CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021514Orig1s010

Trade Name:	DAYTRANA
Generic or Proper Name:	(methylphenidate)
Sponsor:	Noven Pharmaceuticals Inc.
Approval Date:	June 29, 2010
Indication:	Daytrana is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). • Children (ages 6-12): the efficacy of Daytrana in ADHD was established in two 7-week controlled trials in children • Adolescents (ages 13-17): the efficacy of Daytrana in ADHD was established in one 7-week, controlled study in adolescents

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021514/S-009/S-010 **SUPPLEMENT APPROVAL**

Shire Pharmaceuticals
Attention: James Ewing
Manager, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mr. Ewing:

Please refer to the following Supplemental New Drug Applications dated June 30, 2009 (S-009) and September 4, 2009 (S-010), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Daytrana® (methylphenidate) 10mg/9hr, 15mg/9hr, 20mg/9hr, 30mg/9hr transdermal systems.

We also acknowledge receipt of your submissions dated October 22, 2009, December 15, 2009, December 21, 2009, January 5, 2010, January 15, 2010, and June 14, 2010.

These supplemental new drug applications provide for the following changes to product labeling:

- **S-009** – This prior approval supplement provides for the conversion to the Physician's Labeling Rule (PLR) format**.**

- **S-010** – This efficacy supplement provides for the use of Daytrana in the treatment of Attention Deficit and Hyperactivity Disorder (ADHD) in adolescent ages 13 to 17 years.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

We are waiving the pediatric study requirement for ages 0 to 5 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

- The diagnostic criteria and assessment measures for determining efficacy for the treatment of ADHD in children less than 6 years old are not well defined.
- Pharmaceutical treatment in this age group is uncommon.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

As required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email your Regulatory Project Manager at Juliette.Toure@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling and Comprehensive Medication Guide

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21514	SUPPL-10	SHIRE DEVELOPMENT INC	Daytrana System
NDA-21514	SUPPL-9	SHIRE DEVELOPMENT INC	Daytrana System

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
06/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Daytrana® safely and effectively. See full prescribing information for Daytrana.

DAYTRANA® (methylphenidate transdermal system)

Initial U.S. Approval: 2006

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning

- **Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.**

-----RECENT MAJOR CHANGES-----

- Indications and Usage (1), September 2009
- Dosage and Administration (2), September 2009

-----INDICATIONS AND USAGE-----

Daytrana is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

- Children (ages 6-12): the efficacy of Daytrana in ADHD was established in two 7-week controlled trials in children (1)
- Adolescents (ages 13-17): the efficacy of Daytrana in ADHD was established in one 7-week, controlled study in adolescents (1)

-----DOSAGE AND ADMINISTRATION-----

- The recommended starting dose for patients new to or converting from another formulation of methylphenidate is 10 mg. (2)
- Daytrana should be applied to the hip area (using alternating sites) 2 hours before an effect is needed and should be removed 9 hours after application. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. (2)
- Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. (2)
- **Patients should be advised to follow the full instructions for patch use provided in the Medication Guide. (17)**

-----DOSAGE FORM AND STRENGTHS-----

- Transdermal Patch: 10mg/9 hours (1.1 mg/hr), 15mg/9 hours (1.6 mg/hr), 20mg/9 hours (2.2 mg/hr), 30mg/9 hours (3.3 mg/hr)

-----CONTRAINDICATIONS-----

- Known hypersensitivity to methylphenidate (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

-----WARNINGS AND PRECAUTIONS-----

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- Long-Term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients. (5.4
- Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.5)
- Contact Sensitization: Use of Daytrana may lead to contact sensitization. Treatment should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. (5.6)
- External Heat: Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. (5.7)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.8)

