CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	021514
Priority or Standard	Standard
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Division / Office	Division of Psychiatry Products
Reviewer Name(s)	Christina P. Burkhart, M.D.
Review Completion Date	April 7, 2010
Established Name	Methylphenidate Transdermal System
(Proposed) Trade Name	Daytrana
Therapeutic Class	Stimulant
Applicant	Shire Pharmaceuticals
Formulation(s)	Transdermal Patch
Dosing Regimen	12.5, 18.75, 25, 37.5 cm^2 patches
Indication(s)	Attention Deficit Hyperactivity Disorder
Intended Population(s)	Adolescents (ages 13 to 17)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Division take an approvable action for sNDA 21514: methylphenidate transdermal system in the treatment of attention deficit hyperactivity disorder in adolescents aged 13 to 17. In one (1) adequate, well-controlled trial (SPD485-409), the sponsor demonstrated the efficacy of the methylphenidate transdermal system (MTS) in the treatment of adolescent subjects with a primary psychiatric diagnosis of attention deficit hyperactivity disorder (ADHD), as measured by a significant improvement compared to placebo in the Attention Deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS-IV) total score at the end of 7 weeks of treatment. Secondary efficacy measures, including improvement in the Conners' Parent Rating Scale Revised (CPRS-R) total scores, CPRS-R subscales, ADHD subscales, Clinical Global Impressions-Improvement (CGI-I), and Parent Global Assessment (PGA) supported the primary efficacy analysis. MTS was reasonably safe in this trial and in an additional 6 month open-label extension trial (SPD485-410) and a 29 day open-label pharmacokinetic trial (SPD485-106). Based on the data from these 3 trials, there were no important differences in the safety profile compared with the previously known safety profile of MTS as currently approved for the treatment of ADHD in children.

1.2 Risk Benefit Assessment

Most children do not outgrow ADHD but continue to have symptoms as adolescents. According to Barkley (2006),[1] hyperactive children followed to young adulthood had significantly lower educational and job performance, fewer close friends, earlier sexual intercourse and early parenthood. Therefore treatment of ADHD in adolescence can be important.

Methylphenidate has been a mainstay of treatment for ADHD for many years and has a well-known, acceptable safety profile. Since the US approval of MTS through 31 December 2008, it is estimated that more than (b) (4) MTS patches have been dispensed resulting in an estimated (b) (4) person-years of exposure. Like other long-acting methylphenidate preparations, the methylphenidate transdermal system (MTS) offers the convenience of once-daily dosing. MTS also offers some unique benefits. These benefits include the ability to tailor wear-time by removing the patch earlier than

[1] Barkley, Russell: Young Adult Outcome of Hyperactive Children: Adaptive Functioning in Major Life Activities. J. Am. Acad. Child Adolesc. Psychiatry 45:2, February 2006.

9 hours and reduced fluctuations in plasma methylphenidate levels. The MTS also offers an alternative for adolescents who find it difficult to swallow pills.

MTS shares risks similar to other methylphenidate preparations. These include decreased appetite, irritability, nausea, insomnia and decreased weight. In addition, just as MTS has some unique benefits, it also has some unique risks. These unique risks primarily concern application site reactions. MTS has problems primarily with erythema at the application site. Some subjects have had more serious reactions but most have had just the mild erythema. Through postmarketing data, we have learned that there have been significant problems with tight release and adhesive transfer. This remains a concern and the sponsor and the Agency are addressing it. However, it appears that there is a significant subset of patients who find the MTS very effective and useful. Based on the evidence of efficacy and safety in these trials, this reviewer believes that the benefits outweigh the risks and that MTS should be approved for the treatment of ADHD in adolescents.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance would be adequate to manage the risk-benefit profile of MTS in the treatment of ADHD in adolescents. Daytrana also currently has a Medication Guide.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division will discuss possible Phase 4 commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Methylphenidate Transdermal System (MTS) is an adhesive-based matrix transdermal system (patch) that is applied to intact skin. Methylphenidate's chemical name is α-phenyl-2-piperidineacetic acid methyl ester. It is a CNS stimulant currently approved in the United States for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

MTS is supplied as 12.5, 18.75, 25, and 37.5cm^2 patches that deliver respective doses of 10, 15, 20, and 30mg when administered for the recommended 9-hour daily application period.

2.2 Tables of Currently Available Treatments for Proposed Indications

Daytrana is the only stimulant transdermal system approved for the treatment of ADHD in any population. Daytrana is currently approved for the treatment of ADHD in children 6 to 12 years old.

Table 1: Medications Used in the Treatment of ADHD

Drug	Short-acting	Intermediate-acting	Extended Release
Methylphenidate	Ritalin Metadate Methylin	Ritalin SR Metadate ER Methylin ER	Concerta Metadate CD Ritalin LA
Dexmethylphenidate	Focalin	--	Focalin XR
Amphetamine	Dexedrine Dextrostat	Adderall Dexedrine spansule	Adderall XR
Lisdexamfetamine	--	--	Vyvanse
Atomoxetine (SNRI)	--	--	Strattera

2.3 Availability of Proposed Active Ingredient in the United States

Methylphenidate is widely available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Oral formulations of methylphenidate and other stimulants have been associated with serious cardiovascular events including sudden death, CVA, treatment-emergent psychotic or manic symptoms, increased blood pressure, visual disturbances, decreased appetite, weight loss, abdominal pain, delayed sleep onset, and decreased growth. Children may also experience motor tics, most of which are transient.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original NDA submission, submitted by Noven Pharmaceutical, was based on studies in pediatric and adult subjects conducted in support of a 12-hour wear time and higher patch strength for MTS. In 2003, the Agency acknowledged the efficacy of MTS in treating children with ADHD but issued a Non-Approvable Letter due to a sub-optimal safety profile.

Shire conducted and submitted additional studies in children employing a 9-hour MTS wear time. One additional submission was made to address the final remaining issues from the NDA review. This regulatory history is detailed in the table below.

Table 2: New Drug Application Summary for NDA 21-514

Table 1: New Drug Application Summary for NDA 21-514				
Submission Type	**Submission Date**	**Date of FDA Action**	**Action Taken**	**Clinical Program**
Original NDA (Original Noven Development Plan)	27 June 2002	25 April 2003	Non-Approvable	12-hour wear time
Non-Approvable NDA Resubmission	28 June 2005	23 December 2005	Approvable	9-hour wear time
Approvable NDA Resubmission	09 February 2006	06 April 2006	Approval	9-hour wear time

(2.2 CTD Introduction, p. 2)

In accordance with Section 2 of the Pediatric Research Equity Act, Shire submitted Study SPD485-409, the pivotal efficacy study for this submission, to satisfy a post-approval commitment to conduct a study in adolescents (aged 13-17) with ADHD.

2.6 Other Relevant Background Information

Discussions have been ongoing between the applicant and the Agency to gain resolution of product quality issues relating to the problems patients and caregivers have had with removing the release liner of MTS patches ("tight release"). There have also been problems with adhesive transfer. (b) (4)

This information is relevant to this sNDA as study SPD485-409 used patches with the original (b) (4) release liner, and studies SPD485-106 and SPD485-410 used patches with the (b) (4) release liner. According to Shire, the use of the two different release liners has not impacted the safety and efficacy conclusions that are included in this sNDA.

In the filing letter for this sNDA (10/30/2009), the Division noted that "we continue to have grave concerns about your current product related to tight release and adhesive transfer." The Agency strongly reiterated the recommendation that the best resolution to the tight release issue was to reformulate the adhesive matrix. Shire was also instructed that the new formulation must demonstrate bioequivalence with the approved formulation. The Agency also recommended that Shire conduct an *in vivo* adhesion study during the bioequivalence trial and assess sensitization and irritation potentials.

Shire and Noven have undertaken a root cause analysis to determine a solution for the product quality issues. They hope to reach consensus on the solutions with the Agency.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

I reviewed the individual clinical study reports, safety and efficacy summaries, relevant narratives and case report forms (specifically for AEs/Discontinuation of study drug), correspondence with the sponsor, raw data sets (JMP files) and the literature review. I performed a random audit of the accuracy of summary data tables in the individual clinical study reports by comparing the results in the tables with the summary data obtained from the raw data sets. The submission was adequately organized and electronic navigation was not difficult .

3.2 Compliance with Good Clinical Practices

All clinical studies included in this submission appear to have been conducted in accordance with International Conference on Harmonisation Good Clinical Practice, the principles of the declaration of Helsinki, the US Code of Federal Regulations, and the European Union Clinical Trials Directive.

The Division of Scientific Investigations (DSI) inspected two study sites. At one site, 10 subjects were screened and enrolled into the study. Nine (9) subjects completed the study. At the other site, 12 subjects were screened and 4 were enrolled. Three (3) subjects completed the study. At both sites, the study appears to have been conducted adequately, and the data generated by the sites appear acceptable in support of the respective indication.

3.3 Financial Disclosures

Shire's records indicate that (b) (6) have received "significant payments of other sorts" as defined in 21 CFR 54.2(f).

(b) (6) has disclosed a "significant equity interest" as defined in 21 CFR 54.2(b).

Since Study (b) (6) was a double-blind, randomized trial, no investigator would have known the sequence of potential treatment assignments. In addition, multiple sites were utilized and enrollment was limited at each site to ensure that no one site could provide a preponderance of data. Therefore, it is unlikely that the above investigators significantly biased the results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no Chemistry, Manufacturing, and Controls (CMC) information being provided in this submission as there is no new information to report.

As discussed in Section 2.6, there have been problems with the tight release of the liner and adhesive transfer. (b) (4)

4.3 Preclinical Pharmacology/Toxicology

The results of two non-clinical safety studies in juvenile rats were submitted 4 January 2010 with a Four Month Safety Update. The results of the two studies do not change the safety profile of Daytrana.

The studies used an oral MPH formulation. The first study was a preliminary oral toxicity study in the neonatal/juvenile rat (R01525M-SPD503). The purpose of the study was to investigate the influence of guanfacine and methylphenidate, either alone or concurrently, when administered to neonatal/juvenile rats for 15 days. From this data, a suitable dose for a subsequent main juvenile 53 day toxicity study was determined. It was concluded that the high dose level for the combination group in the main juvenile

toxicity study should not exceed 1mg/kg/day of guanfacine and 50mg/kg/day of methylphenidate.

The second study was an oral (gavage) developmental toxicity study in the neonatal/juvenile rat (R01587M-SPD503). The purpose of this study was to investigate the influence of guanfacine and methylphenidate, either alone or co-administered, when administered to neonatal/juvenile rats for 53 days. Based on the results obtained in this study, it was concluded that the NOAEL for male and female juvenile rats was 1mg/kg/day guanfacine and 50mg/kg/day methylphenidate, administered either alone or in combination. The results of the toxicokinetic evaluations indicated that when 1mg/kg/day guanfacine was co-administered with 50mg/kg/day methylphenidate, higher systemic exposure was achieved than when 1 mg/kg/day guanfacine was administered alone. However, this high combination of guanfacine and methylphenidate was considered unlikely to have any long-term detrimental effect and had no adverse effect on fertility or embryonic survival.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Methylphenidate is a CNS stimulant. Its mechanism of action is not known. According to labeling, methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.

4.4.2 Pharmacodynamics

Methylphenidate is a racemic mixture of the *d*- and *l*-enantiomers. The *d*-enantiomer is the more pharmacologically active. *L*-MPH is likely to contribute only 5-10% of the total pharmacological effect of Daytrana.

4.4.3 Pharmacokinetics

The amount of methylphenidate absorbed systemically is a function of both wear time and patch size. Peak plasma levels of MPH are reached at about 9 hours after single application and 8 hours after repeat patch application.

On single dosing with Daytrana, there is a delay of 2 hours before *d*-MPH is detectable. On repeat dosing, low doses of *d*-MPH are detected earlier.

Transdermal absorption of MPH may increase with repeat dosing; on average, steady-state is likely to have been achieved by approximately 14 days of dosing.

With Daytrana, exposure to *l*-MPH is 35% to 65% lower than exposure to *d*-MPH. Little if any *l*-MPH is detectable after administration of an oral MPH formulation.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study Number	Design	Objectives	Test Product; Dosage Regimen	N	Subjects	Duration	Efficacy Results
SPD485-409 **Safety and Efficacy**	Randomized, double-blind, multi-center, parallel group, dose optimization, Placebo-controlled Primary Efficacy Measure: ADHD-RS-IV	Short-term efficacy and safety of MTS vs. placebo in adolescents aged 13-17	12.5, 18.75, 25 and 37.5cm^2 or matching placebo; one patch titrated to acceptable response, worn daily for 9 hours	217 162M 55F	Adolescent subjects (13-17 years of age) with ADHD	5 weeks dose optimization Plus 2 weeks maintenance	-9.96 (-13.39, -6.53) p < 0.001
SPD485-410 **Safety**	Open-label, multicenter, extension; uncontrolled Primary Efficacy Measure: ADHD-RS-IV	Long-term safety and efficacy of MTS in adolescent subjects aged 13-17	12.5, 18.75, 25 and 37.5 cm^2 MTS or matching placebo; one patch titrated to acceptable response, worn daily for 9 hours	162 121M 41F	Adolescent subjects (13-17 years of age) with ADHD	6 months (5 weeks optimization period; 5 months maintenance period)	
SPD485-106 **PK**	Open-label, randomized, multi-center; forced titration	Describe the PK in pediatric and adolescent subjects aged 6-17 yrs after single and escalating doses of MTS; determine extent of accumulation after multiple escalating doses of MTS	**Part I-Fixed Single/Multiple Doses** Treatments A and B (9hr/day): Day 1 single MTS dose (12.5 cm^2); Day 4 MTS (12.5 cm^2) daily for 7days Treatment C: Day 1 single oral dose Concerta (18 mg); Day 4 Concerta (18 mg) daily for 7 days	71 38M 33F	Pediatric and adolescent subjects with ADHD	29 days	

			Part II-Dose Escalation Treatment A (9h/day): MTS (12.5 cm^2) daily for an additional 3 weeks Treatment B (9h/day): Escalating doses of MTS (18.75, 25, and 37.5 cm^2) at weekly intervals; maintained on daily doses at each dose level for 7 days Treatment C: Escalating doses of Concerta (27, 36 and 54 mg) at weekly intervals; maintained at each dose level for 7 days				

5.2 Review Strategy

The clinical study report of the short-term placebo-controlled efficacy Study SPD485-409 was reviewed in detail. Data sets were reviewed and analyzed and compared to the summary data in the report. The Clinical Overview, the Summary of Clinical Efficacy, the Summary of Clinical Safety, applicable literature references, labeling, and the case narratives/CRFs of subjects who discontinued or had serious adverse events were also reviewed in detail. Monthly postmarketing reports submitted by Shire detailing problems with tight release and adhesive transfer were also reviewed.

Dr. Yeh-Fong Chen reviewed the accuracy of the statistical analysis and Dr. Andre Jackson reviewed the pharmacokinetic data in Study SPD485-106.

5.3 Discussion of Individual Studies/Clinical Trials

The submission for this efficacy supplement comprises 3 studies in adolescents with ADHD: a short-term placebo-controlled efficacy study (SPD485-409), a long-term open-label safety extension study (SPD485-410), and a pharmacokinetic study (SPD485-106). Study SPD485-409 is discussed fully in Sections 6 and 7. The design and results

of Study SPD485-410 and Study SPD485-106 are discussed below in Section 5.3. The safety results of these studies will be discussed in Section 7.

Study SPD485-409
Please see Section 6 and 7 for a full discussion of Study SPD485-409.

Study SPD485-410

Study SPD485-410 was an open-label extension study of Study SPD485-409. It was designed to evaluate the safety of MTS for approximately 6 months in adolescent subjects diagnosed with ADHD who had previously received study medication (MTS or placebo) in Study SPD485-409. Efficacy was assessed using the same measures as were used in Study SPD485-409: Attention Deficit/Hyperactivity Disorder-Rating Scale, version 4th Edition (ADHD-RS-IV) total score change from baseline at endpoint, Conners' Parent Rating Scale Revised: Short Form (CPRS-R), Clinical Global Impressions-Improvement (CGI-I), Parent Global Assessment (PGA), and Youth Quality of Life Instrument-Research Version (YQOL-R).

The subjects who entered Study SPD485-410 had to have either completed Study SPD485-409 or completed the 5-week dose-optimization period without having achieved an acceptable response. Subjects who were discontinued from Study SPD485-409 because of a protocol violation, noncompliance, or a serious adverse event were not eligible for Study SPD485-410. A total of 163 subjects from Study SPD485-409 enrolled in Study SPD485-410.

This long-term study consisted of 3 periods: dose optimization, dose maintenance, and follow-up.

Dose Optimization (5 Weeks):
Subjects from Study SPD485-409 were started on MTS treatment at the smallest patch size, 12.5cm^2. Over the 5-week dose-optimization period, subjects were titrated to the highest acceptable dose. Subjects who had not reached an acceptable response (as defined in Study SPD485-409) by Week 5 were to be withdrawn from the study.

Dose Maintenance (5 Months):
Subjects continued to receive the same dose for the next 5 months.

Follow-up (1 Week):
The investigators were required to collect and report both safety and concomitant medication information from subjects in the event that they were notified during this period.

The primary efficacy analysis (ADHD-RS-IV total score change from baseline at endpoint) was performed on the ITT and completers populations. The ITT population

was defined as all subjects who enrolled, received at least 1 dose of MTS, and had at least 1 post-entry assessment of ADHD-RS-IV. The completers analysis population consisted of subjects who completed the 6-month assessment.

The ITT analysis population consisted of 158 subjects and the completers analysis population consisted of 88 subjects. Among the 75 subjects who did not complete the 5-month dose maintenance period, the most commonly reported reasons for early termination were consent withdrawn (36%), lost to follow-up (25%), and AEs (16%). Five subjects (3%) discontinued due to lack of efficacy.

