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

Memorandum

Date: January 27, 2019

From: Peiling Yang, PhD.
Statistical Team Lead, Division of Biometrics I
Office of Biostatistics

Subject: Statistical Review of NDA 212-038

NDA Letter Date:	April 27, 2018
Applicant:	PURDUE
Drug Name:	ADHANSIA XR™ (Methylphenidate Hydrochloride Extended-Release Capsules) 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Submission Locations:	\\CDSESUB1\evsprod\NDA212038\0000 \\CDSESUB1\evsprod\NDA212038\0010 \\CDSESUB1\evsprod\NDA212038\0013
Relevant IND:	118,297

To: File NDA 212-038

This memorandum serves as a secondary review, which includes some essential information and my comments that may differ from the primary statistical review by Dr. Satish Misra. The results included in this memorandum were largely provided by the statistical reviewer Dr. Yang (Kelly) Yang, whose review is included as an appendix in this memorandum.

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1 Background

This application included four efficacy studies to support the proposed indication. The following table highlights some key elements for the 4 studies.

Table 1: Summary of Efficacy Studies

Study ID	Patient Population	Study Design	Doses Investigated
063-009	Adolescents	Parallel-group	Fixed doses: 25, 45, 70 and 85 mg/day
063-010	Adults	Parallel-group	Fixed doses: 25, 45, 70 and 100 mg/day
063-008	Adults	Laboratory, cross-over	Optimal dose: 25, 35, 45, 55, 70, 85, 100 mg/day
063-015	Children	Laboratory classroom, parallel-group	Optimal dose: 25, 35, 45, 55, 70, 85 mg/day

2 Efficacy Studies

2.1 Study -009 (Adolescents)

Protocol Title: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM, MULTI-CENTER STUDY MEASURING THE EFFICACY AND SAFETY OF PRC-063 IN ADOLESCENT ADHD PATIENTS

Study Start Date: 23-Apr-2014
Study End Date: 21-Jan-2015

This study was conducted at 50 centers across the United States and Canada. Subjects were randomized in a 1:1:1:1:1 ratio to 5 treatment groups: placebo, 25 mg/day, 45 mg/day, 70 mg/day and 85 mg/day.

2.1.1 Statistical Analysis Plan

The primary efficacy endpoint was the change from baseline (week 1, visit 2) in the clinician-rated ADHD-5-RS total score to week 5 (visit 6), that is, the change over the 4 weeks double-blind treatment duration.

The primary efficacy analysis was conducted on the Full Analysis (FA) Population, consisting of all randomized subjects who received any study medication and who had any primary outcome measure assessments.

The SAP (statistical analysis plan) last reviewed by FDA was Version 2, dated 08 July 2014 submitted on October 23, 2017 under the serial number eCTD 006. In that version, the primary analysis for the primary endpoint agreed upon was based on mixed model with repeated measures (MMRM) analysis with Dunnett's procedure to control for multiple comparisons with placebo. FDA conveyed the following two messages to the Applicant on SAP Version 2:

(1) The LOCF (last-observed-carried-forward) approach is not an appropriate sensitivity analysis because it requires a very rigorous assumption about missing data;
(2) The covariance structure in the primary analysis MMRM should not allow for any pattern; that is, it should be based on the unstructured "un".

Subsequently the SAP was revised twice (Version 3 and Version 4), but they were never submitted to FDA for review before data unblinding. In the Applicant's Clinical Study Report (CSR), the primary analysis was based on SAP Version 4 + Addendum 1, dated 20 May 2015, where the primary analysis was changed from MMRM to "ANCOVA on Observed Case" (that is, only the completers were included in Analysis of Covariance) and the primary comparison became the comparison of the pooled doses with placebo. In addition, comparisons between individual doses and placebo became secondary.

As summarized in Table 2 below, SAP Version 2 was submitted and reviewed before the study end date (January 21, 2015). After the study ended, the protocol was amended (Amendment 3) to mainly incorporate FDA's statistical comments; essentially, the primary analysis model was still MMRM. However, in SAP version 4 + Addendum 1 (dated May 20, 2015), it was changed to "ANCOVA on Observed Case". In response to FDA's Information Request during the NDA review, the Applicant confirmed that SAP Version 2 was the latest version submitted to FDA for review prior to trial completion and noted that the database lock occurred on the next day of the last SAP amendment.

Regardless of whether the amendment occurred before database lock or not, a major concern with the primary analysis presented in the Applicant's CSR is the handling of missing data because "ANCOVA on Observed Case" generally relies on a very rigorous assumption about missing data, missing completely at random, the same assumption for the LOCF imputation approach. Additionally, analyses on the completers set generally violate the intent-to-treat principle. On the other hand, MMRM (the pre-specified primary analysis in SAP Version 2, last submitted to FDA) includes both completers and dropouts, and requires less rigorous assumption about missing data. Also, to inform dosing, it is necessary to identify the individual dose(s) that demonstrated efficacy, which was the rationale for a fixed-dose study. With that in mind, it does not appear adequate to merely conclude that the drug when all doses were pooled beat placebo.

Table 2: Relevant Submission History (Study -009)

	Version Date or else specified	Key Notes
SAP Version 2	July 8, 2014	Primary analysis based on mixed model with repeated measures (MMRM) analysis with Dunnett's procedure to adjust for multiplicity.
Study End Date	January 21, 2015	
SAP Version 3	February 2, 2015	Not submitted for review
Protocol Amendment 3	March 16, 2015	Primary analysis still based on MMRM with Dunnett's procedure to adjust for multiplicity.
SAP Version 4	April 2, 2015	Not submitted for review
SAP Version 4 + Addendum 1	May 20, 2015	Submitted to eCTD 15 (August 17, 2016), but data were already unblinded and the CSR was already included.
Database Lock	May 21, 2015	

[Source: Applicant's CSR in eCTD 0 and Response to Information Request in eCTD 10.]

Regarding the Applicant's sensitivity analysis based on MCMC (Markov Chain Monte Carlo) multiple imputation method to impute missing data, it was also not included in the SAP last reviewed by FDA. The purpose of the sensitivity analysis should be to explore the impact of wrong assumptions about missing data on the primary efficacy results; however, the imputation method as stated in the Applicant's last version of SAP did not appear sensible for this purpose because it also relied on a very rigorous assumption about missing data.

2.1.2 Core Results

Exclusion of Site 08 from Efficacy Evaluations. The study was conducted at 50 centers across US and Canada. The Applicant noted that, during the course of the study, the monitoring was behind schedule for Site 08 in Canada due to poor source documentation. Per the Applicant's clarification, during the site monitoring prior to database lock and through the ongoing study overnight process, a For Cause Audit was performed at this site and it was determined that data from this site was not reliable because of numerous protocol and Good Clinical Practice (GCP) violations. In this study, 13 adolescents were enrolled at this site. Of those, ten completed the study and three were discontinued early due to withdrawal of consent. Subjects from this site were excluded from the Applicant's primary efficacy evaluations, but still included in the Applicant's primary safety evaluations.

After excluding site 08, a total of 354 subjects were randomized and 352 subjects were included in the primary analysis set (full analysis set). The dropout rate in the full analysis set was near 10% (Table 3).

Table 3: Number of Subjects (Study -009)

	Placebo n	25 mg n	45 mg n	70 mg n	85 mg n	Total n
Randomized	71	71	69	73	70	354
Full Analysis Set	71	71	68	72	70	352
Completers	66	65	64	67	62	324

Subjects from site 08 are excluded from this table.
[Source: Table A-1 of Appendix in this memorandum, provided by FDA statistician Dr. Yang (Kelly) Yang.]

Table 4 summarizes the Applicant's results of the primary efficacy endpoint. In the Applicant's CSR, the primary analysis was "ANCOVA on observed case", that is, on the completers set only. Based on this analysis, only the middle two doses (45 mg and the 70 mg) beat placebo after adjusting for multiplicity using the Dunnett's procedure (the pre-specified multiple testing procedure), with adjusted p-values 0.0155 and 0.0401, respectively. Although the nominal significance level for the high dose 85 mg was less than 0.05, statistical significance was not reached after adjusting for multiplicity using the pre-specified procedure.

Table 4: Primary Efficacy Endpoint: Applicant's Analysis Results (Site 08 Excluded, Study -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-063
CSR Analysis:	LS Mean diff[a]	-2.0	-5.6	-4.9	-4.3	-4.2
ANCOVA on	95% CI	(-6.8, 2.8)	(-10.4, -0.8)	(-9.7, -0.2)	(-9.1, 0.6)	(-7.2, -1.2)
Observed	**p (adjusted)[b]**	0.7031	**0.0155**	**0.0401**	0.1011	0.0067
Case	p (unadjusted)	0.3112	0.0043	0.0115	0.0311	0.0067
SAP 2.0	LS Mean diff[a]	-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

Note: Subjects from site 08 are excluded from this table.
CSR = clinical study report; MMRM = mixed model repeated measures; SAP = statistical analysis plan.
[a] Least square mean difference from placebo in the change from baseline.
[b] Dunnett's adjustment for multiple pairwise comparisons for each active dose group with placebo.
[Source: Extracted from Table 2 in Applicant's Response to Information Request submitted in eCTD sequence 010, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Regarding the prespecified primary analysis MMRM in SAP Version 2 that was agreed upon, the Applicant noted that by SAS default the Dunnett's procedure corrects for all comparisons of each dose group at each timepoint in the repeated-measures model. This tends to lead to a more conservative approach (such as larger adjusted p-values) because unwanted comparisons are also included in multiplicity adjustment. However, the nominal p-values for comparisons of

interest were generally smaller in MMRM analysis, suggesting that both "ANCOVA on Observed Case" and MMRM analysis led to the same conclusions that only the two middle doses beat placebo. This conclusion was confirmed by the FDA statistician Dr. Yang (Kelly) Yang, who derived the adjusted p-values exclusively on the four comparisons of interest (Table 5) based on MMRM with the Dunnett's procedure).

Whether including or excluding site 08, the primary efficacy results were not affected; that is, only 45 mg and 70 mg demonstrated efficacy.

Table 5: Primary Efficacy Endpoint: FDA MMRM Results (Site 08 Excluded, Study -009)

Treatment Group	n	Primary Efficacy Measure: Change from Baseline (Week 1, Visit 2) in ADHD-5-RS Total Score to Week 5 (Visit 6)				
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)	Unadjusted p-value	Adjusted p-value
25 mg	71	37.7 (8.69)	-12.77 (1.35)	-2.18 (-5.94, 1.59)	0.2562	0.5297
45 mg*	68	36.4 (8.52)	-16.03 (1.39)	-5.44 (-9.25, -1.63)	0.0052	0.0170
70 mg*	72	35.9 (8.42)	-15.79 (1.35)	-5.20 (-8.95, -1.44)	0.0069	0.0224
85 mg	70	37.8 (8.13)	-15.03 (1.39)	-4.43 (-8.24, -0.63)	0.0226	0.0692
Placebo	71	37.3 (8.40)	-10.59 (1.35)	--	--	--

n: number of subjects in the full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses that are statistically significantly different from placebo after adjusting for multiplicity.

[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA prior to trial completion.]

Table 6 summarizes the treatment effects, and Figure 1 depicts change from baseline for each dose, at each visit based on MMRM. The 75 mg dose did not seem to provide an additional benefit over the 40 mg dose.

In this study, the Applicant explored a linear trend in dose response, defined by the orthogonal polynomial (-9, -4, 0, 5, 8) in ANCOVA model. Since the p-value for testing the linear trend was 0.0076, the Applicant concluded a linear dose response. However, the results in Table 5 did not support a linear trend for the four doses; in contrast, the data seemed to suggest a flat dose response for the higher three doses. It is to be noted that p-value generally measures the strength of statistical evidence against the null hypothesis (no difference between any two

arms in this case). Rejection of the null hypothesis does not necessarily imply a linear dose response. Other dose response shapes might better fit to the data, but they were not explored.

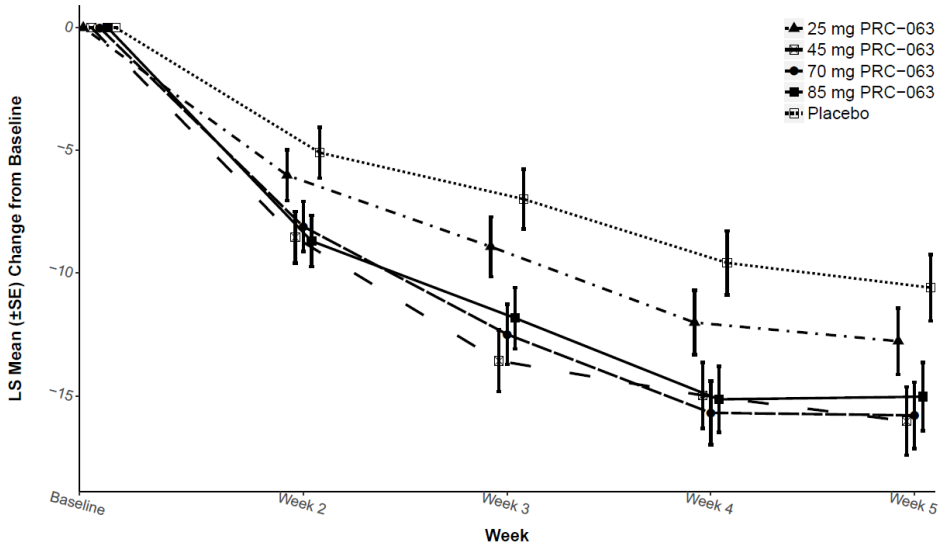
Conclusions: The study demonstrated the efficacy of 45 mg and 70 mg. However, the 70 mg dose did not seem to provide additional benefit over the 45 mg dose.

Table 6: Visit-wise Change from Baseline in ADHD-5-RS Total Score: FDA Results (Site 08 excluded, Study -009)

Time Point	Treatment Group	n	Mean Change from Baseline (SE)	Placebo-subtracted (Unadjusted 95% CI[a])	Unadjusted P-value
Visit 3 (week 2)	25 mg	71	-6.01 (1.03)	-0.91 (-3.77, 1.95)	0.5306
	45 mg	68	-8.54 (1.05)	-3.45 (-6.34, -0.56)	0.0195
	70 mg	72	-8.10 (1.02)	-3.01 (-5.86, -0.16)	0.0387
	85 mg	70	-8.69 (1.04)	-3.60 (-6.47, -0.73)	0.0141
	Placebo	71	-5.09 (1.03)	--	--
Visit 4 (week 3)	25 mg	71	-8.92 (1.22)	-1.94 (-5.33, 1.45)	0.261
	45 mg	66	-13.57 (1.26)	-6.59 (-10.04, -3.15)	0.0002
	70 mg	69	-12.49 (1.23)	-5.50 (-8.91, -2.10)	0.0016
	85 mg	66	-11.83 (1.25)	-4.85 (-8.28, -1.41)	0.0058
	Placebo	71	-6.98 (1.22)	--	--
Visit 5 (week 4)	25 mg	67	-12.01 (1.31)	-2.43 (-6.07, 1.21)	0.1894
	45 mg	64	-14.98 (1.34)	-5.40 (-9.08, -1.71)	0.0043
	70 mg	69	-15.69 (1.30)	-6.11 (-9.74, -2.48)	0.001
	85 mg	64	-15.14 (1.34)	-5.56 (-9.24, -1.88)	0.0032
	Placebo	67	-9.58 (1.31)	--	--
Visit 6 (week 5)	25 mg	65	-12.77 (1.35)	-2.18 (-5.94, 1.59)	0.2562
	45 mg	64	-16.03 (1.39)	-5.44 (-9.25, -1.63)	0.0052
	70 mg	67	-15.79 (1.35)	-5.20 (-8.95, -1.44)	0.0069
	85 mg	62	-15.03 (1.39)	-4.43 (-8.24, -0.63)	0.0226
	Placebo	66	-10.59 (1.35)	--	--

n: number of subjects at the visit; SE: standard error; CI: confidence interval.
[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA prior to trial completion]

Figure 1: Change from Baseline in ADHD-5-RS Total Score Over Time (Site 08 Excluded, Study -009)



[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA]

2.2 Study -010 (Adults)

Protocol Title: PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM, MULTI-CENTER STUDY MEASURING THE EFFICACY AND SAFETY OF PRC-063 IN ADULT ADHD PATIENTS

Study Start Date: April 28, 2014
Study End Date: October 22, 2014

This study was conducted at 34 sites across the United States and Canada. Subjects were randomized in a 1:1:1:1:1 ratio to 5 treatment groups: placebo, 25 mg/day, 45 mg/day, 70 mg/day and 100 mg/day.

