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Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Adult Laboratory Classroom Study of the Efficacy and Safety of PRC-063 (Extended-Release Methylphenidate) for the Treatment of ADHD

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Abstract

Objective: To evaluate the efficacy, safety, and duration of action of the once-daily extended-release methylphenidate formulation PRC-063 for the treatment of ADHD in an adult laboratory classroom (ALC). **Method:** After dose optimization with PRC-063 over 7 weeks, adults with ADHD were randomized to 1 week of double-blind treatment with PRC-063 or placebo that ended with an ALC evaluation. The primary outcome measure was Permanent Product Measure of Performance-Total (PERMP-T) score. **Results:** Of 288 subjects enrolled, 221 completed the ALC visit. PERMP-T score was significantly higher for PRC-063 versus placebo at every assessment from 1 to 16 hours post-dose at the ALC visit and when averaged over 16 hours post-dose (least-squares mean difference 16.3, 95% confidence interval 7.6–24.9). The most frequent adverse events during dose optimization were headache, decreased appetite, and insomnia. **Conclusion:** PRC-063 provided rapid and sustained symptom relief in adults with ADHD and was well tolerated. NCT03618030. *(J. of Att. Dis. 2022; 26(6) 857-869)*

Keywords

adult ADHD, ALC environment, efficacy, methylphenidate, safety, sustained and long-lasting stimulant

Introduction

ADHD affects an estimated 2.5% to 5.0% of the adult population worldwide (Ginsberg et al., 2014). According to World Mental Health Surveys conducted by World Health Organization, the prevalence of ADHD in adults is higher among high- or upper-middle-income countries than low- or lower-middle-income countries (3.0%–3.6% vs. 1.4%) (Fayyad et al., 2017). Common manifestations of ADHD in adults include inattentiveness, disorganization, forgetfulness, impulsivity, and excessive physical activity (Katzman et al., 2019). Functional impairments due to ADHD in adults are varied and do not just affect work performance, but also interfere with other routine activities. These activities may include driving, parenting, and daily household chores, which can begin early in the morning and continue until late evening (Goodman, 2007; Katzman et al., 2019). Hence, many adult patients require an ADHD medication that provides a rapid onset of action when taken in the morning and adequate symptom relief throughout the day.

Methylphenidate is one of the most widely accepted and commonly prescribed drugs for ADHD symptom management, and has proven to be safe and effective in children, adolescents, and adults with ADHD (Fallu et al., 2016; Huss et al., 2014, 2017). In a comprehensive network meta-analysis, methylphenidate was one of the most efficacious drugs in adults based on ratings from both clinicians and patients (Cortese et al., 2018). Moreover, according to

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National Institute for Health and Clinical Excellence guidelines, methylphenidate is the first-line pharmacotherapy for ADHD in adults (NICE, 2018). However, multiple daily dosing with immediate-release methylphenidate formulations can be inconvenient and has been shown to be associated with fluctuations in plasma concentrations and poor treatment adherence (Gajria et al., 2014). Most extended-release methylphenidate formulations only last up to approximately 12 hours, meaning patients often require additional immediate-release booster doses toward the end of the day (Childress et al., 2018; Gormez et al., 2013; Lachaine et al., 2012; Swanson, 2005; Wigal et al., 2018). Therefore, there remains a medical need for an ADHD medication that provides day-long symptom relief (Wigal et al., 2020).

PRC-063 is a beaded, multilayer, extended-release methylphenidate formulation approved in the US (as Adhansia XR®) and Canada (as Foquest®) for the treatment of ADHD in patients 6 years and older. It is designed to provide rapid symptom relief lasting for more than 12 hours when taken once daily in the morning (Wigal et al., 2020). The PRC-063 formulation comprises an immediate-release layer (~20% of the methylphenidate dose) that is immediately released following ingestion and a controlled-release layer (~80% of the methylphenidate dose) with a pH-sensitive, delayed-release polymer coating that prevents any significant release of methylphenidate until after the pH in the gastrointestinal tract reaches 7 or above. PRC-063 has a biphasic pharmacokinetic profile, with an initial peak at ~1.5 hours and a second, higher peak at ~12 hours (Katzman et al., 2020). Steady state is achieved by day 3 of once-daily dosing (Katzman et al., 2020; Weiss et al., 2020; Wigal et al., 2020).

Previous studies have investigated the safety and efficacy of PRC-063 in children, adolescents and adults with ADHD (Childress et al., 2020; Kollins et al., 2016; Weiss et al., 2020; Wigal et al., 2020). In a randomized, double-blind, crossover study conducted in a simulated adult workplace environment (ClinicalTrials.gov identifier NCT02225639), mean Permanent Product Measure of Performance-Total (PERMP-T) score was significantly higher for PRC-063 than for placebo. Mean Swanson, Kotkin, Agler, M-Flynn, and Pelham-Combined (SKAMP-C) score was also higher for PRC-063 than for placebo (Wigal et al., 2020). Moreover, in a 4-week, randomized, double-blind, placebo-controlled parallel-group, multi-center study in adults with ADHD (NCT02139124), PRC-063 was associated with significant improvements in ADHD symptoms based on the ADHD Rating Scale 5 (ADHD-RS-5) (Weiss et al., 2020).

Available methylphenidate formulations often fail to provide an adequate duration of ADHD symptom relief. In the present study, we evaluated the efficacy, safety, and onset and duration of action of PRC-063 in adults with ADHD in an adult laboratory classroom (ALC) environment.

Methods

Overall Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled, dose-optimized, phase 3 ALC study (Swanson et al., 2000) conducted at eight sites in the United States between August 2018 and July 2019 (NCT03618030). The study comprised a screening period of up to 28 days; a 3-day washout period; a 7-week open-label dose-optimization period, during which subjects were titrated from a starting dose of 25 mg to their optimal dose (25, 35, 45, 55, 70, 85, or 100 mg/day) and then underwent a half-day ALC evaluation at the study site; a 1-week double-blind treatment period, including a full-day (16-hour) ALC evaluation at the study site; and safety follow-up 1 week after the last dose of study drug (Figure 1). For each site, central or local institutional review board approval of the study was obtained. Subjects provided written informed consent prior to the initiation of any study-specific procedures. All study-related activities were performed in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and local and national laws.

Participants

Eligible participants were adults aged 18 to 60 years with a diagnosis of any of the three presentations of ADHD (based on Structured Clinical Interview for DSM-5) and an ADHD Rating Scale IV (ADHD-RS-IV) score ≥28 at baseline (i.e., when not receiving treatment). They were also dissatisfied with or not receiving current ADHD therapy or were treatment-naïve. Participants were required to have an IQ ≥80 on the Wechsler Abbreviated Scale of Intelligence II™ (McCrimmon & Smith, 2012) or the Kaufman Brief Intelligence Test–2 (Bain & Jaspers, 2010). Females of child-bearing potential were required to not be pregnant or nursing at screening and to use a clinically accepted method of contraception during the study. Potential participants were excluded from the study if they had a primary or comorbid psychiatric condition other than ADHD; if they or someone they lived with had in the previous 6 months experienced substance abuse or dependence disorder; or if the urine drug test at screening was positive for recreational drugs or for a stimulant other than their current ADHD medication. Other reasons for exclusion included history of allergy, intolerance, hypersensitivity, or non-responsiveness to methylphenidate; history of hypertension, serious cardiac

