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Prescribing decisions should be made based on the approved package insert.*

Proprietary Drug Name:

Daytrana™

Generic Drug Name:

Methylphenidate Transdermal System (MTS)

Therapeutic area and FDA approved indications:

Daytrana is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-12

Name of Sponsor/Company:

Shire Development, Inc.

Title of Study:

A Phase III, Randomized, Double-Blind, Multi-Center, Parallel-Group, Placebo-Controlled, Dose Optimization Study, Designed to Evaluate the Safety and Efficacy of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in Pediatric Patients aged 6-12 with Attention-Deficit/Hyperactivity Disorder (ADHD).

Study Center(s):

Multi-center study (38 centers), US only

Studied period:

23-Aug-2004 – 02-Feb-2005

Phase of Development:

III

Objectives:

Primary

The primary objective of this study was to evaluate, under controlled conditions, the safety and efficacy of MTS compared to placebo with reference to CONCERTA® (Concerta is a registered trademark of Alza Corporation), 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 Diagnostic and Statistical Manual of Mental Disorders, 4th ed. –Text Revision (DSM-IV-TR) criteria.

Secondary

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

Additional secondary objectives of this study were:

- To assess the efficacy of MTS compared to placebo and CONCERTA on the Conner's' Parent Rating Scale-Revised: Short Form (CPRS-R).
- To assess global impressions of ADHD severity and improvement of MTS compared to placebo and CONCERTA from the clinician and parent in response to treatment using Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessments (PGA).
- Evaluation of the safety and tolerability of MTS compared with placebo and CONCERTA with respect to treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and specific evaluation of sleep (Children's Sleep Habits Questionnaire - CSHQ), weight, blood pressure (BP), and heart rate.
- Assessment of the relationship between plasma exposure and the safety and efficacy measures of MTS and CONCERTA via sparse sampling.
- Assessment of skin tolerance to MTS/Placebo Transdermal System (PTS) using the Dermal Evaluation and Response Scale.

Methodology:

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 (10mg/12.5cm², 15mg/18.75cm², 20mg/25cm², and 30mg/37.5cm² doses, expressed as nominal methylphenidate dose delivered over a 9-hour wear time/patch size) compared to placebo with reference to CONCERTA in pediatric subjects diagnosed with ADHD. Subjects visited the study site nine times during the course of approximately 14 weeks. The study consisted of three 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 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 10mg/12.5cm², 15mg/18.75cm², 20mg/25cm², and 30mg/37.5cm² doses, expressed as nominal methylphenidate dose delivered over a 9-hour wear time/patch size) 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 one of the last three 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 five weeks to allow for titration up to the highest dose and one 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 nine hours per day; a new patch was applied each morning at approximately 0700 hours. All subjects were initiated on the MTS/PTS 12.5cm² 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 (ie "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 two 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.

Number of Patients (planned and analyzed):

A total of 282 subjects were enrolled into the study. Following completion of screening and washout, subjects were randomized, in a 1:1:1 ratio (MTS: CONCERTA: Placebo), into the double-blind dose optimization/maintenance period. Subject disposition is presented in the table below.

Subject Disposition				
	Treatment			Total
	MTS	CONCERTA	Placebo	
Enrolled	100	94	88	282
Randomized	100	94	88	282
Discontinued	29	28	56	113
Completed	71	66	32	169
ITT	96	89	85	270
Per Protocol	60	55	26	141
Safety population	98	91	85	274
PK population	72	70	0	142

MTS=Methylphenidate Transdermal System, ITT=Intention-to-Treat; PK=Pharmacokinetic

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were male or female children aged 6-12 years, with a primary diagnosis of ADHD. In addition, all eligible subjects had BP measurements within the 95th percentile, had no comorbid illness that could affect safety or tolerability, had no comorbid psychiatric diagnosis (except ODD), were not known non-responders to psycho stimulant treatment, and had no clinically significant ECG findings or laboratory evaluations at Screening.

Test Product, Dose and Mode of Administration:

MTS (provided as 10mg/12.5cm², 15mg/18.75cm², 20mg/25cm², and 30mg/37.5cm² doses, expressed as nominal methylphenidate dose delivered over a 9-hour wear time/patch size) is designed to deliver *d, l* (*threo*)-methylphenidate transdermally at a continuous rate upon application to intact skin. MTS was applied to a clean, dry, non-oily and non-irritated site on the hip of each subject. Initial placement on the left or right side was decided by the subject or caregiver. Subsequent applications were to be alternated to the opposite side so that the same site was not used for two consecutive applications.