The results of the primary efficacy analysis in the ITT and completers populations are summarized in Table 3 below.

Table 3: ADHD-RS-IV Total Score Change from Baseline and Change from SPD485-410 Entry at Endpoint- ITT Population and Completers

Parameter	ITT N=158	Completers N=88
Endpoint		
Mean	13.8	9.0
Change from Study SPD485-409 Baseline		
Mean	-23	-27.5
p-value	<0.001	<0.001
Change from Study SPD485-410 Entry		
Mean	-5.9	-9.9
p-value	<0.001	<0.001

(Summary of Clinical Efficacy, p. 20)

The results of both the ITT and completers analyses are consistent with maintenance of a long-term treatment benefit for MTS. The results of the secondary efficacy analyses supported the primary analysis. The mean change from baseline CPRS-R total score was -27.6 ($p< 0.001$). At endpoint, 75.9% of subjects were categorized as “improved” on the CGI-I scale and 63.3% of subjects were categorized as “improved” on the PGA scale.

For a discussion of the safety results of Study SPD485-410, please see Section 7.4.5.

Study SPD485-106

Study SPD485-106 was an open-label, randomized, multi-center study with the primary objective of describing the pharmacokinetics and determining the accumulation of *d*-MPH and *l*-MPH in children and adolescents aged 6-17 years with ADHD, after single and multiple escalating doses of MTS worn for 9 hours. The secondary objective was to describe the pharmacokinetics and determine the accumulation of *d*-MPH and *l*-MPH in children and adolescents aged 6-17 years with ADHD, after single and multiple escalating doses of Concerta®.

The study enrolled 35 children (aged 6 to 12) and 36 adolescents (aged 13 to 17). The study consisted of 2 parts: Fixed Single/Multiple Dose and Dose Escalation. Subjects were randomly assigned to receive 1 of 3 treatment regimens (A, B, or C):

Part I-Fixed Single/Multiple Dose
Treatment A: Single dose of MTS (10mg/9 hours; 12.5cm^2)
Treatment B: Single dose of MTS (10mg/9 hours; 12.5cm^2)
Treatment C: Single dose of Concerta 18 mg

After washout of at least 3 days, subjects then received:
Treatment A: MTS (10mg/9 hours; 12.5cm^2) daily for 7 days
Treatment B: MTS (10mg/9 hours; 12.5cm^2) daily for 7 days
Treatment C: Concerta 18 mg daily for 7 days

Part II-Dose Escalation
Treatment A: MTS (10mg/9 hours; 12.5cm^2) daily for an additional 3 weeks
Treatment B: Subjects received escalating doses of MTS 15, 20, and 30 mg/9 hours (18.75cm^2, 25cm^2, and 37.5cm^2) at weekly intervals and were maintained on daily doses at each dose level for 7 days.
Treatment C: Subjects received escalating doses of Concerta 27, 36, and 54 mg at weekly intervals and were maintained on daily doses at each dose level for 7 days.

Serial blood samples for the pharmacokinetic evaluation were drawn pre-dose and at 1, 2, 4, 6, 8, 9, 10, 12, 14, 24, and 30 hours following dose administration on Day 1; pre-dose and at 1, 2, 4, 6, 8, 9, 10, 12, 14, and 24 hours following the dose administration on Days 10 and 31. Trough samples were also taken on Days 17 and 24 for each treatment regimen. Plasma concentration of *d*-MPH and *l*-MPH were determined by liquid chromatography with tandem mass spectrometric detection.

Shire's conclusions from this study include the following:

- Systemic exposure to *d*- and *l*-MPH was consistently greater in children compared with adolescents across all treatments of MTS and Concerta, on all study days.
- A lag in the absorption of *d*- and *l*-MPH, followed by slow absorption, was apparent across both age groups and sexes, following MTS single doses. In general, this lag-time was not apparent after multiple doses.
- Systemic exposure to *l*-MPH was consistently approximately half that of *d*-MPH, across age groups and sexes, following single and multiple doses of MTS. Systemic exposure to *l*-MPH was negligible after single and multiple doses of Concerta.
- Following single and multiple fixed doses, total systemic exposure to *d*-MPH was greater in children when compared with adolescents following multiple dose escalation of both MTS and Concerta.

- Systemic exposure to *d*-MPH in children after multiple escalating doses is 1.4- to 1.6-fold higher for MTS than for Concerta.
- Systemic exposure to *d*-MPH in adolescents after multiple escalating doses of Concerta is modestly higher (9%-29%) than for MTS.

Dr. Jackson is in the process of reviewing this study. His final review is not yet available.

The safety results of Study SPD485-106 will be discussed in Section 7.4.5.

6 Review of Efficacy

Efficacy Summary

The efficacy of MTS in the treatment of adolescent subjects with ADHD, relative to placebo, was demonstrated in Study SPD485-409. At endpoint, the LS mean difference between MTS and placebo in ADHD-RS-IV total score was -9.96 (-13.39 to -6.53; p< 0.001). This primary efficacy result was supported by the analysis at each post-baseline timepoint. Mean change in ADHD-RS-IV total score in the MTS group was significantly greater than placebo at all weekly post-baseline assessments. This primary efficacy analysis was also supported by analyses of ADHD-RS-IV subscale scores, the Per Protocol (PP) analysis and a MMRM analysis for ADHD-RS-IV total scores.

This study also met its key secondary objectives. MTS demonstrated significant improvements in CPRS-R total scores compared with placebo at endpoint and at all weekly post-baseline assessments through Week 7. The key secondary analysis was supported by analyses of CPRS-R subscales, ADHD subscales, CGI-I, and PGA.

6.1 Indication

Study SPD485-409: Treatment of ADHD in Adolescents aged 13-17 years

6.1.1 Methods

Description and Objective of Study

Study SPD485-409 was a Phase 3b, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the efficacy and safety of MTS (10, 15, 20, and 30mg/9 hour doses) compared with placebo, in adolescents aged 13-17 with ADHD.

The primary objective was to evaluate the efficacy of MTS compared with placebo in the treatment of adolescents with ADHD, as determined by the change in the clinician-completed ADHD-RS-IV.

Secondary objectives included:

- Assessing the safety and tolerability of MTS compared with placebo
- Assessing the efficacy of MTS compared with placebo in the home environment as rated by the parent using the Conners' Parent Rating Scale Revised: Short Form (CPRS-R)
- Assessing global impressions of ADHD improvement of MTS compared with placebo from the clinician [Clinical Global Impressions-Improvement (CGI-I)] and parent [Parent Global Assessment (PGA)]
- Assessing subject satisfaction and efficacy of MTS, compared with placebo, as measured by the Youth Quality of Life Instrument-Research Version (YQOL-R)
- Assessing the impact of MTS, compared with placebo, on sleep using the Post Sleep Questionnaire (PSQ)
- Assessing skin tolerability to both MTS and placebo transdermal system (PTS) from the dermal response scale (DRS)
- Assessing the relationship between plasma exposure and the safety and efficacy measures of MTS via sparse sampling

Subject Selection Criteria

Approximately 210 eligible subjects were to be randomized in a 2:1 ratio to receive either MTS (140 planned subjects) or PTS (70 planned subjects).

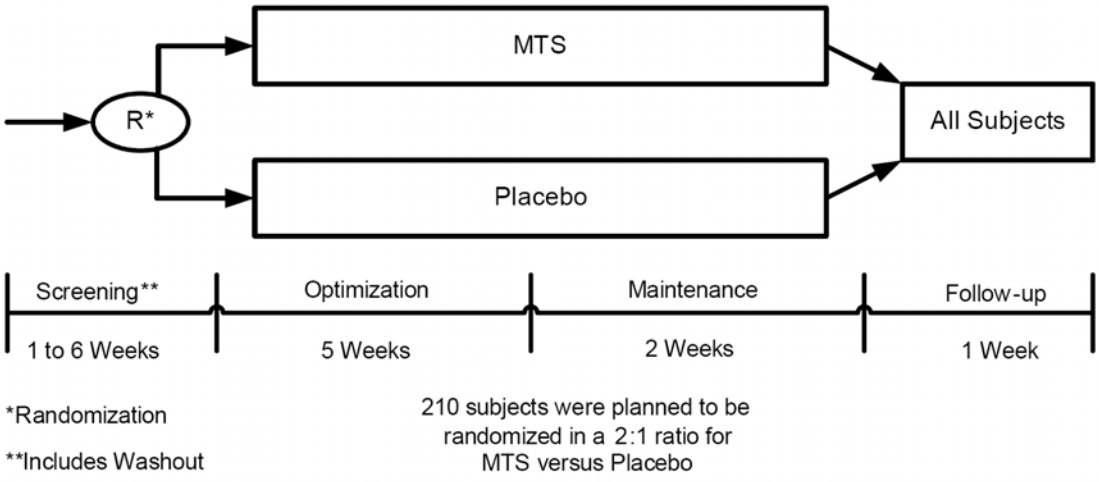
Eligible subjects were outpatient male and female adolescents aged 13-17 years, with a primary diagnosis of ADHD. The diagnosis was based on a structured Kiddie-Schedule for Affective Disorders-Present and Lifetime-Diagnostic Interview (K-SADS-PL). A total score of $\geq$ 26 on the ADHD-RS-IV at baseline, and an IQ score $\geq$ 80 as measured by the Kaufman Brief Intelligence Test were required. In addition, the eligible subjects had to have blood pressures within the 95th percentile for their age, gender, and height and no significant comorbid illnesses, significant ECG findings, or history of skin diseases.

Exclusion criteria included a current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis (except Oppositional Defiant Disorder) that, in the opinion of the investigator, would contraindicate MTS treatment or confound efficacy or safety assessments. Overweight adolescents (BMI > 95th percentile) and those who were known non-responders to psychostimulant treatment were also excluded.

Study Phases

The study consisted of 4 periods: Screening and Washout, Dose Optimization, Dose Maintenance, and Follow-up.

Figure 1: Study Schematic



(Clinical Study report, p. 17)

Screening and Washout Period

Screening occurred approximately 2 weeks prior to washout. The duration of the washout period could be up to 30 days depending on the half-life of the subject's current medication. Prohibited medications to be washed out included investigational compounds, sedatives, anxiolytics, antipsychotics, P450 enzyme-altering agents, psychostimulants, amphetamines, antidepressants, clonidine, norepinephrine reuptake inhibitors (Strattera), antihypertensives (except diuretics), and antihistamines (except non-sedating antihistamines)

Randomization

The randomization schedule was prepared by (b) (4) an Interactive Voice Response System (IVRS) vendor working on behalf of Shire. Eligible subjects were randomized in a 2:1 ratio to MTS or matching PTS and entered the double-blind stepwise dose optimization period.

Double-Blind Dose Optimization

All subjects were started on the MTS/PTS 10mg/12.5cm^2 dose/patch size. Subjects were to wear the patches for 9 hours per day; a new patch was to be applied each morning. Application sites were to be alternated between opposite sides of the body so that the same site was not used on 2 consecutive days. The subject's parent or legally authorized representative (LAR) was required to apply the patch to the subject's hip at approximately 7:00 AM. The subject's parent/LAR also needed to make arrangements for the removal of the patch at approximately 4:00 PM.

The subjects were evaluated weekly and could be titrated to the next highest dosage strength. The dosage strengths are detailed in Table 4.

Table 4: MTS Patch Sizes and Dose Delivered

Patch Size (cm^2)	MPH Content per Patch[a] (mg)	Dosage Rate[b] (mg/hr)	MPH Dose Delivered Over 9 hours (mg)
12.5	27.5	1.1	10
18.75	41.3	1.6	15
25	55	2.2	20
37.5	82.5	3.3	30

[a] Total *d*- and *l*-methylphenidate content in each patch.

[b] Nominal *in vivo* delivery rate per hour in pediatric subjects aged 6–12 years when applied to the hip, based on a 9-hour wear period.

MPH = methylphenidate

(Clinical Study report, p. 26)

Subjects were titrated to an acceptable dose of MTS based upon investigator review of parent rating forms, TEAEs, and clinical judgment using the ADHD-RS-IV. Only one downward titration to the previous dosage strength/patch size was permitted during the Optimization Period. The duration of the optimization period was 5 weeks. Further titration up or down was not allowed after Week 6 or at any time after a subject had received one downward titration. Subjects who had not reached an acceptable (see Table 5) dose by Week 5 were withdrawn from the study. These subjects were allowed to enroll into the open-label extension study (SPD485-410) if they met the eligibility criteria.

Table 5: Subject Response Criteria for Dose Optimization

Condition	Definition	Action
Intolerable	Unacceptable safety profile	Titrate downward to previous Investigational Medicinal Product (IMP) dose. If the adjusted dose strength/patch size also produced an intolerable effect, the subject should be discontinued from the study.
Ineffective	<25% change in ADHD-RS-IV score from baseline with acceptable safety profile	Increase the IMP patch size to the next dosage strength/patch size followed by weekly evaluation
Acceptable	≥25% reduction from baseline in ADHD symptom scores at a given dose, as determined by the ADHD-RS-IV, with an acceptable safety profile	Maintain current dose for the remainder of the study OR increase to the next larger dosage strength/patch size if the current dose is well-tolerated, and in the investigator's opinion the subject would potentially receive further symptom reduction through titration to the next dosage strength/patch size. No further titration was permitted after Visit 6.

(Clinical Study report, p. 19)

Maintenance Period

Subjects who had been successfully titrated to an acceptable dose continued on the same dose for a 2 week maintenance period. Safety and efficacy data continued to be collected.

Follow-up Period

At the End of Study (Week 7) Visit or at the Early Termination Visit, subjects had the option to enroll in the open-label extension study (SPD485-410). Subjects who did not enroll in the open-label study had an additional 7-day safety follow-up period. No scheduled study visit took place at the end of this period but any additional safety information was collected and included in the SPD485-409 clinical database.

For subjects who did enroll in the open-label extension study (SPD485-410), the End of Study Visit or Early Termination Visit became the baseline visit for SPD485-410.

In addition, subjects who discontinued due to an application site reaction may have been contacted up to a year after the last dose to determine subsequent ADHD therapy and tolerability.

Dermal Evaluations

At each visit, the investigator examined both the current and the prior application sites for any signs of skin irritation. The investigator also asked the subject about any skin discomfort at the sites and transdermal adherence was evaluated at the current patch application site. The following 3 scales were used to evaluate the sites and are detailed in the tables below: Dermal Response Scale, Experience of Discomfort and Pruritus, and Transdermal System Adherence. Per protocol, signs of skin irritation or symptoms of discomfort were not recorded as AEs unless they occurred at a site different from the patch application site or required pharmacologic therapy.

Table 6: Dermal Response Scale

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Table 7: Experience of Discomfort and Pruritus

0	No discomfort
1	Mild discomfort
2	Moderate but tolerable discomfort
3	Severe, intolerable discomfort

Table 8: Transdermal System Adherence

0	≥90% adhered (essentially no lift off of the skin)
1	≥75% to <90% adhered (some edges only lifting off of the skin)
2	≥50% to <75% adhered (less than half of the system lifting off of the skin)
3	<50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4	MTS/PTS detached (system completely off the skin)

(Clinical Study report, p. 33)

Efficacy Measure and Statistical Analysis Plan

The Safety population consisted of subjects who were randomized and received at least one dose of the study drug. The Intent-to-Treat (ITT) population consisted of subjects who received at least one dose of the study drug and had one baseline and at least one post-baseline assessment of ADHD-RS-IV. The PP population is a subset of the ITT population consisting of subjects who did not have any major protocol deviations.

The primary efficacy analysis was performed on the ITT population. The primary efficacy measure was Attention Deficit/Hyperactivity Disorder-Rating Scale, version 4th Edition (ADHD-RS-IV) total score change from baseline at endpoint. The endpoint for the primary efficacy measurement was defined as the last post-baseline assessment for which a valid ADHD-RS-IV score was obtained. The primary efficacy variable was assessed using an analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline ADHD-RS-IV score as a covariate. The null hypothesis was that there was no difference between MTS and PTS. The treatment comparisons were tested at the 0.05 significance level and 95 % confidence intervals (CI) were calculated. A sensitivity analysis using mixed-effects model repeated measures (MMRM) was performed to address the effect of incomplete data. A p-value was presented from a paired t-test assessing if the change from baseline to visit/endpoint within each treatment was significantly different from zero.

The key secondary efficacy variable was the CPRS-R (Conners' Parent Rating Scale-Revised: Short Form) total score. Additional secondary assessments included the ADHD-RS-IV subscales (hyperactivity/impulsivity and inattentiveness), the CPRS-R subscales (oppositional, cognitive problems, hyperactivity, and ADHD Index), CGI-S (Clinical Global Impressions-Severity of Illness), CGI-I (Clinical Global Impressions-Improvement), PGA (Parent Global Assessment), and YQOL-R (Youth Quality of Life Instrument-Research Version). The ANCOVA model was used to examine treatment

effects at endpoint and each post-baseline visit for the ADHD-RS-IV subscales, the CPRS-R total scores, and the CPRS-R subscales.
Least squares (LS) mean and 95% CI for the comparison between MTS and PTS were calculated for all secondary endpoints.

The CGI-I and PGA were analyzed by a chi-square test. These 7-point scales were dichotomized to two categories:

Dichotomized CGI-I or PGA	CGI-I or PGA score	
Improvement	1	Very much improved
	2	Much improved
No Improvement	3	Minimally improved
	4	No change
	5	Minimally worse
	6	Much worse
	7	Very much worse

(Clinical Study report, p. 37)

Relationships between efficacy parameters and systemic exposure were also explored using a simple regression analysis model. The efficacy parameter was the dependent variable and the plasma concentration of d-MPH at the 9-hour timepoint was a continuous independent variable. Relationships between relevant safety parameter and systemic exposure to d-MPH were also explored.

