SAFETY 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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder – Rating Scale, Version IV
AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
AST	Aspartate Transaminase (SGOT)
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
cm	Centimeter
CRF	Case Report Form
CSHQ	Children's Sleep Habits Questionnaire
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ID	Identification
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary of Regulatory Activity
mg	Milligram
mL	Milliliter
MPH	Methylphenidate
MTS	Methylphenidate Transdermal System (SPD485)
NDA	New Drug Application
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PK	Pharmacokinetic
PTS	Placebo Transdermal System

RBC	Red Blood Cells
SAE	Serious Adverse Event
SD	Standard Deviation
STP	Summer Treatment Program
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell

1. SAFETY SUMMARY

1.1 Introduction

New Drug Application (NDA) 21-514 was submitted by Noven Pharmaceuticals, Inc. (Noven) on 27 June 2002 for the Methylphenidate Transdermal System (MTS) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients. MTS contains methylphenidate, an approved agent for the treatment of ADHD, in a multi-polymeric adhesive platform, as a means of delivering methylphenidate transdermally during the period of patch wear.

On 25 April 2003, the Agency issued an action letter regarding NDA 21-514. The Agency stated there were unacceptable incidences of insomnia, anorexia, significant weight loss in the short term, and the potential for skin sensitization, and expressed concerns that these adverse events could result in possible growth retardation or other serious adverse consequences with more chronic treatment with MTS due to overexposure of methylphenidate consequent to longer wear time. The Agency believed that decreasing the wear time of the MTS patch might decrease the incidences of insomnia, anorexia, and significant weight loss to acceptable levels. In order to demonstrate such decreases in these adverse events, the Agency would require evidence that a shorter MTS patch wear time was both safe and effective.

Shire Development Inc. (Shire) has joined Noven as a co-partner for the clinical development of MTS. In meetings and correspondence with the Agency, Shire and Noven gained Food and Drug Administration (FDA) concurrence to pursue 3 new Phase II/III studies to address FDA's concerns (Study SPD485-201, an analog laboratory classroom study; Study SPD485-302, a 7-week outpatient naturalistic study; and Study SPD485-303, an ongoing open-label extension study). In addition, 2 MTS pediatric pharmacokinetic studies were conducted (Studies SPD485-101 and SPD485-102). A total of 24 studies now comprise the MTS clinical development program (see Text Table below). Sixteen studies have been conducted in pediatric subjects (4 Phase I, 5 Phase II, 3 Phase III and 4 Long-Term) and 8 studies have been conducted in adults (all Phase I).

Adverse events (AEs) reported in the MTS clinical development program were generally similar in nature to those reported for other methylphenidate formulations. The 2 pivotal studies (SPD485-201 and –302) support the safety of MTS worn for 9 hours in the treatment of ADHD in children.

Table 1: Studies Comprising the MTS Clinical Development Program by Study Type

Study Type	Study Description	Study Number	Number of Subjects
Pediatric Studies			
Pharmacokinetic/ Biopharmaceutic Studies	Single-dose, crossover evaluation of the bioequivalence of 2 application sites (hip and scapula) in pediatric ADHD subjects	N17-005	27
	Multiple-dose, sequential dose escalation evaluation of the pharmacokinetic profile of MTS following 8- and 12-hour wear times in pediatric ADHD subjects	N17-016	12
	Single-dose, crossover evaluation of the relative bioavailability of a 25cm^2 MTS patch at 3 different wear-times (6-hour, 8-hour, and 10-hour) versus a 36mg dose of CONCERTA® in pediatric ADHD subjects	SPD485-101	24
	Single-dose, crossover evaluation of the relative bioavailability of 12.5cm^2, 25cm^2, and 37.5cm^2 MTS patches for a 9-hour wear time versus a 54mg dose of CONCERTA® in pediatric ADHD subjects	SPD485-102	34
Phase II, Controlled, Short-Term Studies (earlier formulation)	Placebo-controlled, multiple-dose, crossover comparison of the pharmacokinetics, safety, and efficacy of MTS and Ritalin in pediatric ADHD subjects in both the community classroom and laboratory setting (24-hour wear time)	N17-002	11
	Placebo-controlled, multiple-dose, crossover safety and efficacy study in pediatric ADHD subjects in a laboratory setting (13-hour wear time)	N17-003	13
Phase II, Controlled, Short-Term Studies	Placebo-controlled, single-dose, crossover safety and efficacy study in pediatric ADHD subjects in a Summer Treatment Program (STP) setting (13 to 16-hour wear time)	N17-009	36
	Placebo-controlled, multiple-dose, crossover safety and efficacy study in pediatric ADHD subjects in a STP setting (6 and 8.5-hour wear times)	N17-015	27
	Placebo-controlled, multiple-dose, crossover safety and efficacy study in pediatric ADHD subjects in the classroom setting (9-hour wear time)	SPD485-201	93
Phase III, Controlled, Short-Term Studies	Placebo- and active-controlled, multiple-dose, parallel-group, dose titration safety and efficacy studies in pediatric ADHD subjects (9-hour wear time for SPD485-302 and 12-hour wear time for N17-010 and –018)	N17-010	210
		N17-018	211
		SPD485-302	282
Uncontrolled, Long-Term Studies	Open-label, long-term safety studies in pediatric ADHD subjects (9-hour wear time for SPD485-303 and 12-hour wear time for N17-011, -013, and –021)	N17-011	118
		N17-013	20*
		N17-021	191
		SPD485-303	289**

Table 1: Studies Comprising the MTS Clinical Development Program by Study Type

Study Type	Study Description	Study Number	Number of Subjects
Adult Studies			
Pharmacokinetic/ Biopharmaceutic Studies	Single-dose, crossover evaluation of dose proportionality in healthy adult subjects (16-hour wear time)	N17-004	14
	Steady-state, crossover comparison of the pharmacokinetic profiles of MTS and Ritalin in healthy adult subjects (16-hour wear time)	N17-006	30
	Single-dose, crossover evaluation of the pharmacokinetic profile and abuse potential of MTS in adult subjects currently abusing stimulants (24-hour wear time)	N17-007	27
	Single-dose, crossover evaluation of 1) the effect of heat on methylphenidate release from MTS and 2) the buccal absorption of methylphenidate from MTS in adult subjects currently abusing stimulants (2, 6, and 8-hour wear times)	N17-012	6
	Evaluation of the pharmacokinetic profile of MTS following repeated application of the same patch in healthy adult subjects (16-hour wear time)	N17-014	6
	Single-dose, crossover comparison of the pharmacokinetic profile of MTS on application to normal and inflamed skin in healthy adult subjects (16-hour wear time)	N17-017	8
Special Safety Studies	Evaluation of skin irritation and sensitization of MTS after repeated applications in healthy adult subjects (24-hour wear time)	N17-008	122
	Evaluation of skin sensitization potential of MTS after repeated applications in healthy adult subjects (24-hour wear time)	N17-020	194

Twelve clinical safety and efficacy studies have been conducted in pediatric ADHD subjects. Six (6) of these studies were adequate and well-controlled studies that are now complete: 3 Phase II dose-finding studies (N17-009, N17-015, and SPD485-201) and 3 Phase III, dose titration studies (N17-010, N17-018, and SPD485-302). Two (2) initial Phase II studies (N17-002 and N17-003) were conducted with an earlier formulation of MTS; Study N17-002 also examined the pharmacokinetics of MTS. Four (4) of the pediatric clinical safety and efficacy studies are long-term, uncontrolled studies (N17-011, N17-013, N17-021, and SPD485-303). The Phase III studies provided the primary evidence of safety for MTS and the Phase II and long-term studies provided supportive evidence of safety in the target population of children with ADHD.

Eleven clinical pharmacology studies examined the pharmacokinetic and pharmacodynamic (PK/PD) properties of MTS. Six (6) of the PK/PD studies (N17-004, N17-006, N17-007, N17-012, N17-014, and N17-017) were conducted in healthy adults (2 of the 6 were conducted in stimulant abusers) and 5 (N17-002, N17-005, N17-016, SPD485-101, and SPD485-102) were conducted in pediatric subjects.

Two (2) specialized safety studies were conducted in healthy adult subjects (Studies N17-008 and N17-020). Study N17-008 examined skin irritation and sensitization related to

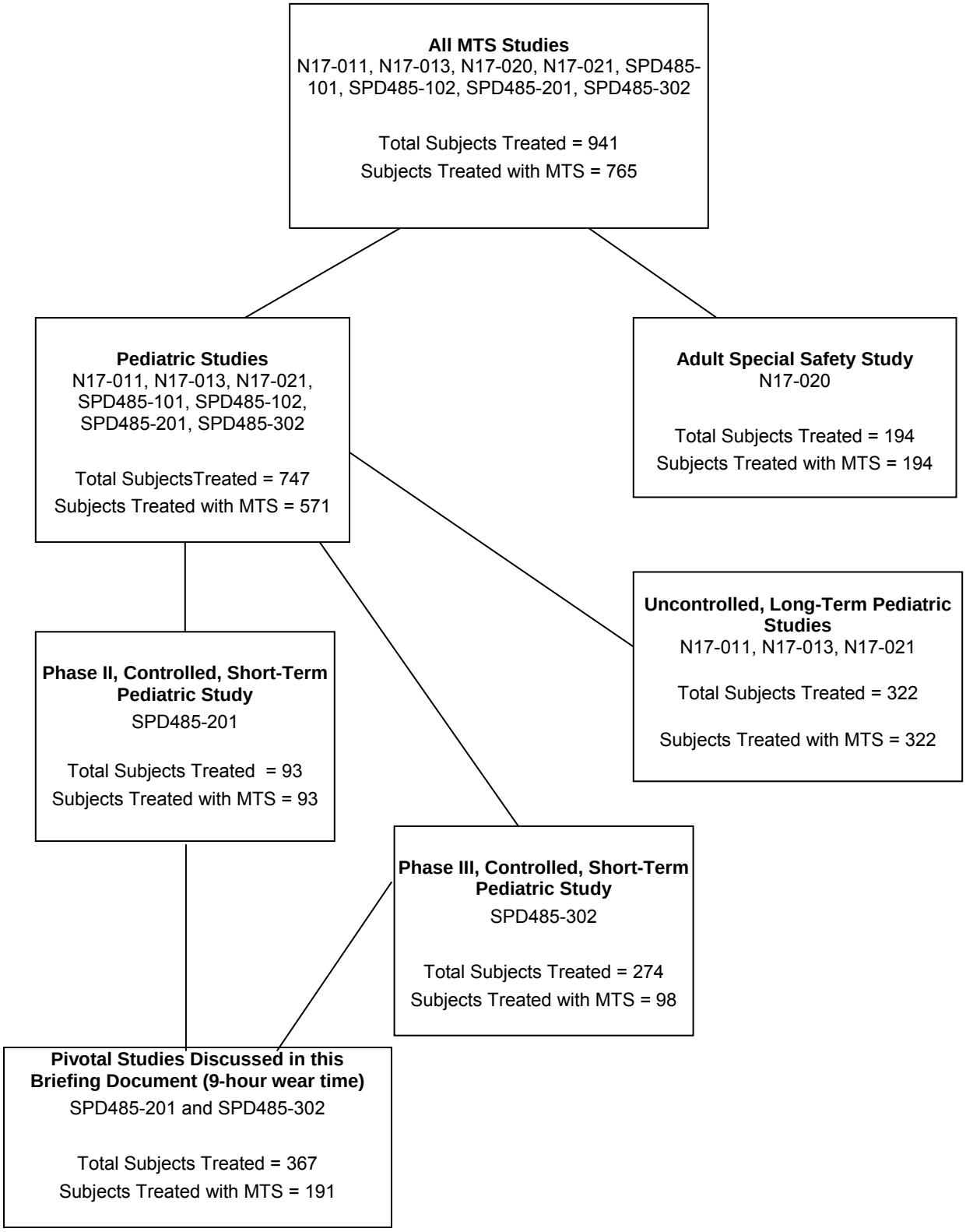
transdermal application with a 24-hour wear period and Study N17-020 examined skin sensitization with 48- to 72-hour wear periods.

Integrated safety data from the long-term, open-label pediatric studies (Studies N17-011, N17-013, and N17-021) are included in this Safety Summary.

Per agreement with the Agency at the Type C Meeting held on 05 April 2005, safety data from the shorter wear time studies were not integrated with data from the longer wear time studies. Study SPD485-303, an open-label study in pediatric ADHD subjects, is currently ongoing.

In this Safety Summary, a total of 941 unique subjects evaluable for safety analysis (i.e., who received at least 1 dose of study treatment) contributed data, including 765 who received MTS (see Text Figure below). A total of 571 pediatric subjects received MTS; 93 in Phase II studies, 98 in Phase III studies and 322 in Long-Term studies. Overall, adverse events (AEs) with MTS (with the intended wear time of 9 hours) are those expected for methylphenidate (as demonstrated in the key 9-hour wear time pivotal studies: SPD485-201 and –302). The incidence of AEs is related to the daily exposure to MTS (both wear time and patch size). In clinical practice, the patch size and wear time can be adjusted to balance efficacy with tolerability. If subjects do not remove the MTS by 9 hours the only effects evident are a slightly higher incidence of adverse events such as anorexia and insomnia.

Figure 1: Overall Disposition of Subjects Included in the MTS Clinical Program



2. PHASE I PHARMACOKINETIC STUDIES (STUDIES SPD485-101 AND SPD485-102)

2.1 Study SPD485-101

2.1.1 Design

Study SPD485-101 was a Phase I, open-label, randomized, single-dose, 4-treatment, 4-period crossover study to assess the pharmacokinetics of the enantiomers of *(threo)*-methylphenidate (*threo*-MPH) after application of the 25cm^2 MTS patch at 3 different wear-times (6-hour, 8-hour, and 10-hour) versus a 36mg oral dose of CONCERTA® in pediatric subjects aged 6-12 with ADHD.

2.1.2 Summary for Study

There were no deaths in this study and no serious AEs. Twenty-two (22) of 24 randomized subjects completed all 4 dosing periods in the study (1 subject was withdrawn for AEs after the second dosing period, and 1 subject missed the second dosing period, but completed all other periods of the study).

Fifteen subjects (63%) reported 1 or more TEAEs during the study. The incidence of subjects reporting TEAEs for the MTS 6-hour, 8-hour, and 10-hour treatment groups; i.e., 3/23 (13%), 7/23 (30%), and 4/23 (17%), respectively, were all lower than for the CONCERTA® group (9/24, 38%). The most frequently reported TEAEs (i.e., frequencies greater than 5% of total episodes) were anorexia, headache, blood pressure increased, and vomiting. Anorexia was reported infrequently in the MTS group with 6-hour wear time (4%), but was reported at a similar frequency to CONCERTA® in the 8-hour and 10-hour wear time groups. Insomnia and weight loss were not reported as AEs in this study.

A total of 85% (29/34) of TEAEs were considered as probably related or possibly related to study drug. All TEAEs, except 1, were mild or moderate in severity.

No clinically significant laboratory abnormalities were reported by the Investigator and there were no laboratory-related AEs. Shifts from a normal range at Baseline to a below normal range at end of study were noted in 1 or more treatment sequence groups for RBC count, hemoglobin, hematocrit, white blood cell (WBC) count, and alanine transaminase (ALT). No other clinically meaningful shifts or trends were noted for laboratory parameters. No clinically meaningful treatment emergent physical findings were noted at study exit.

Compared to Baseline values, statistically significant increases ($p<0.01$) from mean Baseline values for systolic blood pressure, pulse, and respiratory rate were observed at 1 or more post-dose time points in all treatment groups. In general, the observed increases with the MTS treatments were lower or similar to the observed increases for the CONCERTA® group. The Investigator reported AEs of elevated blood pressure for 1 subject during the CONCERTA® dosing period and for 1 subject during the MTS 6-hour dosing period. There

were no clinically significant electrocardiogram (ECG) abnormalities noted by the Investigator at screening or study completion.

2.2 Study SPD485-102

2.2.1 Design

Study SPD485-102 was a Phase I, open-label, randomized, single-dose, 4-treatment, 4-period crossover study designed to determine the relative bioavailability of *d,l*-MPH after application of a 37.5cm^2 MTS patch for a 9-hour wear time and the 54mg dose of CONCERTA® in pediatric subjects with ADHD.

2.2.2 Summary for Study

No deaths, other serious adverse events, discontinuations due to AE or other significant adverse events were reported in this study.