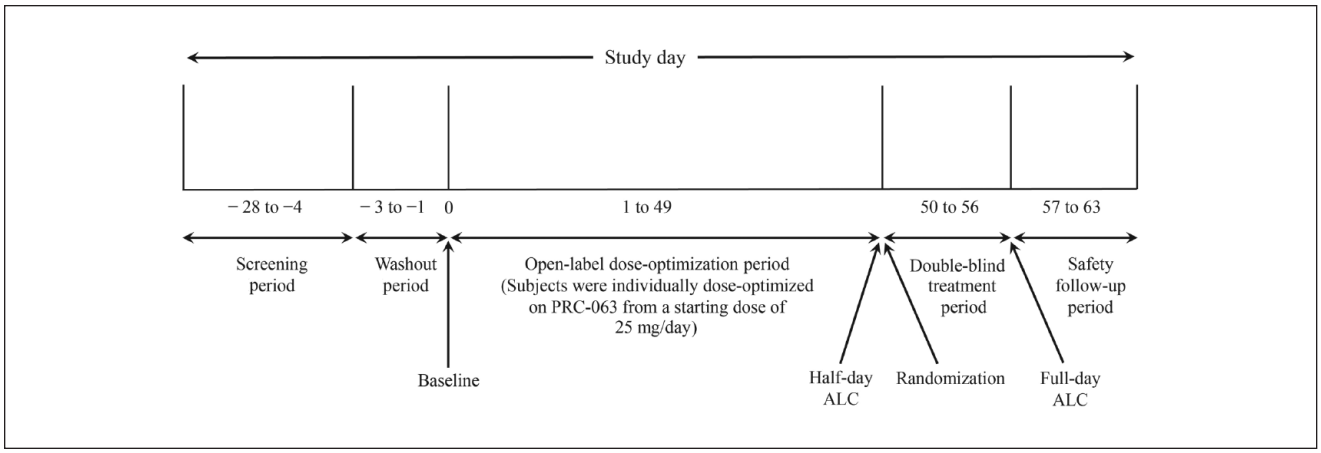

Figure 1. Overall study design.
Note. ALC = adult laboratory classroom.

problems, thyroid disease, or seizures; a clinically significant laboratory or electrocardiogram (ECG) abnormality that meant participation in the study could be detrimental to the subject, in the judgment of the investigator; suicidal ideation or behavior in the previous 2 years; physical, sexual, or emotional abuse in the previous year; and use of an investigational drug in the previous 30 days.

Study Treatment

During the open-label dose-optimization period, subjects took a capsule of PRC-063 (25, 35, 45, 55, 70, 85, or 100 mg) each morning at home. All subjects were initiated at the lowest available dose of PRC-063 (25 mg/day) and had their dose increased weekly until their optimal dose was reached. The dose was considered optimized when there was a ≥30% reduction in ADHD-RS-IV score from baseline, a Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2, and side effects that were tolerable, as assessed by the investigator based on their clinical judgment and a review of efficacy and adverse events (AEs). Subjects who reached their optimal dose but who were expected to benefit from an additional dose increase could have their dose increased further. Subjects whose dose was optimal based on ADHD-RS-IV and CGI-I scores but who were having tolerability issues could have their dose reduced, at the discretion of the investigator. The optimal dose, once reached, was maintained for the remainder of the open-label dose-optimization period and during the double-blind treatment period. Subjects who did not reach an optimal dose by the seventh week of open-label treatment were withdrawn from the study.

Subjects whose PRC-063 dose had been optimized and who completed the half-day ALC assessments were randomized 1:1 to receive either PRC-063 or an identical-looking placebo during the double-blind treatment period. Randomization was applied centrally across all sites using an interactive web response system and was stratified by optimized dose so that, for each dose, approximately half of all subjects received PRC-063 and half received placebo during the double-blind treatment period. Starting from the day after randomization, participants took a capsule of PRC-063 (25, 35, 45, 55, 70, 85, or 100 mg) or placebo each morning at home. On the days of the half-day and full-day ALC evaluations, study drug was administered by staff at the study site after the pre-dose evaluations had been completed.

Assessments and Endpoints

At the half-day ALC visit, participants practiced the assessments that would be completed at the full-day ALC visit. At the full-day ALC visit, subjects completed the PERMP and were assessed for PERMP-T score over 16 hours after dosing (primary endpoint) and time to onset and duration of efficacy of PRC-063 based on PERMP-T score after dosing (key secondary endpoints). Other secondary endpoints included ADHD-RS-IV (with adult prompts) (Adler & Cohen, 2004), CGI-Severity (CGI-S), CGI-I, and SKAMP-C. Safety endpoints included AEs, physical examination, vital signs (blood pressure, heart rate, and body weight), ECG, and clinical laboratory tests (clinical chemistry, hematology, and urinalysis).

For the PERMP (Swanson et al., 2000), subjects were given 400 math problems during the classroom sessions at the ALC visits and were asked to complete as many of them as possible in 10 minutes. The difficulty level of the math problems was individualized based on an assessment of each subject's ability at baseline. Subjects completed the

PERMP before dosing and approximately 0.5, 1, 2, 4, 6, 7.5, 9, 11, 13, 14, 15, and 16 hours after dosing. At each time point, a different selection of problems was used, so that no participant took the same test more than once. PERMP-T score (range 0–800) was calculated as the sum of the number of problems attempted and the number of problems answered correctly. Mean PERMP-T score was calculated as the average of the scores obtained after dosing at the full-day ALC visit.

ADHD-RS-IV (with adult prompts) was assessed at baseline, during open-label dose-optimization, at the half-day ALC visit, and the day before the full-day ALC visit. A clinician-rated scale, the ADHD-RS-IV (Adler & Cohen, 2004; DuPaul, 2006) assesses the current severity of ADHD symptoms. It comprises 18 items grouped into two subscales: inattention (nine items) and hyperactivity/impulsivity (nine items). Each item is scored on a 4-point scale from 0 (not present) to 3 (severe), giving an ADHD-RS-IV total score ranging from 0 to 54. ADHD-RS-IV scores were categorized as 0 to 18 (mild), 19 to 36 (moderate), and 37 to 54 (severe). These categories were defined a priori based on mean per-item scores for the 18 ADHD-RS-IV items.

The CGI-S was assessed at baseline, and both the CGI-S and CGI-I were assessed during open-label dose-optimization and at the half-day and full-day ALC visits. The CGI scales (Busner & Targum, 2007; Guy, 1976) provide a clinician-rated global evaluation of baseline symptom severity (CGI-S) and improvement over time (CGI-I). The CGI-S is used to rate the severity of a patient's illness on a scale of 1 (normal, not at all ill) to 7 (among the most extremely ill patients) and the CGI-I is used to rate improvement from baseline in the patient's overall clinical condition on a scale of 1 (very much improved) to 7 (very much worse).

The SKAMP was assessed by trained observers during the classroom sessions at the half-day and full-day ALC visits. It is a 13-item scale that assesses impairment related to inattention and behavior problems of ADHD (Wigal, 2019; Wigal et al., 1998). SKAMP-C (range 0–78) was calculated by summing the scores for the different SKAMP items, each of which is scored on a 7-point scale ranging from 0 (none) to 6 (maximal impairment).

AEs were recorded from the signing of informed consent through the safety follow-up visit. Reporting of serious adverse events (SAEs) continued for 30 days after the last dose of study drug. Treatment-emergent AEs (TEAEs, events that started or whose severity worsened after the first dose of PRC-063) were assessed for seriousness and relationship to study treatment and were graded according to severity. Study discontinuation due to AEs was recorded.

Statistical Analyses

Analyses of the primary and secondary endpoints were based on the full analysis population, which consisted of all randomized participants who attended the full-day ALC visit, received double-blind study drug at the full-day ALC visit, and had at least one post-dose PERMP-T score during the full-day ALC visit. Analyses of demographic and baseline characteristics and AEs were based on the safety analysis population, which consisted of all participants who received at least one dose of study drug during the open-label dose-optimization period and had at least one post-dose safety assessment. Summary statistics were calculated using SAS v9.4 (SAS Institute Inc., NC, USA).

