Office of Clinical Pharmacology Review

NDA	212038
Link to EDR	\\CDSESUB1\evsprod\nda212038\0000
Submission Date	4/27/18, 2/4/19
Submission Type	505(b)(2), New Formulation
Brand Name	Adhansia XR™
Generic Name	Methylphenidate hydrochloride
Dosage Form and Strength	Extended release capsules, 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg
Route of Administration	Oral
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant	Purdue Pharma, L.P.
Associated IND	(b) (4)
OCP Review Team	Kofi Kumi, Ph.D., Luning (Ada) Zhuang, Ph.D.
OCP Final Signatory	Luning (Ada) Zhuang, Ph.D.

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1. EXECUTIVE SUMMARY

Methylphenidate HCl is central nervous system (CNS) stimulant approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate is available as immediate and extended release formulations such as Ritalin and Concerta, respectively. In this 505(b)(2) application, the Sponsor is partially relying on the Agency's assessment of safety and efficacy, clinical pharmacology and nonclinical toxicology of Ritalin® IR and Concerta®, as the reference listed drugs. Clinical safety and efficacy studies were conducted and included in the application.

The clinical development program for Adhansia XR comprised five efficacy and safety trials, one long-term 6-month open label extension study and seven clinical pharmacology studies. The clinical pharmacology studies evaluated the comparative bioavailability (BA) between Adhansia XR (PRC-063) and immediate release (IR) Ritalin after a single dose and at steady state in adults, pharmacokinetics (PK) in children and adolescents, effect of food on Adhansia XR, effect of alcohol on Adhansia XR, comparative BA with Concerta and between clinical trial and the to be marketed formulations.

The clinical pharmacology findings are summarized below:

- After administration of Adhansia XR, two distinct peak concentrations are observed with the 1st occurring in about 1.5 hours and the 2nd in about 12 hours post dose. This is indicative of the immediate and delayed release components of the formulation

- After administration of 100 mg Adhansia XR daily and 20 mg IR methylphenidate 3 times a day for 5 days in a comparative bioavailability study, exposure to racemic (d,l-) methylphenidate (AUC0-24) and minimum concentration (Cmin) were about 50% and 288% higher after Adhansia XR, respectively. The 1st peak concentration (Cmax) was 22% higher but the 2nd Cmax was similar at steady state. Partial (p) AUC $_{0\text{-}4h}$, pAUC$_{8\text{-}12h}$, pAUC$_{12\text{-}16h}$, pAUC$_{12\text{-}t}$ were about 31%, 13%, 126%, 220% higher, respectively but AUC$_{4\text{-}8h}$ was about 20% lower after Adhansia XR compared to IR methylphenidate at steady state. The exposures were not equivalent except pAUC$_{8\text{-}12h}$. Clinical safety and efficacy studies demonstrated effectiveness at various time points during the day up to 16 hours post dose (refer to medical review)

- AUC$_{0\text{-}inf}$ and AUC$_{0\text{-}t}$ of methylphenidate are equivalent after a single dose administration of 70 mg Adhansia XR and 72 mg Concerta. However, pAUCs (AUC$_{0\text{-}3}$, AUC$_{3\text{-}7}$, AUC$_{7\text{-}12}$, AUC$_{12\text{-}16}$) and Cmax of methylphenidate were not equivalent. Clinical safety and efficacy studies demonstrated effectiveness at various time points during the day up to 16 hours post dose (refer to medical review).

- The higher Cmin observed after administration of Adhansia XR could explain the high incidence of insomnia observed in the clinical safety and efficacy trials in adults and pediatric patients after administration of Adhansia XR (please refer to medical review).

- Adhansia XR can be administered with or without food. The entire contents of Adhansia XR capsule can be sprinkled on applesauce or yogurt and consumed without chewing.

- Since the delayed release coating is dissolved (b) (4) and methylphenidate is released, pH modulators, such as proton pump inhibitors, should be co-administered with caution and based on clinical response, alternate medication used if needed.

An Office of Study Integrity and Surveillance (OSIS) inspection was requested. OSIS declined to inspect the sites and recommended the data should be accepted because OSIS recently inspected the sites and the outcome was classified as No Action Indicated (NAI).

1.1 Recommendation

The office of Clinical Pharmacology (OCP) has reviewed the information in NDA 212038 and supports the approval of Adhansia XR for the treatment of ADHD.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendation and Comments
Supportive evidence of effectiveness	Effectiveness was demonstrated in clinical safety efficacy trials in adults and pediatric patients (6 -17 years).
Bridging between Adhansia XR and the reference products	After a single dose administration of 100 mg Adhansia XR and 20 mg IR methylphenidate (Ritalin) given 3 times, non-dose normalized exposures (Cmax, AUC) to d,l-methylphenidate were not equivalent. However, when the doses were normalized, $AUC_{0\text{-}inf}$ was equivalent. Similar observations were noticed when Adhansia XR and IR methylphenidate were compared at steady state. After a single dose administration of Adhansia XR 70 mg and Concerta Extended Release (ER) 72 mg, exposures ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$) were equivalent but Cmax and partial AUCs were not. Ritalin IR and Concerta ER are reasonable reference products for Adhansia XR.
General dosing instructions	The recommended starting dose of Adhansia XR for ADHD in patients 6 years and older is 25 mg once daily. The dose can be titrated in increments of 10 to 15 mg at intervals of no less than 5 days according to clinical response of the patient. Doses higher than 100 mg have

	not been evaluated. In short-term controlled trials, dosages above 85 mg daily in adults and 70 mg and above daily in pediatric patients did not confer increased effectiveness sufficient to outweigh dose-related adverse reactions. Adhansia XR can be administered with or without food. And can be sprinkled on applesauce or yogurt and consumed without chewing.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No new studies in renal or hepatic impaired subjects were conducted. No new drug interaction studies were conducted. Information in the approved labels for the reference products will be included in the Adhansia XR label
Bridging between the "to-be-marketed" and clinical trial formulations	A comparative bioavailability study demonstrated that the "to-be-marketed" and clinical trial formulations manufactured in USA and Canada, respectively are bioequivalent

1.2 Post Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 The Pharmacology and Clinical Pharmacokinetics

Adhansia XR™ contains a racemic mixture of d- and l-methylphenidate. Methylphenidate is a CNS stimulant approved for the treatment of ADHD. Methylphenidate is classified as a non-catecholamine sympathomimetic that is a direct and indirect adrenergic agonist.

Absorption

Following administration of 100 mg Adhansia XR once daily and 20 mg IR Ritalin administered 3 times a day for 5 days under fasting conditions in a comparative bioavailability study, mean total exposure (AUC_{0-24}) and minimum concentration (Cmin) of racemic (d,l-) methylphenidate for Adhansia XR were about 50% and 288%, respectively higher compared to IR Ritalin and not equivalent at steady state. Partial (p) AUCs (AUC_{0-4h}, AUC_{4-8}, AUC_{12-16} and AUC_{12-t}) were not equivalent except AUC_{8-12h}. Peak 1st and 2nd peak concentration (Cmax) were about 22% and 1.4%, respectively when Adhansia XR was compared to Ritalin IR at steady state. Dose normalized AUC_{0-24h} for racemic methylphenidate was equivalent but Cmax and Cmin were not equivalent.

The bioavailability of Adhansia XR relative to Ritalin IR after a single dose administration was estimated to be about 90% based on dose normalized data.

Following a single dose administration Adhansia XR 70 mg and Concerta 72 (2 x 36) mg, exposure to methylphenidate (AUC_{0-inf}, AUC_{0-t}) was equivalent, however, partial AUCs (AUC_{0-3}, AUC_{3-7}, AUC_{7-12}) were not equivalent. Peak concentration (Cmax) was about 19% lower after administration of Adhansia XR compared to Concerta. The initial release of methylphenidate from Concerta was faster compared to that from Adhansia XR.

