DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-514 (S-10)
Drug Name:	DAYTRANA® (Methylphenidate Transdermal System)
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Applicant:	Shire
Dates:	Date of Document: 9/4/2009
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Review Priority:	Standard
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

After evaluation, the statistical reviewer agreed with the sponsor that the data from Study SPD485-409 supported the efficacy of Methylphenidate Transdermal System (MTS) as a treatment of attention deficit/hyperactivity disorder (ADHD) for adolescent patients.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Methylphenidate Transdermal System (MTS), the first and only patch for the treatment of attention deficit/hyperactivity disorder (ADHD), was already approved in the US based on demonstration of efficacy in two placebo-controlled studies in children. In this submission, three studies in adolescents with ADHD were included, where Study SPD485-409 was the only placebo controlled efficacy study that this statistical review was focused on.

Study SPD485-409 was a phase IIIb randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization study. The primary efficacy measure was

the ADHD Rating Scale, the fourth version edition (ADHD-RS-IV) total score change from baseline at endpoint and one key secondary efficacy assessment was prospectively specified as Conner's Parent Rating Scale Revised: Short Form (CPRS-R).

With significant results shown for both the primary and key secondary endpoint, the sponsor concluded that the efficacy of MTS in the treatment of subjects with ADHD, relative to placebo, was demonstrated in this study.

1.3 STATISTICAL ISSUES AND FINDINGS

The sponsor's efficacy analysis results were not performed based on the study protocol, where patients' data after Week 5 should have been excluded when they did not achieve an acceptable response at Week 5. After removing those patients' post-Week 5 data, the statistical reviewer found that the change in analysis results was too minor to yield a different conclusion.

2. INTRODUCTION

2.1 OVERVIEW

Methylphenidate Transdermal System (MTS), the first and only patch for the treatment of attention deficit/hyperactivity disorder (ADHD), was already approved in the US based on demonstration of efficacy in two placebo-controlled studies in children. In this submission, three studies in adolescents with ADHD were included: a short-term placebo-controlled efficacy study (SPD485-409), a long-term open-label safety extension study (SPD485-106), and a pharmacokinetic study (SPD485-106). Study SPD485-409 was the only study that this statistical review focused on.

Study SPD485-409 was a phase IIIb randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization study. It was designed to evaluate the efficacy and safety of MTS (12.5, 18.75, 25, and 37.5cm^2 patch sizes) compared with placebo in adolescent subjects diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. The study was of 5-week, double-blind, dose-optimization period and was followed by a 2-week, double-blind, maintenance period. The primary efficacy measure was the ADHD Rating Scale, the fourth version edition (ADHD-RS-IV) total score change from baseline at endpoint and one key secondary efficacy assessment was prospectively specified as Conner's Parent Rating Scale Revised: Short Form (CPRS-R).

With significant results shown for both the primary and key secondary endpoint, the sponsor concluded that the efficacy of MTS in the treatment of subjects with ADHD, relative to placebo, was demonstrated in this study.

2.2 DATA SOURCES

The sponsor's submission including data and clinical study report were stored in CDER electronic document room (EDR) with the following link: \\Cdsesub1\evsprod\NDA021514\0026.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study SPD485-409

The study was entitled 'A Phase IIIb, Randomized, Double-blind, Multi-center, Parallel-group, Placebo-controlled, Dose Optimization Study, Designed to Evaluate the Efficacy and Safety of Methylphenidate Transdermal System (MTS) in Adolescents aged 13-17 years with Attention Deficit/Hyperactivity Disorder (ADHD)' and was conducted at 31 investigational sites in the United States.

3.1.1.1 Study Objectives

The primary objective was to evaluate the efficacy of MTS compared with placebo, as determined by the change in the clinician-completed ADHD-RS-IV, in the symptomatic treatment of adolescents (aged 13-17 years) diagnosed with ADHD by DSM-IV-TR criteria.