-----ADVERSE REACTIONS-----

- Children (ages 6-12):The most commonly (≥5% and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia (6.1).
- Adolescents (ages 13-17): The most commonly (>5% and twice the rate of placebo) reported adverse reactions in a placebo-controlled trial in adolescents aged 13-17 included appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia. The majority of subjects in these trials had erythema at the application site (6.1).
- The most common (≥2% of subjects) adverse reaction associated with discontinuations in controlled clinical trials in children or adolescents was application site reactions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Do not use Daytrana in patients currently using or within 2 weeks of using an MAO inhibitor. (7.1)
- Daytrana may increase blood pressure; use cautiously with vasopressors. (7.2)
- Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. (7.3)
- Methylphenidate may inhibit metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants. (7.4)
- Serious adverse events have been reported when using clonidine in combination with methylphenidate, although no causality has been established. (7.5)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus and/or child. Based on animal data, may cause fetal harm. (8.1, 8.3)

Pediatric Use: has not been studied in children under 6 years of age (8.4)

- Geriatric Use: has not been studied in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DRUG DEPENDENCE

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE

Daytrana (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Daytrana in patients diagnosed with ADHD was established in two 7-week controlled clinical trials in children (ages 6-12) and one 7-week, controlled clinical trial in adolescents (ages 13-17).

A diagnosis of ADHD (DSM-IV-TR®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; “on the go;” excessive talking; blurting answers; can’t wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations

The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV-TR® characteristics.

1.2 Need for Comprehensive Treatment Program

Daytrana is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician’s assessment of the chronicity and severity of the patient’s symptoms.

2 DOSAGE AND ADMINISTRATION

It is recommended that Daytrana be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application. Dosage should be titrated to effect. The recommended dose titration schedule is shown in the table below. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient.

Table 1 Daytrana - Recommended Titration Schedule (Patients New to Methylphenidate)

Upward Titration, if Response is Not Maximized				
	Week 1	Week 2	Week 3	Week 4
Patch Size	12.5 cm^2	18.75 cm^2	25 cm^2	37.5 cm^2
Nominal Delivered Dose* (mg/9 hours)	10 mg	15 mg	20 mg	30 mg
Delivery Rate*	(1.1 mg/hr)*	(1.6 mg/hr)*	(2.2 mg/hr)*	(3.3 mg/hr)*

*Nominal *in vivo* delivery rate children and adolescents when applied to the hip, based on a 9-hour wear period.

Patients converting from another formulation of methylphenidate should follow the above titration schedule due to differences in bioavailability of Daytrana compared to other products.

2.1 Application

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal. It is recommended that parents or caregivers apply and remove the patch for children; responsible adolescents may apply or remove the patch themselves if appropriate. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove Daytrana, based on the 9-hour application time.

The adhesive side of Daytrana should be placed on a clean, dry area of the hip. The area selected should not be oily, damaged, or irritated. Apply patch to the hip area, avoiding the waistline, since clothing may cause the patch to rub off. When applying the patch the next morning, place on the opposite hip at a new site if possible.

If patients or caregivers experience difficulty separating the patch from the release liner or observe transfer of adhesive to the liner, tearing and/or other damage to the patch during removal from the liner, the patch should be discarded according to the directions provided below, and a new patch should be applied. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the patch should be discarded.

Daytrana should be applied immediately after opening the individual pouch and removing the protective liner. Do not use if the individual pouch seal is broken or if the patch appears to be damaged. Do not cut patches. Only intact patches should be applied. The patch should then be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact of the patch with the skin, especially around the edges. Exposure to water during bathing, swimming, or showering can affect patch adherence. Patches should not be applied or re-applied with dressings, tape, or other common adhesives. In the event that a patch does not fully adhere to the skin upon application, or becomes partially or fully detached during wear time, the patch should be discarded according to the directions provided in this label [*see Dosage and Administration (2.3)]* and a new patch may be applied at a different site. The total recommended wear time for that day should remain 9 hours regardless of the number of patches used [*see Patient Counseling Information (17.1)].*

All patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch [*see Warnings and Precautions (5.7)].* When heat is applied to Daytrana™ after patch application, both the rate and the extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold (see **CLINICAL PHARMACOLOGY:** Pharmacokinetics/Absorption).