Food (high fat meal, applesauce or yogurt) did not significantly affect the absorption of methylphenidate after administration of Adhansia XR under fed conditions. Therefore, Adhansia XR can be administrated with or without food and it can be sprinkled on applesauce or yogurt and swallowed.

Distribution

Methylphenidate is reported to be to approximately 10% to 33% bound to plasma proteins.

Elimination

The mean elimination half-life of methylphenidate after administration of Adhansia XR is about 7 hours in adults, 5 hours in adolescents (13 -17 years) and 4 -7 hours in children (6 -12 years)

Metabolism

The Sponsor did not conduct radiolabeled studies to determine the metabolism of methylphenidate after administration of Adhansia XR. The following information is from the label of the reference drugs. Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPAA, ritalinic acid), which has little or no pharmacologic activity.

Excretion

The Sponsor did not conduct radiolabeled study. The following information is from the label for Concerta, a reference drug. After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main metabolite was PPAA, accounting for approximately 80% of the dose.

2.2 Dosing and Therapeutic Individualization

The recommended starting dose of Adhansia XR for ADHD in patients 6 years and older is 25 mg once daily. The dose can be titrated in increments of 10 to 15 mg at intervals of no less than 5 days according to clinical response of the patient. Doses higher than 100 mg were not evaluated in clinical studies.

The clinical safety and efficacy trials evaluated doses 25 to 85 mg daily in pediatric patients (6 - 17 years) and 25 mg to 100 mg in adults. The medical reviewer indicated that in short-term controlled safety and efficacy trials, doses above 85 mg daily in adults and 70 mg daily in pediatric patients, respectively do not confer increased effectiveness sufficient to outweigh dose related adverse events (refer to medical review for details).

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The following is recommended to be added to Section 12.3

Adhansia XR contains a racemic mixture of d- and l-methylphenidate and produces two distinct peak concentrations (Cmax). The 1st median (range) time to Cmax (Tmax) occurred at about 1.5 (1- 2.5) hours and the 2nd about 12 (8.5- 16.0) hours after Adhansia XR administration. Following administration of Adhansia XR (100 mg once daily) and 60 mg of immediate-release (IR) methylphenidate (administered as 20 mg three times daily 4 hours apart) under fasted conditions for 5 consecutive days to 21 healthy adult subjects, 1st d,l-methylphenidate mean Cmax was about 22% higher but the 2nd mean Cmax was similar for ADHANSIA XR compared to IR methylphenidate at steady state. The mean extent of exposure (AUC0-24h) and minimum concentration (Cmin) of d,l-methylphenidate were about 50% and 288% higher, respectively for ADHANSIA XR compared to IR methylphenidate at steady state. (Figure 1) Following administration of ADHANSIA XR (100 mg once daily), the steady-state was reached from day 3.

Effect of Food

High fat, high caloric meal (800 to 1000 calories) does not affect the maximum concentration (Cmax) and extent of absorption (AUC) of d,l-methylphenidate when taken with Adhansia XR. The time to maximum concentration (Tmax) was increased by about 1 hour after administration with a high fat meal compared to under fasting conditions. The absorption and exposure to d,l-methylphenidate were similar when Adhansia XR (100 mg) was administered following an overnight fast as an intact capsule or sprinkled on a tablespoonful of applesauce and yogurt in healthy adult subjects.

Effect of Alcohol

In an *in vivo* alcohol interaction study, in fasted healthy adults, Adhansia XR 70 mg capsules with 40% alcohol concentration resulted in a 1.4-fold increase in the peak plasma methylphenidate concentration and a 1.3-fold increase in the extent of absorption.

Pediatric patients

Pharmacokinetic studies of racemic methylphenidate after oral administration of Adhansia XR has been conducted in pediatric subjects (6 – 17 years) with ADHD. Following administration of Adhansia XR, the median 1st and 2nd peak plasma concentration (Tmax) for d, l-methylphenidate occurred in about 2 and 10 hours in children and 2 and 11 hours, respectively in adolescents. The mean plasma elimination half-life for d, l-methylphenidate was about 4 -7 hours in children and 5 hours in adolescents.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Adhansia XR™ is an ER methylphenidate product (b) (4) currently marketed methylphenidate products (e.g. Ritalin, Concerta, Aptensio XR, Cotempla XR ODT) for ADHD. Most currently approved once-daily long-acting methylphenidate treatments for ADHD are reported to have a 9- to 12-hour duration of action.

Adhansia XR contain beads which consist of multiple layers of (b) (4) the components of the formulation (b) (4) Each (b) (4) bead has a methylphenidate IR component (containing 20% of the dose of methylphenidate hydrochloride [HCl]) and a methylphenidate controlled-release (CR) component (containing 80% of the dose of methylphenidate HCl). (b) (4) Adhansia XR will be available in strengths of 25, 35, 45, 55, 70, and 85 mg.

The Sponsor submitted a 505(b)(2) application referencing the Agency's assessment of safety, efficacy, clinical pharmacology, and nonclinical toxicology of Ritalin® IR and Concerta® as the reference listed drugs. The Sponsor does not have the right of reference to the listed drugs.

The clinical development program for Adhansia XR comprised five efficacy and safety trials, one long-term 6-month open label extension study and seven clinical pharmacology studies. The clinical pharmacology studies evaluated the comparative bioavailability (BA) between Adhansia XR (PRC-063) and immediate release (IR) Ritalin after a single dose and at steady state in adults, pharmacokinetics (PK) in children and adolescents, effect of food on Adhansia XR, effect of alcohol on Adhansia XR, comparative BA with Concerta and between clinical trial and the to be marketed formulations. The bioanalytical assay used was a validated chiral assay that determined both the d- and l-methylphenidate isomers. The results presented in this review are for the combined (racemic) values since both isomers contribute to central nervous system (CNS) activity even though the d-isomer is the more potent for CNS effect.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	CNS stimulant
Active moiety	Methylphenidate
QT Prolongation	Not available
General Information	
Bioanalysis	Validated LC/MS/MS; range of 150 to 30000 and 4 to 800 pg/mL for d- and l-methylphenidate, respectively
Maximum tolerated dose or exposure	100 mg
Dose proportionality	25 to 100 mg
Accumulation	None or minimal
Absorption	Two peaks were observed after administration. 1st median (range) Tmax= 1.5 (1 – 2.5) hours, 2nd Tmax = 12 (8.5 – 16) hours. Cmax and AUC increased 1.4-fold and 1.3-fold respectively, when administered with 40% alcohol.
Distribution	Approximately 10% to 33% bound to plasma proteins.
Metabolism	Metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPAA). The metabolite has little or no pharmacological effect
Excretion	After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite is PPAA, accounting for approximately 80% of the dose.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology or biopharmaceutics information provide pivotal or supportive evidences of effectiveness

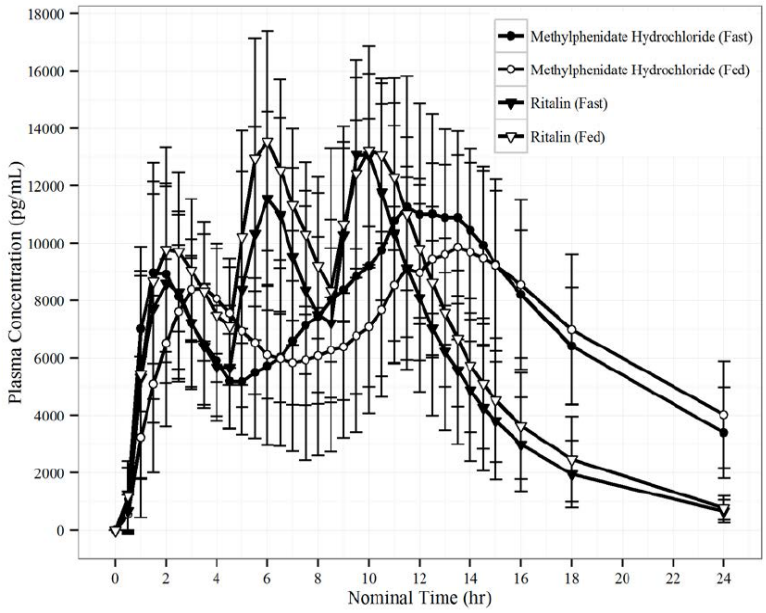
The Sponsor demonstrated that after a single dose and at steady state, the dose-normalized exposure ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}24}$) to methylphenidate was equivalent when 100 mg Adhansia XR given once daily compared to 20 mg Ritalin IR given 3 times daily. However, the dose-normalized partial AUCs were not equivalent and dose-normalized Cmin was 132% higher and dose-normalized Cmax was 40% lower after daily administration of Adhansia XR compared to IR Ritalin. Ritalin has been shown to be effective in treating ADHD and since the dose-normalized exposures ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}24}$) to methylphenidate are equivalent, it supports the expectation that Adhansia XR will be effective in treating ADHD. The difference in dose-normalized partial AUCs suggest that the time frame for onset and duration of effectiveness might be different for Adhansia XR compared to Ritalin IR.

