Office of Clinical Pharmacology Review

NDA#/eCTD:	205831/0065
NDA Type:	Priority
Related IND:	IND104483
Brand Name:	APTENSIO XR®
Generic Name:	Methylphenidate Hydrochloride
Dosage Form:	Capsule
Dosage Strength (mg):	10, 15, 20, 30, 40, 50 and 60
Indications:	ADHD
Sponsor:	Rhodes Pharmaceuticals
Submission Type:	PREA PMR Study Report
Submission Date:	April 11, 2018
OCP Division:	Division I
OND Division:	Division of Psychiatry Product
OCP Review Team:	Di Zhou, PhD, Reviewer; Luning (Ada) Zhuang, PhD, Team Leader

Executive Summary

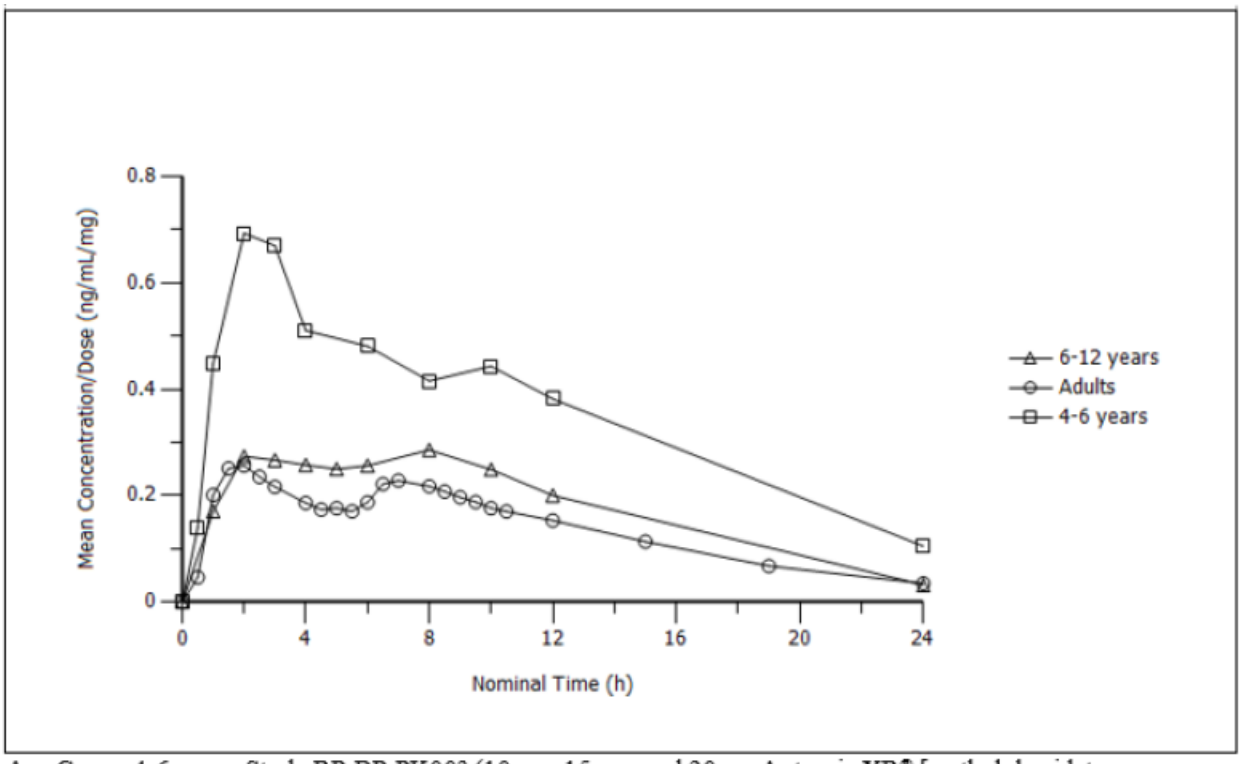
Rhodes Pharmaceuticals, Inc. conducted a pediatric pharmacokinetic study in order to fulfil the post-marketing requirement (#PMR 2899-2) and submitted the study report on April 11, 2018 under NDA 205318. APTENSIO XR® was approved by the FDA on April 17, 2015 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). As described under PMR 2899-2 in the FDA approval letter, one of the required post-marketing studies was "A single-dose, open-label, randomized pharmacokinetic study of Aptensio XR capsules in male or female children (4 to less than 6 years of age) with ADHD in fed condition."

