U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 212038
Supplement #:	
Drug Name:	Adhansia XR (methylphenidate HCL) extended-release capsules
Indication(s):	For the treatment of Attention-deficit/Hyperactivity Disorder (ADHD)
Applicant:	Purdue Pharma
Date(s):	NDA Submission: 27 April 2018
	PDUFA Goal Date: 27 Feb. 2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords: Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1. EXECUTIVE SUMMARY

The proposed indication for PRC-063 is: *PRC-063 is a central nervous system (CNS) stimulant indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).*

The following four relevant phase 3 studies were reviewed in in support of the proposed indication:

Study 063-015 - Children (6-12 Years - USA)

Study 063-009 - Adolescents (12 to 17 Years USA & Canada)

Study 063-008 – Adults (18-60 Years USA)

Study 063-010 Adults (18-60 Years USA & Canada)

The efficacy results from five phase 3 studies the sponsor's claim that ADHANSIA XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older at dose levels of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg extended-release Capsules. Sponsor stated that the recommended starting dose for patients 6 years and older is 25 mg once daily in the morning. Dosage may be increased in increments of (b) (4) mg at intervals of at least 5 days (b) (4)

FDA disagreed on sponsor's analyses based on all doses combined and ANCOVA model for fixed studies 63-009 and 63-010. The sponsor was requested to provide analyses based on individual doses using MMRM (mixed model repeated measures). The results are summarized below:

Study 063-009 - Adolescents (12 to 17 Years USA & Canada) - efficacy was demonstrated on the middle two doses: 45 mg and 75 mg only.

Study 063-010 Adults (18-60 Years USA & Canada - efficacy was demonstrated on the 45 mg and the highest dose 100 mg, not on the 75 mg. The 100 mg did not appear to provide additional benefit to the 45 mg.

Study 063-015 - Children (6-12 Years - USA) - efficacy was demonstrated based on SKAMP compared to placebo

Study 063-008 – Adults (18-60 Years USA) - efficacy was demonstrated based on PERMP-Total Score compared to placebo.

Labeling is under review.

2. INTRODUCTION

2.1 Overview

On April 27, 2018, Purdue Pharma, submitted a 505(b)(2) NDA for Adhansia XR (methylphenidate HCl) extended-release capsules for the proposed indication of the treatment of ADHD. PRC-063 is an extended-release (ER) methylphenidate (MPH) product (b) (4) for the treatment of attention-deficit/hyperactivity disorder (ADHD), and as an alternative to currently approved MPH products for the treatment of ADHD.

Their basis for approval is the demonstration of efficacy of Adhansia XR compared to placebo in their positive pivotal studies in children, adolescents, and adults with ADHD and utilizing our assessment of safety, efficacy, clinical pharmacology, and nonclinical toxicology of methylphenidate hydrochloride from the reference listed drugs-CONCERTA (NDA 021121) and Ritalin (NDA 010187), for which Purdue Pharma (Canada) does not have a right of reference. Methylphenidate once daily products approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in US include Concerta, Metadate CD, Aptensio XR, Focalin XR, Ritalin LA, Quillivant XR and Cotempla XR ODT.

The proposed indication for PRC-063 is:

PRC-063 is a central nervous system (CNS) stimulant indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The clinical development program consists of 10 clinical pharmacology/bioavailability studies (including 3 pilot formulation development studies), Population pharmacokinetic and exposure-response analyses, five adequate and well-controlled efficacy and safety studies, and one long-term, six months, open-label extension study.

The focus of this review is four adequate and well-controlled efficacy and safety studies identified by the sponsor. The efficacy of PRC-063 was established in a randomized, double-blind, parallel-group, placebo-controlled, dose-optimized, phase 3 laboratory classroom study in children 6–12 years of age with a diagnosis of ADHD (Study 063-015) who have been diagnosed with ADHD. Additional data are presented from one randomized, fixed-dose, double-blind, parallel-group, placebo-controlled study in adolescents (age 12–17 years; Study 063-009), two randomized, double-blind, placebo- or active-controlled studies in adults (age ≥ 18 years; Studies 063-008, 063-010).

Study 63-013 for adults (18-60 years USA) entitled “A Randomized, Phase 3, Double-Blind, Crossover Comparison of PRC-063 and Lisdexamfetamine in the Driving Performance of Adults With ADHD” was included in the submission, but not included in this review (b) (4)

There was another six-month open-label extension study (Study 063-012) in adults and adolescents who had completed Studies 063-010 and 063-009 and evaluated safety and adverse events. This study is also not included in this review.

Key information is given in Table 1:

Table 1: List of all studies included in analysis

Study ID, Data Source, Start-End Dates	Study Centers Sample Size	Study Objectives	Age Group	Design & Control	Duration
063-015 04-May-2017 to 28-Aug-2017	Centers = 7	Primary: To assess efficacy of PRC-063 compared to placebo, as measured by the SKAMP-C score during the laboratory classroom. To assess the safety of PRC-063 Key Secondary: To estimate the time to onset and the duration of efficacy of PRC-063 as measured by the SKAMP-C score assessed during the laboratory classroom	**Children** (6- 12 years)	A randomized, double blind, parallel-group, placebo-controlled, dose-optimized, phase 3 study.	up to 7 weeks (up to 6 weeks of open label treatment with PRC-063 followed by 1 week of randomized double blind, treatment with either PRC-063 or placebo)
063-009 23-Apr-2014 to 21-Jan-2015	Centers = 42	To evaluate the clinical efficacy and safety of PRC-063 capsules in adolescents with ADHD.	Adolescents (12–17 years)	A multiple fixed-dose, randomized, parallel group, double-blind, placebo-controlled, phase 3 study.	7 weeks (4 weeks of randomized doubleblind treatment with either PRC-063 or placebo)
063-008 29-Nov-2014 to 21-Mar-2015	Centers = 2	To assess the clinical efficacy, time of onset, and time course of efficacy over 16 hours of PRC-063 capsules versus placebo in adults diagnosed with ADHD in an adult workplace environment.	Adults (18–60 years)	A randomized, double blind, Placebo controlled crossover, titration to optimal dose, phase 3 study.	4-11 weeks (a 2 to 9-week open label titration with PRC-063 followed by two double-blind crossover weeks, each with either PRC-063 or placebo)