Non-dose-normalized AUC0-inf and AUC0-24h after a single dose and at steady state, respectively were not equivalent but Cmax was comparable after administration of Adhansia XR 100 mg daily and Ritalin IR 20 mg 3 times daily. After single dose administration, AUC0-inf was about 50% higher and Cmax was about 10% lower of racemic methylphenidate after Adhansia XR compared to Ritalin IR. Non-dose normalized partial AUCs were not equivalent except for AUC0-4h after a single dose and AUC8-12h at steady state. Non-dose normalized racemic methylphenidate AUC0-24h and Cmin at steady state was about 50% and 288% higher after Adhansia XR compared to Ritalin IR. The results support the effectiveness of Adhansia XR but the exposures after the maximum recommended dose (60 mg) for Ritalin IR is not comparable to the highest dose (100 mg) of Adhansia XR studies in the clinical trials.

The Sponsor demonstrated that after a single dose administration of Adhansia XR compared to Concerta, the exposures (AUC0-inf, AUC0-t) to methylphenidate were equivalent but partial AUCs (0-3, 3-7, 7-12, 12-16, 16 – 24 hours) were not equivalent. Concerta has been demonstrated to be effective in treating ADHD, therefore the equivalent total exposure supports the effectiveness of Adhansia XR in treating ADHD. The difference in partial exposures suggest that the onset and duration of effect might be different. Clinical trials were conducted to demonstrate the efficacy of Adhansia XR versus placebo. Refer to medical review for details.

The Sponsor conducted a comparative bioavailability study comparing Adhansia XR 100 mg administered once daily to IR Ritalin 20 mg administered 3 times a day for one day and daily administration for 5 days. The mean plasma concentration time profile for d,l-methylphenidate and the statistical analysis are provided in the following figures and tables

Figure 1: Mean concentration-time profile for d,l-methylphenidate after single daily dose



Source: Study 063-004

Table 1: Ratios, 90% Geometric Confidence Intervals for Dose-Normalized AUC_{0-T}, AUC_{0-Inf} and Cmax for Racemic (d,l-) Methylphenidate after a Single Daily Dose

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test (A) – Reference (C)	75.56%	71.77%	79.56%	11.35%	25.27%
	Test (B) – Test (A)	97.45%	92.54%	102.62%		
	Test (B) – Reference (D)	62.04%	58.91%	65.33%		
AUC_{0-inf}	Test (A) – Reference (C)	89.75%	85.67%	94.02%	10.25%	26.63%
	Test (B) – Test (A)	101.87%	97.11%	106.87%		
	Test (B) – Reference (D)	77.26%	73.64%	81.05%		
C_{max}	Test (A) – Reference (C)	53.73%	49.69%	58.11%	17.32%	23.26%
	Test (B) – Test (A)	87.49%	80.88%	94.63%		
	Test (B) – Reference (D)	42.82%	39.58%	46.32%		

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Treatment A: PRC-063 (Adhansia XR) 100 (55+45) mg capsule under fasting conditions.

Treatment B: PRC-063 100 mg (55 +45) mg capsule under fed conditions

Treatment C: Ritalin 20 mg 3 times a day under fasting conditions

Treatment D: Ritalin 20 mg 3 times a day under fed conditions

Source: Study 063-004

Table 2: Ratios, 90% Geometric Confidence Intervals for Dose-Normalized Partial AUCs for Racemic (d,l-) Methylphenidate after a Single Dose

Parameter	Treatment Comparisons	Ratio[1] (%)	90% Geometric C.I.[2] Lower (%)	90% Geometric C.I.[2] Upper (%)	Intra-Subject CV (%)
AUC_{0-4}	Test (A) – Reference (C)	63.54	57.58	70.12	5.45
AUC_{4-8}	Test (A) – Reference (C)	37.41	34.69	40.34	5.95
AUC_{8-12}	Test (A) – Reference (C)	50.04	44.78	55.93	5.37
AUC_{12-16}	Test (A) – Reference (C)	121.87	110.77	134.08	6.51
AUC_{12-t}	Test (A) – Reference (C)	157.93	144.91	172.13	7.98
AUC_{0-4}	Test (B) – Reference (D)	46.80	42.39	51.66	5.45
AUC_{4-8}	Test (B) – Reference (D)	35.84	33.23	38.66	5.95
AUC_{8-12}	Test (B) – Reference (D)	38.41	34.35	42.94	5.37
AUC_{12-16}	Test (B) – Reference (D)	91.41	83.05	100.60	6.51
AUC_{12-t}	Test (B) – Reference (D)	129.76	119.02	141.48	7.98

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.

[2] 90% Geometric Confidence Interval using ln-transformed data.

Tests (A and B) = Purdue Pharma, Canada, methylphenidate hydrochloride, 1 x 45 mg CR capsule + 1 x 55 mg CR capsule, for a total daily dose of 100 mg, under fasting (Treatment A) and fed (Treatment B) conditions.

References (C and D) = Novartis Pharmaceuticals Canada Inc., Canada (Ritalin) methylphenidate hydrochloride, 1 x 20 mg IR tablet TID, for a total daily dose of 60 mg, under fasting (Treatment C) and fed (Treatment D) conditions.

Source: Study 063-004 supplement

Table 3: Ratios, 90% Geometric Confidence Intervals for Non-Dose Normalized AUC0-t, AUC0-inf and Cmax for Combined Methylphenidate after a Single Dose

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test (A) – Reference (C)	125.94%	119.62%	132.60%	11.35%	25.27%
	Test (B) – Test (A)	97.45%	92.54%	102.62%		
	Test (B) – Reference (D)	103.40%	98.19%	108.88%		
AUC_{0-inf}	Test (A) – Reference (C)	149.58%	142.78%	156.70%	10.25%	26.63%
	Test (B) – Test (A)	101.87%	97.11%	106.87%		
	Test (B) – Reference (D)	128.77%	122.74%	135.09%		
C_{max}	Test (A) – Reference (C)	89.55%	82.81%	96.84%	17.32%	23.26%
	Test (B) – Test (A)	87.49%	80.88%	94.63%		
	Test (B) – Reference (D)	71.36%	65.97%	77.19%		

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Source: Study 063-004

Table 4: Ratios, 90% Geometric Confidence Intervals for Non-Dose Normalized AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, AUC_{12-16} and AUC_{12-T} for Combined Methylphenidate after a Single Dose