OCP reviewed the study report and has determined that the reported study has fulfilled the pharmacokinetic study requirement for #PMR 2899-2. The PK features in pediatric patients 4 to under 6 years as compared to pediatric patients 6-12 years and adults 18-25 years are summarized below and in Figure 1 and Table 1.

- The overall exposures (AUC0-inf and AUC0-t) increased by 2-3 fold in pediatric patients 4 to under 6 years compared with adults and pediatric patients 6-12 years.
- An approximately 2-fold increase in Cmax was also observed in pediatric patients 4 to under 6 years as compared to adults and pediatric patients 6-12 years.
- Tmax to reach the first peak across different populations are similar (2-3 hrs). Longer half-life was observed in pediatric patients 4 to under 6 years compared with adults and pediatric patients 6-12 years.
- Time to reach the second peak was observed at approximately 10 to 12 hours, which was delayed, compared with adults and pediatric patients 6 to 12 years of age (~ 8 hours)

In addition, based on the safety findings from clinical studies, the increased exposure and delayed time to reach the second peak concentration appears to explain the high degree of insomnia and decreased appetite observed in these patients.

Figure 1 Mean Dose-normalized Methylphenidate Plasma Concentration vs. Time Profiles Across Age Groups



Age Group 4-6 years: Study RP-BP-PK003 (10 mg, 15 mg, and 20 mg Aptensio XR® [methylphenidate hydrochloride] ER capsules)
Age Group 6-12 years: Study 022-001 (20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 80 mg Biphentin® CR [methylphenidate HCl] controlled-release capsules)
Adults (aged 18-45 years): Study RP-BP-PK001 (T1, 80 mg Biphentin® CR [methylphenidate HCl] extended-release capsules)

Adopted from IR response submitted by the sponsor on Feb 22nd, 2019

Table 1 Summary of Dose-Normalized Pharmacokinetic Parameters Following Administration of Aptensio XR in Pediatric Patients 4 to Under 6 Years, 6-12 Years and Adults 18-25 Years.

	Pediatric Patients 4 to Under 6 Years				Pediatric Patients 6-12 Years	Adults 18-25 Years
Parameter	**10 mg (N=5)**	**15 mg (N=3)**	**20 mg (N=2)**	**Total (N=10)**	**20, 30, 40, 50, 60 and 80 mg (N=18)**	**20 mg (N=20)**
Cmax/Dose (ng/mL) Mean±SD	0.81 ± 0.17	0.67±0.04	0.77±0.05	0.76 ±0.13	0.35±0.16	0.31±0.09
AUCinf/Dose (hr*ng/mL) Mean±SD	10.53 ± 2.18	9.38±NE	7.21±NE	9.63 ±2.11	4.50±2.39	3.52±1.50
AUC0-t/Dose (hr*ng/mL) Mean±SD	8.92 ± 2.50	7.90±1.21	7.80±1.76	8.39±1.94	4.23±2.29	3.29±1.35
Tmax (h) Median	2.0	3.0	2.0	2.5	2.5	2.0
T1/2 (h) Mean±SD	4.80 ± 0.46	12.69 ±NE	6.98 ±NE	6.81±3.44	5.07± 1.47	5.04±1.46

*Tmax: time to reach the first peak

Based on these findings, the Office of Clinical Pharmacology recommends the following labeling concepts be included under section 12.3 in the final package insert:

Age

The pharmacokinetics of methylphenidate after APTENSIO XR administration was studied in pediatric patients with ADHD between 4 and 12 years of age. Following administration of APTENSIO XR, the bi-phasic plasma methylphenidate concentrations profile was similar in healthy adult volunteers and pediatric patients with ADHD between 6 to 12 years of age. In pediatric patients with ADHD ages 4 to under 6 years, following oral administration of APTENSIO XR administered as sprinkle over apple sauce, there was a 2- to 3- fold increase in exposure (Cmax and AUC) to methylphenidate. The initial maximum plasma methylphenidate concentrations were observed at 2 to 3 hours, followed by gradual descending concentrations over the next 7 to 8 hours, after which a gradual increase begins, reaching a second peak at approximately 10 to 12 hours, which was delayed, compared with adults and pediatric patients 6 to 12 years of age.

