A Randomized, Double-Blind, Multicenter, Parallel-Group, Placebo-Controlled, Dose-Optimization Study of the Methylphenidate Transdermal System for the Treatment of ADHD in Adolescents

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ABSTRACT

Introduction: The current report evaluates the efficacy and safety of methylphenidate transdermal system (MTS) compared with placebo transdermal system (PTS) in adolescents with attention-deficit/hyperactivity disorder (ADHD).

Methods: A total of 217 subjects participated in a 7-week, randomized, double-blind, multicenter, parallel-group, placebo-controlled, dose-optimization study of MTS (10-, 15-, 20- or 30-mg/9 hours). Subjects were randomized into a 2:1 MTS to PTS ratio and titrated to an optimal dose during an initial 5-week period. Subjects maintained their optimal dose through a subsequent 2-week period. The primary outcome measure was the ADHD-

FOCUS POINTS

- This report describes the therapeutic efficacy and safety of a 7-week, randomized, placebo-controlled, dose-optimization study of methylphenidate (MPH) transdermal system (MTS) in adolescents 13–17 years of age with attention-deficit/hyperactivity disorder (ADHD).
- Notable improvements in ADHD symptoms were observed in subjects treated with MTS compared with subjects treated with a placebo transdermal system as rated by clinicians using the ADHD Rating Scale-IV.
- Improvement was demonstrated in all secondary efficacy measures, including behavior and severity of the subject's condition.
- Reported adverse events included those that are typically observed for oral MPH, with the exception of generally mild application site erythema associated with the transdermal delivery.
- MTS is generally safe and effective in treating adolescents 13–17 years of age with ADHD.

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Rating Scale-IV (ADHD-RS-IV). Safety of MTS was assessed throughout the study by analyzing adverse events, results of physical examinations, laboratory evaluations, vital sign data, electrocardiograms, and dermal evaluations.

Results: Treatment with MTS demonstrated greater reductions from baseline in ADHD-RS-IV total score compared to PTS at endpoint (P <.0001). The majority of the adverse events (98.5%) were mild or moderate in intensity, the most common of which were decreased appetite, headache, irritability, and upper respiratory tract infection. Three subjects in the MTS group discontinued because of an application site reaction.

Conclusions: MTS therapy was generally well-tolerated and resulted in significantly greater improvements in ADHD symptoms in adolescents when compared to PTS.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in youths, with an estimated 4 million cases presenting in the United States among children and adolescents 3–17 years of age.[1] ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity, resulting in impairments within academic, home, and social environments.[2] It is estimated that up to 75% of children with ADHD will continue to experience symptoms and dysfunction that persist into adolescence.[3,4]

Psychostimulants are recognized as first-line of treatment for children and adolescents with ADHD,[5-8] and methylphenidate (MPH) has been established as an effective agent in reducing ADHD symptoms.[9,10] Accordingly, MPH is one of the most frequently prescribed medications for this disorder.[11,12] The mechanism of therapeutic action of MPH is thought to be due to the fact that MPH blocks the uptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space in regions of the brain associated with ADHD.[13,14]

As an alternative to oral extended-release (ER-MPH) and oral immediate-release (IR-MPH) formulations, an MPH transdermal patch is now available. The MPH transdermal system (MTS; Daytrana® [Shire Pharmaceuticals Ireland Ltd., Dublin, Ireland]) was approved by the US Food and Drug Administration in 2006 for the treatment of ADHD in children 6–12 years of age.[15] MTS is a diffusion-based patch, using DOT Matrix® technology (Noven Pharmaceuticals, Miami, Florida), that continuously delivers racemic MPH through contact with skin.[16] The dose of drug delivered depends on the surface area of the patch and the length of time that the patch is worn.[17] The efficacy and tolerability of MTS at doses of 10, 15, 20, and 30 mg with a wear time of 9 hours have been established in two randomized, double-blind, placebo-controlled clinical studies of children 6–12 years of age.[18,19] Transdermal delivery of MPH may be an appropriate treatment option for children with ADHD who might benefit from tailoring the duration of effect or who might have difficulty swallowing oral medications.[20]

On review, we are not aware of published data on the use of MTS as treatment for adolescents 13–17 years of age diagnosed with ADHD. However, it is postulated that MTS may offer benefits similar to those described for children 6–12 years of age with ADHD. The purpose of this study was to test the acute efficacy and safety of MTS for the treatment of ADHD in adolescents.

METHODS

Data were collected at 31 sites across the US. Before the study began, training for efficacy and safety evaluations was reviewed with investigators to ensure reliability across the sites. The institutional review board (IRB) at each site approved the study. The subject agreed to study participation and the subject's parent or legally appointed representative (hereinafter referred to as "parent") provided written consent in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline E6 and applicable regulations. Per IRB approval, subjects were compensated a modest amount for their participation in this study and those who traveled extended distances were compensated to defray fuel costs. In addition, all study medication and medical care was provided free of cost. The study was ~11 months in duration; the first subject consent was obtained on June 28, 2007, and the last follow-up visit was completed on May 19, 2008.