Sample Size

Effect sizes > 0.5 were observed in previous studies of children with ADHD treated with MTS. One hundred and twelve (112) subjects in the MTS treatment group and 56 subjects in the placebo group was determined to provide 85% power to detect an effect size of 0.5 between two treatment groups at the 0.05 significance level.

6.1.2 Demographics

The majority of subjects were male (74.7%) and White (77%). The mean age was 14.6. The age of the study population was evenly divided between the age categories of 13-14 years (52.5%) and 15-17 years (47.5%). The treatment groups were balanced with respect to age, gender, race, and ethnicity.

Table 9: Key Demographic and Baseline Characteristics-Safety Population

Characteristic	**Placebo** N=72	**MTS** N=145	**All** N=217
Age(years)			
Mean (SD)	14.6 (1.42)	14.5 (1.25)	14.6 (1.31)
(Min, Max)	(13, 17)	(13, 17)	(13, 17)
Age Category n(%)			
13-14 years	38 (52.8)	76 (52.4)	114 (52.5)
15-17 years	34 (47.2)	69 (47.6)	103 (47.5)
Gender n(%)			
Male	53 (73.6)	109 (75.2)	162 (74.7)
Female	19 (26.4)	36 (24.8)	55 (25.3)
Race n(%)			
White	56 (77.8)	111 (76.6)	167 (77)
Black or African American	13 (18.1)	27 (18.6)	40 (18.4)
Native Hawaiian or Pacific Islander	0	0	0
Asian	1 (1.4)	0	1 (0.5)
American Indian or Alaska Native	1 (1.4)	0	1 (0.5)
Other	1 (1.4)	7 (4.8)	8 (3.7)
Weight (lb)			
Mean (SD)	128.45 (29.2)	130.18 (25.1)	129.6 (26.5)
(Min, Max)	(68, 203)	(76, 195)	(68, 203)
Height (in)			
Mean (SD)	64.97 (4.3)	65.35 (3.6)	65.23 (3.8)
(Min, Max)	(56.5, 74)	(57, 74.5)	(56.5, 74.5)
BMI (kg/m^2)			
Mean (SD)	21.2 (3.5)	21.3 (2.9)	21.2 (3.1)

(Clinical Study Report, p. 49-50)

The mean age at the first onset of ADHD symptoms was 4.3 years in the placebo group and 4.2 years in the MTS group. The majority of subjects (76.5%) had no prior or current psychiatric comorbidities. Only 50% of the placebo group and 40.7 % of the MTS group had ever used stimulant medication. At baseline, mean ADHD-RS was 36.5 and mean CGI-S was 4.5. The placebo and MTS groups had similar scores at baseline.

Table 10: Baseline ADHD Disease Characteristics- Safety Population

Characteristic	Placebo N=72	Total MTS N=145	All N=217
Age at ADHD Onset (yrs)			
Mean (SD)	4.3 (1.5)	4.2 (1.4)	4.2 (1.4)
(Min, Max)	(0, 7)	(0, 7)	(0, 7)
Duration of ADHD Diagnosis (yrs)			
Mean (SD)	4.4 (3.9)	4.0 (3.7)	4.1 (3.8)
(Min, Max)	(0, 13)	(0, 12)	(0, 13)
Prior Stimulant Medicine Use n%			
Yes	36 (50)	59 (40.7)	95 (43.8)
No	36 (50)	86 (59.3)	122 (56.2)
Any Psychiatric Comorbidities Currently or in the Past: n(%)			
No	57 (79.2)	109 (75.2)	166 (76.5)
Yes	15 (20.8)	36 (24.8)	51 (23.5)
ADHD-RS Total Score at Baseline			
Mean (SD)	36.6 (7.7)	36.4 (7.1)	36.5 (7.3)
(Min, Max)	(26, 54)	(26, 52)	(26, 54)
CPRS-R Total Score at Baseline: n(%)			
Mean (SD)	51.9 (12.7)	49.7 (15.2)	50.4 (14.4)
(Min, Max)	(23, 77)	(6, 79)	(6, 79)
Summary of CGI-S at Baseline			
Mean (SD)	4.6 (0.71)	4.5 (0.66)	4.5 (0.67)
(Min, Max)	(4, 6)	(3, 6)	(3, 6)

(Clinical Study Report, p. 51)

The MTS and PTS treatment groups were consistent with regard to baseline ADHD characteristics. Combined subtype was the most common subtype for both groups. A greater percent of subjects in the PTS group had ODD as a comorbidity compared with the MTS group.

Table 11: ADHD Subtypes and Psychiatric Comorbidities-ITT

Characteristic	**Statistic**	**Placebo** (N=72)	**Total MTS** (N=143)
ADHD Subtype			
Predominantly Inattentive	n (%)	27 (37.5)	55 (38.5)
Predominantly Hyperactive-Impulsive	n (%)	0	1 (0.7)
Combined Subtype	n (%)	45 (62.5)	87 (60.8)
Psychiatric Comorbidities			
Oppositional Defiant Disorder (ODD)	n (%)	9 (12.5)	16 (11)
Simple Phobia	n (%)	0	0
Dysthymia	n (%)	0	1 (> 1)
Other	n (%)	6 (8)	19 (13)

(Clinical Study Report, p.162)

Table 12: Specifics of Psychiatric Comorbidities Termed *Other*

Psychiatric History (other)	**MTS**	**Placebo**
Enuresis	1	1
Enuresis (past)	7	2
Anxiety Disorder (past)	2	-
Adjustment Disorder with Depressed Mood	1	-
Adjustment Disorder with Depressed Mood (past)	3	1
Adjustment Disorder with Anxious Mood	1	-
OCD (past)	1	-
Marijuana Dependency in remission	1	-
GAD/Major Depression	1	-
Marijuana Abuse	1	-
Mild Acute Stress	-	1
Encopresis/Reactive Attachment Disorder/ Separation Anxiety Disorder	-	1
Encopresis	1	-

(Clinical Study Report, p. 39-50)

6.1.3 Subject Disposition

A total of 217 subjects at 31 investigational sites were enrolled and randomized. No center contributed more than 8% of the total 217 randomized subjects to the efficacy analyses. Seventy-two (72) subjects were randomized to PTS and 145 subjects were randomized to MTS. All 217 subjects received at least one administration of study treatment and were included in the safety analysis population. The ITT analysis population included 215 subjects. Two of the subjects in the safety population were

excluded because they did not have at least one post-baseline assessment of ADHD-RS-IV.

A total of 124 (57%) subjects completed the study. The rate of study completion was higher for subjects who received MTS (65.5%) than for subjects who received PTS (40.3%).

Table 13 : Subject Disposition for All Randomized Subjects

Analysis Population	PTS N=72 (%)	MTS N=145 (%)	All N=217 (%)
Randomized	72	145	217
Safety	72 (100)	145 (100)	217 (100)
ITT	72 (100)	143 (98.6)	215 (99.1)
Per Protocol (No Protocol Deviations)	54 (75)	117 (80.7)	171 (78.8)
Completed 7-week Dose Optimization/ Maintenance Period	29 (40.3)	95 (65.5)	124 (57)
Completed 7-week Dose Optimization/ Maintenance Period and Entered Open-Label Study	25 (35)	91 (63)	116 (53)
Did Not Complete 7-week Dose Optimization/ Maintenance Period	43 (60)	50 (34)	93 (43)
Did Not Complete 7-week Dose Optimization/ Maintenance Period and Entered Open-Label Study	28 (39)	19 (13)	47 (22)
Total Subjects Who Entered Open-Label Study	53 (74)	110 (76)	163 (75)

(Clinical Study report, p. 45)

The most common reason for discontinuation was lack of efficacy (22%). The percentage of subjects randomized to placebo (37.5%) who discontinued due to lack of efficacy was higher than in the MTS group (14.5%).

Table 14: Reasons for Termination

Reason for Termination Those who did not complete 7-week Dose Optimization	**Placebo** N=72(%) N=43	**MTS** N=145(%) N=50	**All** N=217(%) N=93
All Adverse Events	2 (2.7)	8 (5.5)	10 (4.6)
Application Site Reaction	0 (0)	3 (2)	3 (1.4)
Protocol Violation	7 (9.7)	12 (8.3)	19 (8.7)
Consent Withdrawn	4 (5.5)	6 (4)	10 (4.6)
Subject Lost to Follow-up	1 (1.4)	1 (<1)	2 (<1)
Lack of Efficacy	27 (37.5)	21 (14.5)	48 (22)
Death	0	0	0
Other	2 (2.7)	2 (1.3)	4 (1.8)

(Clinical Study report, p. 45)

Adverse events leading to termination included loss of appetite, increased irritable mood, sedation, dry mouth, dizziness, and syncope. Protocol violations leading to termination included positive urine drug screens, non-compliance and enrollment in another study. Reasons designated as "other" included *sponsor decision*, *investigator felt response was suboptimal* and *father not available to monitor study medication*.

No trends were apparent between the frequency of discontinuation due to AEs and final MTS patch size.

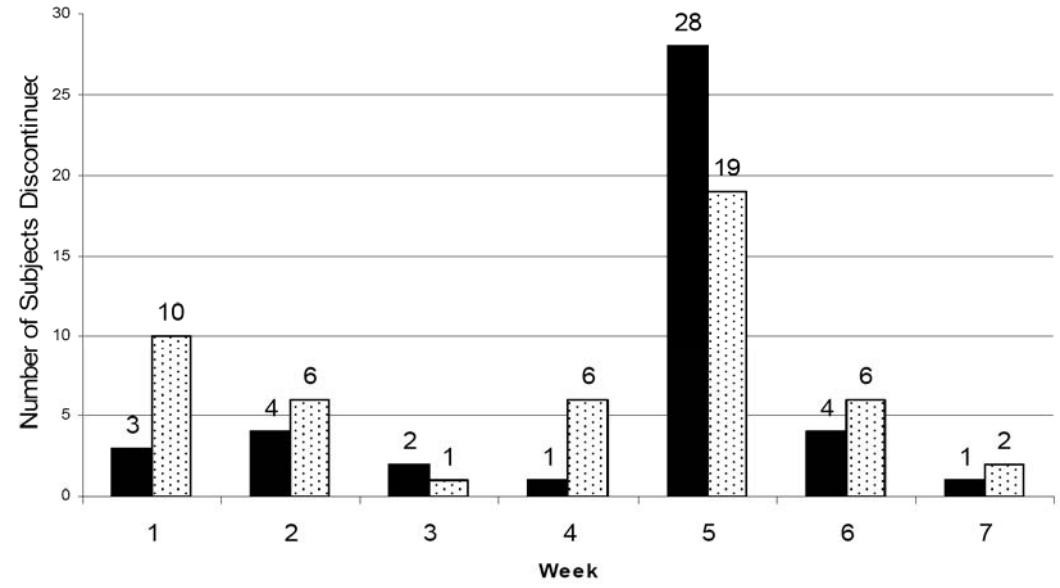
Table 15: Summary of Early Terminations by MTS Final Patch Size (Safety Population)

Reason for Termination	12.5cm^2 n=16	18.75cm^2 n=26	25cm^2 n=29	37.5cm^2 n=74
All Adverse Events	0	4 (15.4)	3 (10.3)	1 (1.4)
Application Site Reaction	0	1 (3.8)	1 (3.4)	1 (1.4)
Protocol Violation	10 (62.5)	1 (3.8)	0	1 (1.4)
Consent Withdrawn	1 (6.3)	3 (11.5)	0	2 (2.7)
Subject Lost to Follow-up	1 (6.3)	0	0	0
Lack of Efficacy	0	0	3 (10.3)	18 (24.3)
Death	0	0	0	0
Other	0	2 (7.7)	0	0

(Clinical Study report, p. 132)

Those subjects who had not achieved an acceptable response by Week 5 were required to withdraw from the study at that time. Figure 2 shows the disproportionately higher rate of early termination in the placebo group relative to the MTS group occurring between Weeks 5 and 6. The majority of these discontinuations (23/27 in PTS group and 16/19 in MTS group) were due to lack of efficacy.

Figure 2: Number of Subjects Discontinued by Week



The randomization ratio 2:1 MTS:placebo should be considered when interpreting the data in the figure.
Data Source: Section 15, Table 1.2.2

Major Protocol Deviations

The percentage of subjects with major protocol deviations was somewhat higher in the placebo group (25%) than the MTS group (19.3%). The most common major protocol deviations were “prohibited medication taken” and “drug compliance.” Prohibited medications taken included Lodrane SR, Adderall XR, Sudafed, phenylephrine, Ambien, and combination products for cough and congestion. Subjects were considered noncompliant if they had an average drug compliance of less than 80% or more than 100%. Most of the subjects who had protocol deviations for drug compliance had compliance greater than 100% (101.9 – 110.6%).

Table 16: Major Protocol Deviations-Safety Population

Parameter	**Placebo** N=72	**MTS** N=145	**All** N=217
Subjects with Major Protocol Deviations	18 (25)	28 (19.3)	46 (21.2)
Drug Compliance	6 (8.3)	13 (9)	19 (8.8)
Inclusion/Exclusion Criteria Failure	1 (1.4)	2 (1.4)	3 (1.4)
Prohibited Medication Taken	7 (9.7)	13 (9)	20 (9.2)
Other	6 (8.3)	4 (2.8)	10 (4.6)

(Clinical Study Report, p.53)

Of ten subjects who had positive urine drug screens at baseline, nine were discontinued from the study in accordance with the protocol. One was inadvertently allowed to continue and was included in the per protocol analysis population.

Twelve subjects in the MTS group and 12 subjects in the placebo group were assessed as not having achieved an acceptable response at Week 5, but were not discontinued from the study as directed by the protocol. As the primary efficacy analysis was based on the ITT population, Shire does not feel that the exclusion of these subjects from the Per Protocol (PP) population should affect the conclusions drawn from the study results.

Dr Yeh-Fong Chen removed the Week 6 and Week 7 data for these 24 subjects and reanalyzed the data. The change from baseline to endpoint was -8.7 for placebo and -18.5 for MTS. This difference of -9.8 was still significant at $p < 0.001$.

Treatment Compliance

The overall mean compliance rate was 95.4% for the placebo group and 95.8% for the MTS group.

Extent of Exposure to Study Drug

This was a dose-optimization study design. Therefore, the number of subjects at each incrementally higher MTS dose level increased over time. Mean duration of exposure to study drug was 41.3 days for the MTS group and 38.8 days for the placebo group.

Table 17: Summary of Subject Drug Exposure-Safety Population

Length of Exposure (days)	Placebo	MTS Total	MTS 12.5cm^2	MTS 18.75cm^2	MTS 25cm^2	MTS 37.5cm^2
n	72	145	145	129	109	76
Mean	38.8	41.3	8.9	11.8	13.8	22.1
Median	40.0	48.0	7.0	7.0	8.0	23.5
(Min, Max)	(5, 61)	(4, 57)	(4, 49)	(3, 44)	(4, 39)	(4, 35)
Total Subject Years Of Exposure	7.6	16.4	3.5	4.2	4.1	4.6

Note: Subjects are counted once in the Total MTS group, but may be counted in more than one MTS patch size group.
(Clinical Study Report, p. 72)

By Week 7, 55% of the MTS group and 80% of the remaining placebo group were on the highest patch size (37.5cm^2)

Table 18: Summary of Patch Size Distribution-Safety Population

Patch Size	**12.5cm^2**		**18.75cm^2**		**25cm^2**		**37.5cm^2**	
Treatment Group	**PTS n**	**MTS n**	**PTS n**	**MTS n**	**PTS n**	**MTS n**	**PTS n**	**MTS n**
Week 1	72	145	0	0	0	0	0	0
Week 2	3	21	66	114	0	0	0	0
Week 3	1	5	7	28	57	96	0	0
Week 4	1	4	6	21	6	43	50	60
Week 5	0	4	5	19	5	26	53	73
Week 6	0	4	4	18	3	24	27	57
Week 7	0 (0%)	4(4.2%)	3 (10 %)	16 (16.7%)	3(10%)	23(24%)	24(80%)	53(55.2%)

Note: subjects may be represented in more than one patch size per week; percentages are calculated out of the number of subjects in the treatment group with dispensing information at that week
(Clinical Study Report, p. 428)

6.1.4 Analysis of Primary Endpoint(s)

The results of the primary efficacy analysis showed a treatment benefit for MTS in the improvement of ADHD-RS-IV total score. The analysis compared MTS with placebo for change from baseline in ADHD-RS-IV total score at endpoint using an ANCOVA with treatment as a factor and baseline ADHD-RS-IV total score as a covariate. The LS mean difference (95% CI) between MTS and placebo was -9.96 (-13.39, -6.53). At endpoint, the LS mean change from baseline in ADHD-RS-IV total score was significantly greater ($p < 0.001$) for the MTS group (-18.8) compared with the placebo group (-8.8).

Table 19: Analysis of LS Mean (SE) Change from Baseline ADHD-RS-IV Total Score (ANCOVA model)-ITT Population

	Placebo N=72	**MTS** N=143	**95% CI LS Mean Difference**	**p-value**
Endpoint LS mean (SE) Difference (MTS-placebo)	 -8.8 (1.42)	 -18.8 (1.01) -9.96	 (-13.39, -6.53)	 <0.001

(Clinical Study Report, p. 59)

Mean ADHD-RS-IV total scores and change from baseline are summarized for endpoint (the last non-missing assessment obtained post-baseline) and at Weeks 5 and 7 in Table 20. Both treatment groups showed a decrease in mean ADHD-RS-IV total scores. The results presented show an increase in mean change from baseline in ADHD-RS-IV total score in the placebo group at Week 7. It is important to remember the details of the protocol. Subjects who had not reached an acceptable response by Week 5 were to have been withdrawn from the study. After Week 5, a higher percentage of subjects were withdrawn from the placebo group than from the MTS group. Shire believes that

the apparent placebo response after Week 5 resulted from "placebo responders" continuing to participate in the study.