Appendix: Review for Individual Study Reports

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CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report #: RP-BP-PK003	**Study Period:** 30-Jul-2016 to 20-Jul-2017
NDA 205831	**Link: \\CDSESUB1\evsprod\NDA205831\0061\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\rp-bp-pk003**
Title	A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules in Male or Female Preschool Children 4 to Under 6 Years of Age with Attention Deficit Hyperactivity Disorder in Fed Condition
Objectives:	To assess methylphenidate pharmacokinetics following a single oral dose of Aptensio XR (methylphenidate hydrochloride) Extended-Release capsules (methylphenidate 10 mg, 15 mg, 20 mg, 30 mg or 40 mg), under fed conditions in male or female children 4 to under 6 years of age with ADHD.

Study Design: This was a single-dose, open-label, one-period, multi-center study in which ten (10) subjects, previously diagnosed with ADHD, received a single oral dose (sprinkled over apple sauce) of Aptensio XR® (methylphenidate hydrochloride). This dose was equivalent to their current total daily methylphenidate dose and was administered under fed conditions. The maximum daily dose in this study did not exceed 20 mg/day.

Patients who met the inclusion criteria, and did not met any exclusion criteria, were instructed to discontinue their current methylphenidate medication for a minimum of 5 days prior to dosing.

Subjects may have been eligible for participation in a 12-month, open-label, extension study (RP-BP-EF004) of Aptensio XR® (methylphenidate hydrochloride) if they completed the end-of-study visit and did not have adverse events (AEs) that suggested poor tolerability to Aptensio.

Administration	Oral
Sampling Times	PK: Blood samples for determination of plasma concentrations of methylphenidate were collected at pre-dose (0 hour) and post-dose at and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours.
PK Parameters	The following pharmacokinetic parameters were calculated: peak concentration in plasma (Cmax), time to peak concentration (Tmax), elimination rate constant (Kel), terminal half-life (T1/2), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC0-t), area under the concentration-time curve from time-zero to 4 hours post-dose (AUC0-4), area under the concentration-time curve from 4 hours to 8 hours post-dose (AUC4-8), area under the concentration-time curve from 8 hours to 12 hours post-dose (AUC8-12), area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC0-inf), apparent clearance (CL/F), and apparent volume of distribution (Vdss/F). Additionally, Cmax, AUC0-t, and AUC0-inf were dose-normalized and CL/F and Vd/F were weight-normalized.
PD Endpoint(s)	NA
PD Parameters	NA
Safety Measures	Safety assessments included adverse events, physical examinations, 12-lead ECGs, vital signs, and blood counts at screening and after treatment with study medication.
Statistical Analysis	
Analytical Method	

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Methylphenidate		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Notes:

Results

Study Population

Table 1 Subject Disposition

		Pre-Treatment	Treatment Phase			
Parameter	Statistics	All Subjects	Methylphenidate 10 mg	Methylphenidate 15 mg	Methylphenidate 20 mg	Total
Number of Subjects Screened	n	10	5	3	2	10
Number of Screen Failures [1]	n	0	NA	NA	NA	NA
Number of Subjects Enrolled	n	10	5	3	2	10
Number of Subjects Who Received Study Drug (Safety Population) [2]	n	10	5	3	2	10
Number of PK Population Subjects [3]	n	10	5	3	2	10
Number of Subjects Who Completed the Study	n	10	5	3	2	10
Number of Subjects Who Terminated the Study Early [4]	n	0	0	0	0	0

Note: [1] The number of screen failures was used as the denominator for percentage calculation of reasons for screen failure.
[2] The 'Safety Population' is defined as all subjects who received at least one dose of study medication.
[3] The 'PK Population' is defined as all safety subjects for whom a pharmacokinetic sample was obtained and analyzed.
[4] The number of early terminations was used as denominator for percentage calculation of reasons for early termination.