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Subjects

Eligible subjects were male or female adolescents 13–17 years of age at the time of signed consent with a primary diagnosis of ADHD according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision[2] criteria and had a total score of ≥26 on the ADHD-Rating Scale-IV (ADHD-RS-IV) at baseline and an IQ score of ≥80 (as measured using the Kaufman Brief Intelligence Test[21]). Prior to receiving study medication, subjects were required to have electrocardiogram (ECG) results within normal range or variants that were not clinically significant as judged by investigators in conjunction with the central laboratory; blood pressure measurements within the 95th percentile for age, gender, and height; and no current or history of skin disease or other skin problems including sensitive skin or signs of skin irritation.

Subjects were excluded from study participation if they had conduct disorder or comorbid psychiatric illnesses (such as clinically significant obsessive compulsive disorder, depressive, or anxiety disorders; posttraumatic stress disorder; psychosis; bipolar illness; or pervasive developmental disorder) that contraindicated treatment with MTS or could confound MTS therapeutic responses. Subjects with a history of structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormalities, or other serious cardiac problems; suicidal ideation; alcohol or other substance abuse (except caffeine or nicotine) within the last 6 months; or seizures during the previous 2 years and those who had a history of being nonresponsive to psychostimulant treatment were also excluded from participation. Subjects receiving clonidine, atomoxetine, antidepressants, sedatives, antipsychotics, anxiolytics, P450 enzyme-altering agents, or other investigational medications within 30 days prior to screening were not eligible to participate in the study.

Study Design and Treatment

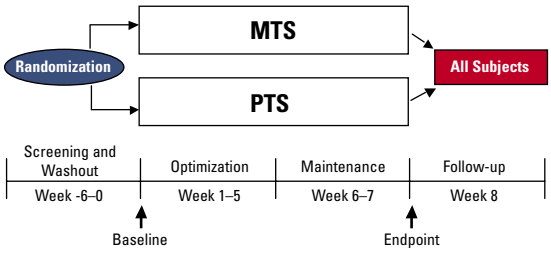
This was a Phase IIIB, randomized, double-blind, parallel-group, placebo-controlled, multicenter, dose-optimization study evaluating the efficacy and safety of MTS (10-, 15-, 20-, or 30-mg/9-hour patches) compared with placebo transdermal system (PTS) in adolescents 13–17 years of age with ADHD. The study consisted of four experimental periods: screening and washout, dose optimization, maintenance, and follow-up (Figure 1).

After written, signed informed consent was obtained, initial eligibility to enter the study was determined at the screening visit, which occurred ~2 weeks prior to washout. At the screening visit, medical and medication history data and subject's concomitant medication usage were reviewed. A psychiatric evaluation based on a semi-structured interview of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version[22] and criteria of the *DSM-IV-TR* were completed. Clinicians collected subjects' vital sign data and urine and serum samples, recorded subjects' height and weight, and performed a resting ECG. After screening was complete, subjects entered a washout period that could last up to 30 days depending on the half-life of subjects' current medication(s).

At baseline, eligible subjects entered the double-blind, stepwise, dose-optimization period and were randomized into a 2:1 ratio of MTS to matching PTS. The ratio for randomization was based on researchers' wishes to reduce the number of patients who would receive placebo during the course of study participation. On study entry, subjects were allocated the next sequential randomization number and received the treatment that corresponded with that randomized number as given by an Interactive Voice Response System. The randomization schedule was produced by computer software that incorporated a standard procedure for generating random numbers.

Patches were applied to subjects' hips once daily (alternating hips each day) and were worn for 9 hours per day. All subjects were initiated on 10 mg MTS and PTS and evaluated after 1 week to determine drug tolerability and efficacy. Titration to the next higher dose was permitted based on tolerability, results of ADHD-RS-IV scores, and

FIGURE 1.
Study design schematic



MTS=methylphenidate transdermal system; PTS=placebo transdermal system.

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review of information gathered from parent rating forms. One downward titration to the previous dose strength was permitted during this period to optimize tolerability and effectiveness.

The goal of the dose-optimization period, during which subjects were seen weekly, was to ensure that subjects were titrated to an optimal dose of medication such that they met a priori criteria for receiving an "acceptable response." An acceptable response to medication was defined as ≥25% decrease from baseline in a subject's ADHD-RS-IV score with minimal side effects. A subject would remain on his or her dose from which he or she achieved an acceptable response for the remainder of the study unless the clinician believed that the subject could receive further symptom reduction from titration to a higher dose.

An "ineffective response" was defined as <25% change in a subject's ADHD-RS-IV score from baseline. If the subject had an ineffective response and was tolerating his or her current dose of medication, the subject was to receive the next higher dose strength for the following week. If, in the clinician's opinion, a favorable response was not achieved at a higher dose, the subject was tapered downward to the previous dose strength.

An "intolerable response" was defined as the subject experiencing an unacceptable safety profile. If the subject had an intolerable response, the subject was titrated downward to the previous dose strength. If the adjusted dose strength also produced an intolerable effect, the subject was discontinued from the study.

No further dose titration was permitted for any subject after week 5 and subjects who had not reached an acceptable response by end of week 5 were withdrawn from the study. Subjects titrated to an acceptable response continued with their optimal dose through the 2-week maintenance period.

During the follow-up period, eligible subjects could opt to enroll into a long-term, open-label extension study, the results of which will be described in a subsequent report. For those subjects who did not enroll in the open-label study, additional safety information was collected for 7 days. However, no scheduled study visits took place for those patients during the follow-up period.