2.2.1 Statistical Analysis Plan

The primary efficacy endpoint was the same as in the adolescent Study -009: the change from baseline (week 1, visit 2) in the clinician-rated ADHD-5-RS total score to week 5 (visit 6), that is, the change over the 4 weeks treatment duration.

As in Study -009, the primary efficacy analysis was conducted on the Full Analysis (FA) Population, consisting of all randomized subjects who received any study medication and who had any primary outcome measure assessments.

The SAP last reviewed by FDA was also SAP Version 2, dated July 08, 2014, submitted under the same serial number eCTD 006 as was SAP Version 2 for Study 009. In both SAPs, the same primary analysis was proposed, that is, MMRM with Dunnett's procedure to control for multiple comparisons with placebo. Hence, FDA conveyed the same comments on statistical analysis to the Applicant for both studies.

As summarized in Table 7 below, the Applicant had SAP Version 3, amended after the study ended and a few days before the database lock date. In SAP Version 3, the primary analysis was also changed to "ANCOVA on Observed Case" with pooled doses compared with placebo, same approach as for Study 009. Please refer to my concerns with this approach as expressed in Section 2.1.1 for Study -009.

Table 7: Relevant Submission History (Study -010)

	Version Date or else specified	**Key Notes**
SAP Version 2	July 8, 2014	Primary analysis based on mixed model with repeated measures (MMRM) analysis with Dunnett's procedure to control for multiple comparisons with placebo
Study End Date	October 22, 2014	
SAP Version 3	January 1, 2015	Submitted to eCTD 15 (August 17, 2016), but data were already unblinded and the CSR was also included.
Database Lock	January 9, 2015	

[Source: Applicant's CSR in eCTD 0 and Response to Information Request in eCTD 10.]

2.2.2 Core Results

A total of 375 subjects were randomized and 368 of them were included in the primary analysis set (full analysis set). The dropout rate in the full analysis set was around 10% (Table 8).

Table 8: Number of Subjects (Study -010)

	25 mg n	**45 mg n**	**70 mg n**	**100 mg n**	**Placebo n**	**Total**
Randomized	77	73	73	74	78	375
Full Analysis Set	75	73	71	72	77	368
Completers	73	69	62	61	69	334

[Source: Table A-8 of Appendix in this memorandum, provided by FDA statistician Dr. Yang (Kelly) Yang.]

Table 9 summarizes the Applicant's results of the primary efficacy endpoint. Like in Study -009, the primary analysis was "ANCOVA on observed case" in the Applicant's CSR. Based on this analysis, only the 45 mg and the highest dose 100 mg demonstrated statistical significance after adjusting for multiplicity using the Dunnett's procedure, with adjusted p-values 0.0013 and 0.0002, respectively. The result from the 70 mg was similar to that from the lowest dose 25 mg. The results from the prespecified primary analysis MMRM in SAP Version 2 (last submitted to FDA before trial completion) were consistent with those from "ANCOVA on Observed Case". Refer to Table 10 for adjust p-values from MMRM analysis.

Table 11 summarizes the treatment effects, and Figure 2 depicts the change from baseline for each dose, at each visit based on MMRM.

Conclusions: The study demonstrated the efficacy of 45 mg and 100 mg, but the 100 mg dose did not seem to provide noticeable advantage over the 45 mg dose. The results for both 25 mg and 70 mg appeared similar to that for placebo.

Table 9: Primary Efficacy Endpoint: Applicant's Analysis Results (Study -010)

Analysis	Change from Baseline (Week 1, Visit 2) in ADHD-5-RS Total Score to Week 5 (Visit 6)					
		25mg	45mg	70mg	100mg	All PRC-063
CSR Analysis: ANCOVA on Observed Case	LS Mean diff[a]	-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)
	p (adjusted)[b]	0.6750	**0.0013**	0.6720	**0.0002**	0.0026
	p (unadjusted)	0.2918	0.0003	0.2899	<0.0001	0.0026
SAP 2.0 Analysis: MMRM	LS Mean diff[a]	-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)
	p (unadjusted)	0.3016	0.0002	0.2287	<0.0001	0.0019

Note: Subjects from site 08 are excluded from this table.
CSR = clinical study report; MMRM = mixed model repeated measures; SAP = statistical analysis plan.
[a] Least square mean difference from placebo in the change from baseline.
[b] Dunnett's adjustment for multiple pairwise comparisons for each active dose group with placebo.
[Source: Extracted from Table 2 in Applicant's Response to Information Request submitted in eCTD sequence 010, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 10: Primary Efficacy Endpoint: FDA Analysis Results (Study -010)

Treatment Group	Primary Efficacy Measure: Change from Baseline (Week 1) in ADHD-5-RS Total Score to Week 5					
	n	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)	Unadjusted p-value	Adjusted p-value
25 mg	75	36.1 (8.14)	-11.63 (1.31)	-1.93 (-5.59, 1.74)	0.3016	0.5919
45 mg*	73	36.5 (7.19)	-16.83 (1.34)	-7.12 (-10.82, -3.43)	0.0002	0.0006
70 mg	71	35.4 (7.44)	-12.00 (1.37)	-2.29 (-6.04, 1.45)	0.2287	0.4889
100 mg*	72	37.0 (7.94)	-17.57 (1.39)	-7.86 (-11.63, -4.09)	<0.0001	0.0003
Placebo	77	35.7 (8.42)	-9.71 (1.32)	--	--	--

n: number of subjects in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses that are statistically significantly different from placebo after adjusting for multiplicity.

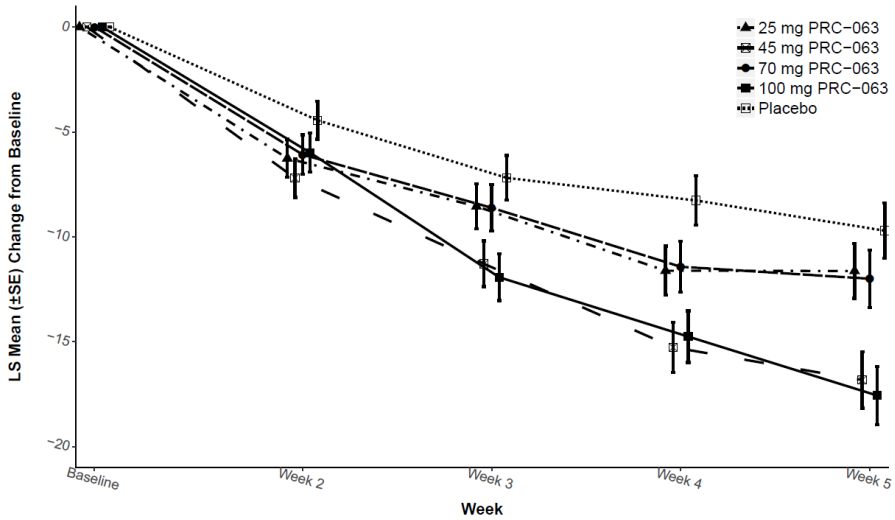
[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA]

Table 11: Visit-wise Change from Baseline in ADHD-5-RS Total Score: FDA Results (Study -010)

Time Point	Treatment Group	n	Mean Change from Baseline (SE)	Placebo-subtracted (Unadjusted 95% CI[a])	Unadjusted P-value
Visit 3 (week 2)	25 mg	75	-6.26 (0.91)	-1.81 (-4.33, 0.70)	0.1577
	45 mg	73	-7.20 (0.92)	-2.75 (-5.29, -0.22)	0.0334
	70 mg	71	-6.08 (0.94)	-1.63 (-4.18, 0.92)	0.2102
	100 mg	72	-5.99 (0.93)	-1.54 (-4.08, 1.01)	0.2355
	Placebo	77	-4.45 (0.90)	--	--
Visit 4 (week 3)	25 mg	73	-8.55 (1.07)	-1.36 (-4.32, 1.61)	0.3686
	45 mg	71	-11.29 (1.09)	-4.10 (-7.09, -1.11)	0.0073
	70 mg	70	-8.62 (1.10)	-1.43 (-4.43, 1.57)	0.3492
	100 mg	67	-11.93 (1.11)	-4.74 (-7.75, -1.72)	0.0022
	Placebo	74	-7.19 (1.06)	--	--
Visit 5 (week 4)	25 mg	73	-11.62 (1.17)	-3.35 (-6.60, -0.10)	0.0432
	45 mg	71	-15.27 (1.19)	-7.00 (-10.27, -3.73)	<.0001
	70 mg	65	-11.43 (1.21)	-3.16 (-6.47, 0.14)	0.0607
	100 mg	62	-14.76 (1.23)	-6.49 (-9.82, -3.16)	0.0001
	Placebo	71	-8.27 (1.17)	--	--
Visit 6 (week 5)	25 mg	73	-11.63 (1.31)	-1.93 (-5.59, 1.74)	0.3016
	45 mg	69	-16.83 (1.34)	-7.12 (-10.82, -3.43)	0.0002
	70 mg	62	-12.00 (1.37)	-2.29 (-6.04, 1.45)	0.2287
	100 mg	61	-17.57 (1.39)	-7.86 (-11.63, -4.09)	<0.0001
	Placebo	69	-9.71 (1.32)	--	--

n: number of subjects at the visit; SE: standard error; CI: confidence interval.
[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA]

Figure 2: Change from Baseline in ADHD-5-RS Total Score Over Time (Study -010)



[Source: FDA statistician Dr. Yang (Kelly) Yang using MMRM analysis prespecified in SAP Version 2 that was last submitted to FDA]

2.3 Study -008 (Adults)

Protocol Title: A RANDOMIZED, DOUBLE-BLIND STUDY OF THE TIME COURSE OF RESPONSE OF PRC-063 IN ADULTS WITH ADHD IN A SIMULATED ADULT WORKPLACE ENVIRONMENT

Study Start Date: November 29, 2014
Study End Date: March 21, 2015

This was a cross-over, optimized-dose study conducted at 2 sites in the United States. PRC-063 methylphenidate hydrochloride controlled-release capsules 25, 35, 45, 55, 70, 85 and 100 mg, are designed to be taken orally once daily in the morning. Subjects were titrated to an optimal dose in an open-label phase of between 2 and 7 weeks, familiarized with study procedures in a practice AWE (Adult Workplace Environment) session and then randomized to one of the two sequences: (i) ACTIVE to PLACEBO or (ii) PLACEBO to ACTIVE, and received one treatment for one week, followed by an AWE session, then crossed over to the other treatment for one week, followed by a second AWE session.

2.3.1 Statistical Analysis Plan

The primary efficacy measure was the mean difference between treatment in the post-dose PERMP (Permanent Product Measure of Performance) total score averaged across all time points on the AWE laboratory day. In each AWE session, efficacy was measured at pre-dose, 1.0, 2.0, 5.0, 8.0, 11.0, 14.0 and 16.0 hours post-dose. The key secondary efficacy measures were time to onset and time course of efficacy. The primary analysis was based on MMRM on the FA (full analysis) population, defined as all randomized subjects who have a pre-dose score and at least one post-dose time point assessment based on the PERMP-T (PERMP Total) score on both AWE laboratory days. The MMRM model contained fixed effect terms for treatment, period, time, treatment-by-time and sequence, where the time factor consisted of 8 levels: pre-dose assessment time and each post-dose assessment time on the laboratory day; that is, the pre-dose measure was considered as a response variable instead of a covariate in the model.

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.

2.3.2 Core Results

As summarized in Table 12, a total of 59 patients were randomized to the study. Of those, 46 (78%) completed the study. There were around 26% dropouts in the treatment sequence "PRC-063 to Placebo" compared with 18% in the other treatment sequence. Since randomization occurred prior to the titration phase, subjects might have been randomized but discontinued prior to receiving randomized treatment, which contributed to the smaller full analysis

population (primary efficacy analysis set) compared with the all-randomized population. Most subjects included in the FA population received the optimal dose 70 mg or higher, and the modal optimal dose was 70 mg (Table 13).

Table 12: Number of Subjects (Study -008)

Category	Treatment Sequence		All Subjects
	PRC-063 to Placebo	Placebo to PRC-063	
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			
AE[a]	5 (16.1%)	2 (7.1%)	7 (11.9%)
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%)

[a] Documented on an AE case report form.
Note: Percentages are based on the total number of subjects randomized to each treatment sequence for all randomized subjects (N). Randomization occurred prior to the titration phase; therefore, subjects may have been randomized but discontinued prior to receiving randomized treatment. The subject discontinuing due to Lack of Response to highest dose discontinued while taking randomized placebo. Subject C6819 discontinued the study due to an AE; however, the subject continued taking study drug and did not discontinue treatment due to the AE.
[Source: Table 4 of Applicant's CSR]

Table 13: Optimized Dose of PRC-063 (Full Analysis Population, Study -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]

Table 14 summarizes the Applicant's primary analysis results of the primary efficacy measure post-dose PERMP-T, averaged over all time points on the AWE laboratory day, where larger scores correspond to better performance. For reference, this table also includes results from the two components PERMP-A (Attempted) and PERMP-C (Corrected) to explore if the primary analysis result was mainly driven by either component. There was a statistically significant difference between PRC-063 and placebo based on the primary efficacy measure post-dose PERMP total score averaged over all time points on the AWE laboratory day. In addition, as

seen in Table 15, statistical significance (at nominal significance level of 0.05) was reached at all time points except the pre-dose hour (regarded as a response variable in the primary analysis) and post-dose hours 5 and 14, suggesting that (i) time of onset occurred at post-dose hour 1 and that (ii) time course of effect was from post-dose hour 1 to hour 2, because statistical testing at hour 5 failed to retain statistical significance.

Table 14: Applicant's Primary Analysis Results of Primary Efficacy Measure: Post-dose PERMP-T (Total) Score Averaged over All Time Points (Study -008)

	Measures Averaged over All Post-dose Time Points on AWE Laboratory Day					
	Primary Efficacy PERMP-T (Total)		**Exploratory** PERMP-A (Attempted)		**Exploratory** PERMP-C (Correct)	
Treatment	**PRC-063**	**Placebo**	**PRC-063**	**Placebo**	**PRC-063**	**Placebo**
n	45	45	45	45	45	45
Mean (SD)	270.2 (81.46)	256.5 (73.86)	137.1 (40.47)	129.8 (36.88)	133.1 (41.03)	126.8 (37.04)
Median	254.1	248.9	130.0	125.8	126.4	122.6
Min, Max	130, 470	109, 428	67, 238	56, 215	63, 232	53, 213
LS Mean (SE)	268.7 (11.24)	255.6 (10.87)	137.1 (5.57)	130.2 (5.45)	131.5 (5.70)	125.6 (5.45)
LS Mean Difference[a] (SE) [95% CI]	**13.05 (4.550) [3.88, 22.23]**		6.95 (2.299) [2.32, 11.59]		5.94 (2.318) [1.27, 10.62]	
Treatment p-value	**0.0064**		0.0042		0.0139	
Period p-value	<0.0001		<0.0001		<0.0001	
Sequence p-value	0.1322		0.0920		0.2284	

n: number of subjects; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean averaged over all post-dose time points.

Note: Larger scores correspond to better performance. Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and treatment-by-time interaction.

[Source: Table 5 of Applicant's CSR; results of PERMP-T confirmed by FDA statistician Dr. Yang (Kelly) Yang]

However, the Applicant observed a noticeable period effect as shown in Table 14 (nominal p-value < 0.001), as well as a noticeable imbalance of pre-dose PERMP total scores between treatments in the group of subjects who were first randomized to PRC-063 then to placebo as shown in Table 16 (nominal p-value 0.0001). This table also illustrates that within each treatment sequence the mean pre-dose scores were larger (better performance) in period 2 than in period 1. The observed period effect may be partially explained by some unknown effects, such as the repeated practice in solving math problems in PERMP.

Table 15: Applicant's PERMP-T Results at Each Time Point (Both Periods Combined, Study -008)

Post-dose Time	**0.0h[b]**	**1.0 h**	**2.0 h**	**5.0 h**	**8.0 h**	**11.0 h**	**14.0 h**	**16.0 h**
LS Mean Diff[a] (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% CI	(-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

LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean at a given hour.

[b] pre-dose.

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. P-values were not adjusted for multiplicity.

[Source: Table 6 of Applicant CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 16: Applicant's Results of Pre-Dose PERMP-T Score by Sequence (Study -008)

Sequence	**PRC-063/Placebo (N=23)**		**Placebo/PRC-063 (N=22)**	
Treatment	PRC-063	Placebo	PRC-063	Placebo
Mean (SD)	201.0 (56.81)	232.5 (64.57)	250.4 (87.45)	239.0 (67.69)
LS Mean (SE)	202.4 (13.31)	233.5 (12.30)	245.6 (13.29)	236.4 (12.38)
LS Mean Difference[a] (SE) [95% CI]	-31.14 (7.388) [-46.04, -16.24]		9.21 (7.425) [-5.76, 24.19]	
p-value	**0.0001**		0.2215	

N: number of subjects; SD: standard deviation; LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.

