EFFICACY SUMMARY

NDA NO: 21-514

Generic Name:	SPD485, *d,l (threo)*-methylphenidate, Methylphenidate Transdermal System (MTS)
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Noven Pharmaceuticals, Inc. 11960 Southwest 144th Street Miami, FL 33186
Agent of Sponsor:	Shire Development Inc. 725 Chesterbrook Boulevard Wayne, PA 19087

TABLE OF CONTENTS

1. INTRODUCTION

Methylphenidate Transdermal System (MTS) is a Class II (CII) central nervous system stimulant that is under investigation for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children. Its active ingredient, methylphenidate (MPH), as an immediate or sustained release tablet, has been used extensively in the treatment of ADHD for the past 30 years. MTS may offer certain advantages over immediate and long-acting oral formulations of MPH. These potential advantages include greater convenience with once-daily administration, reduced blood concentration fluctuation and the elimination of swallowing large extended release tablets which is problematic for small children.

The 9-hour MTS wear time was studied in 2 pivotal trials (SPD485-201 and –302). Study SPD485-201 was an Analog Laboratory Classroom protocol; the results of the Analog Laboratory Classroom study demonstrated an overall effect on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) deportment score during the period of MTS wear (0-9 hours). In study SPD485-302, using the clinician rated Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV), MTS demonstrated significant improvements in overall ADHD symptoms compared to placebo. In this study, CONCERTA® was used as a reference treatment. These 2 studies support the efficacy of MTS worn for 9 hours in the treatment of ADHD in children.

1.1 Condition Background and Current Treatment

ADHD is the most prevalent psychiatric disorder of childhood.[1] It is estimated that 3%-7% of school aged children have ADHD.[2,3,4,5,6] It is also estimated that approximately 6 million men, women, and children in the United States fit the diagnosis of ADHD or 1 of its subcategories.[7]

ADHD consists of a variety of behaviors and personality types. However, the 3 main symptoms of ADHD include inattention, hyperactivity, and impulsivity. These symptoms must appear before age 7, be present for more than 6 months, and must be adversely affecting social, occupational, or school functioning for the diagnosis of ADHD to be made.

ADHD is theorized to result from a deficiency of neurotransmission of dopamine and norepinephrine either through the insufficient sensitivity of the receptors or amount of dopamine produced. Some of the functions associated with sufficient levels of these metabolites in the central nervous system include controlling the ability to shift from an open- to focused-state of awareness and, indirectly, the sense of time.

For the past 30 years, the most common therapy for ADHD has been orally dosed stimulants such as methylphenidate, dextroamphetamine and pemoline. It is believed that these medications may either stimulate the release of dopamine or block its re-uptake. It is felt that increasing dopamine levels results in increasing impulse control and enhancing a more “focused state of awareness.”

Numerous studies have demonstrated the short-term efficacy of these medications, especially MPH, in the treatment of ADHD. In 1994, it was estimated that about 80% of all diagnosed cases of ADHD were treated with MPH.[8] Positive effects on behavior and

academic productivity are well established for stimulant medications such as MPH.[9] Studies have shown that, in children with ADHD, MPH improves classroom functioning, notably by decreasing disruptive behavior and increasing academic productivity, accuracy and improvement in teacher ratings.[10,11,12,13] In addition, MPH has been shown to improve performance in children for a number of cognitive tasks, including measures of attention and memory.[10,14,15,16]

Because of MPH's short half-life (1-3 hours) in immediate release formulations, it must be administered orally twice daily (BID) or 3 times daily (TID) to ensure adequate coverage over the school or work day, with a third dose given after school to cover afternoon behavior. MPH's narrow window of effect on cognitive performance averages 60 to 180 minutes after ingestion, therefore, maximum drug effectiveness is achieved for only a part of the school day in children who take Ritalin (MPH)-Immediate Release (IR) on a BID basis. In addition, problems with dosing BID, especially in school-age children, are compounded when children either forget or refuse to dose at school, or school systems have policies that prohibit the school personnel from administering psychoactive medications. Issues related to compliance, privacy, and the potential diversion of doses have been raised.

In 1983, the development of a once-a-day sustained release (SR) preparation of MPH (Ritalin-SR®) attempted to overcome the problems associated with multiple dose administration of MPH. Ritalin-SR®, available only as a 20mg tablet of methylphenidate hydrochloride, has a bioavailability of 25% with duration of action of 8 hours.[17] The preparation was designed to be equivalent to a BID schedule of 10mg of Ritalin-IR, while avoiding the problems of fluctuation of maximum dose effectiveness and the stigma of multiple dosing of Ritalin-IR. However, published studies have suggested that Ritalin-SR® does not reliably mimic the effects of a 10mg Ritalin-IR regimen.[10,18] Approved SR formulations of MPH have not been widely adopted for clinical use possibly because of the limited range of available doses (only a 20mg SR dose is approved and available for clinical use).[14] It is also possible that because of the pharmacokinetic profile of the existing SR formulation, the onset of efficacy is delayed and the treatment effect is of insufficient duration.[18]

In 2000, another extended-release formulation of methylphenidate (CONCERTA®) reached the market, and has grown in popularity due to its effectiveness through 12 hours after dosing. CONCERTA® is available in doses of 18mg, 27mg, 36mg, 54mg, and 72mg tablets.

Noven Pharmaceuticals, Inc., in collaboration with Shire Development Inc., is developing a transdermal delivery system containing MPH in a multi-polymeric adhesive platform as a means of providing sustained levels of *d,l*-methylphenidate while the patch is worn. The system is designed to release *d,l*-methylphenidate continuously upon application to intact skin. It is anticipated that this transdermal delivery system will provide greater consistency in therapeutic response, and may improve therapeutic efficacy. Transdermal administration of *d,l*-methylphenidate in subjects should result in more stable plasma concentrations over the course of the day that may contribute to a prolonged duration of effect.

2. STUDY OBJECTIVES (STUDY SPD485-201)

The purpose of this study was to evaluate the safety and efficacy of MTS and to characterize the duration of efficacy of MTS in pediatric subjects aged 6-12 compared to placebo.

2.1 Primary Efficacy Objective

The primary objective of this study was to evaluate, under controlled conditions at multiple timepoints throughout the day, the behavioral effects (measured by the SKAMP deportment scale) of MTS compared to placebo in children (aged 6-12) diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) by Diagnostic and Statistical Manual of Mental Disorders, 4th ed. – Text Revision (DSM-IV-TR) criteria.

2.2 Secondary Efficacy Objectives

The main secondary objective was to assess the duration of efficacy of MTS compared to placebo in children with ADHD using the PERMP (Permanent Product Measure of Performance, an age-adjusted math test) administered at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post-application/dosing in a controlled environment.

Other key secondary objectives included the following:

- To evaluate the efficacy of MTS compared to placebo in children with ADHD as measured by the SKAMP Total score.
- To evaluate the efficacy of MTS compared to placebo in children with ADHD as measured by SKAMP sub-scales of attention and quality of work.
- To evaluate the efficacy of MTS compared to placebo in the symptomatic treatment of children with ADHD using the clinician completed Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV).
- To assess global impressions of ADHD severity and improvement from the clinician and parent in response to treatment using Clinical Global Impressions - Improvement (CGI-I) and Parent Global Assessments (PGA).
- To assess the efficacy of MTS compared to placebo in the home environment as rated by the parent using the Conners' Parent Rating Scale – Revised: Short Form (CPRS-R) administered weekly, on 1 weekend day in the morning and afternoon.

3. INVESTIGATIONAL PLAN (STUDY SPD485-201)

3.1 Overall Study Design and Plan

This was a Phase II, randomized, double-blind, multi-center, placebo-controlled, Analog Classroom, crossover study, with an open-label optimization phase, designed to assess the time course of treatment effect, tolerability and safety of MTS ($12.5cm^2$, $18.75cm^2$, $25cm^2$, and $37.5cm^2$ patch sizes) in subjects aged 6-12 diagnosed with ADHD. Subjects visited the study site 9 times during the course of approximately 14 weeks. The study consisted of 4 periods detailed below:

Screening & Washout Period:

Subjects were screened for approximately 2 weeks prior to washout (up to a maximum 28 days).

Open-Label Dose Optimization Period:

The objective of this 5-week period was to ensure subjects were titrated to an optimal dose of MTS (using $12.5cm^2$, $18.75cm^2$, $25cm^2$, and $37.5cm^2$ patch sizes) based upon investigator review of parent rating forms, TEAEs, and clinical judgment (using the ADHD-RS-IV). All subjects were initiated on the MTS $12.5cm^2$ size patch (1/day) and were evaluated after 1 week (7 ± 3 days) for tolerability and effectiveness.The approximate duration of MTS patch wear was 9 hours per day; a new patch was applied each morning upon awakening. Subjects were titrated to the next patch size after a minimum of 1 week on the previous size. Subjects may have been titrated back down to the previous patch size to optimize tolerability. Subject response was categorized by the investigator into 1 of the following 3 conditions:

1. **Intolerable condition:** (unacceptable safety profile): Subject was tapered to a lower MTS patch size (if available). If the lower patch size was not tolerable, the subject was discontinued from the study.
2. **Ineffective condition:** (<25% change in ADHD-RS score with acceptable safety profile): The MTS patch size was increased to the next available dose strength followed by weekly evaluation.
3. **Acceptable condition:** Significant reduction in ADHD symptoms with minimal side effects.