The secondary objectives of this study were:

- To assess the safety and tolerability of MTS compared with placebo based on occurrence of treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and weight

- To assess the efficacy of MTS compared with placebo in the home environment as rated by the parent using the Conners' Parent Rating Scale Revised: Short Form (CPRS-R)

- To assess global impressions of ADHD improvement of MTS compared with placebo from the clinician and parent in response to treatment from Clinical Global Impressions-Improvement (CGI-I) and Parent Global Assessment (PGA)

- To assess subject satisfaction and efficacy of MTS, compared with placebo, as measured by the Youth Quality of Life Instrument-Research Version (YQOL-R)

- To assess the impact of MTS, compared with placebo, on sleep using data collected via the Post Sleep Questionnaire (PSQ)

- To assess skin tolerability to both MTS and placebo transdermal system (PTS), from the dermal response scale (DRS)

- To assess the relationship between plasma exposure and the safety and efficacy measures of MTS via sparse sampling.

3.1.1.2 Study Design

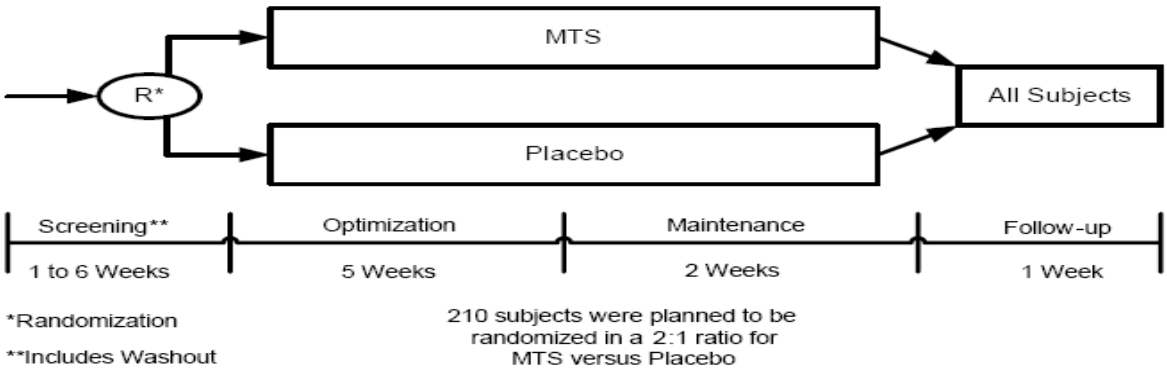
This was a Phase IIIb, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the efficacy and safety of MTS (10, 15, 20, and 30 mg/9 hour doses) compared with placebo in adolescent subjects (aged 13-17 years) with ADHD. Note that the drug was administered through a patch being applied in subject's hip. The patch sizes used in this study for the corresponding MPH delivery rate and total delivered MPH doses are 12.4, 18.75, 25 and 37.5 cm^2, respectively.

Eligible subjects were male or female adolescents aged 13-17 years at the time of signed informed consent, with a primary diagnosis of ADHD, a total score of ≥26 on the ADHD-RS-IV at baseline, and an IQ score ≥80 as measured using the Kaufman Brief Intelligence Test (KBIT).

Approximately 210 eligible subjects were to be randomized in a 2:1 ratio to receive either MTS (140 planned subjects) or PTS (70 planned subjects). Subjects visited the study site nine times during the course of up to 11 weeks.

This study consisted of the four periods: Screening and Washout, Dose Optimization, Dose Maintenance, and Follow-up. The study design schematic is shown in Figure 1.

Figure 1. Study Schematic



Source: Sponsor's Figure 1 of CSR

Reviewer's Note: It was noted that in the dose optimization period, the sponsor used some pre-defined subject response criteria to ensure subjects were titrated to at least an acceptable dose of MT. For those *subjects who had not reached at least an acceptable dose by Week 5, they were planned to be withdrawn from the study.* The definition of determining whether the dose is acceptable is that having at least 25 % reduction from baseline in ADHD-RS-IV scores at a given dose and also having an acceptable safety profile.

3.1.1.3 Efficacy Endpoints and Analyses

The primary efficacy variable was the ADHD-RS-IV total score change from baseline at endpoint. The key secondary efficacy variable was the CPRS-R total score. Additional secondary efficacy variables included the ADHD-RS-IV hyperactive/impulsivity and inattentiveness subscale scores, CPRS-R ADHD index, oppositional, hyperactivity and cognitive subscale scores, the CGI-I, PGA, and YQOL-R perceptual domains and total perceptual score.