Of the 34 subjects randomized to treatment, 26 (76%) reported 1 or more TEAEs during the study. For the reference treatment (CONCERTA®), 39% of subjects (13/33) reported 1 or more events compared to 29% (10/34) for both the 12.5 and 37.5cm^2 MTS treatments, and 44% (15/34) for the 25cm^2 MTS treatment. The TEAEs of highest incidence (i.e., ≥5% of subjects reporting) for the CONCERTA® treatment were vomiting (12%), anorexia (9%), headache (9%), upper abdominal pain (6%), nausea (6%), and increased systolic blood pressure (6%). The TEAEs of highest incidence for the MTS treatments were: headache (12%) for the 12.5cm^2 MTS; headache (9%), vomiting (9%), increased systolic blood pressure (6%), increased body temperature (6%), chest pain (6%), nasopharyngitis (6%), and anorexia (6%) for the 25cm^2 MTS; and headache (6%) and somnolence (6%) for the 37.5cm^2 MTS.

The overall incidence of anorexia in the MTS groups was low (≥6%). Insomnia and weight loss were not reported as AEs by any subjects in this study.

There were no reported adverse events of a severe intensity under any treatment in this trial. A total of 75 treatment emergent adverse events were reported. Of these, 53% (40/75) were of a mild intensity and 47% (35/75) were of moderate intensity. Most adverse events were deemed by the Investigator to be possibly (48%) or probably (21%) related to study treatment.

There appeared to be a trend towards a decrease in mean corpuscular hemoglobin concentration (MCHC), from screening to end of study, for all treatment sequences. This trend was observed with the mean change from baseline (mean changes for all treatment sequences ranging from -23.3 to -26.3g/L). Additionally, shifts from a normal to below normal range were noted for hemoglobin in 21% (7/34) subjects and for MCHC in 21% (7/34) subjects. Additionally, an apparent trend towards an increase in mean corpuscular volume (MCV) were noted for all treatment sequence groups with mean change from baseline values ranging from 6.22 to 8.13fL and in shift analyses, and shift analysis for this parameter indicated only 9% (3/34) shifted from a normal MCV to above normal MCV at the end of the

study. Adverse events for RBC/hemoglobin-related parameters were reported for 12% (4/34) subjects (i.e., CONCERTA®: 1 subject, MTS 25cm^2: 2 subjects and MTS 37.5cm^2: 1 subject). The RBC/hemoglobin-related events were ongoing at the time of study exit for 2 of these subjects. These changes may be attributed to the multiple PK blood draws.

For systolic blood pressure, statistically significant increases ($p<0.01$) in mean change from pre-dose values were observed for the CONCERTA® (maximum mean change: 7.30mmHg at 8 hours) and for the 3 MTS treatments: 12.5cm^2 maximum mean change: 7.09mmHg at 10 hours, 25cm^2 maximum mean change: 5.82mmHg at 10 hours, and 37.5cm^2 maximum mean change: 9.44mmHg at 10 hours. Increased systolic blood pressure was reported as clinically significant for 2 subjects under the CONCERTA® treatment, for 1 subject under the 12.5cm^2 MTS, for 2 subjects under the 25cm^2 MTS and for 1 subject under the 37.5cm^2 MTS. Statistically significant increases in diastolic blood pressure were also observed for the 4 study treatments with maximum increases occurring at 10 hours post-dose and ranging from 3.97mmHg (for the 12.5cm^2 MTS) to 6.62mmHg for the 25cm^2 MTS. Diastolic blood pressure increases were reported as clinically significant for 1 subject each under the 4 study treatments. Statistically significant increases in pulse were also noted for the 4 treatments ranging from 11.15bpm (CONCERTA® at 30h post-dose) to 12.47bpm (37.5cm^2 MTS at 10 hours post-dose).

Immediately before removal of the 12.5cm^2, 25cm^2, and 37.5cm^2 patches, there was no evidence of irritation for 41%, 50%, and 41% of subjects, respectively. At 30 hours post-application, the percentage of subjects with no irritation was at least 85%. Additionally, there was no experience of discomfort for at least 94% of the subjects for each of the treatments.

A relationship was observed between weight loss and exposure based on graphical evaluations and regression analyses. A relationship between efficacy or any other safety parameter and exposure (using the *d*-MPH concentration at 9 hours as a surrogate) was not observed.

3. PHASE II SHORT-TERM PEDIATRIC ANALOG CLASSROOM POPULATION (STUDY SPD485-201)

3.1 Study SPD485-201

3.1.1 Design

Study SPD485-201 was a Phase II, randomized, double-blind, multicenter, 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 were to visit the study site 9 times during the course of approximately 14 weeks.

The study consisted of 4 periods:

- Screening and Washout Period – Subjects were screened for approximately 2 weeks prior to washout. Washout (if applicable) could have been up to 28 days depending upon the half-life of the subject's current medication.

- Open-Label Dose Optimization Period – Eligible subjects entered an open-label 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) based upon investigator review of parent rating forms, treatment emergent adverse events (TEAEs), and clinical judgment (using the Attention Deficit Hyperactivity Disorder-Rating Scale, Version IV [ADHD-RS-IV]). The duration of this period was 5 weeks to allow for titration up to the highest patch size and 1 titration down to a prior patch size, if necessary. No further titration up or down was permitted once subjects had been titrated down.

  The approximate duration of MTS patch wear was to be 9 hours per day; a new patch was applied each morning upon awakening. 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. Subjects could be titrated to the next patch size after a minimum of 1 week on the previous size based on the overall response of the subject. Additionally, subjects could be titrated back down to the previous patch size (once) to optimize tolerability and effectiveness. Subject response was categorized by the investigator into 1 of 3 conditions and associated actions:

  Intolerable condition: (i.e., unacceptable safety profile) Required the subject to be tapered to a lower MTS patch size (if available). However, if the adjusted patch size produced an intolerable effect as well, the subject was discontinued from the study.

  Ineffective condition: (i.e., <25% change in ADHD-RS-IV score with acceptable safety profile) Required increasing the MTS patch size to the next available dose strength followed by weekly evaluation.

Acceptable condition: A response was defined as acceptable if it showed a significant reduction in ADHD symptoms with minimal side effects. Investigators referred to the subject's Baseline ADHD-RS-IV score to aid in dose adjustments. Subjects who had at least a 25% reduction from Baseline in ADHD symptom scores at a given patch size, as determined by the ADHD-RS-IV, were considered to be at an acceptable patch size. Subjects categorized as "acceptable" could have been maintained at that patch size for the remainder of the study (through Visit 7). Alternatively, the subject's patch size could have been increased to the next larger patch size, if their current patch size was well tolerated, and in the Investigator's opinion the subject would potentially receive further symptom reduction through titration to the next patch size. Visit 6 was the last visit at which titration could occur.

Subjects who had **not** reached at least an acceptable patch size (i.e., "Acceptable condition") by Visit 7 were withdrawn from the study.

- Double-Blind, Crossover, Analog Classroom Period – Following completion of the open-label dose optimization period and successful titration to at least an acceptable patch size of MTS by Visit 7, subjects were randomized in a 1:1 ratio to a sequence of 1 week of treatment with each MTS and matching Placebo Transdermal System (PTS) for the double-blind, crossover, analog classroom period. The duration of this period was 2 weeks and each end of week (Saturday) assessment, included both measurement of behavioral effects and plasma collection, and took place in the controlled environment of the analog classroom. During scheduled classroom visits, subjects arrived at the study site at approximately 0615 hours and were dismissed at 1930 hours.

- Follow-Up Period – At the End of Study/Early Termination Visit (Visit 9), eligible subjects had the option to enroll into an open-label extension study (Study SPD485-303). Subjects who did not enroll into the extension continued to be followed for thirty days (±2 days) following the last dose of study drug.

3.2 Brief summary of adverse events: Study 201

Overall, there were a total of 281 AEs reported in this study, 33 of these AEs were recorded pre-dose and 248 were Treatment-Emergent AEs (TEAEs). 184 of the TEAEs were reported during the Open Label Dose Optimization period and 64 were reported during the Double-Blind Analog Classroom period. No deaths and no other SAEs were reported during this study.

3.2.1 Dose Optimization Period

During the Dose Optimization period a total of 184 TEAEs were reported (see the Text Table below).

Table 2: Overall Summary of TEAEs – Dose Optimization Period – Safety Population

TEAEs	MTS 12.5cm² (N=93) n (%) [Events]		MTS 18.75cm² (N=81) n (%) [Events]		MTS 25cm² (N=38) n (%) [Events]		MTS 37.5cm² (N=11) n (%) [Events]	
Total	41 (44.1)	[79]	39 (48.1)	[74]	12 (31.6)	[17]	6 (54.5)	[14]
Related	29 (31.2)	[57]	21 (25.9)	[37]	4 (10.5)	[7]	4 (36.4)	[8]
Severe	1 (1.1)	[1]	0	0	0	0	0	0
AEs Causing Termination	5 (5.4)	[5]	2* (2.5)	[2]	0	0	0	0

Five (5; 5.4%) MTS 12.5cm^2 subjects and 2 MTS 18.75cm^2 subjects reported AEs that led to termination of study drug.

Analog Classroom Period

Overall, 64 TEAEs were reported for the MTS and PTS treatments during the Analog Classroom Period, for the Safety population. More TEAEs were reported for MTS (39 events, 24 subjects, 30.0%) than for PTS (25 events, 18 subjects, 22.5%). A higher frequency of drug related TEAEs were reported for MTS (10 subjects, 12.5%, 14 events) than for PTS (5 subjects, 6.3%, 8 events). For MTS, 1 severe treatment-emergent adverse event (TEAE; 1 subject, 1.3%) and 2 TEAEs causing termination (1 subject, 1.3%) were reported. An overall summary of treatment-emergent adverse events during the Analog Classroom period can be found in the Text Table below.

The relationship between plasma concentrations of *d*-MPH and adverse events was not evaluated due to the low incidence of adverse events during the Analog Classroom period.

Table 3: Overall Summary of Adverse Events – Analog Classroom Period

TEAEs	MTS (N=80) n (%) n (%)	[Events]	PTS (N=80) n (%) n (%)	[Events]
Total	24 (30.0)	[39]	18 (22.5)	[25]
Related	10 (12.5)	[14]	5 (6.3)	[8]
Severe	1 (1.3)	[1]	0	0
AEs Causing Termination	1* (1.3)	[2]	0	0

3.2.2 Description and analysis of adverse events

Most common adverse events

MedDRA version 7.0 was used to code the reported AEs by system organ class (SOC) and Preferred Term. The Text Table below presents a summary of the most commonly reported TEAEs by patch size (reported by ≥5% in any group of subjects). The most commonly reported events were decreased appetite, anorexia, headache, insomnia, and abdominal pain, upper.

Table 4: Most Commonly Reported Treatment-Emergent Adverse Events (≥5% of Subjects): Dose Optimization Period, Safety Population

System Organ Class* Preferred Term	MTS 12.5cm^2 (N = 93)		MTS 18.75cm^2 (N = 81)		MTS 25cm^2 (N = 38)		MTS 37.5cm^2 (N = 11)	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders								
Tachycardia	0	0	0	0	0	0	1	(9.1)
Gastrointestinal disorders								
Abdominal pain upper	5	(5.4)	2	(2.5)	0	0	1	(9.1)
Nausea	1	(1.1)	1	(1.2)	0	0	1	(9.1)
General disorders and administration site conditions								
Application site dermatitis	0	0	0	0	0	0	1	(9.1)
Pyrexia	1	(1.1)	3	(3.7)	1	(2.6)	1	(9.1)
Infections and Infestations								
Nasopharyngitis	0	0	1	(1.2)	0	0	1	(9.1)
Pharyngitis	1	(1.1)	0	0	1	(2.6)	1	(9.1)
Metabolism and nutrition disorders								
Anorexia	7	(7.5)	1	(1.2)	1	(2.6)	1	(9.1)
Decreased appetite	8	(8.6)	6	(7.4)	2	(5.3)	2	(18.2)
Nervous system disorders								
Headache	7	(7.5)	5	(6.2)	1	(2.6)	1	(9.1)
Psychiatric disorders								
Insomnia	5	(5.4)	2	(2.5)	0	0	2	(18.2)
Respiratory disorders, thoracic and mediastinal disorders								
Pharyngolaryngeal pain	1	(1.1)	0	0	1	(2.6)	1	(9.1)

* MedDRA Version 7.0

The Text Table below presents a summary of the most commonly reported TEAEs (reported by ≥2% of subjects).

Table 5: Most Commonly Reported Treatment-Emergent Adverse Events (≥2% of Subjects)- Analog Classroom Period, Safety Population

System Organ Class* Preferred Term	MTS (N = 80) n	(%)	PTS (N = 80) n	(%)
Blood and lymphatic system disorders				
Lymphadenopathy	2	(2.5)	0	0
Gastrointestinal disorders				
Nausea	3	(3.8)	0	0
Infections and infestations				
Nasopharyngitis	1	(1.3)	2	(2.5)
Upper respiratory tract infection	0	0	3	(3.8)
Investigations				
Blood pressure increased	2	(2.5)	0	0
Metabolism and nutrition disorders				
Anorexia	2	(2.5)	0	0
Nervous system disorders				
Headache	3	(3.8)	3	(3.8)
Respiratory, thoracic and mediastinal disorders				
Pharyngolaryngeal pain	2	(2.5)	1	(1.3)
Rhinitis allergic	2	(2.5)	0	0
Skin and subcutaneous tissue disorders				
Rash	1	(1.3)	2	(2.5)

* MedDRA Version 7.0

The Text Table below shows the number of adverse events reported during the Analog Classroom Period (≥2%) by SOC and final patch size for the Safety population.

Table 6: Summary of All Treatment-Emergent Adverse Events (≥2%) by System Organ Class and Preferred Term – Analog Classroom Period Presented by MTS Final Dose Group, Safety Population

System Organ Class* Preferred Term	MTS 12.5cm^2 (N = 7)		MTS 18.75cm^2 (N = 36)		MTS 25cm^2 (N = 28)		MTS 37.5cm^2 (N = 9)	
	n	(%)	n	(%)	n	(%)	n	(%)
Blood and lymphatic system disorders								
Anemia	0	0	1	(2.8)	0	0	0	0
Lymphadenopathy	1	(14.3)	1	(2.8)	0	0	0	0
Ear and labyrinth disorders								
Motion sickness	0	0	0	0	1	(3.6)	0	0
Gastrointestinal Disorders								
Abdominal pain upper	0	0	1	(2.8)	0	0	0	0
Constipation	0	0	1	(2.8)	0	0	0	0
Nausea	0	0	2	(5.6)	1	(3.6)	0	0
Vomiting	0	0	0	0	1	(3.6)	0	0
General disorders and administration site conditions								
Pyrexia	0	0	0	0	1	(3.6)	0	0
Infections and infestations								
Nasopharyngitis	0	0	1	(2.8)	0	0	0	0
Sinusitis	0	0	0	0	1	(3.6)	0	0
Viral infection	0	0	0	0	0	0	1	(11.1)
Injury, poisoning and procedural complications								
Contusion	0	0	0	0	1	(3.6)	0	0
Investigations								
Blood calcium increased	0	0	0	0	0	0	1	(11.1)
Blood creatinine increased	1	(14.3)	0	0	0	0	0	0
Blood glucose increased	1	(14.3)	0	0	0	0	0	0
Blood pressure increased	0	0	2	(5.6)	0	0	0	0
Eosinophil count increased	1	(14.3)	0	0	0	0	0	0
Lymphocyte count increased	1	(14.3)	0	0	0	0	0	0
Metabolism and nutrition disorders								
Anorexia	0	0	1	(2.8)	1	(3.6)	0	0
Musculoskeletal and connective tissue disorders								

Table 6: Summary of All Treatment-Emergent Adverse Events (≥2%) by System Organ Class and Preferred Term – Analog Classroom Period Presented by MTS Final Dose Group, Safety Population

System Organ Class∗ Preferred Term	MTS 12.5cm^2 (N = 7)		MTS 18.75cm^2 (N = 36)		MTS 25cm^2 (N = 28)		MTS 37.5cm^2 (N = 9)	
	n	(%)	n	(%)	n	(%)	n	(%)
Pain in extremity	1	(14.3)	0	0	0	0	0	0
Nervous system disorders								
Headache	1	(14.3)	2	(5.6)	0	0	0	0
Psychiatric disorders								
Aggression	0	0	0	0	1	(3.6)	0	0
Compulsions	0	0	0	0	0	0	1	(11.1)
Crying	0	0	0	0	1	(3.6)	0	0
Disorientation	0	0	0	0	1	(3.6)	0	0
Mood altered	0	0	1	(2.8)	0	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	0	0	0	0	1	(3.6)	0	0
Pharyngolaryngeal pain	0	0	2	(5.6)	0	0	0	0
Rhinitis allergic	0	0	0	0	1	(3.6)	1	(11.1)
Skin and subcutaneous tissue disorders								
Rash	1	(14.3)	0	0	0	0	0	0

∗ MedDRA Version 7.0

3.2.3 Intensity of adverse events

Summaries of TEAEs by intensity (mild, moderate, or severe) and relationship to study drug are presented in Text Tables below (for the Dose Optimization Period and for the Analog Classroom Period).

