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CLINICAL PHARMACOLOGY STUDY PROTOCOL

A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release capsules in Male or Female Pre-School Children 4 to Under 6 years of age with ADHD in Fed Condition

No. RP-BP-PK003, v2.0

VERSION DATE

13 February, 2018

A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules in Male or Female Pre-School Children 4 to Under 6 years of age with ADHD in Fed Condition

Protocol Number: RP-BP-PK003, v2.0

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INVESTIGATOR'S AGREEMENT

I have read the protocol:

RP-BP-PK003: A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules in Male or Female Pre-School Children 4 to Under 6 years of age with ADHD in Fed Condition.

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the trial, without written authorization from Rhodes Pharmaceuticals. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the trial in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that the Sponsor may decide to suspend or prematurely terminate the trial at any time for any reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial, I will communicate my intention immediately in writing to the Sponsor.

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A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules in Male or Female Pre-School Children 4 to Under 6 Years of Age with ADHD in Fed Condition

KEY STUDY PERSONNEL

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A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release, Capsules in Male or Female Pre-School Children 4 to Under 6 Years of Age with ADHD in Fed Condition

STUDY FACILITIES

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PROTOCOL SYNOPSIS

Protocol #:	RP-BP-PK003 Version 2.0
Compound:	Methylphenidate Hydrochloride
Study Title:	A Pharmacokinetic Study of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules in Male or Female Pre-School Children 4 to Under 6 Years of Age with ADHD in Fed Condition
Study Objectives:	To assess the pharmacokinetics of a single dose of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release capsules under fed conditions in male or female children 4 to under 6 years of age with ADHD.
Approximate Number of Subjects Screened:	60
Number of Subjects to Complete	Ten (10)
Study Design, Duration of Treatment:	This will be a multi-center, open-label, single-dose, study to assess the pharmacokinetics of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release capsules in male and female children 4 to under 6 years of age with ADHD in fed condition.
Dosage	10, 15, 20, 30, and 40 mg capsules
Study Duration:	Approximately: 1 year, including screening period and treatment period
Inclusion Criteria:	1. Patient is a male or female between the ages of 4 and under 6 years old. 2. Patient has a history consistent with ADHD, meets the DSM-IV criteria for ADHD, inattentive, hyperactivity or combined. 3. Patient must meet criteria for ADHD diagnosis on KSADS-PL and clinical interview by experienced clinician; symptoms must have been present for at least 6 months. 4. Subject has had prior behavioral treatment or subject's symptoms are severe enough to warrant treatment without prior behavioral treatment, and patient is on a stable dose of either immediate-release or extended-release methylphenidate. 5. Subject must have age- and sex-adjusted ratings of ≥ 90th percentile Total Score on the ADHD-RS-IV Preschool Version, a Clinical Global Impressions -Severity Score of ≥4 and a Child Global Assessment Scale rating of <65 after methylphenidate washout and prior to obtaining pharmacokinetic samples. Ratings may be completed via telephone on day-1. 6. Parents or guardians of patients must have the ability to read and understand the language in which the Informed Consent is written and are mentally and physically competent to provide written informed consents for their child. 7. Patient and/or parent are/is able to understand English in order to provide assent and is otherwise able to comply with the study protocol.

Exclusion Criteria:	1. Patient has allergy to methylphenidate or amphetamines, or history of serious adverse reaction to methylphenidate. 2. Patient has a history of tension, agitation, glaucoma, thyrotoxicosis, tachyarrythmias or severe angina pectoris or patient with serious or unstable medical illness such as asthma, diabetes, or seizures. 3. A history of motor or vocal tics or Tourette's syndrome 4. Patient is receiving MAO inhibitors, anticonvulsants (phenobarbital, phenytoin, primidone), coumarin anticoagulants, presser agents guanethidine, tricyclic antidepressants (imipramine, desipramine, selective serotonin inhibitors (SSRIs), or herbal remedies (e.g., melatonin). 5. Patient has serious hypertension. 6. Patient has a history of disorders of the sensory organs, particularly deafness, severe or profound retardation. 7. Patient has any other unstable psychiatric condition requiring treatment. 8. Patient is at risk for substance abuse. 9. Evidence of current physical, sexual, or emotional abuse 10. Living with anyone who currently abuses stimulants or cocaine 11. History of bipolar disorder in both biological parents
Study Procedures:	Screening Procedures: After obtaining written informed consent from parents, subjects will undergo a complete medical and medication history, demographic data (including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), physical examination, vital signs evaluation (sitting blood pressure, pulse rate, respiration rate, temperature and pulse oximetry), resting 12-lead electrocardiogram (ECG), clinical laboratory tests and concomitant medication within 28 days prior to receiving study drug. On Day 1: subjects will receive a single oral dose of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release.
Confinement and Visits;	Subject will be confined in a play school setting for at least 12 hours after dosing after first blood draw. Subjects will return for all subsequent blood draws.
Washout	Medication discontinued 5 days prior to dosing (i.e., no dose on Day -5)
Sample Collection, Processing, and Storage	A local, topical anesthetic (2.5% lidocaine and 2.5% prilocaine cream) will be applied at the catheter insertion site. Serial Blood samples will be obtained via a catheter placed in the antecubital vein in subject's forearm. Subjects will be distracted which includes listening to songs during catheter insertion and PK sampling. Serial blood samples for determination of methylphenidate plasma concentration and PK analysis will be obtained on Day 1 at time 0 (within 15-30 minutes pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose in K_2EDTA Vacutainer tubes. The blood samples will be processed immediately by centrifugation, and the plasma samples will be stored at approximately -20°C before frozen shipment on dry ice and shipped to Bioanalytical CRO (Worldwide Clinical Trials). Samples will remain frozen until assayed.
Bioanalytical Analysis:	Plasma samples will be analyzed by high-performance liquid chromatography/mass spectrometry (LC/MS) to determine the concentrations of methylphenidate.
Subject Safety	Vital signs, ECG, medical history, physical examination, and clinical laboratory tests within 28 days prior to receiving drug.
Study Exit Procedures	Vital signs, ECG, brief physical examination, laboratory tests, concomitant medications, and adverse events (AEs)