The primary efficacy variable was assessed using an analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline ADHD-RS-IV score as a covariate. A sensitivity analysis of ADHD-RS-IV total score change from baseline was performed on observed data using mixed-effects model repeated measures (MMRM) to address the effect of incomplete data resulting from ET or unavailability.

The same ANCOVA model used for the primary efficacy analysis was applied to examine treatment effects at endpoint and at each post-baseline visit for the ADHD-RS-IV hyperactive/impulsivity and inattentiveness subscales, the CPRS-R total scores, and the CPRS-R ADHD index, oppositional, hyperactivity, and cognitive subscale scores. The CGI-I and PGA were analyzed by a chi-square test. Prior to the analysis, these variables were dichotomized to two categories (Improvement [i.e., CGI-I, PGA=1 or 2] and No Improvement [i.e., CGI-I, PGA=3, 4, 5, 6 or 7]).

3.1.2 Sponsor's Efficacy Analysis Results

3.1.2.1 Disposition of Subjects and Baseline Characteristics

A total of 217 subjects at 31 investigational sites were enrolled and randomized in the study; 72 subjects were randomized to PTS and 145 subjects were randomized to MTS. Although 32 investigational sites were initiated and enrolled subjects, one site did not randomize any subjects. Table 3.1 shows the sponsor's summary of disposition for all randomized subjects. Table 3.2 shows the sponsor's summary of key demographic and baseline characteristics. As shown in Table 3.2, the sponsor concluded that the treatment groups were balanced with respect to age, gender, race, and ethnicity as well as weight, height, and BMI (not shown).

Table 3.1 Subject Disposition for Study SPD 485-409

	Placebo	Total MTS	All
Randomized Population	72	145	217
Safety Population	72	145	217
Intent-to-Treat Population	72	143	215
Completed the 7-Week Dose Optimization/Maintenance Period	29	95	124
Reason(s) for Termination			
Adverse Event	2 (4.7%)	8 (16.0 %)	10 (10.8%)
Protocol Violation	7 (16.3 %)	12 (24.0 %)	19 (20.4%)
Consent Withdrawn	4 (9.3%)	6 (12.0%)	10 (10.8%)
Subject Lost to Follow-Up	1 (2.3%)	1 (2.0%)	2 (2.2%)
Lack of Efficacy	27 (62.8%)	21 (42.0%)	48 (51.6%)
Other	2 (4.7 %)	2 (4.0 %)	4 (4.3%)

Source: Sponsor's Table 7 of CSR

Table 3.2 Sponsor's Summary of Key Demographic and Baseline Characteristics for Safety Population for Study SPD 485-409

Characteristic	Placebo	Total MTS	All
Age (years)			
Mean (SD)	14.6 (1.42)	14.5 (1.25)	14.6 (1.31)
Gender, n(%)			
Male	53 (73.6)	109 (75.2)	162 (74.7)
Female	19 (26.4)	36 (24.8)	55 (25.3)
Race, n(%)			
White	56 (77.8)	111 (76.6)	167 (77.0)
Black or African American	13 (18.1)	27 (18.6)	40 (18.4)
Native Hawaiian or other Pacific Islander	0	0	0
Asian	1 (1.4)	0	1 (0.5)
American Indian or Alaska Native	1 (1.4)	0	1 (0.5)
Other	1 (1.4)	7 (4.8)	8 (3.7)
Weight (lb)			
Mean (SD)	128.45 (29.2)	130.18 (25.10)	129.61 (26.48)
Height (in)			
Mean (SD)	64.97 (4.26)	65.35 (3.57)	65.23 (3.81)
Prior Stimulant Medicine Use, n (%)			
Yes	36 (50.0)	59 (40.7)	95 (43.8)
No	36 (50.0)	86 (59.3)	122 (56.2)

Source: Sponsor's Table 8 of CSR

3.1.2.2 Results for Primary and Secondary Endpoints

Tables 3.3 and 3.4 summarize the sponsor's analysis results for the primary endpoint, ADHD-RS-IV Total score and for the key and other secondary endpoints at each study visit, respectively. As shown in Table 3.3, the LS mean difference (95% C.I.) at endpoint between MTS and placebo was -9.96 (-13.39, -6.53) with p-value <0.001. The sponsor's results clearly indicate a significant treatment benefit for MTS in the improvement of ADHD-RS-IV total score. The sponsor noted that their MMRM analysis results also showed significant difference between MTS and placebo.