Duration of Treatment:

- Duration of Screening period: approximately 2 weeks
- Duration of Washout period (if applicable): 1 to 4 weeks
- Duration of Treatment period: 5 weeks optimization plus 2 weeks maintenance
- Duration of Follow-up: 30 days (±2 days)

Eligible subjects visited the clinic approximately 9 times over the course of approximately 10 weeks. At approximately 30 days (±2 days) post-discontinuation or completion of study drug, a follow-up telephone contact was made to collect information on ongoing AEs and serious adverse events (SAEs) and to collect any new related AEs and new onset SAEs.

Reference Therapy, Dose and Mode of Administration:

CONCERTA is administered orally and uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. It is designed to have 12-hour duration of effect and was provided as overencapsulated 18mg, 27mg, 36mg, and 54mg dose tablets.

Placebo was provided as matching PTS and as matching capsules.

Criteria for Evaluation:

The primary outcome measure of the study was the ADHD-RS-IV. The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0 to 54. The scale may be sub-divided into two sub-scales of 9 items each: hyperactivity/impulsivity and inattentiveness.

The main secondary efficacy measure was the CTRS-R.

Other secondary outcome measures included the CPRS-R, CGI-I, and PGA.

Safety and tolerability assessments included AEs, laboratory tests, vital signs, physical examinations, ECGs, CSHQ, Dermal Evaluations (Dermal Response, Dermal Discomfort and Transdermal System Adherence), and weight.

Pharmacokinetic Evaluations were conducted on subjects at visit 7, 8 or 9 for quantification of *d*-threo-methylphenidate and *d*-threo-methylphenidate in plasma.

Statistical Methods:

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 hypotheses were 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.

The plasma *d*-MPH and *l*-MPH concentrations, collected at hours 7.5, 9.0 and 10.5 hours during a dose maintenance visit, were plotted against time for each of the subjects receiving active treatment. Plots for mean concentration-time data by treatment and by dose were also generated. The plasma concentration-time data was summarized statistically (n, arithmetic mean, SD, coefficient of variation, median, geometric mean, minimum and maximum) by treatment and by dose. Exposure (e.g. predicted AUC) for each subject receiving MTS was estimated from the plasma *d*-MPH concentrations and, if appropriate, any derived parameters were also summarized statistically (n, arithmetic mean, SD, coefficient of variation, median, geometric mean, minimum and maximum) by dose.

Retrospective analyses of data from two previous phase I studies were conducted to select the best of the three sample times (7.5, 9.0, and 10.5 hours) to serve as surrogate for systemic exposure with which to explore relationships with efficacy and safety measures. Exploratory plots and regression analyses were conducted to assess potential relationships with efficacy measures (ADHD-RS-IV, CTRS-R, CPRS-R, CGI, and PGA ratings) and safety measures (e.g. change in systolic BP, diastolic BP, heart rate, pulse, and respiratory rate, and the following TEAEs: weight loss or sleep changes [CSHQ ratings]).

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

Summary – Results:**Subject demographics**

A total of 282 subjects were enrolled and randomized into this study. Eight subjects who were randomized did not receive study medication, thus the Safety population consists of 274 subjects. Site 44 randomized a total of six subjects, five subjects had CRF information submitted, of those 5 only 2 had CRF documentation of receiving study medication. Two subjects from site 44 were included in the safety population but were excluded by the Sponsor for efficacy evaluation due to unreliability of data following a GCP audit. Site 44 was closed by the sponsor and reported to FDA for protocol and GCP non-compliance issues. A total of 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 (5.2%) 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.

The demographic and Baseline characteristics of the study population are presented below.