Study Endpoints:	The primary PK endpoints include • Maximum plasma methylphenidate concentration (Cmax) and dose normalized (Cmax/Dose) • Area under the plasma concentration versus time curve calculated to the last measurable observation (AUC0-t) and dose normalized (AUC0-t/Dose) • Area under the plasma concentration versus time curve extrapolated to infinity (AUC0-inf) and dose normalized (AUC0-inf/Dose) • Apparent clearance (CL/F, where F is fraction of dose determined by bioavailability) and weight normalized (CL/F/Kg) using screening weight • Apparent volume of distribution (Vd/F) and weight normalized Vd/F/Kg using screening weight • Dose and weight normalized dose (mg/kg) The secondary PK endpoints include • Time to Cmax (tmax); • Elimination half-life (t½) • Terminal elimination rate constant (Kel) • AUC0-4 • AUC4-8 • AUC8-12
Statistical Analyses:	Statistics will be conducted on PK parameters. The arithmetic mean (SD) for C_{max}, AUC, half-life, K_{el} and median T_{max} will be calculated. The SAP is attached.
Safety Plan:	During treatment, investigators will actively solicit reports of adverse events that will be recorded and assessed for severity and relationship to study medication. Safety assessments will include physical examinations, vital signs and blood counts at screening and after management with study medication. Vital signs will be assessed pre-dose, and then at specified hours.
Adverse Events	The safety and tolerability of methylphenidate, as assessed by incidence of treatment emergent adverse events (AEs) will be monitored by nursing and medical staff throughout the study and will be recorded
Concomitant Medication:	No other CNS stimulant other than the test medication specifically indicated for the treatment of ADHD will be administered during the course of study. Any concomitant medication will be recorded
Scientific and Ethical Guidelines	This study will be conducted according to the protocol, current ICH and GCP guidelines, the "Declaration of Helsinki" (2008) and all applicable Federal and local government regulations and Institutional research policies and procedures.
IRB Approval	The study will be conducted with the approval of a duly constituted institutional review board (IRB) or ethics committee (EC) in accordance with the requirement of 21 CFR 56 - Institutional Review Boards.

1 INTRODUCTION

1.1 Attention Deficit Hyperactivity Disorder Overview:

Disturbances in attention regulation and activity modulation are perhaps the most common psychiatric disorders in children[1] with reported rates ranging from 4%[2] to 9%.[3] It is four to five times more frequent in boys than girls.[4] Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD).[1]

Children affected by ADHD commonly exhibit disruptive behavior in the classroom, underachieve academically, and tend to have conflictual relations with family members and peers.[5] They experience an inability to sit still and pay attention in class and the negative consequences of such behaviour.[6] Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills.[4] Their academic and social difficulties have far-reaching and long term consequences.[6] For many individuals, the impact of ADHD continues into adulthood.[6]

The DSM-IV defines ADHD as a persistent pattern of inattention/hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.[7] the exact cause of ADHD is not clear, although brain-imaging studies have suggested that the pre-frontal cortex and the basal ganglia are involved. These areas are responsible for "editing" one's behavior and resisting distractions.[8, 9] Other factors include premature birth, maternal alcohol and tobacco use, exposure to lead in early childhood and brain injuries – especially those that involve the prefrontal cortex.[8] Although minimal degrees of head trauma may result in ADD, for the most part, children with ADD do not show evidence of a history of insult.[1]

The mode of therapeutic action of stimulants in ADHD is not completely understood. There is some evidence suggesting that the mechanism whereby methylphenidate produces its mental and behavioral effects is related to a dose-dependent blockade of the dopamine transporter and an increase in extracellular dopamine.[10, 11, 12, 13, 14] Methylphenidate is a racemic mixture comprised of the d- and l-isomers. Only the d-isomer possesses motor stimulant effects.[15]

Methylphenidate should be administered starting at the lowest possible dose. The recommended starting dose of methylphenidate immediate-release tablet in children and adolescents is 5-10 mg three times daily with weekly increments of 5 to 10 mg in the daily dosage. In adults, the daily dosage with the immediate-release tablet ranges between 10 and 60 mg, with an average of 20 to 30 mg. The recommended starting dose of methylphenidate extended-release capsule in adults is 10 to 20 mg once daily and dosage may be adjusted to a maximum of 80 mg taken once daily. Adverse events associated with the use of immediate-release methylphenidate are listed in the product monograph.[16]

Methylphenidate formulations are rapidly absorbed and reach peak (C_{max}) values within 1 to 3 hours following oral ingestion (Ritalin® Label, Concerta® Label, Metadate® Label and Quillivant™ Label).[16, 17, 18, 19] Extended-Release (ER) methylphenidate formulations usually produce two C_{max} values in children and healthy adults, first peak at 1 to 3 hours and second peak occurs 3 to 4 hours later (Concerta®, Quillivant™).[17, 19] ER formulations minimize variability between peak and trough levels that usually occurs with multiple dosing of Immediate-Release (IR) formulations. Bioavailability was similar upon administration of equivalent doses of IR or ER formulations.

Absorption of methylphenidate is essentially complete and rapid, as shown by urinary excretion and minimal fecal elimination. After oral administration of 14C-methylphenidate dose, 50 to 90% of the radioactivity was excreted in urine by 8 to 48 hrs, respectively and fecal elimination accounted for 1.5% and 3.3% of radioactive dose, respectively.[20]

Methylphenidate is metabolized primarily by de-esterification to the inactive metabolite ritalinic acid.[21, 22, 23] This facile process limits the absolute bioavailability to 11 to 53%.[24] The circulating concentrations of ritalinic acid greatly exceed that of the parent drug [25, 26] and urinary elimination of ritalinic acid accounts for 60 to 80% of the dose.[20, 21]

Methylphenidate is excreted almost entirely in the urine, mainly as alpha-phenyl-piperidine acetic acid (PPAA). Methylphenidate and its metabolites exhibit low plasma protein binding (~15%).[27, 28]

There are no clinically significant food effects on methylphenidate bioavailability and this can be administered without regard to food intake (Ritalin® Label, Concerta® Label, Quillivant™ Label).[16, 17, 19].