The primary efficacy analysis used a mixed-model for repeated measures (MMRM) that included the full-day ALC PERMP-T score for each time point as the dependent variable. Fixed effects for treatment, post-dose time point, treatment-by-time interaction, and study site, and covariate terms for pre-dose PERMP-T score and pre-dose PERMP-T score-by-time interaction, were included as independent variables. The MMRM-adjusted least-squares (LS) means for PRC-063 and placebo across the full 16-hour ALC evaluation were compared by *t*-test. A p-value of $<.05$ was considered significant. 95% confidence intervals (CIs) were calculated for the difference between PRC-063 and placebo. A similar analysis was performed for change from pre-dose PERMP-T score. Because the primary efficacy analysis only compared two treatment groups, no adjustment for multiplicity was warranted.

To assess the impact of missing data, sensitivity analyses were performed for the primary efficacy analysis by imputation of the subject's worst post-dose score; imputation of the subject's best post-dose score; imputation of the worst post-dose score for subjects randomized to PRC-063 and the best post-dose score for subjects randomized to placebo (worst case scenario); and Markov Chain Monte Carlo multiple imputation, where missing data was imputed twenty times.

Time to onset of efficacy was defined as the first post-dose time point where the difference in the PERMP-T score between the two treatment groups was statistically significant. Duration of efficacy was defined as the time interval between the onset of efficacy and the offset of efficacy (i.e., the first time point after the onset of efficacy where the difference in PERMP-T score between the two treatment groups was not statistically significant).

For each visit during the open-label dose-optimization and double-blind treatment periods, analysis of covariance models were used to analyze ADHD-RS-IV total score and change from baseline as the dependent variable. The models included fixed effects for treatment and study site as independent variables; baseline ADHD-RS-IV total score was included as a covariate term.

CGI-I scores were dichotomized as treatment responder (1, 2) and non-responder (3, 4, 5, 6, 7). For each time point, numbers and percentages of participants with different CGI-S scores and who were treatment responders and non-responders based on CGI-I were calculated.

SKAMP-C was analyzed in the same way as PERMP-T. For the full-day ALC visit, pre-dose, average post-dose, and average change from pre-dose SKAMP-C scores were calculated.

TEAEs were allocated to either the open-label dose-optimization period or the double-blind treatment period. TEAEs that started in the open-label dose-optimization period and continued into the double-blind treatment period without worsening in severity were allocated to the open-label dose-optimization period; those that worsened in severity during double-blind treatment were allocated to both treatment periods; and those that occurred during safety follow-up were allocated to the double-blind treatment period. Any TEAEs for which a missing or incomplete start made it impossible to determine which study period they started in were allocated to the open-label dose-optimization period.

Sample Size

Based on prior studies of PRC-063 in an adult workplace environment (Wigal et al., 2020), the MMRM-adjusted LS mean difference in PERMP-T score between placebo and PRC-063 was assumed to be at least 35 points, with a common standard deviation (SD) of 75 points. A two-sample *t*-test with a two-sided significance level of 0.05 and at least 90% power required that approximately 200 randomized participants (100 per group) should participate in the full-day ALC evaluation. Assuming a dropout rate of 20% from the start of the open-label dose-optimization period through the half-day ALC evaluation, approximately 250 participants were required to enter the open-label dose-optimization period.

Results

Disposition

In total, 288 subjects were enrolled into the study and received PRC-063 during the open-label dose-optimization period (Figure 2). Of these, 239 subjects (121 for PRC-063 and 118 for placebo) entered the double-blind treatment period, and 221 subjects (113 for PRC-063 and 108 for placebo) completed the full-day ALC.

Forty-nine subjects discontinued the study during the open-label dose-optimization period, of whom 10 discontinued due to AEs (7 while on treatment). During the double-blind treatment period, 10 subjects (five each in the PRC-063 and placebo groups) discontinued the study because of loss to follow-up (PRC-063, $n=1$), non-compliance (placebo, $n=1$), inability to complete the half-day ALC or full-day ALC assessments (PRC-063, $n=2$; placebo, $n=3$), or withdrawal by the subject (PRC-063, $n=2$; placebo, $n=1$). No subjects discontinued double-blind treatment due to AEs.

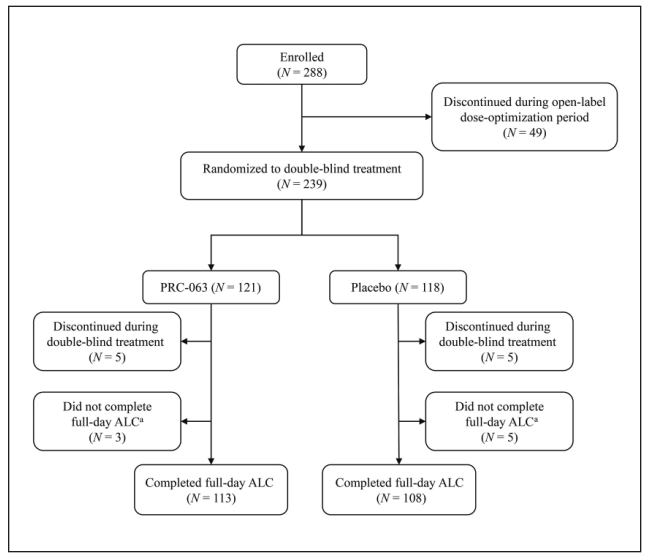

Figure 2. Subject disposition.
Note. ALC = adult laboratory classroom.
[a]Missed some or part of the full-day ALC.

Demographics and Baseline Characteristics

Overall, demographic and baseline characteristics were well balanced between the PRC-063 and placebo groups (Table 1). Median age was 32 years for the PRC-063 group and 31 years for the placebo group and slightly over half of subjects were female (55.1% for PRC-063 and 54.2% for placebo). Most subjects were white (76.0% for PRC-063 and 76.3% for placebo) and not Hispanic or Latino (81.4% for PRC-063 and 78.8% for placebo). A majority of subjects had combined type ADHD (82.0% for PRC-063 and 86.4% for placebo). At baseline, ADHD symptoms were severe based on ADHD-RS-IV total score in 64.7% of subjects in the PRC-063 group and 59.3% in the placebo group. All subjects had moderate to severe illness at baseline based on CGI-S.

PRC-063 Doses Administered

In the last week of the open-label dose-optimization period, the PRC-063 dose was 25 mg/day in five subjects (2.0%), 35 mg/day in 10 subjects (4.0%), 45 mg/day in 30 subjects (12.0%), 55 mg/day in 64 subjects (25.6%), 70 mg/day in 61 subjects (24.4%), 85 mg/day in 46 subjects (18.4%), and 100 mg/day in 34 subjects (13.6%). In the 247 subjects (98.8%) whose PRC-063 dose was considered optimized at the last week of the open-label dose-optimization period, the mean (SD) daily dose was 67.5 (19.4) mg.

Efficacy

Primary endpoint: PERMP-T. During the full-day ALC visit, subjects treated with PRC-063 had a significantly higher LS

Table 1. Demographics and Baseline Characteristics (Safety Analysis Population).