Subjects who had not reached an acceptable patch size by Visit 7 were withdrawn from the study.

Double-Blind, Crossover, Analog Classroom Period:

Following completion of the Dose Optimization period subjects were randomized to a sequence of 1 week of treatment with each of MTS and placebo transdermal patch (PTS). The duration of this period was 2 weeks and each end of week assessment, included both measurement of behavioral effects and plasma collection, and occurred in the controlled environment of the Analog Classroom. During scheduled classroom visits, subjects arrived at the study site at approximately 0615 and were dismissed at approximately 1930.

Follow-up Period:
Subjects who did not enroll into the open-label extension study (protocol SPD485-303) at the End of Study/Early Termination Visit (Visit 9) were followed for 30 days (±2 days) after their last dose of study drug.

The study design is shown in the Text Figure and Text Table below.

Figure 1: Study Design Flow Chart

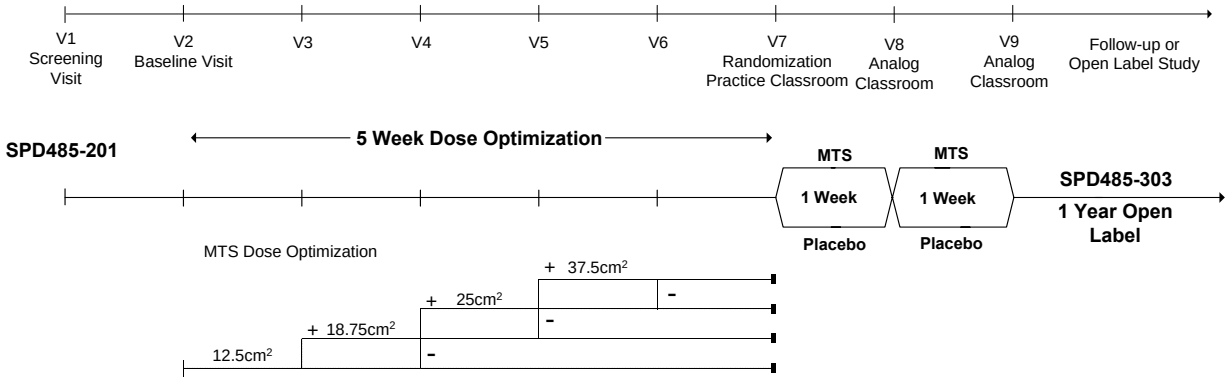


Table 1: Detailed Study Day Schedule

Hour Post Dose	Physical Examination	Vital Signs *	Height	Weight	Biochemistry/Hematology	Urinalysis	12-lead ECG†	Pregnancy Test (FOCP)	ADHD-RS-IV	Patch Removal	CGI-I	PGA & CPRS-R	SKAMP	PERMP	Collect Investigational Product	Distribute Investigational Product	PK Blood Draw§	Dermal Evaluations	CSHQ	AE monitoring ¶	Concomitant medications
Any	✓#		✓#		✓	✓	✓	✓#	✓		✓	✓							✓		
-1.25		✓		✓									✓	✓	✓		✓	✓		✓	✓
0	**Dosing - MTS/PTS Application followed by a Standard Breakfast**																				
0.5																					
1.0																					
1.5																					
2.0		✓											✓	✓			✓				
2.5	**Standard Snack**																				
3.0		✓											✓	✓			✓				
3.5																					
4.0																					
4.5		✓											✓	✓			✓				
5.0	**Standard Lunch**																				
5.5																					
6.0		✓											✓	✓			✓			✓	
6.5																					
7.0																					
7.5		✓											✓	✓			✓				
8.0	**Standard Snack**																				
8.5																					
9.0		✓								✓			✓	✓	✓		✓	✓		✓	
9.5																					
10.0																					
10.5		✓											✓	✓			✓				
11.0	**Standard Dinner**																				
11.5																✓+					
12.0		✓											✓	✓			✓			✓	
12.5	**Dismissal**																				

∗ Included sitting blood pressure, pulse, and respiratory rate. Oral temperature was only collected upon arrival.
† Any time between 1200 and prior to patch removal at Visit 9 only.
¶ Spontaneously reported AEs were collected throughout, non-directed questioning occurred.
+ Conducted at Visit 8 only.
# Conducted at Visit 9 only.
§ Blood sampling for pharmacokinetic analysis was conducted at Visits 8 and 9 only.

3.2 Data Analyses

3.2.1 Statistical analysis plan

3.2.1.1 Study populations

Intention-to-treat population
The Intention-to-Treat (ITT) population was defined as all subjects who were randomized to receive investigational product, received at least 1 application of investigational product, had a SKAMP scale assessment at pre-dose on Visit 8 and had at least 1 SKAMP scale assessment following Visit 8 pre-dose.

3.2.1.2 Analysis variables

The primary efficacy variable was the mean SKAMP deportment scale score over the course of the Analog Classroom session days at 2.0, 3.0, 4.5, 6.0, 7.5 and 9.0 hours. The primary efficacy analysis was the comparison between MTS and placebo and was performed on the ITT population.

The primary efficacy variable was assessed by a mixed linear model with sequence, period and treatment as fixed effects, and subject-within-sequence as a random effect. Based on the same model, the SKAMP deportment scores at each timepoint through the day (2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours) were also analyzed. The time of onset of efficacy was defined as one-half of the time between the first assessment time showing statistical significance and the previous assessment. The loss of efficacy was defined as one-half of the time between an assessment time that showed significance and the subsequent time that failed to show significance. If no loss of significance was found until 12.0 hours, then the loss of efficacy was assigned at 12.5 hours.

Additional statistical analyses of the primary efficacy variable, and analyses of secondary efficacy variables, were considered supportive. The secondary efficacy variables included the PERMP, total SKAMP score, additional SKAMP subscale scores (attention and quality of work), ADHD-RS-IV, CPRS-R, CGI-I and PGA. The PERMP scores were analyzed based on a similar analysis model to that described for the primary efficacy variable. Other SKAMP scores (total, attention and quality of work), ADHD-RS-IV and CPRS-R scores were analyzed similarly. A generalized estimating model was used to analyze the CGI-I and PGA scores during Analog Classroom sessions.

Summary statistics (including number of observations, mean, SD, median, minimum, and maximum) of skin tolerance as well as apparent dose were provided for each treatment, where applicable.

4. STUDY SUBJECTS – RESULTS (STUDY SPD485-201)

4.1 Disposition of Subjects

A total of 127 subjects were screened for the study. There were 34 screen failures, resulting in 93 subjects enrolled.

Ninety-three subjects were enrolled in this study and comprised the safety population. Thirteen subjects were terminated prior to randomization: 7 subjects for AEs, 3 subjects withdrew consent, and 3 subjects for other reasons. Seventy-nine (98.8%) of the 80 randomized subjects completed the study and comprised the ITT population.

4.2 Demographic and Other Baseline Characteristics

A summary of demographics and baseline characteristics for all enrolled subjects is presented below. The mean age of the 93 enrolled subjects was 9.2 years, with 54.8% subjects 6-9 years of age and 45.2% subjects 10-12 years of age. There were 73.1% males and 26.9% females. The majority of subjects were White (68.8%) and of Not Hispanic or Latino (75.3%) ethnicity. The ADHD-RS-IV scores at Baseline ranged from 26-54, with a mean of 41.2. The mean CGI-S at Baseline was 4.3, with the majority of subjects categorized as moderately (55.9%) and markedly (34.4%) ill.

Table 2: Summary of Demographics and Baseline Characteristics: All Enrolled Subjects

Characteristic	Statistic	TPR (N=13)	Treatment Sequence MTS/PTS (N=42)	Treatment Sequence PTS/MTS (N=38)	Overall (N=93)
Age (years):					
	Mean (SD)	9.5 (2.11)	9.4 (1.87)	8.9 (1.56)	9.2 (1.79)
	Median	10	9	8.5	9
	Min, Max	6, 12	6, 12	6, 12	6, 12
Age Category (years):					
6 - 9	n (%)*	6 (46.2)	22 (52.4)	23 (60.5)	51 (54.8)
10 - 12	n (%)	7 (53.8)	20 (47.6)	15 (39.5)	42 (45.2)
Gender					
Male	n (%)	10 (76.9)	31 (73.8)	27 (71.1)	68 (73.1)
Female	n (%)	3 (23.1)	11 (26.2)	11 (28.9)	25 (26.9)
Ethnicity					
Hispanic or Latino	n (%)	4 (30.8)	10 (23.8)	9 (23.7)	23 (24.7)
Not Hispanic or Latino	n (%)	9 (69.2)	32 (76.2)	29 (76.3)	70 (75.3)

Table 2: Summary of Demographics and Baseline Characteristics: All Enrolled Subjects