063-010 28-Apr-2014 to 22-Oct-2014	Centers = 34	To evaluate the clinical efficacy and safety of PRC-063 capsules in adults with ADHD.	Adults (≥ 18 years)	A multiple fixed-dose, randomized, parallelgroup, double-blind, placebo-controlled, phase 3 study.	7 weeks (4 weeks of double-blind treatment with either PRC-063 or placebo)

ADHD = Attention-Deficit/Hyperactivity Disorder; LDX = lisdexamfetamine dimesylate; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn, and Pelham-Combined.
Source: Applicant's study reports 063-015 CSR, 063-008 CSR, 063-010 CSR, 063-009 CSR, 063-012 CSR

2.2 Overview of Clinical Efficacy Studies

The following five clinical studies have been conducted to evaluate the safety and efficacy of PRC-063 in children, adolescents, and adults. The sponsor considered these studies as adequate and well-controlled; and each study was conducted and analyzed in accordance with predefined plans; enrolled subject populations based on standard and well-accepted diagnostic criteria; used designs and endpoints that are common for the evaluation of drug effects in patients with ADHD. Studies 063-009 and 063-010 used a fixed-dose design, in which dose level was assigned randomly and double-blinded, reducing the risk for bias.

- Study 063-015 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center laboratory classroom study to evaluate the safety and efficacy of PRC-063 compared to placebo in children (6–12 years of age) with ADHD.

- Study 063-009 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of PRC-063 in adolescent ADHD patients.

- Study 063-008 was a phase 3, randomized, double-blind, placebo-controlled, crossover study of the time course of response of PRC-063 in adults with ADHD in a simulated adult workplace environment (AWE).

- Study 063-010 was a phase 3, randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PRC-063 in adult ADHD patients.

These studies were considered adequate and well controlled by the sponsor in that:

- The studies were conducted and analyzed in accordance with predefined protocols and statistical analysis plans.

- Patients were diagnosed according to well-accepted criteria, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).

- The studies utilized designs and endpoints that are common for the evaluation of drug effects in patients with ADHD.

- They were double-blind studies. Patients, study staff (including evaluators), and the sponsor (including representatives of the sponsor) were unaware of patient treatment assignment during the double-blind phases of the studies. The only exceptions were certain individuals specified in the protocol, none of whom had direct patient or study staff contact, (*e.g.*, randomization code generation, clinical trial packaging). Capsules (and bottle labels) used during the double-blind phase had matching placebo (Studies 063-015, 063-009, 063-008, and 063-010).

- Treatment (Studies 063-015, 063-009, 063-010) or sequence (Studies 063-008) was assigned in a randomized manner (PRC-063, active control, or placebo), preventing any conscious or unconscious bias in group assignment or sequence.

2.3 Regulatory History

April 30, 2013: Pre-IND meeting granted – written responses only

May 6, 2013 background package submitted.

June 14, 2013 Meeting Minutes Written Responses Only (Pre-IND) sent

Feb 18, 2014 Clinical

August 4, 2015 Clinical

November 1, 2017 Clinical

December 30, 2017 Clinical End of Phase II Clinical Meeting Minutes (Meeting 12 Dec 2017) – Type B

April 10, 2017 – CMC End of Phase II Clinical Meeting Minutes

December 26, 2017 – Pre-NDA Clinical Meeting Minutes (Meeting held on 12 Dec 2017)

January-04-2018, February-01-2018: Email- IND 118297; PRC063 for ADHD - SAP amendment

2.4 Analysis Population

The analysis populations used in five safety and efficacy studies were as follows:

- Safety Population: was defined as all subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment.

- Intent-to-Treat Population: included all subjects who signed the informed consent/assent and received at least 1 dose of open-label treatment.

- Full Analysis (FA) Population: included all randomized subjects who received at least 1 dose of double-blind study medication (the full day laboratory classroom morning dose was mandatory for a subject to be included in this population) and attended the full day laboratory classroom evaluation. The FA population was the primary population for the analysis of the primary and the key secondary efficacy objectives.

- Per-protocol (PP) Population included all subjects from the FA population who completed the study and had no important protocol deviations. The PP population was used to support the findings from the primary efficacy analysis.

2.5 Data Sources

The following data sources were considered in this review:

a) Applicant's study report and datasets
EDR Location: \\CDSESUB1\evsprod\NDA212038\212038.enx
Initial application submitted under sequence 0000 on April 27, 2018

b) Data sets
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c) Software code
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d) Response to FDA Information Request

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. Some issues with the analysis quality emerged during the review. A brief description is as follows:

Efficacy analysis in some studies was based on the comparison of pooled doses with placebo. This was not agreed upon analysis. Efficacy should be demonstrated based on individual doses compared with placebo, not the comparison of pooled doses with placebo. The individual doses that beat placebo with the overall type I error rate controlled based on the pre-specified analysis that was agreed upon should be identified. If efficacy is not demonstrated based on all individual doses compared to placebo, testing on the secondary endpoint cannot proceed because they did not win on all doses with the primary endpoint.

Information Request was sent to the sponsor, and they resubmitted the results of revised analyses for two studies along with SAS codes.

This reviewer found the quality of their revised submissions acceptable and was able to replicate the primary results from the sponsor's Clinical Study Report (CSR).

3.2 Evaluation of Efficacy

Abbreviations used:

ADHD - Attention-Deficit/Hyperactivity Disorder; AWE - adult workplace environment; BA- bioavailability; F - female; IR - immediate-release; LDX – lisdexamfetamine dimesylate; M - male; MPH- methylphenidate; SKAMP-C- Swanson, Kotkin, Agler, M-Flynn, and Pelham-Combined; USA-United States; USP - United States Pharmacopeia.

There were five clinical efficacy studies of PRC-063 in children, adolescents, and adults. Efficacy of each these studies are presented below.

3.2.1 Study 063-015 - Children (6-12 Years - USA)

Study Population: Children (6 to 12 years) with ADHD in USA.

Study Design: A randomized, double-blind, parallel-group, placebo-controlled, dose optimized, simulated classroom environment efficacy phase 3 study in children (age 6 to 12 years) with ADHD in USA.

Primary efficacy endpoint: To assess efficacy of PRC-063 compared to placebo, as measured by the SKAMP-C score during the full day laboratory classroom.