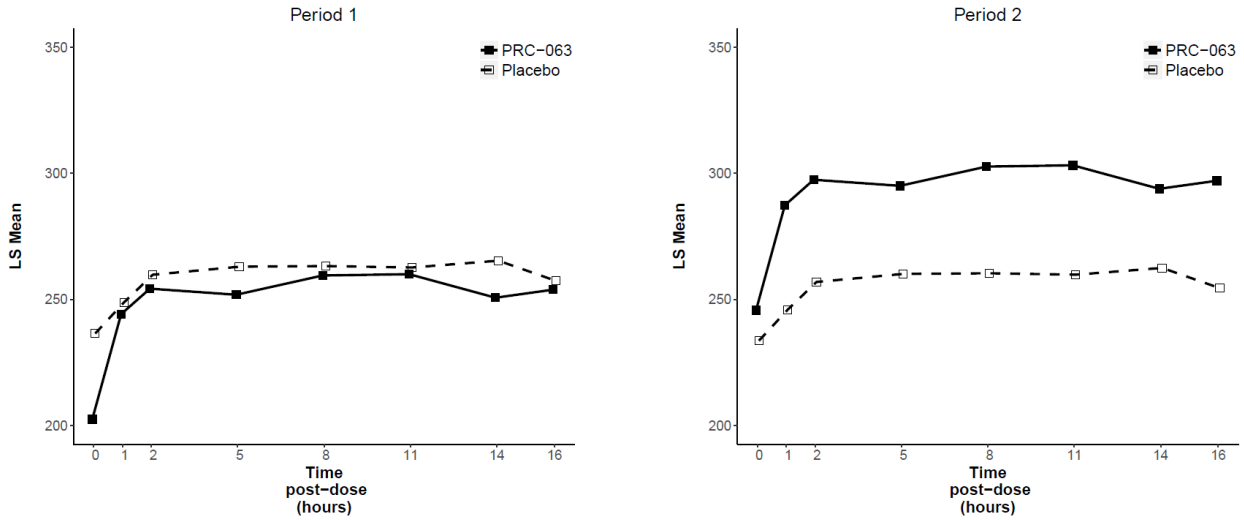
[a] Difference (drug minus placebo) in least-squares mean of pre-dose PERMP-T score.

Note: Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and treatment-by-time interaction.

[Source: Table ST8-10 of Applicant's CSR]

Figure 3 depicts the mean PERMP Total score during the laboratory day for each treatment by period. This figure suggests a strong interaction effect between treatment and period in the following sense: in period 1, the two curves are close to each other with the placebo curve slightly on top of the PRC-063 curve, but in period 2 the positions of the two curves switched and much separated from each other. The strong interaction was already noted at the pre-dose hour. However, in terms of improvement over pre-dose score, the figure suggests a larger improvement with PRC-063 than with placebo in both periods, and the improvement mainly occurred in the first two hours post-dose.

Figure 3: Pre-Specified: PERMP Total Score by Period (Study -008)



Note: Post-dose time at hour 0 corresponds to the pre-dose time.
[Source: FDA sttaistician Dr. Yang (Kelly) Yang]

To address the impact of the strong interaction effect, particularly at the pre-dose hour, the Applicant conducted two ad-hoc MMRM analyses, which were slight modifications from the primary MMRM analysis as following:

(1) **First ad-hoc analysis:** The role of the pre-dose score was changed from a dependent/response variable (in the primary analysis) to a covariate in the model.
(2) **Second ad-hoc analysis:** The response variable was revised from "the outcome score observed at each time point" to "the change from pre-dose score".

As summarized in Table 17 and Table 18, in each ad-hoc analysis, statistical significance was reached at nominal significance level of 0.05 at all post-dose hours except hour 14, suggesting that both ad-hoc analyses led to the same conclusions with each other: (i) time of onset occurred at hour 1, and (ii) time course of effect was from hour 1 through hour 11. Figure 4 and Figure 5 display the efficacy results based on the respective ad hoc analyses.

Conclusions: Because of the noticeable interaction between treatment and period, mainly resulting from the imbalance in pre-dose scores, I agree that the ad-hoc analsyes appear to be more appropriate and consider the (b) (4) .

Table 17: Applicant's First Ad-Hoc Analysis of PERMP Total Score (Study -008)

	Treatment Difference (PRC-063 – Placebo) in **Post-dose PERMP-T Score**						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Diff[a]	27.86	27.60	22.36	30.09	31.32	18.01	30.38
(SE)	(5.595)	(5.932)	(7.060)	(6.112)	(9.390)	(9.836)	(8.446)
95% CI	(16.57, 39.14)	(15.64, 39.56)	(8.12, 36.60)	(17.76, 42.41)	(12.39, 50.26)	(-1.83, 37.84)	(13.35, 47.41)
Treatment p-value	<0.0001	<0.0001	0.0028	<0.0001	0.0018	0.0741	0.0008

LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean at a given hour.

Note: Analyses utilize repeated measures mixed-effects analysis of covariance models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and interaction and pre-dose score as a covariate.

[Source: Table 9 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 18: Applicant's Second Ad-Hoc Analysis of PERMP Total (Study 008)

	Treatment Difference in **Change from Pre-dose PERMP-T Score**						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Diff[a]	28.35	27.37	22.17	29.86	30.58	18.08	29.22
(SE)	(5.744)	(5.905)	(7.033)	(6.126)	(9.369)	(9.746)	(8.238)
95% CI	(16.77, 39.93)	(15.46, 39.28)	(7.99, 36.36)	(17.50, 42.21)	(11.69, 49.48)	(-1.57, 37.74)	(12.60, 45.83)
Treatment p-value	<0.0001	<0.0001	0.0030	<0.0001	0.0022	0.0704	0.0010

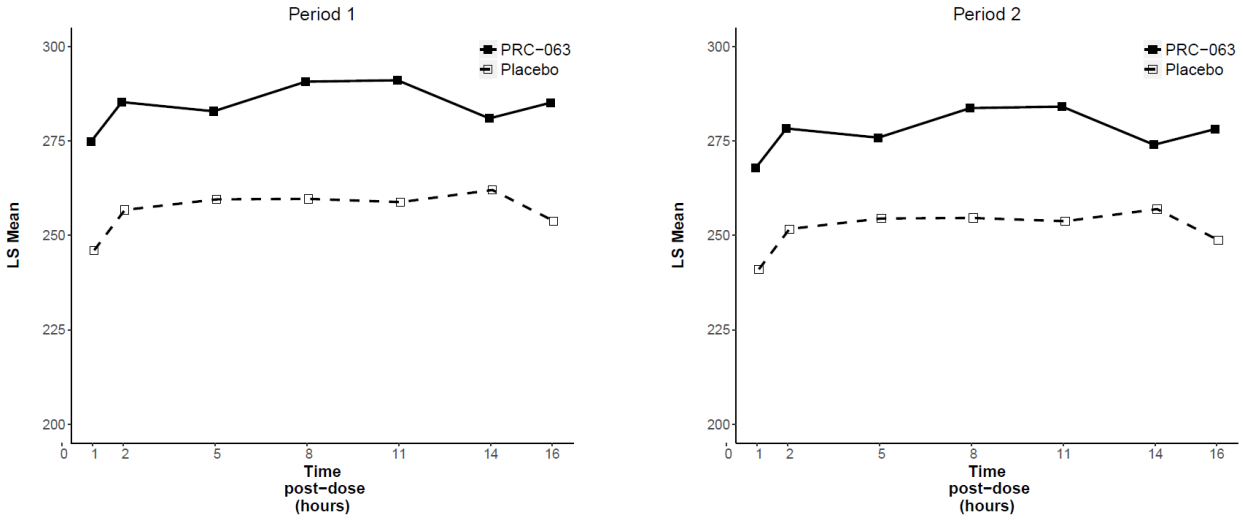
LS Mean: least-squares mean; SE: standard error; CI: confidence interval, not adjusted for multiple comparisons.

[a] Difference (drug minus placebo) in least-squares mean at a given hour.

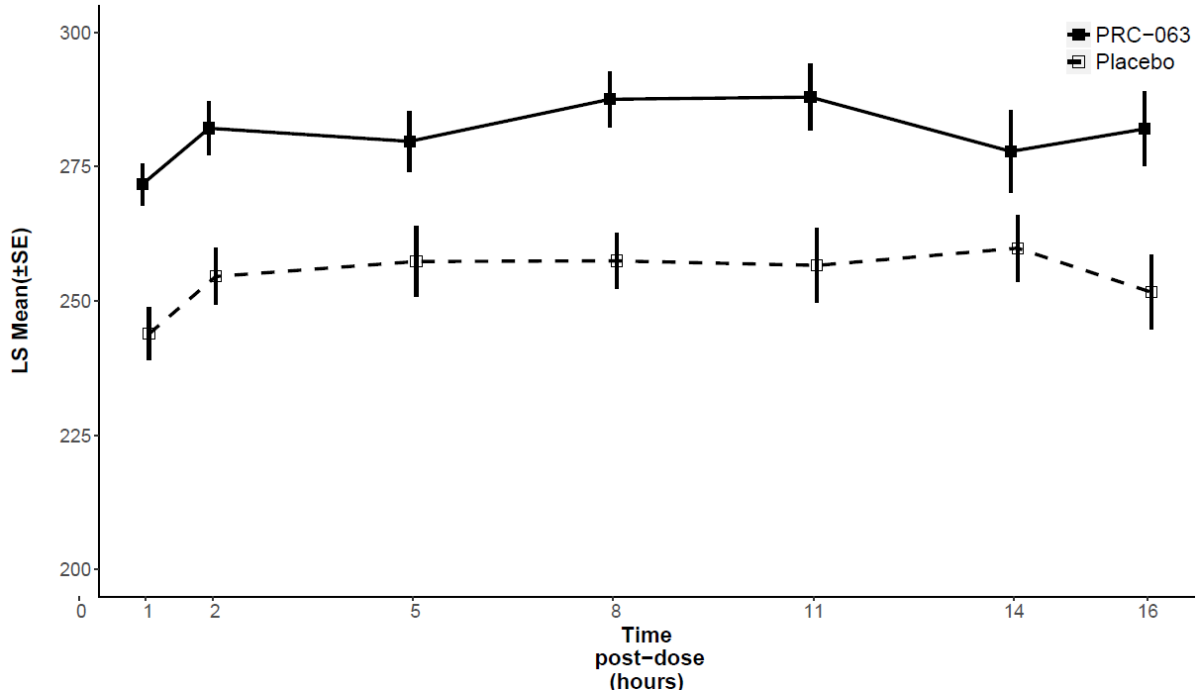
Note: Analyses utilize repeated measures mixed-effects ANOVA models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and treatment-by-time interaction.

[Source: Table 10 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Figure 4: First Ad-Hoc Analysis: PERMP-T (Study 008, by Period and When Both Periods Were Combined)

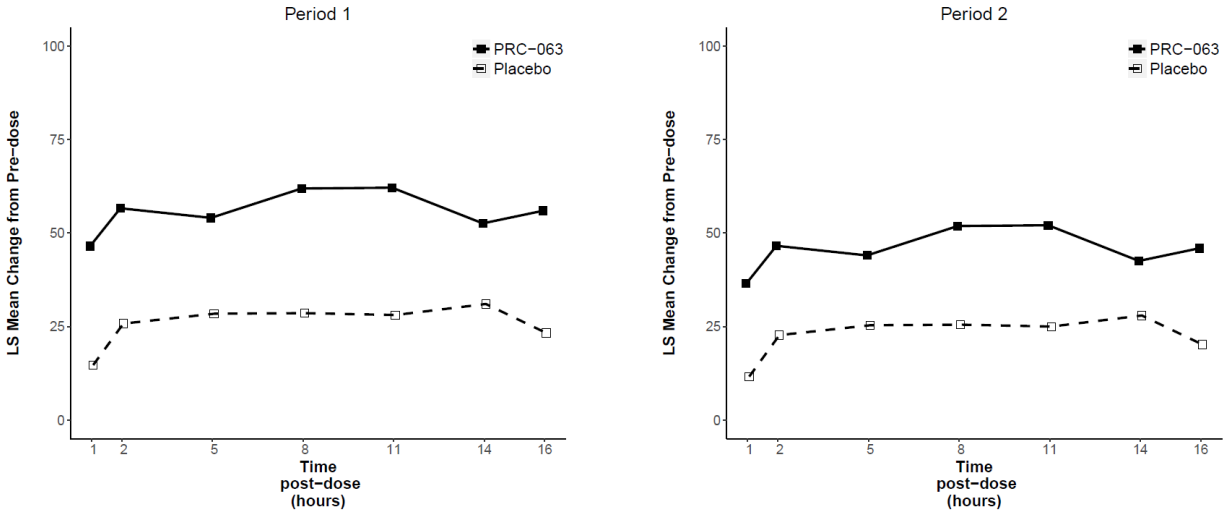


When Both Periods Combined:

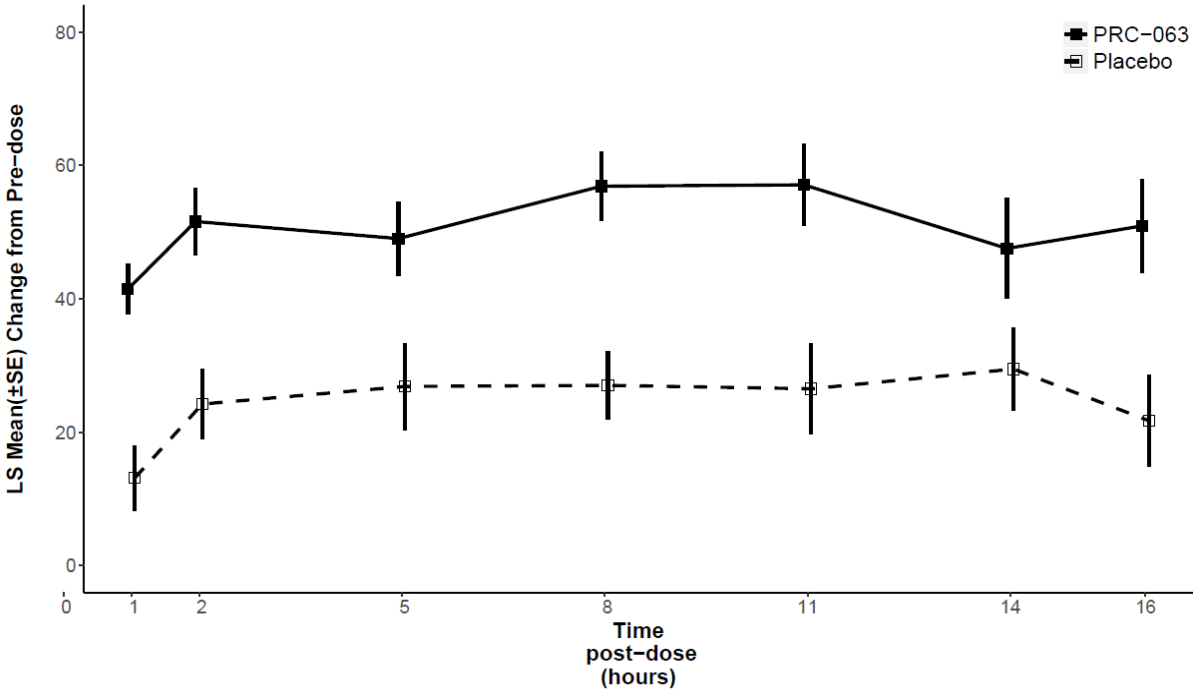


[Source: FDA statistician Dr. Yang (Kelly) Yang]

Figure 5: Second Ad-hoc Analysis: Change in PERMP-T from Pre-dose by Period (Study 008, by Period and When Both Periods Combined)



When Both Periods Combined:



[Source: FDA statistician Dr. Yang (Kelly) Yang]

2.4 Study -015 (Children)

Protocol Title: 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 (6-12 YEARS OF AGE) WITH ADHD

Study Start Date: May 4, 2017
Study End Date: August 28, 2017

This was a parallel-group and dose optimized study at 6 sites in US. PRC-063 methylphenidate hydrochloride controlled-release capsules 25, 35, 45, 55, 70, and 85 mg/day are designed to be taken orally once daily in the morning. Subjects (6 – 12 years old) were titrated to an optimal dose in an open-label phase of 6 weeks, followed by a one-week double-blind treatment period. At the end of the open-label phase (Day 42), subjects were randomized, stratified by individual optimal dose level, to the optimal PRC-063 dose or placebo. On the last day of the double-blind period (Day 49), subjects returned to the clinic to participate in the full day of evaluations in a laboratory classroom setting.