Table 20: Mean ADHD-RS-IV Total Score and Change from Baseline ADHD-RS-IV Total Score-ITT Population

Visit **Mean (SD) ADHD-RS-IV total score**	**Placebo**	**MTS**
Baseline		
n	72	143
Total Score	36.6 (7.71)	36.4 (7.15)
Endpoint		
n	72	143
Total Score	27.7 (12.75)	17.7 (12.2)
Change from baseline	-8.9 (11.73)	-18.7 (13.27)
Week 5		
n	61	121
Total Score	26.2 (12.17)	17.2 (10.78)
Change from baseline	-10.2 (11.19)	-19.3 (11.85)
Week 7		
n	29	96
Total score	18.2 (10.93)	12.6 (9.42)
Change from baseline	-18.5 (12.13)	-24.2 (10.71)

(Clinical Study Report, p. 57-58)

The results of the ANCOVA analysis in the Per Protocol population supported the primary analysis in the ITT population. The MMRM, a sensitivity analysis to explore the effect of early termination or missing data, also showed a statistically significant difference between MTS and placebo.

Treatment differences for the 7 sites with $\geq$ 10 subjects are summarized in Table 21.

Table 21: Summary of Treatment Difference for Centers with at Least 10 Subjects

Center	**Total**	**MTS**		**Placebo**		**Treatment Difference**
State	n	n	Mean ADHD-RS-IV Total Score Change from Baseline At Endpoint	n	Mean ADHD-RS-IV Total Score Change from Baseline At Endpoint	MTS - Placebo
33-KS	16	12	-13.42	4	-5.25	-8.17
21-CA	15	10	-19.2	5	1.6	-20.8
32-TX	15	11	-22.73	4	-12.5	-10.23
10-KY	11	8	-13.75	3	-2.33	-11.42
27-MI	11	5	-11.60	6	-8.33	-3.27
29-VA	10	6	-31.5	4	-13.0	-18.5
35-TN	10	6	-14.33	4	-15.75	1.42

(Clinical Study Report, p. 207)

The 18 items of the ADHD-RS-IV may be grouped into two subscales: hyperactive/impulsivity and inattentiveness. Mean hyperactive/impulsivity and inattentiveness scores decreased progressively over Weeks 1-7. The magnitude of the decrease from baseline was greater for the MTS group than the placebo group. The treatment difference (MTS-PTS) in LS mean showed a statistically significant treatment benefit for MTS in hyperactive/impulsivity and inattentiveness.

Table 22: Analysis of LS Mean Change from Baseline ADHD-RS-IV Subscale Scores at Endpoint (ANCOVA model)-ITT Population

ADHD-RS-IV Subscale	**Placebo N=72**	**MTS** N=143	**95% CI LS Mean Difference**	**p-value**
Hyperactivity/Impulsivity				
LS mean (SE)	-4.1 (0.69)	-8.1 (0.49)		
Difference (MTS-placebo)		-4.02	(-5.68, -2.36)	<0.001
Inattentiveness				
LS mean (SE)	-4.7 (0.83)	-10.7 (0.59)		
Difference (MTS-placebo)		-5.93	(-7.94, -3.92)	<0.001

Note: Endpoint is the last non-missing assessment obtained post-baseline
(Clinical Study Report, p. 60)

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary efficacy variable was the Conners' Parent Rating Scale-Revised Short Version (CPRS-R) total score. Mean CPRS-R total scores decreased progressively over Weeks 1-7 in both treatment groups. The magnitude of the decrease from baseline was greater for the MTS group than the placebo group at all timepoints. At endpoint, the LS mean difference (95% CI) between MTS and placebo in change from baseline CPRS-R total score was -13.48 (-18.48, -8.47). This was significant at the $p < 0.001$ level.

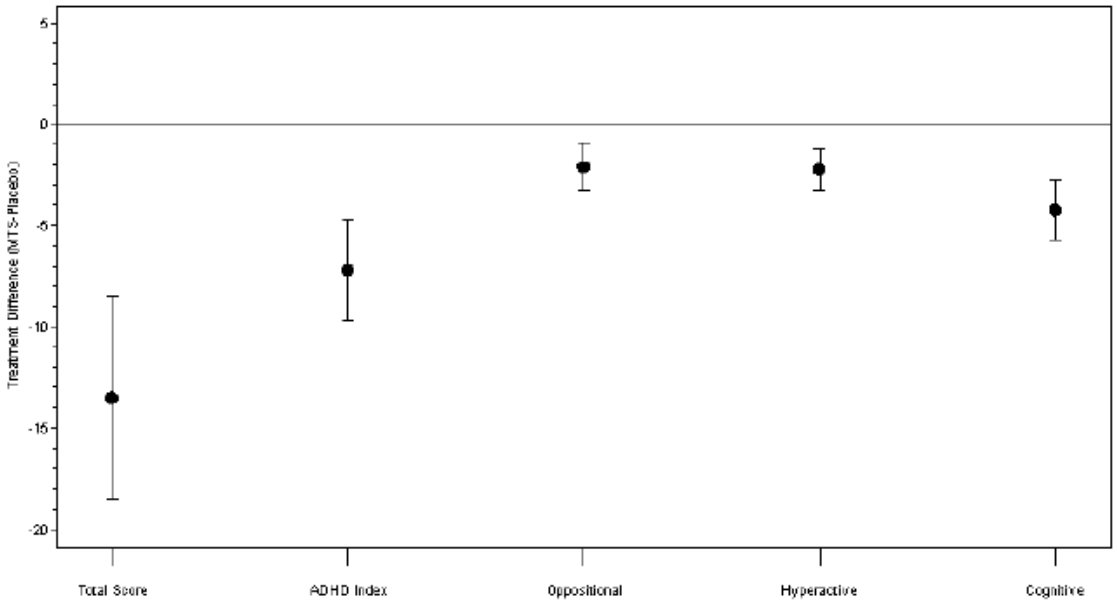
Table 23: Analysis of LS Mean (SE) Change from Baseline CPRS-R Total Score (ANCOVA model)-ITT Population

CPRS-R	**Placebo N=72**	**MTS** N=143	**95% CI LS Mean Difference**	**p-value**
Endpoint				
LS mean (SE)	-7.5 (2.08)	-20.9 (1.45)		
Difference (MTS-placebo)		-13.48	(-18.48, -8.47)	<0.001

Note: Endpoint is the last non-missing assessment obtained post-baseline
(Clinical Study Report, p. 62)

The results of the ANCOVA analysis of change from baseline CPRS-R subscale scores (ADHD Index, Oppositional, Hyperactivity and Cognitive) at endpoint also show a significant treatment benefit for MTS at endpoint for all four CPRS-R subscales ($p<0.001$).

Figure 3 : Plot of Change from Baseline Treatment Differences in LS Means and CIs for CPRS-R Subscale Scores at Endpoint-ITT Population



(Clinical Study Report, p. 1117)

Additional secondary assessments included the Clinical Global Impression-Improvement (CGI-I) scale, the Parent Global Assessment (PGA), and the YQOL-R. At endpoint, the percentage of subjects categorized as "improved" using the dichotomized CGI-I scale was significantly greater for the MTS group (65.5%) compared with the placebo group (30.6%; p<0.001).

Table 24: Analysis of Dichotomized CGI-I-ITT Population

Endpoint Visit	**Placebo N=72**	**MTS N=143**	**Difference in % of Subjects With Improvement (MTS-placebo)**	**p-value**
n	72	142		
Subjects with Improvement: includes CGI-I categories "very much improved" and "much improved" n (%)	22(30.6)	93(65.5)	34.9	<0.001
No Improvement: includes all other categories n (%)	50(69.4)	49(34.5)		

(Clinical Study Report, p. 63)

PGA evaluations were also dichotomized into categories of "improvement" or "no improvement" for analysis. At endpoint, the percentage of subjects categorized as

"improved" was significantly greater for the MTS group (53.1%) compared with the placebo group (20.8%; p < 0.001).

Table 25 : Analysis of Dichotomized PGA-ITT Population

Endpoint Visit	Placebo N=72	MTS N=143	Difference in % of Subjects With Improvement (MTS-placebo)	p-value
n	72	142		
Subjects with Improvement: includes PGA categories "very much improved" and "much improved" n (%)	15(20.8)	76(53.1)	32.3	<0.001
No Improvement: includes all other categories n (%)	57(79.2)	67(46.9)		

(Clinical Study Report, p. 65)

The YQOL-R is a validated 56-item generic instrument for assessing quality of life of adolescents. It consists of 2 domains: contextual and perceptual. Assessment of YQOL-R in this study was introduced through Amendment 1. Approximately 1/3 of subjects in the ITT population did not have a baseline assessment as the study was already actively enrolling. The YQOL-R was assessed at baseline and at the Week 7. No significant treatment benefit was detected for MTS compared with placebo.

Handling of Missing Data

For the ADHD-RS-IV, CPRS-R, and YQOL-R, missing data for individual items were assessed for each assessment of each scale and imputed with the mean score of corresponding assessment and rounded to the nearest integer if the number of items with missing or invalid data was ≤ 20% of total item number. Otherwise, the assessment was set to missing. For CGI and PGA, missing data were not imputed but the last observation was used in the endpoint analysis.

6.1.7 Subpopulations

Subgroup summaries were performed on the primary efficacy variable (ADHD-RS-IV Total Score) for gender, race (white vs. non-white), age group, prior stimulant use and ADHD subtype. No statistical testing was performed on subgroups as the study was not sized for subgroup analyses. A treatment benefit for MTS was seen within subgroups for age, prior stimulant use, and ADHD subtype (Inattentive and Combined). Because the sample sizes for females and non-white subjects were small, Shire felt no meaningful comparisons of treatment effect could be made in these subgroups.

Table 26: Summary of ADHD-RS-IV Total Score Change from Baseline to Endpoint by Subgroups-ITT Population

Subgroup	**Gender**				**Race**			
	Male		Female		White		Non-White	
Treatment Group	PTS	MTS	PTS	MTS	PTS	MTS	PTS	MTS
n	53	107	19	36	56	109	16	34
Mean Change From Baseline ADHD-RS-IV Total Score	-7.1	-19	-13.8	-17.9	-8.1	-19.1	-11.6	-17.6

Subgroup	**Age**			
	13-14		15-17	
Treatment Group	PTS	MTS	PTS	MTS
n	38	76	34	67
Mean Change From Baseline ADHD-RS-IV Total Score	-8.3	-18.6	-9.5	-18.9

Subgroup	**ADHD Subtype**						**Prior Stimulant Use**			
	Inattentive		Hyperactive-Impulsive		Combined		Yes		No	
Treatment Group	PTS	MTS	PTS	MTS	PTS	MTS	PTS	MTS	PTS	MTS
n	27	55	0	1	45	87	36	58	36	85
Mean Change From Baseline ADHD-RS-IV Total Score	-8.0	-14.7	NA	-22	-9.4	-21.2	-6.9	-20.5	-10.8	-17.5

(Clinical Study Report, p. 241, 257, 273, 281, 289, 297, 305, 313, 321)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Change from baseline in ADHD-RS-IV Total Score at endpoint is summarized by patch size in

Table 27. The dose optimization design of the study does not allow for determination of dose-response. It appears that improvement from baseline ADHD-RS-IV Total Score is lower for the two highest MTS dose/patch sizes than for the smaller patch size. Shire cautions that when interpreting these results, it is important to note that the dose optimization design may not allow this conclusion to be drawn and that it can be argued that subjects who are non-responsive to MTS would have been progressively increased in dose to the highest MTS doses studied. Examination of Week 7 data, where non-responders have been eliminated, shows no clinically meaningful difference in treatment effect magnitude across MTS doses.

Table 27: Summary of ADHD-RS-IV Total Score Change from Baseline at Endpoint and Week 7 by MTS Patch Size

Change from Baseline ADHD-RS-IV Total Score	Placebo (N=72)	Total MTS (N=143)	MTS Patch Size			
			12.5cm^2	18.75cm^2	25cm^2	37.5cm^2
At Endpoint						
n	72	143	12	18	25	68
Mean	-8.9	-18.7	-13.1	-25.8	-23.1	-18.6
p-value	<0.001	<0.001				
At Week 7						
n	29	96	4	16	22	48
Mean	-18.5	-24.2	-23.8	-26.4	-25.4	-24.1
p-value	<0.001	<0.001				

(Clinical Study Report, p. 195, 202)

6.1.10 Additional Efficacy Issues/Analyses

A venous blood sample was collected at one of the last three visits (Week 5, 6, or 7/ET) for the measurement of steady-state plasma concentrations of *d*- and *l*-MPH. The samples were collected at the end of the wear-time (9 hours after application).

Of the efficacy parameters explored, only YQOL-R total perceptual score showed a significant correlation to plasma concentrations of *d*-MPH (r=0.357; p=0.002).

Table 28: Analysis of Efficacy Parameters and d-MPH Plasma Concentrations at 9 Hours

Parameter	Regression Coefficient	p-value
ADHD-RS-IV Total Score	-0.059	0.496
CPRS-R Total Score	-0.105	0.408
YQOL-R	0.357	0.002
CGI-I	0.001	0.901
PGA	-0.002	0.822

(Clinical Safety Report, p.1100)

7 Review of Safety

Safety Summary

There were no new or unexpected findings with respect to safety. There were no deaths and only one subject in the MTS group experienced SAEs (2 episodes of syncope). Discontinuations due to adverse events that were probably drug-related included loss of appetite, increased irritable mood, sedation, dry mouth, dizziness, syncope and application site reactions. Drug-related common adverse events included decreased

appetite, irritability, nausea, abdominal discomfort, vomiting, insomnia, weight decreased, and dizziness. The MTS group showed a small increase from baseline in mean systolic blood pressure, diastolic blood pressure, and heart rate. Mean weight decreased from baseline by 1.90 pounds at endpoint in the MTS group.

In summary, the safety data showed no notable safety concerns with Daytrana's use in adolescents. The safety profile appears to be similar to the safety profile of MTS in children and to the safety profile of MPH in general.

7.1 Methods

The clinical study report for Study SPD485-409, the raw data sets, the Summary of Clinical Safety, and the case narratives/CRFs of serious adverse events were reviewed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study SPD485-409 was used to assess safety and efficacy. The safety results from the open-label, long-term Study SPD485-410 and the pharmacokinetic Study SPD485-106 are also discussed in Section 7.4.5.

7.1.2 Categorization of Adverse Events

The sponsor's categorization of adverse events was assessed and found to be adequate. Verbatim terms compared well with the preferred terms. MedDRA Version 7.0 was used. Safety signals did not appear to be diminished through splitting.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of safety data was done. The safety data from the short-term, placebo-controlled study (SPD485-409) are discussed separately from the long-term, open-label study (SPD485-410) and the pharmacokinetic study (SPD485-106).

7.2 Adequacy of Safety Assessments

All tests reasonably applicable were conducted to assess the safety of MTS in adolescents. There was adequate experience with the drug in terms of overall numbers of patients in the target population. Doses and duration of exposure were appropriate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study SPD485-409, the majority of subjects were male and white but the treatment groups were balanced with respect to age, gender, race, and ethnicity.

Overall exposure at appropriate doses/durations of the target population was adequate. Study SPD485-409 was a dose-optimization study design. Therefore, the number of subjects at each incrementally higher MTS dose level increased over time. Mean duration of exposure to study drug was 41.3 days for the MTS group. Total subject years of exposure were 16.4 for the MTS group.

Table 29: Summary of Subject Drug Exposure-Safety Population

Length of Exposure (days)	Placebo	MTS Total	MTS 12.5cm^2	MTS 18.75cm^2	MTS 25cm^2	MTS 37.5cm^2
n	72	145	145	129	109	76
Mean	38.8	41.3	8.9	11.8	13.8	22.1
Median	40.0	48.0	7.0	7.0	8.0	23.5
(Min, Max)	(5, 61)	(4, 57)	(4, 49)	(3, 44)	(4, 39)	(4, 35)
Total Subject Years Of Exposure	7.6	16.4	3.5	4.2	4.1	4.6

Note: Subjects are counted once in the Total MTS group, but may be counted in more than one MTS patch size group.
(Clinical Study Report, p. 72)

Median duration of exposure to MTS for all subjects during Study SPD485-410 was 168 days. The total exposure was 57.6 subject-years. Cumulative MTS exposure in SPD485-409 and SPD485-410 is detailed in Table 56.

Table 30: Cumulative MTS Exposure in SPD485-409 and SPD485-410-Safety Population

Parameter	**Total MTS**
Length of Exposure (days)	
n	198
Mean	136.5
Median	164.5
Length of Exposure Category (days)	n (%)
>90 days	128 (65)
>180 days	85 (43)
Total Subject Years of Exposure	74.0

(Summary of Clinical Safety, p. 14)

7.2.2 Explorations for Dose Response

The dose optimization design of the study does not allow for determination of dose-response relationship. However, exploratory regression analyses of key variables and *d*-MPH plasma concentrations after a 9-hour wear-time were done. A venous blood sample was collected at one of the last three visits (Week 5, 6, or 7/ET) for the measurement of steady-state plasma concentrations of *d*- and *l*-MPH. The results of these regression analyses are discussed further in Section 7.5.1.

7.2.4 Routine Clinical Testing

The routine clinical testing of the subjects appeared to be adequate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Shire adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

There were no unexpected safety concerns. The safety concerns were similar to what has previously been found in the treatment of children with MTS and oral formulations of methylphenidate.

7.3.1 Deaths

There were no deaths reported during this study.

7.3.2 Nonfatal Serious Adverse Events

Two subjects experienced three SAEs. One subject in the MTS group experienced 2 episodes of syncope and one subject in the placebo group experienced negativism.