This increased absorption can be clinically significant and result in overdose of methylphenidate (see **OVERDOSAGE**).

Patches should not be stored in refrigerators or freezers.

2.2 Removal of Daytrana

Daytrana patches should be peeled off slowly. If necessary, patch removal may be facilitated by gently applying an oil-based product (i.e., petroleum jelly, olive oil, or mineral oil) to the patch edges, gently working the oil underneath the patch edges. If any adhesive remains on the skin following patch removal, an oil-based product may be applied to patch sites in an effort to gently loosen and remove any residual adhesive that remains following patch removal.

In the unlikely event that a patch remains tightly adhered despite these measures, the patient or caregiver should contact the physician or pharmacist. Nonmedical adhesive removers and acetone-based products (i.e., nail polish remover) should not be used to remove Daytrana patches or adhesive.

2.3 Disposal of Daytrana

Upon removal of Daytrana, used patches should be folded so that the adhesive side of the patch adheres to itself and should be flushed down the toilet or disposed of in an appropriate lidded container. If the patient stops using the prescription, each unused patch should be removed from its individual pouch, separated from the protective liner, folded onto itself, and disposed of in the same manner as used patches.

The parent or caregiver should be encouraged to record on the administration chart included with each carton the time that each patch was applied and removed. If a patch was removed without the parent or caregiver's knowledge, or if a patch is missing from the tray or outer pouch, the parent or caregiver should be encouraged to ask the child when and how the patch was removed.

2.4 Maintenance/Extended Treatment

There is no body of evidence available from controlled clinical trials to indicate how long the patient with ADHD should be treated with Daytrana. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. The effectiveness of Daytrana for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Daytrana for extended periods should periodically re-evaluate the long-term usefulness of Daytrana for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.5 Dose/Wear Time Reduction and Discontinuation

Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. Plasma concentrations of *d*-methylphenidate generally begin declining when the patch is removed, although absorption may continue for several hours. Individualization of wear time may help manage some of the side effects caused by methylphenidate. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued. Residual methylphenidate remains in used patches when worn as recommended.

3 DOSAGE FORM AND STRENGTHS

Four dosage strengths are available:

Nominal Dose Delivered (mg) Over 9 Hours*	**Dosage Rate* (mg/hr)**	**Patch Size (cm^2)**	**Methylphenidate Content per Patch (mg)**

10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55
30	3.3	37.5	82.5

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Daytrana is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester) *[see Description (11.1)].*

4.2 Agitation

Daytrana is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma

Daytrana is contraindicated in patients with glaucoma.

4.4 Tics

Daytrana is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.1)].*

4.5 Monoamine Oxidase Inhibitors

Daytrana is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

5 WARNINGS and PRECAUTIONS

5.1 Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia *[see Adverse Reactions (6.1)].*

Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.2 Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to none in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility,

patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

5.4 Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.5 Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

5.6 Contact Sensitization

In an open-label study of 305 subjects conducted to characterize dermal reactions in children with ADHD treated with Daytrana using a 9-hour wear time, one subject (0.3%) was confirmed by patch testing to be sensitized to methylphenidate (allergic contact dermatitis). This subject experienced erythema and edema at Daytrana application sites with concurrent urticarial lesions on the abdomen and legs resulting in treatment discontinuation. This subject was not transitioned to oral methylphenidate.

Use of Daytrana may lead to contact sensitization. Daytrana should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Confirmation of a diagnosis of contact sensitization (allergic contact dermatitis) may require further diagnostic testing.

Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. No cases of systemic sensitization have been observed in clinical trials of Daytrana.

Patients who develop contact sensitization to Daytrana and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana may not be able to take methylphenidate in any form.