1.2 Methylphenidate Overview:

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl) acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants.[29]

The psychopharmacologic features of methylphenidate (effects on motor performance and activity, effects on attention and impulsivity, and effects on cognition) have been reviewed by Shaywitz et al. (1984).[1] Because the responses vary considerably at doses from 0.3 to 1.0 mg/kg, titration is required in each case.[30] The smallest effective dose should be maintained. Many children show marked improvement with a single daily dose as low as 0.3 mg/kg; the need for a midday or midafternoon dose is easily determined and the effects are easily monitored.[31]

The efficacy of methylphenidate in improving attention and behavioral symptoms has been supported by many studies. Short-term improvements in school-work production, accuracy and learning and the suggestion that treated children had been helped to take responsibility for the correction of their behavior were noted in a study by Douglas et al. (1985).[32]

1.3 Pharmacokinetics of Methylphenidate:

Stimulant drugs have been used for the management of hyperactive children. However when first used very little was known about the pharmacology and metabolism of these agents, or about the relationship of blood levels to the clinical response.[33] Peak blood levels following the administration of methylphenidate occur at 1 to 3 hours.[20, 34] The half-life of the drug ranges from 2 to 4 hours in adults and children.[20, 28, 35] Hungund et al. (1979) reported on the pharmacokinetics of methylphenidate in four hyperkinetic children.[28] The mean half-life was 2.5 hours. Although there was little variability in this parameter, body clearance varied by a factor of three. This suggested that plasma methylphenidate levels are subject to a considerable degree of inter-patient variability.

The primary route of metabolism for methylphenidate is desterification to ritalinic acid, which accounts for 75% to 91% of total urinary methylphenidate. Other metabolic products arise from p-hydroxylation or oxidation to the lactam. Gualtieri et al. (1982) reported on a series of bioavailability studies using a GC-mass spectrometric analysis to measure methylphenidate blood levels in hyperkinetic children (age 6-13 years), normal adults and hyperactive adults.[36] The serial sampling study revealed adults had a pharmacokinetic profile similar to that in hyperkinetic children. The concentration time profile showed peak levels at 60 to 120 minutes. The peak concentrations had a four-fold range. Elimination half-lives showed a mean of 3.4 hours in adults and one adolescent, and ranged from 2.52 hours to 3.36 hours in children. In another series of studies, one hour serum levels were also measured in 16 hyperactive children, 28 hyperactive children and 22 healthy adult volunteers who were participating in placebo- controlled double-blind crossover studies of methylphenidate. There was the same wide range of serum levels noted in adults and children, and mean serum levels were virtually identical in adults and children.

1.4 Rationale of Dosing:

Immediate-release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. Their rapid onset and offset means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, methylphenidate is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens.[37, 38] Compliance is a major problem for children who require a mid-day or mid-afternoon dose as many schools prohibit children from taking medications during the school day and others often insist that all medications be given by a nurse.

Poor compliance in taking medication may explain, in part, the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate-release methylphenidate led to interest in products with longer effective periods of action. Therefore, a methylphenidate sustained-release formulation was developed. This formulation was chosen for further development because it exhibited an initial rapid rise in plasma concentration in healthy adults (range 18-45 years) similar to Ritalin® with a C_{max} relative to the first dose of Ritalin® IR, a relative Total $AUC_{0\text{-}inf}$ also similar to Ritalin® (study RP-BP-PK001) and its plasma concentration time profile was more prolonged than that of Ritalin® IR. The elimination half-life of immediate-release methylphenidate in study (RP-BP-PK001) was 3.4 hour fasting and 3.15 hours in the fed state, which is consistent with the findings of Gualtieri et al in adults and children.[38, 39] Based upon the 90% CIs, maximum plasma methylphenidate concentrations (C_{max}) and exposure (AUCs) were comparable following Aptensio XR® 80 mg capsule or Aptensio XR® 80 mg sprinkle once daily compared to comparator 3 × 25 mg Ritalin®.[40] We hypothesize that the pharmacokinetics of this new formulation of extended-release methylphenidate will be suitable for once-daily dosing in young children. As requested by FDA, a pharmacokinetic study of Aptensio XR® is required in children aged 4 to under 6 year with ADHD. The maximum daily dose in this pharmacokinetic study will not exceed 40 mg/day in children.

The clinical efficacy of Aptensio XR® was established in two, controlled trials in young children and adolescents. The primary efficacy endpoint of study (RP-BP-EF001) was met. The primary measure of efficacy was the comparison between the average of SKAMP Total Scores for the Aptensio XR®

and placebo arms across treatment assessment days during the Double-Blind phase for the Evaluable population. LS mean post-dose SKAMP Total score was significantly better for Aptensio XR® than for placebo (1.32 vs 2.18, p = 0.0001) with subjects receiving Aptensio XR® having significantly greater improvement in classroom behavior, written work, and general behavior compared with placebo. Once-daily Aptensio XR® was significantly better than placebo in treating children with ADHD in a double-blind manner in laboratory school setting.[40]

Results from a parallel, double-blind, placebo-controlled study (RP-BP-EF002) demonstrated the efficacy of Aptensio XR® relative to placebo in the treatment of ADHD in children and adolescents ages 6 to 18 years (n=221).[40] The primary efficacy endpoint of this study was met. The primary efficacy analysis was to analyze the decrease from baseline (Visit 2) to the end of Week 1 (Visit 3) in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) Total score, comparing the 5 treatment groups (placebo, 10, 15, 20, and 40 mg/day Aptensio XR®). The overall test for whether all treatments had the same mean decrease was the primary result. There was a statistically significant difference among treatments (ANCOVA, treatment p = 0.0046), which indicates that there were differences among study treatments for how much the total score decreased during the Double-Blind phase.

In both studies, no major adverse events were observed other than known for other methylphenidate.

2 OBJECTIVE

To assess the pharmacokinetics of a single dose of Aptensio XR® (Methylphenidate Hydrochloride) Extended-Release Capsules (MPH-MLR or Biphentin®) under fed conditions in male or female children 4 to under 6 years of age with ADHD.