Table 31: List of Subjects with SAEs

Subject ID	Study Treatment	Patch Size at Onset	SAE (PT)	Relationship	Subject Disposition
33-011	MTS	18.75 cm^2 18.75 cm^2	syncope syncope	related related	discontinued discontinued
04-006	Placebo	37.5 cm^2	negativism	not related	discontinued

(Clinical Report, p. 85)

Subject 33-011 was randomized to MTS and started study treatment on 11 Oct 2007. On 24 Oct 2007, the subject reported that he had experienced two episodes of dizziness followed by syncope on 19 Oct 2007 and 22 Oct 2007. Both episodes of

syncope occurred approximately 1 hour after removal of the patch and lasted less than 30 seconds. At the time of the events, the subject was receiving the 18.75 cm^2 patch. The subject's mother discontinued the patch after the second episode of syncope and did not seek further medical attention. No ECGs were done while the subject was on treatment but his screening, baseline, and early termination visit ECGs were reviewed by a pediatric cardiologist. No evidence of structural heart disease or aberrant conduction was found.

7.3.3 Dropouts and/or Discontinuations Due to Adverse Events

Overall, approximately 6% of the MTS group and 3% of the placebo group dropped out of the study secondary to adverse events. This rate is typical to what has been found in previous studies. As discussed above, there were no deaths and only 1 SAE (syncope) in the MTS group which was probably related to the study medication. None of the adverse events leading to discontinuation were new or unexpected.

Table 32: List of Subjects who Discontinued as the Result of an Adverse Event

Table 27 List Of Subjects who Discontinued as the Result of an Adverse Event

Subject ID	Study Treatment	Patch Size at Onset	Preferred Term	Relationship[a]	SAE	Severity
14-004	MTS	37.5 cm^2	application site erythema	related	N	moderate
32-010	MTS	25 cm^2	decreased appetite	related	N	moderate
33-007	MTS	25 cm^2	dry mouth	related	N	moderate
			anorexia	related	N	moderate
			sedation	related	N	mild
33-011	MTS	18.75 cm^2	dizziness	related	N	moderate
			syncope	related	Y	moderate
			syncope	related	Y	moderate
33-013	MTS	18.75 cm^2	psoriasis	not related	N	moderate
			folliculitis	not related	N	moderate
34-007	MTS	18.75 cm^2	somnolence	related	N	moderate
			fatigue	related	N	moderate
35-001	MTS	18.75 cm^2	application site dermatitis	related	N	moderate
40-001	MTS	25 cm^2	application site dermatitis	related	N	severe
04-006	Placebo	37.5 cm^2	negativism	not related	Y	severe
21-005	Placebo	25 cm^2	irritability	related	N	moderate
			mood altered	related	N	moderate

[a] Investigator's assessment of relationship to study drug

Data Source: Section 15, Table 3.3.3.2.A

(Clinical Study Report, p.86)

Adverse events leading to termination included loss of appetite, increased irritable mood, sedation, dry mouth, dizziness, syncope and application site reactions. There were no apparent cases of contact sensitization. The narratives of the subjects in the

MTS group who discontinued secondary to adverse events and application site reactions are summarized below.

Subject 14-004 was a 13-year-old male who discontinued secondary to application site erythema. He had the following application site reactions detailed in Table 33.

Table 33: Subject 14-004

Study Day	Patch Size	Application Site Reaction	Relationship to MTS
Day 11	18.75cm^2	Mild skin irritation	Related
Day 20	25cm^2	Mild application site erythema	Related
Day 32	37.5cm^2	Moderate application site pruritus	Related
Day 33	37.5cm^2	Moderate application site erythema	Related
Day 40-last dose given	37.5cm^2	Moderate application site erythema	Related
Day 42	--	Application site erythema and pruritus resolved (DRS of 2 and EODP of 2)	--

(Clinical Study Report, p. 717)

Subject 32-010 was a 16-year-old female who discontinued secondary to decreased appetite. Her course is summarized in Table 34.

Table 34: Subject 32-010

Study Day	Patch Size	Adverse Events	Relationship to MTS
Day 13	25cm^2	Moderate decreased appetite	Related
Day 17	25cm^2 » 18.75cm^2	Intolerable response to study medication and patch size decreased	Related
Day 41-last dose given	18.75cm^2	Decreased appetite, 6% decrease in weight from baseline	Related

(Clinical Study Report, p. 719)

Subject 33-007 was a 16-year-old male who discontinued due to the adverse events of dry mouth, anorexia, and sedation. His course is summarized in Table 35.

Table 35: Subject 33-007

Study Day	Patch Size	Adverse Events	Relationship to MTS
Day 30	25cm^2	Moderate dry mouth and anorexia	Related
Day 32	25cm^2	Mild sedation	Related
Day 34	discontinued	3.5% weight loss from baseline, dry mouth, sedation, and anorexia	Related

(Clinical Study Report, p. 721)

Subject 33-013 was a 15-year-old female who discontinued secondary to psoriasis and folliculitis. She had a history of dry skin and poison ivy allergy. She developed moderate

psoriasis ("mild psoriatic lesion at base of scalp") on Day 16 and moderate folliculitis on Day 19 which were judged by the investigator not to be related to the study medication. She was treated with clobetasol propionate for the psoriasis and cefalexin for the folliculitis. She also had a mild intercurrent URI. She was discontinued from the study on Day 29. The folliculitis resolved and the psoriasis was downgraded to mild.

Subject 34-007 was a 13-year-old male who discontinued secondary to the adverse events of somnolence and fatigue. On Study Day 15, the subject was reported to have moderate somnolence and moderate fatigue. These adverse events were considered to be related to the study medication. The last dose of the study medication was given 4 days later (Study Day 19) and the subject was discontinued from the study on Study Day 27. The adverse events had resolved by this time.

Subject 35-001 was a 13-year-old male who discontinued secondary to an application site dermatitis. The details of his course are summarized in Table 36.

Table 36: Subject 35-001

Study Day	Patch Size	Adverse Events	Relationship to MTS
Day 2	18.75cm^2	Mild headache	Related
Day 14	18.75cm^2	Mild weight loss	Related
Day 15	18.75cm^2	Mild dizziness	Related
Day 18	18.75cm^2	Moderate application site dermatitis	Related
Day 21	18.75cm^2	Moderate application site dermatitis » treated with topical hydrocortisone; maximal DRS of 3 at this visit	Related
Day 25	Discontinued	Moderate application site dermatitis	Related

(Clinical Study Report, p. 725)

Subject 40-001 was a 13-year-old male who discontinued due to an application site dermatitis (maculopapular rash at patch site bilaterally). The details of his course are summarized in Table 37.

Table 37: Subject 40-001

Study Day	Patch Size	Adverse Events	Relationship to MTS
Day 22	25cm^2	Mild discomfort (burning) with DRS of 3	Related
Day 24	25cm^2	Severe application site dermatitis (maculopapular rash at patch site bilaterally)	Related
Day 27	Discontinued	Application site dermatitis; DRS of 3 and EODP of 2	Related
Day 39	NA	Resolved	NA

(Clinical Study Report, p. 727)

7.3.4 Significant Adverse Events

Overall, 156 subjects (72%) experienced at least one AE. One or more TEAEs were reported for a higher percentage of the subjects in the MTS group (77%) than the placebo group (56%). The MedDRA SOCs with the largest percentages of subjects in the MTS group with one or more TEAEs were Infections and Infestations (30%), Metabolism and Nutrition (30%), Gastrointestinal Disorders (22%), Nervous System Disorders (17%), and Psychiatric Disorders (17%).

Table 38: Summary of Adverse Events-Safety Population

Number (%) of Subjects with one or more adverse events	Placebo N=72	MTS N=145	All N=217
AEs	42 (58.3)	114 (78.6)	156 (71.9)
Treatment-emergent AE (TEAE)	40 (56)	112 (77)	152 (70)
AE leading to discontinuation	2 (2.8)	8 (5.5)	10 (4.6)
Serious Adverse Event (SAE)	1 (1.4)	1 (0.7)	2 (0.9)
Treatment-emergent SAE	1 (1.4)	1 (0.7)	2 (0.9)
AE leading to death	0	0	0

(Clinical Report, p.73)

7.3.5 Submission Specific Primary Safety Concerns

Psychiatric Disorders SOC

One or more TEAEs in the Psychiatric Disorders SOC were reported for 17.2% of subjects in the MTS group and 12.5% of subjects in the placebo group. Two events were reported as severe: anxiety (MTS group) and negativism (SAE in placebo group). The negativism resulted in subject discontinuation. The most frequently reported AEs in the Psychiatric Disorders SOC were irritability (11% in MTS, 6.9% placebo) and insomnia (6.2% MTS, 2.8% placebo). No tics were reported as AEs in this study.

The safety results were also reviewed for psychiatric AEs of interest falling into four broad categories: psychosis/mania events, suicidal ideation, events related to hostility/aggression, and miscellaneous serious behavioral AEs. No psychiatric events of interest were identified. One subject (19-004) in the MTS group “wished she wasn’t alive.” The investigator considered the event to be stress-related, not serious, and of mild intensity. It was coded to a preferred term of *stress symptoms* and felt to be related to extreme work and activity stress in school. The subject’s after-school activities were reduced and she continued in the study.

Stimulant-Related Adverse Events

The frequency of stimulant-related adverse events was higher in the MTS group (47.6%) compared with the placebo group (25%) and higher for females and younger subjects. Four aggregate categories were analyzed: appetite-related, headache-related, affect-related, and insomnia-related.
Appetite-related TEAEs included decreased appetite, anorexia, and weight decreased. The percentage of subjects with one or more appetite-related TEAEs was higher in the MTS group (33.8%) than in the placebo group (4.2%). The majority in the MTS group were of mild severity (71.9%), although two subjects in the MTS group discontinued as a result of an appetite-related AE. One subject (32-010) experienced a decreased appetite and a 6% decrease in weight from baseline to Day 41 and therefore was discontinued from the study. Another subject (33-007) was discontinued secondary to dry mouth, anorexia, and sedation. He experienced a 3.5% loss from his baseline weight after about a month of MTS.

Table 39: Summary of Appetite-Related TEAEs-Safety Population

Parameter	Placebo N=72	Total MTS N=145
Onset day of first appetite-related TEAE Mean	21	13
Duration of appetite-related TEAEs (days) Mean	11.7	23.2
Number of subjects who discontinued as a result of appetite-related TEAE	0	2

(Clinical Study Report, p.78)

The percentage of subjects in the MTS group with newly reported appetite-related AEs was highest at Week 1. Fifty-two percent (52%) of the appetite-related AEs in the MTS group resolved while the subjects were still receiving study medication.

Headache-related AEs included headache, tension headache, migraine, and post-traumatic headache. The frequency of headache-related AEs was similar between the MTS group (13%) and the placebo group (12.5%). None of the headache-related AEs resulted in discontinuation from the study.

Affect-related TEAEs included affect lability, affective disorder, depressed mood, depression, dysphoria, emotional disorder, irritability, and mood altered. The percentage of subjects with affect-related TEAEs was higher for the MTS group (12.4%) than the placebo group (8.3%). The majority (60%) of affect-related TEAEs in the MTS group were mild and resolved while the subjects were on treatment.

Table 40: Summary of Affect-Related TEAEs-Safety Population

Parameter	Placebo N=72	Total MTS N=145
Number (%) of subjects with affect-related TEAE	6 (8.3)	18 (12.4)
Onset of day of first affect-related TEAE	20	13.4
Duration of affect-related TEAEs (days)	15.8	17
Number of subjects who discontinued as a result of affect-related TEAE	1	0
Outcome (%)		
Resolved while on study drug	42.9%	60%
Ongoing	28.6%	30%

(Clinical Study Report, p. 80)

Insomnia-related AEs included insomnia, initial insomnia, and middle insomnia. The percentage of subjects with insomnia-related AEs was higher for the MTS group (9%) than the placebo group (2.8%). All events were of mild or moderate intensity and none resulted in discontinuation from the study. The majority (80%) resolved while the subjects were receiving the study medication. Two subjects in the MTS group required pharmacologic treatment for the insomnia. The majority (69%) of the subjects in the MTS group who experienced an insomnia-related event were in the 13-14 year age group. Overall, the majority of subjects in both groups assessed the quality of their sleep as average or better in the Post Sleep Questionnaire (PSQ).

Table 41 : Summary of PSQ- Safety Population

Question	Placebo n(%)		Total MTS n(%)	
	Baseline N=44	Week 7 N=58	Baseline N=95	Week 7 N=121
Rate the overall quality of your sleep:				
Very Poor	1 (2.3)	2 (3.4)	1 (1.1)	2 (1.7)
Poor	8 (18)	7(12.1)	9 (9.5)	14 (11.6)
Average	10 (22.7)	13 (22)	32 (34)	27 (22.3)
Good	14 (31.8)	18 (31)	34 (35.8)	47 (38.8)
Very good	11 (25)	18 (31)	19 (20)	31 (25.6)

(Clinical Study Report, p. 1092, 1094)

Table 42: Summary of Key Stimulant-Related TEAEs-Safety Population

Table 25 Summary of Key Stimulant-related Treatment-Emergent Adverse Events – Safety Population

AE Category	Placebo N=72	Total MTS N=145
Appetite-related		
Subjects with ≥1event n(%)	3 (4.2)	49 (33.8)
SAE	0	0
Subjects Discontinued	0	2
Total number of events	3	57
Percent of events mild/moderate	33.3%, 66.7%	71.9%, 28.1%
Percent of events resolved on treatment	66.7%	52.6%
Headache-related		
Subjects with ≥1event n(%)	9 (12.5)	19 (13.1)
SAE	0	0
Subjects Discontinued	0	0
Total number of events	9	22
Percent of events mild/moderate	66.7%, 22.2%	68.2%, 27.3%
Percent of events resolved on treatment	77.8%	86.4%
Affect-related		
Subjects with ≥1event n (%)	6 (8.3)	18 (2.4)
SAE	0	0
Subjects Discontinued	1	0
Total number of events	7	20
Percent of events mild/moderate	57.1%, 42.9%	60.0%, 40.0%
Percent of events resolved on treatment	42.9%	60.0%
Insomnia-related		
Subjects with ≥1 event n (%)	2 (2.8)	13 (9.0)
SAE	0	0
Subjects Discontinued	0	0
Total number of events	2	15
Percent of events mild/moderate	100%, 0%	73.3%, 26.7%
Percent of events resolved on treatment	100.0%	80.0%

Appetite-related preferred terms: decreased appetite, anorexia, and weight decreased
Headache-related preferred terms: headache, tension headache, migraine, post-traumatic headache
Affect-related preferred terms: affect lability, affective disorder, depressed mood, depression, dysphoria, emotional disorder, irritability and mood altered
Insomnia-related preferred terms: initial insomnia, insomnia, and middle insomnia
Data Source: Section 15, Table 3.3.8.1.1, Table 3.3.8.2.1, Table 3.3.8.3.1,Table 3.3.8.5.1

(Clinical Study Report, p. 82)

Dizziness-Related Adverse Events

Dizziness-related TEAEs were reported for eight (5.5%) subjects in the MTS group and one (1.4%) subject in the placebo group. One subject (33-011) in the MTS group discontinued due to two serious syncopal events associated with dizziness. The subject was a 14 year old male who had episodes of syncope on Days 9 and 12. Both episodes of syncope occurred approximately 1 hour after removal of the patch and lasted less than 30 seconds. His physical exam, lab work and ECGs were not clinically significant. No ECGs were done while the subject was on treatment but his screening, baseline, and early termination visit ECGs were reviewed by a pediatric cardiologist. No evidence of structural heart disease or aberrant conduction was found.

Application Site and Dermal Reactions

Nine (6.2%) subjects in the MTS group experienced 13 application site reactions. These included burning (2), dermatitis (2), erythema (3), irritation (1), pigmentation changes (1), and pruritus (3). Three subjects discontinued as a result of the application site reaction. One reaction required pharmacologic treatment, topical hydrocortisone. No trend between patch size and number of application site reactions was noted.

One subject (15-008) in the placebo group experienced bleeding and scabbing when the patch was applied directly under the elastic of the patient's underwear. The subject had no further reactions when the patch was applied to the correct site.

The mean Dermal Response Scale (DRS) score for current and prior applications was higher for total MTS than PTS at all weekly visits. The majority of subjects in the placebo group did not have a DRS score > 1. All current and prior DRS scores in the placebo group were $\leq$ 2 except for one subject with a score of 5. In the MTS group, the majority of subjects (90%) had scores $\leq$ 2 and 19% had no dermal reaction. Three subjects in the MTS group had one or more DRS $\geq$ 4. Two subjects experienced a DRS score of 4 and one subject experienced a score of 5.

Dermal Response Scale

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Table 43: Dermal Response Scale Scores by Week-**Placebo Group**

Week	Dermal Response Scale Placebo Group n(%)							
	0	1	2	3	4	5	6	7
1	62 (87)	8 (11)	0	0	0	1(1.4)	0	0
2	60(87)	7(10)	2(2.9)	0	0	0	0	0
3	53(81.5)	8 (12)	4(6)	0	0	0	0	0
4	49(80.3)	9(14.8)	3 (4.9)	0	0	0	0	0
5	50(83.3)	7(11.7)	3(5)	0	0	0	0	0
6	32(94)	0	2(5.9)	0	0	0	0	0
7	22(75.9)	6(20.7)	1(3.4)	0	0	0	0	0

Table 44: Dermal Response Scale Scores by Week-**MTS Group**

Week	Dermal Response Scale MTS group n(%)							
	0	1	2	3	4	5	6	7
1	75 (54)	41(29.5)	23(16.5)	0	0	0	0	0
2	63 (47)	47(35)	22 (16)	1(0.8)	0	0	0	0
3	54(43)	37(29.6)	28(22.4)	4 (3.2)	2(1.6)	0	0	0
4	49(38.9)	43(34)	32(25.4)	1(0.8)	0	1(0.8)	0	0
5	43(35.5)	41(33.9)	36(29.8)	0	0	1(0.8)	0	0
6	42(41.2)	32(31.4)	26(25.5)	2(2)	0	0	0	0
7	39(40.6)	33(34.4)	23(24)	1(1)	0	0	0	0

(Clinical Study Report, p. 1028-1052)

Mean experience of discomfort was low for both treatment groups. Most subjects who experienced discomfort described it as itching for PTS and itching and/or burning for MTS.