5.7 Patients Using External Heat

Patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as hair dryers, heating pads, electric blankets, heated water beds, etc., while wearing the patch. When heat is applied to Daytrana after patch application, both the rate and extent of absorption are significantly increased. The temperature-dependent increase in methylphenidate absorption can be greater than 2-fold *[see Clinical Pharmacology (12.3)]*. This increased absorption can be clinically significant and can result in overdose of methylphenidate [*see Overdosage (10)]*.

5.8 Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS

Detailed information on serious and adverse reactions of particular importance is provided in the *Boxed Warning* and *Warnings and Precautions (5)* sections:

- Drug dependence *[see box Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Marked anxiety, tension, or agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics or a family history of Tourette's syndrome *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.2)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.4)]*
- Visual Disturbance *[see Warnings and Precautions (5.5)]*
- Contact Sensitization *[see Warnings and Precautions (5.6)]*
- External Heat *[see Warnings and Precautions (5.7)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.8)]*

The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in children aged 6-12 included appetite decreased, insomnia, nausea, vomiting, weight decreased, tic, affect lability, and anorexia. The most commonly reported (frequency ≥ 5% and twice the rate of placebo) adverse reactions in a controlled trial in adolescents aged 13-17 were appetite decreased, nausea, insomnia, weight decreased, dizziness, abdominal pain, and anorexia *[see Adverse Reactions (6.1)]*.

The most common (≥2% of subjects) adverse reaction associated with discontinuations in double-blind clinical trials in children or adolescents was application site reactions *[see Adverse Reactions (6.3)]*.[15]

The overall Daytrana development program included exposure to Daytrana in a total of 2,152 participants in clinical trials, including 1,529 children aged 6-12, 223 adolescents aged 13-17, and 400 adults. The 1,752 child and adolescent subjects aged 6-17 years were evaluated in 10 controlled clinical studies, 7 open-label clinical studies, and 5 clinical pharmacology studies. In a combined studies pool of children using Daytrana with a wear time of 9 hours, 212 subjects were exposed for ≥6 months and 115 were exposed for ≥1 year; 85 adolescents have been exposed for ≥6 months. Most patients studied were exposed to Daytrana patch sizes of 12.5 cm^2, 18.75 cm^2, 25 cm^2 or 37.5 cm^2, with a wear time of 9 hours.

In the data presented below, the adverse reactions reported during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals

experiencing adverse reactions without first grouping similar types of events into a smaller number of standardized event categories.

Throughout this section adverse reactions reported are events that were considered to be reasonably associated with the use of Daytrana based on comprehensive assessment of the available adverse event information. A causal association for Daytrana often cannot be reliably established in individual cases. Further, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience

Adverse Reactions Associated With Discontinuation of Treatment

In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The most commonly reported (>1% and twice the rate of placebo) adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%), tics (1%), headache (1%), and irritability (1%).

In a 7-week double-blind, parallel-group, placebo-controlled study in adolescents with ADHD conducted in the outpatient setting, 5.5% (8/145) of patients treated with Daytrana discontinued due to adverse reactions compared with 2.8% (2/72) receiving placebo. The most commonly reported adverse reactions leading to discontinuation in the Daytrana group were application site reaction (2%) and decreased appetite/anorexia (1.4%).

Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Trials

Skin Irritation and Application Site Reactions

Daytrana is a dermal irritant. In addition to the most commonly reported adverse reactions presented in Table 2, the majority of subjects in those studies had minimal to definite skin erythema at the patch application site. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. Erythema is not by itself a manifestation of contact sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site [*see Warnings and Precautions (5.6)*].

Most Commonly Reported Adverse Reactions

Table 2 lists treatment-emergent adverse reactions reported in >1% Daytrana-treated children or adolescents with ADHD in two 7 week double-blind, parallel-group, placebo-controlled studies conducted in the outpatient setting. Overall, in these studies, 75.5% of children and 78.6% of adolescents experienced at least 1 adverse event.