Characteristic	PRC-063 (all doses)	Placebo
N	167	118
Age (years), median (range)	32 (18–60)	31 (18–59)
Sex (*n*, %)		
Male	75 (44.9)	54 (45.8)
Female	92 (55.1)	64 (54.2)
Race (*n*, %)		
American Indian or Alaska Native	0	0
Asian	4 (2.4)	2 (1.7)
Black or African American	31 (18.6)	21 (17.8)
Native Hawaiian or Other Pacific Islander	0	0
White	127 (76.0)	90 (76.3)
Other	5 (3.0)	4 (3.4)
Not reported	0	1 (0.8)
Ethnicity (*n*, %)		
Hispanic or Latino	28 (16.8)	24 (20.3)
Not Hispanic or Latino	136 (81.4)	93 (78.8)
Not reported	3 (1.8)	1 (0.8)
BMI (kg/m^2), mean (SD)	28.47 (6.91)	28.27 (5.94)
ADHD subtype (*n*, %)		
Inattentive	29 (17.4)	15 (12.7)
Hyperactive-impulsive	1 (0.6)	1 (0.8)
Combined	137 (82.0)	102 (86.4)
ADHD-RS-IV total score (*n*, %)		
0–18 (mild)	0	0
19–36 (moderate)	59 (35.3)	48 (40.7)
37–54 (severe)	108 (64.7)	70 (59.3)
CGI-S score (*n*, %)		
1 (normal, not at all ill)	0	0
2 (borderline mentally ill)	0	0
3 (mildly ill)	0	0
4 (moderately ill)	37 (31.9)	44 (38.9)
5 (markedly ill)	55 (47.4)	50 (44.2)
6 (severely ill)	24 (20.7)	19 (16.8)
7 (among the most extremely ill subjects)	0	0

Note. ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; BMI = body mass index; CGI-S = Clinical Global Impressions-Severity; SD = standard deviation.

mean PERMP-T score than those treated with placebo when averaged over 16 hours after dosing (302.9 vs. 286.6; LS mean difference [95% CI]: 16.3 [7.6, 24.9]; $p = .0003$). The sensitivity analyses gave similar results for the LS mean difference between PRC-063 and placebo in PERMP-T score over 16 hours after dosing.

Key secondary endpoints: Time to onset and duration of efficacy of PRC-063 based on PERMP-T. During the full-day ALC visit, the pre-dose LS mean PERMP-T score tended to be slightly lower in the PRC-063 group than in the placebo group (272.5 vs. 285.0; LS mean difference [95% CI]: −12.5 [−36.4, 11.4]) (Figure 3A). Post-dose LS mean PERMP-T scores were significantly higher in the PRC-063 group than in the placebo group at every time point from 1 hour through 16 hours (all $p < .05$). The LS mean change from pre-dose PERMP-T score averaged over 16 hours after dosing was 35.9 for PRC-063 and 19.7 for placebo. The LS mean change from pre-dose PERMP-T score was significantly higher in the PRC-063 group than in the placebo group at all time points starting from 1 hour post-dose (Figure 3B). At 1 hour post-dose, the LS mean change from pre-dose PERMP-T score was 30.6 in the PRC-063 group and 17.2 in the placebo group (LS mean difference [95% CI]: 13.4 [2.8, 24.0]; $p = .0137$). At 2 hours post-dose, the corresponding values were 42.3 for PRC-063 and 22.0 for placebo (LS mean difference [95% CI]: 20.3 [11.0, 29.6]; $p < .0001$) and at 16 hours they were 35.9 for PRC-063 and

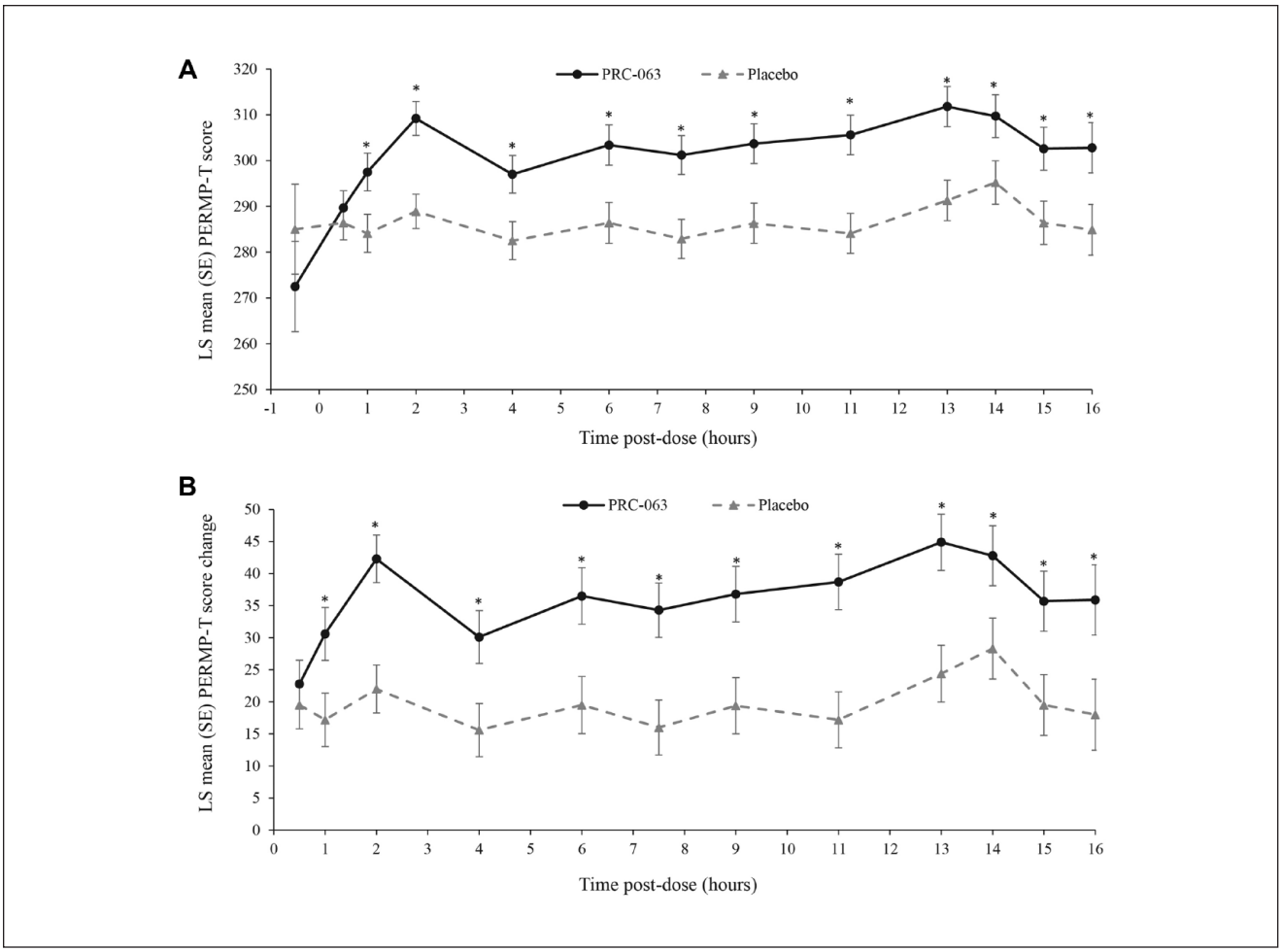

Figure 3. PERMP-T score during the full-day ALC visit (full analysis population): (A) LS mean PERMP-T score and (B) LS mean change in PERMP-T score from pre-dose score.
Note. ALC = adult laboratory classroom; LS = least-squares; PERMP-T = Permanent Product Measure of Performance-Total; SE = standard error.
*$p < .05$ for PRC-063 versus placebo.

18.0 for placebo (LS mean difference [95% CI]: 17.9 [3.2, 32.6]; $p = .0172$).

Other secondary endpoints. *ADHD-RS-IV*. During the open-label dose-optimization period, mean (SD) ADHD-RS-IV total score improved each week as the dose was increased (Figure 4). Mean ADHD-RS-IV total score was lower (indicating less severe symptoms) at the half-day ALC visit than at baseline (12.4 [5.56] vs. 39.2 [6.71]). The mean (SD) difference was −26.8 (7.83). The day before the full-day ALC visit, mean ADHD-RS-IV total score was significantly lower in the PRC-063 group than in the placebo group (15.3 vs. 23.9; LS mean difference [95% CI]: −8.5 [−11.30, −5.75]; $p < .0001$).