Dermal Discomfort scale

0	No discomfort
1	Mild discomfort
2	Moderate but tolerable discomfort
3	Severe, intolerable discomfort

Table 45: Incidence of Type of Dermal Discomfort Experienced -Safety Population

Visit	Experience of Discomfort Scale	MTS Total Group N=145	
		Current n(%)	Prior n(%)
Week 1		n=140	n=139
	0	119 (85)	124 (89.2)
	1 itching	14 (10)	10 (7.2)
	burning	7 (5)	4 (2.9)
	other	1 (0.7)	1 (0.7)
	2 itching	1 (0.7)	0
	burning	1 (0.7)	0
	other	0	0
	3 itching	1 (0.7)	2 (1.4)
	burning	1 (0.7)	1 (0.7)
	other	0	0
Week 7		n=96	n=96
	0	73 (76)	84 (87.5)
	1 itching	17 (17.7)	10 (10.4)
	burning	6 (6.3)	2 (2.1)
	other	0	0
	2 itching	1 (1)	1 (1)
	burning	0	0
	other	0	0
	3 itching	0	0
	burning	0	0
	other	0	0

The AE data were reviewed for reports of rash other than at the application site. One subject in the placebo group had a rash on the arms and chest that was considered unrelated to the study medication. Two subjects in the MTS group had contact dermatitis and two subjects had excoriations (abrasions). All were considered unrelated to the study medication.

Corticosteroid use was reviewed to further track possible skin reactions. It was determined that corticosteroids were received by nine subjects as a prior or concomitant medication. Six of the nine subjects received corticosteroids to treat allergies or asthma. One subject received it for an ear infection and one for the treatment of scalp psoriasis. Only 1 subject in the MTS group received corticosteroid treatment (hydrocortisone cream) for the treatment of an application site reaction.

The mean Transdermal System Adherence (TSA) was similar for MTS and PTS. Five subjects reported a detached MTS patch and no subjects reported a detached PTS patch. The majority of subjects in both groups reported TSA to be ≥ 90%.

Transdermal System Adherence

0	≥90% adhered (essentially no lift off of the skin)
1	≥75% to <90% adhered (some edges only lifting off of the skin)
2	≥50% to <75% adhered (less than half of the system lifting off of the skin)
3	<50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4	MTS/PTS detached (system completely off the skin)

Table 46: Transdermal System Adherence

Week	Group	Transdermal System Adherence				
		0	1	2	3	4
1	Placebo (n=42)	37 (88)	5 (12)	0	0	0
	MTS (n=92)	65 (71)	21 (23)	3 (3.3)	2 (2.2)	1 (1.1)
2	Placebo (n=39)	35 (90)	4 (10)	0	0	0
	MTS (n=90)	67 (74)	19 (21)	3 (3.3)	1 (1.1)	0
3	Placebo (n=46)	40 (87)	3 (6.5)	3 (6.5)	0	0
	MTS (n=85)	57 (67)	21 (25)	4 (4.7)	0	3 (3.5)
4	Placebo (n=36)	31 (86)	3 (8.3)	2 (5.6)	0	0
	MTS (n=92)	71 (77.2)	15 (16.3)	4 (4.3)	2 (2.2)	0
5	Placebo (n=41)	38 (93)	3 (7)	0	0	0
	MTS (n=80)	61 (76)	16 (20)	3 (3.8)	0	0
6	Placebo (n=18)	17 (94.4)	1 (5.6)	0	0	0
	MTS (n=69)	55 (80)	11 (16)	1 (1.4)	1 (1.4)	1 (1.4)
7	Placebo (n=14)	11 (78.6)	3 (21.4)	0	0	0
	MTS (n=61)	50 (82)	10 (16.4)	1 (1.6)	0	0

(Clinical report, p. 1030-1054)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported TEAEs in the MTS group were decreased appetite (25.5%), headache (12.4%), irritability (11%), URI (10.3%), nausea (9.7%), insomnia

(6.2%), weight decreased (5.5%), and dizziness (5.5%). The incidence of headache and URI was similar between MTS and placebo groups.

Table 47: Summary of Treatment-Emergent Adverse Events ≥ 5% in the Total MTS Group by System Organ Class and Preferred Term-Safety Population

System Organ Class Preferred term	Placebo N=72		Total MTS N=145	
Number (%) of subjects with ≥1 event:				
Gastrointestinal disorders				
Nausea	2	(2.8)	14	(9.7)
Infections and infestations				
Upper respiratory tract infection	7	(9.7)	15	(10.3)
Investigations				
Weight decreased	1	(1.4)	8	(5.5)
Metabolism and nutrition disorders				
Decreased appetite	1	(1.4)	37	(25.5)
Nervous system disorders				
Dizziness	1	(1.4)	8	(5.5)
Headache	9	(12.5)	18	(12.4)
Psychiatric disorders				
Insomnia	2	(2.8)	9	(6.2)
Irritability	5	(6.9)	16	(11.0)

(Clinical Study Report, p. 74)

Severity of Adverse Events

TEAEs were rated by intensity. Only 5 subjects were reported to have experienced a severe TEAE: 3 subjects in the MTS group (application site dermatitis, headache and anxiety) and 2 subjects in the placebo group (severe headache and negativism). The percentages of subjects with mild (25% vs. 36.6%) and moderate (27.8% vs. 38.6%) TEAEs were lower in the placebo group than the MTS group.

Relationship of Adverse Events to Study Treatment

The relationship of AEs to study medication was established based on the investigator's judgment. Related TEAEs were reported for 51.7% of subjects in the MTS group (168 events) and 25% of the subjects in the placebo group (33 events). The MedDRA SOCs with the most frequently reported related TEAEs in the MTS group were Metabolism and Nutrition Disorders, Psychiatric Disorders, Gastrointestinal Disorders, and Nervous

System Disorders. The most commonly reported (≥ 5%) related TEAEs in the MTS group were decreased appetite (24.8%), irritability (9.7%), nausea (6.9%), insomnia (7.5%), and dizziness (5.5%).

Table 48: Summary of Related TEAEs-Safety Population

Parameter	**Placebo** N=72 n (%)	**Total MTS** N=145 n (%)
Any related TEAEs	18 (25)	75 (51.7)
Cardiac Disorders		
Tachycardia	0	1 (0.7)
Eye Disorders		
Blepharospasm	1 (1.4)	0
Vision Blurred	0	1 (0.7)
Gastrointestinal Disorder		
Abdominal Discomfort/Pain/Pain Upper/ Stomach Discomfort	0	7 (4.8)
Diarrhea	0	1 (0.7)
Dry Mouth	0	1 (0.7)
Dyspepsia	0	1 (0.7)
Nausea	1 (1.4)	10 (6.9)
Vomiting	0	3 (2.1)
General Disorders and Administration Site Conditions		
Application Site Burning	0	2 (1.4)
Application Site Dermatitis	0	2 (1.4)
Application Site Erythema	0	3 (2.1)
Application Site Irritation	0	1 (0.7)
Application Site Pigmentation Changes	0	1 (0.7)
Application Site Pruritus	0	3 (2.1)
Fatigue	0	5 (3.4)
Sluggishness	0	1 (0.7)
Investigations		
Blood Pressure Increased	0	1 (0.7)
Heart Rate Increased	0	2 (1.4)
Weight Decreased	1 (1.4)	7 (4.8)
Metabolism and Nutrition Disorders		
Anorexia	1 (1.4)	6 (4.1)
Decreased Appetite	1 (1.4)	36 (24.8)
Polydipsia	0	1 (0.7)
Musculoskeletal and Connective Tissue Disorders		
Pain in Extremity	0	1 (0.7)
Nervous System Disorders		
Dizziness	1 (1.4)	8 (5.5)
Headache	5 (6.9)	7 (4.8)
Paresthesia	1 (1.4)	0
Psychomotor Hyperactivity	1 (1.4)	0
Sedation	0	2 (1.4)

Somnolence	5 (6.9)	1 (0.7)
Syncope	0	1 (0.7)
Tension Headache	0	1 (0.7)
Tremor	0	1 (0.7)
Psychiatric Disorder		
Affect Liability	1 (1.4)	0
Anxiety	1 (1.4)	1 (0.7)
Depression	0	1 (0.7)
Emotional Disorder	0	1 (0.7)
Initial Insomnia/Insomnia/Middle Insomnia	2 (2.8)	11 (7.5)
Irritability	4 (5.6)	14 (9.7)
Mood Altered	1 (1.4)	2 (1.4)
Tension	0	1 (0.7)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	0	1 (0.7)
Hemoptysis	0	1 (0.7)
Nasal Congestion	1 (1.4)	2 (1.4)
Pharyngolaryngeal Pain	1 (1.4)	1 (0.7)
Skin and Subcutaneous Tissue Disorders		
Acne	1 (1.4)	0
Pruritus	0	1 (0.7)
Scab	1 (1.4)	0
Vascular Disorders		
Hemorrhage	1 (1.4)	0

(Clinical Study report, p. 499-502)

Examples of AEs determined to be unrelated to the study drug in the MTS group included scleral hemorrhage, some episodes of gastrointestinal symptoms, toothache, pyrexia, tinea, infections (URI, influenza, strep pharyngitis, bronchitis), hordeolum, joint injuries/sprains, burn, dysmenorrhea, epistaxis, acne, psoriasis, and facial swelling.

7.4.2 Laboratory Findings

MTS did not show any clinically meaningful effects on hematology, chemistry, or urinalysis values at Week 7 relative to baseline. No AEs related to abnormalities in hematology or chemistry were reported. An AE of mild proteinuria was reported for one subject in the MTS group.

The percentage of subjects with normal leukocyte counts at screening that shifted to abnormally low was slightly higher in the MTS group (6 subjects; 4.5%) than the placebo group (1 subject; 1.5%). One subject in the MTS group showed a shift in percent lymphocytes from normal to abnormally high and 5 subjects in the MTS group showed a shift in percent lymphocytes from normal to PCI high. Only one subject in the placebo group showed a similar shift.

Shifts in alkaline phosphatase from normal to abnormally high were seen more commonly in the placebo group (4.7%) than the MTS group (2.9%). These elevations in alkaline phosphatase were felt to be related to normal growth spurts in adolescents. Shifts in total bilirubin from normal to abnormally high or PCI high were seen more often in the MTS group (5 subjects; 3.7%) than the placebo group (1 subject; 1.5%). A total of 8 subjects (6 in the MTS group and 2 in the placebo group) had one or more PCI high values for total bilirubin. Liver function tests were normal and the observations of abnormally high bilirubin were not classified as adverse events but rather were considered to be a manifestation of Gilbert's syndrome.

Three subjects (2.2%) in the MTS group showed a shift in urine protein from normal to PCI high. There were no shifts in the placebo group. An AE of mild proteinuria was reported for one subject (29-004) in the MTS group. The proteinuria was not associated with hematuria, hypertension or any other signs or symptoms and was not considered to be related to study treatment by the investigator.

7.4.3 Vital Signs

Pulse rate

Mean pulse rate and change from baseline in mean pulse rate increased over the first 5 weeks of MTS treatment. Pulse rate in the MTS group increased by 6.5 to 7.1 bpm while the placebo group's change in pulse rate from baseline averaged -1.5 to +1.9 bpm. More subjects at endpoint in the MTS group (6.3%) compared to the placebo group (1.4%) showed shifts from normal to PCI high values for pulse. High outlier values for pulse ($\geq$ 100 bpm) were also reported more frequently for the MTS group. The highest treatment-emergent PCI high pulse value reported was 111 bpm.

Table 49: Change from Baseline in Pulse Rate

Parameter	Placebo Mean Change from Baseline	MTS Mean Change from Baseline
Week 7	-1.5	6.7

(Clinical Study Report, p. 806)

There was no clear evidence of a dose response relationship in the MTS group.

Table 50: Change from Baseline in Pulse Rate by Patch Size

Parameter	MTS 12.5cm^2	MTS 18.75cm^2	MTS 25cm^2	MTS 37.5cm^2
Week 7 Mean Change from Baseline in Pulse Rate	12.0	6.4	5.5	6.9

(Clinical Study Report, p. 807-808)

One subject (40-005) in the MTS group experienced an adverse event reported as moderate tachycardia. The maximum pulse rate recorded for this subject was 76bpm at Week 6. Heart rate increased was reported as an AE for 2 subjects in the MTS group. Subject 19-004 exhibited PCI high pulse rate of 109bpm at Week 4 and Subject 28-004 exhibited PCI high pulse rates of 100bpm and 104bpm at Week 6 and 7.

Oral Temperature

Mean oral temperature increased from baseline in the MTS group, with maximal mean increases of +0.25°F observed at Week 7. According to Shire, this observation is consistent with the literature.

Five subjects in the MTS group experienced 6 TEAEs of pyrexia, most in association with infections. All resolved and only one subject had an oral temperature > 100°F.

Blood Pressure

The MTS group showed an increase from baseline in mean systolic and diastolic blood pressure. The greatest mean increases in SBP were observed at Week 6 (+2.4 mmHg), Week 7 (+2.9mmHg), and endpoint (+2.0mmHg). Mean increases in diastolic blood pressure ranged from 0 to +2.3mmHg for Weeks 1-4 and from +1.7 to 2.2mmHg for Weeks 5, 6, and 7.

For the placebo group, mean changes from baseline in SBP were unchanged or negative. Mean changes from baseline in DBP were generally negative for the first 4 weeks but positive and similar in magnitude to the MTS group for Weeks 5-7. At endpoint, mean change from baseline for DBP was slightly higher for the MTS group (+1.9mmHg) compared with the placebo group (+1.1mmHg).
At endpoint, 1.4% of the subjects in the MTS group and no subjects in the placebo group reported a shift from normal to PCI high values for SBP. At endpoint, 0.7% of the subjects in the MTS group and 2.8% of subjects in the placebo group experienced shifts in DBP from normal to PCI high values.

Table 51: PCI SBP and DBP at Baseline and Endpoint

Parameter	Placebo		Total MTS	
	Baseline n (%)	Endpoint n (%)	Baseline n (%)	Endpoint n (%)
Systolic BP				
<90	2 (2.8)	1 (1.4)	2 (1.4)	1 (0.7)
>140	1 (1.4)	0	1 (0.7)	3 (2.1)
Diastolic BP				
<50	1 (1.4)	1 (1.4)	0	2 (1.4)
>85	0	2 (2.8)	0	1 (0.7)

(Clinical Study Report, p. 884)

An AE of moderate blood pressure increased was reported for 1 subject (28-004) in the MTS group. This was a 13-year-old white male with a screening BP of 113/76. At Week 6, his BP was 131/88 and an AE of moderate BP increased was reported.

No subjects discontinued as a result of pulse or BP abnormalities.

Respiratory Rate

Mean respiratory rate was decreased from baseline at all study visits in the MTS group. At endpoint, the MTS group showed a -0.5 change from baseline in respiratory rate (breaths per minute) compared with no change in the placebo group. Shire considers this observation to be of no clinical significance and not consistent with results reported in the literature where increased respiratory rate with MPH were observed.

Weight and Height

Mean weight decreased from baseline by 1.90 pounds at endpoint in the MTS group. Subjects in the placebo group showed small increases in mean weight. In the MTS group, mean weight z-scores declined over the dose optimization period (Weeks 1-5) and stabilized after Week 5. Weight z-scores for the placebo group were greater than baseline at all weekly assessments.

Three subjects in the MTS group showed a weight loss $\geq$ 7% from baseline. No subjects in the placebo group had a similar weight loss. Two subjects in the MTS group discontinued as the result of appetite-related AEs. Weight decreased was reported as an AE for eight subjects in the MTS group and one subject in the placebo group.

Mean height increase was similar between the two treatment groups.

Table 52: Summary of Change from Baseline Weight and Height-Safety Population

Parameter	Placebo N=72		Total MTS N=145	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Mean Weight at Endpoint	131.2	1.77	129.2	-1.9
Weight (z-score) Baseline Endpoint	 0.34 0.42		 0.52 0.44	
Mean Height (in) at Endpoint	65.2	0.24	65.55	0.21

(Clinical Study report, p. 95)

Relationship of Drug Concentration to Vital Signs and Weight

Exploratory regression analyses of vital signs and d-MPH plasma concentrations after a 9-hour wear-time were done. Systolic blood pressure, diastolic blood pressure, and pulse rate showed a significant positive correlation. Weight showed a significant inverse correlation with plasma concentrations of d-MPH.

Table 53: Exploratory Regression Analyses

Parameter	Regression Coefficient	p-value
Systolic BP	0.219	<0.001
Diastolic BP	0.109	0.036
Pulse	0.312	<0.001
Respiration	-.008	0.677
Weight	-.087	<0.001

(Clinical Study report, p.1101)

Table 54: Change in Weight from Baseline by Patch Size

Parameter	MTS 12.5cm^2		MTS 18.75cm^2		MTS 25cm^2		MTS 37.5cm^2	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Mean Weight at Endpoint	139.1	0.02	128.1	-1.78	128.5	-2.53	127.7	-2.08

(Clinical Study report, p.846-847)

7.4.4 Electrocardiograms (ECGs)

The frequency of clinically significant ECG abnormalities was similar between the MTS group (11%) and the placebo group (11.1%).