Characteristic	Statistic	TPR (N=13)	Treatment Sequence MTS/PTS (N=42)	Treatment Sequence PTS/MTS (N=38)	Overall (N=93)
Race					
White	n (%)	8 (61.5)	26 (61.9)	30 (78.9)	64 (68.8)
Black or African American	n (%)	1 (7.7)	4 (9.5)	4 (10.5)	9 (9.7)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0	0
Asian	n (%)	1 (7.7)	2 (4.8)	0	3 (3.2)
American Indian or Alaska Native	n (%)	0	0	0	0
Other	n (%)	3 (23.1)	10 (23.8)	4 (10.5)	17 (18.3)
Weight (lb):					
	Mean (SD)	71.62 (20.35)	73.50 (21.62)	68.27 (13.70)	71.10 (18.54)
	Median	68.4	72	65	68.4
	Min, Max	43.0, 107.5	41.0, 131.1	46.5, 102.0	41.0, 131.1
Height (in):					
	Mean (SD)	54.53(4.44)	54.16(5.28)	53.14(3.34)	53.80(4.45)
	Median	54.5	54	54	54
	Min, Max	47.5 , 61.3	43.5 , 65.0	46.0 , 60.0	43.5 , 65.0
BMI (kg/m^2):					
	Mean (SD)	16.58 (2.48)	17.26(2.58)	16.86 (2.18)	17.01 (2.40)
	Median	16.07	16.83	16.34	16.45
	Min, Max	13.4, 20.6	13.0, 24.4	14.1, 24.1	13.0, 24.4
ADHD-RS-IV :					
	Mean (SD)	38.4 (7.14)	41.6 (8.46)	41.8 (6.64)	41.2 (7.59)
	Median	37	44	41.5	42
	Min, Max	26, 47	26, 53	29, 54	26, 54
CGI-S:					
	Mean (SD)	4.2 (0.60)	4.4 (0.73)	4.3 (0.58)	4.3 (0.65)
	Median	4	4	4	4
	Min, Max	3, 5	3, 6	3, 6	3, 6

* Percentages are based on the number of enrolled subjects in each category.
TPR = Terminated Prior to Randomization

4.3 Prior and Concomitant Therapy

4.3.1 Prior therapy

The majority of subjects, 64 of the 93 subjects enrolled (68.8%) had received ADHD therapy prior to participating in this study and 29 of the 93 subjects (31.2%) reported that they had never received ADHD medication therapy prior to participation in this study. Prior medications were defined as medications with a start or stop date before the first dispensing date of the investigational product. The most common prior medications reported were methylphenidate hydrochloride (33 subjects, 35.5%) and obetrol (21 subjects, 23.7%). Subjects randomized to the MTS/PTS sequence (18 subjects, 42.9%) reported more methylphenidate hydrochloride as a prior medication than subjects randomized to the PTS/MTS sequence (11 subjects, 28.9%).

4.3.2 Concomitant therapy

Concomitant medications were defined as medications with a start and a stop date on or after the first dispensing date of the investigational product. Of the 93 subjects that received MTS treatment, the most common concomitant medications were ibuprofen (16 subjects,17.2%), paracetamol (14 subjects, 15.1%), and loratadine (8 subjects, 8.6%). Paracetamol (4 subjects, 5.0%) was the most common concomitant medication reported for the 80 subjects that received PTS.

4.4 Measurements of Treatment Compliance

The mean compliance rate during the Dose-Optimization period was similar for all MTS patch sizes. The mean (SD) compliance rate ranged from 94.72 (11.76)% for the 12.5cm^2 MTS to 102.38 (6.30)% for the 37.5cm^2 MTS.

The overall mean (SD) compliance rates for the Analog Classroom MTS and PTS treatment periods were similar, 96.83 (9.25)% for MTS and 95.77 (8.33)% for PTS.

5. EFFICACY EVALUATION – RESULTS (STUDY SPD485-201)

5.1 Data Sets Analyzed

All subjects who entered the Baseline Visit were considered enrolled study participants. The ITT population was identified and finalized before the database was locked and the study unblinded.

5.2 Efficacy Results

5.2.1 Primary efficacy variable

5.2.1.1 SKAMP Deportment Scale

ITT Population
The primary objective of this study was to evaluate the behavioral effects (measured by the SKAMP deportment scale) of MTS compared to placebo in children diagnosed with ADHD. The primary efficacy variable was the mean SKAMP deportment scale score over the course of the Analog Classroom session days at 2.0, 3.0, 4.5, 6.0, 7.5 and 9.0 hours. The primary objective was assessed using a mixed model with terms for sequence, period and treatment as fixed effects and subject-within-sequence as a random effect.

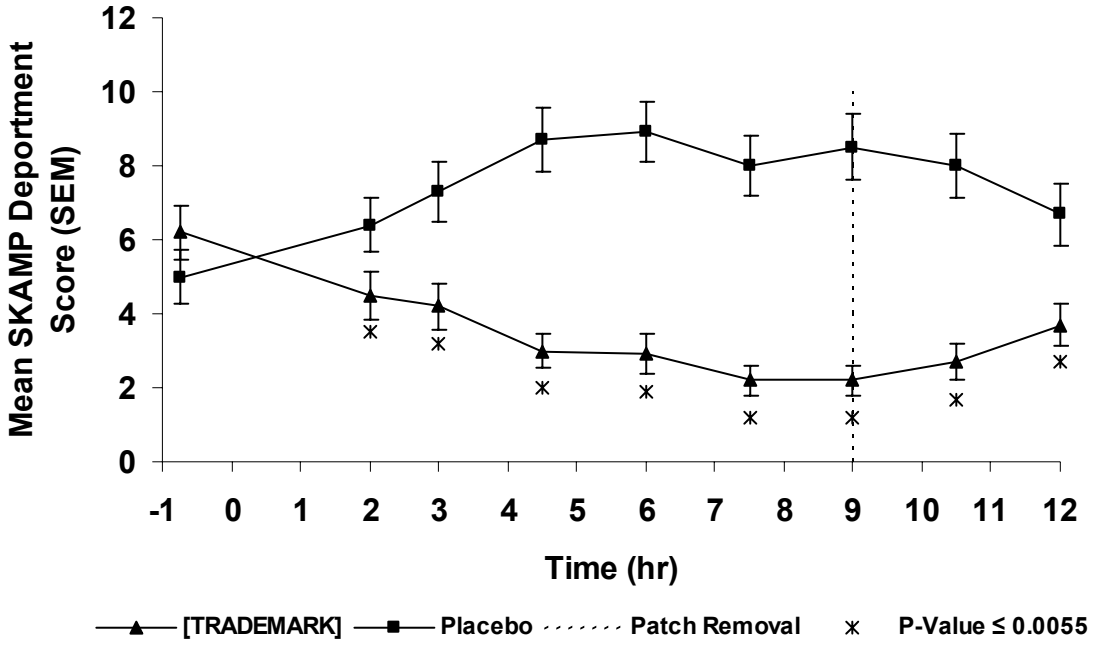
For the ITT population, the LS mean (±SE) SKAMP deportment score for MTS (3.2±0.58) was significantly lower ($p<0.0001$) than that for PTS (8.0±0.58). The LS mean difference in SKAMP deportment scores was -4.8, with a 95% confidence interval of (-5.89, -3.64).

Mean SKAMP deportment scores were significantly lower for MTS compared to PTS at all post-dose timepoints. Moreover, this difference was statistically significant starting with the first post-dose administration timepoint (2.0 hours) and the difference continued to be statistically significant for all timepoints up to and including 12.0 hours post dose.

Table 3: Summary and Analysis of Mean SKAMP Deportment Score During Patch Application (Hours 2.0 – 9.0): ITT Population

Statistic	MTS	PTS
N	79	79
Mean (SD)	3.2 (3.64)	8.0 (6.33)
Median	2.2	7.3
Min, Max	0, 17	0, 29
LS Mean (SE)	3.2 (0.58)	8.0 (0.58)
Difference and 95% CI of LS Means (MTS-PTS)	-4.8 (-5.89, -3.64)	
P-value	<0.0001	

Figure 2: Plot of SKAMP Deportment Score by Timepoint – Analog Classroom Period – ITT Population – Means and One Standard Error



5.2.2 Secondary efficacy variables

5.2.2.1 PERMP Measures

PERMP: Number of Math Problems Attempted

The main secondary objective was to assess the duration of efficacy of MTS compared to placebo in children with ADHD using the PERMP. The LS mean (±SE) PERMP: Number of Math Problems Attempted score for MTS (113.8±6.39) was significantly higher ($p<0.0001$) than that for PTS (86.2±6.39). The LS mean difference in PERMP: Number of Math Problems Attempted scores was 27.5, with a 95% confidence interval of (19.48, 35.59).