Table 3.3 Sponsor's Analysis Results for ADHD-RS-IV Total Score

	Placebo N=72	MTS N=143	95% C.I. LS Mean Difference	p-value
Endpoint	N=72	N=143		
LS mean (SE)	-8.8 (1.42)	-18.8 (1.01)		
Differences (MTS-placebo)		-9.96	(-13.39, -6.53)	<0.001
Week 1	N=72	N=143		
LS mean (SE)	-3.6 (0.87)	-7.0 (0.61)		
Difference (MTS-placebo)		-3.42	(-5.51, -1.33)	0.001
Week 2	N=69	N=134		
LS mean (SE)	-6.0 (1.07)	-10.4 (0.77)		
Difference (MTS-placebo)		-4.48	(-7.08, -1.88)	<0.001
Week 3	N=65	N=128		
LS mean (SE)	-7.1 (1.24)	-15.0 (0.89)		
Difference (MTS-placebo)		-7.98	(-10.99, -4.97)	<0.001
Week 4	N=63	N=128		
LS mean (SE)	-9.5 (1.37)	-17.7 (0.96)		
Difference (MTS-placebo)		-8.20	(-11.51, -4.89)	<0.001
Week 5	N=61	N=121		
LS mean (SE)	-10.2 (1.39)	-19.3 (0.99)		
Difference (MTS-placebo)		-9.05	(-12.42, -5.69)	<0.001
Week 6	N=34	N=102		
LS mean (SE)	-16.0 (1.70)	-23.7 (0.98)		
Difference (MTS-placebo)		-7.70	(-11.59, -3.81)	<0.001
Week 7	N=29	N=96		
LS mean (SE)	-18.6 (1.80)	-24.2 (0.99)		
Difference (MTS-placebo)		-5.66	(-9.71, -1.60)	0.007

Note: LS=least squares; SE=standard error. Source: Sponsor Table 13 of CSR

Table 3.4 Sponsor's Analysis Results for Secondary Endpoints

Variables	Placebo N=72	MTS N=143	95% C.I.	P-value
Change from Baseline to Endpoint				
ADHD-RS-IV Subscale Hyperactivity/Impulsivity				
LS mean (SE)	-4.1 (0.69)	-8.1 (0.49)		
Difference (MTS-placebo)		-4.02	(-5.68, -2.36)	<0.001
ADHD-RS-IV Subscale Inattentiveness				
LS mean (SE)	-4.7 (0.83)	-10.7 (0.59)		
Difference (MTS-placebo)		-5.93	(-7.94, -3.92)	<0.001
CPRS-R Total Score				
LS mean (SE)	-7.5 (2.08)	-20.9 (1.45)		
Difference (MTS-placebo)		-13.48	(-18.48, -8.47)	<0.001
YQOL-R Total Perceptual Scores				
LS mean (SE)	1.3 (1.55)	3.3 (1.06)		
Difference (MTS-placebo)		2.01	(-1.71, 5.73)	0.288
CGI-I	N=72	N=142		
Subjects with improvement n (%)	22 (30.6)	93 (65.5)		
No Improvement n (%)	50 (69.4)	49 (34.5)	34.9	<0.001
PGA	N=72	N=143		
Subjects with improvement n (%)	15 (20.8)	76 (53.1)		
No Improvement n (%)	57 (79.2)	67 (46.9)	32.3	<0.001

Source: Sponsor's Tables 14, 15, 16, 17 and 2.5.2 of CSR.

3.1.3 Statistical Reviewer's Findings and Comments

1. Based on the sponsor's data for the intention to treat (ITT) population, the statistical reviewer confirmed their analysis results for the primary endpoint and the key and other secondary endpoints. However, the medical reviewer notified the statistical reviewer that there were 24 subjects (12 of them were in the MTS group and the other 12 were in the placebo group) who were assessed as not having achieved an acceptable response at Week 5, were not discontinued from the study in accordance with the protocol. The statistical reviewer performed the re-analysis after removing those 24 patients' Week 6 and Week 7 data and found that the change of results was too minor to yield a conclusion different from the sponsor's.

