Protocol No. 063-020

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, ADULT LABORATORY CLASSROOM STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PRC-063 COMPARED TO PLACEBO IN ADULTS WITH ADHD

Sponsor: **PURDUE PHARMA (CANADA)**
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Study Product PRC-063

Study Phase: 3

Date and Version Amendment 2 Final 24 Apr, 2019 version 3.0

[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6 (R2)), and applicable local regulatory requirements.

CONFIDENTIAL

1. SYNOPSIS

NAME OF SPONSOR: Purdue Pharma (Canada)	**PROTOCOL No.:** 063-020
NAME OF STUDY TREATMENT: PRC-063	
TITLE OF STUDY: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Adult Laboratory Classroom Study to Evaluate the Safety and Efficacy of PRC-063 Compared to Placebo in Adults with ADHD	
STUDY CENTERS: Multicenter	
STUDY DURATION: For each subject, the overall duration could be up to 10 weeks, including a 7-day follow-up period. Subjects will be required to visit the clinic up to 10 times over a 10-week period.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: Anticipated Start Date: 20 Aug-2018 Anticipated Stop Date: 14-Jan-2019	
OBJECTIVES: The purpose of this study is to evaluate the clinical efficacy and safety of PRC-063 in adults diagnosed with attention deficit/hyperactivity disorder (ADHD). **Primary Objective:** • To assess the efficacy of PRC-063 compared to placebo as measured by the Permanent Product Measure of Performance-Total (PERMP-T) scores assessed during the full day adult laboratory classroom (ALC) visit [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 for the treatment of ADHD in adults. After providing a written informed consent, subjects will be screened to ascertain their eligibility for the study according to the inclusion and exclusion criteria.

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 [redacted] 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 7-week, open-label, dose-optimization period during which subjects will be titrated from a starting dose of 25 mg/day up to his/her optimal dose (25, 35, 45, 55, 70, 85, or 100 mg/day), and will include one half day evaluation in a practice ALC;
4) Double-blind Treatment Period; 1-week double-blind treatment period which will include one full day evaluation in an ALC;
5) Safety Follow-up Period; 7-day safety follow-up visit after the last dose of study medication.

[redacted]

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

Any protocol-specific activity which is not part of the normal clinical practice of the site must be performed only after obtaining the subject's consent. 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, 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) structured clinical interview (SCID-5-CT), 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), and Columbia-Suicide Severity Rating Scale (C-SSRS), 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.

Washout Period (Day -3 to Day -1)

After receipt of all the test results and confirmation that a subject is eligible to participate in the study, eligible subjects who are currently taking any medication for the treatment of ADHD will begin

a washout period of three days prior to the baseline visit (Day 0). 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)

Baseline will include the following procedures: confirmation of inclusion/exclusion criteria; sitting vital signs, weight; 12-lead ECG; urine pregnancy test (if applicable), ADHD-RS-IV; one PERMP Placement Test; Clinical Global Impressions- Severity (CGI-S); C-SSRS suicidality assessment; concomitant medications and adverse events (AEs). Study medication will be dispensed.

Open-label Dose-optimization Period (Day 1 – Day 49; Week 1 – Week 7)

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 ALC 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 half day practice ALC are being assembled.

Once a subject reaches his/her optimal dose and has been on his/her optimal dose for at least one week, they will be eligible to attend a half day practice ALC. The visit schedule below is an illustration for subjects who participate in the full 7 weeks of dose-optimization.

Clinic Visits: Visit 3 (Day 7 -1, + 3); Visit 4 (Day 14 -1, + 3), Visit 5 (Day 21 -1, + 3), Visit 6 (Day 28 -1, + 3), Visit 7 (Day 35 -1, + 3), Visit 8 (Day 42 -1, + 3)

Telephone Contact: Day 4, Day 11, Day 18, Day 25, Day 32, Day 39, Day 46

Half Day Practice ALC Visit and Randomization: Visit 9 (Day 49 + 3)

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-063 100 mg will take open-label study medication up to Day 49 [end of Week 7]). During the open-label dose-optimization period of up to 7 weeks, the subject will administer the study medication once a day at home in the morning. On the half day practice ALC visit, study medication will be administered by clinic personnel [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-IV 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 9 or subjects who need a dose adjustment on the day of the practice ALC 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 dose-optimization clinic visit: weight, vital signs, ECG, urine pregnancy test (if applicable), ADHD-RS-IV; CGI-I; CGI-S; C-SSRS Since Last Visit; drug dispensing; drug accountability; [redacted] concomitant medications/therapy; two practice PERMP tests, 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, Day 39, and Day 46), to discuss any adverse reactions to PRC-063 or tolerability issues, record any concomitant medications, to remind subjects to take their study medication every day and to bring their study medication container and unused medication to the next clinic visit, [redacted] Subjects will be reminded not to take their study medication at home on the half day practice ALC visit, and to bring their study medication container to the ALC visit.

On the half day practice ALC visit, 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 ALC to become familiar with schedules and procedures. Six [redacted] practice PERMP tests will be completed during the half day practice ALC visit.

Randomization

Subjects who have reached their optimal dose will be randomized in a 1 to 1 ratio during the half day practice ALC to receive double-blind treatment (optimized dose of PRC-063 or placebo) for one 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:

- Optimal dose of open-label PRC-063 for at least 7 days; defined as no change in dose between the week preceding the half day practice ALC visit and the day of the half day practice ALC visit
- Optimal dose of PRC-063 on the half day practice ALC visit in the judgment of the investigator
- No change in medical condition that precludes administration of double-blind treatment
- Complete pre-dose ALC assessments and dosing during the half day practice ALC visit.

