TITLE PAGE

PROTOCOL TITLE	RP-BP-EF003: A Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR®) in Children Ages 4 to Under 6 Years Diagnosed with Attention Deficit-Hyperactivity Disorder (ADHD)
PROTOCOL NO.	RP-BP-EF003, version 2.0, Protocol Dated February 15, 2018
DRUG	Methylphenidate Hydrochloride Extended Release Capsules, MPH-MLR (Aptensio XR®)
INDICATION	Treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in Children 4 to Under 6 Years
CLINICAL PHASE	Phase 4
SPONSOR	Rhodes Pharmaceuticals, LP 498 Washington Street Coventry, RI 02816
COORDINATING INVESTIGATORS	Ann Childress, M.D. Scott Kollins, Ph.D.
IND NO.	#104,624
Monitoring CRO	See Emergency Contact List & Appendices for details

GCP Statement: This study will be performed in compliance with Good Clinical Practices (GCP) guidelines, including the archiving of essential documents.

SYNOPSIS

Name of Company: Rhodes Pharmaceuticals LP	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
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Title of Study: Protocol RP-BP-EF003: A Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR®) in Children Ages 4 to Under 6 Years Diagnosed with Attention Deficit-Hyperactivity Disorder (ADHD)

Coordinating Investigators:

Dr. Ann C. Childress, Center for Psychiatry and Behavioral Medicine Inc., Las Vegas, NV;

Dr. Scott H. Kollins, Professor, Vice-Chair, Director, Department of Psychiatry & Behavioral Sciences, 2608 Erwin Road, Suite 300, Duke University, Durham, NC 27705

Study Drug:

Aptensio XR® 10 mg capsules, AP Aptensio XR® 15 mg capsules, Aptensio XR® 20 mg capsules, Aptensio XR® 30 mg capsules, Aptensio XR® 40 mg capsules

Enrollment: Up to 150 subjects

Number of Study Centers: Up to 10

Duration of Open Label Phase: Six Weeks

Duration of Double-Blind Phase: Two Weeks

Objectives: The objectives of this study are to evaluate the efficacy and safety of Aptensio XR® in treating ADHD in children ages 4 to under 6 years.

Primary Efficacy Objective

- The primary objective of this study is to establish that an optimal dose of Aptensio XR® will result in a significant reduction in ADHD symptoms compared with placebo in children ages 4 to under 6 years.
- The primary efficacy measure is the comparison of the two treatment groups (optimized dose vs placebo) using the change in ADHD-RS-IV Total Score during the double-blind phase, i.e. the change from end of open label phase to end of double blind phase.

Secondary Efficacy Objectives

- As with the primary efficacy objective, secondary efficacy objectives will primarily focus on the double-blind treatment period.
- Secondary efficacy measures will include the comparison of the two treatment groups (optimized dose vs placebo) using the following:
- The change in ADHD-RS-IV hyperactivity/impulsivity and inattention subscales during the double-blind phase

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- The change in CGI-S during the double-blind phase
- The CGI-I at the end of the double-blind phase (this CGI-I evaluates the change from end of open label phase to end of double blind phase)
- The change in Conners EC BEH-P(S) during the double-blind phase.

Safety Evaluation

- Collect spontaneously reported adverse events
- Assess Blood Pressure, Pulse, Height and Weight, ECG, Clinical Laboratory Values
- Assess suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Assess changes in sleep (quantity and quality) patterns using the Child Sleep Habits Questionnaire (CSHQ)

Design and Investigational Plan:

This randomized, double-blind, flexible-dose, placebo-controlled, parallel group study is designed to evaluate Aptensio XR® compared to placebo in preschool age children with ADHD. Male and female children ages 4 years, 0 months to 5 years, 8 months with a diagnosis of ADHD (combined, inattentive or hyperactive/impulsive) will be enrolled.

There will be 6 phases in this study: a screening phase of up to 4 weeks, which will include washout if applicable, an enrollment & parent training phase lasting 2-4 weeks, an eligibility phase of up to 2 weeks to determine eligibility for the open-label phase, a 6-week open-label dose titration phase, a 2 week double-blind phase for Aptensio XR® responders, and a two-week follow-up call after study completion or early discontinuation to assess for ongoing adverse events and concomitant medications.

Up to 150 subjects will be enrolled in this trial to allow for subjects who improve significantly during the behavior training phase and drop-outs. Once 74 subjects have completed the double-blind phase, no additional subjects will be enrolled in the trial. Subjects who are already enrolled at that time will be allowed to complete the trial.