Table 2 Number (%) of Subjects with Commonly Reported Adverse Reactions (≥1% in the Daytrana Group) in 7-Week Placebo-controlled Studies in Either Children or Adolescents- Safety Population

System Organ Class Preferred term	**Adolescents**		**Children**	
	Placebo N = 72	Daytrana N = 145	Placebo N = 85	Daytrana N = 98
Cardiac Disorders				
Tachycardia	0 (0)	1 (0.7)	0 (0)	1 (1.0)
Gastrointestinal disorders				
Abdominal pain	0 (0)	7 (4.8)	5 (5.9)	7 (7.1)
Nausea	2 (2.8)	14 (9.7)	2 (2.4)	12 (12.2)
Vomiting	1 (1.4)	5 (3.4)	4 (4.7)	10 (10.2)
Investigations				
Weight decreased	1 (1.4)	8 (5.5)	0 (0)	9 (9.2)
Metabolism and nutrition disorders				
Anorexia	1 (1.4)	7 (4.8)	1 (1.2)	5 (5.1)
Decreased appetite	1 (1.4)	37 (25.5)	4 (4.7)	25 (25.5)
Nervous system disorders				
Dizziness	1 (1.4)	8 (5.5)	1 (1.2)	0 (0)
Headache	9 (12.5)	18 (12.4)	10 (11.8)	15 (15.3)
Psychiatric disorders				
Affect lability	1 (1.4)	0 (0)	0 (0)	6 (6.1)*
Insomnia	2 (2.8)	9 (6.2)	4 (4.7)	13 (13.3)
Irritability	5 (6.9)	16 (11)	4 (4.7)	7 (7.1)
Tic	0 (0)	0 (0)	0 (0)	7 (7.1)

* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional

Adverse Reactions With the Long-Term Use of Daytrana

In a long-term open-label study of up to 12 months duration in 326 children wearing Daytrana 9 hours daily, the most common (≥10%) adverse reactions were decreased appetite, headache, and weight decreased. A total of 30 subjects (9.2%) were withdrawn from the study due to adverse events and 22 additional subjects (6.7%) discontinued treatment as the result of an application site reaction. Other than application site reactions, affect lability (5 subjects, 1.5%) was the only additional adverse reaction leading to discontinuation reported with a frequency of greater than 1%.

In a long-term open-label study of up to 6 months duration in 162 adolescents wearing Daytrana 9 hours daily, the most common (≥10%) adverse reactions were decreased appetite and headache. A total of 9 subjects (5.5%) were withdrawn from the study due to adverse events and 3 additional subjects (1.9%) discontinued treatment as the result of an application site reaction. Other adverse reactions leading to discontinuation that occurred with a frequency of greater than 1% included affect lability and irritability (2 subjects each, 1.2%).

6.2 Postmarketing Experience

In addition, the following adverse reactions have been identified during the postapproval use of Daytrana. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to Daytrana exposure.

Cardiac Disorders: palpitations

Eye Disorders: visual disturbances, blurred vision, mydriasis, accommodation disorder

General Disorders and Administration Site Disorders: application site reactions such as bleeding, bruising, burn, burning, dermatitis, discharge, discoloration, discomfort, dryness, eczema, edema, erosion, erythema, excoriation, exfoliation, fissure, hyperpigmentation, hypopigmentation, induration, infection, inflammation, irritation, pain, papules, paresthesia, pruritus, rash, scab, swelling, ulcer, urticaria, vesicles, and warmth.

Immune System Disorders: hypersensitivity reactions including generalized erythematous and urticarial rashes, allergic contact dermatitis, angioedema, and anaphylaxis

Investigations: blood pressure increased

Nervous System Disorders: convulsion, dyskinesia

Psychiatric Disorders: transient depressed mood, hallucination, nervousness

Skin and Subcutaneous Tissue Disorders: alopecia

6.3 Adverse Reactions With Oral Methylphenidate Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, pulse increased or decreased

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

Nervous System: drowsiness, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood

Skin/Subcutaneous: scalp hair loss

Neuroleptic Malignant Syndrome: Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

Daytrana should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors *[see Contraindications (4.5)]*.