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
Age Category	6 – 9 (n%)	61 (61.0%)	60 (63.8%)	62 (70.5%)	183 (64.9%)
	10 –12 (n%)	39 (39.0%)	34 (36.2%)	26 (29.5%)	99 (35.1%)
Gender	Male (n%)	60 (60.0%)	62 (66.0%)	65 (73.9%)	187 (66.3%)
	Female (n%)	40 (40.0%)	32 (34.0%)	23 (26.1%)	95 (33.7%)
Ethnicity	Hispanic/Latino (n%)	16 (16.0%)	11 (11.7%)	8 (9.1%)	35 (12.4%)
	Not Hispanic/Latin(n%)	84 (84.0%)	83 (88.3%)	79 (89.8%)	246 (87.2%)
	Missing (n%)			1 (1.1%)	1 (0.4%)
Race	White (n%)	79 (79.0%)	75 (79.8%)	64 (72.7%)	218 (77.3%)
	Black/African American (n%)	11 (11.0%)	13 (13.8%)	17 (19.3%)	41 (14.5%)
	Asian (n%)	2 (2.0%)			2 (0.7%)
	Other (n%)	8 (8.0%)	6 (6.4%)	7 (8.0%)	21 (7.4%)

Efficacy results:

Primary efficacy results: ANCOVA on the primary efficacy outcome, the change in ADHD-RS-IV total score at Endpoint, showed a statistically significant treatment difference between MTS and placebo, as shown below.

**Primary Efficacy Outcome: Change from Baseline in
ADHD-RS-IV Total Score at Endpoint (ITT Population)**

Variable	Treatment	
	MTS (N=96)	Placebo (N=85)
Baseline ADHD-RS-IV		
n	96	85
Mean (SD)	43.0 (7.45)	41.9 (7.43)
Change from Baseline		
n	96	85
Mean (SD)	-24.2 (14.55)	-9.9 (14.06)
Median	-26.0	-5.0
Minimum, Maximum	-54, 10	-48, 17
LS mean (SE)	-24.3 (1.46)	-10.3 (1.54)
Difference (95% CI of LS means*) Active - Placebo	-13.893 (-18.062, -9.724)	NA
P-value (Active - Placebo)	<0.0001	NA

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

Secondary efficacy results: Mean scores in the ADHD-RS-IV subscales, CTRS-R, and CPRS-R demonstrated improvement over Visits 3-9 in all treatment groups, including placebo. Improvements were always larger in the MTS group than in the placebo group.

At Endpoint, chi-square analysis in the ITT population of the ratios of improvement to no improvement showed a statistically significant difference between MTS and placebo for the CGI and PGA assessments.

Results of analyses performed in the PP population were similar to those in the ITT population, but failed more often to demonstrate statistical significance, probably because of the loss of statistical power in the much smaller PP population.

Pharmacokinetic results:

The plasma concentration at patch removal time, 9 hours after application, was selected, on the basis of regression analyses of data from previous studies, as the optimum surrogate for systemic exposure with which to explore relationships with efficacy and safety measures.

For each of the comparable patch sizes and capsule strengths, concentrations for *d*- and *l*-MPH at the 9-hour time point appear to be higher for MTS, as shown below.

Mean (SD) 9 hour plasma <i>d</i>- and <i>l</i>-MPH concentrations (ng/mL) for MTS and CONCERTA					
Patch Size	<i>d</i> -MPH	<i>l</i> -MPH	Capsule Strength	<i>d</i> -MPH	<i>l</i> -MPH
12.5cm ² (N=5)	12.7 (7.42)	6.87 (4.09)	18mg (N=3)	8.65 (1.75)	0.00 (0.00)
18.75cm ² (N=14)	20.1 (15.3)	10.0 (7.08)	27mg (N=13)	11.0 (9.48)	0.852 (2.31)
25cm ² (N=20)	38.6 (17.0)	20.2 (8.64)	36mg (N=23)	20.1 (9.77)	0.178 (0.322)
37.5cm ² (N=33)	47.0 (27.1)	28.6 (20.6)	54mg (N=41)	23.2 (13.2)	0.337 (0.618)

Based on the regression analysis, a relationship was observed between body weight and *d*-MPH concentration (P=0.0002). No relationship was observed between any of the relevant efficacy or any of the other safety parameters and exposure. The table below presents a summary of the regression analysis results.