Parameter	Treatment Comparisons	Ratio[1] (%)	90% Geometric C.I.[2] Lower (%)	Upper (%)	Intra-Subject CV (%)
AUC_{0-4}	Test (A) – Reference (C)	105.90	95.97	116.86	5.45
AUC_{4-8}	Test (A) – Reference (C)	62.35	57.82	67.24	5.95
AUC_{8-12}	Test (A) – Reference (C)	83.40	74.63	93.21	5.37
AUC_{12-16}	Test (A) – Reference (C)	203.12	184.62	223.47	6.51
AUC_{12-t}	Test (A) – Reference (C)	263.22	241.51	286.89	7.98
AUC_{0-4}	Test (B) – Test (A)	86.89	78.71	95.93	5.45
AUC_{4-8}	Test (B) – Test (A)	116.14	107.67	125.29	5.95
AUC_{8-12}	Test (B) – Test (A)	86.25	77.13	96.45	5.37
AUC_{12-16}	Test (B) – Test (A)	92.67	84.19	102.00	6.51
AUC_{12-t}	Test (B) – Test (A)	102.13	93.67	111.35	7.98
AUC_{0-4}	Test (B) – Reference (D)	77.99	70.65	86.10	5.45
AUC_{4-8}	Test (B) – Reference (D)	59.74	55.38	64.44	5.95
AUC_{8-12}	Test (B) – Reference (D)	64.01	57.25	71.57	5.37
AUC_{12-16}	Test (B) – Reference (D)	152.35	138.42	167.67	6.51
AUC_{12-t}	Test (B) – Reference (D)	216.27	198.36	235.79	7.98

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Tests (A and B): Purdue Pharma, Canada, methylphenidate hydrochloride, 1 x 45 mg CR capsule + 1 x 55 mg CR capsule, for a total daily dose of 100 mg, under fasting (Treatment A) and fed (Treatment B) conditions.
References (C and D): Novartis Pharmaceuticals Canada Inc., Canada (Ritalin) methylphenidate hydrochloride, 1 x 20 mg IR tablet TID, for a total daily dose of 60 mg, under fasting (Treatment C) and fed (Treatment D) conditions.

Source: Study 063-004 supplement

The mean plasma concentration time profile for d,l-methylphenidate at steady state is provided in Figure 2. The statistical comparisons are provided in Tables 5 to 8

Figure 2: Mean Concentration-Time Profile for d,l- (Racemic) Methylphenidate for Each Treatment on Day 5 after Daily Dosing

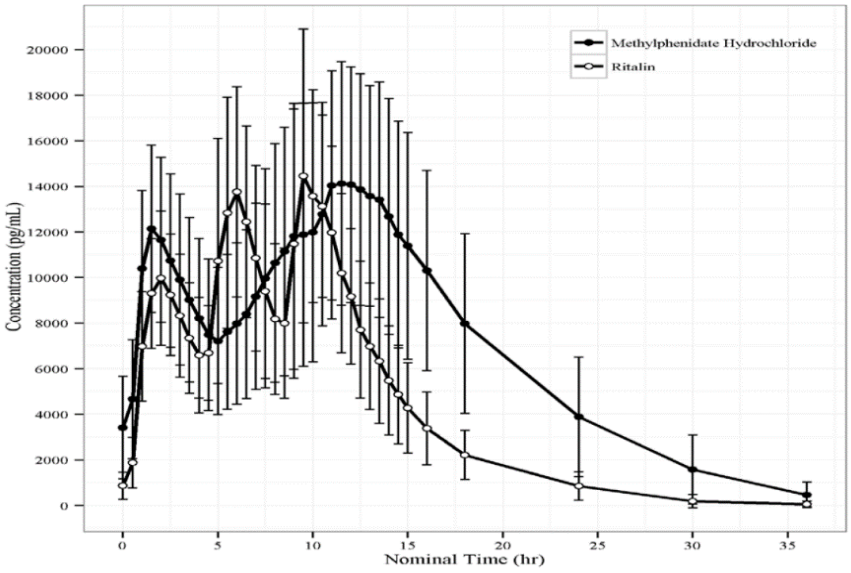


Table 5: Ratios, 90% Geometric Confidence Intervals for Dose-Normalized AUC_{0-24}, Cmax, and Cmin for Racemic (d,l-) Methylphenidate - Day 5 after Daily Dosing

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-24}	Test(A) - Reference(B)	89.39%	86.63%	92.23%	4.84%	31.95%
C_{max}	Test(A) - Reference(B)	60.25%	56.38%	64.39%	10.28%	26.39%
C_{min}	Test(A) - Reference(B)	232.60%	195.58%	276.62%	26.16%	62.33%

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Source study 063-007

Table 6: Ratios, 90% Geometric Confidence Intervals for Dose-Normalized Partial AUCs for Racemic (d,l-) Methylphenidate - Day 5 after Daily Dosing

			90% Geometric C.I.[2]		
Parameter	Treatment Comparisons	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)
AUC_{0-4}	Test (A) – Reference (B)	78.86	74.77	83.17	8.23
AUC_{4-8}	Test (A) – Reference (B)	102.17	92.84	112.44	14.86
AUC_{8-12}	Test (A) – Reference (B)	110.50	101.52	120.27	13.13
AUC_{12-16}	Test (A) – Reference (B)	204.93	188.23	223.12	13.18
AUC_{12-t}	Test (A) – Reference (B)	156.14	140.90	173.01	15.94

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.

[2] 90% Geometric Confidence Interval using ln-transformed data.

Test(A): Purdue Pharma, Canada, methylphenidate hydrochloride, 1 x 45 mg CR capsule + 1 x 55 mg CR capsule, for a total daily dose of 100 mg, under fasting for 5 consecutive days

Reference(B): Novartis Pharmaceuticals Canada Inc., Canada (Ritalin) methylphenidate hydrochloride, 1 x 20 mg IR tablet TID, for a total daily dose of 60 mg, under fasting conditions for 5 consecutive days

Source: Study 063-007 supplement

Table 7: Ratios, 90% Geometric Confidence Intervals for Non-Dose-Normalized AUC0-24, Cmax, and Cmin for Combined Methylphenidate - Day 5 after Daily Dosing

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-24}	Test(A) - Reference(B)	148.98%	144.39%	153.72%	4.84%	31.95%
C_{max}	Test(A) - Reference(B)	100.42%	93.96%	107.32%	10.28%	26.39%
C_{min}	Test(A) - Reference(B)	387.67%	325.97%	461.04%	26.16%	62.33%

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.

[2] 90% Geometric Confidence Interval using ln-transformed data.

Source: Study 063-007

Table 8: Ratios, 90% Geometric Confidence Intervals for Non-Dose-Normalized AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, AUC_{12-16} and AUC_{12-T} for Combined Methylphenidate – Day 5 after Daily Dosing

Non dose-normalised

Parameter	Treatment Comparisons	Ratio[1] (%)	90% Geometric C.I.[2] Lower (%)	90% Geometric C.I.[2] Upper (%)	Intra-Subject CV (%)
AUC_{0-4}	Test (A) – Reference (B)	131.43	124.62	138.62	8.23
AUC_{4-8}	Test (A) – Reference (B)	80.57	73.94	87.79	13.30
AUC_{8-12}	Test (A) – Reference (B)	112.90	102.17	124.75	15.50
AUC_{12-16}	Test (A) – Reference (B)	226.44	209.12	245.20	12.32
AUC_{12-t}	Test (A) – Reference (B)	319.97	294.52	347.62	12.84

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.

[2] 90% Geometric Confidence Interval using ln-transformed data.