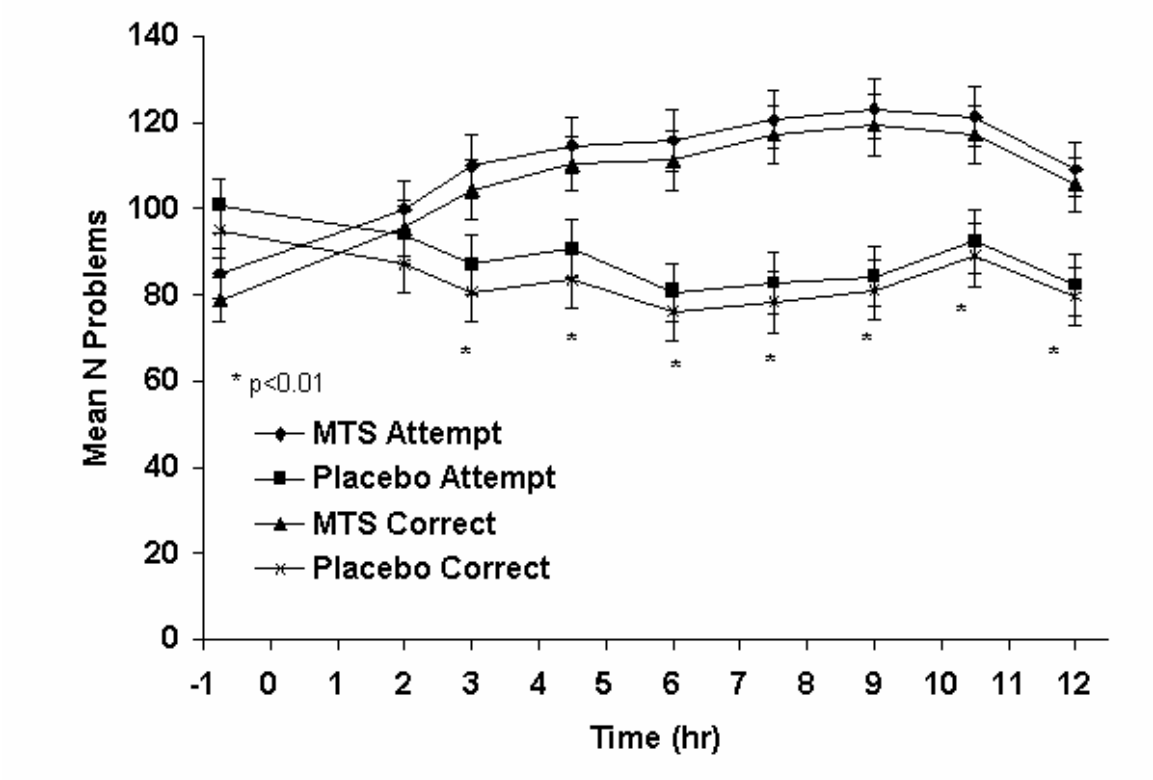
Mean MTS PERMP: Number of Math Problems Attempted scores were slightly lower than the mean PTS PERMP: Number of Math Problems Attempted scores at pre-dose and were higher at all timepoints after 2.0 hours post-dose. Moreover, the difference was statistically significant starting at 3 hours post-dose and continuing up to and including the 12.0 hours post-dose timepoint. For the analysis by timepoint, the largest mean difference in PERMP Number of Math Problems Attempted scores was observed at 9.0 hours post-dose in the ITT population.

Table 4: Summary and Analysis of Mean PERMP, Number of Math Problems Attempted: ITT Population

Statistic	MTS	PTS
N	79	79
Mean* (SD)	113.9 (56.80)	86.7 (57.15)
Median	99.3	71.5
Min, Max*	30, 305	9, 381
LS Mean (SE)	113.8 (6.39)	86.2 (6.39)
Difference and 95% CI of LS Means (MTS-PTS)	27.5 (19.48, 35.59)	
P-value	<0.0001	

* mean, min and max scores shown based on analysis of mean data score for each visit averaged over all timepoints.

Figure 3: Plot of PERMP Score – Number of Math Problems Attempted and Correct – Analog Classroom Period – ITT Population – Means and One Standard Error



PERMP: Number of Math Problems Correct
For the ITT population, the LS mean (±SE) PERMP: Number of Math Problems Correct score for MTS (109.4±6.34) was significantly higher (p<0.0001) than that for PTS (80.7±6.34). The LS mean difference in PERMP: Number of Math Problems Correct scores was 28.7, with a 95 % confidence interval of (21.09, 36.34).

Mean MTS PERMP number correct scores were lower than the mean PTS PERMP number correct scores at pre-dose and were significantly higher at all timepoints after 2.0 hours post-dose. The largest difference in mean PERMP number correct scores between the MTS and PTS groups was observed at 7.5 hours post-dose.

Table 5: Summary and Analysis of Mean PERMP, Number of Math Problems Correct – ITT Population

Statistic	MTS	PTS
N	79	79
Mean (SD)	109.5 (56.25)	81.2 (56.92)
Median	94.5	65.8
Min, Max	29, 305	9, 380
LS Mean (SE)	109.4 (6.34)	80.7 (6.34)
Difference and 95% CI of LS Means (MTS-PTS)	28.7 (21.09, 36.34)	
P-value	<0.0001	

PERMP: Sum of Number of Math Problems Attempted and Correct
In the ITT population, the LS mean (±SE) PERMP: Sum of Number of Math Problems Attempted and Correct score for MTS (223.2±12.67) was significantly higher (p<0.0001) than that for PTS (167.0±12.67). The LS mean difference in PERMP: Sum of Number of Math Problems Attempted and Correct scores was 56.3, with a 95% confidence interval of (40.74, 71.76).

5.2.2.2 Other SKAMP Scales/Subscales

SKAMP Total Score
In the ITT population, the MTS LS mean (±SE) (9.4±0.99) was significantly lower (p<0.0001) than the PTS LS mean (±SE) (17.9±0.99). The 95% confidence interval for the LS mean difference (MTS-PTS) of -8.5 was (-10.2, -6.79).

SKAMP Attention Subscale Score
The MTS LS mean (±SE) (1.6±0.28) was significantly less (p<0.0001) than the PTS LS mean (±SE) (3.4±0.28) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -1.7 was (-2.23, -1.25).

SKAMP Quality of Work Subscale Score
The MTS LS mean (±SE) (4.5±0.31) was significantly less (p<0.0001) than the PTS LS mean (±SE) (6.5±0.31) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -2.0 was (-2.49, -1.50).

5.2.2.3 ADHD Rating Scale – IV

ADHD-RS-IV Total Score
Analog Classroom Period
For the ITT population, the MTS LS mean (±SE) (16.3±1.24) was significantly less (p<0.0001) than the PTS LS mean (±SE) (32.7±1.23). The 95% confidence interval for the LS mean difference (MTS-PTS) of -16.5 was (-19.8, -13.1).

Table 6: Summary and Analysis of ADHD-RS-IV Total Score – Analog Classroom Period – ITT Population

Statistic	MTS	PTS
N	78	79
Mean (SD)	16.3 (9.96)	32.8 (11.99)
Median	15.5	35.0
Min, Max	0, 45	1, 54
LS Mean (SE)	16.3 (1.24)	32.7 (1.23)
Difference and 95% CI of LS Means (MTS-PTS)	-16.5 (-19.80, -13.14)	
P-value	<0.0001	

Gender Analysis
In the ITT population, for MTS compared to PTS, the mean ADHD Total score was lower for male and female subjects.

For MTS, the mean ADHD Total score for was lower for male subjects compared to female subjects.

Race Analysis
In the ITT population, for MTS compared to PTS, the mean ADHD Total score was lower for White, Black, and Other subjects.

ADHD-RS-IV Subscale Score: Hyperactivity/Impulsivity

Analog Classroom Period
The MTS LS mean (±SE) (7.2±0.69) was significantly less (p<0.0001) than the PTS LS mean (±SE) (15.8±0.68) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -8.6 was (-10.4, -6.85).

ADHD-RS-IV Subscale Score: Inattentiveness

Analog Classroom Period
The MTS LS mean (±SE) (9.0±0.70) was significantly less (p<0.0001) than the PTS LS mean (±SE) (16.9±0.70) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -7.9 was (-9.57, -6.14).

5.2.2.4 Clinical Global Impressions Scales

Analog Classroom Period
In the ITT population, a significantly (p<0.0001) larger number of MTS subjects than PTS subjects were rated as improved. For Period 1 (V8), 33 (80.5%) MTS subjects and 6 (15.8%) PTS subjects were rated as showing improvement. For Period 2 (V9), 30 (78.9%) MTS subjects and 3 (7.3%) PTS subjects were rated as showing improvement.

5.2.2.5 Parent's Global Assessment

Analog Classroom Period
In the ITT population, a significantly (p<0.0001) larger number of MTS subjects than PTS subjects were rated as showing improvement. For Period 1 (V8), 27 (65.9%) MTS subjects and 9 (24.3%) PTS subjects were rated as showing improvement. For Period 2 (V9), 29 (76.3%) MTS subjects and 3 (7.3%) PTS subjects were rated as showing improvement.

5.2.2.6 Conners' Parent Rating Scale – Revised Short Version

CPRS-R Total Score

Analog Classroom Period
The MTS LS mean (±SE) (20.2±2.11) was significantly lower (p<0.0001) than the PTS LS mean (±SE) (35.3±2.21) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -15.1 was (-20.5, -9.66).

CPRS-R ADHD Score

Analog Classroom Period
The MTS LS mean (±SE) (10.7±1.05) was significantly less (p<0.0001) than the PTS LS mean (±SE) (17.4±1.09) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -6.7 was (-9.34, -4.08).

CPRS-R Oppositional Score

Analog Classroom Period
The MTS LS mean (±SE) (3.5±0.50) was significantly less (p<0.0001) than the PTS LS mean (±SE) (6.0±0.52) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -2.5 was (-3.60, -1.41).

CPRS-R Hyperactivity Score

Analog Classroom Period
The MTS LS mean (±SE) (3.5±0.54) was significantly less (p<0.0001) than the PTS LS mean (±SE) (7.6±0.57) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -4.1 was (-5.45, -2.76).