Double-blind Treatment

Administration of double-blind study medication will begin on the day after randomization and continue for seven days. During the double-blind treatment period of 1 week (7 days), study medication will be administered once daily at home in the morning. During the double-blind

treatment period, every day, [redacted] On the last day of the double-blind period, subjects will attend a full day ALC visit and study drug will be administered by the clinic staff after all pre-dose assessments have been completed.

Subjects will arrive around 6:00 am and depart around 12:00 am (midnight). The full day ALC visit will consist of [redacted] PERMP tests within 30 minutes prior to dosing (pre-dose), and at 0.5, 1, 2, 4, 6, 7.5, 9, 11, 13, 14, 15, and 16 hours following administration of study drug. The following assessments will also be completed: weight, vital signs (once between 10 and 16 hours post-dose), ECG (once between 10 and 16 hours post-dose), [redacted] urine pregnancy test (if applicable), ADHD-RS-IV, CGI-S, CGI-I, C-SSRS suicidality assessment, drug accountability, concomitant medications; and AEs.

End of Study Assessments

End of study assessments will occur during the full day ALC visit after the 6-hour post-dose assessment, or within three 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 three days after the last dose of study medication.

Safety Follow-up

Subjects will have a safety follow-up approximately seven days after last dose of study medication to assess AEs and concomitant medications/therapy. 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) are confirmed.

Inclusion Criteria:

1. Males or females 18 to 60 years of age, inclusive
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. Norplant System];
4. Diagnosis of ADHD (any type: combined, predominately hyperactive impulsive type or predominately inattentive type) by a psychiatrist, psychologist, or licensed allied healthcare professional using the Structured Clinical Interview for DSM-5 (SCID-5): Clinical Trials Version (SCID-5-CT);
5. Ratings on the ADHD-RS-IV based on Visit 2 data when the subject is not receiving treatment for ADHD must be equal to or greater than 28;
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. Minimum level of intellectual functioning, as determined by an intelligent quotient (IQ) score of 80 or above based on a documented IQ assessment such as the WASI-II vocabulary and matrix reasoning components, or the KBIT-2;
8. Must have the ability to complete PERMP assessment;
9. Subject is willing and able to comply with all the protocol requirements.

Exclusion Criteria:

1. Elevated blood pressure, defined as any values above 89 mmHg diastolic or 139 mmHg systolic at screening and/or baseline;
2. Is a known non-responder to methylphenidate treatment (defined as used at various doses for at least four weeks at each dose with little or no clinical benefit in the last 10 years);
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 living with subject 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. A subject with a positive urine drug screen for Tetrahydrocannabinol (THC) at the screening visit may participate in the study after receiving approval by medical monitor and the subject must agree to abstain from using marijuana and THC containing products for the duration of study. For such subjects, abstinence should be confirmed

through one or two random, unscheduled urine drug screens conducted at the discretion of the Investigator;

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;
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 (QTcF greater than 450 msec for males or 470 msec for female is exclusionary) 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 occurring within the past two years as assessed at screening.

NUMBER OF SUBJECTS: A sufficient number of subjects will be screened and entered into the dose-optimization period such that approximately 200 subjects will be randomized. It is expected that 200 subjects will complete the full day ALC assessments.

STUDY TREATMENT(S):

Test Product, Dose and Mode of Administration:
PRC-063 capsules (25, 35, 45, 55, 70, 85, or 100 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 7 weeks, and with double-blind study medication (PRC-063 or placebo) for up to 1 week (7 days), for a total treatment duration of up to 8 weeks.

STUDY EVALUATIONS:

Primary Efficacy Endpoint:

- Post-dose PERMP-T scores measured on the full day ALC visit

[redacted]

- [redacted]

Safety Endpoints:

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

STATISTICAL METHODS:

The primary efficacy analysis will use a mixed model for repeated measures (MMRM) which includes the full day ALC visit PERMP-T scores from each time point as the multivariate normally distributed dependent variable. The independent variables in the model include fixed effects for treatment (2 levels), time (12 post-dose times), treatment-by-time interaction, investigative site (number of sites), and covariate terms for the pre-dose PERMP-T score and pre-dose PERMP-T score-by-time interaction (which allows the pre-dose covariate parameter to change over time). An unstructured covariance matrix will be used to model the covariance among the repeated measures. However, in the unlikely event that the model does not converge, an alternative covariance matrix will be used which is appropriate for the repeated measurements (e.g., heterogeneous first-order autoregressive). Since this is a repeated measures analysis with potential missing data, the Kenward-Roger approximation will be used for calculating the denominator degrees of freedom and adjusting standard errors. The Full Analysis population will be used to generate the primary efficacy results and the Per-Protocol population will be used to provide supportive information. The repeated measures model-adjusted means (LS-means) for PRC-063 and placebo will be compared statistically using a t-test with an overall 5% significance level to evaluate efficacy. The estimated difference of the two LS-means provides an overall treatment effect across the entire 16-hour ALC evaluation, and an accompanying 95% confidence interval will portray the precision of the estimated effect. The null and alternative hypotheses used to evaluate efficacy for the primary endpoint are:

- Null hypothesis: The group means for PRC-063 and placebo are equal.
- Alternative hypothesis: The group means for PRC-063 and placebo are not equal.

The sample size estimate was based on the overall mean treatment difference from the MMRM. Assuming an average PERMP-T score treatment difference of 35 and a common standard deviation of 75, a total sample size of 200 (100 per treatment group) randomized subjects is sufficient to achieve at least 90% power with a 0.05, two-sided significance level. Approximately 250 subjects will enter the dose-optimization period to allow for an expected dropout rate of 20% prior to randomization. A blinded sample size re-estimation will be performed when approximately 75% of the planned randomized subjects have completed their full day ALC visit.

DATE AND VERSION: 24 April 2019, Version 3.0