2.4.1 Statistical Analysis Plan

The primary efficacy measure was the mean SKAMP-C (Swanson, Kotkin, Agler, M-Flynn and Pelham Combined) score averaged across the laboratory classroom day after dosing. On that day, efficacy was assessed within 30 minutes prior to dosing and at hours 1, 2, 4, 6, 8, 10, 12 and 13 post-dose. The key secondary efficacy measures were time to onset and time course of efficacy.

The primary analysis was based on MMRM on the FA (full analysis) population, defined as 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 laboratory classroom day (that is, must have at least one SKAMP evaluation on this day). The response (dependent) variable in the MMRM analysis was the post-dose SKAMP-C score at each assessed time point during the laboratory classroom. MMRM model contained fixed effects for treatment, time, treatment-by-time interaction, investigative site, and covariate terms for the pre-dose SKAMP-C score and pre-dose SKAMP-C score-by-time interaction.

2.4.2 Core Results

A total of 148 patients were randomized to the double-blind phase and 147 of them were included in the FA population. In the double-blind phase, 75 subjects were randomized to PRC-063 and 73 to placebo. Among those randomized to PRC-063, most subjects received 45 mg or 55 mg. One subject randomized to PRC-063 25 mg was excluded from the primary efficacy analysis because of failure to meet the FA population definition.

Table 19: Number (%) of Subjects (Study -015)

	Optimal PRC-063 Dose						Total PRC-063	Total Placebo	Total Subjects
	25 mg	35 mg	45 mg	55 mg	70 mg	85 mg			
Randomized	9	15	20	19	8	4	75	73	148
Completed*	8	15	20	19	8	4	74	73	147

*Completed study to the full day laboratory classroom
[Source: Table 3 of Applicant's CSR]

Based on the primary analysis results (Table 20, where larger scores correspond to more severe symptoms), 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. The onset of time was at hour 1 and the effect lasted throughout hour 13 post-dose (Table 21). The time course of effect is displayed in Figure 6.

Conclusions: This study demonstrated that PRC-063 was superior to placebo in reducing SKAMP-C total score and that the time course of effect started from hour 1 through hour 13.

Table 20: Primary Efficacy Results – Post-dose SKAMP-C Score Averaged Over All Time Points on Laboratory Classroom Day (Study -015)

Treatment Group	Mean Pre-Dose Score on Classroom Day (SD)	LS Mean (SE) for the Classroom day	Placebo-subtracted Difference[a] (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)	--

N: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a]Least-Squares Mean Difference (drug minus placebo).
Larger scores represent more severe symptoms.
[Source: Table 14.2.1.1.1 and Table 14.2.1.1.4 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Table 21: Secondary Efficacy Results – Post-dose SKAMP-C Scores at Each Time Point (Study -015)

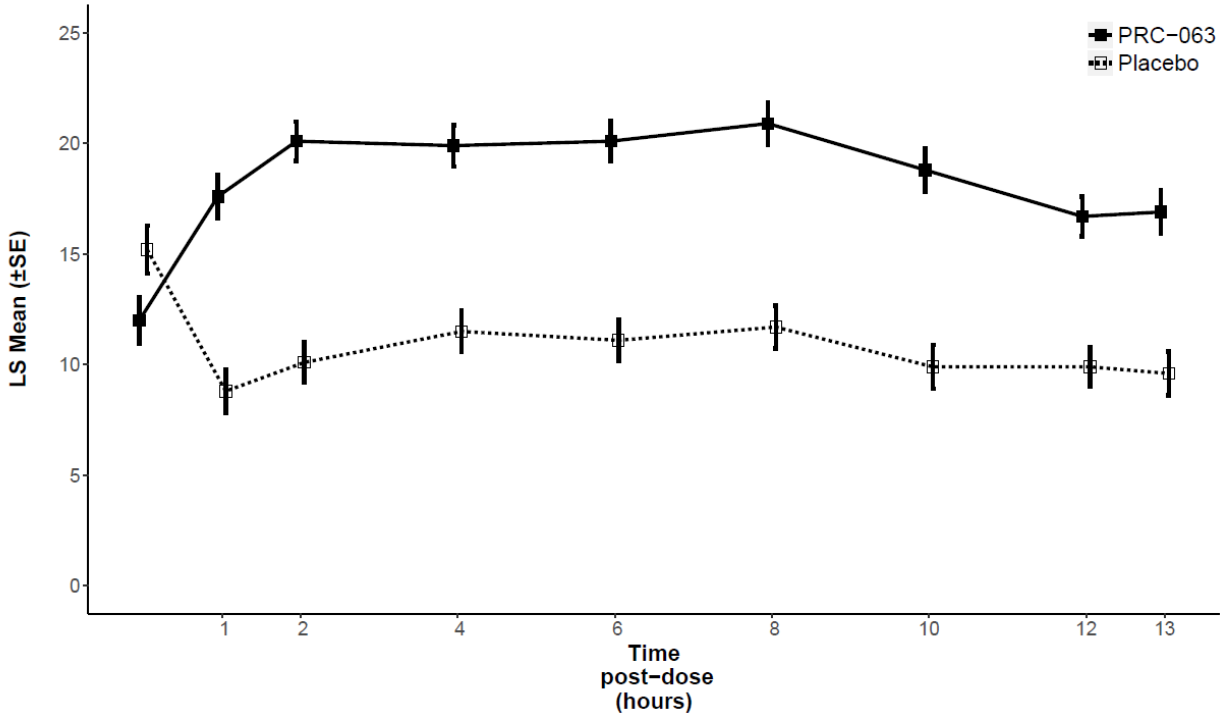
Post-Dose Hour	PRC-063 [N=74] LS Means (SE)	Placebo [N=73] LS Means (SE)	LS Mean Difference[a] (SE)	95% CI	p-value
hour 1	8.8 (0.98)	17.6 (0.97)	-8.8 (1.36)	(-11.5, -6.1)	< 0.0001
hour 2	10.1 (0.90)	20.1 (0.89)	-10.1 (1.25)	(-12.5, -7.6)	< 0.0001
hour 4	11.5 (0.94)	19.9 (0.93)	-8.4 (1.31)	(-11.0, -5.9)	< 0.0001
hour 6	11.1 (0.93)	20.1 (0.92)	-9.0 (1.30)	(-11.6, -6.4)	< 0.0001
hour 8	11.7 (0.97)	20.9 (0.96)	-9.1 (1.35)	(-11.8, -6.5)	< 0.0001
hour 10	9.9 (0.98)	18.8 (0.97)	-8.9 (1.37)	(-11.6, -6.2)	< 0.0001
hour 12	9.9 (0.91)	16.7 (0.90)	-6.8 (1.26)	(-9.3, -4.3)	< 0.0001
hour 13	9.6 (0.99)	16.9 (0.98)	-7.3 (1.38)	(-10.1, -4.6)	< 0.0001

CI = confidence interval; LS = least squares; SE = standard error; p-values are not adjusted for multiplicity.

[a]Least-Squares Mean Difference (drug minus placebo).

[Source: Table 9 and 10 of Applicant's CSR, confirmed by FDA statistician Dr. Yang (Kelly) Yang]

Figure 6: SKAMP-C Scores by Treatment During the Full Day Classroom (Study -015)



[Source: FDA statistician Dr. Yang (Kelly) Yang]

2.5 Exploratory Subgroup Analyses Results

Below summarize the subgroup analysis results explored by Dr. Yang (Kelly) Yang. For more details, please refer to the Appendix.

[1] Gender:

- For the fixed-dose studies -009 (adolescents) and -010 (adults), there did not suggest a consistent dose response between genders. However, the sample size in each dose group within each gender was relatively small, particularly in study -009, where less than one third of the subjects were females.

- For both laboratory studies -008 (adults) and -015 (children), the data suggested a consistent trend in favor of PRC-063 in both genders.

[2] Race: Race was explored by white vs. others (including multi-racial subjects) in studies -009, -010, and -15. It was not explored in study -008 because almost all subjects were white.

- For study -009, approximately 69% of the subjects were white. There did not appear to be a consistent dose response between the two strata. However, the sample size in the "others" was quite small. For study -010, approximately 85% of the subjects were white.

- For study -015, approximately 55% of the subjects were white. The results appeared to be consistent between the two strata.

[3] Age: Age effect was not explored. Among the four studies, one (study -015) was conducted in children and another (study -009) was conducted in adolescents. The remaining two studies (-008 and -010) were conducted in adults, but for study -008 all subjects were < 65 years old and for study -010 almost all subjects were < 65 years old.

[4] Country: Both studies -009 and -010 were conducted in US and Canada, but more than 80% of subjects were from US. The results in US were similar to those when both countries were combined.

3 APPENDIX (Provided by Statistical Reviewer Dr. Yang (Kelly) Yang)

APPEARS THIS WAY ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	NDA 212-038
Letter Date:	April 27, 2018
Applicant:	PURDUE
Drug Name:	ADHANSIA XR™ (Methylphenidate Hydrochloride Extended-Release Capsules) 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Submission Locations:	\\CDSESUB1\evsprod\NDA212038\0000 \\CDSESUB1\evsprod\NDA212038\0010 \\CDSESUB1\evsprod\NDA212038\0013
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Yang (Kelly) Yang, Ph.D.

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A.1 Study 063-009

This study was a multiple-dose, randomized, double-blind, placebo-controlled, parallel-group assessment of the clinical efficacy and safety of PRC-063 in adolescents with ADHD.

Table A-1: Number of Subjects (Study -009)

	Placebo n (%)	**25 mg n (%)**	**45 mg n (%)**	**70 mg n (%)**	**85 mg n (%)**	**Total n (%)**
Randomized	71	71	69	73	70	354
Full Analysis Set	71 (100.0)	71 (100.0)	68 (98.6)	72 (98.6)	70 (100.0)	352 (99.4)
Completers	66 (93.0)	65 (91.5)	64 (92.8)	67 (91.8)	62 (88.6)	324 (91.5)

Subjects from site 08 are excluded from this table.
Note: The reviewer found that 2 subjects dropped out of the trial right after the baseline; those 2 subjects should not be included in the Full Analysis Set.
One subject in 85mg group was marked as uncompleted in the applicant's dataset, but the reviewer found that this subject had completed the trial.
[Source: Reviewer's table]

Table A-2: Analysis Using ANCOVA Model: Clinician-Rated ADHD-5-RS (Completers in FA Population, Site 08 Excluded, Study -009)

Time Point	**Treatment Group**	**n**	**LS Mean Change from Baseline**	**SE**	**Difference in LS Means**	**Unadjusted 95% CI[a]**	**Unadjusted P-value[a]**	**Adjusted P-value[b]**
Visit 6	25 mg PRC-063	65	-12.95	1.39	-1.98	(-5.81, 1.86)	0.3112	0.7031
	45 mg PRC-063	64	-16.60	1.39	-5.63	(-9.47, -1.78)	0.0043	0.0155
	70 mg PRC-063	67	-15.89	1.36	-4.91	(-8.72, -1.11)	0.0115	0.0401
	85 mg PRC-063	62	-15.25	1.42	-4.27	(-8.15, -0.39)	0.0311	0.1011
	Placebo	66	-10.98	1.37	--	--	--	--

Note: Analyses utilize ANCOVA models with Dunnett's adjustments for multiple pairwise comparisons for each active dose group with placebo. The model includes terms for treatment and baseline Clinician ADHD-5-RS score as a covariate. Subjects from site 08 are excluded from this table.
[a]: The unadjusted CIs and unadjusted P-values in the table above were calculated by the reviewer.
[b]: The p-values were adjusted for multiple comparisons using Dunnett's procedure in the Applicant's table.
[Source: Applicant's clinical study report PRC-063-0089 Table ST 8- 12 except unadjusted CIs and unadjusted p-values in the table, which are from this reviewer.]

Table A-3: Analysis Using ANCOVA Model: Clinician-Rated ADHD-5-RS (Completers in FA Population, Site 08 Included, Study -009)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI	Unadjusted P-value	Adjusted P-value
Visit 6	25 mg PRC-063	66	-12.92	1.36	-1.98	(-6.67, 2.71)	0.3005	0.6872
	45 mg PRC-063	66	-16.38	1.36	-5.44	(-10.13, 0.76)	0.0046	0.0167
	70 mg PRC-063	69	-15.89	1.33	-4.95	(-9.59, -0.31)	0.0092	0.0323
	85 mg PRC-063	64	-15.22	1.38	-4.28	(-9.00, 0.45)	0.0268	0.0884
	Placebo	68	-10.94	1.34	--	--	--	--

Note: Analyses utilize ANCOVA models with Dunnett's adjustments for multiple pairwise comparisons for each active dose group with placebo. The model includes terms for treatment and baseline Clinician ADHD-5-RS score as a covariate.

[Source: Reviewer's table.]

This reviewer performed the Dunnett's procedure using R package "Mediana" and confirmed that statistical significance was achieved for the 45 mg (adjusted P-value= 0.017), 70 mg (adjusted P-value= 0.0224) after the adjustment for multiplicity (See Table below).

Table A-4: Analysis Using MMRM: Clinician-Rated ADHD-5-RS (FA Population, Site 08 Excluded, Study -009)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]	Adjusted P-value[b]
Visit 6	25 mg PRC-063	65	-12.77	1.35	-2.18	(-5.94, 1.59)	0.2562	0.5297
	45 mg PRC-063	64	-16.03	1.39	-5.44	(-9.25, -1.63)	0.0052	0.0170
	70 mg PRC-063	67	-15.79	1.35	-5.20	(-8.95, -1.44)	0.0069	0.0224
	85 mg PRC-063	62	-15.03	1.39	-4.43	(-8.24, -0.63)	0.0226	0.0692
	Placebo	66	-10.59	1.35	--	--	--	--

Note: Analyses utilize MMRM. Estimates, standard errors (SE), two-sided confidence intervals (CIs) and two-sided p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix. The AIC OF MMRM with UN covariance matrix is 9174.4.

n: number of subjects at the visit; LS mean: least-squares mean; SE: standard error; CI: confidence interval.

[a] not adjusted for multiple dose groups compared with placebo.

[b] p-values adjusted based on Dunnett's method for multiple pairwise comparisons for each active dose group with placebo.

[Source: Reviewer's Table.]

Table A-5: Clinician-Rated ADHD-5-RS Visit-wise Comparisons Using MMRM Analysis (FA Population, Site 08 Excluded, Study -009)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]
Visit 3	25 mg PRC-063	71	-6.01	1.03	-0.91	(-3.77, 1.95)	0.5306
	45 mg PRC-063	68	-8.54	1.05	-3.45	(-6.34, -0.56)	0.0195
	70 mg PRC-063	72	-8.10	1.02	-3.01	(-5.86, -0.16)	0.0387
	85 mg PRC-063	70	-8.69	1.04	-3.60	(-6.47, -0.73)	0.0141
	Placebo	71	-5.09	1.03	--	--	--
Visit 4	25 mg PRC-063	71	-8.92	1.22	-1.94	(-5.33, 1.45)	0.261
	45 mg PRC-063	66	-13.57	1.26	-6.59	(-10.04, -3.15)	0.0002
	70 mg PRC-063	69	-12.49	1.23	-5.50	(-8.91, -2.10)	0.0016
	85 mg PRC-063	66	-11.83	1.25	-4.85	(-8.28, -1.41)	0.0058
	Placebo	71	-6.98	1.22	--	--	--
Visit 5	25 mg PRC-063	67	-12.01	1.31	-2.43	(-6.07, 1.21)	0.1894
	45 mg PRC-063	64	-14.98	1.34	-5.40	(-9.08, -1.71)	0.0043
	70 mg PRC-063	69	-15.69	1.30	-6.11	(-9.74, -2.48)	0.001
	85 mg PRC-063	64	-15.14	1.34	-5.56	(-9.24, -1.88)	0.0032
	Placebo	67	-9.58	1.31	--	--	--

Note: Estimates, standard errors (SE), two-sided confidence intervals (CIs) and two-sided p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

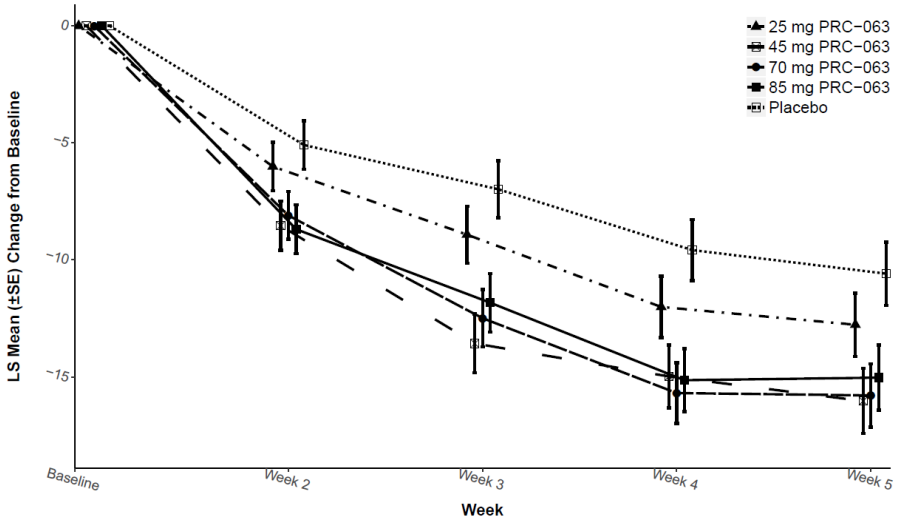
n: number of subjects at the visit; LS mean: least-squares mean; SE: standard error; CI: confidence interval.