3 STUDY DESIGN SUMMARY:

This is a single-dose, open-label, one-period study in which approximately 60 children with ADHD subjects will be screened in order for ten (10) subjects to complete the study. Subjects will be assigned numbers in an ascending order, based on successful completion of the screening process.

Patients who withdraw from the study will not be replaced.

During the study period, 1.0 mL blood samples will be obtained prior to dose administration and at selected times through 24 hours after dose administration. A total of 11 pharmacokinetic blood samples will be collected from each subject. Plasma pharmacokinetic samples will be analyzed for methylphenidate using a validated analytical method. Appropriate pharmacokinetic parameters will be calculated for each formulation using non-compartmental methods.

Eligible patients will receive a total daily dose equivalent to their current total methylphenidate daily dose as a sprinkle over apple sauce or yogurt.

Table 1 summarizes events proposed for the study.

3.1 Open-Label, Long-Term, Extension Study

Subjects may be eligible for participation in a 12-month open-label extension study of MPH-MLR if they complete the End of Study visit and do not have adverse events that suggest poor tolerability to MPH-MLR. Subjects who enroll in the open-label extension may do so at the End of Study Visit.

Table 1: Schedule of Events

Evaluations	Screening Visit (Days -28 to -1)	Day (-5)	Day (-1)	Day 1										End of Study
				Hours after dosing										
				0	0.5	1	2	3	4	6	8	10	12	24[1]
Informed Consent & Assent	X													
Medical / Medication History	X		X											
K-SADS-PL Structured Interview	X													
ADHD-RS-IV Preschool version			X											
Child Global Assessment (CGAS)			X											
Clinical Global Impressions-Severity (CGI-S)			X											
Discontinue current methylphenidate dosing		X												
Urine drug screen for methylphenidate	X													
Physical Examination[2]	X													X[2]
Admission				X										
Vital Signs[3]	X			X			X		X		X		X	X
Verify Inclusion/Exclusion Criteria	X	X	X	X										
Resting 12-Lead ECG	X			X			X		X		X		X	X
Clinical Laboratory/urine/ Serology Tests	X													
Clinical Laboratory Chemistry and Hematology	X													X
Holter Monitor Application				X										
Holter Monitor Removal														X
Study Drug Dosing				X										
Blood for PK Analysis				X	X	X	X	X	X	X	X	X	X	X
AE Assessment				X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medication	X		X	X	X	X	X	X	X	X	X	X	X	X

[1] End of Study Visit
[2] A complete physical examination will be performed at Screening and a limited physical examination will be performed prior to discharge from the study.
[3] Screening vital signs include sitting blood pressure, pulse rate, weight, height, temperature, respiration rate and pulse oximetry. Vital signs will be obtained within 60 minutes prior to dosing and prior to discharge from the study. For full schedule of vital signs measurements see Table 2

4 SUBJECT SELECTION

4.1 Inclusion Criteria

All subjects must satisfy the following criteria to be considered for study participation:

- Patient is a male or female between the ages of 4 and under 6 years old.
- Patient has a history consistent with ADHD, meets the DSM-IV criteria for ADHD, inattentive, hyperactivity or combined.
- Patient must meet criteria for ADHD diagnosis on K-SADS-PL and clinical interview by experienced clinician; symptoms must have been present for at least 6 months.
- Subject has had prior behavioral treatment or patient's symptoms are severe enough to warrant treatment without prior behavioral treatment, and patient is on a stable dose of either immediate-release or extended-release methylphenidate.
- Subject must have age- and sex-adjusted ratings of ≥ 90th percentile Total Score on the ADHD-RS-IV Preschool Version, a Clinical Global Impressions-Severity Score of ≥4 and a Child Global Assessment Scale rating of <65 after methylphenidate washout and prior to obtaining pharmacokinetic samples. Ratings may be completed via telephone on day-1.
- Parents or guardians of patients must have the ability to read and understand the language in which the Informed Consent is written and are mentally and physically competent to provide written informed consents for their child.
- Patient and/or parent are/is able to understand English in order to provide assent and is otherwise able to comply with the study protocol.

4.2 Exclusion Criteria

Subjects will be excluded for any of the following:

- Patient has allergy to methylphenidate or amphetamines, or history of serious adverse reaction to methylphenidate.
- Patient has a history of tension, agitation, glaucoma, thyrotoxicosis, tachy-arrythmias or severe angina pectoris or patient with serious or unstable medical illness such as asthma, diabetes or seizures.
- A history of motor or vocal tics or Tourette's syndrome.
- Patient is receiving MAO inhibitors, anticonvulsants (phenobarbital, phenytoin, primidone), coumarin anticoagulants, presser agents guanethidine, tricyclic antidepressants (imipramine, desipramine, selective serotonin inhibitors (SSRIs) or herbal remedies (e.g., melatonin).
- Patient has serious hypertension.
- Patient has a history of disorders of the sensory organs, particularly deafness, severe or profound retardation.
- Patient has any other unstable psychiatric condition requiring treatment.
- Patient is at risk for substance abuse.

- Evidence of current physical, sexual or emotional abuse
- Living with anyone who currently abuses stimulants or cocaine
- History of bipolar disorder in both biological parents.

4.3 Inclusion of subjects without prior non-pharmacological therapy

Broad guidelines for consideration of inclusion of subjects without prior non-pharmacological therapy will include the following:

- ADHD-RS Preschool Version score >50
- CGI-S score >5
- CGAS score <40

Additional consideration will be given to (i) parent-reported behavioral severity, (ii) specific concerns regarding safety of the child in his/her environment and (iii) the investigator's judgment regarding likelihood of success of non-pharmacologic therapy.
Investigators will document the specific rationale for assessing severity and impairment in cases where children are to be enrolled without a history of non-pharmacological treatment. These cases will be reviewed by the medical monitor and/or the coordinating PI(s).

4.4 Restrictions

Parent should not give any over the counter (OTC) medication to his/her child within 7 days prior to the first dose of study medication until the end-of-study visit without evaluation and approval by the study investigator.

Parent must not give any other medication prior to the first dose of study medication until the end-of-study visit other than prescribed to control ADHD without evaluation and approval by the study investigator.