Summary of Exposure-Response Regression Analysis on Safety and Efficacy Variables					
Efficacy and Safety Variables	N	Slope	Intercept	R ²	Significance F
ADHD Rating Scale - Change From Baseline	72	-0.0196	18.9812	0.001052	0.7853
CGI-I Results	72	-0.0021	1.9969	0.002362	0.6831
CGI-S Result	72	0.0057	4.4083	0.03872	0.0952
CSHQ - Change From Baseline	72	-0.0035	-3.5274	0.000175	0.9109
CPRS - Change From Baseline	65	-0.1267	-23.4790	0.02456	0.2089
CTRS - Change From Baseline	72	-0.0870	-13.8115	0.01011	0.4292
Systolic Blood Pressure - Change From Baseline	72	0.0403	0.4878	0.01307	0.3355
Diastolic Blood Pressure - Change From Baseline	72	0.0592	-0.0022	0.03108	0.1357
PGA Result	72	-0.0044	2.3955	0.008765	0.4308
Heart Rate - Change From Baseline	70	0.1266	5.9196	0.04718	0.0688
Pulse - Change From Baseline	72	0.0519	4.1030	0.008138	0.4479
Respiratory Rate - Change From Baseline	72	0.0024	0.5691	0.0003736	0.8711
Weight - Change From Baseline	72	-0.0471	0.0264	0.1761	0.0002197

Safety results:

The results of this study showed that a MTS target wear time of 9 hours led to a similar rate of AEs as in a similar dose of CONCERTA administered in a double-blind-double-dummy fashion.

Treatment-Emergent Adverse Events: Overall, 74 (75.5%) subjects reported 286 TEAEs in the MTS group, 63 (69.2%) subjects reported 179 TEAEs in the CONCERTA group, and 49 (57.6%) subjects reported 108 TEAEs in the placebo group. The most commonly reported TEAEs among the two active treatment groups were decreased appetite and headache.

The incidence of treatment-emergent insomnia, nausea, decreased weight, and anorexia was slightly higher in the MTS group compared to CONCERTA, however the numbers are within the reported ranges for other methylphenidate products. The most common adverse events (≥5% in MTS group AND >2X Placebo) are presented in the following table.

Summary of Treatment-Emergent Adverse Events – Safety population (>5% in MTS AND >2X Placebo)

Adverse Event (Preferred Term)	Number (%) of subjects reporting AE					
	MTS (N=98)		CONCERTA (N=91)		Placebo (N=85)	
No. subjects with ≥1 AE	74	(75.5)	63	(69.2)	49	(57.6)
Decreased appetite	25	(25.5)	17	(18.7)	4	(4.7)
Insomnia	13	(13.3)	7	(7.7)	4	(4.7)
Nausea	12	(12.2)	7	(7.7)	2	(2.4)
Vomiting	10	(10.2)	9	(9.9)	4	(4.7)
Weight decreased	9	(9.2)	7	(7.7)	0	(0.0)
Tic	7	(7.1)	1	(1.1)	0	(0.0)
Affect liability	6	(6.1)	3	(3.3)	0	(0.0)
Nasal congestion	6	(6.1)	3	(3.3)	1	(1.2)
Anorexia	5	(5.1)	3	(3.3)	1	(1.2)
Nasopharyngitis	5	(5.1)	4	(4.4)	2	(2.4)

The majority of TEAEs were transient and mild to moderate in intensity.

Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events: No deaths or other serious adverse events occurred in this study. Eleven subjects reported events that led to termination of study drug; 7 subjects (7.1%) in the MTS group, 3 subjects (3.3%) in the CONCERTA group, and 1 subject (1.2%) in the placebo group. Two subjects in the MTS group discontinued due to application site reactions.

Clinical Laboratory Evaluations: There were no clinically meaningful changes in mean change from Screening to Visit 9 or in the pattern in the occurrence of abnormal values in hematology, chemistry, or urinalysis.

Vital Signs: Small increases in mean systolic and diastolic BP Baseline were noted in both the MTS and CONCERTA groups compared to the placebo group; however the changes were not clinically significant and were similar between the MTS and CONCERTA treatment groups.

In the MTS group, there was no increase in the number of subjects with systolic BP, diastolic BP, or respiration rate measurements above the normal range compared to Baseline.

The number of subjects with pulse measurements above the normal range was higher at most visits compared to the number of subjects with above normal pulse values at Baseline, however the incidence of pulse values above the normal range was generally similar between the active treatment groups.

There was a small increase in the number of subjects with weight measurements below the normal range between Baseline and Visit 9 in the MTS group. One subject (1.0%) in the MTS group had a weight at Baseline that was below the normal range. At Visit 9, 3 (3.1%) MTS subjects had weight measurements below the normal range.