Efficacy Measures

The primary efficacy measure was the ADHD-RS-IV,[23] an 18-item scale that evaluates the severity of ADHD symptoms. Clinicians completed the ADHD-RS-IV at baseline and each study visit. The 18 items can be divided into two scales to derive hyperactive/impulsivity and inattentiveness scores. Secondary measures included the Conners' Parent Rating Scales-Revised Short Form (CPRS-R),[24] Clinical Global Impressions scales (CGI; CGI-Severity scale [CGI-S] and CGI-Improvement scale [GCI-I]),[25] and the Parent Global Assessment (PGA), a parent-completed variation on the CGI-I. Using the 27-question CPRS-R, parents evaluated their child's behavior on the last weekend day before each study visit starting with the baseline visit. The severity of the subject's condition was rated by clinicians at baseline using the CGI-S scale. At subsequent study visits, the subject's improvement relative to baseline was evaluated using the CGI-I scale. In addition, parents also rated their child's behavior and symptom improvement using the 7-point PGA scale.

Safety Measures

Safety was assessed through adverse event (AE) monitoring, physician examinations, clinical laboratory evaluations, vital sign measurements, and ECG data. AEs were monitored at each study visit and assessed through a general inquiry given by an investigator or qualified evaluator. The investigator assessed the severity and suspected relationship of spontaneously reported AEs to study treatment at each study visit. Physical examinations, height measurements, and clinical laboratory evaluations (hematology, serum chemistry, and urinalysis tests) were performed at screening and at the final double-blind study visit. Vital signs (including oral temperature, systolic and diastolic blood pressure, pulse, and respiratory rate) and weight measurements were obtained at screening, baseline, and at all study visits. A 12-lead ECG evaluation was obtained at screening, baseline, week 5, and the final double-blind study visit. The investigator determined the clinical significance of any physical examination, height, or vital sign measurement that was outside of the normal range. Clinically significant deviations from those measurements recorded at screening were reported as an AE. Reference ranges from clinical laboratory measures were supplied by Covance Central Laboratory Services (Indianapolis, Indiana) and were used to assess clinical significance. ECGs were analyzed by Covance Cardiac Safety Services (Reno, Nevada), and the investigator determined, based on normal ranges, whether the ECG was normal, abnor-

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mal but not clinically significant, or abnormal and clinically significant. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 7.0.

A dermal evaluation was completed at each study visit beginning at week 1 to assess skin reactions or irritations, skin discomfort, and transdermal system adherence at the current and prior application site. The dermal response scale (DRS) was used to evaluate observed skin findings: 0=no evidence of irritation; 1=minimal erythema; 2=definite erythema; 3=erythema and papules; 4=definite edema; 5=erythema, edema, and papules; 6=vesicular eruption; and 7=strong reaction beyond the site. The Experience of Discomfort and Pruritus Scale (EODP) was used to evaluate the overall level of discomfort at the patch application site: 0=no discomfort; 1=mild discomfort; 2=moderate but tolerable discomfort; and 3=severe, intolerable discomfort. If discomfort was present (score ≥1), then the type of discomfort (burning, itching, or other) was specified. The Transdermal System Adherence (TSA) scale was used to examine the adherence of the patch at the current application site: 0=≥90% adhered (essentially no lift off the skin); 1=≥75% to <90% adhered (some edges only lifting off of the skin); 2=≥50% to <75% adhered (less than half of the system lifting off of the skin); 3=<50% adhered but not detached (more than half of the system lifting off of the skin without falling off); or 4=MTS detached (system completely off the skin). Signs of skin irritation or symptoms of discomfort in subjects were not recorded as AEs unless they occurred at a site different from the site of application, or if the application site required pharmacologic treatment.

Statistical Analysis

The results of previous studies were used to estimate the number of subjects to be randomized into this study. The randomization ratio was 2:1 for MTS and PTS. Using 85% power to detect an effect size of 0.5 between active treatment and placebo at the significance level of 5%, it was estimated that 112 subjects were needed for MTS groups and 56 for the PTS groups. Assuming a 20% dropout rate, ~210 subjects (140 for MTS and 70 for PTS) were required for the study.

Data collected across the 31 sites were entered into a clinical database for management. The clinical database was reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study medicine and at least one postbaseline primary efficacy assessment. The primary efficacy variable was defined as the ADHD-RS-IV total score change from baseline at endpoint. This variable was assessed using analysis of covariance (ANCOVA) with treatment as a factor and baseline ADHD-RS-IV total score as a covariate. The null hypothesis was that there was no difference between MTS and PTS. The same ANCOVA model used for the primary efficacy analysis was applied to examine treatment effects of the CPRS-R total scores, and the total scores of ADHD-RS-IV subscales. Scores for CGI-I and PGA were evaluated by comparing scores obtained at week 1 (the first consistent collection of these ratings) and scores obtained at endpoint. Scores for CGI-I and PGA were dichotomized to two categories ("very much improved" and "much improved" into one category and "minimally improved," "no change," "minimally worse," "much worse," and "very much worse" into the other). The dichotomized scores were then analyzed using a chi-square test to evaluate differences of the improvement rates between treatment groups at each study visit and endpoint. Effect sizes were calculated as the least square mean difference divided by the square root of the mean square error.