Parent must not give beverages and foods containing grapefruit, poppy seeds or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end- of-study visit. Parents should avoid giving above products to his/her children; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study investigator based on the potential for interaction with the study drug.

4.5 Screening

The principal investigator and co-investigators will identify patients who meet the selection criteria. After parents give informed consent, screening may begin immediately or an appointment will be made for a screening visit. Each potential study patient will have the following assessments by the Investigator or designee within 28 days prior to study start: medical history and demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm) and BMI (kg/m^2). The K-SADS-PL, a semi-structured interview, will be administered by qualified and trained clinicians to confirm ADHD diagnosis and determine whether psychiatric comorbidities are present. Each potential participant will receive a physical examination, ECG, lab sampling for hematology, serum chemistry and serological testing, and a urinalysis. A urine drug screen to confirm methylphenidate dosing will be performed. The ECG will be performed after subject has been in supine position for a minimum of 5 minutes. Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs will be enrolled in the study. The informed consent documents will be discussed with each parent,

and each individual parent will sign an informed consent document for the study prior to any study-specific procedures being performed. The patient's current total daily dose of immediate- release or extended-release methylphenidate will be recorded.

4.5.1 Clinic - Day (-5):

Patients who meet the entry criteria will discontinue their current methylphenidate medication to enable washout for a minimum of 5 days prior to dosing.

4.5.2 Clinic - Day (-1):

The parent will provide any updates to the child's medical history, pre-existing conditions, concomitant medication information, and past or present difficulty with inattention, hyperactivity, impulsivity, defiance, conduct problems and developmental disabilities. ADHD severity and functioning will be quantified prior to dosing using the (i) ADHD-RS-IV Preschool version, (ii) Child Global Assessment (CGAS) and (iii) Clinical Global Impressions-Severity (CGI-S) scales.

4.5.3 Clinic – Day (1):

On the day of dosing: Vital signs will be measured as described in Table 2. An indwelling catheter will be inserted prior to the morning dose and a pre-dose plasma sample will be obtained. Patients will receive a total dose as single Aptensio XR® capsule. A standardized breakfast consisting of cereal with milk, juice and toast will be provided before dosing. Patients will be assigned to various regimens based on previously targeted methylphenidate dose. After receiving the morning dose, patients will remain in the clinic for 12 hours during which time plasma samples will be collected at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose.

During the day, patients will be provided with meals or snacks consisting of pizza, milk, juice or water or other age appropriate food. After the 12 hour sample, the catheter will be removed and the patients will be discharged. Patients will subsequently return to the clinic the following morning.

Parents will be instructed not to give any CNS stimulant, including supplemental methylphenidate, other to what is prescribed by the principal investigator.

4.5.4 End of Study Visit:

The patient will return to the clinic the next morning for a 24 hour blood draw. At this time, the patients will resume their usual treatment and will receive a single daily dose of CR or IR methylphenidate as per previous prescription. The patient will complete end of study procedures as described in Section 5.6.

4.6 Laboratory Tests

A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform the following clinical laboratory tests for this study:

4.6.1 Hematology

The following will be evaluated: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count (RBC), and platelet count.

4.6.2 Serum Chemistry

The following will be evaluated: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, and glucose.

4.6.3 Serology

Blood will be tested for hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV).

4.6.4 Urinalysis

The following will be evaluated by an automated or manual urine "dipstick" method: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed.

5 STUDY PROCEDURES

5.1 Subject Assignment

Approximately sixty (60) subjects will be screened in this study. Ten (10) subjects will be selected for dosing. Each selected subject will receive an assigned treatment dose to equal the patient's current total daily dose of immediate-release or extended-release methylphenidate.
The maximum duration of the study from screening to study completion will be approximately 1 year. This is an open-label study without treatment blinding.

5.2 Check-In Procedures

Parents of patients will be asked to affirm that the exclusion criteria and restrictions have not been violated since the screening. Parent's response will be documented.

5.3 Confinement

Patient will be admitted to the research center at an appropriate time in the morning prior to study drug administration. Patients will be given breakfast. Subjects will remain in the research center until completion of the 12-hour procedures for each study period and return for outpatient visits at approximately 24 hours after dose.

5.4 Meals/Beverages

5.4.1 Meals

Patients will be given breakfast. A standardized breakfast consisting of cereal with milk, juice and toast will be provided before dosing. During the day, patients will be provided with meals or snacks consisting of pizza, milk, juice or water or other age appropriate food.

5.4.2 Beverages

Water will be allowed *ad lib* and will be encouraged to drink water.

5.5 Drug Administration

5.5.1 Administration of Study Medication

Drug will be administered as a sprinkle over apple sauce or yogurt.

5.5.2 Blood Sampling, Processing and Shipment

A total of 11 mL (11 × 1 mL samples) will be collected for pharmacokinetic analysis. In addition, approximately 5 mL of blood will be collected for screening and the end-of-study clinical laboratory evaluations. The total volume of blood collected will not exceed 21 mL.

A local, topical anesthetic (2.5% lidocaine and 2.5% prilocaine cream) will be applied at the catheter insertion site. Serial Blood samples will be obtained via a catheter placed in the antecubital vein in subject's forearm. Subjects will be distracted which includes listening to songs during catheter insertion and PK sampling. Serial blood samples for determination of methylphenidate plasma concentration and PK analysis will be obtained on Day 1 at time 0 (within 15-30 minutes pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose in K2-EDTA Vacutainer tubes. Samples will immediately be placed in an ice bath where they will remain throughout processing.

Blood samples collected up to and including 24 hours post-dose within ± 2 minutes of scheduled time will not be considered deviations, however, exact time will be recorded. Blood samples will be centrifuged at approximately 3000 rpm for 10 minutes at 4 degrees Centigrade. The resulting plasma samples will be harvested and transferred into two appropriately labeled polypropylene screw-cap tubes. Use tubes supplied by Simport, Part # T310-1A, 12.5 x 42 mm, 1.2 mL tubes. Pharmacokinetic samples will be placed in a storage freezer at minus 20 degrees Centigrade or lower within 60 minutes of blood draw. Samples will remain frozen until assayed. A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the study master file.