Heart Rate and RR Interval

Heart rate increased from baseline at endpoint (+5.1bpm) and RR decreased from baseline at endpoint in the MTS group. No clear dose response was seen but subjects receiving the 37.5cm^2 patch showed the greatest mean increase in HR from baseline at endpoint (+7.4bpm).

No treatment-emergent PCI high HR intervals were seen in the placebo group. No subjects in the placebo group had HR > 110bpm. Ten subjects in the MTS group had treatment-emergent PCI high HR. Two subjects who were receiving the 37.5cm^2 patch had HR > 110bpm. Subject 28-004 had a HR of 140bpm at Week 7. Besides the AE of

moderate increased heart rate, the subject had AEs of mild decreased appetite, severe increased anxiety, and moderate increased blood pressure. Subject 36-003 had a HR of 115bpm at Week 5 that returned to normal (83bpm) at Week 7.

PR Interval

No clinically meaningful changes in PR interval were seen for either treatment group.

QRS Interval

No clinically meaningful changes in QRS interval were seen for either treatment group.

QT/QTc Interval

After QT was corrected using the Fridericia method, no clinically meaningful changes from baseline in mean QTcF were seen. A higher percentage of subjects in the MTS group (4.2-10.9%) showed QTcF increases of ≥ 30-59 msec compared with the placebo group (1.4-5%).

Two subjects in the MTS group had one or more QTcF interval durations ≥ 450 msec. Subject 21-008 had a QTcF of 409 at screening and a QTcF of 451 at Week 7 (PCI HR at 104bpm). The QTcF of 451 was considered PCI by the ECG central laboratory and not clinically significant by the investigator. Subject 33-007 had a baseline QTcF of 461 msec. The subject discontinued after 34 days as a result of noncardiac-related AEs of sedation, dry mouth, and loss of appetite. The QTcF was 419 msec at the early termination visit.

Table 55: Summary of ECG Results-Safety Population

Parameter (Mean Value at Endpoint)	Placebo N=72		Total MTS N=145	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Mean Heart Rate (bpm)	69	-1.7	75.1	5.1
Mean PR Interval (msec)	140.2	-0.4	141.8	-0.7
Mean QRS Interval(msec)	87.1	-0.2	85.9	-0.6
Mean RR Interval (msec)	890.3	22.4	821.3	-53.6
Mean QTcF (msec)	392.3	-0.8	391.1	-1.3

(Clinical Study report, p.929-947)

7.4.5 Safety Data from Study SPD485-410 and Study SPD485-106

Long-term Safety Data from Study SPD485-410

In general, the category and frequency of adverse events were similar to those found in Study SPD485-409 and in a previous open-label long-term study in children.

Exposure

Median duration of exposure to MTS for all subjects during Study SPD485-410 was 168 days. The total exposure was 57.6 subject-years. Cumulative MTS exposure in SPD485-409 and SPD485-410 is detailed in Table 56.

Table 56: Cumulative MTS Exposure in SPD485-409 and SPD485-410-Safety Population

Parameter	Total MTS
Length of Exposure (days)	
n	198
Mean	136.5
Median	164.5
Length of Exposure Category (days)	n (%)
>90 days	128 (65)
>180 days	85 (43)
Total Subject Years of Exposure	74.0

(Summary of Clinical Safety, p. 14)

Disposition

A total of 163 subjects enrolled in Study SPD485-410. Seventy-five subjects did not complete the 5-month dose maintenance period. The most commonly reported reasons for early termination were consent withdrawn (36%), lost to follow-up (25.3%), and adverse events (16%). The AEs leading to discontinuation that were reported for more than 1 subject were: application site reaction (3 subjects), irritability (2 subjects), and affect lability (2 subjects).

Table 57: List of Subjects in Study SPD484-410 Who Discontinued as Result of Adverse Event

Subject ID	Patch Size	Preferred Term	Related	SAE	Severity
SPD485-410					
04-001	25cm^2	Social avoidant behavior	Y	N	moderate
08-003	25cm^2	Application site reaction	Y	N	moderate
11-006	18.75cm^2	Decreased appetite[c]	Y	N	moderate
		Weight decreased[c]	Y	N	moderate
		Compulsions	Y	N	moderate
21-006	37.5cm^2	Affect lability	Y	N	moderate
		Irritability	Y	N	moderate
25-013	25cm^2	Clonic convulsion	N	Y	mild
27-001	37.5cm^2	Application site burning	Y	N	severe
27-006	37.5cm^2	Nausea	Y	N	moderate
28-006	12.5cm^2	Anxiety	Y	N	moderate
29-002	18.75cm^2	Affect lability	Y	N	moderate
30-009	37.5cm^2	Hallucination, auditory	Y	Y	moderate
		Hallucination, visual	Y	Y	moderate
35-005	37.5cm^2	Application site erythema	Y	N	moderate
		Application site oedema	Y	N	moderate
		Application site pruritus	Y	N	moderate
37-007	12.5cm^2	Irritability	Y	N	mild

(Summary of Clinical Safety, p.27)

Deaths and Serious Adverse Events

There were no deaths.

Four subjects had 5 SAEs during the study: clonic convulsion, grand mal convulsion, auditory and visual hallucinations, and syncope. Only the episodes of auditory and visual hallucinations were considered related to the study drug.

The investigator did not consider the episode of syncope upon standing to be related to MTS. A pediatric cardiologist reviewed the ECGs of the subject (35-010) who experienced syncope. There were no findings indicative of structural heart disease or accessory conduction pathway. The syncopal event was felt to be neurocardiogenic or vasovagal in nature.

The episodes of seizures were also felt to be unrelated to MTS. One subject (34-002) experienced a grand mal convulsion while playing video games 6 days after completing the study treatment (MTS 37.5 cm^2). He was on an oral MPH product at the time. He was hospitalized and evaluated. The oral MPH was discontinued. Except for a “mildly abnormal” EEG, his test results were negative.

Another subject (25-013) experienced a mild clonic convulsion and MTS was discontinued. CT and MRI showed a cavernous hemangioma and anticonvulsant treatment was started. The subject's mother subsequently reported that the subject had previously experienced "daily seizures with vomiting" prior to the start of the MTS treatment.

Subject 35-009 experienced SAEs of auditory and visual hallucinations which led to hospitalization. The subject had no prior history of hallucinations or psychiatric disorders. The subject recovered promptly after the MTS was discontinued. Therefore, the investigator considered these hallucinations to be related to the study drug.

Table 58: Subjects with SAEs in Study SPD485-410

Subject ID	MTS Patch Size at Onset	Sex/Age	SAE Preferred Term	Related	Discontinued
25-013	MTS 25cm^2	M/13	Clonic convulsion	N	Y
30-009	MTS 37.5 cm^2	F/13	Hallucination, auditory Hallucination, visual	Y Y	Y Y
34-002	None (event occurred after completion of study)	M/13	Grand mal convulsion	N	N
35-010	MTS 37.5cm^2	M/15	Syncope	N	N

(Summary of Clinical Safety, p.25)

Adverse Events

Overall, 133 (82%) subjects had at least one AE and 119 (73.5%) subjects had at least one TEAE.

Table 59: Summary of Adverse Events in SPD485-410 Safety Population

Event	Antecedent Treatment In Study SPD485-409		All MTS N=162
	Placebo N=53	MTS N=109	
AE	46 (87%)	87 (80%)	133 (82%)
TEAE	43 (81%)	76 (70%)	119 (73.5%)
Treatment-emergent SAE	1 (1.9%)	2 (1.8%)	3 (1.9%)
AE Leading to Death	0	0	0

(Summary of Clinical Safety, p.17)

Key stimulant-related TEAEs were also analyzed. Four categories were determined: appetite-related, headache-related, affect-related, and insomnia-related. No unexpected stimulant-related events were observed.

Table 60: Summary of Key Stimulant-related TEAEs in SPD485-410--Safety Population

AE Category Subjects with ≥ 1 event: n (%)	MTS N=162
Appetite-related	32 (19.8%)
SAE	0
Subjects discontinued	0
% resolved on treatment	44.4%
Headache-related	21 (13%)
SAE	0
Subjects discontinued	0
% resolved on treatment	91.3%
Affect-related	15 (9.3%)
SAE	0
Subjects discontinued	3
% resolved on treatment	68.4%
Insomnia-related	7 (4.3%)
SAE	0
Subjects discontinued	0
% resolved on treatment	66.7%

(Summary of Clinical Safety, p.31)

Common Adverse Events

The most commonly reported TEAEs were decreased appetite (15.4%), headache (11.7%), URI (10.5%), nasopharyngitis (8%), and irritability (6.2%). These results were consistent with the short-term antecedent study in adolescents (SPD485-409) and generally similar to the common TEAEs seen in a long-term study in children (SPD485-303).

Table 61: Common TEAEs in Long-term Open-label Studies in Adolescents and Children

Table 8: Commonly Reported Treatment-emergent Adverse Events (≥5%) in Long-term Open-label Studies of MTS in either Adolescents (SPD485-410) or Children (SPD485-303) - Safety Population

System Organ Class Preferred term n (%)	SPD485-410[a] Adolescents N=162	SPD485-303[b, c] Children N=326
Gastrointestinal Disorders		
Abdominal pain, upper	6 (3.7)	27 (8.3)
Nausea	3 (1.9)	20 (6.1)
Vomiting	3 (1.9)	23 (7.1)
General Disorders and Administration Site Conditions		
Pyrexia	3 (1.9)	33 (10.1)
Infections and Infestations		
Nasopharyngitis	13 (8.0)	24 (7.4)
Upper respiratory tract infection	17 (10.5)	40 (12.3)
Investigations		
Weight decreased	5 (3.1)	33 (10.1)
Metabolism and Nutrition Disorders		
Decreased Appetite	25 (15.4)	81 (24.8)
Nervous System Disorders		
Headache	19 (11.7)	54 (16.6)
Psychiatric Disorders		
Insomnia	5 (3.1)	29 (8.9)
Irritability	10 (6.2)	20 (6.1)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	1 (0.6)	38 (11.7)
Nasal congestion	4 (2.5)	18 (5.5)
Pharyngolaryngeal pain	5 (3.1)	19 (5.8)

[a] MTS treatment duration up to 6 months
[b] MTS treatment duration up to 12 months
[c] SPD485-303 was previously submitted as part of the NDA 21-514 resubmission (28 Jun 2005)

(Summary of Clinical Safety, p.19)

Application-site and Dermal Reactions

There were 14 AEs that were ASRs. Only one report (application site burning) was termed severe. One event (application site reaction) required pharmacologic treatment with desloratadine. Three subjects discontinued as the result of an ASR. No trend between patch size and the frequency of ASRs was apparent.

Table 62: Summary of Application-site Reactions

Event	Number
Application site pruritus	6
Application site burning	2
Application site reaction	2
Application site erythema	1
Application site irritation	1
Application site pigmentation change	1
Application site edema	1
Application site dryness	1

(Summary of Clinical Safety, p.33)

Mean dermal response scores ranged from 0.7 to 1 for current applications and 0.2 to 0.4 for prior applications. The majority of subjects (83.5%) had maximum current DRS score of 1, 2, or 3. Only 14.6% had no dermal reactions. Four subjects had a maximum score of 5 and were wearing the 37.5cm^2 patch. No subjects had scores > 5.

Clinical Laboratory Evaluations

No laboratory-related TEAEs were identified as signals of concern.

Vital Signs: Pulse Rate

The mean change from SPD485-409 baseline was +5.2bpm at endpoint and +7.3bpm at Month 6. Fourteen subjects had a pulse rate ≥ 110bpm and 2 had a pulse rate ≥ 120bpm. Two subjects experience mild or moderate non-serious AEs related to heart rate.

Vital Signs: Blood Pressure

Increases on mean SBP and DBP from SPD485-409 baseline were observed at all visits throughout the study. At endpoint, mean increase from baseline was 4.2mmHg for SBP and 1.7mmHg for DBP. No dose-response trends were noted between patch size and BP.

Growth—Body Weight

Upon entry into SPD485-410, mean weight was lower for subjects in the antecedent MTS group than the placebo group. At endpoint for SPD485-410, mean weight was similar between the antecedent MTS and placebo groups. Overall, mean weight increased from SPD485-409 baseline by 1.72 lbs at endpoint and 2.47 lbs at Month 6. However, 38.6% of all subjects exhibited a measurable weight loss from SPD485-409 baseline at endpoint and 59.5% showed a measurable weight gain. In addition, 24 subjects exhibited at least 1 observation of ≥ 7% decrease in weight from SPD485-409

baseline. Most of these observations were not at study completion indicating the weight decrease was not progressive.

Growth—Height

Height was not affected by MTS. At endpoint in SPD485-410, subjects had an overall mean increase of 0.82 inches from SPD485-409 screening.

Electrocardiogram

Clinically significant ECG abnormalities were reported for 18.5% of subjects in SPD485-410. None were associated with an SAE or resulted in discontinuation from the study.

At endpoint, the overall mean increase in HR from SPD485-409 baseline was +5.9bpm. No significant effects on PR or QRS were observed. After QT interval was corrected for HR (QTcF), no significant changes from baseline were noted.

Post Sleep Questionnaire

The majority of subjects (91%) assessed the quality of their sleep as average or better after 6 months of MTS treatment. Insomnia-related TEAEs were reported of 4.3% of subjects and did not result in early discontinuation.

Subgroups—Gender

Decreased appetite and upper abdominal pain were reported more frequently among males than females.

Subgroups—Age

The frequency of psychiatric disorders in the MTS group was higher in the younger age group across both studies. In SPD485-410, the frequency of psychiatric disorders was 22.5% in the 13-14 year age group and 13.7% in the 15-17 year age group. Decreased appetite was also reported more frequently in the younger age group.

Subgroups—Race

No significant differences were evident. However the number of non-white subjects was small.

Safety Data from Study SPD485-106

Safety was assessed by collection of AEs, vital signs, ECGs, physical examination, and clinical laboratory tests (biochemistry, hematology, and urinalysis). There were no

deaths or SAEs. There were no significant AEs. There were no withdrawals due to AEs or application-site reactions. The TEAEs were known to be associated with MPH treatment or were typical intercurrent conditions in children and adolescents.

Exposure

Subjects who completed the study received 29 doses of either MTS or Concerta.

Compliance

The compliance rate in each of the age/treatment groups was at least 98.6%. Scores consistently indicated good adherence of MTS.

Adverse Events

The TEAEs were either known to be associated with MPH treatment (abdominal pain and decreased appetite) or were typical intercurrent conditions in children and adolescents (cough and URI). Most TEAEs were experienced by only one subject per group.

Table 63: Number of Subjects Who Experienced at Least One TEAE

Age Group	**MTS Fixed** N=12C/13A n (%)	**MTS Escalating** N=12C/12A n (%)	**Concerta** N=11C/11A n (%)
Children	6 (50%)	6 (50%)	6 (54.5%)
Adolescents	6 (46.2%)	8 (66.7%)	5 (45.5%)

(SPD485-106 Clinical Study Report, p. 100)

Table 64: Treatment-Emergent Adverse Events in Adolescents—Safety Population

Table 35: Treatment-Emergent Adverse Events in Adolescents (Aged 13-17 Years), Safety Population			
System Organ Class	Number (%) of subjects reporting adverse event		
Adverse Event (Preferred Term)	MTS Fixed Dose (N=13)	MTS Escalating Doses (N=12)	CONCERTA® (N=11)
All adverse events	**6 (46.2)**	**8 (66.7)**	**5 (45.5)**
Gastrointestinal Disorders	**2 (15.4)**	**0**	**1 (9.1)**
Abdominal discomfort	0	0	1 (9.1)
Abdominal pain upper	1 (7.7)	0	0
Gastroesophageal reflux disease	1 (7.7)	0	0
General Disorders and Administrative Site Conditions	**4 (30.8)**	**2 (16.7)**	**0**
Application site erythema	1 (7.7)	1 (8.3)	0
Application site pruritus	0	1 (8.3)	0
Catheter site pain	1 (7.7)	0	0
Fatigue	1 (7.7)	1 (8.3)	0
Feeling hot	1 (7.7)	0	0
Infusion site pain	1 (7.7)	0	0
Venipuncture site pain	1 (7.7)	0	0
Infections and Infestations	**1 (7.7)**	**1 (8.3)**	**1 (9.1)**
Influenza	1 (7.7)	0	0
Upper respiratory tract infection	0	1 (8.3)	1 (9.1)
Injury, Poisoning, and Procedural Complications	**1 (7.7)**	**1 (8.3)**	**0**
Contusion	0	1 (8.3)	0
Fall	0	1 (8.3)	0
Laceration	0	1 (8.3)	0
Post procedural nausea	1 (7.7)	0	0
Post procedural pain	0	1 (8.3)	0
Road traffic accident	1 (7.7)	0	0
Investigations	**1 (7.7)**	**0**	**0**
Heart rate increased	1 (7.7)	0	0
Metabolism and Nutrition Disorders	**1 (7.7)**	**2 (16.7)**	**0**
Anorexia	0	1 (8.3)	0
Decreased appetite	1 (7.7)	1 (8.3)	0

Table 35: Treatment-Emergent Adverse Events in Adolescents (Aged 13-17 Years), Safety Population			
System Organ Class Adverse Event (Preferred Term)	Number (%) of subjects reporting adverse event		
	MTS Fixed Dose (N=13)	MTS Escalating Doses (N=12)	CONCERTA® (N=11)
Nervous System Disorders	**1 (7.7)**	**5 (41.7)**	**4 (36.4)**
Dizziness	1 (7.7)	1 (8.3)	0
Headache	0	2 (16.7)	3 (27.3)
Lethargy	0	0	1 (9.1)
Paraesthesia	0	1 (8.3)	0
Tremor	0	1 (8.3)	0
Respiratory, Thoracic, and Mediastinal Disorders	**2 (15.4)**	**2 (16.7)**	**1 (9.1)**
Cough	0	0	1 (9.1)
Dyspnoea	1 (7.7)	0	0
Nasal congestion	0	1 (8.3)	0
Pharyngolaryngeal pain	1 (7.7)	1 (8.3)	0

Source: Section 14, Table 3.1

((SPD485-106 Clinical Study Report, p. 103-104)

Laboratory Values

There was no clinically meaningful changes in mean values in hematology, chemistry, or urinalysis.

