NAME OF SPONSOR: Purdue Pharma	**PROTOCOL No.:** 063-015
NAME OF STUDY TREATMENT: PRC-063	
TITLE OF STUDY: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Laboratory Classroom Study to Evaluate the Safety and Efficacy of PRC-063 Compared to Placebo in Children (6-12 years of age) with ADHD	
STUDY CENTERS: Multicenter.	
STUDY DURATION: For each subject, the overall duration including screening, could be up to a maximum of 10 to 12 weeks.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The expected enrolment duration is approximately 2 months.	

OBJECTIVES:

Primary Objectives:

- To assess efficacy of PRC-063 compared to placebo, as measured by the Swanson, Kotkin, Agler, M-Flynn and Pelham-Combined (SKAMP-Combined or SKAMP-C) score during the full day laboratory classroom
- To assess safety of PRC-063

Key Secondary Objective:

- To estimate the time to onset and the duration of efficacy of PRC-063 as measured by the SKAMP-C score assessed during the full day laboratory classroom

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- [redacted]
- [redacted]

[redacted]

[redacted]

STUDY DESIGN AND METHODOLOGY:

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

The study will have the following periods:

1) Screening Period: up to 28 days;
2) 3-day Washout Period: for washout and collection of baseline diary information. Some medications may require a washout period greater than 3-days or a dose taper, depending on the product labelling recommendations;
3) Open-label, Dose-Optimization Period: up to a 6-week open-label dose-optimization period during which subjects will be titrated from a starting dose of 25 mg up to his/her optimal dose (25, 35, 45, 55, 70 and 85 mg/day);
4) Double-Blind Treatment Period: 1-week double-blind period which will include 1 full day of evaluations in a laboratory classroom;
5) Safety Follow-up Period: 1-week safety follow-up after the last dose of study medication.

[redacted]

Screening Period (Visit 1, Day -28 to Day -4)

Screening assessments will only proceed once written informed consent/assent is obtained. The screening period may take up to 28 days. However, there is no minimum number of days for screening, and subjects may start washout as soon as eligibility is confirmed.

Following receipt of informed consent/assent, the following procedures and assessments will be done: inclusion/exclusion criteria, psychiatric history, diagnosis of ADHD using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and confirmed by the Kiddie – Schedule for Affective Disorders and Schizophrenia for School Age Children – Present and Lifetime DSM-5 version (K-SADS-PL) interview; demographics, medical and medication history including current pharmacological and non-pharmacological treatment for ADHD, physical examination including height and weight, vital signs (while seated), 12-lead electrocardiogram (ECG), clinical laboratory tests including urine drug screen, serology, urine pregnancy test for subjects of child-bearing potential (a serum pregnancy test will be done only if the urine pregnancy test is positive), a documented IQ assessment such as the Wechsler Abbreviated Scale of Intelligence II (WASI-II) or Kaufman Brief Intelligence Test-Second Edition (KBIT-2), Clinical Global Impressions –Severity (CGI-S), and Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Baseline/Screening version. Positive findings for suicidal ideation and/or suicidal behaviors are exclusionary. Appropriate interventions and follow-up measures will be implemented in such cases.

[redacted]

[redacted]

Washout Period (Day -3 to Day -1)

After receipt of the screening tests results and confirmation of inclusion and exclusion criteria, all eligible subjects will be asked to stop all their current treatments (medication and non-pharmacologic treatments) for ADHD and all subjects will begin a 3-day washout period prior to the baseline visit. Some medications may require a washout period greater than 3-days or a dose taper, depending on the product labelling recommendations. All pharmacological and non-pharmacological treatments for ADHD must be discontinued during the washout period and for the duration of the study.

[redacted]

Baseline (Visit 2, Day 0)

The baseline visit will include the following procedures: confirmation of inclusion/exclusion criteria, weight, sitting vital signs, 12-lead ECG, urine pregnancy test (if applicable), a single level-finding Permanent Product Measure of Performance (PERMP) math test, ADHD-RS-5; CGI-S; C-SSRS Children's Since Last Visit; concomitant therapy and adverse events (AEs). Subjects will be dispensed study medication for the next week, and given instructions for administration of study medication [redacted].