2. For the purpose of exploration, the following Figures 1 to 4 show the empirical cumulative distribution functions (CDF) for patients' improvement to Week 5 and, respectively to Week 7, respectively, on the primary and secondary outcome measures.

Figure 1 Empirical Distribution Function of Change in ADHD-RS-IV Total score (By Week 5 LOCF data)

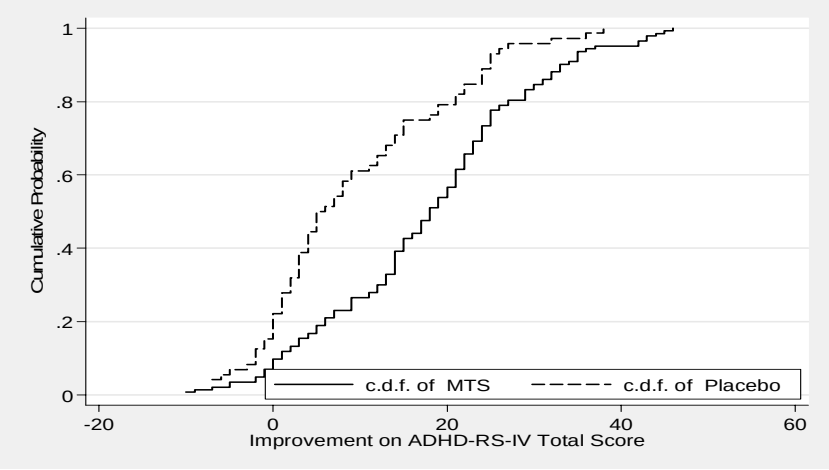
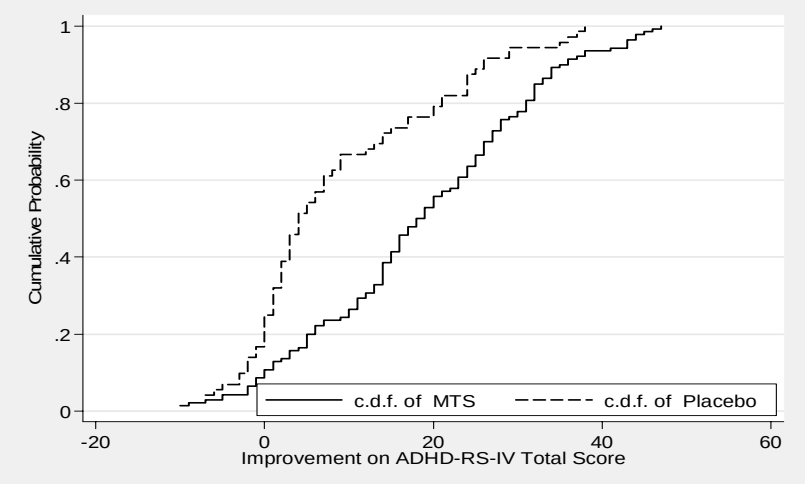


Figure 2 Empirical Distribution Function of Change in ADHD-RS-IV Total score (By Week 7 LOCF data)



Note that for easiness to comprehend, the cumulative probability was calculated based on patients' improvement (i.e., baseline measurement minus the measurement at Week 5 or Week 7), not on their changes from baseline to the visit data directly.

Although the primary endpoint and secondary endpoints were based on the change from baseline to the end visit data, i.e., Week 7, in addition to the CDF results by Week 7 LOCF data, similar plots were produced by Week 5 LOCF data to check the impact of the high dropouts as the dropout rate at the end of the study, i.e., Week 7 was 42%. It appears that the high dropout rate at Week 7 was a result of a forced withdrawal rule at Week 5 (when there was only 15% of patients dropped out) to discontinue patients who did not reach an acceptable dose; therefore, similar CDF plots at Week 5 were given to exam whether the Week 7 CDF plot was interpretable.