For the 184 TEAEs reported during the Dose Optimization Period, 123 were mild, 60 moderate, and 1 was severe. One (1) severe event of joint sprain was reported for a subject on MTS 12.5cm^2 and 1 severe event of cough was reported pre-dose.

Table 7: Summary of Treatment-Emergent Adverse Events by Severity (Intensity) – Dose Optimization Period, Safety Population

	MTS 12.5cm² (N=93)		MTS 18.75cm² (N=81)		MTS 25cm² (N=38)		MTS 37.5cm² (N=11)	
Severity	n (%)	[Events]	n (%)	[Events]	n (%)	[Events]	n (%)	[Events]
Mild	28 (30.1)	[52]	28 (34.6)	[47]	9 (23.7)	[13]	4 (36.4)	[11]
Moderate	12 (12.9)	[26]	11 (13.6)	[27]	3 (7.9)	[4]	2 (18.2)	[3]
Severe	1 (1.1)	[1]	0	0	0	0	0	0

For the 64 TEAEs reported during the Analog Classroom Period, 39 were mild, 24 moderate, and 1 was severe. For the MTS group, 22 mild (12 subjects), 16 moderate (11 subjects), and 1 severe (1 subject) events were reported. The SOC and preferred term for the severe event reported were psychiatric disorders, mood altered. For the PTS group, 17 mild (14 subjects) and 8 moderate (4 subjects) events were reported.

Table 8: Summary of Treatment Emergent Adverse Events by Severity (Intensity) –Analog Classroom Period – Safety Population

	MTS (N=80)		PTS (N=80)	
Severity	n (%)	[Events]	n (%)	[Events]
Mild	12 (15.0)	[22]	14 (17.5)	[17]
Moderate	11 (13.8)	[16]	4 (5.0)	[8]
Severe	1 (1.3)	[1]	0	0

Relationship of adverse events to treatment

Of the 184 TEAEs reported during the Dose Optimization Period, 109 events related to study drug were reported (see the Text Table below). The distribution of related events by MTS were: MTS 12.5cm^2 (57 events, 29 subjects [31.2%]), MTS 18.75cm^2 (37 events, 21 subjects [25.9%]), MTS 25cm^2 (7 events, 4 subjects [10.5%]), and MTS 37.5cm^2 (8 events, 4 subjects [36.4%]).

Table 9: Summary of Related and Unrelated Adverse Events – Dose Optimization Period – Safety Population								
Relationship	MTS 12.5cm² (N=93) n (%)	[Events]	MTS 18.75cm² (N=81) n (%)	[Events]	MTS 25cm² (N=38) n (%)	[Events]	MTS 37.5cm² (N=11) n (%)	[Events]
Related	29 (31.2)	[57]	21 (25.9)	[37]	4 (10.5)	[7]	4 (36.4)	[8]
Unrelated	18 (19.4)	[22]	25 (30.9)	[37]	8 (21.1)	[10]	3 (27.3)	[6]

For the 64 TEAEs reported during the Analog Classroom Period, 22 events related to study drug were reported for MTS (14 events, 10 subjects [12.5%]) and PTS (8 events, 5 subjects [6.3%]) (see the Text Table below). The most common related events reported were anorexia (MTS, 2 events, 2 subjects [2.5%]), blood pressure increased (MTS, 2 events, 2 subjects [2.5%]) and headache (MTS, 2 events, 2 subjects [2.5%]).

Table 10: Summary of Related and Unrelated Adverse Events – Analog Classroom Period – Safety Population				
Relationship	MTS (N=80) n (%)	[Events]	PTS (N=80) n (%)	[Events]
Related	10 (12.5)	[14]	5 (6.3)	[8]
Unrelated	16 (20.0)	[25]	15 (18.8)	[17]

Summary of adverse events by final patch sizes

The text tables below present the overall summary of adverse events by final MTS and PTS patch sizes in the Analog Classroom Safety population.

Table 11: Overall Summary of Treatment Emergent Adverse Events By Final MTS Patch Size – Analog Classroom Period - Safety Population							
MTS 12.5cm² (N=7) n (%)	[Events]	MTS 18.75cm² (N=36) n (%)	[Events]	MTS 25cm² (N=28) n (%)	[Events]	MTS 37.5cm² (N=9) n (%)	[Events]
4 (57.1)	[8]	11 (30.6)	[15]	6 (21.4)	[12]	3 (33.3)	[4]

Table 12: Overall Summary of Treatment Emergent Adverse Events By Final PTS Patch Size – Analog Classroom Period - Safety Population							
PTS 12.5cm² (N=7)		PTS 18.75cm² (N=36)		PTS 25cm² (N=28)		PTS 37.5cm² (N=9)	
n (%)	[Events]	n (%)	[Events]	n (%)	[Events]	n (%)	[Events]
3 (42.9)	[3]	6 (16.7)	[13]	7 (25.0)	[7]	2 (22.2)	[2]

3.2.3.1 Deaths, Serious Adverse Events and Discontinuations Due To Adverse Events

Deaths and Serious Adverse Events
No deaths or serious adverse events were reported in this study.

Discontinuations Due To Adverse Events
Eight (8) subjects were discontinued from the study early due to adverse events (see the Text Table below).

Table 13: Summary of Adverse Events Leading to Discontinuation, Safety Population (Study SPD485-201)

Subject	Study Period	Treatment	Adverse Event
01-012	Dose Optimization	MTS 12.5cm^2	Tic/Vocal Tics
02-007	Dose Optimization	MTS 12.5cm^2	Tic
02-023	Dose Optimization	MTS 12.5cm^2	Application Site Rash
05-012	Dose Optimization	MTS 12.5cm^2	Decreased Appetite
02-015	Dose Optimization	MTS 18.75cm^2	Application Site Rash
02-024	Dose Optimization	MTS 18.75cm^2	Elevated QTc Values
05-007	Dose Optimization	MTS 18.75cm^2	Decreased Appetite
01-014	Analog Classroom	MTS 18.75cm^2	Elevated blood pressure; Increased moodiness

During the Dose Optimization period 7 subjects were discontinued, 4 on MTS 12.5cm^2 and 3 on MTS 18.75cm^2. MTS 12.5cm^2 subjects were discontinued for tic (2 subjects), application site rash (1 subject), and decreased appetite (1 subject). The 3 MTS 18.75cm^2 subjects were discontinued for application site rash (1 subject), elevated QTc values (1 subject) and decreased appetite (1 subject).

During the final Analog Classroom, Period 2 (V9), 1 subject (01-014) had his patch removed early, due to the TEAEs of blood pressure increased and mood altered events (increased moodiness). However, the subject remained at the study site and completed the Visit 9 classroom period and was therefore marked a study completer.

3.2.4 Clinical Laboratory Evaluation

Individual subject changes

A total of 5 subjects were identified as having treatment-emergent abnormal values for hematology and/or chemistry.

Hematology

Three (3) subjects had treatment-emergent abnormal hematology values. Two (2) subjects had eosinophil values greater than 10% and 1 subject had a platelet count less than 75.0 GI/L.

Clinical chemistry

Three (3) subjects had treatment-emergent abnormal chemistry. Two (2) subjects had serum potassium values greater than 5.5 mmol/L and 1 subject had a serum potassium value of less than 3.0 mmol/L. One (1) subject had a calcium value of less than 2.10 mmol/L and 1 subject had a serum sodium value of greater than 150 mmol/L.

Urinalysis

There were no subjects with treatment-emergent abnormal urinalysis values.

Other Safety Data

3.2.5 Physical examination

Seven (7) clinically significant physical examination findings were reported in this study at Visit 9/end of study (EOS)/early termination (ET), Head, Ears, Eyes, Nose and Throat, 1 event, Musculoskeletal, 1 event, Neurological, 1 event, and Skin, 4 events. Subject 02-007 had a CS Neurological PE finding of (Tic – Eye). This subject was discontinued from the study early due to this tic. Subject 02-015 had a CS Skin PE finding of (Post Inflammatory Hyperpigmentation at Patch Site). This subject was discontinued from the study early due to application site rash.

3.2.6 Vital signs

Dose Optimization Period

Systolic Blood Pressure

Percentages of subjects with SBP out of range were comparable during the first 6 visits, with slight increase in percentages in the below normal range category at the higher patch sizes. Percentages of subjects with SBP below the normal range appeared slightly higher for the $25cm^2$ and $37.5cm^2$ patch sizes for the pre-dose and first 3 post-dose measurements at Visit 7.

Diastolic Blood Pressure

Percentages of subjects with DBP below the normal range were generally comparable for Visits 3 to 6 and for Visit 7. However, a greater number of subjects on the 25cm^2 patch size showed lower values than the other patch sizes at Visit 7.

Pulse

Percentages of subjects with pulse outside the normal range were generally comparable for Visits 3 to 6 and for Visit 7. Percentages of subjects with pulse above the normal range were higher in the 25cm^2 and 37.5 cm^2 patch sizes for the first 3 post-dose measurements of Visit 7.

Respiration Rate

No out of range measurements from Visit 4 to Visit 6 were reported. Also, very few out of range values were reported at Visit 7.

Weight

Mean (Min, Max), weight loss reflected by a negative change from Baseline and gain reflected by a positive change from Baseline, in pounds, through the dose optimization period (Visit 7) was -0.9 (-2.5, 1.1) for the 12.5 cm^2 patch size, -1.4 (-5.5, 2.0) for the 18.75cm^2 patch size, -2.4 (-9.5, 5.0) for the 25cm^2 patch size and -2.3 (-7.1, 0.5) for the 37.5cm^2 patch size. The majority of out of range measurements for weight fell into the above normal range category.

Temperature

Percentages of subjects with out of range measurements of temperature were generally comparable for Visits 3 to 6. Out of range measurements at Visit 7 pre-dose were mostly in the below normal range category.

Analog Classroom Period

Systolic Blood Pressure

Fewer MTS than PTS subjects had out of range post-dose SBP measurements for Visit 8, with no major differences reported for Visit 9. For MTS and PTS, small and similar increases in the number of subjects with above normal range SBP were reported for Visits 8 and 9, at all post-dose timepoints. For PTS treatment, the number of subjects with below normal range SBP was increased relative to MTS at most post-dose timepoints at Visit 8, with no differences reported at Visit 9.

Diastolic Blood Pressure

Fewer MTS than PTS subjects had out of range post-dose DBP measurements for Visit 8. There were slightly more subjects in the below normal range for MTS compared to PTS at Visit 9. For MTS and PTS, very few increases in the number of subjects with above normal range DBP were reported for Visits 8 and 9, at all post-dose timepoints. For PTS treatment, the number of subjects with below normal range DBP was increased at all post-dose timepoints relative to MTS at Visit 8, with no differences reported at Visit 9.

Pulse

Out of range post-dose pulse measurements at Visit 8 are similar for MTS and PTS. For PTS treatment, the number of subjects with above normal range pulse was increased relative to MTS for most post-dose timepoints at Visits 8 and 9.

Respiration Rate

Very few out of range respiration rate measurements were reported for MTS and PTS treatments at Visits 8 and 9.

Temperature

Out of range measurements for Visit 8 and 9 pre-dose were mostly in the below normal range category and percentages of subjects was comparable between MTS and PTS.

Weight

Mean (Min, Max), weight loss reflected by a negative change from Baseline and gain reflected by a positive change from Baseline, in pounds, through the Analog Classroom period (Visit 8) was -2.2 (-8.9, 2.0) for the MTS group, and -0.6 (-7.5, 3.5) for the PTS group Mean (Min, Max), weight loss reflected through the end of the Analog Classroom period (Visit 9) was -1.3 (-11.6, 4.0) for the MTS group, and -0.6 (-5.5, 6.0) for the PTS group. The majority of out of range measurements for weight fell into the above normal range category.

At Visit 8 pre-dose, above normal range weight was reported for more MTS (6 subjects, 14.3%) than PTS (3 subjects, 7.9%) subjects. At Visit 9 pre-dose, above normal range weight was reported for more PTS (7 subjects, 16.7%) than MTS (3 subjects, 7.9%) subjects. A summary of z-scores for weight, height and BMI are presented in the Text Table below.

Table 14: Summary of Z-Scores: All Enrolled Subjects

Z-Score			Treatment Sequence			
			TPR	**MTS/PTS**	**PTS/MTS**	**Overall**
		Statistic	(N=13)	(N=42)	(N=38)	(N=93)
Weight	Screening	n	10	41	38	89
		Mean (SD)	-0.41 (1.277)	-0.11 (0.995)	0.04 (0.751)	-0.08 (0.935)
		Median	0.05	-0.08	-0.03	-0.06
		Min, Max	-2.5, 1.5	-2.2, 2.2	-1.7, 2.2	-2.5, 2.2
	Visit 9 (Wk 7)/	n	10	41	38	89
	EOS/ET	Mean (SD)	-0.39 (1.315)	-0.16 (0.998)	-0.07 (0.765)	-0.15 (0.941)
		Median	0.01	-0.13	-0.15	-0.14
		Min, Max	-2.6, 1.6	-2.1, 2.0	-1.5, 2.0	-2.6, 2.0
Height	Screening	n	10	41	38	89
		Mean (SD)	-0.07 (1.048)	-0.14 (0.914)	0.03 (0.810)	-0.06 (0.880)
		Median	-0.13	-0.14	0.06	-0.06
		Min, Max	-1.6, 1.5	-2.0, 1.4	-1.5, 2.6	-2.0, 2.6
	Visit 9 (Wk 7)/	n	10	41	38	89
	EOS/ET	Mean (SD)	-0.08 (1.077)	-0.14 (0.927)	0.11 (0.980)	-0.03 (0.963)
		Median	-0.23	-0.26	-0.02	-0.07
		Min, Max	-1.7, 1.4	-1.9, 1.5	-1.4, 3.3	-1.9, 3.3
BMI	Screening	n	10	41	38	89
		Mean (SD)	-0.56 (1.236)	-0.04 (1.077)	0.04 (0.854)	-0.07 (1.011)
		Median	-0.65	0.06	0.08	0.06
		Min, Max	-2.4, 1.5	-2.6, 2.2	-1.7, 2.1	-2.6, 2.2
	Visit 9 (Wk 7)/	n	10	41	38	89
	EOS/ET	Mean (SD)	-0.50 (1.260)	-0.12 (1.076)	-0.23 (1.077)	-0.21 (1.091)
		Median	-0.40	0.05	-0.10	-0.17
		Min, Max	-2.4, 1.4	-2.3, 2.1	-3.4, 1.9	-3.4, 2.1

SD = standard deviation.

3.2.7 Electrocardiogram (ECG)

Dose Optimization Period

An abnormal, ECG result was reported for 1 subject (1.1%) at pre-dose Baseline. This subject (02-024) was terminated prior to randomization due to prolonged QT interval at Visit 7. There were very few qualitative changes in ECG interpretation from Baseline to Visit 7 for all MTS doses. All QT, QTcB, and QTcF interval results were less than 500 msec for all MTS doses.

One (1) subject (Site 05, Subject 017) had an increase of 62 msec in QTcB from Baseline (387 msec) to Visit 7 (449 msec). This subject was on the 25cm^2 patch and the overall ECG impression was found to be abnormal, not clinically significant. The overall ECG impression at Baseline was normal and at study completion was abnormal, not clinically significant.

Analog Classroom Period

There were no abnormal CS ECG results reported. All QT, QTcB, and QTcF interval results were less than 500 msec for both MTS/PTS and PTS/MTS treatment sequences.

3.2.8 Other safety parameters measured

Dermal Evaluations

Dermal evaluations were conducted at each visit to assess the prior and current application site for the presence or absence of primary skin reactions and other signs of skin irritation in the areas of patch wear.

Dose Optimization Period

At the end of the Dose Optimization Period (Visit 7), the majority of subjects reported no evidence of irritation or minimal evidence of irritation and no discomfort or mild discomfort at both the current and prior application sites. In addition, patch adherence was judged to be greater than 90% adhered for most (86%) patches. The number of assessments rated higher than a 1 on the Dermal Response Scale and the Experience of Discomfort and Pruritus scale, as well as the number of patches less than 90% adhered are presented in the Text Table below.