Table 2 Summary of demographics

Parameter	Statistics	Methylphenidate 10 mg (N=5)	Methylphenidate 15 mg (N=3)	Methylphenidate 20 mg (N=2)	Total (N=10)
Age at Baseline (Months)	Mean (SD)	61.0 (8.03)	63.3 (5.51)	70.5 (0.71)	63.6 (7.06)
	Median	64.0	63.0	70.5	65.0
	Min, Max	49, 69	58, 69	70, 71	49, 71
Sex Male	n (%)	4 (80.0)	2 (66.7)	1 (50.0)	7 (70.0)
Female	n (%)	1 (20.0)	1 (33.3)	1 (50.0)	3 (30.0)
Race White/Caucasian	n (%)	0	1 (33.3)	1 (50.0)	2 (20.0)
Black or African American	n (%)	4 (80.0)	1 (33.3)	1 (50.0)	6 (60.0)
Other Black/Hispanic	n (%)	1 (20.0)	1 (33.3)	0	2 (20.0)
Ethnicity Hispanic or Latino	n (%)	1 (20.0)	1 (33.3)	1 (50.0)	3 (30.0)
Not Hispanic or Latino	n (%)	4 (80.0)	2 (66.7)	1 (50.0)	7 (70.0)
Prior Methylphenidate treatment was discontinued 5 days prior to PK dosing (Yes)	n (%)	5 (100)	3 (100)	2 (100)	10 (100)
Height (cm)	Mean (SD)	113.4 (4.51)	113.0 (4.36)	118.0 (1.41)	114.2 (4.18)
	Median	116.0	115.0	118.0	116.0
	Min, Max	108, 117	108, 116	117, 119	108, 119
Weight (kg)	Mean (SD)	19.7 (1.76)	19.6 (2.65)	21.3 (3.68)	20.0 (2.22)
	Median	19.6	20.6	21.3	20.1
	Min, Max	17.7, 22.1	16.6, 21.6	18.7, 23.9	16.6, 23.9
BMI (kg/m^2)	Mean (SD)	15.3 (0.55)	15.3 (0.98)	15.3 (2.26)	15.3 (0.96)
	Median	15.2	15.6	15.3	15.4
	Min, Max	14.6, 16.1	14.2, 16.1	13.7, 16.9	13.7, 16.9
Hepatitis C Antibody Negative	n (%)	5 (100)	3 (100)	2 (100)	10 (100)
Human Immunodeficiency Virus (HIV) Negative	n (%)	5 (100)	3 (100)	2 (100)	10 (100)

Results

Table 3 Pharmacokinetic Parameters of Methylphenidate

Parameter	Methylphenidate 10 mg (n=5)				Methylphenidate 15 mg (n=3)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max}[a] (h)	5	2.00 (1.0, 3.0)			3	3.00 (3.0, 12.0)		
C_{max} (ng/mL)	5	8.07	1.702	21.891	3	10.09	0.620	6.061
C_{max}/Dose (ng/mL/mg)	5	0.81	0.170	21.891	3	0.67	0.041	6.061
AUC_{0-4} (h*ng/mL)	5	21.8	7.056	36.691	3	25.69	3.669	13.921
AUC_{4-8} (h*ng/mL)	5	19.81	3.141	15.644	3	25.72	2.715	10.735
AUC_{8-12} (h*ng/mL)	5	19.73	5.103	24.952	3	20.73	6.342	29.354
AUC_{0-t} (h*ng/mL)	5	89.18	25.047	30.150	3	118.49	18.211	14.976
AUC_{0-t}/Dose (h*ng/mL/mg)	5	8.92	2.505	30.150	3	7.90	1.214	14.976
AUC_{0-inf} (h*ng/mL)	3	105.26	21.831	19.971	1	140.68	NE	NE
AUC_{0-inf}/Dose (h*ng/mL/mg)	3	10.53	2.183	19.971	1	9.38	NE	NE
K_{el} (h^{-1})	3	0.15	0.015	NC	1	0.05	NE	NC
$T_{1/2}$ (h)	3	4.80	0.466	NC	1	12.69	NE	NC
CL/F (L/h)	3	97.51	18.095	19.971	1	106.63	NE	NE
V_d/F (L)	3	682.49	182.605	30.291	1	1952.17	NE	NE
CL/F/kg (L/h/kg)	3	4.88	0.942	19.955	1	5.18	NE	NE
V_d/F/kg (L/mg)	3	34.18	9.493	30.153	1	94.77	NE	NE
Dose/Weight (mg/kg)	5	0.51	0.045	8.929	3	0.78	0.112	14.104