All statistical testing was performed at the 5% significance level. Summary statistics are summarized as follows: mean and standard error (SE) of the mean are presented for the total ADHD-RS-IV scores at baseline, endpoint, and the change from baseline to endpoint; least squares mean and SE are presented for ADHD-RS-IV and CPRS-R scores at each study visit and endpoint; and number of observations and percentage of improvement are presented for CGI-I and PGA scores at each study visit and endpoint.

Safety assessments and dermal evaluations were analyzed using descriptive statistics based on the observed data for the safety population, defined as all randomized subjects who received at least one dose of study medicine. AEs were considered to be treatment-emergent if they began or worsened on or after the first patch application, and occurred before or at the same time as the last patch application in this study.

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RESULTS

Study Population

Subject disposition is illustrated in Table 1. A total of 217 subjects were enrolled and randomized in the study; 145 and 72 subjects were randomized to receive MTS and PTS, respectively. All 217 subjects received at least one dose of study medication and were included in the safety population. The ITT population was composed of 215 subjects; 2 subjects were excluded from the ITT population due to the lack of the postbaseline ADHD-RS-IV assessment. A total of 124 subjects completed the 7-week dose-optimization/dose-maintenance period and were considered to have completed the study.

The demographic and baseline characteristics for the safety population are displayed in Table 2. The majority (76.5% [MTS=109, PTS=57]) of subjects reported no prior or current psychiatric comorbidities at baseline. On study entry, the overall mean (SD) ADHD-RS-IV symptom severity for subjects was 36.5 (7.32). The overall mean (SD) CPRS-R total score was 50.4 (14.45) and the mean (SD) CGI-S score at baseline was 4.5 (0.67). Based on CGI-S scores obtained at baseline, the majority of subjects were rated as moderately ill (54.4%) or markedly ill (35.5%).

At the end of the dose-optimization period, most subjects in the MTS group had progressed to the MTS 20- or 30-mg dose and at week 7, 4.2%, 16.7%, 24.0%, and 55.2% of subjects were receiving MTS doses of 10, 15, 20, and 30 mg, respectively. The median exposure time to MTS was 48 days (range, 4–57 days). Median exposure time, by MTS dose, was 7 days (range, 4–49 days), 7 days (range, 3–44 days), 8 days (range, 4–39 days), and 23.5 days (range, 4–35 days) with the 10-, 15-, 20-, and 30-mg doses, respectively.

Efficacy

ADHD-RS-IV Total and Subscale Scores

Improved ADHD symptoms were reported in the ITT population for both MTS and PTS treatment groups as demonstrated by a decrease in ADHD-RS-IV mean total scores beginning at the first postbaseline assessment through week 7 and at endpoint. At baseline, ADHD-RS-IV mean (SD) total scores for MTS and PTS were 36.4 (7.15) and 36.6 (7.71) compared with 17.7 (12.20) and 27.7 (12.75) at endpoint, respectively. The magnitude of the change from baseline in ADHD-RS-IV total score for the MTS group was greater at all study visits and endpoint compared to the PTS group. At endpoint, the least squares mean difference was significantly greater for the MTS group compared to the PTS group ($P<.001$, difference=-9.96, 95% confidence interval [CI]=-13.39 to -6.53) indicating significant treatment benefit for MTS in improving ADHD-RS-IV total score when compared to placebo (Figure 2). The ADHD-RS-IV total score effect

TABLE 1.
Disposition for All Enrolled Subjects

	Number (%) of Subjects		
Study Subjects and Analysis Populations	***MTS***	***PTS***	***Total***
Enrolled and randomized	145	72	217
Safety	145 (100.0)	72 (100.0)	217 (100.0)
Intent-to-treat	143 (98.6)	72 (100.0)	215 (99.1)
Completed 7-week dose-optimization/dose-maintenance period	95 (65.5)	29 (40.3)	124 (57.1)
• Enrolled in open-label extension study*	91 (95.8)	25 (86.2)	116 (93.5)
Did not complete 7-week dose-optimization/dose-maintenance period	50 (34.5)	43 (59.7)	93 (42.9)
• Enrolled in open-label extension study†,‡	19 (38.0)	28 (65.1)	47 (50.5)
Reasons for discontinuation‡			
Adverse event	8 (16.0)	2 (4.7)	10 (10.8)
Application site reaction	3 (6.0)	0 (0.0)	3 (3.2)
Protocol violation	12 (24.0)	7 (16.3)	19 (20.4)
Consent withdrawn	6 (12.0)	4 (9.3)	10 (10.8)
Lost to follow-up	1 (2.0)	1 (2.3)	2 (2.2)
Lack of efficacy	21 (42.0)	27 (62.8)	48 (51.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (4.0)	2 (4.7)	4 (4.3)

* Percentages are based on the number of subjects who completed the 7-week dose-optimization/dose-maintenance period.

† To continue on in the open-label extension study, subjects either completed all required study visits or completed the 5-week dose-optimization period without achieving an acceptable condition and were not discontinued from the current study due to a protocol violation, noncompliance, an adverse event, or a serious adverse event.

‡ Percentages are based on the number of subjects who did not complete the 7-week dose-optimization/dose-maintenance period.