Open-label Dose-Optimization Period (Day 1 – Day 42; Week 1 – Week 6)

Following initial dosing with 25 mg, subjects will attend weekly clinic visits until they reach their optimal dose. Once subjects have reached their optimal dose, they will be eligible to participate in a half day practice laboratory classroom and be eligible for randomization. However, if necessary, subjects could continue to receive their optimized dose of PRC-063 while the required number of participants for the laboratory classroom are being assembled.

The visit schedule below is an illustration for subjects who participate in the full 6 weeks of dose-optimization.

- Clinic Visits: Visit 3 (Day 7 + 3); Visit 4 (Day 14 + 3), Visit 5 (Day 21 + 3), Visit 6 (Day 28 + 3), Visit 7 (Day 35 + 3)
- Half Day Practice Laboratory Classroom: Visit 8 (Day 42 + 3)
- Telephone Contact: Day 4, Day 11, Day 18, Day 25, Day 32, Day 39

Administration of daily open-label study medication will begin on Day 1 (the day following the baseline visit) and continue up to randomization (for example, subjects who optimize to PRC-063 85 mg, will take open-label study medication up to Day 42 [end of Week 6]). During the open-label dose-optimization period of up to 6 weeks, a parent or caregiver will administer the study medication once a day at home in the morning. On the half day practice laboratory classroom visit, study medication will be administered by clinic personnel. [redacted]

[redacted]

Subjects will return to the clinic every week. At clinic visits, subjects will be adjusted to the next available dose at weekly intervals, until their optimal dose is reached. Optimal dose will be defined as the dose that will produce a reduction in ADHD-RS-5 score ≥ 30% from Visit 2, and CGI-I score of 1 or 2 with tolerable side effects. Subjects who meet the definition for optimal dose and are tolerating the dose well, but may benefit from additional dose increases may have their dose further optimized. If a higher dose is not tolerated, subjects may step down 1 dose level. Tolerability will be determined by the investigator, based on review of AEs and clinical judgment. Once reached, the optimal dose will be maintained for the remainder of the dose-optimization period, and this dose will be used in the double-blind period. Subjects who have reached their optimal dose but are having tolerability issues may have one downward dose adjustment at the discretion of the investigator. Subjects who do not reach an optimal dose by Visit 8 or subjects who need a dose adjustment on the day of the practice laboratory classroom will be discontinued from the study. Subjects who are discontinued early from the study will complete the end of study assessments.

The following procedures will be included at each clinic visit: weight, vital signs, ECG, urine pregnancy test (if applicable), ADHD-RS-5; CGI-I; CGI-S; C-SSRS Children's Since Last Visit; drug dispensing; drug accountability; [redacted] concomitant medications/therapy; and AEs.

Study staff will contact each subject approximately 4 days after the baseline visit and after each dose-optimization clinic visit (approximately Day 4, Day 11, Day 18, Day 25, Day 32, and Day 39) to discuss any adverse reactions to PRC-063 or tolerability issues, and to remind subjects to take their study medication every day, bring their study medication container and unused medication to the next clinic visi[redacted]. Subjects will be reminded not to take their study medication at home on the half day practice laboratory classroom visit, and to bring their study medication container to the laboratory classroom visit.

On the half day practice laboratory classroom, study medication will be administered by clinic personnel after all pre-dose assessments have been completed. During this visit, along with the usual clinic assessments, subjects will attend a half-day practice laboratory classroom with analog classroom sessions to become familiar with classroom schedules and procedures. Three SKAMP assessments, and 3 practice PERMP tests will be completed during the practice laboratory classroom visit.

Randomization: Subjects who have reached their optimal dose will be randomized in a 1 to 1 ratio after they have completed the half day practice laboratory classroom to receive double-blind treatment (optimized dose of PRC-063 or placebo) for 1 week (7 days). Randomization will be stratified by individual dose level so that approximately half the subjects within each dose level will receive PRC-063 and half will receive placebo. Subjects will be eligible for randomization if they meet the following criteria:

- Stable dose of open-label PRC-063 for at least 1 week; defined as no change in dose between the week preceding the half day practice classroom visit and the day of the half day practice classroom visit

- Optimal dose of PRC-063 on the half day practice classroom visit in the judgment of the investigator
- No change in medical condition that precludes administration of double-blind treatment
- Complete pre-dose and post-dose laboratory classroom assessments during the half day practice classroom visit.