Vital Signs

Table 65: Number of Adolescent Subjects with Outlier Vital Sign Values at End of Study

Vital Sign	**MTS Fixed N=13 n (%)**	**MTS Escalating N=12 n (%)**	**Concerta N=11 n (%)**
Systolic BP < 100 mmHg	3 (25)	1 (8.3)	1 (9.1)
Diastolic BP > 85 mmHg	0	2 (16.7)	1 (9.1)
Pulse > 100	1 (8.3)	0	2 (18.2)
Weight > 7% change from baseline	0	1 (8.3)	0

(SPD485-106 Clinical Study Report, p. 107)

Electrocardiograms

In the 6-12 year age group, no subjects experienced a shift from normal baseline. In the 13-17 year age group, one subject in the Concerta group experienced a shift from normal to abnormal end of study ECG result.

Dermal Evaluations

No relationships between dermal evaluations or application-site reactions with increasing MTS dose or repeat dosing of MTS were apparent. No subjects withdrew as the result of an application-site reaction. Most subjects had a dermal response of either no evidence of irritation or minimal erythema. Only one subject (03-009) had a significant dermal response score. A 12-year-old female in the MTS escalating dose group had a dermal response score of definite edema (DRS 4) on Day 1 but subsequent scores were minimal erythema or less.

In summary, both MTS and Concerta were well tolerated in Study SPD485-106. No significant safety concerns were raised.

7.4.6 Immunogenicity

No new information is available from the clinical studies of this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no clear evidence of a dose response relationship when patch size and adverse events were analyzed. The dose optimization design of the study does not allow for determination of dose-response. However, exploratory regression analyses of key variables and *d*-MPH plasma concentrations after a 9-hour wear-time were done. Exploratory regression analyses of vital signs and d-MPH plasma concentrations showed that systolic blood pressure, diastolic blood pressure, and pulse rate were significantly positively correlated. In contrast, weight showed a significant inverse correlation with plasma concentrations of d-MPH.

MPH plasma concentration was determined by sparse sampling in Study SPD485-409. A venous blood sample was collected at one of the last three visits (Week 5, 6, or 7/ET) for the measurement of steady-state plasma concentrations of *d*- and *l*-MPH. Mean plasma concentrations were observed to increase with dose. However, there was no suggestion of dose-proportionality.

7.5.3 Drug-Demographic Interactions

Study SPD485-409

The percentage of subjects in the MTS group reporting one or more AEs was generally similar within the subgroups of gender, race, age, and prior stimulant medication use (Table 66)

Increased application site reactions accounted for the difference in TEAEs between males (15%) and females (2.8%) in the General Disorders and Administration Site Conditions SOC. Decreased appetite accounted for the difference in TEAEs between White (37%) and Non-White (8.8%) in the Metabolism and Nutrition Disorders SOC.
.
Irritability was higher in the 13-14 year age group (25%) than the 15-17 year age group (8.7%) and higher in the MTS group (7.2%) than the placebo group (2.9%). Dizziness was also reported more frequently in the younger MTS age group.

Psychiatric Disorders were reported more frequently in subjects who had no prior stimulant use. In the MTS group, anorexia, irritability, and decreased appetite were reported more frequently for subjects with no prior stimulant use.

Table 66: Summary of TEAEs by Subgroup

Parameter	Gender MTS Group		Race MTS Group		Age MTS Group		Prior Stimulant Use MTS Group	
	Male N=109 n (%)	Female N=36 n (%)	White N=111 n (%)	Non-White N=34 n (%)	13-14 N=76 n (%)	15-17 N=69 n (%)	No N=86 n (%)	Yes N=59) n (%)
Any TEAEs	83(76)	29(81)	88(79)	24(70)	61(80)	51(74)	69(80)	43(73)
Cardiac Disorders	1(0.9)	1 (2.8)	1(0.9)	1(2.9)	0	2(2.9)	2(2.3)	0
Eye Disorders	2 (1.8)	0	1(0.9)	1(2.9)	0	2(2.9)	1(1.2)	1(1.7)
Gastrointestinal Disorder	23(21)	9(25)	25(22)	7(21)	16(21)	16(23)	19(22)	13(22)
General Disorders and Administration Site Conditions	16(15)	1(2.8)	13(12)	4(12)	10(13)	7(10)	9(10)	8(14)
Application site reaction	12(11)	0	12(11)	0	8(11)	4(6)	4(4.6)	8(14)
Infections and Infestations	29(27)	15(42)	36(32)	8(23)	23(30)	21(30)	23(27)	21(36)
Injury, Poisoning and Procedural Complication	8(7)	4(11)	9(8.1)	3(8.8)	6(7.9)	6(8.7)	2(2.3)	5(8.5)

Investigations	7(6)	3(8.3)	8(7.2)	2(5.9)	7(9.2)	3(4.3)	9(10)	1(1.7)
Metabolism and Nutrition Disorders	31(28)	13(36)	41(37)	3(8.8)	26(34)	18(26)	31(36)	13(22)
Decreased Appetite	25(23)	12(33)	35(31)	2(5.9)	21(28)	16(23)	25(29)	12(20)
Musculoskeletal and Connective Tissue Disorders	3(5.7)	0	3(2.7)	3(8.8)	2(2.6)	4(5.8)	4(4.7)	2(3.4)
Neoplasms Benign, Malignant and Unspecified	1(0.9)	0	1(0.9)	0	1(1.3)	0	0	1(1.7)
Nervous System Disorders	16(15)	9(25)	17(15)	8(23)	14(18)	11(16)	19(22)	6(10)
Psychiatric Disorder	16(15)	9(25)	20(18)	5(15)	19(25)	6(8.7)	22(26)	3(5.1)
Renal and Urinary Disorders	1 (0.9)	0	0	1(2.9)	1(1.3)	0	1(1.2)	0
Reproductive System and Breast Disorders	0	1 (2.8)	1(3.1*)	0	1(6.7*)	0	1(4.8*)	0
Respiratory, Thoracic, and Mediastinal Disorders	9(8.3)	3(8.3)	10(9)	2(5.9)	7(9.2)	5(7.2)	4(4.7)	8(14)
Skin and Subcutaneous Tissue Disorders	5(4.6)	3(8.3)	7(6.3)	1(2.9)	5(6.6)	3(4.3)	5(5.8)	3(5.1)

(Clinical Study Report, p.564-614)
*Gender Specific AEs have percentages calculated out of the number of female subjects in the safety population.

7.5.5 Drug-Drug Interactions

No formal studies of drug-drug interaction have been performed with MTS.

7.6.2 Human Carcinogenicity

No new information is available from the clinical studies of this submission.

7.6.2 Human Reproduction and Pregnancy Data

No new information is available from the clinical studies of this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

See sections 7.4.3 and 7.4.5 for information on the effect of MTS on weight and height in adolescents.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is available from the clinical studies of this submission. The current label bears a black box warning concerning drug dependence and abuse potential.

7.7 Additional Submissions / Safety Issues

A Four Month Safety Update was submitted by Shire on 4 January 2010. The report states that during the period of September 4, 2009 to January 4, 2010 there have been no clinical studies initiated or ongoing for Daytrana and that there have been no significant changes in its safety profile. The report also notes that Daytrana is not currently marketed in other countries. Finally, a summary of reports of nonclinical studies conducted in juvenile rats was submitted with this safety update. These studies are discussed in Section 4.3.

8 Postmarket Experience

The United States is the only country where marketing authorization for MTS has been obtained. Since US approval through 31 December 2008, it is estimated that more than (b) (4) MTS patches have been dispensed resulting in an estimated (b) (4) person-years of exposure. Children account for 63% of MTS use and adolescents account for 24% of MTS use.

Table 67: Estimate* of Daytrana Prescriptions Dispensed by Age

Years	Prescriptions	% of Total
0-5	(b) (4)	(b) (4)
6-12		
13-17		
18+		
Unspecified		

*Data provided by (b) (4)

(Shire Pharmacovigilance & Risk Management, p. 5)

Shire reviewed all AEs in the Shire Global Safety System received from spontaneous sources, regulatory agencies, and the literature from the date of approval (6 April 2006) through 05 January 2009. In general, the safety profile of MTS appears to be similar in children and adolescents. Few events were reported more frequently in adolescents than children. There were higher reporting rates in adolescents of serious aggression,

nonserious irregular heart rate, and hypersomnia. These cases were further analyzed by Shire.

There were 4 cases of serious aggression and all involved 13-year-old males. In 1 case the information indicated a possible association with MTS. The other 3 cases were considered unrelated or of indeterminate causality.

There were 2 nonserious cases of irregular heart rate. The information provided was insufficient to assess causality.

There were 2 nonserious cases of hypersomnia. According to Shire, these cases could have been related to the known effect of MTS.

Less dermal site reactions were reported in adolescents than children.

Table 68: Dermal Site Reactions in Children versus Adolescents

PT	Children		Adolescents	
	Count	Events/ 1000PY	Count	Events/ 1000PY
Pharmaceutical Product Complaint	2263	24.4	381	10.8
Application site erythema	1672	18.0	268	7.6
Application site pruritus	958	10.3	166	4.7
Application site irritation	876	9.4	194	5.5
Application site rash	294	3.2	54	1.5
Application site pain	227	2.4	52	1.5
Application site dryness	162	1.7	0	0
Application site urticaria	161	1.7	0	0
Application site swelling	135	1.5	0	0

(Shire Pharmacovigilance & Risk Management, p. 6-7)

In summary, Shire's review of the postmarketing data showed no notable safety concerns with Daytrana's use in adolescents. The safety profile appears to be similar to that of children.

9 Appendices

9.1 Literature Review/References

There was no summary of the review of the literature in this submission. Under literature review, 79 articles were cited with links to the articles. Several of the articles were funded by Shire. Only a few articles referred specifically to the use of MTS. Even fewer referred to the use of MTS in adolescents. Most of the articles addressed the diagnosis and treatment of ADHD, the benefits and limitations of MPH in general, and the metabolism of MPH. I will summarize the key points from 13 of the most relevant articles in the following paragraphs. In general the safety data in these articles are consistent with the safety data obtained from the studies in this sNDA.

Persistence of ADHD into Adulthood

Several articles supported Shire's contention that ADHD in childhood can persist into adulthood. Up to 50% of children diagnosed with ADHD may have symptoms persisting into adolescence (Liu 2005). Studies using the DSM-IV criteria have shown prevalence rates of ADHD in adolescents to be as high as 9.5%. Most children do not out grow ADHD but continue to have symptoms of ADHD as adolescents and adults, especially if they had severe symptoms or were treated with medications (Katragadda 2007).

Barkley (2006) reported on the adaptive functioning of hyperactive and control children in Wisconsin followed to young adulthood. The hyperactive group had significantly lower educational performance and attainment. The hyperactive group also had been fired from more jobs and had lower job performance. Socially, the hyperactive group had fewer close friends, earlier sexual intercourse, and early parenthood. They also were more likely to have been treated for sexually transmitted disease.

Benefits of Using Once-a-day MPH Dosing Regimens

Many articles cited the benefits of using once-a-day regimens of MPH. These benefits include improved adherence because of the simplicity of the regimen and avoidance of the embarrassment of using medications at school or work (Katragadda 2007). According to Taylor (2004), from the school's point of view, it is hard to overstate the advantage that comes if dispensing a controlled medication is no longer on the list of school responsibilities.

Benefits specific to MTS include not having to swallow a pill and the added flexibility of allowing termination of drug delivery at any time simply by removing the patch (Patrick 2009). Wilens' (2008) findings from a trial involving the treatment of children with ADHD

in an Analog Classroom setting suggest that the duration of medication effect is related to the wear time of the patch and may be tailored to accommodate the schedules of patients. Positive effects were evident 2 hours after the patch was applied. Drug effects diminished between 2 and 4 hours after patch removal. MTS did not produce any serious adverse events. Adverse events were generally mild or moderate and were typical of those seen with MPH treatment (decreased appetite, headache, and insomnia). Wilens concludes that MTS provides a mechanism to vary the exposure to MPH flexibly based on individual needs.

Effect of MPH on Height and Weight

Several articles addressed the effect of stimulants on height and weight. Farone's (2008) conclusion was that stimulants in childhood modestly reduced expected height and weight but that over time these effects attenuate and that ultimate adult growth parameters are not affected. Katragadda (2007) agreed that most long-term follow-up studies seem to show a temporary reduction in growth rate during childhood and early adolescent periods in active stimulant treatment followed by a growth pattern ultimately leading to the full expected adult height. However, exploratory analyses from the follow-up phase of the Multimodal Treatment Study of ADHD suggest that consistent use of stimulant medication was associated with maintenance of effectiveness but continued mild growth suppression (MTA Cooperative Group 2004). Finally, Poulton (2005) tried to clarify the confusion. The author reviewed 29 studies and concluded that many studies do not stand up to rigorous analysis. However, the author concluded that doctors treating children with stimulant medication should anticipate a reduction in height velocity and growth should be closely monitored but that it would appear that most children achieve a satisfactory adult height.

Abuse Potential of MPH

The abuse potential of MPH was also addressed in several articles. Kollins (1998) examined the acute behavioral effects of orally administered sustained-release MPH, immediate-release MPH, and placebo in 10 healthy volunteers. The author notes that previous research shows that the rate of onset of a drug's effect is an important determinant of its abuse potential. The findings of this experiment are consistent with this previous research and suggest that the abuse potential of IR methylphenidate may be greater than that of SR methylphenidate.

Katragadda (2007) concludes that early treatment of ADHD is likely to prevent, rather than promote, substance abuse disorder in the future and that Daytrana seems to have a lower risk for abuse potential. He contends that most patients prescribed stimulants for ADHD do not abuse them and that using long-acting formulations may be helpful in reducing the risk of abuse. This view is echoed by Taylor (2004) who states that available clinical data suggest that the net effect of treating children and young people

with ADHD with stimulant medication is to protect against, rather than lead to, later substance misuse.

Patrick (2009) in a review article voices some concern about the abuse potential of the patch. He states that on average, only 36% of the MPH contained in an MTS is absorbed during a 9 hour application. Therefore, a substantial amount of drug remains in the system after removal from a patient. This residual content represents a potential source of MPH diversion or accidental poisoning. The patch is also subject to unscheduled/ unauthorized removal with potential for diversion.

Patrick's article also describes how MPH free base can be expected to be extracted from MTS using any number of commercially available non-polar organic solvents (lighter fluid, lantern fuel, or cold weather engine starter). However, as the free base, MPH can no longer be solubilized in water, thus eliminating the potential for IV abuse (Levine et al., 1986). MPH free base should also prevent intranasal abuse (Barrett et al., 2005) due to its inability to be dissolved in the moist mucosal sinuses. MPH is expected to primarily pyrolyze rather than volatilize under flame which limits the abuse potential of MPH by smoking.

Role of the Isomers of MPH

Several articles discussed the role of MPH and its isomers in the treatment of ADHD. When *dl-threo*-MPH is orally administered, the plasma concentrations of *d-threo*-MPH are higher than those of *l-threo*-MPH. With MTS, both hepatic and enteric "first-pass" metabolism is circumvented. Because of this plasma concentrations of *d-threo*-MPH are consistent with those produced by oral formulations, but the relative concentrations of *l-threo*-MPH are much higher. However, *d-threo*-MPH is the more potent and abundant of the two isomers and is the major contributor of both efficacy and adverse effects (Heal 2006).

Patrick discussed an interaction between ethanol and *l*-MPH. *L*-MPH-ethanol interaction was accompanied by a 40% mean elevation of *d*-MPH plasma C_{max} and 25% increase in *d*-MPH exposure (AUC). Elevation in these parameters has been associated with an increase in abuse liability (Patrick 2009).

Cutaneous Reactions to MTS

Patrick (2009) describes a controlled study in which 18 of 133 subjects were confirmed to have become sensitized after intentionally applying MTS to the same skin site for 3 weeks. This 13.5% sensitization rate underscores the importance of alternating skin application sites. According to the author, cutaneous adverse events with MPH are not limited to administration by the transdermal route and successful desensitization to oral MPH induced rash has been reported (Confino-Cohen and Goldberg, 2005).

Recommendations from a dermatology expert panel consensus meeting are described in an article by Warshaw (2008). In September 2007, a group of child psychiatrists, pediatricians, developmental pediatricians, and pediatric neurologists who treat ADHD and have experience with MTS convened to discuss cutaneous reactions in relation to its use. Information collected from the meeting and from Shire's clinical database was reviewed by a panel of 3 dermatologic clinical experts in contact dermatitis and 1 pediatric dermatologist. Their recommendations are summarized in this article. The panel concluded that mild to moderate erythema is a common cutaneous effect with MTS use, and is generally not a cause for discontinuation if seen in isolation. Irritant contact dermatitis is relatively common and can be reduced and treated by alternating patch sites. Allergic contact dermatitis (ACD) and allergic contact urticaria (ACU) are rare when MTS is worn as directed. MTS should be discontinued if ACD is suspected.

9.2 Labeling Recommendations

Currently, the Division and the sponsor are negotiating language for labeling.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned.

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

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CHRISTINA P BURKHART
04/07/2010

ROBERT L LEVIN
04/13/2010
Comments will follow in a team leader review memo.