The samples will be transferred in two separate shipments to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. Primary samples shall be shipped separate from back-up samples. Prior to shipment, the samples will be appropriately packed in a Styrofoam cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 72 hours for remote shipments. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. All frozen pharmacokinetic samples will be transferred with accompanying documentation to:

Worldwide Clinical Trials
Early Phase Services/Bioanalytical Sciences, Inc.
Attention: Ian David
8609 Cross Park Drive
Austin, Texas 78754
Telephone: 512.834.7766
Fax: 512.834.1165

5.6 End-of-Study Procedures

A brief physical examination, an ECG, and vital signs measurements (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be performed on the day of study discharge. The vital signs measurements should be completed prior to the 24 hour blood collection. The ECG will be performed after subject has been in supine position for a minimum of 5 minutes. Blood will be collected for the same hematology and chemistry tests performed during screening. Adverse events and changes in concomitant medications will be assessed. When possible, end-of-study procedures will be performed in the event of a subject's early termination from the study.

5.7 Safety Monitoring and Procedures

A full set of vital signs will be measured at screening and at -0.5 hours pre-dose, at 2, 4, 6, 8, 12 and 24 hours post-dose as given in Table 2.

Table 2: Schedule of Vital Signs Measurements

Time point	Blood Pressure (mmHg)	Pulse (Beats/min)	Temperature (°C)	Respiration rate (Breaths/min)	Pulse oximetry (SpO_2; %)
Screening	X	X	X	X	X
-0.5 hours	X	X	X	X	X
2 hours post-dose	X	X		X	X
4 hours post-dose	X	X		X	X
8 hours post-dose	X	X		X	X
12 house post-dose	X	X	X	X	X
24 hours post-dose	X	X	X	X	X

Electrocardiogram (Holter, provided by eResearch Technology, Inc.) will be monitored from pre-dose until completion of 24 hours post dose, and additional vital signs measurements may be performed as deemed medically necessary by research personnel. All vital signs measurements will be taken after the subject has completed a minimum 3-minute sit.

Subjects will be closely monitored during the confinement period in the research facility. Subjects will be instructed to inform the study physician and/or research personnel and/or parent of any adverse events (AEs) that occur at any time during the study.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

Medical emergency personnel trained in advanced cardiac life support will be on site to monitor subjects during the confinement period in the research center. Emergency medical equipment including but not limited to intubation equipment and pulse oximetry shall be maintained on site to administer appropriate medical care should it be required. A physician will remain on site after each dose administration and will be available immediately.

6 ADVERSE EVENTS

Subjects will be monitored for any adverse events (AEs) and Serious Adverse Events (SAEs) from the beginning of confinement until the end-of-study visit. The Investigator or a medically qualified designee will review each event. The Investigator or a Sub-Investigator will assess its relationship to the study drug. Each sign or symptom will be graded for severity, and the date and time of onset, cessation and resolution will be recorded. Treatment of any adverse reactions will be evaluated and

managed by a physician at the study site. All non-serious AEs will be reported on a regular basis or as specified by the Sponsor. Adverse events will be monitored and documented using MeDRA terminology.[42]

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without judgment to causality. An AE can arise from any use of the drug (eg, off-label, use in combinations with another drug) and from any route of administration, formulation, or dose, including an overdose.

6.1.2 Life-Threatening Adverse Event/Life-Threatening Suspected Adverse Reaction

A life-threatening AE/life-threatening suspected adverse reaction, in the view of either the Investigator or sponsor, places the patient or subject at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death.

6.1.3 Serious Adverse Event/Serious Suspected Adverse Reaction

A Serious Adverse Events (SAE) or serious suspected adverse reaction, in the view of either the investigator or sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.4 Unexpected Adverse Event/Unexpected Suspected Adverse Reaction

An unexpected AE/unexpected suspected adverse reaction is an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

6.2 Serious Adverse Event Reporting

The Investigator or designee will notify the appropriate sponsor contact immediately after the SAE detection, observation, or report of occurrence. The sponsor contact information for SAE reported is provided below:

Akwete Lex Adjei, Ph.D.
Executive Director, Product Development
Rhodes Pharmaceuticals, L.P.
498 Washington Street

Coventry, Rhode Island 02816
Phone: 401-262-9408;
Fax: 401-262-9403

Email: akwete.adjei@pharma.com

These SAE reports must contain the following information:

1. Study name/number
2. Study drug
3. Investigator details (name, phone, fax, e-mail)
4. Subject number
5. Subject initials
6. Subject demographics
7. MedWatch 3500 form
8. Clinical event
    i. Description
    ii. Date of onset
    iii. Treatment (drug, dose, dosage form)
    iv. Adverse event relationship to study drug
    v. Action taken regarding study drug in direct relationship to the adverse event
9. If the adverse event was fatal or life-threatening.
10. If hospitalized, hospital records.
11. Cause of death (whether or not the death was related to study drug)
12. Autopsy findings (if available)

Any new SAE that occurs beyond one month after the study period and is considered to be possibly related to the Investigational Medicinal Product (IMP) should be recorded and reported immediately to the Sponsor.

The person responsible for the study shall take care that the study has been carried out in accordance with pharmacovigilance local regulations.

All serious event reporting will adhere to 21 CFR 312.32 for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (IRB) will be notified of the alert reports per Food and Drug Administration (FDA) regulations.

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the case report form (CRF).

6.3 Relationship to Study Treatment

The relationship between the AE and the investigational product will be determined by the Principal Investigator or Sub-Investigator on the basis of his/her clinical judgment and the following definitions:

1= **Related:**

The AE follows a reasonable temporal sequence from the study product administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study,

concurrent diseases, or concomitant medications).

The AE follows a reasonable temporal sequence from the study product administration, and represents a known reaction to the drug under study or other drugs in its class, or is predicted by the known pharmacological properties of the drug.

The AE resolves with discontinuation of the investigational product and/or recurs with rechallenge, if applicable.

2 = **Not Related**:

The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

7 GENERAL CONSIDERATIONS

7.1 Basic Principles

This research will be carried out in accordance with the protocol, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6), and applicable regulatory requirements(s) including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

7.2 Protocol Approval

The protocol, informed consent and assent must be approved by the IRB.