Key Secondary endpoint: To estimate the time to onset and the duration of efficacy of PRC-063 as measured by the SKAMP-C score assessed during the full day laboratory classroom.

Treatment Doses: PRC-063 or matching placebo 25, 35, 45, 55, 70 or 85 mg

Number of subjects: 156 enrolled

Study Duration: up to 7 weeks (up to 6 weeks of open-label treatment with PRC-063 followed by 1 week of randomized double-blind, treatment with either PRC-063 or placebo)

3.2.2 Study 063-009 - Adolescents (12 to 17 Years USA & Canada)

Study Population: Adolescents (12 to 17 years) with ADHD in USA & Canada.

Study Design: A multiple fixed-dose, randomized, parallel-group, double-blind, placebo-controlled, phase 3 study.

Primary efficacy endpoint: To evaluate the clinical efficacy of PRC-063 capsules in adolescents with ADHD.

Treatment Doses: **Active** PRC-063 or matching placebo 25, 45, 70 or 85 mg oral capsules administered once daily in the morning

Number of subjects: 367 randomized, 323 completed

Study Duration: 7 weeks (4 weeks of randomized double-blind treatment with either PRC-063 or placebo)

3.2.3 Study 063-008 – Adults (18-60 Years USA)

Study Population: Adults (18 to 60 years) with ADHD in USA.

Study Design: A randomized, double-blind, placebo-controlled, crossover, titration to optimal dose, phase 3 study in USA.

Primary efficacy endpoint: To assess the clinical efficacy, time of onset, and time course of efficacy over 16 hours of PRC 063 capsules versus placebo in adults diagnosed with ADHD in an AWE setting (USA)

Treatment Doses: Active PRC-063 or matching placebo 25, 35, 45, 55, 70, 85 or 100 mg (titrated to effect) oral capsules administered once daily in the morning

Number of subjects: 59 randomized, 46 completed

Study Duration: 4-11 weeks (a 2 to 9 week open-label titration with PRC-063 followed by two double-blind crossover weeks, each with either PRC-063 or placebo)

3.2.4 Study 063-010 Adults (18-60 Years USA & Canada)

Study Population: Adults (18 to 60 years) with ADHD in USA & Canada.

Study Design: A multiple fixed-dose, randomized, parallel-group, double-blind, placebo-controlled, phase 3 study.

Primary efficacy endpoint: To evaluate the clinical efficacy and safety of PRC-063 capsules in adults with ADHD.

Treatment Doses: Active PRC-063 or matching placebo 25, 70 or 100 mg oral capsules administered once daily in the morning

Number of subjects: 375 randomized, 333 completed

Study Duration: 7 weeks (4 weeks of double-blind treatment with either PRC-063 or placebo)

3.3 Clinical Efficacy Results

3.3.1 Study 063-015 - Children (6 to 12 years) with ADHD in USA

Study 063-015 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, laboratory classroom study to evaluate the safety and efficacy of PRC-063 compared to placebo in children (6 to 12 years of age) with ADHD.

The population for efficacy analyses comprised 147 subjects, 73 who received placebo and 74 who received PRC-063. Median ages were 9 years for children, all patients enrolled in the efficacy and safety studies were diagnosed with ADHD according to DSM-5 criteria. All studies allowed for ADHD inattentive, hyperactive- impulsive, or combined types.

Patients received ADHANSIA XR 25, 35, 45, 55, or 70 mg during a 6-week, open-label, dose-optimization period, followed by a 1-week, randomized, placebo-controlled, double-blind treatment phase. After 1 week of double-blind treatment, patients were evaluated at pre-dose and 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose on the analog classroom day using the

Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale, a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting.

The primary efficacy endpoint was the difference between ADHANSIA XR and placebo in mean SKAMP-Combined score averaged across the 8 sessions on the analog classroom day. ADHANSIA XR demonstrated a statistically significant response over placebo. SKAMP-C ranges from 0 to 78, where lower scores indicate less severe symptoms.

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 the full day laboratory classroom.

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 greater than 3-days or a dose taper, depending on the product labelling 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 and 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.

Results:

A total of 156 subjects met the entry criteria, were enrolled into the study and attended the baseline visit of the open-label period. Of these, 148 subjects were randomized into the double-blind period, 147 subjects completed to the full day laboratory visit, and 140 subjects completed to the safety follow-up visit. Overall, the median age was 9 years (range 6 to 12 years), 65.4% were males, 55.8% were white, and 84.0% were of the ADHD subtype "combined."

The primary efficacy endpoint was the difference between ADHANSIA XR and placebo in mean SKAMP-Combined score averaged across the 8 sessions on the analog classroom day. ADHANSIA XR demonstrated a statistically significant response over placebo. The secondary efficacy endpoints were onset and duration of clinical effect, as assessed by the treatment difference in SKAMP-Combined scores at post-dose time points. The SKAMP scores were also statistically significantly lower (improved) at all time points (1, 2, 4, 6, 8, 10, 12, 13-hours) post-dose with ADHANSIA XR compared to placebo (Figure 1).

Table 2 presents SKAMP-C scores. Table 2 shows that LS Mean change from pre-dose score was -8.6 with 95% Confidence Interval ranging from -10.6 to -6.6. Figure 1 shows that the effect an onset within 1 hour of treatment, and a duration of effect continuing for up to and including 13 hours post-dose.