CGI-S. During the open-label dose-optimization period, all 229 subjects were moderately to severely ill at baseline, as defined by a CGI-S score of 4–6. At the half-day ALC visit, 220 subjects (96.1%: 110 [94.8%] who were subsequently randomized to PRC-063 and 110 [97.3%] randomized to placebo) showed a shift to being not at all ill, borderline mentally ill, or mildly ill, as defined by a CGI-S score of 1–3. At the full-day ALC visit, 90 subjects (77.6%) in the PRC-063 group and 47 subjects (41.6%) in the placebo group had a CGI-S score of 1–3.

CGI-I. At the half-day ALC visit, all 229 subjects were responders, as defined by a CGI-I score of 1–2. At the full-day ALC visit, 106 subjects (91.4%) in the PRC-063 group

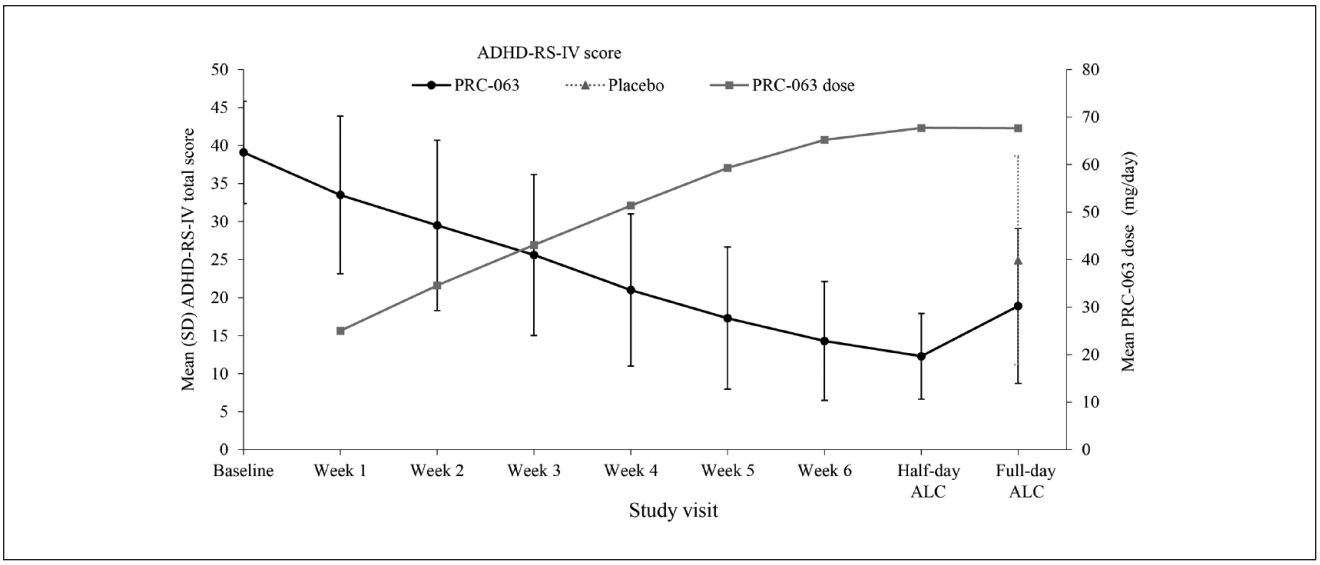

Figure 4. Mean ADHD-RS-IV total score and mean PRC-063 dose by study visit (full analysis population).
Note. ADHD-RS-IV = ADHD Rating Scale IV; ALC = adult laboratory classroom; SD = standard deviation.

and 80 subjects (70.8%) in the placebo group were responders (CGI-I score 1–2).

SKAMP-C. During the full-day ALC visit, subjects treated with PRC-063 had a significantly lower (better) LS mean SKAMP-C score than those treated with placebo when averaged over 16 hours after dosing (9.1 vs. 11.4; LS mean difference [95% CI]: −2.3 [−3.1, −1.5]; $p < .0001$). Moreover, post-dose LS mean SKAMP-C scores were significantly lower in the PRC-063 group than in the placebo group at every time point from 1 hour through 16 hours (all $p < .05$) (Figure 5).

Safety

During the open-label dose-optimization period, 209 subjects (73.3%) experienced ≥1 TEAEs and 188 subjects (66.0%) experienced ≥1 treatment-related AEs (Table 2). Headache ($n = 61$, 21.4%), decreased appetite ($n = 61$, 21.4%), and insomnia ($n = 46$, 16.1%) were the most frequently reported TEAEs. Nine subjects (3.2%) experienced initial insomnia. Most TEAEs were of mild or moderate severity. No correlation between PRC-063 dose level and incidence of TEAEs and treatment-related AEs was observed. Seven subjects (2.5%) discontinued the study because of TEAEs: jitteriness, heart palpitations, irritability, anxiety, nausea, headache, and acute paranoia. The TEAE of acute paranoia that led to study discontinuation was also an SAE. It was reported in a subject during treatment with 25 mg PRC-063 in the first week of the open-label dose-optimization period and was assessed as possibly related to study drug.

Following 7 weeks of open-label treatment, there was no evidence of increasing weight loss with increasing PRC-063 dose level (Supplemental Table 1). Slight increases from baseline, with no obvious dose-relationship, were observed for mean changes in systolic blood pressure, diastolic blood pressure, and heart rate.

A total of 231 subjects (117 for PRC-063 and 114 for placebo) completed the safety follow-up visit after the end of the double-blind treatment period. The overall incidence of TEAEs and treatment-related AEs during double-blind treatment was higher in the PRC-063 group (20.7% and 11.6%, respectively) than in the placebo group (15.3% and 5.9%, respectively) (Table 2). The most frequently reported TEAEs were headache (PRC-063: $n = 5$, 4.1%; placebo: $n = 3$, 2.5%), fatigue (PRC-063: $n = 4$, 3.3%; placebo: $n = 1$, 0.8%), upper respiratory tract infection (PRC-063: $n = 2$, 1.7%; placebo: $n = 3$, 2.5%), insomnia (both treatment groups: $n = 2$, 1.7%), and irritability, nausea, and dysmenorrhea (PRC-063: $n = 2$ each, 1.7%). In both treatment groups, all TEAEs were of mild or moderate severity. There were no TEAEs of initial insomnia during double-blind treatment. There was no correlation between PRC-063 dose level and incidence of TEAEs and treatment-related AEs. There were no SAEs or TEAEs that led to study discontinuation in either treatment group during double-blind treatment.

There were no clinically meaningful changes in mean values for clinical chemistry, hematology, or urinalysis parameters between screening and the end of the double-blind treatment period. Clinically significant vital sign and ECG abnormalities are shown in Supplementary Table 2. For PRC-063, clinically significant vital sign abnormalities