[a] not adjusted for multiple dose groups compared with placebo.

[Source: Reviewer's table.]

As shown in Figure A-1, the LS mean decreases in the ADHD-5-RS total scores in all PRC-063 dose groups were numerically greater than placebo beginning at Week 2 and continuing through Week 5. The mean decrease in three higher dose groups was also numerically greater than 25mg group at later visits. Overall, compared to placebo, the plot supported that all PRC-063 doses numerically improved the ADHD-5-RS total score after 5 weeks of treatment, but the superiority to placebo was statistically significant only for the middle two doses after adjusting for multiplicity.

Figure A-1: Clinician-Rated ADHD-5-RS Total Scores (FA Population, Study -009)



[Source: Reviewer's plot.]

Table A-6: Primary Analysis Using MMRM with Toeplitz Covariance Matrix: Clinician-Rated ADHD-5-RS (FA Population, Site 08 Excluded, Study -009)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]	Adjusted P-value[b]
Visit 6	25 mg PRC-063	65	-12.81	1.24	-2.12	(-5.55, 1.30)	0.2238	0.9288
	45 mg PRC-063	64	-16.17	1.26	-5.48	(-8.94, -2.03)	0.0019	0.0261
	70 mg PRC-063	67	-15.82	1.23	-5.13	(-8.54, -1.72)	0.0033	0.0422
	85 mg PRC-063	62	-15.10	1.26	-4.41	(-7.87, -0.94)	0.0127	0.1378
	Placebo	66	-10.69	1.23	--	--	--	--

The AIC of MMRM with Toeplitz covariance matrix is 9257.6.
[a] not adjusted for multiple dose groups compared with placebo.
[b] p-values adjusted based on Dunnett's method for multiple pairwise comparisons with placebo.
[Source: Reviewer's table.]

Table A-7: Primary Analysis Using MMRM with Toeplitz Covariance Matrix Using Sandwich Estimator: Clinician-Rated ADHD-5-RS (FA Population, Site 08 Excluded, Study -009)

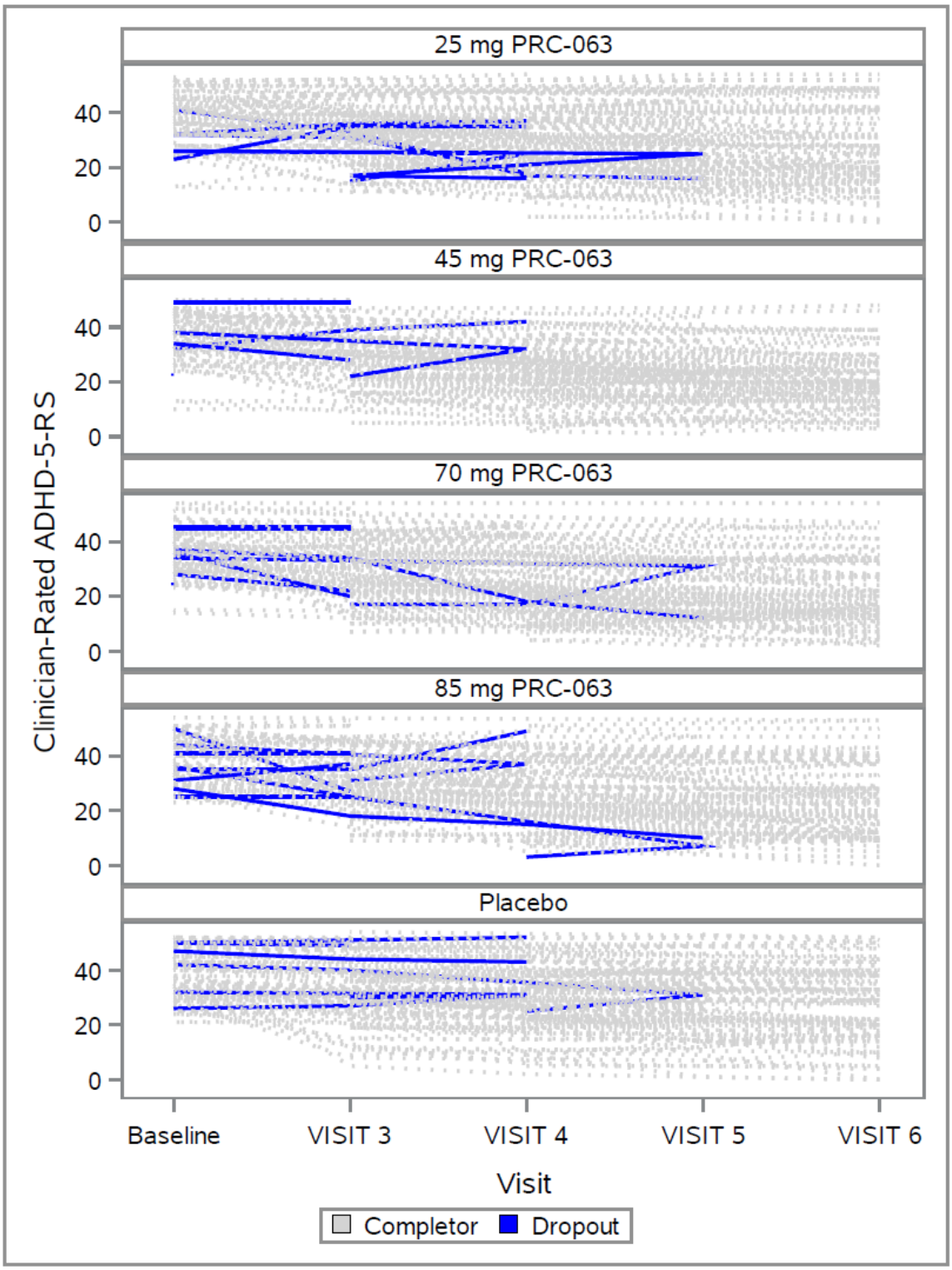
Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]	Adjusted P-value[b]
Visit 6	25 mg PRC-063	65	-12.81	1.41	-2.12	(-6.09, 1.84)	0.2935	0.9615
	45 mg PRC-063	64	-16.17	1.23	-5.48	(-9.20, -1.76)	0.0039	0.0442
	70 mg PRC-063	67	-15.82	1.29	-5.13	(-8.91, -1.34)	0.008	0.082
	85 mg PRC-063	62	-15.10	1.37	-4.41	(-8.31, -0.50)	0.0272	0.2261
	Placebo	66	-10.69	1.44	--	--	--	--

[a] not adjusted for multiple dose groups compared with placebo.
[b] p-values adjusted based on Dunnett's method for multiple pairwise comparisons with placebo.
[Source: Reviewer's table.]

The Applicant conducted a sensitivity analysis using the same ANCOVA structure and a Markov Chain Monte Carlo (MCMC) imputation for missing data. This reviewer found that the missing data was imputed randomly without any missing assumption. Thus, this sensitivity analysis was essentially performed based on the assumption of missing completely at random (MCAR); thus, it is not sensible to assess the performance of ANCOVA model under the deviation of missing assumption.

Most of the dropouts seemed to have the similar patterns with the completers in each treatment group before they discontinued from the study. Thus, it was reasonable to suspect that MAR assumption is reasonable (See figure below).

Figure A-2: Individual-Patient Longitudinal Profiles in Clinician-Rated ADHD-5-RS by Arm (FA Population, Study -009)



[Source: Reviewer's plot]

A.2 Study 063-010

This was a multiple-dose, randomized, double-blind, placebo-controlled, parallel group assessment of the clinical efficacy and safety of PRC-063 in 360 adults, male and female subjects with ADHD.

Table A-8: Number of Subjects (Study -010)

	25 mg n (%)	45 mg n (%)	70 mg n (%)	100 mg n (%)	Placebo n (%)	Total
Randomized	77	73	73	74	78	375
Full Analysis Set	75 (97.4)	73 (100)	71 (97.3)	72 (97.3)	77 (98.7)	368 (98.1)
Completers	73 (94.8)	69 (94.5)	62 (84.9)	61 (82.4)	69 (88.5)	334 (89.1)

Note: The reviewer found that 7 subjects dropped out of the trial right after the baseline; those 7 subjects should not be included in the Full Analysis Set.
One subject in 70mg group was marked as uncompleted in the applicant's dataset, but the reviewer found that this subject had completed the trial.
[Source: Reviewer's table]

Table A-9: Analysis Using ANCOVA model: Clinician-Rated ADHD-5-RS (Completers in FA Population, Study -010)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]	Adjusted P-value[b]
Visit 6	25 mg PRC-063	73	-11.80	1.30	-1.97	(-5.65, 1.70)	0.2918	0.675
	45 mg PRC-063	69	-16.70	1.34	-6.88	(-10.61, -3.15)	0.0003	0.0013
	70 mg PRC-063	62	-11.89	1.41	-2.06	(-5.89, 1.77)	0.2899	0.672
	100 mg PRC-063	61	-17.88	1.43	-8.06	(-11.91, -4.20)	<.0001	0.0002
	Placebo	69	-9.82	1.34	--	--	--	--

Note: Analyses utilize ANCOVA models with Dunnett's adjustments for multiple pairwise comparisons for each active dose group with placebo. The models include terms for treatment and baseline Clinician ADHD-5-RS score as a covariate.
[a]: The unadjusted CIs and unadjusted P-values in the table above were calculated by the reviewer.
[b]: The p-values were adjusted for multiple comparisons using Dunnett's procedure.
[Source: Table ST 8- 12 except unadjusted CIs and unadjusted p-values in the table, which are from this reviewer.]

This reviewer performed the Dunnett's procedure using R package "Mediana" and confirmed that statistical significance was achieved for the 45 mg (adjusted P-value= 0.0006), and 100 mg (adjusted P-value= 0.0003) after the adjustment for multiplicity. Refer to the Table below.

Table A-10: Analysis using MMRM: Clinician-Rated ADHD-5-RS (FA Population, Study -010)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]	Adjusted P-value[b]
Visit 6	25 mg PRC-063	73	-11.63	1.31	-1.93	(-5.59, 1.74)	0.3016	0.5919
	45 mg PRC-063	69	-16.83	1.34	-7.12	(-10.82, -3.43)	0.0002	**0.0006**
	70 mg PRC-063	62	-12.00	1.37	-2.29	(-6.04, 1.45)	0.2287	0.4889
	100 mg PRC-063	61	-17.57	1.39	-7.86	(-11.63, -4.09)	<.0001	**0.0003**
	Placebo	69	-9.71	1.32	--	--	--	--

Note: Analyses utilize MMRM. Estimates, standard errors (SE), two-sided confidence intervals (CIs) and two-sided p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

n: number of subjects at the visit; LS mean: least-squares mean; SE: standard error; CI: confidence interval.

[a]: not adjusted for multiple comparisons with placebo.

[b]: The p-values were adjusted for multiple comparisons using Dunnett's procedure.

[Source: Reviewer's table.]

Table A-11: Clinician-Rated ADHD-5-RS Visit-wise Comparisons Using MMRM Analysis (FA Population, Study -010)

Time Point	Treatment Group	n	LS Mean Change from Baseline	SE	Difference in LS Means	Unadjusted 95% CI[a]	Unadjusted P-value[a]
Visit 3	25 mg PRC-063	75	-6.26	0.91	-1.81	(-4.33, 0.70)	0.1577
	45 mg PRC-063	73	-7.20	0.92	-2.75	(-5.29, -0.22)	0.0334
	70 mg PRC-063	71	-6.08	0.94	-1.63	(-4.18, 0.92)	0.2102
	100 mg PRC-063	72	-5.99	0.93	-1.54	(-4.08, 1.01)	0.2355
	Placebo	77	-4.45	0.90	--	--	--
Visit 4	25 mg PRC-063	73	-8.55	1.07	-1.36	(-4.32, 1.61)	0.3686
	45 mg PRC-063	71	-11.29	1.09	-4.10	(-7.09, -1.11)	0.0073
	70 mg PRC-063	70	-8.62	1.10	-1.43	(-4.43, 1.57)	0.3492
	100 mg PRC-063	67	-11.93	1.11	-4.74	(-7.75, -1.72)	0.0022
	Placebo	74	-7.19	1.06	--	--	--
Visit 5	25 mg PRC-063	73	-11.62	1.17	-3.35	(-6.60, -0.10)	0.0432
	45 mg PRC-063	71	-15.27	1.19	-7.00	(-10.27, -3.73)	<.0001
	70 mg PRC-063	65	-11.43	1.21	-3.16	(-6.47, 0.14)	0.0607
	100 mg PRC-063	62	-14.76	1.23	-6.49	(-9.82, -3.16)	0.0001
	Placebo	71	-8.27	1.17	--	--	--

Note: Analyses utilize MMRM. Estimates, standard errors (SE), two-sided confidence intervals (CIs) and two-sided p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

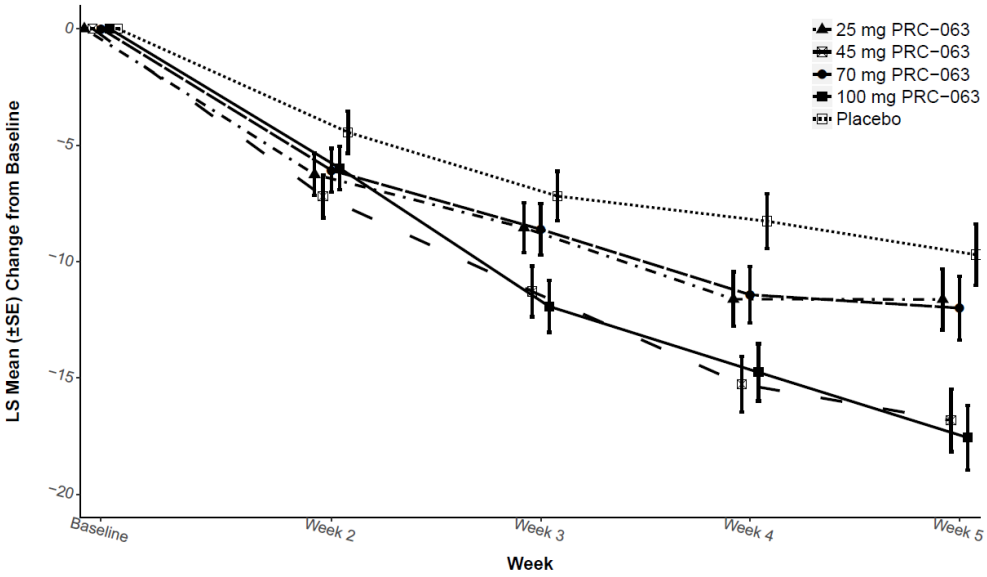
n: number of subjects at the visit; LS mean: least-squares mean; SE: standard error; CI: confidence interval.

[a]: not adjusted for multiple comparisons with placebo.

[Source: Reviewer's table.]

As shown in Figure A-3, the LS mean decreases in the ADHD-5-RS total scores in all PRC-063 dose groups were numerically greater than placebo beginning at Week 2 and continuing through Week 5. The mean decreases in the 45 mg and 100 mg dose groups were numerically greater than the other groups at later visits. Overall, compared to placebo, the plot supported that all PRC-063 doses numerically improved the ADHD-5-RS total score after 5 weeks of treatment, but the superiority to placebo was statistically significant for the 45 mg and the 100 mg only.