7.3 Institutional Review Board

This protocol will be reviewed by an appropriate IRB and study enrollment will not commence until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the U.S. Code of Federal Regulations (21 CFR Part 56).

7.4 Informed Consent Form and Assent

Before implementation of the study, the investigator will provide the sponsor with a copy of the IRB approved consent form, printed on the investigator's or institution's letterhead. All patients will be fully informed of the nature and purpose of the study and will give verbal assent and a parent or guardian will provide written consent prior to entry into the study. A copy of the consent form will be given to the parent or guardian and the original retained by the Investigator/site. Parent or guardian will be informed of any significant new findings that could affect their decision that their child will remain in the study.

7.5 Investigator's Brochure

Prior to the start of the study the principal investigator will be provided with an Investigator's Brochure (IB). The IB will be carefully reviewed by the investigator prior to patient enrolment.

7.6 Protocol Modifications

Neither the investigator nor the sponsor will modify the protocol without first obtaining the

concurrence of the other. All changes must be submitted to the IRB. Protocol modifications that impact on patient safety or the validity of the study must be approved by the IRB and the FDA before implementation.

7.7 Qualified Investigator Undertaking

Before initiation of the study, the investigator will supply the sponsor with a completed Qualified Investigator Undertaking. A curriculum vitae and current medical license will also be provided for all investigators and all co-investigators.

7.8 Indications for Subject Withdrawal

Parent will be free to withdraw his/her children at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

The final report will include reasons for withdrawals. In the event of an early termination, patient will undergo the procedures described in Section 5.6. If necessary, subjects will be followed up at the request of the Principal Investigator.

If a subject experiences emesis within 2-4 hours of dosing (based on 2 times the T_{max} of methylphenidate of approximately 1-2 hours), the subject will be discontinued from the study and his/her pharmacokinetic samples will not be analyzed. If emesis occurs after 4 hours, the subject will be retained in the study and his/her pharmacokinetic samples will be analyzed.

7.9 Termination of the Study

The Principal Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

7.10 Treatment of Outliers

If anomalous pharmacokinetic results are noted for a subject, the pharmacokinetic data for the patients in question may be reviewed to determine if the patients is a statistical outlier. The outlier test will be performed using the Grubb's Test (T Procedure) applied to the Test/Reference ratio for the relevant pharmacokinetic parameters, C_{max}, AUC_{last}, and AUC_{inf} in particular. If the subject is determined to be a statistical outlier, the statistical analyses (e.g., ANOVA) will be performed with and without the outlier in the analysis data set. Both ANOVA results, i.e., without the outlier (primary analysis) and with the outlier (secondary analysis), will be reported. In the event of outliers, a redose challenge study will be conducted to either confirm or reject the outlier.

7.11 Documentation

All documents pertaining to the study, including a copy of the approved protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act (HIPAA) documents, completed CRFs (where applicable), drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study (not merely the Investigator's portion of the study, if it

involved more than one investigator) is completed, terminated, or discontinued, and the FDA is notified.

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, the FDA, other government offices, and the IRB.

7.12 Trial Monitoring

Sponsor personnel (or designees) will be responsible for monitoring the study to ensure compliance with the protocol and GCP. Compliance may be verified by one or more of the following methods: on-site visits, frequent communication with the Investigator, and/or review of CRFs and source documents. The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities and the IRB.

7.13 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

7.14 Quality Control and Quality Assurance Audits

The raw data generated during the conduct of the study as well as reports will undergo a thorough Quality Control (QC) check and random Quality Assurance (QA) process for conformance to this protocol and all the governing Standard Operating Procedures (SOPs) by auditors from the QA departments of Worldwide Clinical Trials (WCT). The final report will contain a statement for quality assurance duly signed by a qualified representative of the Quality Assurance department.

7.15 Archiving

All raw data generated during the clinical phase of this study, together with an original of this protocol, signed ICFs, and an original of the final report will be archived according to the ICH guideline for good clinical practice.

7.16 Confidentiality of Data

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, FDA, other government offices, and the IRB.

All reports and subject samples will be identified only by Study Identification Number and initials to maintain subject confidentiality.

7.17 Publication Policy

Results of the study including all obtained data will be the property of the Sponsor of this study. For any publication pertaining to the data or results of study, a written approval of Sponsor will be obtained prior to communicating for publication and the manuscript will be sent for Sponsor's approval, if the Sponsor asks to do so.

7.18 Investigator Responsibilities

The Investigator will agree to conduct the study in accordance with the relevant, current protocol and to only make changes in a protocol after notifying the Sponsor, except when necessary to protect the

safety, rights, or welfare of subjects, and to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

8 PHARMACOKINETIC ANALYSIS

8.1 Analytical Methodology

Plasma samples will be analyzed for methylphenidate using a validated assay. The samples from all evaluable subjects completing the study will be analyzed.

Incurred sample reproducibility will be performed and reported per WCT SOPs.

8.2 Pharmacokinetic Parameters

Pharmacokinetic parameters for methylphenidate will be calculated using non-compartmental analysis. The pharmacokinetic parameters that will be determined are detailed in **below**

Pharmacokinetic Parameter	**Definition**
C_{max}	Maximum observed plasma concentration
C_{max} / Dose	Dose normalized C_{max}
AUC_{0-t}	Area under the plasma concentration-time curve from dosing to the final sample with a concentration greater than limit of quantitation (LOQ)
AUC_{0-t} / Dose	Dose normalized AUC_{0-t}
AUC_{0-inf}	Area under the plasma concentration-time curve from dosing extrapolated to infinity. AUC_{0-inf} is calculated as $AUC_{0-t} + C_{last}/K_{el}$ where C_{last} is the final sample with a concentration greater than LOQ and K_{el} is the terminal elimination rate constant
AUC_{0-inf} / Dose	Dose normalized AUC_{0-inf}
CL/F	Apparent clearance
CL/F/Kg	Weight normalized Apparent clearance
V_d/F	Apparent volume of distribution
V_d/F/Kg	Weight normalized Apparent volume of distribution
t_{max}	Time of maximum observed plasma concentration: Time to C_{max}
$t_{½}$	Elimination half-life: $0.693/K_{el}$
K_{el}	Terminal elimination rate constant
Dose and weight normalized dose	Dose and weight normalized dose (mg/kg)
AUC_{0-4}	Area under the plasma concentration-time curve from dosing to 4 hours
AUC_{4-8}	Area under the plasma concentration-time curve from 4 hours to 8 hours
AUC_{8-12}	Area under the plasma concentration-time curve from 8 hours to 12 hours

F - Fraction of dose determined by bioavailability

The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data. The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time.