MTS=methylphenidate transdermal system; PTS=placebo transdermal system

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size was calculated to be -.83 (95% CI, -1.12 to .53) at endpoint, indicative of a superior response for MTS when compared to placebo. The least squares mean difference (MTS–PTS) in ADHD-RS-IV total score and effect size for each study visit and endpoint are shown in Table 3.

TABLE 2.
Demographics and Baseline Characteristics (Safety Population)

Characteristic	MTS (n=145)	PTS (n=72)	Total (n=217)
Age, mean (SD) years	14.5 (1.3)	14.6 (1.4)	14.6 (1.3)
Gender, n (%)			
Male	109 (75.2)	53 (73.6)	162 (74.7)
Female	36 (24.8)	19 (26.4)	55 (25.3)
Race, n (%)			
White	111 (76.6)	56 (77.8)	167 (77.0)
African American	27 (18.6)	13 (18.1)	40 (18.4)
Asian	0	1 (1.4)	1 (0.5)
American Indian or Alaska Native	0	1 (1.4)	1 (0.5)
Other	7 (4.8)	1 (1.4)	8 (3.7)
Weight, mean (SD) lbs.	130.2 (25.1)	128.5 (29.2)	129.6 (26.5)
Height, mean (SD) in.	65.4 (3.6)	65.0 (4.3)	65.2 (3.8)
Prior stimulant medication use, n (%)			
Yes	59 (40.7)	36 (50.0)	95 (43.8)
No	86 (59.3)	36 (50.0)	122 (56.2)
ADHD-RS-IV total score (SD)	36.4 (7.1)	36.6 (7.7)	36.5 (7.3)
CPRS-R total score (SD)	49.7 (15.2)	51.9 (12.7)	50.4 (14.5)
CGI-S score (SD)	4.5 (0.7)	4.6 (0.7)	4.5 (0.7)
CGI-S summary, n (%)			
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	1 (0.7)	0	1 (0.5)
Moderately ill	77 (53.1)	41 (56.9)	118 (54.4)
Markedly ill	55 (37.9)	22 (30.6)	77 (35.5)
Severely ill	12 (8.3)	9 (12.5)	21 (9.7)
Among the most extremely ill subjects	0	0	0

MTS=methylphenidate transdermal system; PTS=placebo transdermal system; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; CPRS-R=Conners' Parent Rating Scale-Revised; CGI-I=Clinical Global Impressions-Severity.

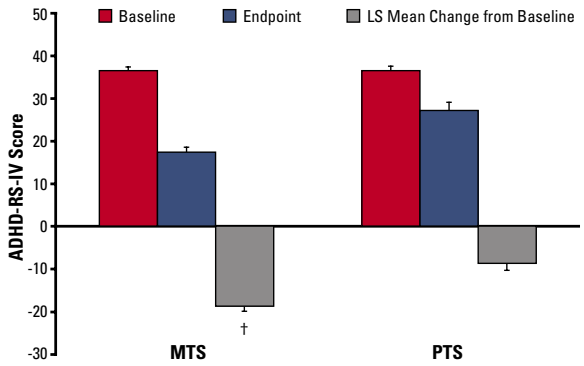
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Similar results were seen with the ADHD-RS-IV subscales scores; mean hyperactivity/impulsivity and inattentiveness scores decreased progressively over weeks 1–7 and the magnitude of the decrease from baseline was greater for the MTS group than for the PTS group at all study visits. At endpoint, the least square mean difference was significantly greater for the MTS group compared to the PTS group for hyperactivity/impulsivity (P<.001, difference=-4.02, 95% CI=-5.68 to -2.36) and inattention (P<.001, difference=-5.93, 95% CI=-7.94 to -3.92), suggesting statistically significant superior treatment benefit for MTS on both ADHD-RS-IV subscale scores.

CPRS-R Total Score

The MTS group showed greater improvement over the PTS group in CPRS-R mean total scores from baseline to endpoint. The mean change from baseline in CPRS-R total score was significantly greater for the MTS group compared with the PTS group at each study visit. At endpoint, the least square mean difference between MTS and PTS was significantly different (P<.001, difference=-13.48, 95% CI=-18.48 to -8.47). The CPRS-R total score effect size was calculated to be -.78 (95% CI, -1.08 to -.48) indicating a more favorable response for MTS when compared to placebo. The least squares mean difference (MTS–PTS) in

FIGURE 2.
Least squares mean from baseline to endpoint of ADHD-RS-IV mean total scores (ITT population)*



* Endpoint is last nonmissing assessment obtained post-baseline. Error bars indicate standard error of the mean.

† P<.001 for difference between MTS and PTS treatment.

ADHD-RS-IV=ADHD-Rating Scale-IV; ITT=intent to treat; LS=least squares; MTS=methylphenidate transdermal system; PTS=placebo transdermal system.

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CPRS-R total score and effect size for each study visit and endpoint is displayed in Table 3.

CGI-I and PGA Scores

Statistically significant improvement was observed for mean global response ratings from clinicians and parents (Table 3 and Figure 3). At endpoint, a greater proportion of subjects evaluated in the MTS group (93/142, 65.5%) were rated as "very much improved" or "much improved" using the CGI-I scale, compared with the PTS group (22/72, 30.6%), $P<.001$. In addition, the number of subjects who were "very much improved" or "much improved" as rated by the PGA scale was higher in the MTS group (76/143, 53.1%) compared to subjects in the PTS group (15/72, 20.8%), $P<.001$, at endpoint.