Figure A-3: Clinician-Rated ADHD-5-RS Total Scores (FA Population)

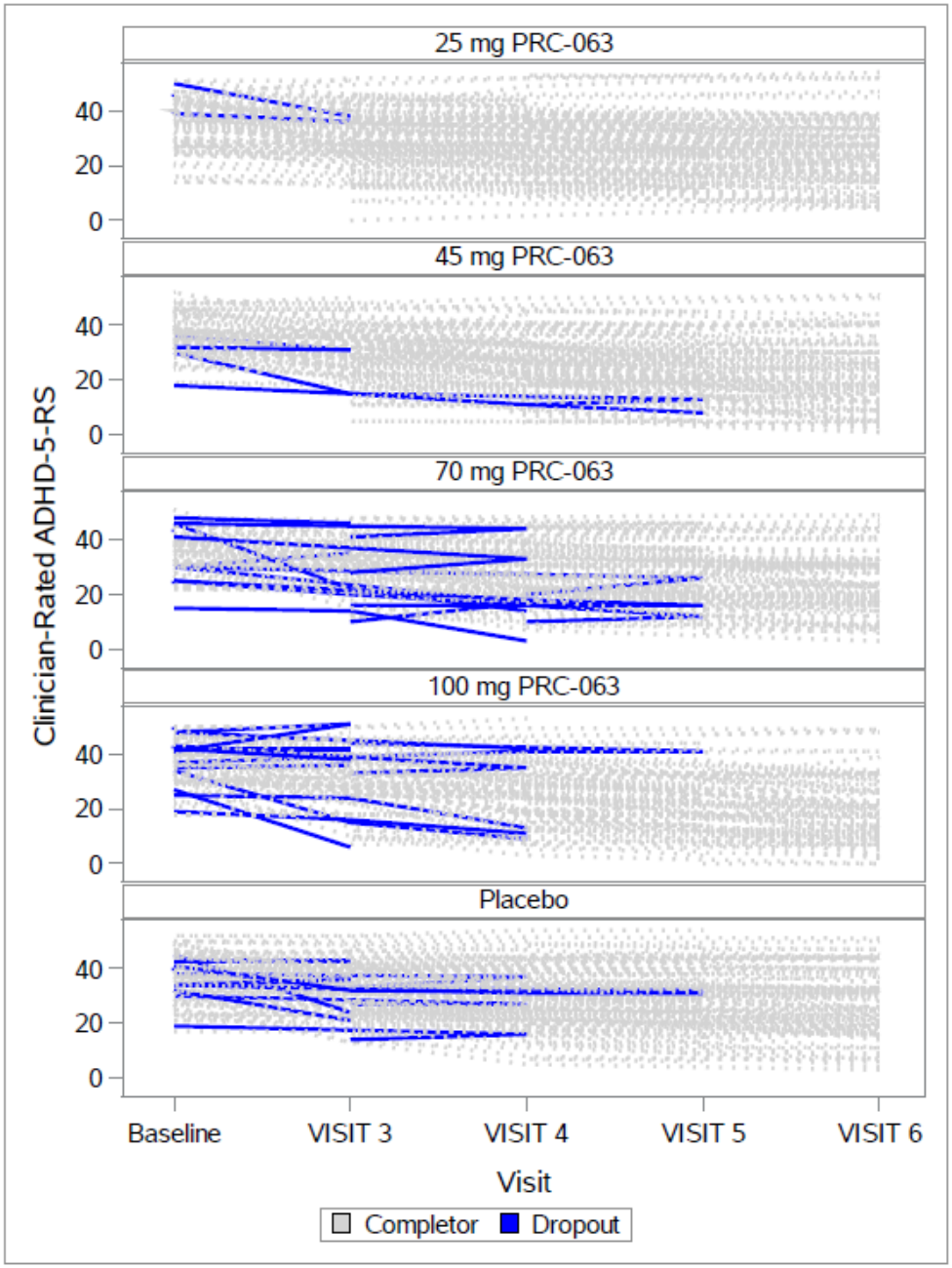


[Source: Reviewer's plot.]

The Applicant conducted a sensitivity analysis using the same ANCOVA structure and a Markov Chain Monte Carlo (MCMC) imputation for missing data. This reviewer found that the missing data was imputed randomly without any missing assumption. Thus, this sensitivity analysis was essentially performed based on the assumption of missing completely at random (MCAR); thus, it is not sensible to assess the performance of ANCOVA model under the deviation of missing assumption.

Most of the dropouts had the similar patterns with the completers in each treatment group before they discontinued from the study. Thus, it was reasonable to suspect that MAR assumption is reasonable. See the figure below.

Figure A-4: Individual-patient Longitudinal Profiles in Clinician-Rated ADHD-5-RS (FA Population, Study -010)



[Source: Reviewer's table]

A.3 Study 063-008

This was 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 diagnosed with ADHD in an AWE setting.

Table A-12: Primary Efficacy Analysis: PERMP-T (Total) Scores During the Full Day laboratory Classroom (FA Population, N = 45, Study -008)

	Treatment Group	
	PRC-063	Placebo
Lease Square		
Mean	268.7	255.6
SE	11.24	10.87
Difference in Least Square		
Mean	13.05	
SE	4.55	
95% CI	(3.88, 22.23)	
Treatment P-value	0.0064	
Period p-value	<0.0001	
Sequence p-value	0.1322	

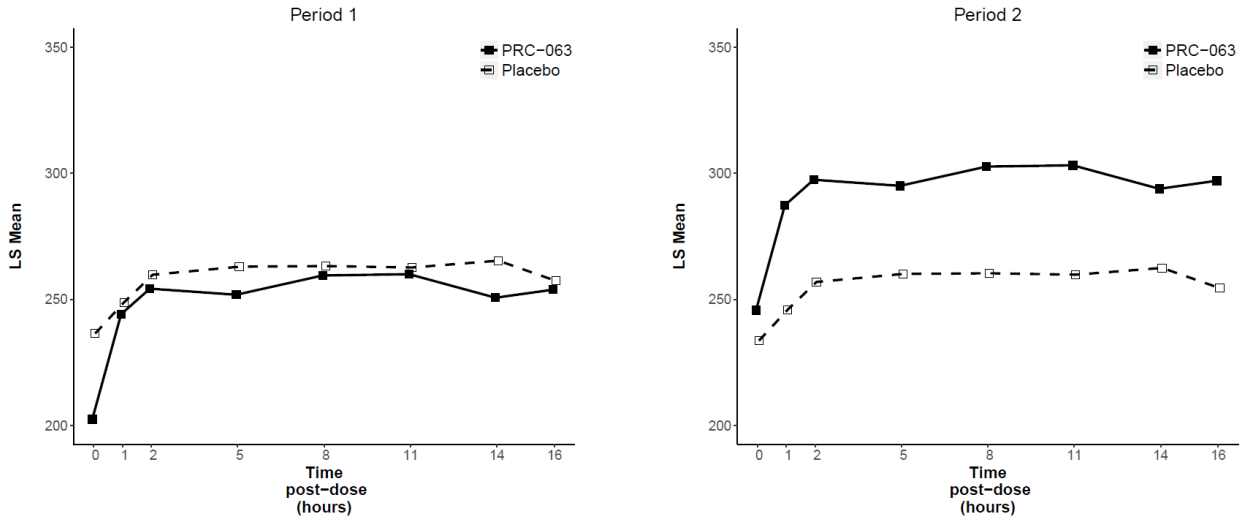
Note: P values and associated estimates are estimated from a repeated-measure mixed model with PERMP-T as the response variable, fixed effects of treatment, period, sequence, time, and treatment-by-time interaction, assuming an unstructured covariance matrix. The pre-dose score was considered as a response variable in the model.
[Source: Applicant's clinical study report PRC-063-008 Table 5, verified by the reviewer.]

Table A-13: Key Secondary Efficacy Analysis: Analysis of PERMP-Total Scores by Time (FA Population, N = 45, Study -008)

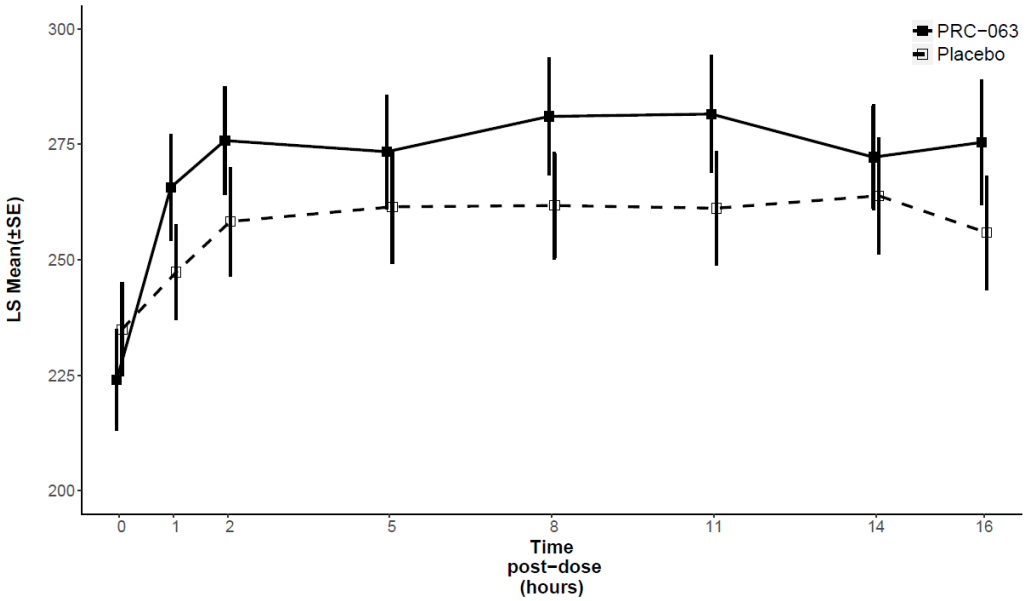
	0.0h	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
LS Mean Difference	-10.96	18.37	17.52	11.93	19.30	20.38	8.36	19.56
(SE)	(6.448)	(6.388)	(6.378)	(6.620)	(5.667)	(8.946)	(7.078)	(6.521)
95% Confidence Interval	(-23.97, 2.04)	(5.49, 31.25)	(4.66, 30.38)	(-1.42, 25.28)	(7.87, 30.72)	(2.33, 38.42)	(-5.92, 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: Applicant's clinical study report PRC-063-008 Table 6, verified by the reviewer.]

Figure A-5: PERMP-Total Score (LS mean) by Period and When Both Periods Were Combined (Study -008)



When Both Periods Were Combined:



[Source: Reviewer's plot.]

Table A-14: Applicant's First Ad-Hoc Analysis (Pre-dose Score as a Covariate) of PERMP-Total Score (FA Population, N = 45, Study -008)

	Treatment Group	
	PRC-063	Placebo
Lease Square		
Mean	281.3	254.5
SE	4.33	4.63
Difference in Least Square		
Mean	26.80	
SE	5.76	
95% CI	(15.19, 38.41)	
Treatment P-value	<0.0001	
Period p-value	0.1314	
Sequence p-value	0.8549	

Note: Analyses utilize repeated measures mixed-effects analysis of covariance 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 and a covariate for the pre-dose score, assuming an unstructured covariance matrix. [Source: Applicant's clinical study report PRC-063-008 Table ST 8-10a, verified by the reviewer.]

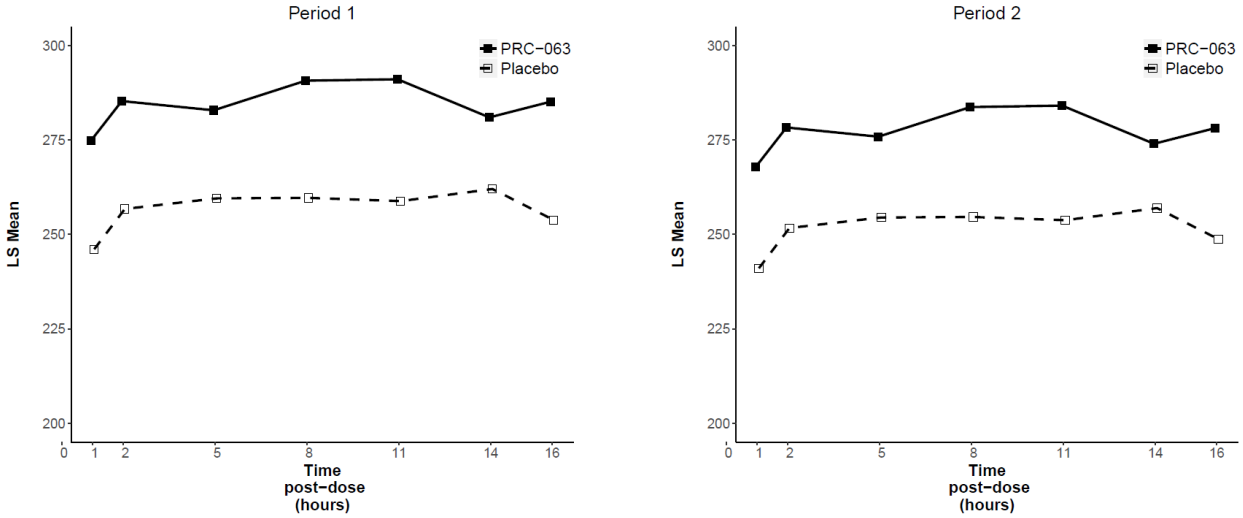
A strong period effect was found in the primary analysis. The Applicant thought that a strong period effect may be due to significant pre-dose differences. They conducted the ad-hoc analyses by including pre-dose as a covariate or using change from pre-dose score as a response variable. The period effect was not significant in both ad-hoc analyses. The statistically significant differences were observed starting at 1.0 hour post-dose, but the difference was not statistically significant at 14 hours post-dose.

Table A-15: Applicant's First Ad-Hoc Analysis (Pre-dose Score as a Covariate) of PERMP-Total Score – Treatment Difference by Time (Study -008)

	Treatment Difference (PRC-063 – Placebo) in Post-dose PERMP-T Score						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
Lease Square Mean							
PRC-063	271.72	282.17	279.72	287.56	287.96	277.85	282.03
(SE)	3.60	4.75	5.30	4.91	5.81	7.37	6.63
Placebo	243.87	254.57	257.36	257.47	256.63	259.84	251.65
(SE)	4.5742	4.972	6.2301	4.9104	6.538	5.8927	6.5842
LS Mean Difference	27.86	27.6	22.36	30.09	31.32	18.01	30.38
(SE)	-5.595	-5.932	-7.06	-6.112	-9.39	-9.836	-8.446
95% Confidence	(16.57,	(15.64,	(8.12,	(17.76,	(12.39,	(-1.83,	(13.35,
Interval	39.14)	39.56)	36.60)	42.41)	50.26)	37.84)	47.41)
Treatment p-value	<0.0001	<0.0001	0.0028	<0.0001	0.0018	0.0741	0.0008

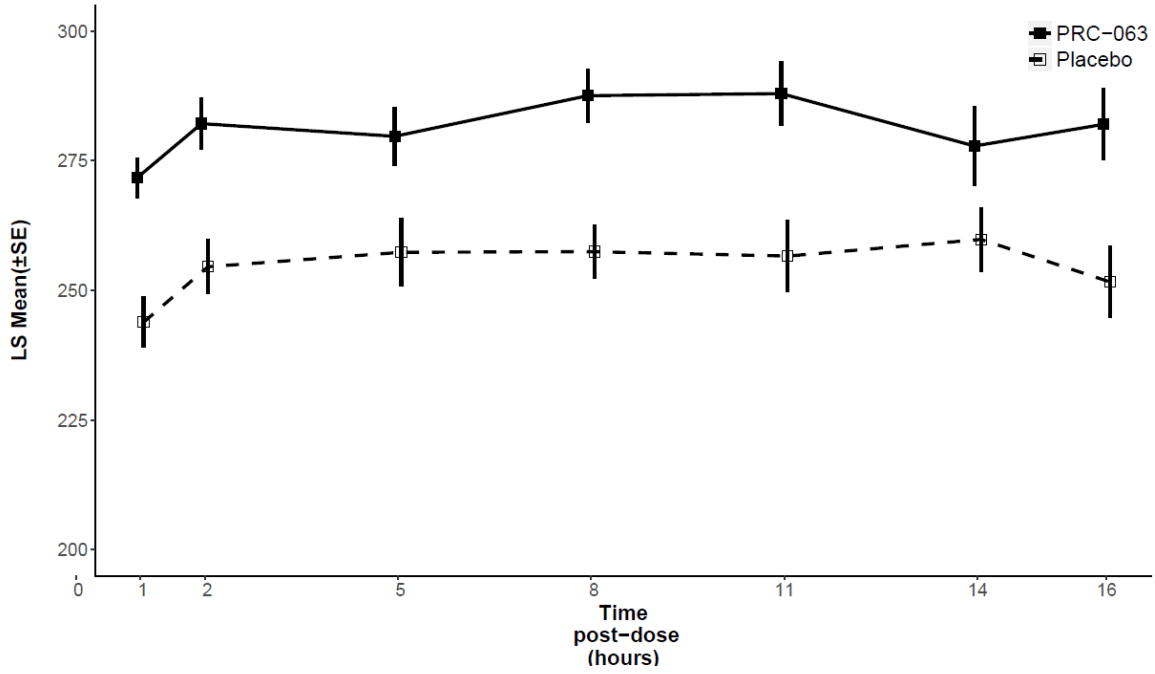
Note: Analyses utilize repeated measures mixed-effects analysis of covariance models for comparing the active treatment with placebo. The model for all subjects includes terms for treatment, period, sequence, time, and interaction and a covariate for baseline score. P-values were not adjusted for multiplicity.
[Source: Top portion (results from individual treatments) was from this reviewer. Bottom portion (comparisons between treatments) was from Applicant's clinical study report PRC-063-008 Table 9, verified by the reviewer.]