Table 15: Dermal Evaluations: Dose Optimization Period – Visit 7				
Dermal Evaluation	**Patch Size**			
	12.5cm^2	**18.75cm^2**	**25.0cm^2**	**37.5cm^2**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Dermal Response Scale				
Total Number of Application Sites Assessed	N=18	N=72	N=55	N=18
Application Sites With More Than Minimal Erythema (> 1 on Dermal Response Scale)	4 (22)	3 (4)	8 (15)	3 (17)
Experience of Discomfort and Pruritus				
Total Number of Application Sites Assessed	N=18	N=72	N=55	N=18
Application Sites With More Than Mild Discomfort (> 1 on Experience of Discomfort and Pruritus Scale)	4 (22)	1 (1)	4 (7)	0
Transdermal System Adherence				
Total Number of Patches Evaluated	N=4	N=28	N=24	N=8
Patches Less than 90 % Adhered (> 0 on Transdermal System Adherence Scale)	2 (50)	5 (18)	1 (4)	1 (13)

* Table represents Dermal Evaluations reported at Visit 7 only.

Analog Classroom Period

During the Analog Classroom Period, dermal evaluations for the prior application site were performed pre-dose. Dermal assessments for the current application site were conducted around the time of patch removal, approximately 9 hours after application. The evaluator assessed the appearance of the site, queried for discomfort and evaluated patch adherence. The number of assessments rated higher than a 1 on the Dermal Response Scale and the Experience of Discomfort and Pruritus scale, as well as the number of patches less than 90% adhered are presented in the Text Table below.

Table 16: Dermal Evaluations: Analog Classroom Period				
Dermal Evaluation	**Visit 8**		**Visit 9**	
	MTS n (%)	**PTS n (%)**	**MTS n (%)**	**PTS n (%)**
Dermal Response Scale				
Total Number of Application Sites Assessed	N=82	N=74	N=75	N=80
Application Sites With More Than Minimal Erythema (> 1 on Dermal Response Scale)	25 (30)	2 (3)	18 (24)	5 (6)
Experience of Discomfort and Pruritus				
Total Number of Application Sites Assessed	N=79	N=72	N=75	N=80
Application Sites With More Than Mild Discomfort (> 1 on Experience of Discomfort and Pruritus Scale)	0	0	2 (3)	0
Transdermal System Adherence				
Total Number of Patches Evaluated	N=40	N=36	N=31	N=34
Number of Patches Less than 90% Adhered (> 0 on Transdermal System Adherence Scale)	9 (23)	5 (14)	11 (35)	5 (15)

These results indicate that patches containing MPH are slightly more irritating than placebo patches. Examinations of the distribution scores indicate that 2 of the 154 MTS application sites (1%) evaluated during the Analog Classroom were evaluated by the subjects as having more than mild discomfort. Patch adherence was good with the majority (72%) of patches having more than 90% of surface area still adhered to skin by the end of the classroom day.

Overall, the patch was well tolerated with site irritation and discomfort limited to a small number of sites. Reactions were localized and skin adherence was very good.

Sleep Evaluation: Child's Sleep Habits Questionnaire

The impact of MTS compared with placebo on sleep was assessed using data collected via the Children's Sleep Habits Questionnaire (CSHQ) and by adverse event analysis. The CSHQ is designed to screen for the most common sleep problems in children aged 4 to 12. This scale was chosen because it evaluates sleep in children by assessing common themes around sleep quality and quantity, as well as by asking the parent if the sleep behavior reported was a problem.

The results of the CSHQ at the end of the open-label Dose Optimization Period, with the exception of the subjects who discontinued before randomization to the double-blind Analog Classroom Periods, are presented in the Text Table below.

Table 17: CSHQ: Dose Optimization Period – Baseline and Mean Change from Baseline Scores – Visit 7*

Parameter	Baseline (Week 0) Pre-dose n=92 Mean (SD)	Visit 7 (Week 5) Patch Size 12.5cm² n=9 Mean (SD)	18.75cm² n=35 Mean (SD)	25.0cm² n=28 Mean (SD)	37.5cm² n=9 Mean (SD)
CSHQ Score	45.9 (9.81)	N/A			
Items Identified as a Problem	3.0 (4.28)				
Change from Baseline	N/A	1.0 (9.99)	-0.9 (8.93)	-1.0 (6.14)	-4.0 (4.92)
Change in Items Identified as a Problem		-1.4 (3.71)	-1.6 (3.42)	-0.8 (4.24)	-1.8 (3.23)

* Table represents CSHQ scores for subjects who were still enrolled in the study at Visit 7.

The mean score of the CSHQ at the Baseline Visit was 45.9 points, indicating a moderate degree of sleep problems. The mean number of sleep items identified as a problem was 3.0. By the end of the Dose Optimization Period, subjects who did not terminate from the study had a reduction in the number of sleep problems identified and overall small changes in the total sleep scores.

In the Analog Classroom Period of the study, subjects had already titrated to at least an acceptable dose of MTS for both efficacy and safety. The results for the changes from baseline in the CSHQ are presented in the Text Table below.

Table 18: CSHQ: Analog Classroom Period – Baseline and Mean Change from Baseline Scores

Parameter	Baseline (Week 0) Pre-dose n=92 Mean (SD)	Visit 8 (Week 6) MTS n=41 Mean (SD)	PTS n=37 Mean (SD)	Visit 9 (Week 7) MTS n=37 Mean (SD)	PTS n=41 Mean (SD)
CSHQ Score	45.9 (9.81)	N/A			
Items Identified as a Problem	3.0 (4.28)				
Change from Baseline	N/A	-0.3 (10.14)	-2.1 (6.48)	-1.5 (6.83)	-0.6 (10.21)
Change in Items Identified as a Problem		-0.4 (5.07)	-1.7 (4.37)	-1.6 (4.17)	-0.9 (4.68)

During the Analog Classroom Period, CSHQ analysis indicated small changes in the overall mean CSHQ, as well as the mean number of problems identified. There was an obvious difference in the 2 randomization groups as those randomized to the MTS/PTS sequence had mean change scores that were lower as a group than those in the PTS/MTS group. This difference persisted when the groups were crossed over to the opposite treatment during the second week of the Analog Classroom Period.

Taken together, these results confirm that children with ADHD demonstrate sleep problems at baseline, after previous treatments have been discontinued and before treatment with MTS has started. The effects of MTS treatment on the CSHQ indicate little effect of MTS on the total score as well as the number of sleep problems reported, both when open-label and double-blind treatments are administered. The effects of MPH on an individual's ability to fall asleep are well known; however, the scores are highly variable in individual subjects and the baseline score does not seem to correlate with the ability to predict sleep problems during treatment with MTS.

The overall incidence of insomnia during Dose Optimization was low at 9.7% (9 events, 9 subjects).

3.2.9 Summary for Study

This short-term, Analog Classroom study had an open-label Dose Optimization period of 5 weeks where Investigators could increase the MTS patch size to optimal effect on ADHD symptoms and for tolerability to methylphenidate and the patch. During the 2-week Analog Classroom period, the MTS or PTS patch size was fixed for the week prior to the first classroom session. Subjects were randomized to PTS or MTS at the optimized patch size to a sequence of 1 week of treatment with each MTS and matching PTS.

Overall, MTS was well tolerated during both the open label and the double-blind periods. There were no deaths or SAEs reported in any period.

During the open-label Dose Optimization period, the most common adverse events were headache, decreased appetite/anorexia, abdominal pain and insomnia. These events are well known adverse drug reactions of methylphenidate administered orally. The incidence of anorexia ranged from 1% in the 18.75cm^2 group to 9% in the 37.5cm^2 group. Two (2) subjects discontinued from the study during the Dose Optimization Phase due to decreased appetite.

The low incidence of adverse events in the double-blind period is likely due to the selection of subjects and patch sizes that were optimized in the open-label period. Thus patients were selected to be tolerant of their MTS. The incidence of anorexia during the double-blind analog classroom period was 3% in the MTS treated group.

The effects of MTS patches on dermal evaluations revealed that most subjects had little to no reaction to the patch. Those effects noted were typically mild to moderate in severity ($\leq$2 on the Experience of Discomfort and Pruritus Dermal Evaluation). Only 2 subjects terminated due to application site reactions. These were moderate in intensity and resolved on discontinuation of treatment and mild topical therapy.

There was no evidence of sensitization to MPH in this short study as evidenced by skin reactions at sites of previous application or by generalized skin rash. Patients receiving PTS had a lower number of reactions than did patients receiving active MTS. The study was not designed to elicit sensitization to MPH or patch components and the rapid resolution of all application site reactions indicates that irritation was the main reaction observed.

Methylphenidate appears to cause a slightly higher incidence of skin irritation when presented in the context of MTS.

The effects of MTS on sleep habits were also evaluated in this study. At baseline, the mean score on the CSHQ was approximately 46 points (on a 100-point scale). This indicates a mild to moderate degree of sleep problems and this is confirmed by the number of sleep items identified as problematic by the parents who completed the questionnaire. There appears to be a small number of subjects sensitive to the effects of methylphenidate who have deterioration of their sleep scores and an increase in the number of problems at the lowest dose of MTS. Whether a longer period of treatment at the lower dose will allow tolerance to these effects was not studied. The lack of overall effect of MTS on sleep is further confirmed by the scores in the double-blind classroom periods. The groups appeared to be different between MTS and PTS in the first period. However, after crossing over to the alternate treatment, the results are similar indicating that MTS was having minimal to no effect on sleep as evaluated by the CSHQ. Overall adverse events of insomnia were low in this study and no subject discontinued for insomnia.

There were no relevant effects of MTS on vital signs in this study. Pulse rate typically increased in subjects receiving MTS and PTS after patch application. This did not appear to be dose related. Blood pressure changes were confined to isolated increases in systolic and diastolic blood pressure (BP) and were not consistent. Two (2) subjects reported an AE of weight decrease during the Dose Optimization Period. Weight decrease was not reported as an AE during the Analog Classroom Period. The mean z-score for weight did not change appreciably between the visits.

Overall, MTS was well tolerated in this study. The primary adverse effects observed were anorexia, decreased appetite, abdominal pain, headache and insomnia. All these effects are known adverse effects of methylphenidate and do not appear to occur at a greater frequency or severity than reported in the approved labeling for these products.

4. PHASE III CONTROLLED PEDIATRIC POPULATION WITH CONCERTA® COMPARATOR (STUDY SPD485-302)

4.1 Study SPD485-302

4.1.1 Design

Study SPD485-302 was a Phase III, randomized, double-blind, multicenter, 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 and 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:

- Screening & Washout Period – Subjects were screened for approximately 2 weeks prior to washout. Washout (if applicable) 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). 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 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 12.5cm2 size patch (1/day) and the CONCERTA®/matching placebo 18mg dose (1/day), and were evaluated after 1 week (7±2days) for tolerability and effectiveness. Subjects may have been titrated to the next patch size/dosage strength 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:

  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/dosage strength produced an intolerable effect as well, the subject was to be discontinued from the study.

Ineffective condition: (i.e., <25% change in ADHD-RS-IV score with acceptable safety profile): Required increasing the MTS size/CONCERTA® dose to the next available dose strength followed by weekly evaluation.

Acceptable condition: A response was defined as acceptable if a subject showed at least a 25% reduction in ADHD symptoms with minimal side effects. Investigators were to refer to the subject's Baseline ADHD-RS-IV score to aid in dose adjustments. Subjects categorized as "acceptable" may have been maintained at their current dose for the remainder of the study (through Visit 7). Alternatively, the subject's dose could have been increased to the next larger patch size/dosage size, if the current dose was well tolerated, and in the Investigator's opinion the subject would potentially receive further symptom reduction through titration to the next patch size/dosage size. Visit 6 was the last visit at which titration could occur.

Subjects who did not reach at least an acceptable dose (i.e., "Acceptable condition") by Visit 7, were withdrawn from the study. Eligible subjects were allowed to enroll into an open-label extension study (SPD485-303).

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/PTS and CONCERTA®/matching placebo occurred for 2 weeks.

- Follow-Up Period – At the End of Study/Early Termination Visit (Visit 9), eligible subjects had the option to enroll into an open-label extension study (Study SPD485-303). Subjects who did not enroll into the extension study continued to be followed for thirty days (±2 days) following the last dose of study drug.

4.2 Extent of Exposure

The mean duration of exposure was similar between the MTS and CONCERTA® groups, while mean exposure was slightly lower in the placebo group. The mean (SD) length of exposure was 45.0 (8.96), 44.5 (11.06), and 36.5 (14.54) days in the MTS, CONCERTA®, and placebo groups, respectively.

As expected by study design, the number of subjects as each successive dose level increased each week during the Dose Optimization Period. At the end of the Dose Optimization Period, the majority of subjects in the MTS and CONCERTA® groups had progressed to the highest 2 dose levels. Fifty-four (55.1%) subjects were receiving 25cm^2 or 37.5cm^2 MTS units at Visit 7, while 52 (57.2%) subjects were receiving 36mg or 54mg CONCERTA®.

The intended patch wear time was 9 hours. Parents were instructed to remove the patch at 1600 hours regardless of the time the patch was applied. Mean (SD) patch wear time during the study was consistent and ranged between 8.70 (0.507) and 9.46 (0.531) hours.

4.3 Adverse Events

4.3.1 Brief summary of 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. Of these treatment-emergent AEs, 63 (64.3%) subjects in the MTS group, 47 (51.6%) subjects in the CONCERTA® group and 23 (27.1%) subjects in the placebo group had AEs that were assessed by investigators as being related to study treatment.

The most commonly reported TEAEs among the 2 active treatment groups were decreased appetite and headache.

The majority of all AEs were assessed as having a mild or moderate intensity. Three (3) subjects, 1 each in the MTS, CONCERTA®, and placebo groups, reported a total of 5 AEs that were assessed as severe.

There were no deaths or other SAEs reported during 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 (2) subjects in the MTS group discontinued due to application site reactions. These application site reactions were documented on the dermal evaluation form of the case report form (CRF) and not captured as AEs.

4.3.2 Description and analysis of adverse events

4.3.2.1 Most common adverse events ≥5% in any treatment group

The Text Table below presents a summary of the most commonly reported TEAEs regardless of causality or intensity that had an incidence of at least 5% in any treatment group. The most commonly reported TEAEs among the 2 active treatment groups were decreased appetite and headache. Other commonly reported TEAEs included insomnia, nausea, upper abdominal pain, and vomiting. The percentage of subjects reporting treatment-emergent insomnia and nausea was higher in the MTS group compared to CONCERTA®. The percentage of subjects reporting treatment-emergent upper abdominal pain was higher in the CONCERTA® group compared to MTS. The percentage of subject reporting vomiting was similar between the 2 active treatment groups

Other AEs of interest include anorexia, decreased weight, and events related to the skin. The number of subjects reporting treatment-emergent anorexia and decreased weight was slightly higher in the MTS group compared to CONCERTA®. The number of subjects in the MTS, CONCERTA®, and placebo group with TEAEs related to the skin was 6 (6.1%), 1 (1.1%), and 2 (2.4%), respectively. Investigators were to examine the dermal study drug application site and rate their findings on a dermal evaluation form. Two (2) of the 6

skin-related AEs in the MTS group were associated with the study drug application. One (1) subject (21-003) was reported to have moderate itching of the hip, while the other (32-001) reported moderate hip irritation. Neither subject received treatment for the skin event.

Table 19: Most Commonly Reported Treatment-Emergent Adverse Events (≥5%; all Causalities in any Treatment Group) – Safety Population

System Organ Class* / 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)
Gastrointestinal Disorders						
Abdominal pain upper	7	(7.1)	9	(9.9)	5	(5.9)
Nausea	12	(12.2)	7	(7.7)	2	(2.4)
Vomiting	10	(10.2)	9	(9.9)	4	(4.7)
General Disorders and Administrative Site Conditions						
Pyrexia	2	(2.0)	4	(4.4)	8	(9.4)
Infections and Infestations						
Nasopharyngitis	5	(5.1)	4	(4.4)	2	(2.4)
Investigations						
Weight decreased	9	(9.2)	7	(7.7)	0	
Metabolism and Nutrition Disorders						
Anorexia	5	(5.1)	3	(3.3)	1	(1.2)
Decreased appetite	25	(25.5)	17	(18.7)	4	(4.7)
Nervous System Disorders						
Headache	15	(15.3)	18	(19.8)	10	(11.8)
Psychiatric Disorders						
Affect lability	6	(6.1)	3	(3.3)	0	
Insomnia	13	(13.3)	7	(7.7)	4	(4.7)
Irritability	7	(7.1)	7	(7.7)	4	(4.7)
Tic	7	(7.1)	1	(1.1)	0	
Respiratory						
Cough	7	(7.1)	5	(5.5)	4	(4.7)
Nasal congestion	6	(6.1)	3	(3.3)	1	(1.2)
Pharyngolaryngeal pain	6	(6.1)	3	(3.3)	5	(5.9)

The Text Table below presents a summary of the most commonly reported TEAEs regardless of causality or intensity that had an incidence of at least 5% in the MTS group and occurred at an incidence that was 2 times the incidence in the placebo group. The most commonly reported TEAEs that occurred at an incidence of at least 5% in the MTS group and at least 2 times the incidence of the placebo group were decreased appetite, insomnia, and nausea.