Phase 1: Screening

The screening /washout period can last up to 4 weeks.

Phase 2: Enrolment & Parent Training

Eligible subjects will be enrolled in the study at Visit 2 and families will begin 4 parent training sessions. Sessions will last up to 90 minutes. The frequency of parent training sessions may be >4 days - <10 days apart. Families are expected to complete all 4 sessions of behavioural training within a 4 week period.

With consultation from the medical monitor/coordinating PI's, parents will be allowed to skip the behaviour management phase if the primary caregiver has participated in behaviour management therapy in the last 12 months with minimal benefit and/or the subject's ADHD symptoms are severe enough to warrant moving immediately to the medication phase of the trial.

Phase 3: Eligibility for Open Label Phase

At Visit 6, eligibility to continue to the open-label phase will be determined. Subjects who have less than

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a 30% improvement on the ADHD-RS-IV and a Clinical Global Impression-Improvement (CGI-I) of 3 (minimally improved or less) will undergo medical screening.

Subjects who are eligible to continue to the open-label phase based on lack of improvement of ADHD symptoms and medical criteria will start open-label treatment. Up to 2 weeks may elapse between Visits 6 and 7 to allow for laboratory results to be obtained. However, the interval between visit 6 and 7 can be <2 weeks if the laboratory test and ECG results are available.

Phase 4: Six-week Open-Label Phase

Subjects will begin Aptensio XR® 10 mg at the morning following Visit 7. At weekly visits (Visits 8-13), dosing may be maintained or increased until an optimal dose or the maximum dose is reached. The ADHD-RS-IV rating scale will be used to determine optimal dose. An optimal dose is a dose that produces a reduction of ADHD symptoms of at least 30% from Visit 7 with a CGI-I of "much improved" or "very much improved" with tolerable side effects. Subjects who meet improvement criteria but may benefit from additional dose increases, may have their dose further optimized. If a higher dose is not tolerated, subjects may step down one dose level.

Phase 5: Two-week Double-Blind Phase

Subjects who have ≥30% response on the ADHD-RS-IV and a CGI of "much" or "very much improved" at the end of Visit 13 will enter the two-week parallel double-blind phase where they will be randomized to receive their best optimal dose of Aptensio XR® or placebo.

Subjects who have a ≥50% worsening of symptoms on the ADHD-RS-IV from Visit 13 and a CGI-I of 6 or 7 (much worse or very much worse) at Visit 14 will be eligible to discontinue the double-blind phase and enter the open-label extension study at investigator discretion after completing end of study (Visit 15) procedures.

- At Visit 15, subjects will complete the double-blind phase and complete end of study procedures.

Phase 6: Follow-up Phone Call

- A follow-up phone call will occur approximately two weeks after treatment discontinuation to assess for ongoing adverse events and concomitant medications.

Proposed Statistical Analysis:

The primary analysis will be an analysis of the change in ADHD-RS-IV Total Score during the double blind phase, comparing the change of subjects on placebo to the change of subjects on their optimal dose of Aptensio XR®.

The primary efficacy population is the Evaluable population which includes all randomized subjects who were administered double-blind study medication, who completed ADHD-RS-IV assessments at the end of the open-label phase and at the end of the double-blind phase, and who did not have any major protocol violations. The Intent to Treat population will include all randomized subjects who were administered any double-blind study medication.

The primary efficacy measure will be the ADHD-RS-IV Total Score. The primary analysis will be a two-way analysis of variance (terms for site and treatment) using each subjects' change in ADHD-RS-IV

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Total Score during the double-blind phase. Treatment will have two values, Aptensio XR® and placebo. Statistical tests will be two-sided and p-values less than or equal to 0.05 will be considered statistically significant. The primary efficacy analysis will use the Efficacy population, and the same analysis will be repeated with the ITT population.

Secondary efficacy measures will be the ADHD-RS-IV hyperactivity/impulsivity and inattention subscale scores, CGI-S, CGI-I, and Conners EC BEH-P(S). Analysis of the ADHD-RS-IV subscale scores and the Conners EC BEH–P(S) score will be the same as for ADHD-RS-IV Total Score. Analysis of the change in CGI-S from end of open label versus to end of double blind will be a Mantel-Haenszel test stratified on site. Analysis of CGI-I at end of double blind phase (comparing end of double-blind to end of open-label) will be a Mantel Haenszel test stratified on site.

All treatment-emergent adverse events will be summarized by number of subjects reporting. Separate analyses will be done for the open-label phase and for the double-blind phase.