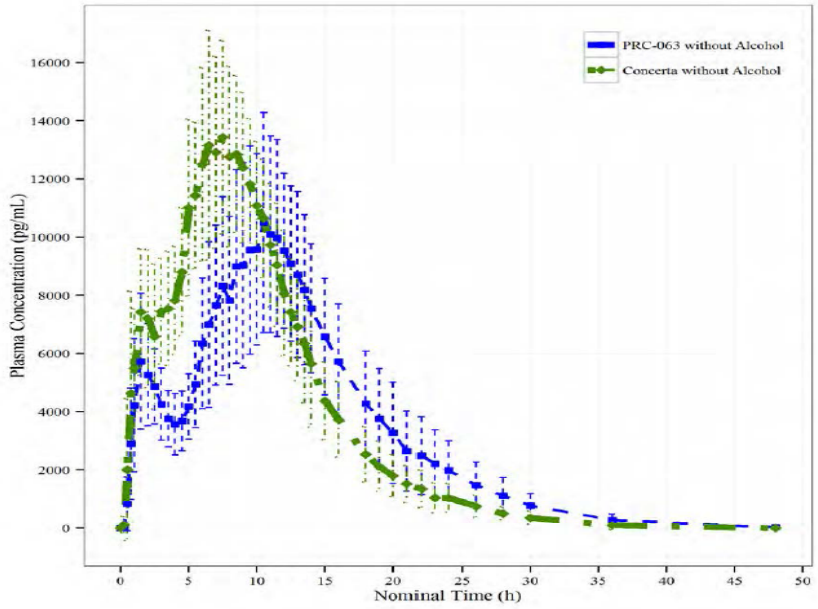
Test(A): Purdue Pharma, Canada, methylphenidate hydrochloride, 1 x 45 mg CR capsule + 1 x 55 mg CR capsule, for a total daily dose of 100 mg, under fasting for 5 consecutive days

Reference(B): Novartis Pharmaceuticals Canada Inc., Canada (Ritalin) methylphenidate hydrochloride, 1 x 20 mg IR tablet TID, for a total daily dose of 60 mg, under fasting conditions for 5 consecutive days

Source: Study 063-007 Supplement

The Sponsor conducted a comparative bioavailability study evaluating exposure of methylphenidate after administration of a single dose of 70 mg Adhansia XR and 72 mg Concerta. The mean plasma concentration-time profile of methylphenidate after a single dose administration of Adhansia XR and Concerta to healthy adult volunteers is provided in Figure 3

Figure 3: Mean (±SD) Concentration-Time Profile for Racemic (d,l-) Methylphenidate after a Single Dose Administration of 70 Mg Adhansia XR and 72 Mg Concerta



Source: Study 063-16

Table 9: Ratio and 90% Geometric Confidence Intervals for Racemic (d,l-) Methylphenidate after a Single Dose Administration of 70 mg Adhansia XR and Concerta 72 mg under Fasting Conditions

Parameter	Treatment Comparisons	Ratio (%)	90% CI Lower	90% CI Upper
AUC_{0-t}	Adhansia XR – Concerta	95.18	90.76	99.81
AUC_{0-inf}	Adhansia XR – Concerta	95.47	91.10	100.05
AUC_{0-24}	Adhansia XR - Concerta	90.45	86.82	94.22
AUC_{0-3}	Adhansia XR - Concerta	73.16	68.57	78.05
AUC_{3-7}	Adhansia XR - Concerta	48.40	45.39	51.62
AUC_{7-12}	Adhansia XR - Concerta	81.64	74.34	89.65
AUC_{12-16}	Adhansia XR - Concerta	138.40	123.78	154.76
AUC_{16-24}	Adhansia XR - Concerta	175.95	150.57	205.61
Cmax	Adhansia XR - Concerta	81.52	74.11	89.68

Source: Study 063-016 supplement

The 90% confidence interval (CI) around the mean ratio for AUC (0-inf, 0-t, 0-24 hours) is contained within the 80% to 125% regulatory criteria for bioequivalence. However, the partial exposures and Cmax are outside the 80% to 125% indicating there are not equivalent.

The partial AUCs evaluated are those recommended for Concerta ER. Additional or new partial AUCs for Adhansia XR may be needed for Adhansia XR since the shape of the pharmacokinetic curve is not the same as that for Concerta and Adhansia XR is supposed to last for up to16 hours as opposed to Concerta that lasts for about 12 hours.

One of the most frequent treatment emergent adverse events observed in the clinical studies in adults and adolescents is insomnia (Tables 10 to 12). The minimum concentration (Cmin) of methylphenidate at steady state is about 132% higher after administration of Adhansia XR compared to IR Ritalin in adults and could explain the high degree of insomnia observed in adults and adolescent patients on Adhansia XR.

Table 10: Adverse Events that Occurred More Frequently on PRC-063 (Adhansia XR) than on Placebo During the Double-blind Period – Adults

Preferred Term [n (%)]	Placebo (N=126) n (%)	PRC-063 25 mg (N=223) n (%)	PRC-063 35 mg (N=0) n (%)	PRC-063 45 mg (N=219) n (%)	PRC-063 55 mg (N=5) n (%)	PRC-063 70 mg (N=150) n (%)	PRC-063 85 mg (N=12) n (%)	PRC-063 100 mg (N=75) n (%)	All PRC-063 Subjects (N=343) n (%)
Any TEAE	55 (43.7)	97 (43.5)	0 (0.0)	91 (41.6)	1 (20.0)	57 (38.0)	6 (50.0)	25 (33.3)	206 (60.1)
Insomnia	4 (3.2)	24 (10.8)	0 (0.0)	12 (5.5)	0 (0.0)	9 (6.0)	0 (0.0)	4 (5.3)	47 (13.7)
Decreased appetite	2 (1.6)	14 (6.3)	0 (0.0)	12 (5.5)	0 (0.0)	8 (5.3)	4 (33.3)	3 (4.0)	41 (12.0)
Dry mouth	4 (3.2)	11 (4.9)	0 (0.0)	9 (4.1)	0 (0.0)	8 (5.3)	0 (0.0)	2 (2.7)	30 (8.7)
Initial insomnia	2 (1.6)	8 (3.6)	0 (0.0)	5 (2.3)	1 (20.0)	5 (3.3)	1 (8.3)	2 (2.7)	21 (6.1)
Nausea	3 (2.4)	7 (3.1)	0 (0.0)	7 (3.2)	0 (0.0)	5 (3.3)	0 (0.0)	1 (1.3)	19 (5.5)
Feeling jittery	1 (0.8)	4 (1.8)	0 (0.0)	4 (1.8)	0 (0.0)	5 (3.3)	0 (0.0)	1 (1.3)	13 (3.8)
Diarrhoea	1 (0.8)	3 (1.3)	0 (0.0)	5 (2.3)	0 (0.0)	2 (1.3)	0 (0.0)	1 (1.3)	11 (3.2)
Weight decreased	1 (0.8)	4 (1.8)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.7)	3 (25.0)	1 (1.3)	11 (3.2)
Anxiety	1 (0.8)	1 (0.4)	0 (0.0)	5 (2.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	7 (2.0)

Note: More frequently is defined as a rate on Total PRC-063 that is $\geq$ 2% and greater than twice the rate of the placebo group.
Note: Safety Grouping 1.1 includes adults in studies 063-008 (double-blind period) and 063-010 (double-blind).
Adverse events are coded using MedDRA Version 20.0. Only treatment-emergent adverse events are summarized. For each preferred term, subjects are included only once per treatment/dose, even if they experienced multiple events in that preferred term.
Subjects are presented by actual treatment/dose at onset of adverse event.

Source: Sponsor's summary of clinical safety Table 2.7.4-24

Table 11: Adverse Events that Occurred More Frequently on PRC-063 (Adhansia XR) than on Placebo During the Double-blind Period – Adolescents

Preferred Term [n (%)]	Placebo (N=74) n (%)	PRC-063 25 mg (N=220) n (%)	PRC-063 45 mg (N=212) n (%)	PRC-063 70 mg (N=141) n (%)	PRC-063 85 mg (N=66) n (%)	All PRC-063 Subjects (N=292) n (%)
Any TEAE	35 (47.3)	99 (45.0)	92 (43.4)	44 (31.2)	20 (30.3)	189 (64.7)
Decreased appetite	0 (0.0)	27 (12.3)	21 (9.9)	11 (7.8)	2 (3.0)	59 (20.2)
Weight decreased	0 (0.0)	4 (1.8)	8 (3.8)	5 (3.5)	1 (1.5)	18 (6.2)
Insomnia	1 (1.4)	7 (3.2)	6 (2.8)	2 (1.4)	3 (4.5)	18 (6.2)
Abdominal pain upper	2 (2.7)	10 (4.5)	6 (2.8)	3 (2.1)	0 (0.0)	17 (5.8)
Initial insomnia	1 (1.4)	8 (3.6)	4 (1.9)	2 (1.4)	1 (1.5)	15 (5.1)
Dizziness	1 (1.4)	5 (2.3)	4 (1.9)	2 (1.4)	1 (1.5)	11 (3.8)
Dry mouth	1 (1.4)	3 (1.4)	3 (1.4)	2 (1.4)	0 (0.0)	8 (2.7)
Vomiting	0 (0.0)	2 (0.9)	3 (1.4)	1 (0.7)	1 (1.5)	7 (2.4)

Note: More frequently is defined as a rate on Total PRC-063 that is ≥ 2% and greater than twice the rate of the placebo group.
Note: Safety Grouping 1.2 includes adolescents in study 063-009 (double blind).
Adverse events are coded using MedDRA Version 20.0. Only treatment-emergent adverse events are summarized. For each preferred term, subjects are included only once per treatment/dose, even if they experienced multiple events in that preferred term.
Subjects are presented by actual treatment/dose at onset of adverse event.
Note: Subjects from dose titration studies may be presented in more than one column. In column "Total PRC-063 Subjects," each subject who received PRC-063 is counted only once.