Table 20: Most Commonly Reported Treatment-Emergent Adverse Events (≥5% in MTS and >2X Placebo) – Safety Population

System Organ Class* 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 lability	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)

*MedDRA Version 7.0,

4.3.2.2 Intensity of adverse events

Of the 573 TEAEs reported among the 274 subjects in the Safety population, 417 events were judged mild in intensity and reported by 132 (48.2%) subjects, 152 moderate AEs were reported by 52 (19.0%) subjects, and 4 severe TEAEs were reported by 3 (1.1%) subjects.

The majority of TEAEs were mild in intensity in the MTS (54 subjects, 55.1%) group, while slightly lower percentage of subjects in the CONCERTA® group (44 subjects, 48.4%) had mild AEs. For most of the commonly reported AEs, the percentage of subjects with AEs that were assessed as mild was higher than those assessed as moderate or severe.

The 5 severe AEs (includes 1 non-treatment–emergent AE) reported included abnormal alanine aminotransferase, abnormal aspartate aminotransferase, syncope, and 2 occurrences of aggression. Subject 24-003 (MTS) had 2 single severe episodes of aggression. One (1) episode of aggression occurred 6 days after treatment was stopped. Both events resolved the same day as they started and no treatment was given or action was taken to resolve the events. In the investigator's opinion, the events were assessed as

unrelated to study drug. Subject 31-004 (CONCERTA®) had a single episode of severe syncope. The event resolved without treatment on the same day it began. As a result of the event, study drug was discontinued. In the investigator's opinion, the event was assessed as possibly related to study drug. Subject 54-001 (Placebo) had a single event each of severe abnormal alanine aminotransferase and abnormal aspartate aminotransferase. In the investigator's opinion, these events were assessed as unrelated to study drug.

4.3.2.3 Relationship of adverse events to treatment

Of the 621 AEs reported, 336 were judged related to study drug and were reported by 134 (48.9%) of the 274 subjects in the Safety population. The number of subjects in the MTS, CONCERTA®, and placebo group that had AEs judged to be related to study drug were 63 (64.3%), 48 (52.7%), and 23 (27.1%), respectively (see the Text Table below). The 3 related AEs with the highest percentage of subjects reporting among the 2 active treatment groups were decreased appetite (25 subjects, 25.5% MTS and 18 subjects, 19.8% CONCERTA®), insomnia (13 subjects, 13.3% MTS and 7 subjects, 7.7% CONCERTA®), and headache (11 subjects, 11.2% MTS and 15 subjects, 16.5% CONCERTA®). The percentage of subjects reporting drug-related decreased appetite and insomnia was slightly higher in the MTS group compared to the CONCERTA® group.

The number of subjects reporting treatment-related anorexia and decreased weight was slightly higher in the MTS group (5 subjects, 5.1% and 9 subjects, 9.2%, respectively) compared to CONCERTA® (3 subjects, 3.3% and 6 subjects, 6.6%, respectively).

Table 21: Summary of Study Drug Related and Unrelated Adverse Events – Safety Population

	Number (%) of subjects reporting AE					
	MTS (N=98)		CONCERTA® (N=91)		Placebo (N=85)	
Related AEs*	63	(64.3)	48	(52.7)	23	(27.1)
Unrelated AEs	52	(53.1)	44	(48.4)	46	(54.1)

* Related AEs include those events with a relationship of possibly related, probably related, or a missing relationship.

4.3.2.4 Adverse events during Dose Maintenance Period

The Text Tables below present the overall summary of adverse events by final MTS, CONCERTA®, and Placebo dose during the Dose Maintenance Period for the Safety population, respectively.

Table 22: Overall Summary of Treatment-Emergent Adverse Events During the Dose Maintenance Period by Final MTS Size – Safety Population

MTS 12.5cm² (N=5)		MTS 18.75cm² (N=16)		MTS 25cm² (N=26)		MTS 37.5cm² (N=24)	
Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
4 (80.0)	11	5 (31.3)	6	7 (26.9)	8	8 (33.3)	11

Table 23: Overall Summary of Treatment-Emergent Adverse Events During the Dose Maintenance Period by Final CONCERTA® Dose – Safety Population

CONCERTA® 18mg (N=3)		CONCERTA® 27mg (N=13)		CONCERTA® 36mg (N=21)		CONCERTA® 54mg (N=28)	
Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
0 (0.0)	0	3 (23.1)	5	4 (19.0)	5	7 (25.0)	11

Table 24: Overall Summary of Treatment-Emergent Adverse Events During the Dose Maintenance Period for Placebo arm by Final PTS* Size – Safety Population

PTS 12.5cm² (N=0)		PTS 18.75cm² (N=6)		PTS 25cm² (N=6)		PTS 37.5cm² (N=21)	
Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
0 (0.0)	0	2 (33.3)	2	1 (16.7)	1	7 (33.3)	8

* Subjects in Placebo arm also received a Placebo capsule, Relationship of adverse events to gender

No clinically important differences in TEAEs by age, gender or ethnic origin were noted.

4.4 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Significant Adverse Events

4.4.1 Deaths

No deaths occurred in this study.

4.4.2 Other serious adverse events

No serious adverse events occurred in this study.

4.4.3 Discontinuations due to adverse events

All subjects discontinued due to an AE are identified in the Text Table below.

Table 25: Summary of Adverse Events Leading to Discontinuation – Safety Population

Treatment	Subject ID	Gender/Age/Race	AE	Relationship
MTS	12-002	M/6/W	Tics	Probably
	15-002	M/9/W	Application site reaction	Probably
	19-003	F/9/W	Application site erythema	Probably
	28-019	M/7/W	Headaches	Possibly
	29-010	M/10/W	Irritability Crying Confusional state	Possibly Possibly Possibly
	45-013	F/6/H	Viral infection	Unrelated
	65-012	F/7/W	Infectious mononucleosis	Unrelated
CONCERTA®	31-004	M11/W	Syncope	Possibly
	39-007	M/12/W	Abdominal pain	Unrelated
	41-008	M/6/W	Aggression Anger Headache	Possibly Possibly Possibly
Placebo	11-003	M/9/W	Worsening ADHD symptoms	Unrelated

M=Male, F=Female, W=White, H=Hispanic

4.4.4 Other significant adverse events

No other significant adverse events occurred in this study.

4.4.4.1 Other significant adverse events

There were no other significant AEs during the study.

4.4.5 Analysis and discussion of deaths, other serious adverse events, discontinuations due to adverse events and other significant adverse events

No subject died or reported a serious adverse event (SAE) during the study.

Eleven subjects reported 1 or more AEs that led to study drug termination. The events that led to study drug termination should not be considered unexpected in the population under study in this trial, considering the medical histories and disease characteristics of these subjects.

4.5 Clinical Laboratory Evaluation

4.5.1 Brief summary of laboratory parameters findings

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. A few clinically significant treatment-emergent laboratory values were reported, however it is unlikely that they were related to study drug treatment.

4.5.2 Individual subject changes

4.5.2.1 Hematology

There was no pattern in the occurrence of abnormal values for hematology parameters from Screening to Visit 9.

4.5.2.2 Clinical chemistry

There was no pattern in the occurrence of abnormal values for chemistry parameters from Screening to Visit 9.

4.5.2.3 Urinalysis

There was no pattern in the occurrence of abnormal values for urinalysis parameters from Screening to Visit 9.

4.5.3 Individual clinically significant abnormalities

4.5.3.1 Hematology

No subject had a treatment-emergent abnormal hematology value that was assessed by the investigator as clinically significant.

4.5.3.2 Clinical chemistry

As shown in the Text Table below, 2 subjects had treatment-emergent laboratory values that were considered by the investigator to be clinically significant. All 4 of these abnormal clinically significant chemistry values were reported as AEs and assessed as unrelated to study drug.

Table 26: Clinically Significant Treatment-Emergent Abnormal Chemistry Values – Safety Population

Treatment	Subject ID	Parameter	Normal Range	Screening Value	Visit 9 Value	Reported as AE	Relationship to study drug
CONCERTA®	11-001	ALT	6-34U/L	15U/L	300U/L	Yes	Unrelated
		AST	10-40U/L	30U/L	162U/L	Yes	Unrelated
Placebo	54-001	ALT	6-34U/L	25U/L	102U/L	Yes	Unrelated
		AST	10-40U/L	40U/L	101U/L	Yes	Unrelated

AST = Aspartate Transaminase.

Additionally, subject 34-018 (CONCERTA®, 18mg) reported an AE of an increase in blood glucose. The abnormal glucose level did not occur at a regular scheduled laboratory measurement and therefore no assessment of clinical significance was recorded. The subject had a Screening blood glucose level of 9.3mmol/L. The subject was randomized to CONCERTA® and was receiving 18mg at the time of the event. The event occurred approximately 2 days after starting CONCERTA®. The subject did not have a history of diabetes. The event was mild in intensity and, in the investigator's opinion, unrelated to study drug. The subject received no treatment for the event and the event resolved the same day it began.

4.5.3.3 Urinalysis

No subject was reported as having a clinically significant abnormal urinalysis value.

4.6 Other Safety Data

4.6.1 Vital signs, height and weight

There was very little difference between MTS and placebo (0.5 v 0.6mmHg) for change from baseline for SBP at Visit 8. There was a small increase in mean change from Baseline in systolic BP at Visits 6, 7, 8, and 9 in both the MTS and CONCERTA® groups compared to the placebo group. The maximum mean increases in systolic BP from Baseline were seen at Visit 7 (+1.3mmHg) in the MTS group and at Visits 6 and 7 (+1.6mmHg) in the CONCERTA® group. The changes noted in systolic BP were not clinically significant and were similar between the MTS and CONCERTA® treatment groups.

Similarly, a small increase in mean change from Baseline in diastolic BP was noted at most visits in the MTS and CONCERTA® groups. The maximum mean increases in diastolic BP from Baseline were seen at Visit 7 in the MTS (+1.6mmHg) group and at Visit 8 in the CONCERTA® (+2.7mmHg) group. The changes noted in diastolic BP were not clinically significant, however were generally higher in the CONCERTA® group compared to the MTS group.

There were no notable differences in mean change from Baseline in pulse between the 3 treatment groups at most visits. At Visit 9, an increase in mean change from Baseline in pulse was noted in the MTS (+5.2bpm) and CONCERTA® (+4.7bpm) compared to the placebo (+1.0bpm) group.

There was a decrease in mean change from Baseline in weight at all post-Baseline visits (3-9) in both the MTS and CONCERTA® groups, while subjects in the placebo group had an increase in mean weight change from Baseline. The maximum mean decrease in weight from Baseline was seen at Visit 8 in both the MTS (-2.2lbs) and CONCERTA® (-2.1lbs) groups. The maximum mean increase in weight from Baseline in the placebo group was also seen at Visit 8 (+2.1lbs). The decrease in mean change from Baseline in weight was similar in the MTS and CONCERTA® groups.

There were no notable differences in mean change from Baseline in respiration rate or temperature between the 3 treatment groups at any visit.

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. There were no CONCERTA®-treated subjects who had Baseline systolic BP measurements above the normal range, however while receiving CONCERTA® several subjects had systolic BP measurement above the normal range.

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 and placebo. At Visit 8, the incidence of pulse values above the normal range was similar between the 2 active treatment groups, yet higher than in the placebo group.

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 (1) 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. There was no change in the number of subject with weight measurements below the normal range in the CONCERTA® or placebo groups. Of note the MTS group had the highest number of subjects (19 subjects, 19.4%) with Baseline weights above the normal range.

There was no pattern in the occurrence of abnormal values for temperature values, although the number of subjects with above and below normal values was higher in the 2 active treatment groups compared to placebo.

A summary of z-scores for height, weight, and BMI at Screening and at Visit 9/EOS/ET for all enrolled subject is presented in the Text Table below. The mean z-score for weight was lower at Visit 9 compared to Screening in the MTS and CONCERTA® groups. The mean z-score for height was relatively unchanged from Screening to Visit 9 in all 3 treatment groups. Mean z-scores for BMI was lower at Visit 9 compared to Screening in the MTS and CONCERTA® groups.

Table 27: Summary of Z-Scores - All Enrolled Subjects

Z-Score		Statistic	MTS (N=100)	CONCERTA® (N=94)	Placebo (N=88)	Overall (N=282)
Weight	Screening	n	92	89	77	258
		Mean (SD)	0.05 (1.075)	0.28 (0.933)	0.15 (0.927)	0.16 (0.985)
		Median	0.04	0.21	0.13	0.11
		Min, Max	-2.7, 2.5	-2.1, 2.2	-2.1., 2.8	-2.7, 2.8
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.21 (1.168)	0.04 (0.926)	0.24 (0.937)	0.01 (1.034)
		Median	-0.24	-0.10	0.24	-0.08
		Min, Max	-2.9, 2.4	-2.3, 1.9	-1.8, 2.8	-2.9, 2.8
Height	Screening	n	92	89	77	258
		Mean (SD)	-0.05 (1.025)	0.12 (0.906)	-0.00 (1.078)	0.02 (1.001)
		Median	0.08	0.13	-0.03	0.07
		Min, Max	-2.8, 2.1	-1.8, 2.2	-4.0, 2.6	-4.0, 2.6
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.08 (1.053)	0.11 (0.972)	0.02 (1.007)	0.01 (1.011)
		Median	-0.03	0.07	0.03	0.04
		Min, Max	-2.9, 2.2	-1.7, 4.0	-2.7, 2.6	-2.9, 4.0
BMI	Screening	n	92	89	77	258
		Mean (SD)	0.13 (1.027)	0.30 (1.091)	0.25 (0.954)	0.22 (1.028)
		Median	0.12	0.38	0.22	0.22
		Min, Max	-2.4, 2.3	-4.2, 2.2	-3.1, 2.3	-4.2, 2.3
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.23 (1.170)	-0.06 (1.232)	0.34 (0.984)	0.00 (1.160)
		Median	-0.27	0.02	0.32	0.03
		Min, Max	-2.9, 2.2	-6.0, 2.0	-3.0, 2.4	-6.0, 2.4

Two (2) subjects had abnormal vital sign values reported as AEs. Subject 29-010 (MTS) was reported to have a continuous decrease in BP starting approximately 1 month after starting MTS. The onset of the event was at Visit 7, during a regularly schedule vital sign measurement. At the time of the event the subject was receiving 25cm^2 MTS. The subject had a Baseline BP of 102/78mmHg. The subject's BP was 74/58mmHg at the time of the

event and no repeat or follow-up was performed. The event was moderate in intensity and, in the investigator's opinion, possibly related to study drug.

Subject 43-008 (CONCERTA®) was reported to have an intermittent increase in pulse approximately 1 week after starting CONCERTA®. At the time of the event onset the subject was receiving 27mg CONCERTA®. The subject had a screening and Baseline pulse of 86bpm and 100bpm, respectively. The subject's pulse at the time of the event is unknown, however the event resolved the same day. The event was mild in intensity and, in the investigator's opinion, possibly related to study drug.

4.6.2 Electrocardiogram

No clinically important 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). No clinically important mean change from Baseline was noted for QTcF in the MTS group.

At Visit 7, the incidence of subjects with a 30-60msec change from Baseline in QTcB was higher in the MTS group (11.2%) compared to the CONCERTA® (3.3%) and placebo group (1.2%). A similar trend was noted in QTcF, however the incidence of 30-60msec changes from Baseline was lower in the 2 active treatment groups compared to QTcB. Three (3) subjects had a >60msec change from Baseline in QT, QTcB, and/or QTcF.

Subject 41-014 in the MTS group had a >60msec increase from Baseline in QTcB and QTcF interval at Visit 7. The subject had a Baseline QTcB and average heart rate of 376msec and 66bpm, respectively. At Visit 7, the subject's QTcB had increased to 471msec with an average heart rate of 91bpm while receiving 25cm^2 MTS. At Visit 9, the subject's QTcB and average heart rate were 432msec and 87bpm. The subject also had similar changes in QTcF, while the uncorrected QT interval was within normal limits at all measurements.