After one week of double-blind treatment, children treated with PRC-063 (all dose groups combined) also had improved attention, as measured by the PERMP-T, improved ADHD-5-RS scores, and improvement as measured by CGI-I

Table 2: SKAMP-C Scores during the Full Day Laboratory Classroom (FA Population)

Statistics	PRC-063 (N=74)	Placebo (N=73)
Pre-dose score		
N	74	73
Mean (SD)	14.4 (10.58)	11.5 (7.13)
Median	11.5	10.0
Q1 , Q3	8.0, 18.0	6.0, 15.0
Min, Max	4, 59	0, 34
LS Mean (SE)	15.2 (1.08)	12.0 (1.07)
LS Mean Difference (SE)	**3.1 (1.48)**	
95% CI	**(0.2, 6.1)**	
p-value	**0.0367**	
Primary Efficacy Analysis: Average post-dose score		
N	74	73
Mean (SD)	11.4 (6.88)	18.2 (9.01)
Median	9.5	15.8
Q1 , Q3	6.8, 13.9	11.3, 23.0
Min, Max	3.5, 36.6	3.9, 42.9
LS Mean (SE)	10.3 (0.74)	18.9 (0.73)
LS Mean Difference (SE)	**-8.6 (1.02)**	

95% CI	**(-10.6, -6.6)**	
p-value	**< 0.001**	
Average change from pre-dose score		
N	74	73
Mean (SD)	-3.0 (7.21)	6.7 (7.81
Median	-1.6	5.9
Q1 , Q3	-5.8, 1.1	0.9, 9.9
Min, Max	-29.1, 11.6	-6.6, 27.4
LS Mean (SE)	-2.7 (0.74)	5.9 (0.73)
LS Mean Difference (SE)	**-8.6 (1.02)**	
95% CI	**(-10.6, -6.6)**	
p-value	**< 0.001**	

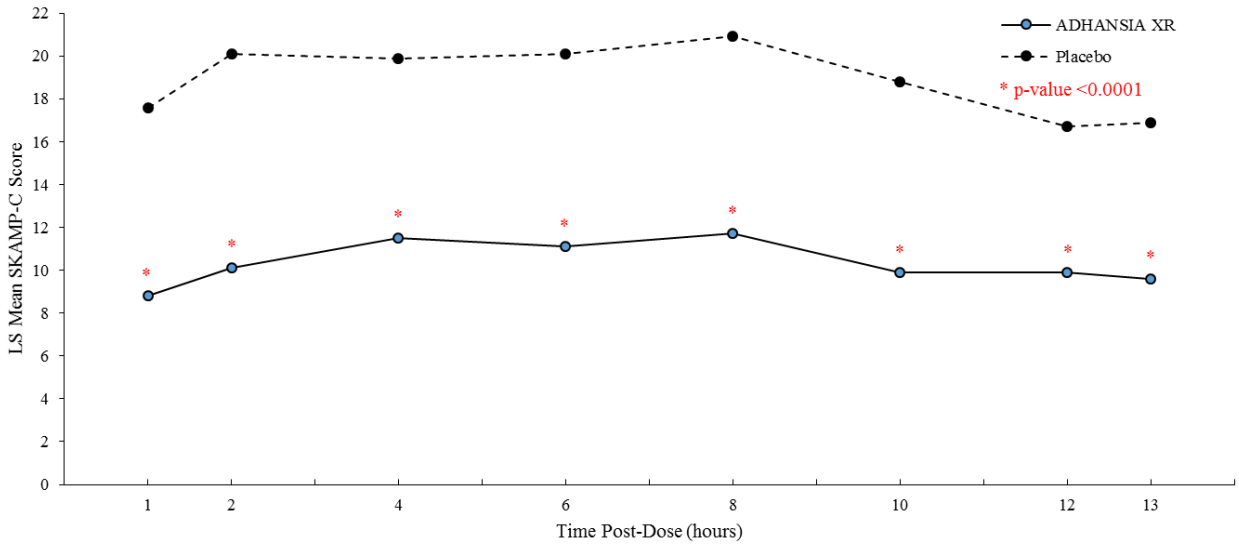
CI = confidence interval; FA = full analysis; LS = least-squares; ANOVA = analysis of variance, MMRM = mixed model repeated measures; SD = standard deviation; SE = standard error

SKAMP-C = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale

Source: Sponsor's 063-015 CSR, Table 14.2.1.1.1 and this reviewer analyses

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 the full day laboratory classroom. The following Figure 1 shows that the effect had an onset within 1 hour of treatment, and a duration of effect continuing for up to and including 13 hours post-dose

Figure 1: SKAMP-Combined Scores during the Full Day Laboratory Classroom Visit – by Time (FA Population)



LS = least-squares; FA = full analysis; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined Score; p-values from mixed model repeated measure analysis

Source: 063-015 CSR, Figure 14.2.1.1.4.1

Conclusions:

This study successfully demonstrated significant improvements in attention and ADHD symptoms in children 6 to 12 years of age (inclusive) who received optimized oral doses of PRC-063 (ranging from 25 to 85 mg daily) compared to placebo.

3.3.2 Study 063-009 - *Adolescents* (12 to 17 years) with ADHD in USA & Canada

Study 063-009 was a multiple fixed-dose, randomized, double-blind, placebo controlled, parallel-group phase 3 study in 367 (Planned: 360 subjects. Randomized: 367 subjects. Completed: 323) subjects. adolescent (12-17 years), male and female subjects with ADHD conducted to assess the clinical efficacy and safety of PRC-063 in adolescents with ADHD. The subjects were randomized 1:1:1:1:1 to receive placebo or active 25, 45, 70, or 85 mg PRC-063 capsules once-daily in the morning and underwent a two-week, double-blind forced dose-titration period followed by a two-week evaluation period. Subjects underwent post-treatment assessments that included ADHD-5-RS and CGI-I. The purpose was to evaluate the clinical efficacy of PRC-063 capsules in adolescents with ADHD.

The primary analysis, as per SAP 4.0, was an analysis of covariance (ANCOVA) model including terms for treatment and baseline Clinician ADHD-5-RS total score as a covariate. The primary efficacy analysis was on the Clinician ADHD-5-RS total score at Visit 6

(following the second week of the evaluation period) and was based on observed data. The primary analysis was performed in the Full Analysis (FA) population, defined as all randomized subjects who received any amount of study medication and who had any ADHD5-RS assessments

FDA differed from this analysis method as per statistical analysis plan (SAP) submitted in eCTD Sequence 0006 (letter dated 23 October 2014) and agreed upon, the primary analysis should be based on repeated measures analysis (instead of ANCOVA on Observed Case). FDA also pointed out that per the ICH E9 guidance, the primary analysis set should be based on the intent-to-treat population. Analysis on Observe Case data set requires a very strong assumption about missing data. Unless the dropout rates are nearly zero, the assumption is unlikely to hold. In addition, the labeling should describe which dose(s) beat placebo. A statistical significance based on all doses pooled would not suffice to support efficacy.

The sponsor was requested to provide the efficacy results based on the pre-specified primary analysis in the SAP that was submitted to FDA, with FDA's comments incorporated, and to provide executable SAS code along with the detailed algorithm.