Parameter	Methylphenidate 20 mg (n=2)				Methylphenidate Total (n=10)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max}[a] (h)	2	2.00 (2.0, 2.0)			10	2.50 (1.0, 12.0)		
C_{max} (ng/mL)	2	15.45	1.061	6.879	10	10.16	3.184	31.246
C_{max}/Dose (ng/mL/mg)	2	0.77	0.053	6.879	10	0.76	0.132	16.863
AUC_{0-4} (h*ng/mL)	2	42.01	2.929	6.987	10	27.01	9.577	38.635
AUC_{4-8} (h*ng/mL)	2	38.26	10.706	28.935	10	25.27	8.539	30.776
AUC_{8-12} (h*ng/mL)	2	28.20	9.482	35.320	10	21.72	6.507	28.624
AUC_{0-t} (h*ng/mL)	2	155.95	35.209	23.069	10	111.33	34.962	33.691
AUC_{0-t}/Dose (h*ng/mL/mg)	2	7.80	1.760	23.069	10	8.39	1.943	23.180
AUC_{0-inf} (h*ng/mL)	1	144.26	NE	NE	5	120.14	25.598	22.552
AUC_{0-inf}/Dose (h*ng/mL/mg)	1	7.21	NE	NE	5	9.63	2.112	21.328
K_{el} (h^{-1})	1	0.10	NE	NC	5	0.12	0.042	NC
$T_{1/2}$ (h)	1	6.98	NE	NC	5	6.81	3.436	NC
CL/F (L/h)	1	138.64	NE	NE	5	107.56	21.937	21.328
V_d/F (L)	1	1396.96	NE	NE	5	1079.32	592.002	59.932
CL/F/kg (L/h/kg)	1	5.80	NE	NE	5	5.13	0.776	16.252
V_d/F/kg (L/mg)	1	58.45	NE	NE	5	51.15	27.384	55.387
Dose/Weight (mg/kg)	2	0.95	0.165	17.481	10	0.68	0.205	29.827

[a] T_{max} is presented as median (minimum, maximum)
NE = Not Estimable
NC = Not calculated

Figure 1 Mean Methylphenidate Plasma Concentration Time Plots (Linear and Semi-Log Scales)