Subject 27-010 in the CONCERTA® group had a >60msec increase in QT interval from Baseline at Visit 9/EOS/ET. This subject had a Baseline QT interval and average heart rate of 282msec and 117bpm, respectively. At an early termination visit approximately 2 weeks after Baseline, the subject's QT interval and average heart rate were 358msec and 80bpm, respectively. The subject was discontinued from the study due to lack of study drug compliance. No follow-up ECG was performed.

Subject 28-006 in the placebo group had a >60msec increase from Baseline in QTcB and QTcF interval at Visit 9/EOS/ET. This subject had a Baseline QTcB and QTcF of 343msec and 316msec, respectively. The subject's Baseline average heart rate was 98bpm. At an early termination visit approximately 1 week after Baseline, the subject's QTcB, QTcF, and average heart rate were 425msec, 388msec, and 104bpm, respectively. The subject was discontinued from the study for worsening behavior. No follow-up ECG was performed.

No subject had a QT, QTcB, or QTcF ≥500msec.

The incidence of normal and abnormal not clinically significant ECG results was generally similar between the 3 treatment groups throughout the study. No subject had a clinically significant abnormal ECG during the study.

A relatively large portion of subjects in all 3 treatment groups had abnormal ECGs at Screening and Baseline that were deemed not clinically significant. There was no significant difference in the relative frequency of the abnormal ECG findings among the 3 groups. A reason for the relatively large number of abnormal ECG findings was the stringent guidelines provided for reporting ECG abnormalities to the central ECG reading service by the sponsor. This was a deliberate, conservative strategy to ensure that all instances of potentially exclusionary findings were highlighted for careful review. Thus, minor abnormalities of rate and rhythm and waveform were classified as abnormal when in usual clinical practice, the findings would have likely been judged as not clinically significant. Accordingly, when abnormal findings of this type were received by investigators, the ECG findings were judged by them as not clinically significant.

4.6.3 Physical examination

Four (4) subjects had clinically significant abnormal physical examination findings at Visit 9 that were not present at Screening.

Table 28: Clinically Significant Treatment-Emergent Abnormal Physical Examination Results – Safety population

Treatment	Subject ID	Examination	Visit	Abnormality Description
MTS	12-002	Neurological	9/EOS/ET	Tics (eye blinking)
	15-002	Skin	9/EOS/ET	Maculopapular rash at patch application sites
	18-003	Other	9/EOS/ET	Itch of eyes induces grimacing and rubbing
	23-001	Skin	9/EOS/ET	Mild erythema under patch right hip

There was no pattern in the occurrence of abnormal values for physical examination findings from Screening to Visit 9, except for possibly the skin. There was a slightly higher shift from a normal skin examination at Screening to an abnormal skin examination at Visit 9 in the MTS group, presumably due to irritation at the patch application site. The majority of the abnormal skin examinations were considered not clinically significant.

4.6.4 Dermal evaluations

4.6.4.1 Dermal response scale

Starting with the first optimization visit post-Baseline, the physician Investigator examined both the current and the prior application sites for the presence or absence of primary skin reactions and other signs of skin irritation in the areas of patch-wear. Observed findings of erythema, edema, papules and vesicles were graded on a scale ranging from 0 (no irritation) to 7 (strong reaction). Signs of skin irritation were not to be recorded in the adverse event section of the CRF unless they occurred at a site different from the system application site.

The mean dermal response score was generally higher in the MTS group at all visits compared to the CONCERTA® and placebo groups. The mean dermal response scores across all visits in the MTS group ranged +0.5 - +1.0. Mean dermal response scores across all visits in the CONCERTA® and placebo groups ranged 0.0 - +0.3. The maximum dermal response score obtained was 4 (definite edema) in the MTS group, 5 (erythema, edema, and papules) in the CONCERTA® group, and 3 (erythema and papules) in the placebo group.

At all visits, the majority of subjects in the MTS group reported no evidence of irritation or minimal erythema, while the majority of subjects in the CONCERTA® and placebo groups reported no evidence of irritation.

4.6.4.2 Dermal discomfort

Other skin evaluations performed at each MTS/PTS application site included experience of discomfort and pruritus. The evaluator asked the subject, "Are you experiencing any discomfort (as it relates to the MTS/PTS)?" The overall level of discomfort was rated from 0, for no discomfort to 3, for severe, intolerable discomfort. If the discomfort was Mild, Moderate, or Severe, the evaluator asked the subject, "What kind of overall discomfort did you experience?" and collected discomfort information specific to the symptoms (itching, burning, or other).

The mean dermal discomfort score was generally higher in the MTS group at all visits compared to the CONCERTA® and placebo groups. The highest mean increase in dermal discomfort score in the MTS group was seen at Visit 6 (+0.3 left and +0.3 right). Mean dermal discomfort scores across all visits in the CONCERTA® and placebo groups ranged 0.0 - +0.2. The maximum dermal discomfort score obtained was 3 (severe, intolerable discomfort) in the MTS group, 2 (moderate, but tolerable discomfort) in the CONCERTA® group, and 3 in the placebo group. The majority of subjects in the MTS group reported no dermal discomfort. Most subjects who experienced dermal discomfort reported the discomfort as itching.

4.6.4.3 Transdermal system adherence

At each visit, the Investigator also examined transdermal system adherence for the current MTS/PTS site. Findings were recorded as an estimate of the percentage of the transdermal system surface in contact with the skin ranging from 0 (≥ 90% adhered) to 4 (MTS/PTS detached).

The mean transdermal system adherence score was generally similar in all 3 treatment groups and the majority of subjects in all groups reported the transdermal system adherence to be ≥ 90%.

4.6.5 Sleep Questionnaire

The impact of MTS compared with placebo and CONCERTA® on sleep was assessed using data collected via the CSHQ. The questionnaire, designed to screen for the most common sleep problems in children aged 4-12 years, assesses sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The CSHQ has 33 questions, responses range from 1 (rarely occurring) to 3 (usually occurring) with total scores ranging from 33 to 99. Bedtime, total sleep time, nightly waking periods, and waking time was also recorded. Parents and/or legal guardians responded on the basis of the child's sleep habits over the past week. Assessments were performed at Baseline (Visit 2) and Visits 3 through 9.

A summary of the total CSHQ scores in the Safety population is presented in the Text Table below. The mean total CSHQ score was lower at each visit compared to Baseline in all 3 treatment groups. The reduction in mean total CSHQ score appeared to be larger in the MTS group compared to the CONCERTA® or placebo group, however the differences were small.

Similarly, there was a reduction at all visits in the mean total number of problems reported in all treatment groups. There appeared to be little difference in the magnitude of mean reduction in the number of problems between the 3 treatment groups.

Table 29: Mean (SD) Change from Baseline in Total CSHQ – Safety population

	MTS (N=98)	CONCERTA® (N=91)	Placebo (N=85)
Baseline - Total Score	50.0 (9.95)	48.0 (10.43)	48.0 (9.47)
Visit 3	-2.3 (5.63)	-2.1 (4.80)	-1.9 (4.73)
Visit 4	-3.0 (5.14)	-2.5 (7.10)	-1.5 (5.81)
Visit 5	-4.1 (6.37)	-2.2 (7.45)	-2.5 (4.93)
Visit 6	-3.8 (6.45)	-1.8 (7.60)	-2.2 (5.60)
Visit 7	-4.7 (6.01)	-4.1 (6.66)	-3.4 (5.70)
Visit 8	- 4.6 (5.97)	-3.3 (7.12)	-4.3 (6.35)
Visit 9/EOS/ET	- 3.9 (6.53)	-3.0 (7.75)	-3.2 (5.55)
Baseline – No. of Problems	5.2 (6.27)	4.2 (4.31)	4.1 (4.82)
Visit 3	-0.8 (3.44)	-1.3 (2.64)	-1.1 (3.11)
Visit 4	-1.3 (3.73)	-1.6 (3.61)	-1.0 (4.35)
Visit 5	-1.5 (4.11)	-1.7 (3.75)	-1.3 (4.13)
Visit 6	-1.7 (4.28)	-1.6 (3.68)	-1.4 (4.40)
Visit 7	-2.2 (4.73)	-2.0 (3.55)	-2.6 (4.83)
Visit 8	-2.4 (4.35)	-1.9 (3.69)	-3.5 (4.20)
Visit 9/EOS/ET	-1.8 (4.53)	-1.9 (3.45)	-1.3 (4.81)

4.6.6 Summary for study

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

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 2 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 percentage of subjects reporting treatment-emergent upper abdominal pain was higher in the CONCERTA® group compared to MTS.

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

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 (2) subjects in the MTS group discontinued due to application site reactions.

With regards to 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.

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 (1) 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.

For ECG evaluations, 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 Visit 7 (6.2msec) and Visit 9 (6.9msec), however no clinically significant mean change from Baseline was noted for QTcF.

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.

All subjects had an assessment of mild to moderate sleep problems at Baseline. The mean total CSHQ score was lower at each visit compared to Baseline in each of the 3 treatment groups. The number of sleep items recorded as a problem also decreased in all 3 groups over the study. There was no adverse effect of MTS recorded in the population when sleep was assessed using a targeted questionnaire.

5. LONG-TERM OPEN-LABEL POPULATION (STUDIES N17-011, N17-013, N17-021)

5.1 Study N17-011

5.1.1 Design

Study N17-011 was an open-label, safety and tolerability study in children aged 6-13 who had a diagnosis of ADHD. The objectives of this study were to collect long-term safety and tolerability data of MTS in pediatric ADHD subjects. The secondary objective was to assess long-term skin tolerance and patch adhesion of MTS.

5.2 Study N17-013

5.2.1 Design

Study N17-013 was a 2-center, open-label study that enrolled pediatric subjects who had completed either Study N17-011 or N17-015, and had their ADHD symptoms well controlled on MTS. Subjects continuing from Study N17-011 were allowed to receive MTS until commercial availability. Subjects from N17-015 could continue using MTS for at least 9 months; the protocol was later amended to allow treatment until commercial availability. The starting MTS dose for each patient in Study N17-013 depended on the patient's previous study. Subjects continuing from Study N17-011 started on the MTS dose they were taking at the completion of that study, either 6.25cm^2, 12.5cm^2, or 25cm^2. Subjects continuing from Study N17-015 began at 25cm^2 MTS. In Study N17-013, the MTS dose was flexible and was administered in doses of 6.25cm^2, 12.5cm^2, 18.75cm^2, 25cm^2 and 37.5cm^2. Dose and wear time adjustments were allowed, based on parent and Investigator assessment of safety, efficacy, and patch tolerability. Following Screening and Baseline assessments, subjects were evaluated at the clinic every 3 months; medication-dispensing visits occurred monthly.

5.3 Study N17-021

5.3.1 Design

Study N17-021 was a multicenter, open-label, safety study designed to (1) collect long-term safety and tolerability data of MTS in children diagnosed with ADHD, and (2) assess long-term skin tolerance and adhesion of MTS. Subjects who completed Study N17-018 were eligible to participate in Study N17-021, if the Investigator thought that the patient would benefit from MTS treatment. For subjects who discontinued early from Study N17-018, completion of at least 1 dose titration was required to enroll in Study N17-021. Study drug was administered in doses of 6.25cm^2, 12.5cm^2, 18.75cm^2, 25cm^2, 37.5cm^2, and 50cm^2 MTS. The initial dose for all subjects was 12.5cm^2 MTS. Dose adjustments were allowed to a maximum of 50cm^2 MTS. Dose adjustment was based on parent and Investigator

assessment of safety, efficacy (based on Investigator rating of Clinical Global Impressions-Improvement; CGI-I), and patch tolerability. Participation in Study N17-021 consisted of 3 consecutive dose adjustment visits (adjustments to the optimum dose must have been completed within 3 weeks) followed by monthly maintenance visits.

The original protocol allowed for 8 months of open-label treatment. The duration of treatment was extended for an additional 32 months with the incorporation of 3 protocol amendments: Amendment 1, Revision 2 – 06 June 2002 (14 months), Amendment 2 – 02 July 2003 (6 months), and Amendment 3 – 11 December 2003 (12 months). Because of the Sponsor's decision to terminate the study early, the protocol was amended a fourth time, Amendment 4 dated 03 December 2004. Amendment 4 required that all subjects discontinue the study as of 23 December 2004. Subjects not completed at the end of the Study N17-021 were allowed to enter Study SPD485-303.

5.3.1.1 Deaths, Serious Adverse Events and Discontinuations Due To Adverse Events

Deaths and Serious Adverse Events
There were no deaths during Study N17-021.

Three (3) subjects had SAEs; none of the SAEs were considered by the Investigators to be related to study treatment. Two (2) of the SAEs were outbursts of hostility leading to hospitalization. The third SAE was an occurrence of dehydration after an episode of vomiting that followed an outpatient procedure. Narratives for these subjects are provided below.

Subject 03-04 was a 12-year-old male with a history of aggressive behavior diagnosed in September 2000, 2 years before entering the study. Concomitant medication at the time of the SAE was Zovirax 5% ointment. The subject was admitted to the hospital psychiatric ward on 03 October 2003 after exhibiting violent and aggressive behavior toward his mother. The subject was experiencing irritability and insomnia at the time of this SAE. The subject was treated with Zyprexa 2.5mg, and the aggressive behavior resolved the next day. The subject was discharged from the hospital on 06 October 2003. The subject's mother was advised to discontinue study medication, but she continued to administer the patches until 21 October 2003. The Investigator considered the relationship of the SAE to study treatment to be unlikely.

Subject 16-06 was an 8-year-old female who had a history of chicken pox in 1997, seasonal allergies since 1998, and dehydration after a viral illness in 2001. Concomitant medication at the time of the SAE was 1 multivitamin tablet daily. On 26 July 2002, the subject underwent an elective outpatient procedure to remove fatty deposits from her left arm as a result of a recent sprain. After the procedure, she began vomiting, reportedly as an adverse reaction to the anesthesia used for the procedure. She was admitted to the hospital later that day because of dehydration from the vomiting. She was treated with intravenous fluids and phenergan. On 27 July 2002, she was discharged from the hospital. Study medication had been stopped on 25 July before the outpatient procedure, but was resumed on 28 July the day after discharge. The Investigator considered the SAE to be not related to study treatment.

Subject 18-17 was an 11-year-old male who was admitted to the hospital for acute behavior management. On 25 September 2003, the subject's mother reported that the subject began having severe temper outbursts including setting a fire in his bedroom and threatening to run away. The subject was admitted to the hospital on the same day. The subject was discharged from the hospital on 28 September 2003. The subject's discharge medications were Concerta® 18mg, Zoloft 50mg, and Risperdal 1mg. Physical or sexual abuse by an older sibling was being investigated as a cause for the subject's anger. The subject was withdrawn from the study. The Investigator considered the SAE to be not related to study treatment.

Discontinuations Due to Adverse Events
A total of 45 (24%) subjects were withdrawn from the study because of AEs. The most common AEs leading to withdrawal were application site reaction (12, 6%), anorexia (7, 4%), and insomnia (7, 4%).

5.4 Long-term Open-label Population (Studies N17-011, N17-013, N17-021)

Deaths and Serious Adverse Events
No deaths occurred in the Long-Term Pediatric Population. Three (3) SAEs occurred. Two (2) SAEs involved hospitalization for outbursts of hostility and 1 SAE was for dehydration following an elective outpatient procedure. An IND Safety Report for the dehydration SAE was submitted to the FDA on 05 August 2002.

Discontinuations Due To Adverse Events
The Text Table below summarizes the AEs leading to discontinuation that were reported by more than a single subject (≥0.5%).

Table 30: Number (%) of Subjects with Adverse Events Leading to Discontinuation Occurring in 2 or More Subjects (Long-Term Pediatric Population)

Body System COSTART Term*	MTS (N=322) n (%)
Any Adverse Event	50 (16)
Digestive System	
Anorexia	8 (3)
Nervous System	
Insomnia	8 (3)
Nervousness	5 (2)
Hostility	3 (1)
Agitation	2 (1)
Anxiety	2 (1)
Emotional Lability	2 (1)
Hallucinations	2 (1)
Hyperkinesia	2 (1)
Metabolic and Nutritional	
Weight Loss	3 (1)
Weight Gain	2 (1)
Skin and Appendages	
Application Site Reaction	13 (4)
Eczema	2 (1)
Maculopapular Rash	2 (1)
Rash	2 (1)

* COSTART Version 5, 1995, was used to code the reported AEs by Body System and COSTART Term.

The most common AEs leading to discontinuation (≥2%) in the Long-Term Pediatric Population were application site reaction (4%), anorexia (3%), insomnia (3%), and nervousness (2%).