CPRS-R Cognitive Score

Analog Classroom Period
The MTS LS mean (±SE) (5.0±0.62) was significantly less (p<0.0001) than the PTS LS mean (±SE) (8.5±0.65) in the ITT population. The 95% confidence interval for the LS mean difference (MTS-PTS) of -3.5 was (-4.98, -1.98).

5.2.3 Statistical/analytical issues

The normality of SKAMP residuals was examined through histograms, normal q-q plots, and plots of residuals versus fitted values.

5.2.4 Efficacy conclusions

This study was designed to demonstrate the effects of treatment with MTS on children with ADHD through direct observation of behaviors and objective measurement of mathematical productivity in the analog classroom setting. The analog classroom protocol has been developed specifically to test stimulant medications in the treatment of ADHD in a highly controlled environment. The design of the analog classroom protocol allows for the precise measurement of surrogate responses to medications used to treat this disorder of childhood.[19] In this study the primary and main secondary surrogate response measures were the deportment subscale of the SKAMP and the PERMP.

In the ITT population, there were significant improvements in mean SKAMP deportment scores in the MTS group compared with the PTS group (difference = -4.8; 95% Confidence Interval -5.89, -3.64) beginning at 2 hours post-patch application through hour 9. Thus, the primary endpoint of this study was achieved with the demonstration of significantly lower mean SKAMP deportment scores in the MTS group.

Since the overall effect of MTS on the primary efficacy variable was statistically significant when compared to placebo, the SKAMP deportment scores at each analog classroom timepoint were analyzed in order to measure the onset and duration of effect of MTS. The results showed that all SKAMP deportment scores were significantly lower than placebo at each timepoint examined. The onset of efficacy was evident at the first post-dose time-point (hour 2) where MTS was superior to PTS. The duration of efficacy lasted through the final post application time-point (hour 12).

The onset of efficacy was defined as one-half of the time between the first assessment time showing significance and the previous assessment. Likewise, the loss of efficacy was defined as one-half of the time between the last assessment time showing significance and the subsequent time that failed to show significance. If no loss of efficacy were found then the loss of efficacy would be assigned at 12.5 hours. The onset of efficacy observed in this

study is thus defined as occurring at 1 hour and the loss of efficacy at 12.5 hours. Therefore, the 9-hour period of patch wear resulted in an 11.5-hour duration of effect.

The main secondary endpoint was analyzed using the same model described above for the primary efficacy variable. The main secondary endpoint was defined as the measurement of the mean PERMP: Number of Math Problems Attempted and Number of Math Problems Correct scores, for the ITT population, beginning 2 hours post application of the MTS or PTS patches through hour 9. The results showed significant improvements in the MTS group compared with the PTS group during the Analog Classroom day in both categories (Attempted and Correct) (Number of Math Problems Attempted: difference = 27.5; 95% CI 19.48 to 35.59) and (Number of Math Problems Correct: difference = 28.7; 95% CI 21.09 to 36.34). Therefore, the main secondary endpoint of this study was achieved with the demonstration of significantly higher mean PERMP: Attempted and Correct scores compared to PTS.

The onset and duration of effect, as measured by the PERMP (Attempted and Correct), were similar to those seen using the SKAMP deportment scores. At the first post-dose time-point (hour 2), for the Number Attempted and the Number Correct there was no statistical significance between MTS and PTS. The difference between MTS and PTS became significant at the second post-dose time-point (hour 3) for both the Number Attempted and the Number Correct. Therefore the onset of efficacy as measured by the PERMP is defined as occurring at 2.5 hours and the loss of efficacy at 12.5 hours. Therefore, the 9-hour period of patch wear resulted in a 10-hour duration of effect.

All of the primary and secondary endpoints analyzed in this study showed significance as presented in the text table below.

Table 7: Summary of Efficacy Endpoints (ITT Population)

Efficacy Variable	Hour/Overall	P Value
SKAMP deportment subscale	Overall	<0.0001
SKAMP deportment by timepoint	2 hr – 12 hr	≤0.0055
PERMP: Number of Math Problems Attempted	Overall	<0.0001
PERMP: Number of Math Problems Attempted	3 hr – 12 hr	≤0.0003
PERMP: Number of Math Problems Correct	Overall	<0.0001
PERMP: Number of Math Problems Correct	3 hr – 12 hr	<0.0001
SKAMP Total Score	Overall	<0.0001
SKAMP Subscale Score: Attention	Overall	<0.0001
SKAMP Subscale Score: Quality of Work	Overall	<0.0001
ADHD-RS-IV Total Score	Overall	<0.0001

Table 7: Summary of Efficacy Endpoints (ITT Population)		
Efficacy Variable	Hour/Overall	P Value
ADHD-RS-IV Subscale Score: Hyperactivity/Impulsivity	Overall	<0.0001
ADHD-RS-IV Subscale Score: Inattentiveness	Overall	<0.0001
CPRS-R Total Score	Overall	<0.0001
CPRS-R Total score by Timepoint	1100	<0.0001
	1500	
CPRS-R Subscale Score: ADHD	Overall	<0.0001
CPRS-R Subscale Score: Oppositional	Overall	<0.0001
CPRS-R Subscale Score: Hyperactivity	Overall	<0.0001
CPRS-R Subscale Score: Cognitive	Overall	<0.0001
CGI – I	Overall	<0.0001
PGA	Overall	<0.0001

Efficacy was demonstrated by the significant ADHD symptom reductions seen in the MTS group in the total ADHD-RS-IV scores, as well as in the separate sub-scale scores of hyperactivity/impulsivity and inattentiveness, when compared to the PTS group. In addition, Clinicians rated efficacy based on improvement in ADHD symptoms using the CGI rating scale. The results of the CGI analysis showed that a significantly greater number of subjects treated with MTS showed improvement over PTS treated subjects.

Efficacy, as measured by the assessment of the child's parent/caregiver using the CPRS-R rating scale, was demonstrated by the significant symptom reduction seen in ADHD symptoms in the MTS group when compared to the PTS group, in total, by timepoint (1100 and 1500), and using all sub-scale scores (ADHD, Oppositional, Hyperactivity, and Cognitive). In addition to the CPRS-R, Parents/Guardians rated efficacy based on improvement using the PGA rating scale. The results of the PGA analysis showed that a significantly greater number of subjects treated with MTS showed improvement when compared to PTS-treated subjects.

Overall, this study showed significant differences in all primary and secondary efficacy variables in MTS-treated subjects when compared to PTS-treated subjects. The MTS group demonstrated significant improvements in subjective measurements of behavior as rated by teachers, clinicians and parents. In addition, the PERMP, an objective assessment of math productivity in the classroom, showed significant improvements. The onset of effect was apparent by the 2.0 hour timepoint and persisted for the duration of the classroom observation period as measured by the SKAMP deportment scale. Therefore, we conclude that treatment with MTS in this study reduced ADHD symptoms as measured by a wide assortment of both subjective and objective standard measurements.

6. STUDY OBJECTIVES (STUDY SPD485-302)

6.1 Primary Efficacy Objective

The primary objective of this study was to evaluate, under controlled conditions, the safety and efficacy of SPD485 (MTS) compared to placebo with reference to CONCERTA®, as determined by the change in the clinician completed Attention-Deficit/Hyperactivity Disorder-Rating Scale, Version IV (ADHD-RS-IV), in the symptomatic treatment of children (aged 6-12) diagnosed with ADHD by the Diagnostic and Statistical manual of Mental Disorders, 4th ed.–text revision (DSM-IV-TR) criteria.

6.2 Secondary Efficacy Objectives

The main secondary objective was to assess the efficacy of MTS compared to placebo with reference to CONCERTA® in an academic setting using the change in the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R). The CTRS-R was completed by the subject's teacher in the morning and afternoon, 2 days per week during the study.

Other key secondary objectives included the following:

- To assess the efficacy of MTS compared to placebo with reference to CONCERTA® in the home environment as rated by the parent using the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) administered weekly, on 1 weekend day in the morning and afternoon.

- To assess global impressions of ADHD severity and improvement of MTS compared to placebo with reference to CONCERTA® from the clinician and parent in response to treatment using Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessments (PGA).

7. INVESTIGATIONAL PLAN (STUDY SPD485-302)

7.1 Overall Study Design and Plan

This was a Phase III, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the safety and efficacy of MTS (12.5cm^2, 18.75cm^2, 25cm^2, and 37.5cm^2 patch sizes) compared to placebo with reference to CONCERTA® in pediatric subjects diagnosed with ADHD. Subjects visited the study site 9 times during the course of approximately 14 weeks. The study consisted of 3 periods detailed below:

Screening & Washout Period

Subjects were screened approximately 2 weeks prior to washout. Washout was up to 28 days depending upon the half-life of the subject's medication requiring washout.

Double-Blind Dose Optimization/Maintenance Period

Eligible subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA®, or matching placebo and entered the double-blind stepwise dose optimization period. The objective of this period was to ensure subjects were titrated to at least an acceptable dose of MTS (using 12.5cm^2, 18.75cm^2, 25cm^2, and 37.5cm^2 patch sizes) or CONCERTA® (using 18mg, 27mg, 36mg, and 54mg dosage strengths) based upon investigator review of parent and teacher rating forms,TEAEs, and clinical judgment (using the ADHD-RS-IV). During 1 of the last 3 visits, Visit 7, 8 or 9, three venous blood samples were drawn at 7.5 hr, 9.0 hr, and 10.5 hr post dosing for Pharmacokinetic (PK) evaluation. The duration of this period was 5 weeks to allow for titration up to the highest dose and 1 titration down to a prior dose level, if necessary. No further titration up or down was permitted once subjects had been titrated down.