The sponsor submitted the required efficacy analyses as well as SAS codes.

The revised analysis uses a mixed model repeated measures (MMRM) analysis with terms for treatment, visit, treatment by visit interaction, and baseline Clinician ADHD-5-RS total score and an unstructured covariance structure. The clinician ADHD-5-RS total score at all post-baseline visits were included in the analysis. Missing data were not imputed but handled in the analysis via the use of the MMRM. The results from this revised analysis, as well as the primary and sensitivity analyses defined in SAP 4.0 and presented in the CSR, are presented in Table 3. Subjects from site 08 are excluded from all analyses.

Table 3: LS Mean Difference versus Placebo (95% Confidence Intervals) for Change from Baseline in Clinician-Rated ADHD-5-RS

		25mg	45mg	70mg	85mg	All PRC-063
Analyses: ANCOVA (terms for treatment and baseline score)						
Primary FA population Placebo n=66	n	65	64	67	62	
	Mean	-2.0	-5.6	-4.9	-4.3	-4.2
	95% CI	(-6.8, 2.8)	(-10.4, -0.8)	(--9.7, -0.2)	(-9.1. 0.6)	(-7.2, -1.2)
	Adjusted p	0.7031	0.0155	0.0401	0.1011	0.0067
SAP 2.0 Analysis: MMRM terms for treatment, visit, treatment by visit interaction and baseline score, Unstructured covariance structure						
MMRM	n	65	64	67	62	258

FA n = 65 Placebo n=66	Mean	-2.2	-5.4	-5.2	-4.4	-4.3
	95% CI	(-5.9, 1.6)	(-9.2, -1.6)	(-9.0, -1.4)	(-8.2, -0.6)	(-7.3, -1.3)
	Unadjusted p	0.2562	0.0052	0.0069	0.0226	0.0049

Dunnett's adjustment for multiple pairwise comparisons for each active dose group with placebo.
CSR = clinical study report; FA = full analysis; MCMC = Markov chain Monte Carlo; MMRM = mixed model repeated measures; SAP = statistical analysis plan.
Source: CSR Table ST 8-12 & ST 8-13

Efficacy was not demonstrated for all individual doses compared with placebo. At the 25 mg dose level, the mean difference was smaller and not statistically significant for both ANCOVA and MMRM methods. At the 85 mg dose level, the mean difference was smaller but not statistically significant based on ANCOVA analyses, but statistically significant based on MMRM analyses.

Therefore, efficacy was demonstrated at 45mg, 70mg, and 85 mg that beat placebo with overall type I error controlled using MMRM analysis.

3.3.3 Study 063-008 – Adults (18-60 years-USA) diagnosed with ADHD in an AWE setting

O**bjective:** to assess the clinical efficacy, time of onset, and time course of efficacy over 16 hours following administration of PRC-063 compared to placebo in adults diagnosed with ADHD in a Simulated Adult Workplace Environment (AWE) setting.

Study Design: Study 063-008 was a randomized, double-blind, placebo-controlled, crossover study in adult male and female ADHD subjects conducted to assess clinical efficacy, the time of onset, and time course of efficacy of PRC-063 as measured by the PERMP score. Subjects were titrated to an optimal dose (25, 35, 45, 55, 70, 85, or 100 mg PRC-063 daily) in an open-label period of between two and nine weeks, familiarized with study procedures in a practice AWE session, and then randomized to 1 of 2 treatment sequences (ACTIVE to PLACEBO or PLACEBO to ACTIVE). Subjects received treatment once daily in the morning for 5 to 10 days prior to each AWE session and during the AWE session.

Number of Subjects: Planned: 60 subjects. Randomized: 59 subjects. Completed: 46 subjects.

Statistical Methods:

The primary endpoint was the mean between-treatment PERMP-T score across the AWE sessions. PERMP-T scores are calculated by adding the number of questions attempted (PERMP-A) to the number of questions correct (PERMP-C) at each time point. The full Analysis (FA) population consisted of all randomized subjects who had taken any study medication and had baseline and at least one post-dose PERMP on both AWE study days.

Main secondary outcome measure was 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 1.0, 2.0, 5.0, 8.0, 11.0, 14.0 and 16.0 hours post dose.

Effect size and two-sided 95% CIs were calculated for the difference between treatments at each time point for the PERMP-T assessments.

Duration of Treatment: Subjects received open label medication during a 2 to 9 week dose titration, followed by a double-blind crossover of one week of placebo treatment and one week of active treatment.

Treatment Schedule: Visit 2a to Visit 3, subjects received open label PRC-063. Visit 3 to Visit 4, subjects received either active or placebo PRC-063 at their optimized dose. Visit 4 to Visit 5, subjects received the alternate treatment (either active or placebo PRC-063) at the same optimized dose.

Results (Study 063-008)

Primary Endpoint

After one week of double-blind treatment, subjects treated with PRC-063 (all dose groups combined) had improved attention, as measured by the PERMP-T, compared with subjects receiving placebo across all time points. Results of the primary analysis are presented in the following Table 4. LS mean difference (SE) between PRC-063 and Placebo was 13.05 (4.550) and 95% CI (3.88, 22.23). The PERMP-A and PERMP-C were consistent with the PERMP-T score. PRC-063 improves attention, as measured by PERMP, over the 16 hours after administration.

Table 4: Permanent Product Measure of Productivity Total Score across All Time Points (Full Analysis Population)

	PRC-063	Placebo
N Randomized (Safety)	59	
N Full Analysis (FA)	45 (76.3%)	
Male (FA)	16 (35.6%	
White (FA)	40 (88.9%)	
Median Age (FA)	27	
Age range (FA)	18-58 Years	
Mean (SD)	270.2 (81.46)	256.5 (73.86)
Median	254.1	248.9
Min, max	130, 470	109, 428
LS mean (SE)-Baseline	235.0 (9.78)	224.0 (10.69)
LS mean (SE)-PRC-063	268.7 (11.24)	255.6 (10.87)
LS mean difference (SE)	13.05 (4.550)	
95% CI	(3.88, 22.23)	
p-value	0.0064	
Period p-value	<0.001	
Sequence p-value	0.1322	

Source: 063-008 CSR, Table ST 8-16
Source: Table ST 8- 10, Table ST 8- 11, and Table ST 8- 12

Secondary Endpoint (Major) –Study 063-008

Secondary analysis included the onset and time course of efficacy of PRC-063 compared with those of placebo as measured by the PERMP-T at pre-dose and 1.0, 2.0, 5.0, 8.0, 11.0, 14.0, and 16.0 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 first 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.