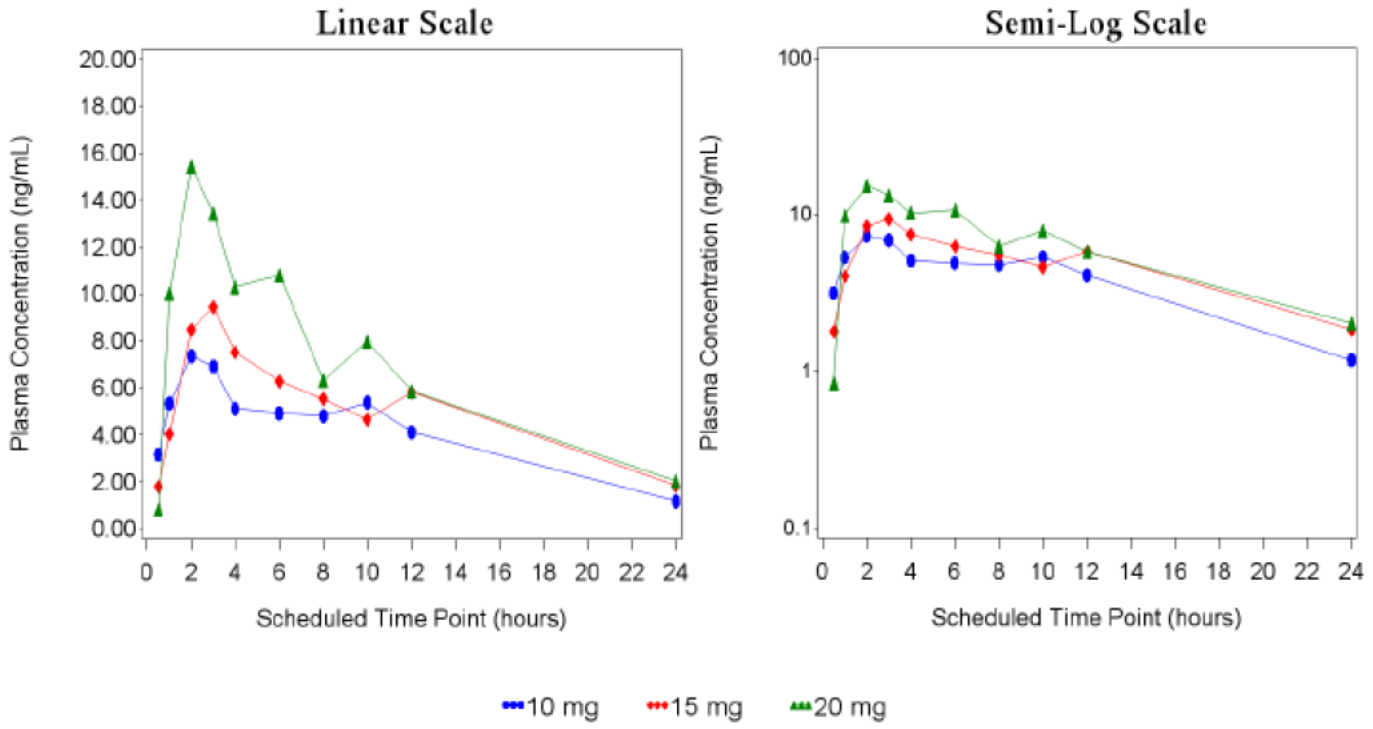


Table 4 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Methylphenidate following a Single Dose of Aptensio XR

Parameter	Comparison	Ratio[a]	90% CI of Ratio[b]
AUC_{0-t}/Dose (h*ng/mL/mg)	Methylphenidate 15 mg vs Methylphenidate 10 mg	0.91	(0.64, 1.29)
	Methylphenidate 20 mg vs Methylphenidate 10 mg	0.89	(0.60, 1.33)
AUC_{0-inf}/Dose (h*ng/mL/mg)	Methylphenidate 15 mg vs Methylphenidate 10 mg	0.90	(0.46, 1.76)
	Methylphenidate 20 mg vs Methylphenidate 10 mg	0.69	(0.36, 1.35)
C_{max}/Dose (ng/mL/mg)	Methylphenidate 15 mg vs Methylphenidate 10 mg	0.85	(0.67, 1.07)
	Methylphenidate 20 mg vs Methylphenidate 10 mg	0.97	(0.74, 1.27)

[a] Ratio(%) = Geometric Mean (Test, 15 mg and 20 mg)/Geometric Mean (Ref, 10 mg))
Geometric Means are based on Least Squares Mean of log-transformed parameter values
[b] 90% Confidence Interval (CI)

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

What is the maximum tolerated dose? 60 mg/day for patients 6 years and above

Comments

Internal Comments

1. *Study Design: The design elements are consistent with the expectations for pediatric pharmacokinetic studies.*
   Age Range: 4 to under 6 years
   Gender: the distribution of gender is not even [7 male and 3 female]. It is acceptable considering the nature of this study

Sample Size: 10
PK samples: Sufficient to cover 3 half-life of the Aptensio XR with intensive samples collected immediately postdose to evaluate Tmax, Cmax and AUC0-inf.
Compound measured: Methylphenidate

2. *Study Conduct (Protocol deviation): There were 25 protocol deviations and 6 of them are PK related. These 6 PK samples have deviated sampling time from 1-6 minutes. However, we do not anticipate that the quality of pharmacokinetic assessment will be compromised with the minor deviation of these 6 PK samples.*

3. *Data Analysis (Outlier): All patients participating in the trial were included for pharmacokinetic analysis. No outlier was identified and excluded from data analysis.*

4. *Discussion:*

Based on previous OCP review dated on 3/27/2015, at mean level, Aptensio XR pharmacokinetic profiles in adults and in pediatric patients 6-12 yrs old both show double peaks with a similar shape (as shown in Figure 2 and Table 5), with pediatric patients receiving different doses demonstrated large variability in the shape of their respective mean pharmacokinetic profiles.