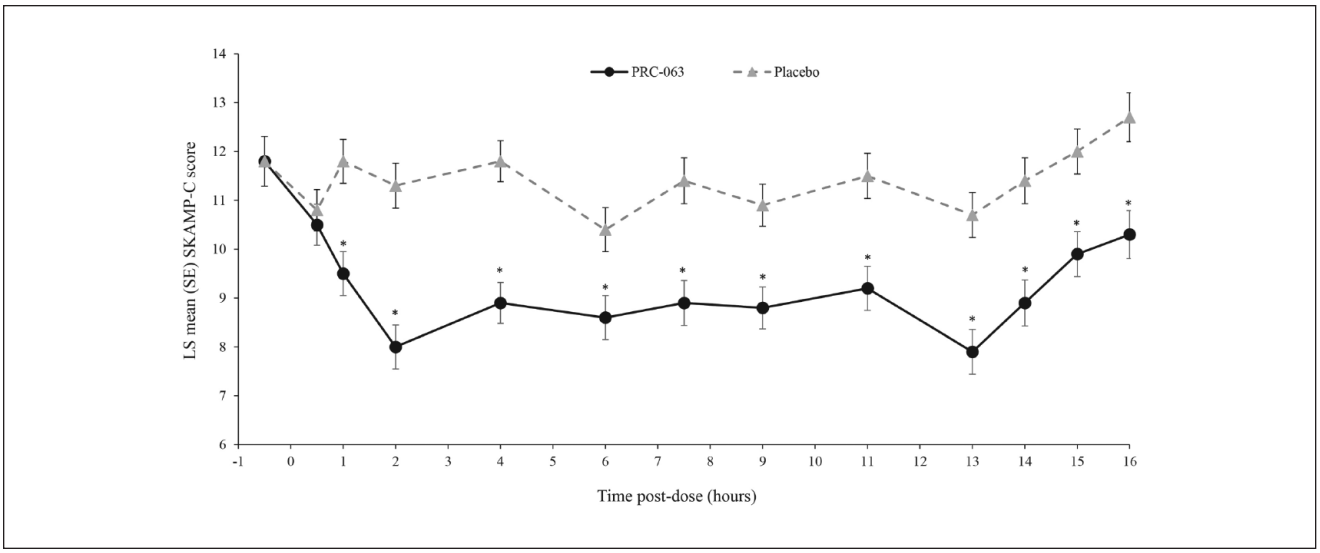

Figure 5. SKAMP-C score during the full-day ALC visit (full analysis population).
Note. ALC = adult laboratory classroom; LS = least-squares; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn, and Pelham-Combined; SE = standard error.
*$p < .05$ for PRC-063 versus placebo.

were weight decreased ($n = 4$), heart rate increased ($n = 5$), systolic blood pressure increased ($n = 2$), and diastolic blood pressure increased ($n = 6$) during the open-label dose-optimization period, and blood pressure increased ($n = 1$) during the double-blind treatment period. There was no obvious association between the incidence of clinically significant vital sign abnormalities and PRC-063 dose level. Clinically significant ECG abnormalities during the open-label dose-optimization period were tachycardia ($n = 6$), palpitations ($n = 3$), bradycardia ($n = 1$), and sinus tachycardia ($n = 1$). There were no clinically significant ECG abnormalities during the double-blind treatment period. All clinically significant vital sign and ECG abnormalities were assessed as TEAEs of mild or moderate severity.

Discussion

Results of the present study support the efficacy of the approved methylphenidate preparation PRC-063 for the treatment of ADHD in adults. Compared to subjects treated with placebo, those treated with PRC-063 demonstrated a significantly greater ability to sustain attention during the full-day ALC visit, as measured by mean PERMP-T score over the first 16 hours post-dose. Moreover, improvements in attention were significantly higher in subjects treated with PRC-063 at each time point from 1 hour through 16 hours post-dose. Therefore, the onset of action of PRC-063 was 1 hour and the duration of efficacy was 16 hours. Consistent with these findings, observer ratings of behavior based on mean SKAMP-C score were better in the PRC-063 group than in the placebo group during the full-day ALC visit, indicating a lower level of impairment in typical classroom behaviors (Wigal et al., 1998). Improvements in ADHD symptoms, as assessed by ADHD-RS-IV total score, were significantly better in subjects who received PRC-063 compared with those who received placebo. These observations were further corroborated by data showing that, at the full-day ALC visit, 77.6% of subjects who received PRC-063 were at worst mildly ill based on CGI-S and 91.4% were responders based on CGI-I.

While an extended-release mixed amphetamine salt formulation with a duration of action of up to 16 hours after dosing is currently available (SHP465) (Wigal, Brams, et al., 2018; Wigal, Childress, et al., 2018), most extended-release methylphenidate formulations have not demonstrated symptom relief for longer than 12 hours (Childress et al., 2018; Weiss et al., 2020). Adults are typically awake for approximately 16 hours a day, and some adults with ADHD have indicated a preference for a 16-hour preparation, including those with a higher work burden, night work, or stress (Erensen et al., 2020). The 1-hour onset of clinical effect of PRC-063, as measured in the present study, might translate to treatment coverage of adults with ADHD during the morning routine, a stressful and attention-demanding part of the day that may include driving, parenting, and other activities of daily living. Coupled with the long duration of action, measured at 16 hours in this study, it suggests that PRC-063 could address the medical need for a stimulant preparation that provides fast and sustained symptom relief in adults. The efficacy findings of the current study can be correlated with pharmacokinetic data relating to plasma methylphenidate concentrations after intake of PRC-063 (Katzman et al., 2020). The early onset of action and sustained effects of PRC-063 can be attributed to the

Table 2. Summary of Treatment-Emergent Adverse Events (Safety Analysis Population).

	PCR-063 dose at onset of AE (mg/day)								
AE category	25	35	45	55	70	85	100	All doses	Placebo
Open-label dose-optimization period									
N[a]	285	274	255	220	155	86	34	285	–
Any TEAE, *n* (%)	117 (41.1)	84 (30.7)	77 (30.2)	77 (35.0)	48 (31.0)	22 (25.6)	6 (17.6)	209 (73.3)	–
Severe TEAE, *n* (%)	4 (1.4)	0	0	2 (0.9)	1 (0.6)	0	0	7 (2.5)	–
SAE, *n* (%)	1 (0.4)	0	0	0	0	0	0	1 (0.4)	–
Treatment-related AE, *n* (%)	102 (35.8)	66 (24.1)	50 (19.6)	55 (25.0)	31 (20.0)	15 (17.4)	4 (11.8)	188 (66.0)	–
TEAE leading to withdrawal[b], *n* (%)	4 (1.4)	1 (0.4)	0	0	2 (1.3)	0	0	7 (2.5)	–
TEAEs occurring in ≥5% of patients, *n* (%)									
Headache	28 (9.8)	14 (5.1)	13 (5.1)	16 (7.3)	3 (1.9)	3 (3.5)	1 (2.9)	61 (21.4)	
Decreased appetite	29 (10.2)	13 (4.7)	8 (3.1)	6 (2.7)	2 (1.3)	2 (2.3)	1 (2.9)	61 (21.4)	
Insomnia	20 (7.0)	10 (3.6)	6 (2.4)	6 (2.7)	4 (2.6)	1 (1.2)	2 (5.9)	46 (16.1)	
Irritability	7 (2.5)	7 (2.6)	4 (1.6)	6 (2.7)	1 (0.6)	2 (2.3)	2 (5.9)	27 (9.5)	
Upper respiratory tract infection	3 (1.1)	3 (1.1)	9 (3.5)	6 (2.7)	3 (1.9)	2 (2.3)	0	26 (9.1)	
Dry mouth	13 (4.6)	4 (1.5)	5 (2.0)	4 (1.8)	2 (1.3)	1 (1.2)	0	25 (8.8)	
Nausea	11 (3.9)	3 (1.1)	1 (0.4)	4 (1.8)	2 (1.3)	0	0	20 (7.0)	
Anxiety	3 (1.1)	4 (1.5)	3 (1.2)	2 (0.9)	3 (1.9)	1 (1.2)	2 (5.9)	17 (6.0)	
Fatigue	4 (1.4)	2 (0.7)	3 (1.2)	4 (1.8)	1 (0.6)	2 (2.3)	0	15 (5.3)	
Double-blind treatment period									
N[c]	3	4	15	31	30	22	16	121	118
Any TEAE, *n* (%)	0	1 (25.0)	3 (20.0)	5 (16.1)	5 (16.7)	8 (36.4)	3 (18.8)	25 (20.7)	18 (15.3)
Severe TEAE, *n*	0	0	0	0	0	0	0	0	0
SAE, *n*	0	0	0	0	0	0	0	0	0
Treatment-related AE, *n* (%)	0	0	1 (6.7)	3 (9.7)	3 (10.0)	6 (27.3)	1 (6.3)	14 (11.6)	7 (5.9)
TEAE leading to withdrawal, *n*	0	0	0	0	0	0	0	0	0

Note. AE = adverse event; CRF = case report form; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a]Number of subjects in the safety analysis population who received the dose at least once during the open-label dose-optimization period.
[b]An additional three subjects discontinued the study due to AEs: two subjects who had AE onset at screening/baseline and therefore could not be assigned to a dose level and one subject who had an AE leading to discontinuation that was captured on the discontinuation CRF page, but not on the AE CRF page.
[c]Number of subjects in the safety analysis population who received the dose/treatment during the double-blind treatment period.

early peak (~1.5 hours) for the immediate-release layer, later peak (~12 hours) for the controlled-release layer, and low amount of fluctuation between peak and trough levels during repeated, once-daily dosing (Katzman et al., 2020).