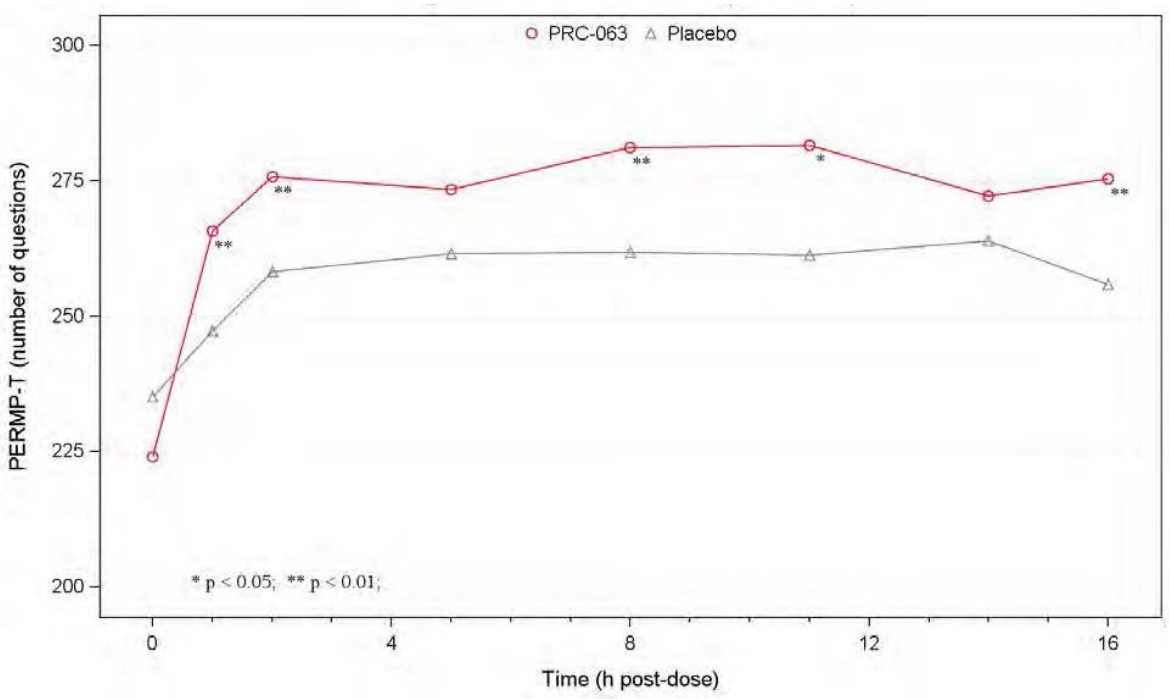
Subjects in the FA population receiving PRC-063 had a significant improvement in attention compared with subjects receiving placebo; the difference had an onset by 1.0-hour post-dose and a duration of efficacy of 16.0 hours, but the difference was marginally significant at 5 hours and not significant at 14 hours post-dose.

Table 5: PERMP-T Difference between PRC-063 and Placebo (Raw Score)

	0.0h	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Difference (SE)	-10.96 (6.448)	18.37 (6.388)	17.52 (6.378)	11.93 (6.620)	19.30 (5.667)	20.38 (8.946)	8.36 (7.078)	19.56 (6.521)
95% Confidence Interval	(-23.97, 2.04)	(5.49, 31.25)	(4.66, 30.38)	(-1.42, 25.28)	(7.87, 30.72)	(2.33, 38.42)	(-5.92, 22.63)	(6.40, 32.71)
p-value	0.0963	0.0063	0.0088	0.0786	0.0014	0.0278	0.2442	0.0045

Note: Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model for all subjects includes terms for treatment, period, sequence, time, and treatment-by-time interaction.
Source: CSR Table ST 8- 10

Figure 2: PERMP-Total Score (Mean Raw Score)



Source: CSR Study 83-008 Table ST 8- 10 and Figure 3

3.3.4 Study 063-010 – Adults diagnosed with ADHD (18-60 Years USA & Canada)

O**bjective:** to evaluate the clinical efficacy and safety of PRC-063 in adults with ADHD.

Study Design: Study 063-010 was a multiple fixed-dose, randomized, double-blind, placebo-controlled, parallel-group study in 375 (Planned: 360 subjects. Randomized: 375 subjects.

Completed: 333 subjects) adult, male and female subjects with ADHD conducted to assess the clinical efficacy and safety of PRC-063 in adults with ADHD.in adult male and female subjects with ADHD. Subjects were randomized to one of five treatment groups and received PRC-063 or placebo for 20 to 40 days. The study had four phases: (1) screening, washout and a one-week baseline; (2) forced-dose titration over a two-week period; (3) evaluation over a two week period; and (4) a 14-day safety follow-up. Subjects were required to visit six times. There was one Screening Visit (Phase 1), one Baseline Visit (Phase 2), two Titration Visits (Phase 2) and two Evaluation Visits (Phase 3).

Statistical Methods: The primary endpoint was to evaluate the clinical efficacy and safety of PRC-063 capsules in adults with ADHD. **Treatment Doses** were Active PRC-063 or matching placebo 25, 70 or 100 mg oral capsules administered once daily in the morning. A total of 375 patients were randomized and 333 patients completed. The study duration was 7 weeks (4 weeks of double-blind treatment with either PRC-063 or placebo)

The primary efficacy analysis was the between-treatment comparison of the Clinician ADHD-5-RS total score at Visit 6, following the second week of the evaluation period. Secondary Endpoint(s) included the Clinician-rated ADHD-5-RS (Phase 3 vs Phase 1 (Baseline)) within treatment;

The Sponsor defined analysis was based on an analysis of covariance (ANCOVA) model including terms for treatment and baseline Clinician ADHD-5-RS total score as a covariate. Between-treatment group differences in least-square (LS) means were calculated for the separate dose levels compared to placebo and two-sided 95% CIs for the treatment differences were calculated.