7.2 Vasopressor Agents

Because of a possible effect on blood pressure, Daytrana should be used cautiously with pressor agents.

7.3 Hypotension Agents

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

7.4 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

7.5 Clonidine

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C - Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity.

Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of Daytrana on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Daytrana should be administered to a nursing woman only if the potential benefit justifies the potential risk to the child.

8.4 Pediatric Use

Daytrana should not be used in children under six years of age, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

Studies with transdermal methylphenidate have not been performed in juvenile animals. In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Daytrana has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Daytrana is classified as a Schedule II controlled substance by federal regulation.

9.2 Abuse

See warning containing drug abuse information [*see Boxed Warning*].

9.3 Dependence

See warning containing drug dependence information [*see Boxed Warning*].

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

10.2 Recommended Treatment

Remove all patches immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the patch, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

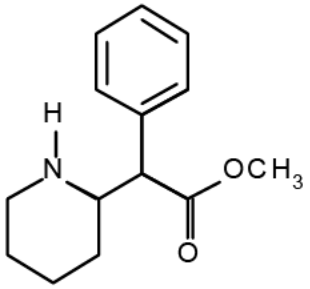
Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Daytrana overdosage has not been established.

10.3 Poison Control Center

As with the management of all overdosages, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

11 DESCRIPTION

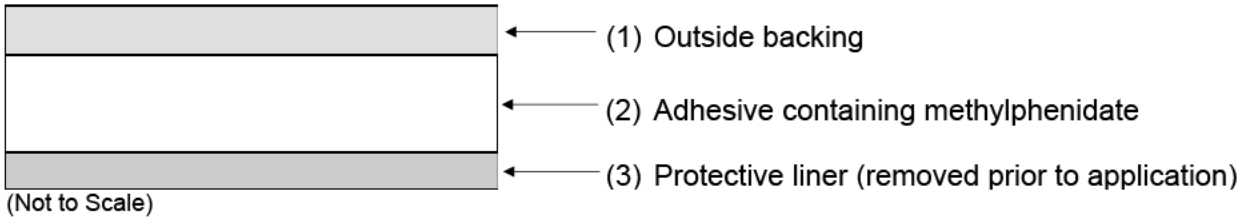
Daytrana is an adhesive-based matrix transdermal system (patch) that is applied to intact skin. The chemical name for methylphenidate is α-phenyl-2-piperidineacetic acid methyl ester. It is a white to off-white powder and is soluble in alcohol, ethyl acetate, and ether. Methylphenidate is practically insoluble in water and petrol ether. Its molecular weight is 233.31. Its empirical formula is $C_{14}H_{19}NO_2$. The structural formula of methylphenidate is:



11.1 Patch Components

Daytrana contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time.

The patch consists of three layers, as seen in the figure below (cross-section of the patch).



(Not to Scale)

Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation incorporating Noven Pharmaceuticals, Inc.'s DOT Matrix™ transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate, and (3) a fluoropolymer-coated polyester protective liner which is attached to the adhesive surface and must be removed before the patch can be used.

The active component of the patch is methylphenidate. The remaining components are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but 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.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer.

12.3 Pharmacokinetics

The pharmacokinetics of Daytrana when applied to the hip for 9 hours have been studied in ADHD patients 6 to 17 years old.

Absorption

The amount of methylphenidate absorbed systemically is a function of both wear time and patch size. In patients with ADHD, peak plasma levels of methylphenidate are reached at about 10 hours after single application and 8 hours after repeat patch applications (12.5 cm^2 to 37.5 cm^2) when worn up to 9 hours.

On single dosing with Daytrana to children or adolescents, there was a delay of, on average, 2 hours before *d*-methylphenidate was detectable in the circulation. On repeat dosing, low concentrations (1.2-3.0 ng/mL in children and 0.5-1.7ng/mL in adolescents, on average across the dose range) were observed earlier in the profile, due to carry-over effect. Following the application of Daytrana once daily with a 9 hour wear time, the mean pharmacokinetic parameters of *d*-methylphenidate in children and adolescents with ADHD after 4 weeks of therapy are summarized in Table 3.