The duration of MTS/PTS (Placebo Transdermal System) patch wear was 9 hours per day; a new patch was applied each morning at approximately 0700 hours. All subjects were initiated on the MTS/PTS 12.5cm^2 size patch (1/day) and the CONCERTA®/matching placebo 18mg dose (1/day), and were evaluated after 1 week (7±2 days) for tolerability and effectiveness. Titration to the next patch size/dosage strength was allowed after a minimum of 1 week on the previous size/dose based on the overall response of the subject. Additionally, subjects may have been titrated back down to the previous patch size/dosage strength (once) to optimize tolerability and effectiveness. Subject response was categorized by the investigator into 1 of 3 conditions and associated actions:

1. **Intolerable condition:** (i.e., unacceptable safety profile) Required the subject to be tapered to a lower MTS size/CONCERTA® dose (if available). However, if the adjusted patch size/dose strength produced an intolerable effect as well, the subject was to be discontinued from the study.
2. **Ineffective condition:** (i.e.,<25% change in ADHD-RS score with acceptable safety profile) Required increasing the MTS size/CONCERTA® dose to the next available dose strength followed by weekly evaluation.
3. **Acceptable condition:** A response was defined as acceptable if a subject showed at least a 25% reduction in ADHD symptoms with minimal side effects.

Subjects who did not reach at least an acceptable dose (i.e., "Acceptable condition") by Visit 7, were withdrawn from the study. Subjects completing Visit 7 (Week 5) were permitted to enroll in the SPD485-303 open-label study.

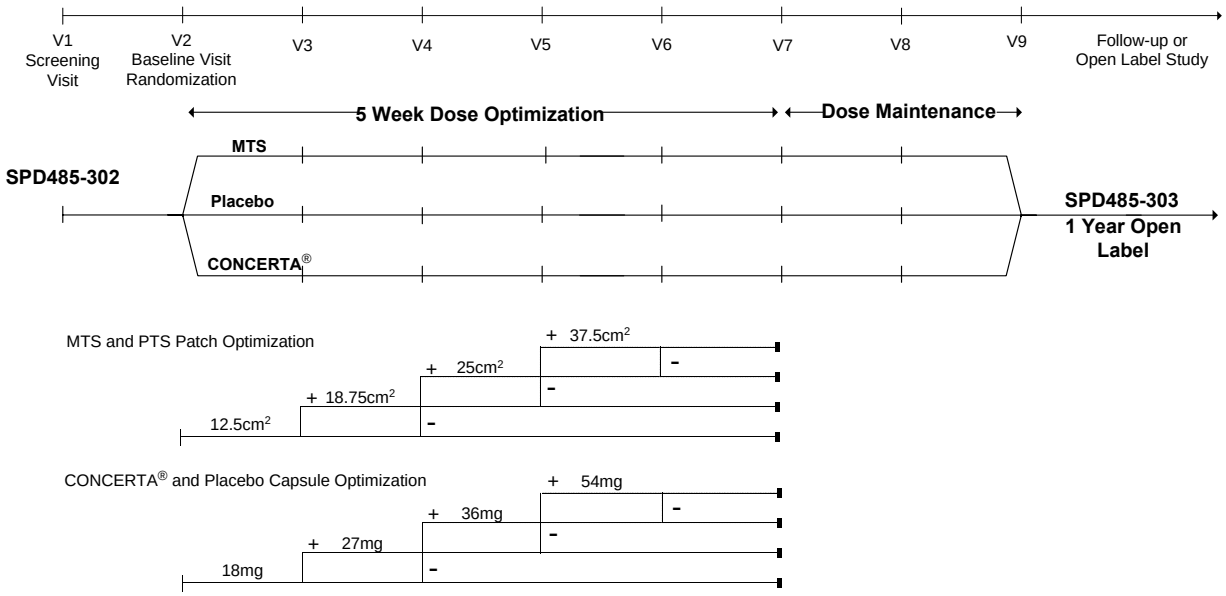
Following successful titration to at least an acceptable dose of MTS/CONCERTA®/Placebo by Visit 7, subjects maintained the dose through the maintenance period. Double-blind assessment of the safety and efficacy of MTS/CONCERTA®/Placebo proceeded for 2 weeks.

Follow-Up Period:

At the End of Study Visit (Visit 9), eligible subjects had the option to enroll into an open-label extension study (protocol SPD485-303). For those subjects who enrolled in the open-label study, Visit 9 also served as the Baseline Visit for SPD485-303. Subjects who did not enroll into the extension continued to be followed for thirty days (±2 days) following their last dose of study drug.

The study design flowchart is shown below in the Text Figure below.

Figure 4: Study Design Flow Chart



7.2 Data Analyses

7.2.1 Statistical analysis plan

7.2.1.1 Study populations

Intention-to-treat population
The Intent-to-Treat (ITT) population was defined as all subjects who were randomized to receive investigational product, received at least 1 dose of investigational product and had a Baseline primary efficacy assessment and at least 1 primary efficacy assessment post-Baseline.

7.2.1.2 Analysis variables

The primary efficacy assessment was defined as the ADHD-RS-IV total scores. The Baseline consisted of the ADHD-RS-IV total score obtained at Visit 2. The endpoint of the primary efficacy assessment was defined as the last post-Baseline assessment for which a valid ADHD-RS-IV score was obtained. The primary efficacy variable was the ADHD-RS-IV change from Baseline score at the endpoint. The null hypothesis was that there was no difference between MTS and placebo. The primary efficacy analysis was performed on the

ITT population. The null hypothesis was tested using the analysis of covariance (ANCOVA) model with treatment as a factor and Baseline ADHD-RS-IV score as a covariate.

The main secondary efficacy assessment was the CTRS-R total scores. The other secondary efficacy assessments included the CPRS-R, CGI-I and PGA. The endpoint of these secondary efficacy assessments was defined as the last post-Baseline assessment for which a valid value was obtained.

Continuous variables were analyzed using the same ANCOVA model described above to examine the treatment effects in the change from Baseline score at endpoint for the ITT population. Categorical variables were analyzed using a chi-square test.

Summary descriptive statistics were presented by treatment group populations. Continuous variables were summarized using a number of observations, mean, standard deviation (SD), median, minimum, and maximum values for each treatment group. Categorical values were summarized using number of observations and percentages.

8. STUDY SUBJECTS – RESULTS (STUDY SPD485-302)

8.1 Disposition of Subjects

A total of 282 subjects were enrolled, from 38 sites across the country, and randomized into this study. Eight (8) subjects who were randomized did not receive study medication, thus the Safety population consists of 274 subjects. Two (2) subjects did not have an ADHD assessment at Baseline and at least 1 post-dose assessment, and 2 additional subjects were included in the safety population but excluded from the efficacy population by the Sponsor due to unreliability of data, thus 270 subjects comprised the ITT population. A total of 113 (40.1%) randomized subjects did not complete the study; 61 (21.6%) continued into open-label study SPD485-303, 16 (5.7%) withdrew for reasons categorized as other, 14 (5.0%) withdrew consent, 9 (3.2%) discontinued due to an AE, 5 (1.8%) had a protocol violation, and 4 (1.4%) were lost to follow-up.

Of the 282 randomized subjects, 270 remained in the ITT population.

8.2 Demographic and Other Baseline Characteristics

A summary of demographics and Baseline characteristics for all randomized subjects is presented in the Text Table below. The age, gender, and ethnicity were similar in all 3 treatment groups within the randomized population. All characteristics of the enrolled, randomized, and ITT populations were similar for all 3 treatment groups.

Table 8: Subject Demographics and Baseline Characteristics - All Randomized Subjects

Characteristic	Category/Parameter	MTS (N=100)	CONCERTA® (N=94)	Placebo (N=88)	Total (N=282)
Age (years)	Mean	8.9	8.8	8.5	8.8
	SD	1.96	1.94	1.91	1.94
	Median	9.0	9.0	9.0	9.0
	Min-Max	6 - 12	6 - 12	6 - 12	6 – 12
Age Category n (%)	6–9 years	61 (61.0%)	60 (63.8%)	62 (70.5%)	183 (64.9%)
	10-12 years	39 (39.0%)	34 (36.2%)	26 (29.5%)	99 (35.1%)
Gender n(%)	Male	60 (60.0%)	62 (66.0%)	65 (73.9%)	187 (66.3%)
	Female	40 (40.0%)	32 (34.0%)	23 (26.1%)	95 (33.7%)
Ethnicity n(%)	Hispanic/Latino	16 (16.0%)	11 (11.7%)	8 (9.1%)	35 (12.4%)
	Not Hispanic/Latino	84 (84.0%)	83 (88.3%)	79 (89.8%)	246 (87.2%)
	Missing			1 (1.1%)	1 (0.4%)
Race n(%)	White	79 (79.0%)	75 (79.8%)	64 (72.7%)	218 (77.3%)
	Black/African American	11 (11.0%)	13 (13.8%)	17 (19.3%)	41 (14.5%)
	Asian	2 (2.0%)	0 (0%)	0 (0.0%)	2 (0.7%)
	Other	8 (8.0%)	6 (6.4%)	7 (8.0%)	21 (7.4%)
Weight (lb)	Mean	72.9	73.0	68.7	71.6
	SD	24.09	20.89	19.18	21.60
	Median	68.2	69.8	62.5	67.2
	Min-Max	37.0 – 148.3	41.0 -144.5	40.0 – 135.0	37.0 - 148.3
Height (in)	Mean	53.4	53.2	52.4	53.1
	SD	5.39	4.97	5.14	5.17
	Median	54.0	52.5	52.3	52.6
	Min-Max	42.3 – 68.0	42.9 – 66.5	39.2 – 65.8	39.2 – 68.0
BMI (kg/m^2)	Mean	17.5	17.8	17.3	17.5
	SD	2.98	2.79	2.31	2.72
	Median	16.7	17.5	16.6	16.8
	Min-Max	13.4 – 27.6	12.1 – 28.7	12.5 – 25.2	12.1 – 28.7
ADHD-RS-IV	Mean	43.1	43.4	42.1	42.9
	SD	7.39	7.11	7.41	7.30
	Median	44.0	45.0	43.0	44.0
	Min-Max	28 – 54	19 – 54	27 – 54	19 – 54