Diagnosis and Main Criteria for Inclusion:

1. Male and female subjects ages 48 months to 68 months inclusive at time of consent
2. Meets DSM-5 criteria for ADHD, combined, hyperactive/impulsive or inattentive presentation made during a clinical interview by an experienced clinician and confirmed with Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)
3. ADHD symptoms must have been present for at least six months
4. Age- and sex-adjusted ratings of ≥ 90th percentile Total Score on the ADHD-RS-IV Preschool Version (rated over past six months)
5. Score of <65 on the Child Global Assessment Scale
6. Must have a score of ≥4 on the Clinical Global Impressions Severity (CGI-S) at Visit 2 (subjects who are granted a waiver to bypass parental training (and do not have a visit 2) are still qualified to continue in the study based on their CGI-S score at screening)
7. Estimated IQ ≥80 on the Kaufman Brief Intelligence Test, Second Edition (KBIT-2)
8. The subject has a parent or legal guardian who will give written informed consent for the subject to participate in the study
9. Subject and parent or legal guardian must be able to speak and understand English
10. Subject must live with primary caretaker/rater and have been living with primary caretaker for at least 6 months
11. Subject and parent or legally authorized representative must be willing and able to comply with all requirements of this protocol
12. Systolic and diastolic blood pressure below the 95th percentile for age and gender

Exclusion Criteria:

1. The subject has had a lack of response to a trial of adequate dose and duration of MPH or intolerance to previous MPH treatment

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2. The subject is using any other current psychotropic medication except clonidine, guanfacine, atomoxetine and /or stimulants or has taken an investigational drug in the 30 days prior to screening
3. The subject has used monoamine oxidase inhibitors within 14 days of the screening visit
4. The subject plans to use prohibited drugs or agents at any point between the screening visit and the end of the study.
5. Use of anticonvulsants, antidepressants or antipsychotics in the 30 days prior to screening
6. The subject should not start any additional psychotherapy outside of the trial during the duration of the study
7. The subject has a history of chronic vocal or motor tics or Tourette's syndrome
8. The subject has any clinically significant ECG abnormalities at screening
9. The subject has any major medical conditions that would interfere with involvement in a study or could be affected negatively by methylphenidate
10. The subject has chronic medical illnesses including a seizure disorder (excluding a history of febrile seizures), severe hypertension, untreated thyroid disease, known structural cardiac abnormalities, serious arrhythmias, cardiomyopathy, glaucoma, or a family history of sudden death
11. History (in the past 12 months) or presence of clinically significant cardiovascular, cerebrovascular, renal, hepatic, gastrointestinal, pulmonary, immunological, hematological, endocrine, or neurological disease that in the opinion of the investigator could put the subject at risk if he/she participates in the trial or could confound study results
12. Family history (parent or sibling) of structural cardiovascular disease
13. Current or recent (past 12 months) history of drug abuse in someone living in the subject's home
14. Current symptoms or history of major psychiatric illness (for example schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, depression, severe anxiety disorder, obsessive compulsive disorder or autistic spectrum disorder) in addition to ADHD that requires treatment with additional medication or, in the opinion of the PI, would contraindicate study participation
15. History or presence of suicidal ideation or significant self-injurious behavior
16. The subject shows evidence of current physical, sexual, or emotional abuse
17. Both biological parents of the subject have a history of bipolar disorder

Ethics:

This study will be conducted in compliance with Standard Operating Procedures of the Contract Research Organization (CRO), designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

1. Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients") and all its accepted amendments to this date concerning medical

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research in humans

2. ICH Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use
3. US Code of Federal Regulations dealing with clinical studies (21 CFR §50 and 21 CFR §56 concerning Patient Consent and IRB regulations)

Independent Ethics Committee or Institutional Review Board

The study protocol, amendments, and informed consent form (ICF) will be reviewed and approved by an Institutional Review Board (IRB) for each study site in accordance with the United States Food and Drug Administration (FDA) regulations set forth in 21 Code of Federal Regulations (CFR) §50 and 21 CFR §56.

Subject Informed Consent

The informed consent forms (ICF) will be reviewed and approved by each IRB. The Investigator will conduct a brief interview over the telephone or in person and then meet with prospective participants and their parent or legally authorized representative to discuss the study and to give written informed consent to take part in the study if they choose to participate. Subject's parent or legally authorized representative will provide a signature of informed consent indicating that they have understood the purpose of and procedures required for the study, and willingness to participate in the study. Documentation of assent will be required by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions. Only after consent and assent have been provided would initial psychiatric and medical evaluations be conducted.