FDA differed from this analysis method for the same reasons as provided in the Study **063-0**09. The sponsor submitted the required efficacy analyses as well as SAS codes.

The revised analysis uses a mixed model repeated measures (MMRM) analysis with terms for treatment, visit, treatment by visit interaction, and baseline Clinician ADHD-5-RS total score and an unstructured covariance structure. The clinician ADHD-5-RS total score at all post-baseline visits were included in the analysis. Missing data were not imputed but handled in the analysis via the use of the MMRM. The results from this revised analysis, as well as the primary and sensitivity analyses defined in SAP 3.0 and presented in the CSR, are presented in Table 5. Subjects from site 08 are excluded from all analyses.

Table 6: LS Mean Difference versus Placebo (95% Confidence Intervals) for Change from Baseline in Clinician-Rated ADHD-5-RS

		25mg	45mg	70mg	100mg	All PRC-063
CSR Analyses: ANCOVA (terms for treatment and baseline score (CSR Table ST 8-11 & ST 8-14)						
Primary FA population Placebo n=69	n	73	69	62	61	
	Mean	-2.0	-6.9	-2.1	-8.1	-4.7
	95% CI	(-6.6, 2.6)	(-11.5, -2.2)	(-6.8, 2.7)	(-12.9,-3.2)	(-7.7, -1.6)
	Adjusted p	0.6750	0.0013	0.6720	0.0002	0.0026
SAP 2.0 Analysis: MMRM terms for treatment, visit, treatment by visit interaction and baseline score, Unstructured covariance structure						
MMRM	n	73	69	62	61	265
FA n = 65 Placebo n=69	Mean	-1.9	-7.1	-2.3	-7.9	-4.7
	95% CI	(-5.6, 1.7)	(-10.8, -3.4)	(-6.0, 1.4)	(-11.6, -4.1)	(-7.7, -1.8)
	Unadjusted p	0.3016	0.0002	0.2287	<0.0001	0.0019

Source: CSR Tables ST 8-11 & ST 8-14

Dunnett's adjustment for multiple pairwise comparisons for each active dose group with placebo.

CSR = clinical study report; FA = full analysis; MCMC = Markov chain Monte Carlo; MMRM = mixed model repeated measures; SAP = statistical analysis plan.

For both methods, at the 25 mg dose level, the mean difference was smaller (-2.0) and not statistically significant. At the 70 mg dose level, the mean difference was smaller (-2.3) and not statistically significant.

Therefore, efficacy was demonstrated at 45 mg, and 100 mg that beat placebo with overall type I error controlled using MMRM analysis.

3.4 Evaluation of Safety – Please see clinical report

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

All patients enrolled in the efficacy and safety studies were diagnosed with ADHD according to DSM-5 criteria. All studies allowed for ADHD inattentive. Hyperactive-impulsive or combined types.

Median ages were 9 years for children, 14 years for adolescents, 27 and 35 years for two studies for adults. The proportion of subjects who were female was 34.7% for children, 32.5% for adolescents, 64.4% and 52.8% for two studies for adults.

Table 7 below provides demographics and change from baseline or placebo subjects in Efficacy Studies in this review by Gender, and Race (Full Analysis Population)

Table 7: Demographics and Change from Baseline or Placebo Subjects in Efficacy Studies in this review by Gender, and Race (Full Analysis Population)

Demographic Characteristic	063-015 (Children)	063-009 (adolescents)	063-008 (Adults)	063-010 (Adults)
Age (tears)				
N	45	367	45	375
Mean (SD)	9.4 (1.85)	14.3 (1.6)	32.2 (11.06)	36.0 (11.9)
Median	9.0	14.0	27.0	35.0
Min, Max	6,12	12, 17	18, 58	18, 72
Gender n (%)				
Male	16 (35.6)	248 (67.6)	16 (35.6)	177 (47.2)
Female	29 (64.4)	119 (32.4)	29 (64.4)	198 (52.8)
Change from Baseline/ Placebo				
Male Means (SD)	36.99 (42.05)	-13.2 (11.5)	-10.1 (12.6)	-12.5 (11.3)
(95% CI)	(14.6, 59.4)	(-14.7, -11.7)	(-17.1, -3.1)	(-14.4, -10.6)
Female Means (SD)	41.4 (32.4)	-15.0 (11.5)	-15.7 (10.6)	-14.1 (12.6)
(95% CI)	(29.0, 53.7)	(-17.1, -12.9)	(-19.7, -11.7)	(-16.0, -12.2)
Race				
White	40 (88.9)	255 (69.5)	40 (88.9)	317 (84.5)
Black	3 (6.7)	79 (21.5)	3 (6.7)	41 (10.9)
Other	2 (4.4)	33 (9/0)	2 (4.4)	17 (4.6)
Change from Baseline/ Placebo				
White - Means (SD)	38.4 (36.2)	-13.2 (11.0)	-13.7 (12.1)	-13.1 (12.0)
95% CI	(26.8, 50.1)	(-14.6, -11.4)	(-17.6, -9.7)	(-14.4, -11.6)
Black - Means (SD)	44.8 (20.7)	-16.1 (12.9)	-17.3 (3.1)	-15.1 (12.9)
95% CI	(-44.0, 133.7)	(-19.0, -13.2)	(-24.9, -9.7)	(-19.7, -10.4)
Other- Means (SD)	59.7 (34.9)	-12.5 (11.4)	-11 (1.4)	-16.2 (12.0)
95% CI	(-254,.3, 373.7)	(-16.5, -8.5)	(-23.7, 1.7)	(-23.8, -8.6)

Source: CSR Table 2.7.3-10 & this reviewer's analyses

Conclusion: In spite of small sample sizes in several cells, the trend in gender is similar between male and female. Due to overwhelming majority of Whites in Race, no conclusion can be drawn about Race.

The sponsor was requested to perform exploratory subgroup analysis by country using MMRM and to provide related data sets. The sponsor compiled. The results as provided by the sponsor are given in the Table 8 below.