8.3 Prior and Concomitant Therapy

8.3.1 Prior therapy

Prior medications were defined as medications with a start or stop date before the first dispensing date of study drug. A total of 115 of the 274 subjects in the Safety population (42.0%) received 1 or more prior medications. The overall number of subjects with prior medication use was slightly higher in the MTS group (49 subjects, 50.0%) compared to the CONCERTA® (35 subjects, 38.5%) and placebo (31 subjects, 36.5%) groups. The most common prior medications reported were methylphenidate hydrochloride (34 subjects, 12.4%), mixed salts amphetamine (OBETROL®) (26 subjects, 9.5%), the oral antihistamines fexofenadine and loratadine (15 subjects, 5.5%), and multivitamins (15 subjects, 5.5%).

Of all enrolled subjects, approximately 43% had received or were taking 1 or more medications to treat ADHD prior to entering the Screening and Wash-out Period of the study, while approximately 57% had not received a medication to treat ADHD. The overall number of subjects with prior ADHD medication use was slightly higher in the MTS group (approximately 18%) compared to the CONCERTA® (approximately 13%) and placebo (approximately 12%) groups.

8.3.2 Concomitant therapy

Concomitant medications were defined as any medication with a start or stop date on or after the first dispensing of study drug. The overall number of subjects with concomitant medication use was similar between the 3 treatment groups. The most commonly used concomitant medications were paracetamol (34 subjects, 12.4%), ibuprofen (31 subjects, 11.3%), the oral antihistamines fexofenadine and loratadine (20 subjects, 7.3%), and multivitamins (15 subjects, 5.5%).

9. EFFICACY EVALUATION – RESULTS (STUDY SPD485-302)

9.1 Data Sets Analyzed

Data from subjects who were randomized, received at least 1 dose of investigational product, and had a Baseline primary efficacy assessment and at least 1 primary post-Baseline efficacy assessment comprised the ITT data set, 270 subjects (MTS, N=96, CONCERTA®, N=89 and placebo, N=85). 12 subjects were excluded from the ITT population. Data from 5 of the 7 valid subjects excluded from the ITT population were excluded because there was no documentation to indicate they received investigational product, and 2 subjects did not have Baseline and post-Baseline primary efficacy assessments. The ITT data set was used for primary and secondary efficacy summaries and analyses.

9.2 Primary Efficacy Variable at Baseline

The primary efficacy variable was the change in the ADHD-RS-IV total score at Endpoint (last valid post-Baseline evaluation) from Baseline (Visit 2); therefore there are no values for the primary efficacy variable at Baseline.

9.3 Efficacy Results

9.3.1 Primary efficacy assessment: ADHD-RS-IV total score

9.3.1.1 Summary of ADHD-RS-IV total score

Mean total scores decreased progressively over Visits 3-9 in all 3 treatment groups. Mean (SD) ADHD-RS-IV total scores at Visit 3 were 35.9 (11.16), 34.1 (12.01), and 37.4 (10.85) for subjects in the ITT population treated with MTS, CONCERTA®, and placebo, respectively; at Visit 9 the corresponding scores were 12.4 (9.15), 15.6 (10.64), and 18.6 (12.07). At Endpoint, the mean ADHD-RS-IV total scores were 18.8 (14.56), 21.8 (14.61), and 32.1 (15.00) for subjects treated with MTS, CONCERTA®, and placebo, respectively.

9.3.1.2 Analysis of change in ADHD-RS-IV total score

The decrease in the adjusted mean ADHD-RS-IV total score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

ANCOVA showed statistically significant differences in the LS mean (i.e., adjusted for Baseline score) change from Baseline in ADHD-RS-IV total score in subjects treated with MTS and subjects treated with placebo in the ITT population at Visits 4-9; the difference was

not significant at Visit 3, however, after 1 week of treatment. A comparison of change scores between subjects in the ITT population treated with CONCERTA® and placebo showed statistically significant differences at Visits 3-7; but the difference was not significant at Visits 8 or 9. By-visit comparisons of MTS and CONCERTA® showed no statistically significant difference at any visit.

Table 9: Primary Efficacy Outcome: Change from Baseline in ADHD-RS-IV Total Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
Baseline ADHD-RS-IV Total Score			
n	96	89	85
Mean (SD)	43.0 (7.45)	43.8 (6.65)	41.9 (7.43)
Change from Baseline			
n	96	89	85
Mean (SD)	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
Median	-26.0	-23.0	-5.0
Minimum, Maximum	-54, 10	-45, 13	-48, 17
LS mean (SE)	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
Difference (95% CI of LS means*) Active - Placebo	-13.893 (-18.062, -9.724)	-11.319 (-15.579, -7.059)	NA
P-value (Active - Placebo)	<0.0001	<0.0001	NA
Difference (95% CI of LS means) MTS - CONCERTA®	-2.574 (-6.690, 1.541)		NA
P-value (MTS - CONCERTA®)	0.2192		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares; NA, not applicable

9.3.1.3 Analysis of change in ADHD-RS-IV subscale score for hyperactivity/impulsivity

The decrease in the adjusted mean ADHD-RS-IV hyperactivity/impulsivity score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Table 10: Change from Baseline in ADHD-RS-IV Hyperactivity/Impulsivity Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
Baseline ADHD-RS-IV hyperactivity/impulsivity score			
n	96	89	85
Mean (SD)	20.3 (5.70)	21.0 (4.84)	19.6 (5.77)
Change from Baseline			
n	96	89	85
Mean (SD)	-11.8 (7.84)	-10.9 (8.06)	-4.8 (6.86)
Median	-12.0	-11.0	-2.0
Minimum, Maximum	-27, 8	-26, 10	-25, 10
LS mean (SE)	-11.8 (0.73)	-10.6 (0.76)	-5.2 (0.78)
Difference (95% CI of LS means*) Active - Placebo	-6.645 (-8.757, -4.532)	-5.421 (-7.581, -3.261)	NA
P-value (Active - Placebo)	<0.0001	<0.0001	NA
Difference (95% CI of LS means) MTS - CONCERTA®	-1.224 (-3.311, 0.863)		NA
P-value (MTS - CONCERTA®)	0.2493		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares; NA, not applicable

9.3.1.4 Analysis of change in ADHD-RS-IV subscale score for inattentiveness

The Text Table below presents an analysis of the change in ADHD-RS-IV inattentiveness score at Endpoint from Baseline in subjects treated with MTS compared to placebo with reference to CONCERTA® in the ITT population. The decrease in the adjusted mean ADHD-RS-IV inattentiveness score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Table 11: Change from Baseline in ADHD-RS-IV Inattentiveness Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
Baseline ADHD-RS-IV inattentiveness score			
n	96	89	85
Mean (SD)	22.7 (3.48)	22.8 (3.78)	22.4 (3.67)
Change from Baseline			
n	96	89	85
Mean (SD)	-12.4 (7.73)	-11.1 (7.62)	-5.1 (7.88)
Median	-14.0	-13.0	-2.0
Minimum, Maximum	-27, 3	-24, 3	-24, 12
LS mean (SE)	-12.4 (0.78)	-11.0 (0.81)	-5.2 (0.83)
Difference (95% CI of LS means*) Active - Placebo	-7.252 (-9.490, -5.014)	-5.888 (-8.167, -3.608)	NA
P-value (Active - Placebo)	<0.0001	<0.0001	NA
Difference (95% CI of LS means) MTS - CONCERTA®	-1.364 (-3.574, 0.845)		NA
P-value (MTS - CONCERTA®)	0.2251		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares; NA, not applicable

9.3.2 Secondary efficacy assessments

The CTRS-R was identified in the protocol as the main secondary efficacy assessment for this study. Other secondary efficacy assessments were the CPRS-R, the CGI, and the PGA.

9.3.2.1 Conners' ADHD Rating Scale – Teacher (CTRS-R)

The score at each visit represents an average of scores taken twice daily at Baseline (week before Visit 2) and twice daily 2 days a week during treatment.

CTRS-R total score
Summary of CTRS-R total score
Mean CTRS-R total scores generally decreased progressively over Visits 3-9.