Source: Sponsor's Summary of Clinical Safety Table 2.7.4-23

Table 12: Adverse Events that Occurred More Frequently on PRC-063 (Adhansia XR) than on Placebo During the Double-blind Period – Children

Preferred Term [n (%)]	Placebo (N=73) n (%)	PRC-063 25 mg (N=9) n (%)	PRC-063 35 mg (N=15) n (%)	PRC-063 45 mg (N=20) n (%)	PRC-063 55 mg (N=19) n (%)	PRC-063 70 mg (N=8) n (%)	PRC-063 85 mg (N=4) n (%)	All PRC-063 Subjects (N=75) n (%)
Any TEAE	7 (9.6)	3 (33.3)	2 (13.3)	5 (25.0)	3 (15.8)	3 (37.5)	2 (50.0)	18 (24.0)
Heart rate increased	1 (1.4)	0	0	1 (5.0)	1 (5.3)	1 (12.5)	0	3 (4.0)
Vomiting	0	1 (11.1)	0	0	1 (5.3)	0	0	2 (2.7)
Headache	0	0	0	0	0	1 (12.5)	1 (25.0)	2 (2.7)
Upper respiratory tract infection	0	0	0	1 (5.0)	0	0	1 (25.0)	2 (2.7)

Note: More frequently is defined as a rate on Total PRC-063 that is ≥ 2% and greater than twice the rate of the placebo group.
Note: Safety Grouping 1.3 includes children in study 063-015 (double blind).
Adverse events are coded using MedDRA Version 20.0. Only Treatment-emergent adverse events are summarized. For each preferred term, subjects are included only once per treatment/dose, even if they experienced multiple events in that preferred term.
Subjects are presented by actual treatment/dose at onset of adverse event.
Note: Subjects from dose titration studies may be presented in more than one column. In column "Total PRC-063 Subjects," each subject who received PRC-063 is counted only once.

Source: Sponsor's Summary of Clinical Safety Table 2.7.4-22.

3.3.2 Is the proposed general dosing regimen appropriate for the general population for which the indication is being sought?

Yes. Based on the results of clinical efficacy and safety trials conducted in adults and pediatric patients (6 -17 years), the following dosing regimen is proposed.

The recommended starting dose of Adhansia XR for patients 6 years or older is 25 mg once daily. Titrate the dose in increments of 10 to 15 mg at intervals of no less than 5 days and individualize according to the needs and response of the patient. Doses higher than 100 mg have not been evaluated in clinical trials. In short-term controlled trials, dosages above 85 mg daily in adults and 70 mg and above daily in pediatric patients do not confer increased effectiveness sufficient to outweigh the disproportionate increase in dose-related adverse reactions

Table 13 contains summary of the safety and efficacy studies with doses studied. Please refer to the medical review for the Agency's analysis

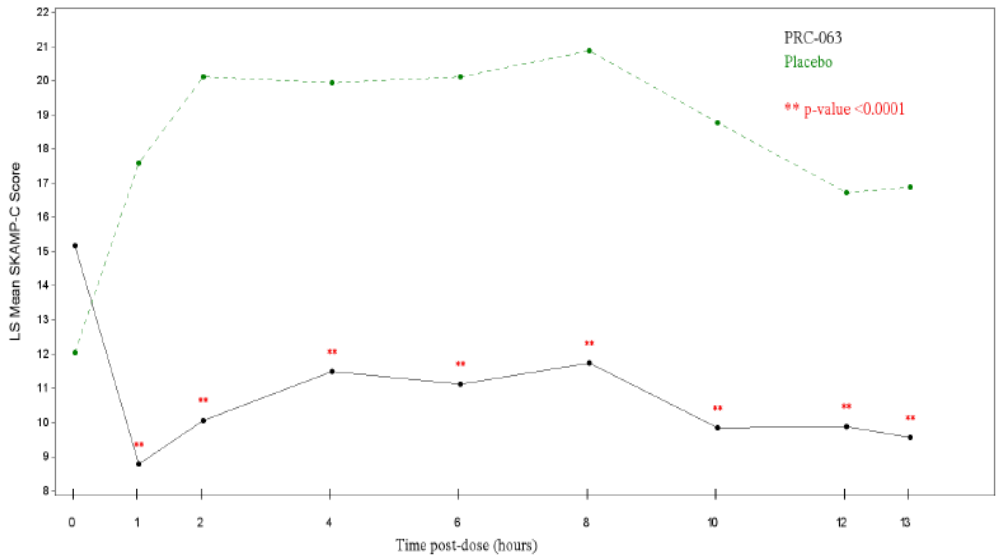
Table 13: Summary of Safety and Efficacy Studies in The Clinical Development Program of Adhansia XR in Adults and Pediatric Patients

Study Number / Country	Objectives	Treatment Doses	Study Population	No. Subjects	Study Duration	Design
Safety and Efficacy						
063-015/ USA	Primary: To assess efficacy of PRC-063 compared to placebo, as measured by the SKAMP-C score during the full day 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 full day laboratory classroom.	PRC-063 or matching placebo 25, 35, 45, 55, 70 or 85 mg	Children (6 to 12 years) with ADHD	156 enrolled	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)	A randomized, double-blind, parallel-group, placebo-controlled, dose-optimized, phase 3 study.
063-009/ USA & Canada	To evaluate the clinical efficacy and safety of PRC-063 capsules in adolescents with ADHD.	Active PRC-063 or matching placebo 25, 45, 70, or 85 mg oral capsules administered once daily in the morning	Adolescents (12 to 17 years) with ADHD	367 randomized, 323 completed	7 weeks (4 weeks of randomized double-blind treatment with either PRC-063 or placebo)	A multiple fixed-dose, randomized, parallel-group, double-blind, placebo-controlled, phase 3 study.
063-008/ USA	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.	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	Adults (18 to 60 years) with ADHD	59 randomized, 46 completed	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)	A randomized, double-blind, placebo-controlled crossover, titration to optimal dose, phase 3 study.
063-010/ USA & Canada	To evaluate the clinical efficacy and safety of PRC-063 capsules in adults with ADHD.	Active PRC-063 or matching placebo 25, 45, 70, or 100 mg oral capsules administered once daily in the morning	Adults (≥ 18 years) with ADHD	375 randomized, 333 completed	7 weeks (4 weeks of double-blind treatment with either PRC-063 or placebo)	A multiple fixed-dose, randomized, parallel-group, double-blind, placebo-controlled, phase 3 study.
063-012/ USA & Canada	To evaluate the long-term clinical efficacy and safety of PRC-063 capsules in adults and adolescents with ADHD.	PRC-063 25, 35, 45, 55, 70, 85 or 100 mg (100 mg for adults only)	Adults and adolescents with ADHD who had completed 063-009 or 063-010	363 entered, 246 completed	Up to 6 months of open-label treatment with PRC-063	A 6 month, open-label, phase 3 extension study for subjects who had completed 063-010 or 063-009.