Figure A-6: Applicant's First Ad-Hoc Analysis **(**Pre-dose Score as a Covariate) of PERMP-Total Score – LS Means in Each Period and When Both Periods Were Combined (Study -008)



Note: LS mean was estimated by repeated measures mixed-effects analysis of covariance models at baseline PERMP-Total score of 230.

When Both Periods Were Combined:



[Source: Reviewer's plot.]

Table A-16: Applicant's Second Ad-Hoc Analysis (Measuring Change from Pre-dose) of PERMP-Total Score (FA Population, N=45, Study -008)

	Treatment Group	
	PRC-063	Placebo
Lease Square		
Mean	50.7	24.1
SE	4.33	4.61
Difference in Least Square		
Mean	26.52	
SE	5.73	
95% CI	(14.97, 38.07)	
Treatment P-value	<0.0001	
Period p-value	0.1064	
Sequence p-value	0.4899	

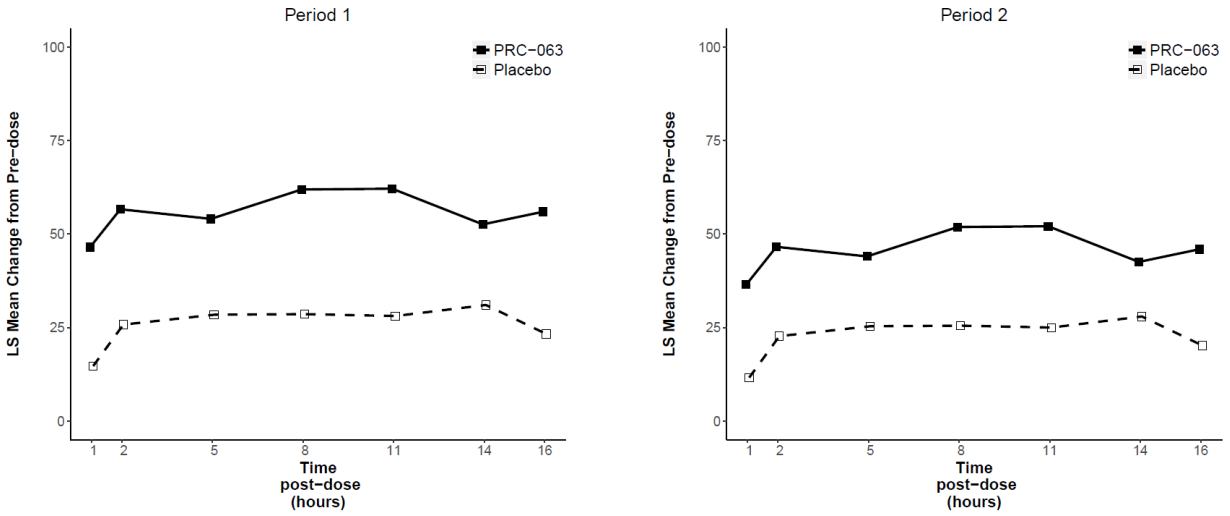
Note: Analyses utilize repeated measures mixed-effects analysis of variance models for comparing the active treatment with placebo. The model includes terms for treatment, period, sequence, time, and treatment-by-time interaction, assuming an unstructured covariance matrix.
[Source: Applicant's clinical study report PRC-063-008 Table ST 8- 10a, verified by the reviewer.]

Table A-17: Applicant's Second Ad-Hoc Analysis (Measuring Change from Pre-dose) of PERMP-Total Score - Treatment Difference by Time (Study -008)

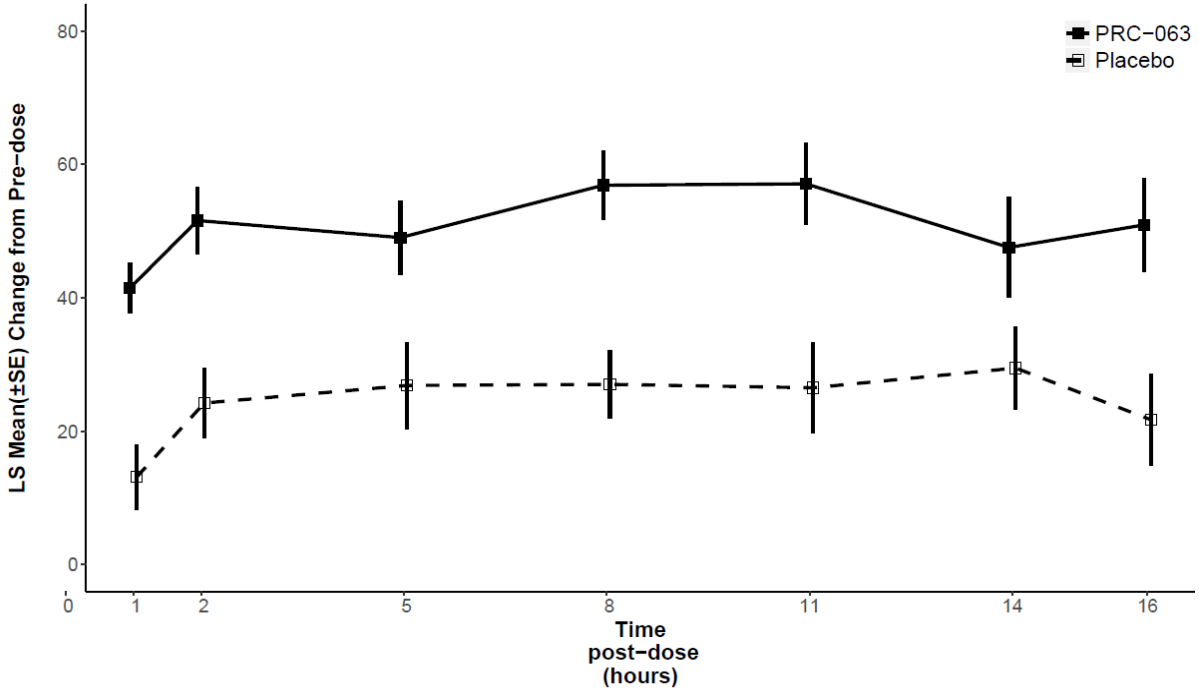
	Treatment Difference (PRC-063 – Placebo) in Change from Pre-dose Score						
	1.0 h	2.0 h	5.0 h	8.0 h	11.0 h	14.0 h	16.0 h
Lease Square Mean							
PRC-063	41.49	51.61	49.04	56.90	57.11	47.56	50.95
(SE)	3.48	4.75	5.29	4.87	5.87	7.27	6.76
Placebo	13.14	24.24	26.87	27.04	26.53	29.48	21.73
(SE)	4.64	4.96	6.23	4.86	6.50	5.93	6.54
LS Mean Difference	28.35	27.37	22.17	29.86	30.58	18.08	29.22
(SE)	(5.744)	(5.905)	(7.033)	(6.126)	(9.369)	(9.746)	(8.238)
95% Confidence Interval	(16.77, 39.93)	(15.46, 39.28)	(7.99, 36.36)	(17.50, 42.21)	(11.69, 49.48)	(-1.57, 37.74)	(12.60, 45.83)
Treatment p-value	<0.0001	<0.0001	0.0030	<0.0001	0.0022	0.0704	0.0010

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. P-values were not adjusted for multiplicity.
[Source: Top portion (results from individual treatments) is from this reviewer. Bottom portion (comparisons between treatments) was from Applicant's clinical study report PRC-063-008 Table 10, verified by the reviewer.]

Figure A-7: Applicant's Second Ad-Hoc Analysis (Measuring Change from Pre-dose) of PERMP-Total Score – LS Mean Change from Pre-dose in Each Period and When Both Periods Were Combined (Study -008)



When Both Periods Were Combined:



Note: LS mean change from pre-dose score was estimated by repeated measures mixed-effects analysis of covariance models.
[Source: Reviewer's plot.]

This reviewer also assessed treatment effect based on the data from Phase 1 only. Treatment effect based on Phase 1 data became statistically significant only after adjusting the pre-dose difference by treating pre-dose score as a covariate instead of a response variable (Table A-18 and Table A-19).

Table A-18: Reviewer's Analysis of PERMP-Total Scores – Pre-dose Score as a Response (Applicant's Pre-specified Analysis) and Including Data from Period 1 Only (Study -008)

	Treatment Group	
	PRC-063	LDX
Lease Square		
Mean	245.14	256.45
SE	14.52	14.85
Difference in Least Square		
Mean	-11.31	
SE	20.77	
95% CI	(-52.19, 29.57)	
P value	0.5864	

Note: Analyses utilize repeated measures mixed-effects analysis of covariance models for comparing the active treatment with placebo. The model for all subjects includes terms for treatment, time, and treatment-by-time interaction, assuming an unstructured covariance matrix. Pre-dose score is treated as a response variable.

Table A-19: Reviewer's Analysis of PERMP-Total Scores – Pre-dose Score as a Covariate and Including Data from Period 1 only (Study -008)

	Treatment Group	
	PRC-063	LDX
Lease Square		
Mean	264.45	235.71
SE	4.96	5.09
Difference in Least Square		
Mean	28.74	
SE	7.27	
95% CI	(14.43, 43.04)	
P value	<.0001	

Note: Analyses utilize repeated measures mixed-effects analysis of covariance models for comparing the active treatment with placebo. The model for all subjects includes terms for treatment, time, treatment-by-time interaction and a covariate for pre-dose score, assuming an unstructured covariance matrix.

A.4 Study 063-0015

This was a randomized, double-blind, parallel group, placebo-controlled, dose optimized, phase 3 study to evaluate the safety and efficacy of PRC-063 25, 35, 45, 55, 70, or 85 mg/day versus placebo for the treatment of ADHD in pediatric subjects ≥ 6 years of age and ≤ 12 years of age.

Table A-20: Primary Efficacy Analysis: SKAMP Combined (SKAMP-C) Scores During The Full Day Laboratory Classroom (FA Population, N = 147, Study -015)

	Treatment Group	
	PRC-063	Placebo
Lease Square		
Mean	10.3	18.9
SE	0.74	0.73
95% CI	(8.85, 11.79)	(17.44, 20.33)
Difference in Least Square		
Mean	-8.6	
SE	1.02	
95% CI	(-10.59, -2.89)	
P value	<.0001	

Note: P values and associated estimates are estimated from a repeated-measure mixed model with SKAMP-C as the response variable, fixed effects of Treatment Group, Site, Post-dose Hours, Post-dose Hours × Treatment Group interaction, and covariate terms for the pre-dose score and pre-dose score*time interaction, assuming an unstructured covariance matrix.
[Source: Applicant's clinical study report PRC-063-015 Table 9, verified by the reviewer]

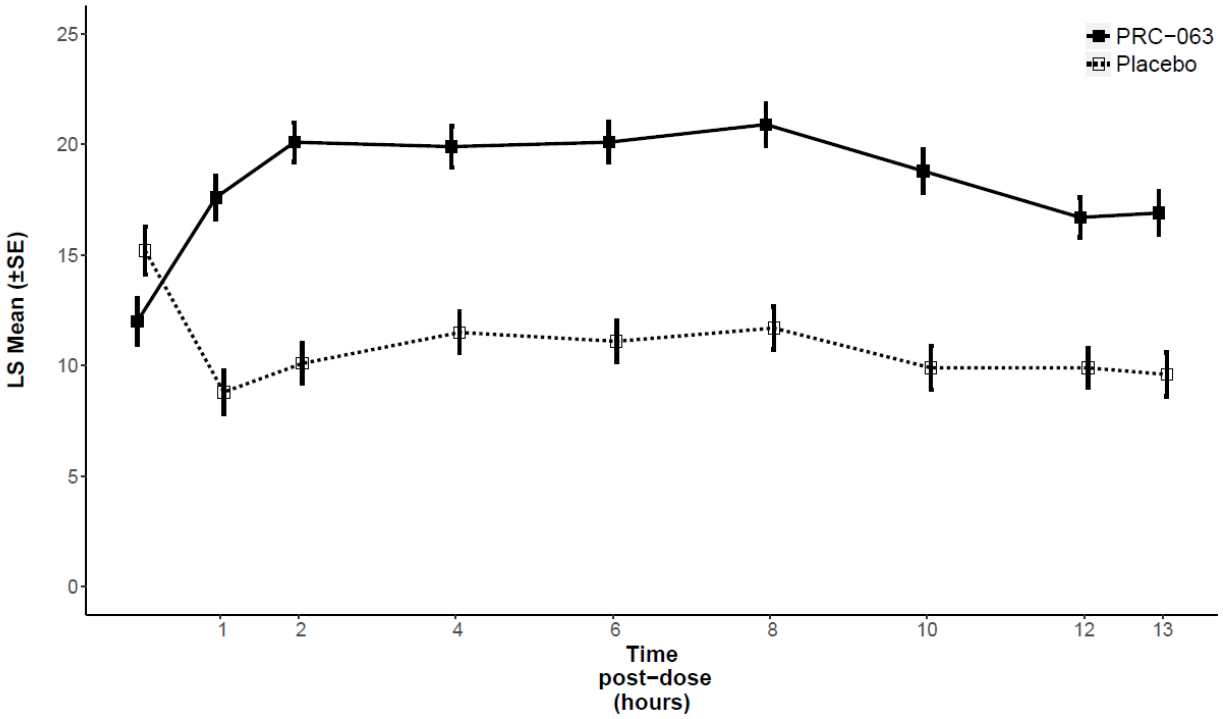
In the FA population, the PRC-063 group had statistically significant improvements over the placebo group ($p < 0.0001$) when the SKAMP-C scores were averaged over the 13-hour full day laboratory classroom (average post-dose score, primary efficacy analysis). The LS mean difference was -8.6 (95% CI: -10.6, -6.6). Table 22 presents the SKAMP-C scores during the full day laboratory classroom by time in the FA population. The SKAMP-C scores were statistically significantly improved in the PRC-063 group versus the placebo group ($p < 0.0001$) at each time point (1, 2, 4, 6, 8, 10, 12 and 13 hours post-dose) from 1 hour post-dose to 13 hours post-dose. Therefore, the onset of efficacy was 1 hour and the duration of efficacy was ≥ 12 hours.

Table A-21: Key Secondary Efficacy Analysis: Analysis of SKAMP-Combined Scores by Post-dose Hours (FA Population, N = 147, Study -015)

		Lease Square			Difference in Least Square			
Post-dose Hours	Treatment Group	Mean	SE	95% CI	Mean	SE	95% CI	P Value
1	PRC-063	8.8	0.98	(6.9, 10.7)	-8.8	1.36	(-11.5, -6.1)	< 0.0001
	Placebo	17.6	0.97	(15.7, 19.5)				
2	PRC-063	10.1	0.90	(8.3, 11.8)	-10.1	1.25	(-12.5, -7.6)	< 0.0001
	Placebo	20.1	0.89	(18.4, 21.9)				
4	PRC-063	11.5	0.94	(9.6, 13.4)	-8.4	1.31	(-11.0, -5.9)	< 0.0001
	Placebo	19.9	0.93	(18.1, 21.8)				
6	PRC-063	11.1	0.93	(9.3, 13.0)	-9.0	1.3	(-11.6, -6.4)	< 0.0001
	Placebo	20.1	0.92	(18.3, 22.0)				
8	PRC-063	11.7	0.97	(9.8, 13.6)	-9.1	1.35	(-11.8, -6.5)	< 0.0001
	Placebo	20.9	0.96	(19.0, 22.8)				
10	PRC-063	9.9	0.98	(7.9, 11.8)	-8.9	1.37	(-11.6, -6.2)	< 0.0001
	Placebo	18.8	0.97	(16.9, 20.7)				
12	PRC-063	9.9	0.91	(8.1, 11.7)	-6.8	1.26	(-9.3, -4.3)	< 0.0001
	Placebo	16.7	0.90	(14.9, 18.8)				
13	PRC-063	9.6	0.99	(7.6, 11.5)	-7.3	1.38	(-10.1, -4.6)	< 0.0001
	Placebo	16.9	0.98	(14.9, 18.8)				

Note: P values (unadjusted for multiplicity) and associated estimates are estimated from a repeated-measure mixed model with SKAMP-C as the response variable, fixed effects of Treatment Group, Site, Post-dose Hours, Post-dose Hours × Treatment Group interaction, and covariate terms for the pre-dose score and pre-dose score*time interaction, assuming an unstructured covariance matrix.
[Source: Applicant's clinical study report PRC-063-015 Table 10, verified by the reviewer]

Figure A-8: SKAMP-Combined Scores During The Full Day Laboratory Classroom Visit – by Time (FA Population, Study -015)



Note: SKAMP-C post-dose score were analyzed with an MMRM model on the individual SKAMP-C scores with fixed effects for treatment, time (repeated effect for each subject), treatment*time interaction, site, and covariate terms for the pre-dose score and pre-dose score*time interaction. Pre-dose scores (at hour zero) were analyzed with an ANOVA model on individual SKAMP-C pre-dose scores with fixed effects for treatment and site.
[Source: Reviewer's Plot]

The SKAMP-C pre-dose score evaluated on the morning of the full day laboratory classroom indicated that the placebo group had less severe symptoms than the PRC-063 group with LS mean difference of 3.1 ($p = 0.0367$) prior to dosing. Thus, we also examined the treatment effect based on the average change of SKAMP-Combined scores from pre-dose. The PRC-063 group still had statistically significant improvements over the placebo group.