5.4.1 Summary for studies

At the time of this Safety Summary data cut-off, 7 pediatric subjects were receiving ongoing, open-label MTS treatment in the Long-Term Studies N17-013 and N17-021. In the Long-Term Pediatric Population (Studies N17-011, N17-013 and N17-021), 322 subjects have

been treated with MTS; 91 (28%) subjects have completed. The 3 most frequently reported reasons for discontinuation were "other" reasons (n=78, 24%), AEs (n=49, 15%), lost to follow-up (n=32, 10%), and lack of efficacy (n=28, 9%).

Subject/patient exposure to MTS was measured in days of treatment. In the Long-Term Pediatric Population, 322 subjects received at least 1 application of MTS in doses ranging from 6.25cm^2 to 50cm^2. In this population, 117 subjects received MTS for more than 6 months, 108 subjects received MTS for more than 9 months and 89 subjects received MTS for more than 1 year. The most common patch sizes used in the Long-Term Pediatric Population were MTS 12.5cm^2 (n=304, 94%) and/or 25cm^2 (n=244, 76%).

Evaluation of TEAEs in the Long-Term Pediatric Population revealed that 309 (96%) subjects reported at least 1 TEAE. The most commonly reported TEAEs (≥10%) were application site reaction (n=290, 90%), anorexia (n=113, 35%), insomnia (n=81, 25%), headache (n=72, 22%), viral infection (n=71, 22%), accidental injury (n=41, 13%), fever (n=40, 12%), cough increased (n=40, 12%), abdominal pain (n=39, 12%), vomiting (n=38, 12%), nervousness (n=36, 11%), weight loss (n=36, 11%), and pharyngitis (n=35, 11%). Other than application site reaction, these TEAEs are not unexpected in a pediatric population exposed to a stimulant and followed for an extended period of time.

When TEAEs in the Long-Term Pediatric Population were grouped by onset of days of MTS treatment from the start of the Long-Term Study, anorexia (n=66, 20%) and insomnia (n=54, 17%), 2 of the TEAEs commonly associated with stimulant use, were most frequently reported during Days 1-29 with fewer onsets during later time periods.

There were no deaths in the long-term studies. Three (3) SAEs have been reported in subjects participating in the long-term studies, 1 of dehydration, reported by an MTS-treated patient following unrelated elective surgery. An IND Safety Report for dehydration was submitted to the FDA on 05 August 2002. The 2 other SAEs were outbursts of hostility leading to hospitalization.

In the ongoing Long-Term Studies, 50 (16%) subjects have discontinued due to an AE. The most common AEs leading to discontinuation reported by subjects in the Long-Term Pediatric Population were application site reaction, insomnia, anorexia, and nervousness.

There was some association between increases in the rates of occurrence of anorexia and increases in most common patch size and cumulative patch size. Decreasing patch size was approximately as effective as discontinuation of treatment in achieving resolution for all TEAEs of clinical interest. For example, decreasing wear time generally was useful in resolving anorexia (loss of appetite; 68%) and insomnia (90%), as demonstrated in long-term study N17-021. This indicates that removing the patch earlier in the evening may be an effective strategy for those subjects who experience anorexia (decreased appetite) and insomnia.

Evaluation of clinical laboratory data, and vital signs other than weight loss for the Long-Term Pediatric Population did not suggest a clinically important effect of exposure to MTS. Early weight loss was observed in some subjects treated with MTS.

A relationship was observed between weight loss and exposure to MTS. Although treatment with MTS may be associated with reductions in expected height, weight, and body mass index (BMI), these reductions are small and attenuate with time. Although this does not eliminate the need for physicians to monitor growth, as they should for all stimulant-based ADHD formulations, it suggests that deficits in growth should not be a clinical concern for most subjects treated with MTS. This is entirely consistent with what is found in other methylphenidate products.

Results from the Long-Term Studies support evidence that MTS can potentially cause skin discomfort and irritation. There appears to be a dose relationship between skin discomfort and irritation and MTS dose, but overall, MTS was well tolerated.

6. SPECIAL SAFETY STUDY – DERMATOLOGICAL SENSITIVITY STUDY (N17-020)

6.1 Study N17-020

6.1.1 Design

Study N17-020 was a single-center study that evaluated MTS, PTS, and saline for the induction of contact sensitization by applications to the skin of healthy adult male and female subjects. The study design was single-blind crossover, and placebo-controlled with all subjects receiving all test articles.

Utilizing the Jordan-King modification of the Draize procedure, each subject initially received 50cm^2 MTS, 50cm^2 PTS, and 0.2mL saline (negative control) applied to the upper back for 48 (±4) hours for a total of 4 days per week and 72 (±8) hours for a total of 3 days per week. After Day 2 of the induction period, the MTS and PTS patch size was reduced from 50cm^2 to 25cm^2 because of an unexpectedly high incidence of adverse events leading to discontinuation. Thus, there were 9 induction applications to the same site on the back over a period of approximately 3 weeks (i.e., application of 3 treatments per week for 3 weeks). Sites were evaluated for irritation 30 minutes to 1 hour post-removal. Following the induction period, the subjects did not receive application of test articles for approximately 2 weeks.

At challenge, each test article was applied to a naïve site for 48 hours to test for reactions indicative of contact sensitization. The sites were scored 48 (±4) and 96 (±8) hours after patch application.

To confirm sensitization, subjects with positive challenge reactions were re-challenged approximately 8 weeks later with the test articles applied to a naïve site for 48 hours. Visual assessment of skin sensitization began at 30 minutes to 1 hour post-removal and ended at 96 hours post-removal.

6.1.1.1 Deaths, Serious Adverse Events and Discontinuations Due To Adverse Events

Deaths and Serious Adverse Events
No deaths were reported during Study N17-020.

Serious AEs were reported by 2 subjects during the study. Subject 135 was hospitalized on 16 December 2002, with severe diarrhea and chest pain; these events were considered by the Investigator to be possibly related to study medication. Subject 349 was hospitalized on 04 January 2003, with severe abdominal pain, which was considered unlikely to be related to study medication.

Subject 135/ETS (25cm^2), a 64-year-old male, received the first MTS application on 2 December 2002. The subject was withdrawn from the study because of hospitalization for severe, intermittent diarrhea (diarrhea) that started 15 December 2002 and severe, continuous pain chest (chest pain) that began on 14 December 2002. The subject also

reported moderate continuous asthenia (decreased energy) starting on 11 December 2002. The subject had received 4 days of treatment with the 50cm² MTS patch and 12 days of treatment with the 25cm² MTS patch.

Subject 135 was admitted to the hospital on 16 December 2002 for diarrhea and chest pain. The subject received 3 tablets of lomotril for the diarrhea. Hospital records indicated the subject's primary care physician felt the diarrhea was probably an acute gastroenteritis. There was no evidence of pre-existing cardiovascular or pulmonary conditions at Screening based on the medical history reported by the subject and the physical exam. Hospital records indicated that blood tests and a stress test conducted at the hospital ruled out myocardial infarction. An abnormal ECG was obtained at the hospital and the subject's primary care physician's impression was possible ischemia; however, the subject had a catheterization in 1999. Consult's impressions were: stress test unremarkable due to an inability to reach the target heart rate; some aortic valvular sclerosis noted; and chest X-ray was consistent with chronic obstructive pulmonary disease. The diarrhea resolved on 16 December 2002 and the chest pain resolved on 18 December 2002. Based on the information available, the Investigator considered the chest pain, diarrhea, and decreased energy to be possibly related to the study treatment.

Subject 349/SAB (25cm^2), a 30-year-old female, received the first MTS application on 02 December 2002. The subject was withdrawn from the study on 04 January 2003 because of hospitalization for severe, continuous abdominal pain (abdominal pain) that began that same day. The subject was admitted to the hospital on 04 January 2003 and released on 05 January 2003. The abdominal pain had started as moderate and continuous on 03 January 2003. Severe, intermittent abdominal pain (shooting abdominal pain) also began on 03 January 2003. After withdrawal from the study, the subject experienced mild, continuous abdominal pain (dull ache abdominal pain) beginning on 04 January 2003 and mild, intermittent abdominal pain (dull ache abdominal pain) beginning on 14 January 2003. Mild, continuous abdominal pain (tenderness abdominal region) began on 06 January 2003 and changed to mild and intermittent on 14 January 2003. The subject had last received MTS 11 days prior to withdrawal, after having received 4 days of treatment with the 50cm² MTS patch and 17 days of treatment with the 25cm² MTS patch.

On 03 January 2003, prior to hospitalization, the Subject 349 took simethicone (3 gel caps) for the abdominal pain. While hospitalized, the subject received intravenous meperidine (dose unknown) and intravenous ketorolac (dose unknown) for pain. The subject also received oxycodone (2 tablets) and methaxalone (dose unknown) post-discharge for pain. The abdominal pain resolved on 05 January 2003 and the shooting abdominal pain resolved on 04 January 2003. The continuous dull ache abdominal pain resolved on 04 January 2003 while the dull ache abdominal pain and the "tenderness abdominal region" resolved on 18 January 2003. Prior to beginning the study, the subject had gastric bypass surgery on 28 October 2002. Admission and discharge summaries from the hospital have been requested, but have not been forthcoming. The Investigator considered the abdominal pain to be unlikely related to the study treatment and likely related to the gastric bypass surgery the subject had had in October 2002.

Discontinuations Due To Adverse Events
A total of 33 subjects (17.0%) discontinued from the study due to AEs. The majority of those subjects discontinued treatment due to side effects associated with stimulant exposure. In this study evaluating MTS for skin sensitization, the patches were applied in ways not intended for clinical use (e.g., lack of titration, prolonged exposure, non-ADHD subjects). Patch size was decreased from 50cm^2 after 2 doses to 25cm^2 (Doses 3 - 9) due to these stimulant-related AEs.

6.2 Summary for study

A total of 183 subjects (94%) reported at least 1 TEAE. TEAEs were numerous during the second induction visit, so the original patch size was reduced by 50% (from 50cm^2 to 25cm^2) starting with the third induction visit. Most of the symptoms reported as TEAEs were considered to be related to methylphenidate. Since all subjects received all treatments during induction, TEAEs were not reported by individual test article. Thirty-three subjects (17.0%) discontinued from the study due to AEs. Two (2) subjects experienced SAEs; 1 subject experienced diarrhea and chest pain (both considered by the Investigator to be possibly related to study medication) and a second subject experienced abdominal pain (considered by the Investigator to be unlikely related to study medication). There were no deaths during the study. The most commonly reported TEAEs were insomnia (81%), headache (49%) and anorexia (31%).

There was definite sensitization to MTS in 18 of 133 subjects who completed the Challenge and Rechallenge Phases. In 3 others, the results were suggestive of sensitization. A full Challenge and Rechallenge Period was needed in 11 other subjects, and it is likely that at least 1 of these subjects would have become sensitized to MTS. Thus the rate of sensitization ranged from 13% - 22% under the conditions of this protocol. MTS was more irritating than both the placebo TS and the negative control (normal saline).

7. NONCLINICAL SUMMARY

Since methylphenidate has been on the market for several decades, a considerable amount of information has been published on its nonclinical toxicity profile. Further, only selected pertinent toxicity studies were conducted by Noven and Shire to support the safety of methylphenidate as a transdermal delivery system in the current application.

Acute behavioral toxicity of the *d*- and *l*-enantiomers and the racemate was evaluated using functional observational battery and rota-rod tests. Rats were dosed orally with vehicle, 1-50, 1-500 or 2-100mg/kg of *d-, l*-, or *d,l*-MPH respectively. Overall both tests showed a ranking of potency, namely *dl*- >*d*- > *l*- enantiomer.

Oral gavage dosing of rats for 90 days with *d*-, and *d,l*-MPH produced significant clinical observations and some changes in body weight , clinical pathology and organ weight, which mostly resolved after a 30-day recovery period. Based on body weight changes, No Observed Adverse Effect Level (NOAEL) for *d*-MPH was 20mg/kg/day, an area under the curve (AUC) exposure estimated to be in the region of 500ng.h/mL, and toxicities of *d*- and *d,l*-MPH were similar at equivalent doses of *d*-enantiomer. The NOAEL for *d*-MPH was 41-fold pediatric dose (1.5-fold based on exposure).

Oral gavage dosing of dogs for 90 days with *d*-, and *d,l*-MPH produced minimal, reversible toxicity. Based on bodyweight changes, NOAEL for *d*-MPH in beagle dogs was 3mg/kg/day (an AUC exposure estimated to be in the region of 38ng.h/mL) and toxicities of *d*- and *d,l*-MPH were similar at equivalent doses of *d*-enantiomer. The NOAEL for *d*-MPH was 6-fold the clinical pediatric dose (0.11-fold based on AUC of *d*-MPH).

d-, *l*- and *d,l*-MPH were evaluated in the bacterial reverse mutation and mouse lymphoma assays with and without S9, and in a bone marrow micronucleus test in mice. Methylphenidate-associated toxicity was observed in the mammalian tests, but none of the 3 compounds tested induced mutagenic or clastogenic effects. The results were consistent with the conclusion that methylphenidate does not present a carcinogenic risk to humans.

In a rat oral gavage developmental toxicity study, a reduction in maternal body weight gain for the high doses (20 and 40mg/kg *d*-MPH and racemate respectively), and for the 6mg/kg *d*-methylphenidate groups may not have been attributable to maternal toxicity, as methylphenidate is a known appetite suppressant. Maternal reproductive parameters were unaffected and there were no gross fetal, soft tissue or skeletal alterations. Some fetal increases in all alterations for 6 and 20mg/kg *d*-MPH were principally reversible delays in sternal and pelvic variations; these were not considered treatment-related because the associated litter incidences were not statistically different between groups and incidences were within the historical control range. Neither *d*- nor *d,l*-MPH was considered a selective developmental toxicant to the rat. The high doses were therefore the NOAEL for developmental effects; the high dose for *d,l*-MPH was 40mg/kg/day (AUC exposure of 1500ng.h/mL to *d*-MPH). The NOAEL for *d,l*-MPH was 41-fold the clinical pediatric dose (about 5-fold based on exposure).

In a rabbit oral gavage developmental toxicity study, maternal reproductive parameters were unaffected and there were no gross fetal, soft tissue or skeletal alterations. Neither *d*- nor *d,l*--MPH were considered selective developmental toxicants based on these studies. The high doses were therefore the NOAEL for developmental effects; the high dose in the rabbit for *dl*-methylphenidate was 200mg/kg/day (AUC exposure of 500ng.h/mL to *d*-MPH). The NOAEL for *d,l*-MPH was 204-fold pediatric dose (1.5-fold based on *d*-MPH AUC).

A rat peri- and post-natal study, dosing F_0 rats by gavage, using *d*-MPH and racemate, showed findings that included reduced maternal body weight gain in both high doses, and hyperreactivity-related signs; the equivalent high doses, of 20 and 40mg/kg/day of *d*- and *d,l*-MPH, respectively, showed similar changes, or slightly greater changes for the racemate. However, the F_0 generation did not show any abnormal natural delivery or litter observations; nor did F_1 animals show any significant changes in reproductive parameters. The high doses were therefore the NOAEL for reproductive effects; the high dose for *d,l*-MPH was 40mg/kg/day (AUC exposure of 1600ng.h/mL to *d*-MPH). The NOAEL for *d,l*-MPH was 41-fold the clinical pediatric dose (5-fold based on *d*-MPH AUC).

There was a tendency for dosing with racemate to yield higher C_{max} (maximum concentration) and AUC systemic exposures to *d*-MPH than the equivalent dose of *d*-MPH.

Radiolabeled brain kinetic studies in baboons and rats using the racemate showed a higher global uptake of radioactivity in the brain of both species for the *l*-enantiomer (as a metabolite) than for the *d*-enantiomer.

A study using single high doses (25, 50 and 100mg/kg) in mice decreased hepatic CYP450, inhibited CYP1A and CYP2E1 catalytic activity and decreased polypeptide levels of CYP3A. Lower oral doses for 2 weeks (2.5, 5 and 10mg/kg/day) decreased hepatic CYP450, at 5 and 10mg/kg and inhibited and decreased its polypeptide levels. However other studies using human hepatic microsomes *in vitro* indicated that *d*-, *l*-, and *d,l*-MPH were not reversible- or irreversible-type inhibitors of cytochromes P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 and there was no substantive difference in inhibition potential between *d*- and *l*-MPH.

Animal toxicity studies of dermal application of MPH petrolatum in 3 species demonstrated macro- and microscopic signs of irritation at the site of application, but no evidence of pre-neoplastic change in the skin. No other opthamological, clinical pathological or necroscopic effects were found in these studies.