Figure 3 Empirical Distribution Function of Change in CPRS-R Total score (By Week 5 LOCF data)

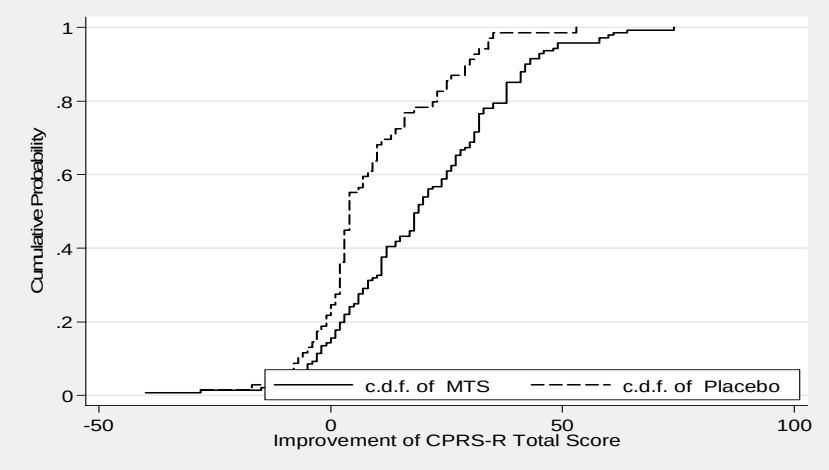
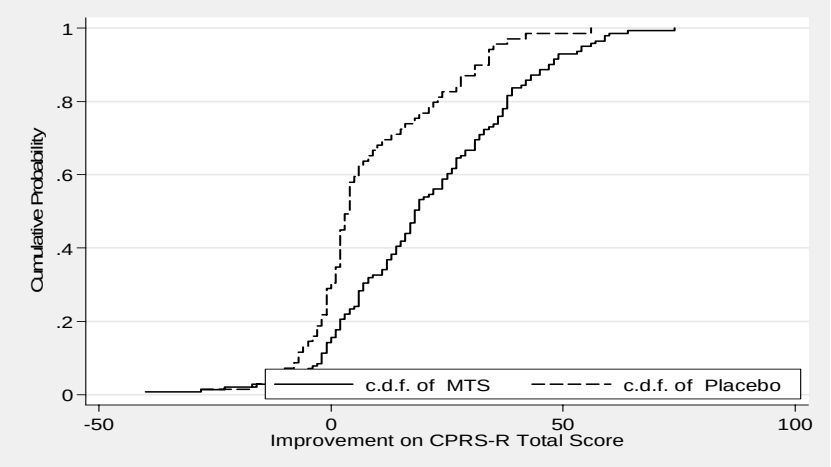


Figure 4 Empirical Distribution Function of Change in CPRS-R Total score (By Week 7 LOCF data)



It appears that for both the primary and key secondary endpoint, the CDF plots by Week 5 LOCF data and by Week 7 LOCF data were similar but with a bigger separation between the MTS and placebo in Week 7 LOCF analysis. This suggests that due to high dropouts the results of the Week 7 LOCF analysis exaggerated the difference between MTS and placebo. Therefore, the plots based on Week 7 LOCF data should be interpreted with great caution.

It is also interesting to note that from both sets of plots (either by Week 5 LOCF data or by Week 7 LOCF data), even though the range of changes are different for the ADHD-RS-IV Total score and also CPRS-R Total score, the largest separation between MTS and placebo curves both occurred around point 10 in both scores. It tells us that the large difference between MTS and placebo appeared to show in patients who had at most the 10 points improvements.

3.2 EVALUATION OF SAFETY

Please refer to the medical review for the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed subgroup analyses for gender, race, age, prior stimulant medicine use and ADHD subtype using the primary efficacy variable, ADHD-RS-IV Total score. Their analysis results are presented in Tables 4.1 and 4.2. According to the results, they concluded that a treatment benefit for MTS was seen within the subgroups for age, prior stimulant use, and ADHD subtype (Inattentive and Combined). The sponsor's analysis results have been confirmed by the statistical reviewer.