Source: Sponsor's clinical overview Table 2.5-1

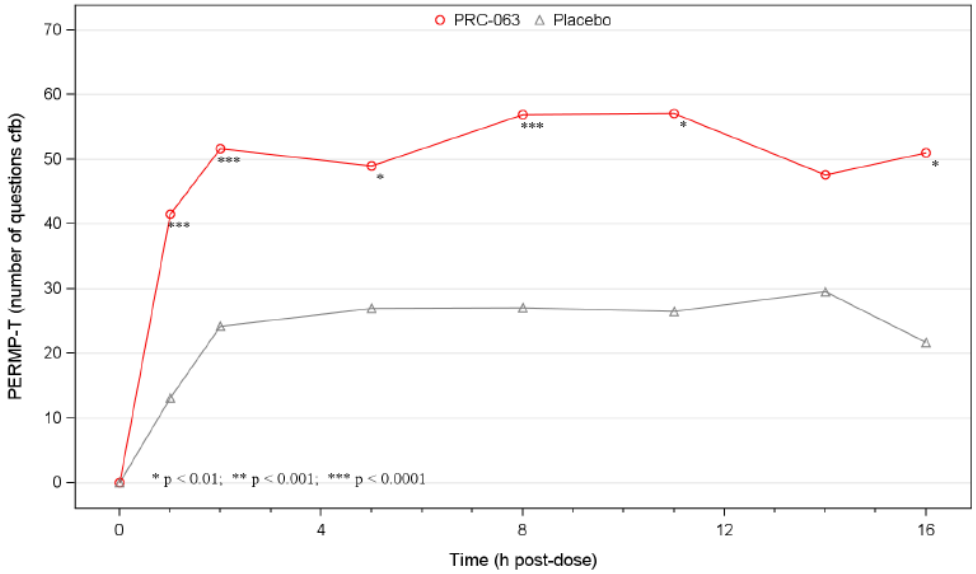
The Sponsor's efficacy results for children and adults are presented graphically Figures 4 and 5. Please refer to the medical review for the Agency's evaluation

Figure 4: SKAMP Combined Scores during the Full Day Laboratory Classroom Visit – by Time (Full Analysis Population)- Children



Source: Sponsor's summary of Clinical Efficacy Figure 2.7.3-1

Figure 5: 063-008: Mean Change from Pre-dose in Permanent Product Measure of Productivity – Total Score (Full Analysis Population) - Adults



cfb = change from baseline; PERMP-T = Mean Change from Pre-dose in Permanent Product Measure of Performance – Total Score.

Source: Sponsor's summary of clinical efficacy Figure 2.7.3-3

Table 14 contains summary of the efficacy results per the Sponsor's analysis. Please refer to the medical review for the Agency's analysis.

Table 14: Primary Results from the Efficacy Studies

Study	Age range (years)	Primary endpoint	Treatment	N	LS mean (SE) Baseline	LS mean (SE) Primary Analysis	LS mean (SE) Change from Baseline	LS mean difference (95% CI)	Treatment p-value
063-015	6–12	SKAMP-C (all laboratory classroom time points after 1 week DB treatment)	PRC-063	74	15.2 (1.08)	10.3 (0.74)	-2.7	-8.6 (-10.6, -6.6)	<0.0001
			Placebo	73	12.0 (1.07)	18.9 (0.73)	5.9		
063-009	12–17	Clinician-rated ADHD-5-RS (end of 2 weeks DB treatment)	PRC-063	258	37.0 (8.44)[a]	22.1 (12.19)[a]	-15.17	-4.2 (-7.2, -1.2)	0.0067
			Placebo	66	37.3 (8.40)[a]	26.2 (13.81)[a]	-10.98		
063-008	18–58	PERMP-T (all AWE time points after 1 week DB treatment)	PRC-063	45	224.0 (10.69)	268.7 (11.24)	-	13.05 (3.88, 22.23)	0.0064
			Placebo	45	235.0 (9.78)	255.6 (10.87)	-		
063-010	18–72	ADHD-5-RS (end of 2 weeks DB treatment)	PRC-063	297	36.3 (7.68)[a]	21.8 (11.97)[a]	-14.49	-4.7 (-7.7, -1.6)	0.0026
			Placebo	78	35.7 (8.42)[a]	26.1 (11.99)[a]	-9.82		
063-013	19–35	TDQ score (across driving simulator day after 21 days DB treatment)	PRC-063	44	-	99.9 (1.84)	-	-0.3 (-2.4, 1.8)	0.793
			LDX	44	-	100.1 (1.84)	-		
063-012		ADHD-5-RS (Month 6)[b]							
	12-17	Adolescents	PRC-063	123	36.4 (9.39)[a]	14.3 (10.08)[a]	-	-22.0 (-24.0, -20.1)[c]	<0.0001[c]
	18-66	Adults	PRC-063	124	36.1 (7.38)[a]	11.3 (7.56)[a]		-24.8 (-26.6, -23.0)[c]	<0.0001[c]

ADHD-5-RS = ADHD Rating Scale, DSM-5 Version; AWE = Adult Workplace Environment; CI = confidence interval; DB = double-blind; LDX = lisdexamfetamine dimesylate; LS = least squares; PERMP-T = Permanent Product Measure of Performance – Total Score; SE = standard error; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined Score; TDQ = Tactical Driving Quotient.

Source: Sponsor's summary of clinical efficacy Table 2.7.3-12

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. No studies in renal and hepatic impaired patients were included in this 505(b)(2) application

Applicable information in the approved labels for Ritalin IR and Concerta ER (reference drugs) will be included in the Adhansia XR label.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No, there was no significant food-drug interaction. Adhansia XR can be administered with or without food. The contents of Adhansia XR can be sprinkled on apple sauce or yogurt and swallowed.

No new drug interaction studies were conducted for this 505(b)(2) application. The drug interaction information in the labels for the reference drugs is appropriate to be included in the label for Adhansia XR. The methylphenidate in the controlled release portion of Adhansia XR is [redacted](b) (4), cautionary information about administering with pH modulators will be added to the drug interaction section of the label.

The Sponsor conducted a pharmacokinetic study comparing the effect of high fat, high caloric meal (FDA breakfast, 800 – 1000 calories) on the absorption of methylphenidate after a single

dose administration of Adhansia XR. The 90% CI around the mean ratio for the total exposures (AUC0-t, AUC0-inf) and Cmax to racemic methylphenidate after administration of Adhansia XR with food and under fasting conditions was within the regulatory criteria of 80% to 125%. The partial AUCs were also within the 80% to 125% except AUC_{0-4} and AUC_{8-12} There is no significant difference in the two methods of administration (Figure 1, Table 15). Median Tmax was delayed about 1 hour after administration under fed compared to fasting conditions. The difference in $pAUC_{0-4}$ and $pAUC_{8-12}$ is not expected to be clinically meaningful.