In this study, pre-dose PERMP-T scores at the full-day ALC visit tended to be slightly lower for PRC-063 than for placebo, although the difference was not significant. While this may partly explain why there was no significant difference in PERMP-T score at 0.5 hour post-dose, the change from pre-dose PERMP-T score at 0.5 hour post-dose was comparable in the PRC-063 and placebo groups.

The PRC-063-induced improvements in inattention and behavior problems based on SKAMP-C scores mirror what was previously seen in PRC-063-treated children with ADHD in a laboratory school setting (Childress et al., 2020). SKAMP scores of adult subjects on drug do not always differ from those on placebo, because the SKAMP was designed to rate functional impairments in attention and behaviors in children in classroom settings and includes items specifically applicable to oppositional defiant disorder and conduct disorder (Childress et al., 2019). In addition, while SKAMP items applicable to ADHD behaviors (e.g., "attending to tasks") can be challenging for children with ADHD, they may be much simpler for an adult, even if they have significant ADHD symptoms.

The PRC-063 dose was titrated weekly during the open-label dose-optimization period, and most subjects showed improvements week over week in ADHD symptoms based on ADHD-RS-IV, CGI-S, and CGI-I scores. Compared with the pre-randomization half-day ALC visit, when all subjects were receiving open-label PRC-063, mean ADHD-RS-IV total score at the full-day ALC visit following 1 week of double-blind treatment was slightly higher (worse) for PRC-063 and much higher for placebo. After randomization, some subjects who received placebo may have experienced relapse of their ADHD symptoms due to discontinuation of active treatment, which is reported to occur relatively rapidly with stimulants (Buitelaar et al., 2015). Nonetheless, mean ADHD-RS-IV total score was lower (better) at the full-day ALC visit than at baseline, even for the placebo group. This may be partly due to the benefit of the PRC-063 treatment they had received during the open-label dose-optimization period. Alternatively, subjects may have developed effective ADHD symptom-reducing habits during the open-label dose-optimization period and then applied them during double-blind treatment period. Improvements based on CGI scores suggest that PRC-063 may have had positive effects on the consequences of ADHD, including functioning and quality of life.

Similar to previous studies of PRC-063 (Childress et al., 2020; Weiss et al., 2020; Wigal et al., 2020), PRC-063 was generally safe and well tolerated, with an AE profile typical of stimulants and no findings of new trends or safety issues. There was no evidence of an increasing incidence of common treatment-related AEs with increasing PRC-063 dose in this study. The rates of insomnia (16.1%) and initial insomnia (3.2%) during the open-label dose-optimization period compare favorably with the rates of 28.6% to 44.2% for insomnia and 4.8% to 7.0% for initial insomnia for different doses of SHP465 in a similarly-designed simulated adult workplace study (Wigal, Brams, et al., 2018). Moreover, only two subjects (1.7%) in each treatment group in the present study reported insomnia during the double-blind treatment period. However, the 1-week duration of double-blind treatment should be considered when interpreting the AE data for this treatment period, and the overall AE findings should be compared with real-world clinical data before deriving any definitive conclusions about PRC-063-related AEs.

This study has a number of limitations, including that it was a simulated classroom study of short duration, and not a naturalistic, real-world study. Moreover, no subjects received placebo during the open-label dose-optimization period, which limits interpretation of TEAEs. This was compounded by the fact that AEs that developed during the open-label dose-optimization period and continued into the double-blind treatment period without a change in severity were only counted as AEs once for open-label treatment, which may have led to underestimation of AE rates during double-blind treatment. Generalizability of the study findings is limited by the exclusion of potential participants with comorbid psychiatric diagnoses. Up to two-thirds of adults with ADHD are reported to have psychiatric comorbidities (Pineiro-Dieguez et al., 2016), so the current study sample may not be representative of the general population of adults with ADHD.

Conclusion

This study demonstrates the efficacy and safety of PRC-063 in adults with ADHD. Compared with placebo, PRC-063 provided rapid and sustained improvements in attention based on PERMP-T and in inattention/ADHD behaviors based on SKAMP-C over a 16-hour period, and improvements in ADHD symptomatology over the study duration. The safety data are consistent with prior studies of long-acting methylphenidate products in adults with ADHD. These findings address the medical need for a robust, long-lasting methylphenidate formulation in this currently underserved patient population.

Authors' Note

This study was presented in part as a poster at the American Professional Society of ADHD and Related Disorders (APSARD) Annual Meeting, January 17 to 19, 2020, Washington, D.C. Sailaja Bhaskar is currently employed at Imbrium Therapeutics L.P., a subsidiary of Purdue Pharma L.P., and Graeme Donnelly is currently employed at Purdue Pharma (Canada).

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Data Sharing

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

References

Adler, L., & Cohen, J. (2004). Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *The Psychiatric Clinics of North America*, *27*(2), 187–201.

Bain, S. K., & Jaspers, K. E. (2010). Test review: Review of Kaufman Brief Intelligence Test, Second Edition:

Kaufman, A. S., & Kaufman, N. L. (2004). Kaufman Brief Intelligence Test, Second Edition. Bloomington, MN: Pearson, Inc. *Journal of Psychoeducational Assessment*, *28*(2), 167–174.

Buitelaar, J., Asherson, P., Soutullo, C., Colla, M., Adams, D. H., Tanaka, Y., Haynes, V. S., Escobar, R., & Upadhyaya, H. (2015). Differences in maintenance of response upon discontinuation across medication treatments in attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology*, *25*(10), 1611–1621.

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont)*, *4*(7), 28–37.

Childress, A. C., Brams, M. N., Cutler, A. J., Donnelly, G. A. E., & Bhaskar, S. (2020). Efficacy and safety of multilayer, extended-release methylphenidate (PRC-063) in children 6-12 years of age with attention-deficit/hyperactivity disorder: A laboratory classroom study. *Journal of Child Adolescent Psychopharmacology*, *30*(10), 580–589.

Childress, A., Mehrotra, S., Gobburu, J., McLean, A., DeSousa, N. J., & Incledon, B. (2018). Single-dose pharmacokinetics of HLD200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *28*(1), 10–18.

Childress, A. C., Newcorn, J. H., & Cutler, A. J. (2019). Gender effects in the efficacy of racemic amphetamine sulfate in children with attention-deficit/hyperactivity disorder. *Advances in Therapy*, *36*(6), 1370–1387.

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., Atkinson, L. Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H.-C., Shokraneh, F., Xia, J., & Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *Lancet Psychiatry*, *5*(9), 727–738.

DuPaul, G. J., Power, T. J., Anastopoulos, A. D., & Reid, R. (2006). ADHD rating scale-IV: Checklists, norms, and clinical interpretation. *Journal of Psychoeducational Assessment*, *24*(2), 172–178.

Erensen, J. G., Beusterien, K., Cambron-Mellott, M. J., Hallissey, B., Matos, J., & Mikl, J. (2020). *Unlocking patient preferences for long-acting treatments for ADHD: Results of a discrete choice experiment* [Poster]. 2020 American Professional Society of ADHD and Related Disorders (APSARD) Annual Meeting. Washington, D.C., United States.