4.1 GENDER, RACE and AGE

Table 4.1 Sponsor's Subgroup Analysis for Gender, Race and Age

Subgroup	Placebo	Total MTS	MTS Patch Size			
			12.5 cm^2	18.75 cm^2	25 cm^2	37.5 cm^2
Male						
N	53	107	7	13	19	53
Change from Baseline Mean (SD)	-7.1 (10.74)	-19.0 (13.31)	-12.9 (9.39)	-26.1 (11.87)	-22.8 (13.34)	-18.9 (13.58)
Female						
N	19	36	5	5	6	15
Change from Baseline Mean (SD)	-13.8 (13.20)	-17.9 (13.31)	-13.4 (11.41)	-25.2 (4.60)	-24.0 (12.36)	-17.7 (15.52)
White						
N	56	109	9	16	23	48
Change from Baseline Mean (SD)	-8.1 (11.66)	-19.1 (12.88)	-13.4 (10.85)	-26.4 (10.09)	-22.5 (12.86)	-19.0 (12.79)
Non-White						
N	16	34	3	2	2	20
Change from Baseline Mean (SD)	-11.6 (11.96)	-17.6 (14.61)	-12.0 (7.21)	-21.0 (14.14)	-30.5 (14.85)	-17.8 (16.66)

Subgroup	Placebo	Total MTS	MTS Patch Size			
			12.5 cm^2	18.75 cm^2	25 cm^2	37.5 cm^2
Age Group: 13-14 years						
N	38	76	5	10	11	40
Change from Baseline Mean (SD)	-8.3 (12.45)	-18.6 (11.99)	-14.4 (6.69)	-20.1 (8.01)	-24.7 (12.10)	-19.1 (13.19)
Age Group: 15-17 years						
N	34	67	7	8	14	28
Change from Baseline Mean (SD)	-9.5 (11.02)	-18.9 (14.68)	-12.1 (11.95)	-33.0 (8.12)	-21.9 (13.76)	-18.0 (15.13)

Source: Sponsor's Tables 2.1.3.1, 2.1.3.2 and 2.1.3.3 of CSR.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 4.2 Sponsor's Subgroup Analysis for Prior Stimulant Medicine Use, ADHD Subtype,

Subgroup	Placebo	Total MTS	MTS Patch Size			
			12.5 cm^2	18.75 cm^2	25 cm^2	37.5 cm^2
Prior Stimulant Medicine Use : No						
N	36	85	6	12	11	45
Change from Baseline Mean (SD)	-10.8 (11.91)	-17.5 (13.30)	-10.0 (10.20)	-23.9 (10.27)	-24.5 (13.67)	-16.60 (13.64)
Prior Stimulant Medicine Use : Yes						
N	36	58	6	6	14	23
Change from Baseline Mean (SD)	-6.9 (11.37)	-20.5 (13.14)	-16.2 (9.13)	-29.7 (9.85)	-22.1 (12.62)	-22.7 (13.84)
ADHD Subtype: Predominantly Inattentive						
N	27	55	7	8	8	24
Change from Baseline Mean (SD)	-8.0 (11.34)	-14.7 (11.00)	-7.6 (8.48)	-23.3 (6.25)	-15.8 (9.66)	-15.0 (12.70)
ADHD Subtype: Predominantly Hyperactive-impulsive						
N		1	1			
Change from Baseline Mean (SD)		-22.0	-22.0			
ADHD Subtype: Combined Subtype						
N	45	87	4	10	17	44
Change from Baseline Mean (SD)	-9.4 (12.05)	-21.2 (14.08)	-20.5 (5.97)	-27.9 (12.51)	-26.6 (12.95)	-20.6 (14.30)

Source: Sponsor's Tables 2.1.3.4 and 2.1.3.5 of CSR.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The sponsor's efficacy analysis results were not performed based on the study protocol, where patients' data after Week 5 should have been excluded when they did not achieve an acceptable response at Week 5. After removing those patients' post-Week 5 data, the statistical reviewer found that the change in analysis results was too minor to yield a different conclusion.

5.2 CONCLUSIONS AND RECOMMENDATIONS

After evaluation, the statistical reviewer agreed with the sponsor that the data from Study SPD485-409 supported the efficacy of Methylphenidate Transdermal System (MTS) as a treatment of attention deficit/hyperactivity disorder (ADHD) for adolescent patients.

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Mathematical Statistician

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21514	SUPPL-10	SHIRE DEVELOPMENT INC	Daytrana System

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