Double-blind Treatment Period (Week 6 - Week 7)

Administration of daily double-blind study medication will begin on the day after randomization and continue for 7 days. During the double-blind treatment period of 1 week, study medication will be administered once daily at home in the morning. On the last day of the double-blind period, subjects will attend a full day laboratory classroom and study drug will be administered by the clinic staff after all pre-dose assessments have been completed. [redacted]

On the last day of the 1-week double-blind treatment period, subjects will participate in the full day laboratory classroom. Subjects will arrive around 6:00 am and depart around 9:00 pm. The full day laboratory classroom will consist of PERMP tests and SKAMP assessments within 30 minutes prior to dosing and at 1, 2, 4, 6, 8, 10, 12 and 13 hours following administration of study medication.

In addition, the following procedures will be included: weight, vital signs (once between 10 and 13 hours post-dose), ECG (once between 10 and 13 hours post-dose), urine pregnancy test (if applicable), ADHD-RS-5 (may be completed the day before the full day classroom visit at the discretion of the investigator); CGI-I; CGI-S; C-SSRS Children's Since Last Visit; concomitant medications/therapy; and AEs.

End of Study Assessments

End of study assessments will occur after the 6 hour post-dose assessment of the full day laboratory classroom visit, or within 3 days after the last dose of study medication. For subjects who discontinue from the study early, end of study assessments should be performed at the time of discontinuation or within 3 days after the last dose of study medication.

Safety Follow-up

Subjects will be followed up approximately 7 days after last dose of study medication to assess AEs, concomitant medications/therapy and to complete the C-SSRS Children's Since Last Visit. The Safety Follow-up can be conducted in-person or over the telephone, at the investigator's discretion.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Subjects cannot be enrolled before all inclusion criteria (including test results) and exclusion criteria are confirmed.

Inclusion Criteria:

1. Males or females greater than or equal to 6 and less than or equal to 12 years of age
2. Females who are non-pregnant and non-nursing
3. Females of child-bearing potential who agree to practice a clinically accepted method of contraception during the study and for at least one month prior to study dosing and one month following completion of the study. Acceptable contraceptive methods include abstinence, oral contraception, surgical sterilization (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), intrauterine device, or diaphragm in addition to spermicidal foam and condom on male partner, or systemic contraception (e.g. levonorgestrel-releasing implant)
4. Diagnosis of ADHD (any type: combined, predominately hyperactive impulsive type or predominately inattentive type) by a psychiatrist, psychologist, developmental pediatrician or licensed allied healthcare professional using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and confirmed by administration of a structured diagnostic interview using the Kiddie – Schedule for Affective Disorders and Schizophrenia for School Age Children – Present and Lifetime DSM-5 version (K-SADS-PL)
5. Ratings on the ADHD-RS-5 based on Visit 2 data when the subject is not receiving treatment for ADHD must be ≥ 90th percentile normative value for gender and age in at least 1 of the categories: total score, inattentive subscale or hyperactive/impulse subscale
6. Unsatisfied with his or her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD. Inclusion of subjects who are naïve to pharmacological therapy for ADHD is permitted
7. Must be functioning at an age-appropriate level intellectually as determined by an intelligence quotient of ≥ 80 on a documented IQ assessment such as the Wechsler Abbreviated Scale of Intelligence II™ (WASI-II) vocabulary and matrix reasoning components, or the Kaufman Brief Intelligence Test, Second Edition (KBIT-2)
8. Must have the ability to complete the PERMP assessments
9. Have parental consent (signed informed consent form) and written or verbal assent from the subject
10. Subject and parent(s)/caregiver are willing and able to comply with all the protocol requirements and parent(s) or caregiver must be able to provide transportation for the subject to and from the analog classroom visits

Exclusion Criteria:

1. Has blood pressure and pulse greater than the 95th percentile for age and gender
2. Is a known non-responder to methylphenidate treatment
3. Has a documented allergy, intolerance, or hypersensitivity to methylphenidate
4. Has current or recent history (within the past 6 months) of drug abuse or dependence disorder in the subject or the immediate family or by someone living at the participant's' home or positive urine drug screen for stimulant medication (other than currently prescribed stimulant for the treatment of ADHD) or drugs of abuse at the screening visit