Fallu, A., Dabouz, F., Furtado, M., Anand, L., & Katzman, M. A. (2016). A randomized, double-blind, cross-over, phase IV trial of oros-methylphenidate (CONCERTA((®))) and generic novo-methylphenidate ER-C (NOVO-generic). *Therapeutic Advances in Psychopharmacology*, *6*(4), 237–251.

Fayyad, J., Sampson, N. A., Hwang, I., Adamowski, T., Aguilar-Gaxiola, S., Al-Hamzawi, A., Andrade, L. H. S. G., Borges, G., de Girolamo, G., Florescu, S., Gureje, O., Haro, J. M., Hu, C., Karam, E. G., Lee, S., Navarro-Mateu, F., O'Neill, S., Pennell, B.-E., Piazza, M., . . . Kessler, R. C. (2017). The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. *Attention Deficit and Hyperactivity Disorders*, *9*(1), 47–65.

Gajria, K., Lu, M., Sikirica, V., Greven, P., Zhong, Y., Qin, P., & Xie, J. (2014). Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder – A systematic literature review. *Neuropsychiatric Disease and Treatment*, *10*, 1543–1569.

Ginsberg, Y., Quintero, J., Anand, E., Casillas, M., & Upadhyaya, H. P. (2014). Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: A review of the literature. *The Primary Care Companion for CNS Disorders*, *16*(3), PCC.13r01600.

Goodman, D. W. (2007). The consequences of attention-deficit/hyperactivity disorder in adults. *Journal of Psychiatric Practice*, *13*(5), 318–327.

Gormez, V., Avery, B., & Mann, H. (2013). Switching from immediate release to sustained release methylphenidate in the treatment of children and adolescents with attention deficit/hyperactivity disorder. *European Review for Medical and Pharmacological Sciences*, *17*(17), 2345–2349.

Guy, W. (1976). *Clinical Global Impressions. ECDEU Assessment Manual for Psychopharmacology—Revised* (pp. 217–222). U.S. Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs.

Huss, M., Duhan, P., Gandhi, P., Chen, C. W., Spannhuth, C., & Kumar, V. (2017). Methylphenidate dose optimization for ADHD treatment: Review of safety, efficacy, and clinical necessity. *Neuropsychiatric Disease and Treatment*, *13*, 1741–1751.

Huss, M., Ginsberg, Y., Tvedten, T., Arngrim, T., Philipsen, A., Carter, K., Chen, C.-W., & Kumar, V. (2014). Methylphenidate hydrochloride modified-release in adults with attention deficit hyperactivity disorder: A randomized double-blind placebo-controlled trial. *Advances in Therapy*, *31*(1), 44–65.

Katzman, M., Mattingly, G., Klassen, L. J., Cataldo, M. J., & Donnelly, G. A. E. (2020). Randomized controlled crossover trials of the pharmacokinetics of PRC-063, a novel multilayer extended-release formulation of methylphenidate, in healthy adults. *Journal of Clinical Psychopharmacology*, *40*(6), 579–587.

Katzman, M. A., Armata, R. S., Fotinos, K., Fine, A., Furtado, M., Canzonieri, A., Lokuge, S., Sherifi, E., & Sternat, T. (2019). Attention deficit hyperactivity disorder and its effects in the Canadian workplace. *EC Psychology and Psychiatry*, *8.4*, 278–288.

Kollins, S., Cutler, A., Khattak, S., Weiss, M., Donnelly, G., & Reiz, J. (2016). *A randomized, double-blind, placebo-controlled, multicenter study measuring the efficacy and safety of a novel, extended-release formulation of methylphenidate (PRC-063) in adolescents with attention-deficit/hyperactivity disorder* [Poster presentation]. Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), New York, NY, United States.

Lachaine, J., Beauchemin, C., Sasane, R., & Hodgkins, P. S. (2012). Treatment patterns, adherence, and persistence in ADHD: A Canadian perspective. *Postgraduate Medicine*, *124*(3), 139–148.

McCrimmon, A. W., & Smith, A. D. (2012). Review of the Wechsler abbreviated scale of intelligence, second edition (WASI-II). *Journal of Psychoeducational Assessment*, *31*(3), 337–341.

NICE. (2018). Attention deficit hyperactivity disorder: Diagnosis and management. *National Institute for Health and Care Excellence*. Retrieved February 11, 2021, from https://www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933

Pineiro-Dieguez, B., Balanza-Martinez, V., Garcia-Garcia, P., Soler-Lopez, B., & Group, C. A. T. S. (2016). Psychiatric comorbidity at the time of diagnosis in adults with ADHD: The CAT study. *Journal of Attention Disorders*, *20*(12), 1066–1075.

Swanson, J. M. (2005). Long-acting stimulants: Development and dosing. *The Canadian Child and Adolescent Psychiatry Review, 14*(suppl 1), 4–9.

Swanson, J. M., Agler, D., Fineberg, E., Wigal, S., Flynn, D., Fineberg, K., Quintana, Y., & Talebi, H. (2000). University of California, Irvine, laboratory school protocol for pharmacokinetic and pharmacodynamic studies. In L. Greenhill & B. Osman (Eds.), *Ritalin: Theory and practice* (2nd ed., pp. 405–430). Mary Ann Liebert.

Weiss, M. D., Childress, A. C., & Donnelly, G. A. E. (2020). Efficacy and safety of PRC-063, extended-release multilayer methylphenidate in adults with ADHD including 6-month open-label extension. *Journal of Attention Disorders*. Advance online publication. https://doi.org//10.1177/1087054719896853

Wigal, S. B. (2019). Laboratory school protocol mini-review: Use of direct observational and objective measures to assess ADHD treatment response across the lifespan. *Frontiers in Psychology*, *10*, 1796.

Wigal, S. B., Childress, A., Berry, S. A., Belden, H. W., Chappell, P., Wajsbrot, D. B., Nagraj, P., Abbas, R., & Palumbo, D. (2018). Optimization of methylphenidate extended-release chewable tablet dose in children with ADHD: Open-label dose optimization in a laboratory classroom study. *Journal of Child and Adolescent Psychopharmacology*, *28*(5), 314–321.

Wigal, S. B., Gupta, S., Guinta, D., & Swanson, J. M. (1998). Reliability and validity of the SKAMP rating scale in a laboratory school setting. *Psychopharmacology Bulletin*, *34*(1), 47–53.

Wigal, S. B., Wigal, T., Childress, A., Donnelly, G. A. E., & Reiz, J. L. (2020). The time course of effect of multilayer-release methylphenidate hydrochloride capsules: A randomized, double-blind study of adults with ADHD in a simulated adult workplace environment. *Journal of Attention Disorders*, *24*(3), 373–383.

Wigal, T., Brams, M., Frick, G., Yan, B., & Madhoo, M. (2018). A randomized, double-blind study of SHP465 mixed amphetamine salts extended-release in adults with ADHD using a simulated adult workplace design. *Postgraduate Medicine*, *130*(5), 481–493.

Wigal, T., Childress, A., Frick, G., Yan, B., Wigal, S., & Madhoo, M. (2018). Effects of SHP465 mixed amphetamine salts in adults with ADHD in a simulated adult workplace environment. *Postgraduate Medicine*, *130*(1), 111–121.

Author Biographies

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Andrea H. Marraffino is a Principal Investigator at Meridien Research, Inc. (Maitland, FL), specializing in all phases of CNS disorder clinical trials. She also supports pharmaceutical companies and clinical research organizations as a clinical trials consultant and subject matter expert. Dr. Marraffino earned degrees from Virginia Commonwealth University, University of Texas, and University of Central Florida.

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Graeme Donnelly has been involved in clinical research and the development of pharmacotherapies for the treatment of ADHD for 20 years.