Safety

During the study period, 386 treatment-emergent AEs (TEAEs) were reported in 112 (77.2%) of the 145 subjects receiving MTS and 40 (55.6%) of the 72 subjects receiving PTS. Of these, 201 AEs were considered treatment-related by investigators in 75 (51.7%) subjects receiving MTS and 18 (25.0%) subjects receiving PTS treatment. The majority (381/386, 98.7%) of TEAEs were mild to moderate in intensity. In the MTS group, the most frequently reported TEAEs included decreased appetite (25.5%), headache (12.4%), irritability (11.0%), and upper respiratory tract infection (10.3%). TEAEs are summarized by treatment group in Table 4.

A total of three serious AEs (SAEs) were reported by two subjects; one subject in each treatment group discontinued from the study due to these SAEs. A subject receiving 15 mg MTS experienced two episodes of syncope; both incidences were judged to be of moderate severity and related to study treatment by the investigator. Each syncope episode occurred approximately 1 hour after patch removal and was <30 seconds in duration. The subject had no clinically notable medical history and results of the ECG assessments at the early termination visit were not deemed to be clinically signifi-

TABLE 3.
Summary of Difference (MTS–PTS) Between Two Treatment Groups for Efficacy Measures (ITT population)

	Week							
Measure	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***Endpoint****
ADHD-RS-IV Total								
LS Mean	-3.42	-4.48	-7.98	-8.20	-9.05	-7.70	-5.66	-9.96
P value†	.001	<.001	<.001	<.001	<.001	<.001	.007	<.001
Effect Size	-.47	-.50	-.80	-.75	-.83	-.78	-.58	-.83
CPRS-R Total								
LS Mean	-4.25	-4.67	-8.82	-10.75	-13.76	-12.83	-10.74	-13.48
P value†	.013	.017	<.001	<.001	<.001	<.001	.001	<.001
Effect Size	-.37	-.37	-.61	-.68	-.88	-.85	-.73	-.78
CGI-I								
Difference in %‡	10.0	18.3	27.8	35.4	31.1	18.6	16.5	34.9
P value§	.044	.005	<.001	<.001	<.001	.022	.045	<.001
PGA								
Difference in %‡	7.0	14.5	30.7	27.0	31.6	22.5	28.4	32.3
P value§	.108	.014	<.001	<.001	<.001	.020	.005	<.001

*Endpoint is the last nonmissing assessment obtained postbaseline.

†Based on Type III tests from an analysis of covariance model for the change from baseline.

‡Includes CGI-I or PGA categories "very much improved" and "much improved."

§*P* values are based on a chi-square statistic for pairwise differences between the treatment groups.

MTS=methylphenidate transdermal system; PTS=placebo transdermal system; ITT=intent to treat; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; LS=least squares; CPRS-R=Conners' Parent Rating Scale-Revised; CGI-I=Clinical Global Impressions-Improvement; PGA=Parent Global Assessment.

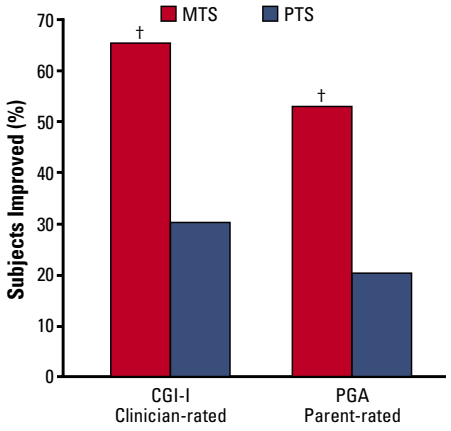
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cant by a pediatric cardiologist. Per the protocol, events of syncope (including these isolated, brief occurrences) were considered important medical events and therefore required to be reported as SAEs. A subject receiving 30 mg PTS reported oppositional behavior (negativism), which was judged as severe and not related to treatment. It was noted that at the time of the event, the subject had a fight with a family member and ran away from home. The subject was later admitted to an inpatient hospital. The subject had no clinically notable general medical history. No deaths were reported in the study.

A total of 10 (4.6%) subjects experienced 17 TEAEs that ultimately led to study discontinuation. Eight subjects in the MTS group experienced 14 AEs including one report each of application site erythema, decreased appetite, dry mouth, anorexia, sedation, dizziness, psoriasis, folliculitis, somnolence, and fatigue as well as two reports each of application site dermatitis and syncope in the MTS group that led to study discontinuation. In the PTS group, two subjects experienced a total of three AEs; one report each of negativism, irritability, and mood-alteration.

FIGURE 3.
Percentage of subjects at endpoint showing improvement using the CGI-I and PGA rating scales for MTS and PTS treatment groups (ITT population)*



* Endpoint is last nonmissing assessment obtained postbaseline.

† $P<.001$ for difference in percentage of subjects with improvement for MTS versus PTS for both CGI-I and PGA ratings.

CGI-I=Clinical Global Impressions-Improvement; PGA=Parent Global Assessment; MTS=methylphenidate transdermal system; PTS=placebo transdermal system; ITT=intent to treat.