The overall exposures (AUC0-inf and AUC0-t) increased by 2-3 fold in pediatric patients 4 to under 6 yrs compared with adults and pediatric patients 6-12 yrs. An approximately 2-fold increase in Cmax was also observed in pediatric patients 4 to under 6 yrs as compared to adults and pediatric patients 6-12 yrs. Tmax for the first peak across different populations are similar (2-3 hrs). In addition, longer half-life was observed in pediatric patients 4 to under 6 yrs compared with adults and pediatric patients 6-12 yrs.

However, it should be noted that Tmax for the second peak varies in pediatric patients 4 to under 6 yrs, ranging from 6-12 hours. A scrutiny of individual PK profiles of the ten subjects in the study demonstrated that the three peaks observed for the 20 mg group is due to interindividual variability. Excluding this variability, the second peak appears 10-12 hours in general, later than the ones observed in adults and pediatric patients 6-12 years (8 hours). An approximately 3-4 fold increase in the second Cmax was also observed in pediatric patients 4 to under 6 yrs as compared to adults and pediatric patients 6-12 yrs.

Based on the safety findings from the randomized, double-blind, placebo-controlled, flexible-dose titration study (RP-BP-EF003), during the 6-week open label dose optimization period, the most common adverse events were decreased appetite (18.5% of subjects), insomnia (15.1%), decreased weight (14.2%), and irritability (13.4%); all of which were considered by the Investigator to be mild or moderate in severity except for one instance of severe insomnia. During the 2-week double blind phase, the most commonly reported AEs in the Aptensio XR® group considered by the Investigator related to treatment were hypertension (7.7% of subjects), and emotional poverty, negativism, pollakiuria, onychophagia, decreased appetite hypertension, and tachycardia (2.6% each).

In the 12-month open label safety study (RP-BP-EF004, dose up to 60 mg), a total of 283 TEAEs were reported in 65 (73.0%) subjects during the maintenance phase. These TEAEs included insomnia (8 [9.0%] subjects), upper respiratory tract infection (8 [9.0%] subjects), Nasopharyngitis (10 [11.2%] subjects), weight loss (16 [18.0%] subjects), decreased appetite (16 [18.0%] subjects), upper abdominal

pain (6 [6.7%] subjects), cough (7 [7.9%] subjects), headache (5 [5.6%] subjects), hypertension (6 [6.7%] subjects) and vomiting (4 [4.5%] subjects). Overall, approximately 66% of the patients discontinued the study.

The increased exposure and delayed time to reach the second peak concentration might explain the high degree of insomnia and decreased appetite observed in these patients.