5. Has untreated thyroid disease, glaucoma, Gilles de la Tourette's disorder, chronic tics or a history of seizures during the last 2 years (except simple febrile seizures), or a tic disorder. Mild medication-induced tics are not exclusionary
6. Primary and/or comorbid psychiatric diagnosis other than ADHD with the exception of simple phobias, motor skill disorders, communication disorders, learning disorders and adjustment disorders so long as such disorder is judged not to interfere with study participation or the safety of the subject or other participants. Children meeting conduct disorder or oppositional defiant disorder criteria but without history of prominent aggressive outbursts that could interfere with study participation or the safety of the subject or other participants will be allowed to enroll at the discretion of the investigator
7. Subjects with a family history (first degree relatives) of sudden cardiac death require review and approval by the medical monitor for participation in the study
8. Has a current or recent history of hypertension, symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug
9. Any clinically significant abnormality or clinically significant abnormal laboratory test, urine test, or ECG result found during medical screening, or has a concurrent medical condition that, in the opinion of the investigator, could cause participation in this study to be detrimental to the subject
10. Has used any investigational drug within 30 days of the screening visit
11. Has a known history of physical, sexual, or emotional abuse in the last year
12. Has a medical history of hepatitis A, B, C or human immunodeficiency virus, or tests positive for any of these at screening (subjects who have received the hepatitis A vaccine and test positive for hepatitis A may be included in the study, at the discretion of the investigator)
13. Has a positive urine pregnancy test (if applicable) at screening
14. Has positive findings on C-SSRS for suicidal ideation or behaviors at screening.

NUMBER OF SUBJECTS:

Based on prior studies, the average difference between the mean SKAMP-Combined score for the placebo and PRC-063 treatment arms is assumed to be at least 0.50 units with a common standard deviation of 0.85 units. A two-sample t-test with a 5% (2-sided) significance level and at least 88% power requires approximately 116 subjects (58 per treatment arm) to participate in the full day laboratory classroom evaluations.

Assuming a dropout rate of 20% from the start of the dose-optimization to the classroom evaluation, approximately 145 subjects will be required to enter the dose-optimization period of the study.

STUDY TREATMENT(S):

Test Product, Dose and Mode of Administration:
PRC-063 capsules (25, 35, 45, 55, 70, or 85 mg), administered orally, once daily

Reference Therapy, Dose and Mode of Administration:
Placebo capsules, administered orally, once daily

DURATION OF TREATMENT: Each subject will be treated with open-label PRC-063 for up to 6 weeks, and with double-blind study medication (PRC-063 or placebo) for up to 1 week, for a total treatment duration of up to 7 weeks.

STUDY EVALUATIONS:

Primary Efficacy Endpoint:

- Mean SKAMP-C score assessed during the full day laboratory classroom. Multiple SKAMP assessments will be completed throughout the day. The mean SKAMP-C score for each subject will be the average of all SKAMP-C scores collected during the full day laboratory classroom, with the exception of the SKAMP-C score prior to dosing

Key Secondary Efficacy Endpoint

- SKAMP-C scores assessed at all time points during the full day laboratory classroom

[redacted]

Safety Endpoints:

- Adverse events (AEs), [redacted] weight, suicidality - assessed using C-SSRS, concomitant medications/therapy, clinical laboratory tests, vital signs, and ECGs.

STATISTICAL METHODS:

The primary efficacy and key secondary efficacy analyses will use a repeated measures model which includes the full day laboratory classroom SKAMP-C scores from each time point as the dependent variable. The independent variables in the model include fixed effects for treatment, time, treatment-by-time interaction, investigative site, and covariate terms for the pre-dose SKAMP-C score and pre-dose SKAMP-C score-by-time interaction. The full analysis set will be used to generate the primary efficacy results and the per-protocol population will be used to provide supportive information.

The mean SKAMP-C score and SKAMP-C scores at each time point from the classroom will be summarized descriptively by raw means, standard deviations, and a 5-number summary (minimum, 1st quartile, median, 3rd quartile, maximum). The change from the pre-dose SKAMP-C score at each time point will be summarized similarly. The least-squares (LS)-means will be shown for each treatment group along with the difference between the treatment LS-means. A 95% confidence interval for the difference and a p-value that statistically compares the 2 treatments will also be displayed.

The key secondary efficacy analysis will be the onset and duration of efficacy of PRC-063 which will be calculated from the SKAMP-C scores at each time point on the full day laboratory classroom by assessing treatment differences at each time point.

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Summary statistics will be provided for safety endpoints.

[redacted]

DATE AND VERSION: 11 July 2017, version 4.0