Electrocardiogram: No clinically significant mean changes from Baseline were noted for QT, QRS, PR, RR intervals or HR in the MTS group. A small increase in change from Baseline was noted in the MTS group for QTcB at Visits 7 (+6.2msec) and 9 (+6.9msec), however no clinically significant mean change from Baseline was noted for QTcF.

Physical Examination: There was no pattern in the occurrence of abnormal values for physical examination findings from Screening to Visit 9, except for possibly the skin.

Dermal Evaluations: The mean dermal response and dermal discomfort scores were generally higher in the MTS group at all visits compared to the CONCERTA and placebo groups. However, most subjects who experienced dermal discomfort reported the discomfort as itching.

Sleep Questionnaire: All subjects had an assessment of a mild to moderate sleep problems at Baseline. The mean total CSHQ score was lower at each visit compared to Baseline in each of the three

treatment groups. The number of sleep items recorded as a problem also decreased in all three groups over the study. There was no adverse effect of MTS recorded in the population when sleep was assessed using a targeted questionnaire.

Overall Summary:

- MTS demonstrated significant improvement in the ADHD-RS-IV total score at endpoint 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 at endpoint between MTS and CONCERTA groups.
- MTS demonstrated significant improvements in CPRS-R total score.
- Mean rating scale scores decreased over time in all treatment groups, indicating not only the expected treatment effect, but a placebo effect, as well; however, quantitative differences in mean scores were generally apparent between active and placebo groups, with much larger treatment effects after active treatment.
- Improvements in ADHD symptoms in subjects receiving MTS were noted by clinicians, parents and teachers.
- There were generally no effects of race or gender on the effects of MTS compared to placebo on ADHD-RS-IV total scores.
- In the PK/PD analysis no relationship between efficacy or any other safety parameter and exposure (using the α -MPH concentration at 9 hours as a surrogate) was observed, based on graphical evaluations and regression analyses.
- Higher concentrations after 9 hours of wear time for MTS versus 9 hours after dosing for CONCERTA suggest that the systemic exposure after MTS is greater than after CONCERTA.
- MTS was well tolerated by subjects in this study.
- Adverse events in the MTS group were those typical for methylphenidate, i.e. decreased appetite, headache, anorexia, insomnia and weight loss. The incidence of these events was slightly higher in the MTS group when compared to CONCERTA, but all events were within the range reported for other oral methylphenidate products.
- The majority of AEs were transient and mild to moderate in intensity. Three subjects, one each in the MTS, CONCERTA, and placebo groups, reported a total of five AEs that were assessed as severe.
- Eleven subjects reported events that led to termination of study drug; 7 subjects (7.1%) in the MTS group, 3 subjects (3.3%) in the CONCERTA group, and 1 subject (1.2%) in the placebo group. Two subjects in the MTS group discontinued due to application site reactions.
- There were no clinically meaningful changes in mean change from Screening to Visit 9 or in the pattern in the occurrence of abnormal values in hematology, chemistry, or urinalysis. Abnormal clinically significant changes were reported in ALT and AST (CONCERTA), ALT and AST (placebo) and glucose (placebo) and none were considered related to treatment.
- Small increases in mean systolic and diastolic BP Baseline were noted in both the MTS and CONCERTA groups compared to the placebo group; however the changes were not clinically significant and were similar between the MTS and CONCERTA treatment groups.

- There was a small increase in the number of subjects with weight measurements below the normal range between Baseline and Visit 9 in the MTS group. One subject (1.0%) in the MTS group had a weight at Baseline that was below the normal range. At Visit 9, 3 (3.1%) MTS subjects had weight measurements below the normal range. Weight loss was reported as an AE in 9 subjects in MTS group and 7 subjects in CONCERTA group. A relationship was observed between weight loss and exposure based on graphical evaluations and regression analyses
- No clinically significant mean changes from Baseline were noted for QT, QRS, PR, RR intervals or HR in the MTS group.
- The dermal response and dermal discomfort scores were generally higher in the MTS group at all visits compared to the CONCERTA and placebo groups. However, most subjects who experienced dermal discomfort reported the discomfort as itching.
- All subjects had an assessment of a mild to moderate sleep problems at Baseline. The mean total CSHQ score was lower at each visit compared to Baseline in each of the three treatment groups. The number of sleep items recorded as a problem also decreased in all three groups over the study. There was no adverse effect of MTS recorded in the population when sleep was assessed using a targeted questionnaire.

Date of Report:

3 June 2005