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For those subjects that discontinued due to an application-related AE, a maximum DRS score of 2 (one subject receiving 30 mg MTS) and 3 (one subject each receiving 20 mg MTS and 15 mg MTS) were recorded.

No clinically meaningful changes were detected in hematology, serum chemistry, or urinalysis from screening to end of study.

Changes in blood pressure and pulse rate typically seen with stimulant therapy[26] occurred in subjects throughout this study. For subjects treated with MTS, the greatest mean increase from baseline in systolic blood pressure (2.9 mm Hg) was observed at week 7, while the mean changes from baseline in diastolic blood pressure ranged from 0.0 to 2.3 mm Hg. Mean pulse rate and change from baseline in mean pulse increased during the first 5 weeks of MTS treatment with a mean (SD) change of 6.5 (11.65) beats per minute (bpm) observed for the MTS group at endpoint. There were several AEs related to the vital sign observations for MTS treatment: one report each of tachycardia, palpitations, increased blood pressure, and dyspnea as well as two reports each of increased heart rate and syncope and a total of six reports of pyrexia. The incidences of pyrexia were considered not related to treatment. No subject discontinued as a result of pulse or blood pressure abnormalities.

TABLE 4.
Most Commonly Reported Treatment-Emergent Adverse Events (≥5% of total MTS subjects) (safety population)

	Subjects, n (%)	
Adverse Event (preferred term)	***MTS (n=145)***	***PTS (n=72)***
Decreased appetite	37 (25.5)	1 (1.4)
Headache	18 (12.4)	9 (12.5)
Irritability	16 (11.0)	5 (6.9)
Upper respiratory tract infection	15 (10.3)	7 (9.7)
Nausea	14 (9.7)	2 (2.8)
Insomnia	9 (6.2)	2 (2.8)
Dizziness	8 (5.5)	1 (1.4)
Weight decreased	8 (5.5)	1 (1.4)

MTS=methylphenidate transdermal system; PTS=placebo transdermal system.

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The frequency of clinically significant ECG abnormalities at any time point during the study, as judged by investigators in conjunction with the central laboratory, was similar between both treatment groups; 11.0% for MTS and 11.1% for PTS. In the MTS group, mean (SD) heart rate change increased from baseline to 5.1 (12.53) bpm at endpoint. For the PTS group, mean change in heart rate was -1.7 (9.03) bpm at endpoint. Two subjects receiving MTS experienced potentially clinically important heart rate elevations >110 bpm and no subjects receiving PTS experienced a heart rate elevation >110 bpm. No clinically meaningful changes in the PR or QRS interval were observed for either treatment group. Two subjects in the MTS group showed potentially clinically important high PR interval durations. However, no subject had a potentially clinically important QRS interval measurement. A small decrease from baseline in mean (SD) QT interval duration of -9.2 (25.24) msec were observed in the MTS group at endpoint. After the Fridericia method was used to correct QT, there were no clinically meaningful changes from baseline in mean (SD) QTcF interval at endpoint (-1.3 [16.70] msec). Two subjects receiving MTS had ≥1 QTcF interval durations ≥450 msec at various timepoints during the study; however, no AEs were reported in association with the QTcF observations.

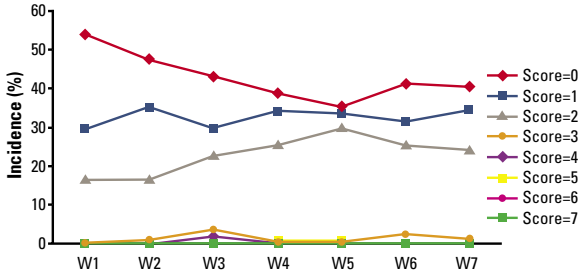
AEs associated with weight decrease were observed for eight subjects (5.5%, nine events) in the MTS group and one subject (1.4%, one event) in the PTS group. Of the nine events experienced by subjects in the MTS group, eight were considered related to study treatment, five resolved while subjects were receiving treatment, and four were ongoing in subjects at study endpoint. None of these weight decrease–related events required a change in MTS dose. Of AEs related to weight decrease, weight loss in the MTS group ranged from 0.9%–7.1%. In general, mean weight declined over the dose-optimization period and stabilized for the remainder of the study. In the MTS group, mean (SD) weight decreased from baseline by 1.90 (3.870) pounds at endpoint. Subjects in the PTS group showed a small mean (SD) weight increase from baseline of 1.77 (4.385) pounds at endpoint. Overall, 67.8% of subjects in the MTS group exhibited weight loss from baseline compared with 27.8% of subjects in the PTS group at endpoint. The mean (SD) height increase during the 7-week duration of study treatment was similar among both treatment groups: 0.21 (0.479) inches for the MTS group and 0.24 (0.500) inches for the PTS group. Mean (SD) body mass index (BMI) values decreased slightly in the MTS group from screening by 0.29 (0.763) at endpoint, while mean BMI values increased in the PTS group from screening by 0.31 (0.883) at endpoint.

