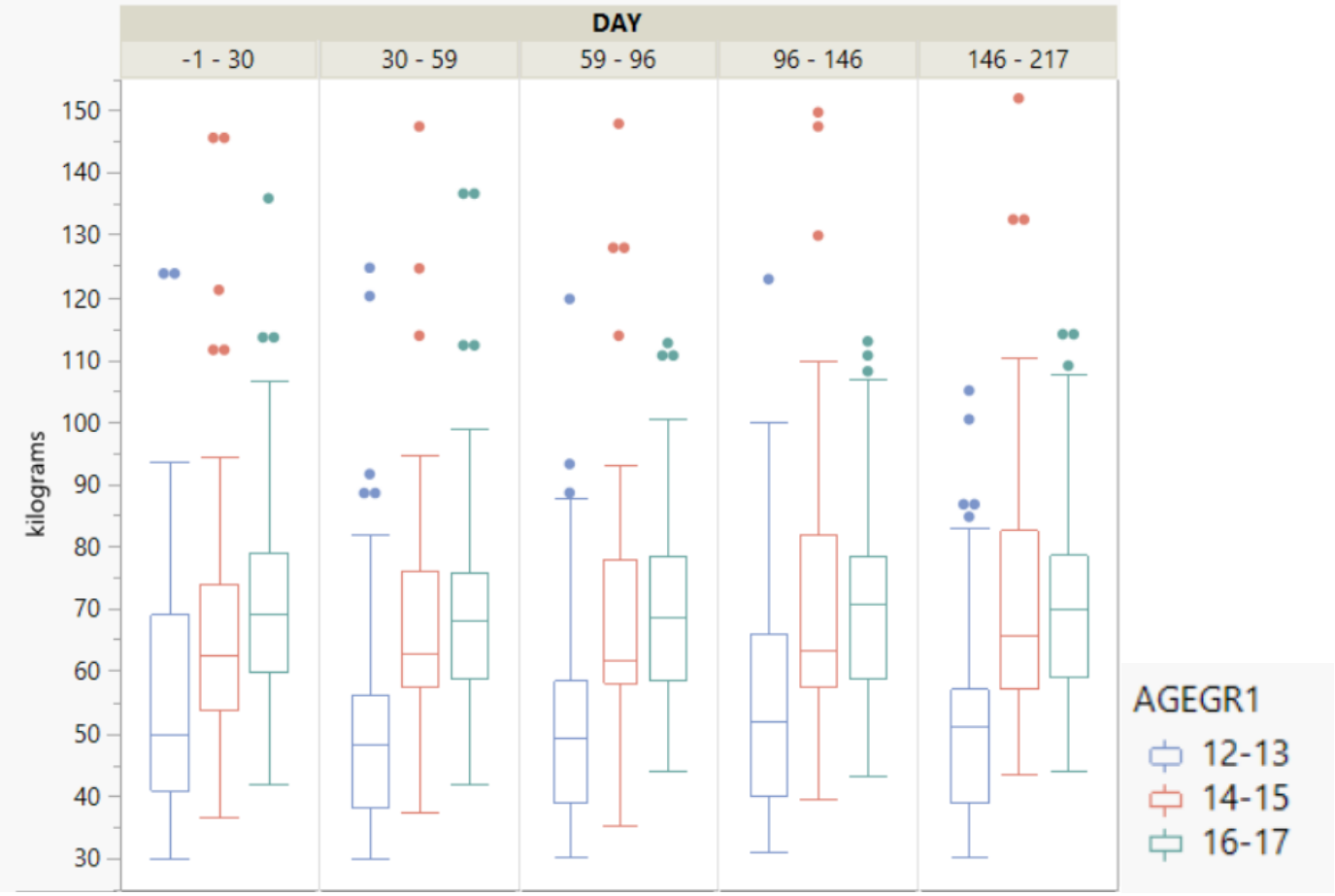
7.5.A. Protocol 063-012 long-term safety

Study 063-012 enrolled adolescents (n=176) and adults (n=184) who completed Studies 063-009 and -010. It was an open-label 6-month study. Generally, no unexpected TEAEs were observed in either population over time.

However, my focus of reviewing this uncontrolled trial was to analyze the impact of PRC-063 on adolescents' growth, especially the youngest patients (12 to 13 years) because methylphenidate is known to cause long-term growth suppression. In Study 063-009, decreased appetite was reported in 20.1% of the PRC-063-treated subjects and zero reports in the placebo group. I evaluated if the decreased appetite led to clinically meaningful weight decrease over 6 months.