Elimination half-life ($T_{½}$) will be calculated according to the following equation: $T_{½} = 0.693 / \lambda_Z$
Area under the curve to the final sample with a concentration greater than the LOQ (AUC_{last}) will be calculated using the linear trapezoidal method and extrapolated to infinity using:

$$AUC_{inf} = AUC_{last} + C_{last} / \lambda_Z$$

Where C_{last} is the final concentration ≥LOQ.

C_{max} and AUC will be dose normalized. Apparent clearance (Cls) and apparent volume of distribution will be reported

Secondary pharmacokinetic endpoints will be the respective time to C_{max} (t_{max}), the elimination half-life (t½), and the terminal elimination rate constant (K_{el}) will be calculated.

All evaluable subjects will be included in the pharmacokinetic analysis. Pharmacokinetic calculations will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation) and/or SAS® (Version 9.3, SAS Institute Inc.).

All the derived PK parameters described above will be listed. The PK parameters will be summarized by dose groups. For AUC, C_{max}, CL/F/kg, Vd/F/kg, CL/F, Vd/F and the normalized results, the following summary statistics will be calculated: median, maximum, minimum, arithmetic mean, standard deviation, CV, geometric mean, 95% confidence interval for the geometric mean, and standard deviation of $\log_e$ transformed data. For other parameters, median, maximum, minimum, arithmetic mean, and standard deviation will be calculated.

Comparison of the PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} will be performed using an analysis of variance (ANOVA) model with dose group as the only factor in the model. The lowest dose group will be selected as the reference group and other dose groups will be compared to the reference group in a pairwise fashion. If the number of subjects in each dose group is too sparse, additional analyses with grouping certain dose levels together may be carried out. This decision will be based on subjects' dosing records and will be made before database lock.

The $\log_e$ transformed normalized parameter will be used in the analyses

8.3 Statistical Analysis

Comparison of the PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} will be performed using an analysis of variance (ANOVA) model with dose group as the only factor in the model. The lowest dose group will be selected as the reference group and other dose groups will be compared to the reference group in a pairwise fashion. If the number of subjects in each dose group is too sparse, additional analyses with grouping certain dose levels together may be carried out. This decision will be based on subjects' dosing records and will be made before database lock.

The $\log_e$ transformed normalized parameter will be used in the analyses. The point estimate of the ratio of the dose normalized PK parameters with associated 90% confidence interval will be presented Statistical analyses will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation) and SAS® (Version 9.3, SAS Institute Inc.).

9 FACILITIES

ANALYTICAL LABORATORY

Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc.

8609 Cross Park Drive
Austin, Texas 78754
Phone: 512-834-7766

10 DRUG SUPPLIES

Rhodes Pharmaceuticals or designee will supply sufficient quantities of the study drug to allow completion of this study. Study drug formulations methylphenidate 10, 15, 20, 30 and 40 mg capsule will be shipped to the clinical site pursuant to site SOPs. The lot numbers of the drugs along with the expiration dates (where available) will be recorded and copies of the Certificate of Analysis (where available) will be maintained on file. As methylphenidate is a scheduled drug it should always be locked and dispensed under strict supervision.

Records will be maintained of the receipt and dispensation of the drugs supplied. At the conclusion of the study, any unused drug product will be stored as per FDA and DEA guidelines.

11 FINAL REPORT

A final report (eCTD format) will be the responsibility of WCT and will signed and approved by the qualified Investigator. Data will be provided in CDISK format.

12 ADMINISTRATIVE ISSUES

The Investigator is referred to the Aptensio XR® package insert, Investigator Brochure, or information provided during the study initiation visit, information provided by the study monitor, and ICH Guidelines for Good Clinical Practice for information regarding the study drug, details, or general considerations to be followed during the course of this study.

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14 APPENDICES

14.1. K-SADS-PL

The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. Probes and objective criteria are provided to rate individual symptoms. Since ADHD criteria and impairment in preschool children is essentially the same in DSM-IV and DSM-5, the K-SADS-PL can be used to confirm the diagnosis. This interview has been used successfully to determine diagnoses in subjects aged 4 to 5 years. The K-SADS-PL is administered at the Screening Visit.[42]

14.2 ADHD Rating Scale (ADHD-RS-IV) Preschool Version

The ADHD-RS-IV Preschool Version will be used to determine ADHD symptomatology and severity.[43] The Investigator or other designated, qualified individual will perform the assessment. ADHD-RS-IV Preschool Version is an 18 item adaptation of the original ADHD-RS-IV which is a measure of ADHD symptomatology. For the Preschool Version symptom statements are modified to better capture behavior that is developmentally inappropriate for children aged 3-5 years. The ADHD-RS-IV preschool version assessment is administered at the Day (-1) visit.

14.3 Clinical Global Impressions-Severity (CGI-S) Scale

This scale provides a global rating of illness severity and improvement during the trial[44]. The subject is rated relative to the clinician's past experience with other patients who have the same diagnosis. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). The CGI-S assessment is administered at the Day (-1) visit.

14.4 Children's Global Assessment Scale (CGAS)

This scale provides a global measure of functioning for children and adolescents.[45] Each assessment is a single numerical rating from 1 – 100 ('1' represents subjects requiring constant (24 hour) supervision, while '100' represents subjects displays superior functioning.) The 100 point scale is arbitrarily subdivided into 10 subgroups that are used to classify the assessment (e.g. 100-91: superior functioning in all areas, 90-81: good functioning in all areas). The CGAS assessment is administered at the Day (-1) visit.