The potential for MTS to induce dermal toxicity has been investigated in rabbits. In 2 studies, 2 x 2.5 cm^2 patches, each containing 6.75 mg MPH, and 2 placebo patches were applied for 24 hours to the backs of rabbits. Application sites were evaluated for erythema and edema immediately prior to removal and up to 48 hours after removal. Both the active and placebo patches produced well defined to moderate-to-severe erythema and very slight-to-moderate edema in intact and abraded skin, thought to be due to the mechanical trauma resulting from patch removal. Both active and placebo patches were therefore considered to be moderate irritants. No evidence of necrosis was found. Microscopic changes included mild epidermal inflammation, minimal to mild epidermal hyperplasia, and minimal hyperkeratosis and indicated that the active test material was generally well tolerated but was slightly more

irritating than the placebo material. A further study investigated the relative level of irritation in intact and abraded sites and demonstrated that abrading the skin did not affect the results.

The potential for MTS to act as a delayed contact sensitizing agent has been studied using the standard occluded patch guinea pig model. MTS was not found to act as a dermal sensitizer in this model, in which animals were treated with repeat application of MTS or placebo patch 3 times a week for 3 weeks.

In summary, animal dermal toxicity studies have shown MTS to be a moderate irritant but have demonstrated that MTS does not act as an agent for delayed contact sensitization.

8. OVERALL SUMMARY AND CONCLUSIONS

8.1 Deaths, SAEs and Discontinuations due to AEs in Pivotal Studies (SPD485-201 and –302)

Few subjects discontinued due to adverse events (AEs) indicating good acceptance of MTS by subjects, parents, and physicians. The most common AEs leading to discontinuation reported by subjects were application site reaction, anorexia, insomnia, and nervousness. The majority of subjects reporting insomnia and anorexia did not discontinue MTS therapy because of these events. In the pivotal 9-hour wear time studies (SPD485-201 and –302), 15 MTS-treated subjects were discontinued early due to adverse events. Deaths and serious adverse events did not occur in the 9-hour wear time studies included in the Resubmission.

8.2 Summary of TEAEs of Clinical Interest for Approved ADHD Products

For comparison with MTS data reported in this Safety Summary, the frequencies of insomnia, anorexia and weight loss (based on package inserts) are summarized in the Text Table below for approved oral methylphenidate ADHD products.

Table 31: Summary of Treatment-Emergent Adverse Events of Special Interest for Approved ADHD Products

Adverse Event	(%) of subjects reporting TEAEs			
	CONCERTA® (N=106)	FOCALIN™ (N=79)	METADATE CD® (N=188)	Ritalin LA® (N=65)
Anorexia	4%	6%	9%	3%
Insomnia	4%	NR	5%	3%
Weight loss	NR	NR	NR	NR

NR: Not reported

CONCERTA®: Treatment-emergent events in a 4-week, placebo-controlled clinical trial, regardless of causality, for which the incidence for patients treated with CONCERTA was at least 1% and greater than the incidence among placebo-treated patients.

FOCALIN™: Events, regardless of causality, for which the incidence for patients treated with Focalin was at least 5% and twice the incidence among placebo-treated patients.

METADATE CD®: Treatment-emergent events in a pool of 3-4 week clinical trials, regardless of causality, for which the incidence for patients treated with METADATE was at least 5% and greater than the incidence among placebo-treated patients.

Ritalin LA®: Treatment-emergent adverse events with an incidence >2% among Ritalin LA-treated subjects during a 2-week, double-blind clinical study.

8.3 Summary of Safety Data from the Placebo-Controlled Studies (SPD485-201 and –302)

Study SPD485-201 was an Analog Classroom study that consisted of an open-label dose optimization period of 5 weeks where Investigators could increase patch size to optimal effect on ADHD symptoms and for tolerability to methylphenidate and the patch, followed by a 2-week Analog Classroom period. The dose of MTS or PTS was fixed for the week prior to the first classroom session. Subjects were randomized to placebo or active MTS at the optimized patch size. Study SPD485-302 was a 7-week outpatient study in which eligible subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA®, or matching placebo. The study had a 5-week double-blind stepwise dose optimization period to titrate 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). Subjects remained on the optimized dose for 2 weeks.

The safety assessments conducted in these studies indicate that the overall safety profile of MTS is consistent with the published results of other approved methylphenidate products. The majority of adverse events were mild to moderate intensity, transient and typically resolved with continued dosing. There were no deaths or SAEs reported in either study. In the pivotal 9-hour wear time studies (SPD485-201 and –302), 15 MTS-treated subjects were discontinued early due to adverse events.

MTS was well tolerated during both the dose-optimization and the fixed-dose periods. During the open-label dose optimization periods, the most common adverse events were headache, decreased appetite/anorexia, abdominal pain and insomnia. These events are well known adverse drug reactions of methylphenidate administered orally. The incidence of these TEAEs is not higher than the numbers in the approved package labeling for these drugs. The

low incidence of adverse events in the double-blind period is likely due to the selection of subjects and doses that were optimized in the open-label period. Thus subjects were selected to be tolerant of their dose of MTS as well as for the behavioral effects.

The incidence of stimulant-related adverse events in previous MTS studies (with longer wear times than 9 hours) is presented in the Text Table below.

Table 32: Summary of Adverse Events in Previous MTS Studies (≥ 9-hour Wear Time)

Adverse Event*	MTS N=202		Placebo N=212	
	N	%	N	%
Headache	29	(14)	13	(6)
Abdominal Pain	27	(13)	12	(6)
Anorexia	68	(34)	4	(2)
Weight Loss	11	(5)	1	(1)
Insomnia	47	(23)	8	(4)
Twitching	10	(5)	0	

* COSTART Version 5, 1995, was used to code the reported AEs by Body System and COSTART Term.

The overall safety profile of MTS worn for 9 hours was similar to that of CONCERTA® and both had a higher incidence of adverse events than did placebo subjects. The most frequent adverse events reported in the active treatment arms of Study SPD485-302 are presented in the Text Table below. The adverse events occurring at a slightly higher frequency in the MTS group include decreased appetite, insomnia, anorexia and tics. The remainder of the events in the table occurred at similar frequencies in both MTS and CONCERTA® groups.

Table 33: Summary of Treatment-Emergent Adverse Events – Study SPD485-302 (≥5% in MTS and >2X Placebo)

Adverse Event*	Number (%) of subjects reporting TEAE					
	MTS (N=98)		CONCERTA® (N=91)		Placebo (N=85)	
No. subjects with ≥1 TEAE	74	(76)	63	(69)	49	(58)
Decreased appetite	25	(26)	17	(19)	4	(5)
Insomnia	13	(13)	7	(8)	4	(5)
Nausea	12	(12)	7	(8)	2	(2)
Vomiting	10	(10)	9	(10)	4	(5)
Weight decreased	9	(9)	7	(8)	0	
Tic	7	(7)	1	(1)	0	
Affect lability	6	(6)	3	(3)	0	
Nasal congestion	6	(6)	3	(3)	1	(1)
Anorexia	5	(5)	3	(3)	1	(1)
Nasopharyngitis	5	(5)	4	(4)	2	(2)

* MedDRA Version 7.0 was used to code the reported AEs by System Organ Class (SOC) and Preferred Term.

These methylphenidate related events occurred at a much lower frequency in this study where patch application time was 9 hours compared to the previous Noven studies where the patch wear time was 12 hours. Decreasing the wear time from 12 to 9 hours, decreased the relative incidence of adverse events. The incidence of adverse events in MTS was generally similar to that in CONCERTA® group. The majority of events reported in both the MTS and CONCERTA® groups were mild to moderate in intensity, transient and typically resolved with continuation of treatment.

While MTS had a slightly higher percentage of TEAEs than did CONCERTA®, the numbers are within those reported in the literature for methylphenidate treatments. The adverse event of tics occurred in a considerably higher number of subjects in the MTS group than in the CONCERTA® group. Overall, there were 9 episodes of tic in 7 MTS treated subjects while there was 1 event of tic in a single CONCERTA® subject. One (1) subject discontinued due to tic in the MTS group. The remaining subjects had tics of mild intensity. All subjects continued in the study with no treatment of tics required. Most tics resolved within 8 – 9 days and only 4 subjects continued to experience tics throughout the study. The incidence of tic in this study is similar to the incidence reported in the literature in ADHD children treated with a variety of stimulants. The literature cites an incidence of tic with methylphenidate treatment of between 5%[1] and 7%.[2] Thus, in this study the numbers of subjects experiencing tics are within the incidence, intensity and outcomes reported in the literature for methylphenidate therapy of ADHD.

The issue of insomnia and sleep disturbances was addressed using a sleep questionnaire (CSHQ) specifically designed to assess sleep disturbances in children of school age. At

Baseline, the population had no significant sleep disturbances outside of normal variations as reported by parents. Throughout the study, the CSHQ total score decreased in all groups. Similarly, the number of items assessed as a problem on the sleep questionnaire also decreased in all 3 groups. The lack of overall effect of MTS on sleep is further confirmed by the scores in the double-blind classroom periods from Study SPD485-201. The groups appeared to be different between MTS and PTS in the first period. However, after crossing over to the alternate treatment, the results are similar indicating that MTS was having minimal to no effect on sleep as evaluated by the CSHQ. It appears that while there is a small proportion of the childhood population that experiences insomnia or sleep problems with methylphenidate treatment, most subjects have no changes in sleep habits or problems while treated for ADHD with methylphenidate.

8.4 Summary of Safety Data from the Open-Label Studies (N17-011, -013, and –021)

Based on the long-term exposure data collected for this Safety Summary, the TEAE and clinical evaluations indicate an acceptable safety profile for MTS in the treatment of pediatric ADHD. Commonly encountered TEAEs were those expected to be associated with use of stimulant medication, (insomnia, anorexia, and headache) or associated with the transdermal delivery system (application site reaction). There were no deaths and 3 SAEs reported in these studies.

A total of 45 (24%) subjects were withdrawn from the study because of AEs. The most common AEs leading to discontinuation were application site reaction, anorexia, insomnia, and nervousness. Anorexia and insomnia were most frequently reported during Days 1 - 29 with fewer onsets during later time periods. The majority of subjects reporting insomnia and anorexia did not discontinue MTS therapy because of these events.

An analysis of trend in monthly change in height, weight, and body mass index (BMI) in Study N17-021 indicated that subjects continued to grow during the study (overall median rate of 0.16in/month during the entire course of the study) with little observable relationship to cumulative patch size; the median trend in weight gain was highest for subjects in the highest range of cumulative patch size (patch size greater than 16000cm^2), the trend at this cumulative patch size was the only trend significantly greater than zero. The mean monthly trends in BMI were negative and significantly different from zero at cumulative patch sizes below 16000cm^2, but the trend was not significantly different from zero at the highest cumulative patch size range with a median value of zero. These results suggest that effects of MTS on growth may diminish with longer exposure. Other studies have shown similar results with long-term stimulant exposure. In a study of long-term exposure to MPH, the investigators observed decreases in the inhibition of height gain after 2 years of treatment. Similar results were seen in a study of long-term exposure to dextroamphetamine. In the current study, growth rate did not seem to have a strong relationship to MTS treatment over the duration of exposure.

Most occurrences of TEAEs of interest (anorexia, headache, insomnia, nervousness, and weight loss) were mild to moderate and of limited duration. There was some association between increases in the rates of occurrence of anorexia and increases in most common patch size and cumulative patch size. The relationship between these 2 measures was less

clear for insomnia and nervousness. Only anorexia showed a consistent pattern of increased rate of occurrence with increased mean daily patch size. There was no clear relationship between any of these measures and headache or weight loss. When analyzed for severity and patch size, the patch sizes did not correlate with severity. Most of the severe TEAEs occurred at the lower patch sizes. Decreasing patch size was approximately as effective as discontinuation of treatment in achieving resolution for all TEAEs of clinical interest. Decreasing wear time was also associated with lower incidences of anorexia and insomnia in achieving resolution. This indicates that removing the patch earlier in the evening may be an effective strategy for those subjects who report anorexia (decreased appetite) and insomnia.

There were no clinically significant changes in hematology, serum chemistry or pulse rate in MTS-treated subjects. Increased systolic blood pressure was reported as clinically significant for 2 subjects under the CONCERTA® treatment, for 1 subject under the 12.5cm^2 MTS, for 2 subjects under the 25cm^2 MTS and for 1 subject under the 37.5cm^2 MTS and diastolic blood pressure increases were reported as clinically significant for 1 subject each under the 4 study treatments in study SPD485-102. There was a modest dose relationship between skin discomfort and irritation and MTS dose, but overall, MTS was well tolerated.

8.5 Summary of Growth Data

Height and weight data from the long-term, open-label Study N17-021 was assessed using z-score analyses compared to normalized height and weight data from the Centers for Disease Control and Prevention (CDC) historical control growth charts. The results demonstrated that for subjects who participated for 2 or more years, the mean deficits were 2.0cm for height, 3.9kg for weight and 1.5 units for BMI. The mean deficit rates per year were 0.68cm for height, 1.3kg for weight and 0.49 units for BMI. The results are similar to those reported for other stimulants. Subjects who dropped out tended to have smaller growth deficits than subjects who did not drop out.

Subjects with ADHD treated with MTS demonstrated continued growth during the treatment phase of observation. The growth deficits attenuated over time; the rate of growth was mostly negative in the first year of the study but mostly positive in the third year of the study.

Growth deficits were dose related for weight and BMI but not height. The correlation between the height and weight deficits was 0.44, which suggests that some of the height deficit may be due to the stimulant-induced loss of appetite. Prior stimulant therapy predicted small deficits for weight and BMI but not height.

8.6 Summary of Skin Sensitization Data

Results from the clinical studies indicate that MTS is potentially irritating. Application site reaction was reported frequently by subjects during MTS treatment. The majority of ratings of discomfort and dermal irritation were mild or non-existent. A dermal irritation study in adult volunteers (N17-017) suggested that application of the MTS to irritated skin is more irritating than to normal skin and alters the absorption of methylphenidate.

In a special study examining the sensitization potential of MTS in a laboratory setting (N17-008), 1 patient out of 116 had confirmed sensitization. An additional patient was suspected of

being sensitized to MTS, but the observation could not be confirmed due to the lack of follow-up. In a second sensitization study (N17-020), the sensitization rate to MTS ranged from about 13% - 22%. MTS was significantly more irritating than both the placebo TS and the negative control (normal saline) in this study.

8.7 Conclusions

The safety assessments indicate that the overall safety profile of MTS is consistent with the published results of other approved methylphenidate products. The majority of adverse events were mild to moderate in intensity, transient and typically resolved with continued dosing. Commonly encountered TEAEs were those expected to be associated with use of stimulant medication, (insomnia, anorexia, and headache) or associated with the transdermal delivery system (application site reaction). Decreasing the patch wear time from 12 to 9 hours decreased the relative incidence of adverse events. The adverse events in MTS-treated subjects were similar to those in the CONCERTA® group. There was some association between increases in the rates of occurrence of anorexia and increases in most common patch size and cumulative patch size. Decreasing patch size was approximately as effective as discontinuation of treatment in achieving resolution for all TEAEs of clinical interest. Decreasing wear time was also effective for anorexia (68%) and insomnia (90%) in achieving resolution. This indicates that removing the patch earlier in the evening may be an effective strategy for those subjects who report anorexia (decreased appetite) and insomnia.

Few subjects discontinued due to AEs indicating good acceptance of MTS by subjects, parents, and physicians. The most common AEs leading to discontinuation reported by subjects were application site reaction, anorexia, insomnia, and nervousness. The majority of subjects reporting insomnia and anorexia did not discontinue MTS therapy because of these events.

A relationship was observed between weight loss and exposure to MTS. Although treatment with MTS may be associated with reductions in expected height, weight, and BMI, these reductions are, on average, small, attenuate with time, and do not cause the large majority of subjects to become extremely short or thin. Although this does not eliminate the need for physicians to monitor growth, as they should for all stimulant formulations, it suggests that deficits in growth should not be a clinical concern for most subjects treated with MTS, especially given the range of strategies available to manage these deficits.

There were no clinically significant changes in hematology, serum chemistry, or pulse rate in MTS-treated subjects. Small mean increases in systolic and diastolic blood pressure and heart rate were observed and are consistent with the known effects of methylphenidate. There was a modest dose relationship between skin discomfort and irritation and MTS dose, but overall, MTS was well tolerated. Application site reaction was commonly reported.

In summary, the AE and clinical evaluations conducted during the clinical development program indicate an acceptable safety profile for MTS. Because MTS is a mild dermal irritant, application site reaction may be a common yet tolerable event in MTS-treated subjects. No other unexpected safety risks beyond those commonly associated with stimulant medications were identified.

9. REFERENCES

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