Overall, mean DRS scores were low across all visits and MTS doses, indicating that most reactions consisted of mild erythema (0.6–1.0 for current application and 0.1–0.3 for prior application site) as illustrated in Figure 4. However, there were three incidences of scores ≥4: two subjects (receiving 15 mg and 20 mg MTS) experienced a maximum DRS score of 4, and one subject (receiving 30 mg MTS) experienced a maximum DRS score of 5. Mean EODP scores were low for subjects treated with MTS (0.1–0.3 for current and prior application sites) during the 7-week study period, with most subjects describing the discomfort as itching and/or burning. Overall, TSA was reported to be ≥90%, and the mean TSA score was similar at all assessments. At endpoint, only five subjects reported a detached MTS patch.

DISCUSSION

The current study provides evidence to suggest that MTS may be a beneficial treatment for adolescents diagnosed with ADHD. Subjects

FIGURE 4.
Dermal response at current application site per postbaseline visit during MTS treatment (safety population)



Dermal Response Scale scores range from 0–7, where 0=no evidence of irritation; 1=minimal erythema; 2=definite erythema; 3=erythema and papules; 4=definite edema; 5=erythema, edema, and papules; 6=vesicular eruption; and 7=strong reaction beyond site.

MTS=methylphenidate transdermal system; W=week.

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treated with MTS had significant improvements in ADHD symptoms compared with subjects treated with PTS, as determined by the ADHD-RS-IV total score. Significant statistical improvement was noted in the least squares change from baseline on the ADHD-RS-IV scale in the MTS group during the first postbaseline assessment and continued through study endpoint. A similar trend was noted in ADHD-RS-IV subscale scores of hyperactivity/impulsivity and inattention. Analogous results have been reported in other clinical studies of stimulant treatment for adolescents with ADHD including mixed amphetamine salts[27,28] and an osmotic-release oral system of MPH (OROS® MPH; Alza Corporation, Mountain View, California).[29] In addition, significant improvement was demonstrated in all secondary efficacy measures including CPRS-R total scores, CGI-I scores, and PGA scores.

The results from AE reports suggest that the safety profile of MTS treatment in adolescent subjects, using a flexible dosing regimen (10–30 mg), is consistent with AEs reported in previous studies of MTS in subjects 6–12 years of age using a 9-hour wear time[19,20] and AEs reported in studies of oral ADHD medication treatment, with the exception of application site irritation.[30-32] The most common TEAEs reported in this study included decreased appetite, headache, irritability, and upper respiratory tract infection. No deaths were reported in this study.

Importantly, no clinically meaningful changes were detected in the laboratory assessments and ECGs from screening to end of study. Although the two incidences of syncope in one subject receiving MTS treatment were considered medically significant, there was no indication of structural heart disease or cardiac conduction abnormalities in the ECG administered at the early termination visit for this patient. It is possible that these episodes were associated with neurocardiogenic syncope, which has been reported to peak during adolescence.[33]

Of subjects receiving MTS treatment, ~70% experienced measurable weight loss over the duration of the study. Mean weight generally declined from baseline over the dose-optimization period and showed gradual attenuation during the 2-week dose-maintenance period. For AEs related to weight decrease, overall weight loss ranged from 0.9% to 7.1% in the MTS group. Of note, only three subjects experienced weight loss ≥7% from baseline. As appetite suppression and weight loss are common symptoms associated with stimulant medications[5] and only a small number of subjects experienced a significant decrease in weight, such results are not clinically meaningful for most individual subjects.

The incidence of dermal response was generally similar across all MTS doses and was consistent with previous observations for MTS in subjects 6–12 years of age with ADHD.[18-20] Most reports consisted of mild or definite erythema with no or mild discomfort. Such skin reactions are anticipated, as MPH is a dermal irritant.[15]

Of subjects who completed the 7-week study, 93.5% (116/124) opted to enter the open-label study in which all subjects received MTS. Of these, four subjects receiving MTS and four subjects receiving PTS treatment did not continue on with the extension study. Information regarding determinants about the decision not to enroll is unavailable. The authors note that the following could be potential reasons for not enrolling into an extension study: relocation to a different city or an unwillingness to participate in the number of study visits and the number of study-related procedures, when compared to routine practice, for a long-term study. Of subjects who did not complete this 7-week study, 50.5% (47/93) were eligible (per inclusion and exclusion criteria) and enrolled in the extension study. This included subjects who completed the 5-week dose-optimization period without achieving an acceptable condition (ie, ≥25% decrease from baseline in a subject's ADHD-RS-IV score with minimal side effects).

Limitations

Although this study was designed to evaluate the efficacy of MTS, it was not designed to characterize the duration of treatment effect. Moreover, due to the short duration of this study, these results do not characterize the long-term effects of treatment with MTS. Although a reduction in ADHD symptoms was observed by clinicians during the 7-week study of MTS in adolescents, no teacher-rated measures were used to ascertain effectiveness in an academic setting. Consequently, the results of this study should not be used to suggest MTS improves academic performance in adolescents.

It is important to note that subjects who failed to respond to psychostimulants in the past and those with conduct disorder and other psychiatric comorbidities were excluded from the study. In addition, youths with substantive gen-

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eral medical conditions were also not enrolled into this clinical trial. Therefore, the results of this study should not be extrapolated to these patient populations.

CONCLUSION

In this 7-week, randomized, double-blind, placebo-controlled study, MTS was shown to be effacious, as rated by clinicians and parents, in treating ADHD in adolescents. Reported AEs included those that are typical for oral MPH, with the exception of generally mild application site erythema associated with transdermal delivery of MPH. ***CNS***

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