Analysis of change in CTRS-R total score

The Text Table below presents an analysis of the change in the CTRS-R total score at Endpoint from Baseline in subjects treated with MTS compared to placebo with reference to CONCERTA® in the ITT population. The decrease in the adjusted mean CTRS-R total score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Table 12: Change from Baseline in CTRS-R Total Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
Baseline CTRS-R total score			
N	82	78	77
Mean (SD)	34.9 (18.97)	34.9 (18.89)	39.1 (18.79)
Change from Baseline			
n	82	76	74
Mean (SD)	-14.9 (18.71)	-17.0 (15.94)	-6.1 (16.09)
Median	-13.5	-15.0	-5.0
Minimum, Maximum	-57, 42	-66, 21	-44, 29
LS mean (SE)	-15.3 (1.69)	-17.5 (1.75)	-5.1 (1.78)
Difference (95% CI of LS means*) Active - Placebo	-10.186 (-15.028, -5.345)	-12.417 (-17.350, -7.484)	NA
P-value (Active - Placebo)	<0.0001	<0.0001	NA
Difference (95% CI of LS means) MTS - CONCERTA®	2.231 (-2.562, 7.024)		NA
P-value (MTS - CONCERTA®)	0.3600		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares; NA, not applicable

Summary of CTRS-R analyses

The study met its main secondary objective. MTS demonstrated significant improvements in CTRS-R total scores compared with placebo.

- MTS demonstrated significant improvements in CTRS-R scores for ADHD index, oppositional, hyperactivity, and cognitive problem subscales compared with placebo.

- The change in CTRS-R total and subscale scores for the CONCERTA® group were significantly improved compared with placebo.
- There were no significant differences in CTRS-R total or subscale scores between MTS and CONCERTA® groups.

9.3.2.2 Conners' ADHD Rating Scale – Parent (CPRS-R)

At each visit, parent ratings made at 1100 and 1500 hours are summarized and analyzed separately and also analyzed using a daily average.

CPRS-R total score

Summary of CPRS-R total score

The decrease in the adjusted mean CPRS-R total score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Analysis of change in mean CPRS-R total score

The Text Table below presents an analysis of the change in the mean CPRS-R total score at Endpoint from Baseline in subjects treated with MTS compared to placebo with reference to CONCERTA® in the ITT population. The decrease in the adjusted mean for the mean CPRS-R total score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Table 13: Change from Baseline in Mean (Daily Average) CPRS-R Total Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
N	85	83	75
Mean (SD)	-28.4 (19.84)	-22.9 (20.44)	-13.8 (19.49)
Median	-29.0	-23.0	-7.0
Minimum, Maximum	-72, 43	-70, 44	-63, 18
LS mean (SE)	-27.8 (2.08)	-23.0 (2.10)	-14.4 (2.22)
Difference (95% CI of LS means*) Active - Placebo	-13.419 (-19.419, -7.419)	-8.590 (-14.607, -2.572)	NA
P-value (Active - Placebo)	<0.0001	0.0053	NA
Difference (95% CI of LS means) MTS - CONCERTA®	-4.829 (-10.661, 1.002)		NA
P-value (MTS - CONCERTA®)	0.1041		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares; NA, not applicable

Summary of CPRS-R analyses
Among other secondary objectives, MTS demonstrated significant improvements in CPRS-R total score and scores for ADHD index, oppositional, hyperactivity, and cognitive subscales, compared with placebo, except for the oppositional subscale at 1500 hours.

- The change in CPRS-R total and subscale scores for the CONCERTA® group were also significantly improved compared with placebo, except for the oppositional subscale at 1100 hours, 1500 hours, and daily average.
- There were statistically significant differences between MTS and CONCERTA® for CPRS-R hyperactivity subscale scores at 1500 hours and daily average, with a treatment difference in favor of MTS.

9.3.2.3 Clinical Global Impressions (CGI) scale

The clinicians' weekly ratings of subjects' improvement from Baseline were dichotomized into categories of "improvement" ("very much improved" and "much improved") or "no improvement" (all other descriptive categories) for summary and analysis.

Chi-square analysis showed a statistically significant difference between MTS and placebo at all visits, as well as at Endpoint ($p<0.0001$). There was also a statistically significant difference between CONCERTA® and placebo at all visits and at Endpoint ($p<0.0001$), as well.

9.3.2.4 Parent Global Assessment (PGA)

As was done for the CGI, the parents' weekly ratings of subjects' improvement from Baseline were dichotomized into categories of "improvement" ("very much improved" and "much improved") or "no improvement" (all other descriptive categories) for summary and analysis.

Chi-square analysis showed a statistically significant difference between MTS and placebo at Visits 3-9 and at Endpoint ($p<0.0001$). There was a statistically significant difference between CONCERTA® and placebo at Visits 5-7, only, and at Endpoint ($p<0.0001$).

9.3.3 Efficacy conclusions

The efficacy of MTS in the treatment of subjects with ADHD, relative to placebo, with reference to CONCERTA®, was demonstrated in this study:

- The study met its primary objective. MTS demonstrated significant improvements in ADHD-RS-IV total scores compared with placebo.
    - MTS demonstrated significant improvements in scores for the ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscales.
    - The change in ADHD-RS-IV total score and subscale scores for the CONCERTA® group were also significantly improved compared with placebo.
    - There were no significant differences in ADHD-RS-IV total or subscale scores at endpoint between MTS and CONCERTA® groups.
- The study met its main secondary objective. MTS demonstrated significant improvements in CTRS-R total scores compared with placebo.
- Among other secondary objectives, MTS demonstrated significant improvements in CPRS-R total score and scores for ADHD index, oppositional, hyperactivity, and cognitive subscales, compared with placebo, except for the oppositional subscale at 1500 hours.
- Responses to the CGI showed a statistically significant improvement from Baseline at Endpoint between MTS and placebo and between CONCERTA® and placebo.
- Responses to the PGA showed a statistically significant improvement from Baseline at Endpoint between MTS and placebo and between CONCERTA® and placebo.

10. OVERALL EFFICACY CONCLUSIONS (STUDIES SPD485-201 AND –302)

The clinical evidence suggests that MTS offers a transdermal once daily treatment for ADHD.

The purpose of study SPD485-201 was to evaluate the safety and efficacy of MTS and to characterize the duration of efficacy of MTS in pediatric subjects aged 6-12 compared to placebo. The primary objective of this study was to evaluate, under controlled conditions at multiple timepoints throughout the day, the behavioral effects (measured by the SKAMP deportment scale) of MTS compared to placebo in children (aged 6-12) diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) by Diagnostic and Statistical Manual of Mental Disorders, 4th ed. – Text Revision (DSM-IV-TR) criteria. The main secondary objective was to assess the duration of efficacy of MTS compared to placebo in children with ADHD using the Permanent Product Measure of Performance; age-adjusted math test (PERMP) administered at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application/dosing in a controlled environment. Additional secondary objectives included: Attention Deficit Hyperactivity Disorder-Rating Scale-IV (ADHD-RS-IV), Clinical Global Impressions (CGI-S and CGI-I), Parent's Global Assessment, and Conners' Parent Rating Scale – Revised: Short Form (CPRS-R).

Overall, this study showed significant differences in all primary and secondary efficacy variables in MTS-treated subjects when compared to PTS-treated subjects. The MTS group demonstrated significant improvements in subjective measurements of behavior as rated by teachers, clinicians and parents. In addition, the PERMP, an objective assessment of math productivity in the classroom, showed significant improvements. The onset of effect was apparent by the 2.0 hour timepoint and persisted for the duration of the classroom observation period as measured by the SKAMP deportment scale. Therefore, we conclude that treatment with MTS in this study was successful in reducing ADHD symptoms as measured by a wide assortment of both subjective and objective standard measurements.

Study SPD485-302 was a Phase III, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the safety and efficacy of MTS ($12.5cm^2$, $18.75cm^2$, $25cm^2$, and $37.5cm^2$ patch sizes) compared to placebo with reference to CONCERTA® in pediatric subjects diagnosed with ADHD. Subjects visited the study site 9 times during the course of approximately 14 weeks.

The primary efficacy measurement was defined as the ADHD-RS-IV total scores. The Baseline consisted of the ADHD-RS-IV total score obtained at Baseline (Visit 2). The endpoint of the primary efficacy measurement was defined as the last post-Baseline assessment for which a valid ADHD-RS-IV score was obtained. The primary efficacy variable was the ADHD-RS-IV change score at the Endpoint from Baseline.

The efficacy of MTS in the treatment of subjects with ADHD, relative to placebo, with reference to CONCERTA®, was demonstrated in this study:

The study met its primary objective. MTS demonstrated significant improvements in ADHD-RS-IV total scores compared with placebo. MTS demonstrated significant improvements in scores for the ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscales. The change in ADHD-RS-IV total score and subscale scores for the CONCERTA® group were

also significantly improved compared with placebo. There were no significant differences in ADHD-RS-IV total or subscale scores at endpoint between MTS and CONCERTA® groups. The study also met its main secondary objectives: Conners' Teacher Rating Scale – Revised: Short Form (CTRS-R), Conners' Parent Rating Scale – Revised: Short Form (CPRS-R), Clinical Global Impressions – Improvement (CGI-I) and Parent Global Assessment (PGA).

In summary, the clinical studies of MTS met the objectives for treatment of ADHD utilizing once-daily dosing with titration-to-effect based on dose and a recommended wear time of 9 hours for the patient.

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