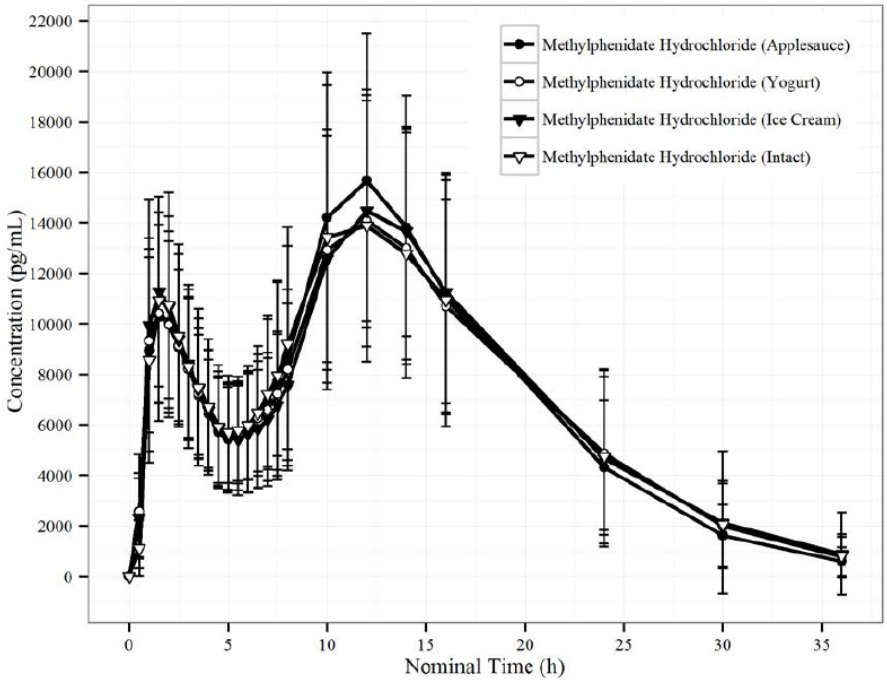
Table 15: Ratios, 90% geometric confidence intervals (CI) for AUC0-t, AUC0-inf, Cmax and partial AUCs for d,l-methylphenidate

Parameter	Treatment Comparisons	Ratio	90% CI Lower	90% CI Upper
AUC_{0-t}	Treatment B-A	97.45%	92.54%	102.62%
AUC_{0-inf}		101.87%	97.11%	106.87%
Cmax		87.49%	80.88%	94.63%
AUC_{0-4}		86.89%	78.71%	95.93
AUC_{4-8}		116.14%	107.67	125.29
AUC_{8-12}		86.25%	77.13%	96.45
AUC_{12-16}		92.67%	84.19%	102.00%
AUC_{12-t}		102.13	93.67%	111.35%

Treatment A: Adhansia XR 100 mg under fasting conditions; Treatment B: Adhansia XR 100 mg under fed conditions. Source: Study 063-004 and supplement

The Sponsor evaluated the effect of sprinkling the contact of Adhansia XR onto applesauce, yogurt or ice cream and showed that there is no significant difference in absorption of methylphenidate. Since methylphenidate is recommended to be administered in the morning and the possible health implications, we recommended that ice cream should not be used as a vehicle for administering sprinkled methylphenidate. Median Tmax was delayed 1-2 hours after sprinkling on applesauce, yogurt or ice cream compared to when it was swallowed intact. Figure 6 is the mean plasma concentration time profile for racemic methylphenidate after sprinkling the contents of Adhansia XR capsule on applesauce, ice cream and yogurt before swallowing it.

Figure 6: Mean Concentration-Time Profile for Racemic (d,l-) Methylphenidate for Each Treatment



Source: Study 063-005

Table 11: Ratios, 90% Geometric Confidence Intervals for AUC_{0-t}, AUC_{0-inf}, and Cmax for Racemic (d,l-) Methylphenidate

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	90% Geometric C.I.[2] Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test(A) - Reference(D)	98.92%	95.42%	102.56%	8.15%	31.32%
	Test(B) - Reference(D)	98.74%	95.23%	102.37%		
	Test(C) - Reference(D)	101.16%	97.58%	104.87%		
AUC_{0-inf}	Test(A) - Reference(D)	98.13%	94.70%	101.68%	8.04%	32.19%
	Test(B) - Reference(D)	98.69%	95.23%	102.27%		
	Test(C) - Reference(D)	101.55%	98.00%	105.22%		
C_{max}	Test(A) - Reference(D)	108.35%	100.03%	117.36%	18.16%	27.29%
	Test(B) - Reference(D)	100.15%	92.44%	108.49%		
	Test(C) - Reference(D)	105.68%	97.57%	114.46%		

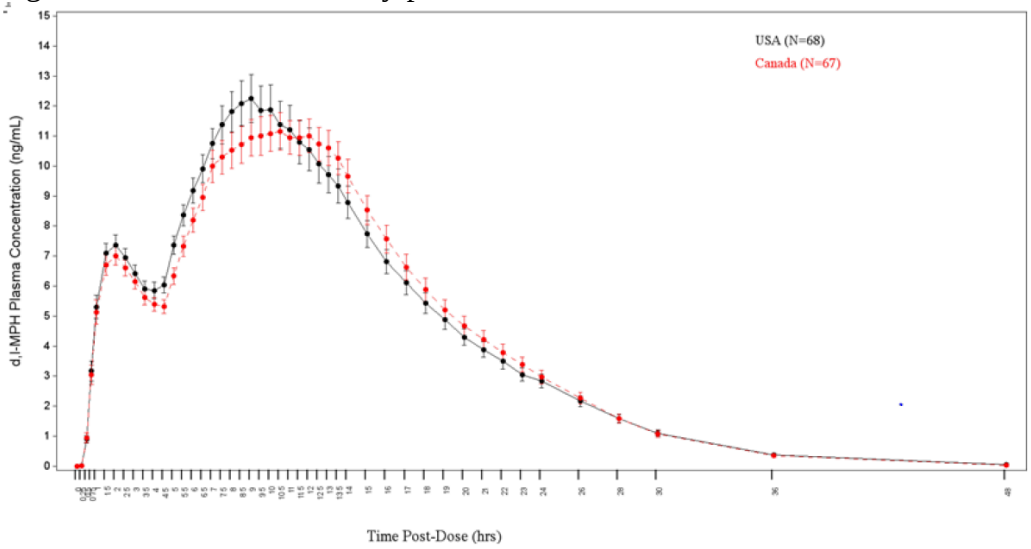
[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Treatment A: sprinkled on applesauce; Treatment B: sprinkled on yogurt; Treatment C: sprinkled on ice-cream; Treatment D: intact under fasting conditions
Source: Study 063-005

The Sponsor demonstrated that “to-be-marketed” formulation manufactured in USA is bioequivalent to the clinical trial formulation manufactured in Canada.

The Sponsor conducted a comparative bioavailability to evaluate manufacturing site change for Adhansia XR. The clinical trial formulations were manufactured in Canada but the “to-be-marketed” formulation will be manufactured in USA. Figure 7 shows the mean concentration time profile for methylphenidate after administration of 85 mg of Adhansia XR manufactured in USA versus that made in Canada.

Figure 7: Mean ±SD d,l-Methylphenidate Plasma Concentration Time Profiles



Source: Study 063-18

Table 16 present the bioequivalence statistical analysis for combined d,l-Methylphenidate between 85 mg capsules manufactured in the USA and Canada.

Table 16: Statistical Analysis for d,l-Methylphenidate

	Geometric LS Mean		LS Mean Ratio (Test/Ref)		
Pharmacokinetic Parameters	**USA (Test)**	**Canada (Ref)**	**Estimate**	**%CV**	**90% CI**
C_{max} (ng/mL)	12.62	12.23	1.03	17.1	(0.98, 1.09)
$AUC_{0\text{-}inf}$ (h*ng/mL)	180.83	180.53	1.00	7.0	(0.98, 1.02)
$AUC_{0\text{-}3}$ (h*ng/mL)	14.63	13.52	1.08	19.9	(1.02, 1.15)
$AUC_{3\text{-}7}$ (h*ng/mL)	29.21	26.28	1.11	10.6	(1.08, 1.15)
$AUC_{7\text{-}t}$ (h*ng/mL)	134.01	137.79	0.97	8.5	(0.95, 1.00)

CI = confidence interval; %CV = coefficient of variation; LS = least squares; Ref = reference; USA = United States of America

Source: Study 063-18

The exposures (Cmax, AUC and pAUCs) were equivalent, therefore, the change in manufacturing site should not have significant effect of the exposures to methylphenidate. The Agency's product specific guidance recommends the pAUCs evaluated based on the shape of the pharmacokinetic curve and duration of Concerta extended release capsules. For this comparison, the recommended pAUCs for Concerta was used and are reasonable. Additional pAUCs or new pAUCs may be needed in future since the shape is different and duration of effect after Administration of Adhansia XR is longer compared to Concerta.

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/s/

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