Table 8: Clinician-Rated ADHD-5-RS Repeated Measures Analysis by Country (FA Population, Studies 063-009 and 063-010)

ADHD-5-RS	25 mg PRC-063	45 mg PRC-063	70 mg PRC-063	85 mg PRC-063	All Doses PRC-063	Placebo
Study 063-009						
Canada						
N	13	13	15	12	53	13
Visit 6 LS Mean cfb	-13.22	-13.43	-11.24	-12.97	-12.63	-6.06
LS Mean cfb Diff from Placebo	-7.2	-7.4	-5.2	-6.9	-6.6	---
P value	0.0592	0.0540	0.1545	0.0835	0.0268	---
USA						
N	58	56	58	58	230	58
Visit 6 LS Mean cfb	-12.60	-16.74	-17.03	-15.34	-15.39	-11.61
LS Mean cfb Diff from Placebo	-1.0	-5.1	-5.4	-3.7	-3.8	---
P value	0.6470	0.0197	0.0132	0.0866	0.0282	---
Study 063-010						
Canada						
N	9	10	10	9	38	10
Visit 6 LS Mean cfb	-16.08	-16.80	-9.99	-14.60	-14.21	-12.65
LS Mean cfb Diff from Placebo	-3.4	-4.2	2.7	-2.0	-1.6	---
P value	0.4110	0.3247	0.5147	0.6437	0.6479	---
USA						
N	68	63	63	65	259	68
Visit 6 LS Mean cfb	-11.00	-16.89	-12.37	-18.01	-14.49	-9.48
LS Mean cfb Diff from Placebo	-1.5	-7.4	-2.9	-8.5	-5.0	---
P value	0.4587	0.0004	0.1711	<0.0001	0.0028	---

Source: Sponsor's Table response to Information Request Jan 18, 2019
CI = Confidence Interval; cfb = change from baseline; LS = least-squares

Conclusion: for the 063-010 adult study, LS mean changes from baseline (cfb) were greater for active treatment than for placebo across all doses, except for 70 mg PRC-063 (n=10) in the adult study. In study 063-009, the placebo response at Canadian sites was lower than at US sites (LS mean cfb of -6.06 vs. -11.61). The sample sizes in several cells are small, it is difficult to draw conclusions.

ADHANSIA XR has not been studied in the patients over the age of 65 years.

4.2 Other Special/Subgroup Populations

There were no other special/subgroup populations identified.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor stated that the primary efficacy variable for both the adolescent fixed dose (Study 063-009) and adult fixed dose (Study 063-010) studies was to demonstrate the efficacy of ADHANSIA XR for all doses combined) versus placebo. Both studies were adequately powered to assess efficacy of all combined doses of ADHANSIA XR compared to placebo per sponsor.

Also, the sponsor's primary analysis was based on an analysis of covariance (ANCOVA) model including terms for treatment and baseline Clinician ADHD-5-RS total score as a covariate.

FDA differed from this analysis method as per statistical analysis plan (SAP) submitted in eCTD Sequence 0006 (letter dated 23 October 2014) and agreed upon, the primary analysis should be based on repeated measures analysis (instead of ANCOVA on Observed Case). FDA also pointed out that per the ICH E9 guidance, the primary analysis set should be based on the intent-to-treat population. Analysis on Observe Case data set requires a very strong assumption about missing data. Unless the dropout rates are nearly zero, the assumption is unlikely to hold. In addition, the labeling should describe which dose(s) beat placebo. A statistical significance based on all doses pooled would not suffice to support efficacy. The sponsor was requested to provide the efficacy results based on the pre-specified primary analysis in the SAP that was submitted to FDA, with FDA's comments incorporated, and to provide executable SAS code along with the detailed algorithm. The sponsor submitted the required efficacy analyses as well as SAS codes.

Based on the adolescent fixed-dose study 009, efficacy was demonstrated on the middle two doses: 45 mg and 75 mg only. In addition, the 70 mg did not appear to add additional benefit to the 45 mg. Based on the adult fixed-dose study 010, efficacy was demonstrated on the 45 mg and the highest dose 100 mg, not on the 75 mg. The 100 mg did not appear to provide additional benefit to the 45 mg. Also, the observed treatment effect for the 75 mg was very similar to the lowest dose 25 mg. These two studies did not suggest a sensible nor consistent dose response

relationship. In both studies, exploratory subgroup analyses by gender did not suggest consistent trends between genders either.

5.2 Conclusions and Recommendations

The proposed indication for PRC-063 is: *PRC-063 is a central nervous system (CNS) stimulant indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).*

The following four relevant phase 3 studies were reviewed in in support of the proposed indication:

Study 063-015 - Children (6-12 Years - USA)

Study 063-009 - Adolescents (12 to 17 Years USA & Canada)

Study 063-008 – Adults (18-60 Years USA)

Study 063-010 Adults (18-60 Years USA & Canada)

The efficacy results from five phase 3 studies the sponsor's claim that ADHANSIA XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older at dose levels of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg extended-release Capsules. Sponsor stated that the recommended starting dose for patients 6 years and older is 25 mg once daily in the morning. Dosage may be increased in increments of (b) (4) mg at intervals of at least 5 days (b) (4)

FDA disagreed on sponsor's analyses based on all doses combined and ANCOVA model for fixed studies 63-009 and 63-010. The sponsor was requested to provide analyses based on individual doses using MMRM (mixed model repeated measures). The results are summarized below:

Study 063-009 - Adolescents (12 to 17 Years USA & Canada) - efficacy was demonstrated on the middle two doses: 45 mg and 75 mg only.

Study 063-010 Adults (18-60 Years USA & Canada - efficacy was demonstrated on the 45 mg and the highest dose 100 mg, not on the 75 mg. The 100 mg did not appear to provide additional benefit to the 45 mg.

Study 063-015 - Children (6-12 Years - USA) - efficacy was demonstrated based on SKAMP compared to placebo

Study 063-008 – Adults (18-60 Years USA) - efficacy was demonstrated based on PERMP-Total Score compared to placebo.

Labeling is under review.

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Date: January 27, 2019

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/s/

SATISH C MISRA
01/28/2019 02:58:24 PM

PEILING YANG
01/29/2019 12:57:19 PM
I acknowledge the completion of Dr. Misra’s statistical review. However, I disagree with many of his comments. Readers should refer to my memorandum for a core statistical review of this NDA.

HSIEN MING J HUNG
02/01/2019 04:09:54 PM
I acknowledge the receipt of this review. However, this stat review does not provide analyses of the efficacy results that are critical to statistical interpretation. I agree with Dr. Peiling Yang's assessment.