Adolescent subjects' weight was recorded generally on Days 1, 30, 60, 90, 120, 150, and 190, (i.e., monthly), during the study. I analyzed changes in weight over time by using review tools from JMP Clinical 6.0. The age groups' (12 to 13, 14 to 15, and 16 to 17 years) average weight remained unchanged over 6 months' time as illustrated in Figure 8. With the older age groups (14 to 17 years), little natural weight gain might be expected in 6 months.

Figure 8: Average Weight by Age Group Over Time



[Source: Reviewer created]

To further assess weight loss or gain in the 12- to 13-year-old group, I reviewed the patients' PRC-063 doses. Table 23 lists the number of patients by dose. In the lower dose group of subjects (n=19) taking 45 (n=9) and 55 mg (n=10) doses, 6 subjects (6/19, 31.5%) lost weight (-0.5 kg min, -5.8 kg max, -2.3 kg mean). Thirteen subjects (13/19, 68.4%) gained weight during the study (1.1 kg min, 5.7 kg max, 3.6 kg mean). One subject had zero change in weight. In the highest dose group (n=22) of 85 mg, 8 subjects (36.3%) lost weight (-0.9 kg min, -7.5 kg max, -2.6 kg mean) and 14 (63.6%) gained weight (0.46 kg min, 13.0 kg max, 5.3 kg mean) over the 6-month safety study. Younger adolescents in the lower dose group had no difference in weight loss or gain compared to the 85-mg PRC-063 dose group. Also, more subjects gained weight than lost, so I concluded that 6 months was not enough time to see growth suppression with PRC-063 and there was no identified dose-related issue.

Table 23: Number of Youngest Adolescents by Dose (Study 063-012)

N=60
12 to 13 years

	TRT01A			
	45 mg PRC-063	55 mg PRC-063	70 mg PRC-063	85 mg PRC-063
	9	12	17	22

[Source: Reviewer created]

To confirm my findings of no dose-related weight loss, I plotted the 12- to 13-year-old subjects' weights at the end of Study 063-012 for those on the 85-mg dose (n=22) over the Center for Disease Control's (CDC) recognized growth chart by age and weight. I used the male growth chart because there were twice as many adolescent males as females in the study.

My findings were that 5/22 ended the study at the 10th or less weight percentile on the CDC growth chart. The other 17 subjects taking 85 mg ended study in the 75th (n=5) or ≥90th (n=12) percentile on the CDC growth chart. In conclusion, the adolescents taking PRC-063 did not appear to have clinically significant growth suppression after continuing the drug for over 7 months (4-week 063-009 + 6-month 063-012).

It will be important to evaluate growth suppression from the long-term safety data being required by the PMR for a 1-year study of PRC-063 in the most vulnerable pediatric patients (4 to 12 years).

7.5.1 Dose Dependency for Adverse Events

Refer to Section 7.4.1.2 in Study 063-009 for discussion of dose-dependent TEAEs.

7.5.2 Time Dependency for Adverse Events

Refer to Figure 4, Time to Discontinuations in Section 7.3.3.2 of Study 063-009.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not Applicable; data as per RLD.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable; data as per RLD.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable; data as per RLD.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to planned pediatric studies in Section 1.4 and Section 7.5.A. for the discussion of long-term weight changes in adolescents (12 to 17 years).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses occurred during the study of PRC-063. Refer to Section 4.5 for discussion on potential for abuse of extended-release methylphenidate. Other data is per RLD.

7.6.5 Submission-Specific Primary Safety Concerns

No submission-specific primary safety concerns were identified with the 505(b)(2) application.

7.7 Additional Safety Issue

Not applicable.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

The application contained over 70 literature references on methylphenidate, including Applicant's White Papers on gastrointestinal motility and adverse events of PRC-063. No new information about methylphenidate was identified.

9.2 Labeling Recommendations

The clinical sections of the label, Sections 6 and 14, were extensively rewritten. The Adverse Reactions section removed (b) (4). The Clinical Trials section removed (b) (4).

At the end of the review cycle, during labeling negotiations, the Applicant proposed to (b) (4) For example, (b) (4)

(b) (4)

. This percentages in the tables changed slightly, along with some other proposals from the Applicant. Because the clinical meaningfulness did not drastically change with the percentages, we decided to accept the proposed percentages instead of using mine.

9.3 Advisory Committee Meeting

The 505(b)(2) application relies on the findings of safety and efficacy of Ritalin IR and there were no questions for an Advisory Committee.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER on behalf of NANCY C DICKINSON
02/26/2019 03:09:31 PM

BERNARD A FISCHER
02/26/2019 03:10:34 PM
Acting Lead Medical Officer