Table A-22: Reviewer's Analysis: Average Change from Pre-dose SKAMP Combined Scores During the Full Day Laboratory Classroom (FA Population, N = 147, Study -015)

	Treatment Group	
	PRC-063	Placebo
Lease Square		
Mean	-3.62	6.32
SE	0.88	0.87
95% CI	(-5.35, -1.88)	(4.59, 8.05)
Difference in Least Square		
Mean	-9.94	
SE	1.21	
95% CI	(-12.32, -7.55)	
P value	<.0001	

Note: P values and associated estimates are estimated from a repeated-measure mixed model with SKAMP-C as the response variable, fixed effects of Treatment Group, Site, Post-dose Hours, Post-dose Hours × Treatment Group interaction, assuming an unstructured covariance matrix.
[Source: Reviewer's table.]

A.5 Exploratory Subgroup Analyses

A.5.1 Study 063-009

Table A-23: Subgroup Analysis by Gender (Study -009)

Gender	Treatment Group (n)	**Primary Efficacy Measure**: Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
Male	PRC-063 25 mg (n=50)	37.48 (9.39)	-12.36 (1.59)	-2.32 (2.28) [-6.81, 2.17]
	PRC-063 45 mg (n=50)	37.10 (8.31)	-16.90 (1.59)	-6.86 (2.28) [-11.35, -2.37]
	PRC-063 70 mg (n=46)	36.13 (8.06)	-13.70 (1.68)	-3.66 (2.34) [-8.28, 0.96]
	PRC-063 85 mg (n=44)	36.91 (8.10)	-13.85 (1.74)	-3.81 (2.39) [-8.52, 0.90]
	Placebo (n=47)	37.55 (8.06)	-10.04 (1.64)	--
Female	PRC-063 25 mg (n=21)	38.29 (6.91)	-13.66 (2.55)	-1.95 (3.49) [-8.87, 4.98]
	PRC-063 45 mg (n=18)	35.33 (8.76)	-13.63(2.79)	-1.92 (3.66) [-9.18, 5.34]
	PRC-063 70 mg (n=26)	36.04 (9.03)	-19.24 (2.27)	-7.52 (3.29) [-14.04, -1.00]
	PRC-063 85 mg (n=26)	39.27 (8.12)	-16.84 (2.31)	-5.13 (3.32) [-11.71, 1.45]
	Placebo (n=24)	36.71 (9.17)	-11.72 (2.38)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).
[Source: Reviewer's Table]

Table A-24: Subgroup Analysis by Race (Study -009)

Race	Treatment Group (n)	**Primary Efficacy Measure**: Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
White	PRC-063 25 mg (n=49)	38.14 (8.18)	-13.35 (1.59)	-3.73(2.19) [-8.06, 0.59]
	PRC-063 45 mg (n=42)	35.26 (8.82)	-13.68 (1.72)	-4.06(2.29) [-8.57, 0.44]
	PRC-063 70 mg (n=51)	35.98 (8.65)	-15.64 (1.54)	-6.02(2.16) [-10.28, -1.76]
	PRC-063 85 mg (n=48)	36.96 (8.28)	-14.86 (1.63)	-5.24(2.23) [-9.63, -0.85]
	Placebo (n=52)	36.40 (8.40)	-9.62 (1.51)	--
Others[b]	PRC-063 25 mg (n=22)	36.77 (9.88)	-11.87 (2.61)	1.27(3.88) [-6.43,8.97]
	PRC-063 45 mg (n=26)	38.85 (7.29)	-19.71 (2.4)	-6.56(3.74) [-13.97,0.85]
	PRC-063 70 mg (n=21)	36.38 (7.8)	-16.1 (2.72)	-2.96(3.96) [-10.81,4.89]
	PRC-063 85 mg (n=22)	39.59 (7.66)	-15.43 (2.63)	-2.29(3.89) [-10.00,5.41]
	Placebo (n=19)	39.63 (8.14)	-13.14 (2.87)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).
[b]The patients with multi-racial were categorized to be "Others".
[Source: Reviewer's Table]

Table A-25: Subgroup Analysis by Country (Study -009)

Country	Treatment Group (n)	**Primary Efficacy Measure:** Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
US	PRC-063 25 mg (n=58)	37.17 (8.94)	-12.6 (1.53)	-0.99 (2.16) [-5.23, 3.26]
	PRC-063 45 mg (n=55)	36.22 (8.72)	-16.74 (1.57)	-5.13 (2.19) [-9.44, -0.83]
	PRC-063 70 mg (n=57)	35.47 (7.77)	-17.03 (1.55)	-5.42 (2.17) [-9.70, -1.14]
	PRC-063 85 mg (n=58)	37 (7.89)	-15.34 (1.55)	-3.73(2.17) [-8.00, 0.54]
	Placebo (n=58)	36.76 (8.33)	-11.61 (1.52)	--
Canada	PRC-063 25 mg (n=13)	40.15 (7.27)	-13.22 (2.61)	-7.16 (3.72) [-14.61,0.29]
	PRC-063 45 mg (n=13)	38.39 (6.92)	-13.43 (2.65)	-7.37 (3.74) [-14.87,0.13]
	PRC-063 70 mg (n=15)	38.47 (10.27)	-11.24 (2.42)	-5.18 (3.59) [-12.37,2.01]
	PRC-063 85 mg (n=12)	41.58 (8.51)	-12.97 (2.89)	-6.91 (3.92) [-14.77,0.95]
	Placebo (n=13)	39.54 (8.63)	-6.06 (2.65)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).

[Source: Applicant's Clinical Responses to Information Request Table 1 except mean baseline score, standard error (SE), standard deviation (SD) and CIs in the table.]

A.5.2 Study 063-010

Table A-26: Subgroup Analysis by Gender (Study -010)

Gender	Treatment Group (n)	**Primary Efficacy Measure:** Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
Male	PRC-063 25 mg (n=36)	34.19(9.64)	-12.95 (1.78)	-5.13 (2.57) [-10.21, -0.05]
	PRC-063 45 mg (n=37)	35.05 (7.01)	-13.05 (1.77)	-5.22 (2.56) [-10.28, -0.17]
	PRC-063 70 mg (n=37)	34.54(6.86)	-11.7 (1.83)	-3.88 (2.60) [-9.01, 1.26]
	PRC-063 100 mg (n=30)	37.17 (7.16)	-18.17 (2.07)	-10.35 (2.79) [-15.85, -4.84]
	Placebo (n=35)	33.66 (7.58)	-7.83 (1.86)	--
Female	PRC-063 25 mg (n=39)	37.59(6.23)	-10.40 (1.90)	0.81 (2.64) [-4.41, 6.02]
	PRC-063 45 mg (n=36)	38.03 (7.16)	-20.70 (1.98)	-9.5 (2.7) [-14.83, -4.16]
	PRC-063 70 mg (n=34)	36.41(7.86)	-12.20 (2.02)	-1.00 (2.74) [-6.40, 4.40]
	PRC-063 100 mg (n=42)	36.52(8.45)	-17.19 (1.87)	-5.99 (2.62) [-11.17, -0.82]
	Placebo (n=42)	37.38(8.88)	-11.20 (1.84)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).
[Source: Reviewer's Table]

Table A-27: Subgroup Analysis by Race (Study -010)

Gender	Treatment Group (n)	**Primary Efficacy Measure:** Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
White	PRC-063 25 mg (n=67)	35.54(8.26)	-12.05 (1.36)	-3.52 (1.95) [-7.36,0.32]
	PRC-063 45 mg (n=57)	36.53 (7.39)	-15.37 (1.47)	-6.84 (2.03) [-10.84,-2.85]
	PRC-063 70 mg (n=66)	35.09(7.39)	-11.43 (1.39)	-2.9 (1.97) [-6.78,0.98]
	PRC-063 100 mg (n=58)	37.72(7.49)	-18.3 (1.52)	-9.77 (2.07) [-13.83,-5.7]
	Placebo (n=64)	35.97 (8.10)	-8.53 (1.4)	--
Others[b]	PRC-063 25 mg (n=8)	39.5 (6.89)	-7.76 (4.34)	8.19 (5.64) [-3.20,19.57]
	PRC-063 45 mg (n=16)	36.50 (6.67)	-22.13 (3.14)	-6.19 (4.74) [-15.77,3.38]
	PRC-063 70 mg (n=5)	40.00 (5.70)	-20.61 (5.71)	-4.67 (6.75) [-18.27,8.94]
	PRC-063 100 mg (n=14)	32.93(8.62)	-15.05 (3.38)	0.89 (4.87) [-8.95,10.73]
	Placebo (n=13)	34.31(10.34)	-15.94 (3.55)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).
[b]The patients with multi-racial were categorized to be "Others".
[Source: Reviewer's Table]

Table A-28: Subgroup Analysis by Country (Study -010)

Gender	Treatment Group (n)	**Primary Efficacy Measure:** Change from Baseline in ADHD-5-RS Total Score Over 4 Weeks of Double-blind Phase		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
US	PRC-063 25 mg (n=66)	36.08(8.44)	-11(1.44)	-1.52 (2.04) [-5.54, 2.5]
	PRC-063 45 mg (n=63)	36.17(7.27)	-16.89(1.48)	-7.41 (2.07) [-11.47, -3.34]
	PRC-063 70 mg (n=61)	35.3(7.71)	-12.37(1.53)	-2.89 (2.10) [-7.03, 1.25]
	PRC-063 100 mg (n=63)	36.84(7.99)	-18.01(1.53)	-8.53 (2.11) [-12.67, -4.38]
	Placebo (n=67)	35.88(8.67)	-9.48(1.44)	--
Canada	PRC-063 25 mg (n=9)	35.11(6.19)	-16.08(2.83)	-3.43 (4.13) [-11.77, 4.91]
	PRC-063 45 mg (n=10)	38.7(6.63)	-16.8(2.82)	-4.16 (4.17) [-12.57, 4.26]
	PRC-063 70 mg (n=10)	36.3(4.95)	-9.99(2.68)	2.66 (4.05) [-5.51, 10.83]
	PRC-063 100 mg (n=9)	36.44(7.65)	-14.6(2.91)	-1.96 (4.2) [-10.43, 6.52]
	Placebo (n=10)	34.4(7.2)	-12.65(3.03)	--

n: number of patients in full analysis set; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).

[Source: Applicant's Clinical Responses to Information Request Table 1 except mean baseline score, standard error (SE), standard deviation (SD) and CIs in the table.]

A.5.3 Study 063-008

Table A-29: Subgroup Analysis by Gender – Post-dose PERMP-T Scores Averaged Over All Time Points on Laboratory Classroom Day (Study -008)

Gender	Treatment Group (n)	**Primary Efficacy Measure:** Post-Dose PERMP-T Score Averaged Over All Time Points on AWE Laboratory Day		
		Mean Pre-Dose Score on Classroom Day (SD)	LS Mean Post-Dose Score (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
Male	PRC-063 (n=16)	228.63 (71.79)	274.25 (7.14)	27.06 (9.03) [8.83, 45.29]
	Placebo (n=16)	230.50 (60.26)	247.19 (7.63)	
Female	PRC-063 (n=29)	223.17 (80.50)	285.77 (5.54)	28.30 (7.38) [13.41, 43.20]
	Placebo (n=29)	238.55 (69.00)	257.46 (5.85)	

n: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on model with treatment, period, sequence, time, and treatment-by-subgroup interaction as fixed factors, and baseline score as a covariate.

[Source: Reviewer's Table]

A.5.4 Study 063-015

Table A-30: Subgroup Analysis by Optimal Dose – SKAMP-C Scores Averaged Across All Time Points on Laboratory Classroom Day (Study -015)

Optimal Dose	Treatment Group (n)	**Primary Efficacy Measure:** Post-Dose SKAMP-C Score Averaged Over All Time Points on Laboratory Classroom Day		
		Mean Pre-Dose Score on Classroom Day (SD)	LS Mean Post-Dose Score (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
25 mg	PRC-063 (n=8)	11.8 (5.60)	12.8 (2.64)	-1.2 (3.76) [-9.2, 6.9]
	Placebo (n=8)	9.9 (3.40)	14.0 (2.46)	
35 mg	PRC-063 (n=15)	12.5 (5.55)	9.5 (0.74)	-4.7 (1.03) [-6.8, -2.7]
	Placebo (n=15)	10.5 (7.45)	14.2 (0.80)	
45 mg	PRC-063 (n=20)	16.7 (12.50)	12.7 (1.25)	-8.1 (1.51) [-11.2, -5.1]
	Placebo (n=20)	13.6 (9.44)	20.8 (1.29)	
55 mg	PRC-063 (n=19)	13.0 (9.92)	9.6 (1.34)	-12.6 (1.71) [-16.1, -9.2]
	Placebo (n=19)	11.9 (6.27)	22.2 (1.27)	
70 mg	PRC-063 (n=8)	19.5 (17.29)	10.4 (2.88)	-10.7 (4.12) [-19.7, -1.7]
	Placebo (n=8)	9.3 (5.09)	21.1 (2.57)	
85 mg	PRC-063 (n=4)	12.0 (8.16)	10.0 (1.15)	-13.0 (2.57) [-19.3, -6.8]
	Placebo (n=3)	11.0 (5.29)	23.1 (2.39)	

n: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).
Note: SKAMP-C ranges from 0 to 78, where lower scores indicate less severe symptoms. The same analysis models are used for each by group as in the primary efficacy analyses.
[Source: Table 11 and Table 14.2.1.1.5 of Applicant's CSR, verified by reviewer]

Table A-31: Subgroup Analysis by Gender and Race– Post-dose SKAMP-C Scores Averaged Over All Time Points on Laboratory Classroom Day (Study -015)

	Treatment Group (n)	**Primary Efficacy Measure**: Post-Dose SKAMP-C Score Averaged Over All Time Points on Laboratory Classroom Day		
		Mean Pre-Dose Score on Classroom Day (SD)	LS Mean Post-Dose Score (SE)	Placebo-subtracted Difference[a] (SE) [95% CI]
Gender				
Male	PRC-063 (n=47)	14.6 (9.49)	11.3 (0.99)	-9.5 (1.35) [-12.2, -6.8]
	Placebo (n=49)	13.0 (7.68)	20.8 (0.95)	
Female	PRC-063 (n=27)	14.8 (2.03)	8.6 (0.95)	-6.3 (1.32) [-9.01, -3.69]
	Placebo (n=24)	9.8 (2.42)	15.0 (1.12)	
Race				
White	PRC-063 (n=47)	10.15 (7.56)	10.78 (1.04)	-8.07(1.48) [-11.00, -5.13]
	Placebo (n=34)	17.91 (12.49)	18.84 (1.17)	
Non-white	PRC-063 (n=27)	9.11 (6.00)	8.84 (1.30)	-9.01 (1.44) [-11.89, -6.12]
	Placebo (n=39)	16.28 (9.51)	17.85 (0.97)	

n: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a]Least-Squares Mean Difference (drug minus placebo).

Note: SKAMP-C ranges from 0 to 78, where lower scores indicate less severe symptoms. The same analysis models are used for each by group as in the primary efficacy analyses.

[Source: Subgroup analysis by gender was based on Table 14.2.1.1.7 of Applicant's CSR. Subgroup analysis by race was conducted by reviewer.]

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/s/

PEILING YANG
01/29/2019 03:11:46 PM

YANG YANG
01/29/2019 04:41:53 PM

HSIEN MING J HUNG
02/01/2019 04:12:30 PM
Statistical interpretation of the trial results should completely depend on this review/memo.