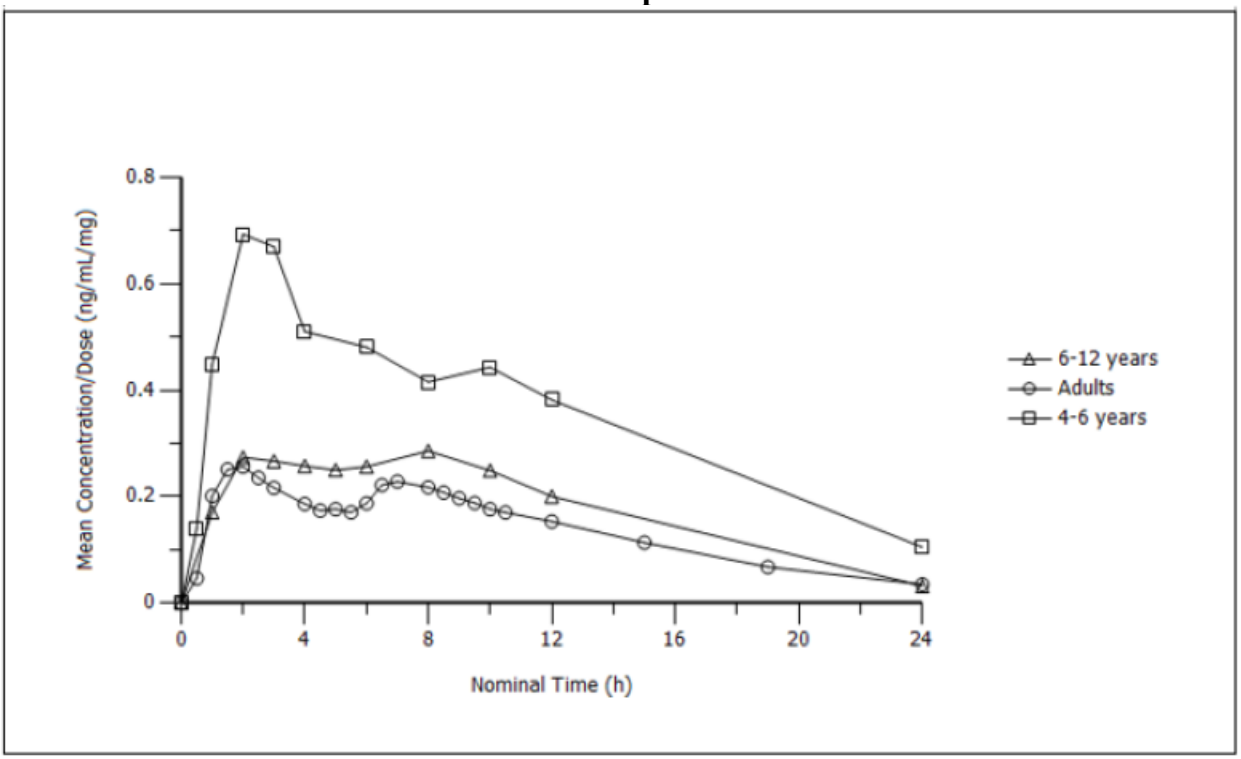
Overall, the PK study report appears to be acceptable. The final pediatric dosing strategy will rely on the safety and efficacy findings from the clinical studies.

Table 5 Summary of Dose-Normalized Pharmacokinetic Parameters Following Administration of Aptensio XR in Pediatric Patients 4 to under 6 Years, 6-12 Years and Adults 18-25 Years.

	Pediatric Patients 4 to under 6 Years				**Pediatric Patients 6-12 Years**	**Adults 18-25 Years**
Parameter	**10 mg (N=5)**	**15 mg (N=3)**	**20 mg (N=2)**	**Total (N=10)**	**20, 30, 40, 50, 60 and 80 mg (N=18)**	**20 mg (N=20)**
Cmax/Dose (ng/mL) Mean±SD	0.81 ± 0.17	0.67±0.04	0.77±0.05	0.76 ±0.13	0.35±0.16	0.31±0.09
AUCinf/Dose (hr*ng/mL) Mean±SD	10.53 ± 2.18 (N=3)	9.38±NE (N=1)	7.21±NE (N=1)	9.63 ±2.11 (N=5)	4.50±2.39	3.52±1.50
AUC0-t/Dose (hr*ng/mL) Mean±SD	8.92 ± 2.50	7.90±1.21	7.80±1.76	8.39±1.94	4.23±2.29	3.29±1.35
***Tmax (h) Median**	2.0	3.0	2.0	2.5	2.5	2.0
T1/2 (h) Mean±SD	4.80 ± 0.46 (N=3)	12.69 ±NE (N=1)	6.98 ±NE (N=1)	6.81±3.44 (N=5)	5.07± 1.47	5.04±1.46

*Tmax: time to reach the first peak

Figure 2 Mean Dose-normalized Methylphenidate Plasma Concentration vs. Time Profiles Across Age Groups



Age Group 4-6 years: Study RP-BP-PK003 (10 mg, 15 mg, and 20 mg Aptensio XR® [methylphenidate hydrochloride] ER capsules)
Age Group 6-12 years: Study 022-001 (20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 80 mg Biphentin® CR [methylphenidate HCl] controlled-release capsules)
Adults (aged 18-45 years): Study RP-BP-PK001 (T1, 80 mg Biphentin® CR [methylphenidate HCl] extended-release capsules)

Adopted from IR response submitted by the sponsor on Feb 22nd, 2019

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

/s/

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