Table 3
Mean Plasma *d*-Methylphenidate Pharmacokinetic Parameters After Repeated 9-Hour Applications of Daytrana or Oral ER-MPH for up to 28 days to Pediatric ADHD Patients (Aged 6 – 17 years)

Children				
Parameter	Daytrana[1] 12.5 cm^2 (N=12)	Daytrana[2] 37.5 cm^2 (N=10)	Oral ER-MPH[3] 18 mg	Oral ER-MPH[3] 54 mg
C_{ssmax} (ng/mL)	15.7 ± 9.39	42.9 ± 22.4	8.37 ± 4.14	26.1 ± 11.2

C_{ssmin} (ng/mL)	1.04 ± 1.17	1.96 ± 1.73	0.708 ± 1.08	1.19 ± 1.54
AUC_{ss} (ng·hr/mL)	163 ± 101	447 ± 230	97.7 ± 67.0	317 ± 160
t_{lag} (h)[4]	0 (0 – 2.0)	0 (0 – 1.0)	0	0
Adolescents				
C_{ssmax} (ng/mL)	8.32 ± 4.60	16.5 ± 6.94	5.23 ± 1.72	18.0 ± 6.97
C_{ssmin} (ng/mL)	0.544 ± 0.383	1.02 ± 0.629	0.360 ± 0.478	1.50 ± 0.937
AUC_{ss} (ng·hr/mL)	85.7 ± 50.0	167 ± 66.0	59.7 ± 19.1	216 ± 80.8
t_{lag} (h)[4]	0 (0 – 2.0)	0 (0 – 2.0)	0	0

[1]Dose maintained fixed for 28 days;
[2]Dose escalated at 7 day intervals from 12.5 cm^2 through 18.75 cm^2 and 25 cm^2 to 37.5 cm^2;
[3]Dose escalated at 7 day intervals from 18 mg through 27 mg and 36 mg to 54 mg; [4]Median (minimum – maximum); t_{lag} = Last Sampling Time Prior to Time of First Quantifiable Plasma Concentration

Following administration of Daytrana 12.5 cm^2 to pediatric and adolescent ADHD patients daily for 7 days, there were 13% and 14% increases, respectively, in steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC0_{-\infty}$); after 28 days administration, these increments increased to 64% and 76%, respectively. C_{max} increased by nearly 69% and 100% within 4 weeks of daily administration of the starting dose in children and adolescents, respectively.

The observed exposures with Daytrana could not be explained by drug accumulation predicted from observed single dose pharmacokinetics, and there was no evidence that clearance or rate of elimination changed between single and repeat dosing. Neither were they explainable by differences in dosing patterns between treatments, age, race, or gender. This suggests that transdermal absorption of methylphenidate may increase with repeat dosing with Daytrana; on average, steady-state is likely to have been achieved by approximately 14 days of dosing.

In the single- and multiple-dose study described above, exposure to *l*-methylphenidate was 46% of the exposure to *d*-methylphenidate in children and 40% in adolescents. *l*-methylphenidate is less pharmacologically active than *d*-methylphenidate *[see Pharmacodynamics (12.2)]*.

In a phase 2 PK/PD study in children aged 6-12 years, 2/3 of patients had 2-hour *d*-MPH concentrations < 5 ng/mL on chronic dosing, and at 3 hours 40% of patients had *d*-MPH concentrations < 5 ng/mL *[see Clinical Studies (14)].*

When Daytrana is applied to inflamed skin, both the rate and extent of absorption are increased as compared with intact skin. When applied to inflamed skin, lag time is no greater than 1 hour, T_{max} is 4 hours, and both C_{max} and AUC are approximately 3-fold higher.

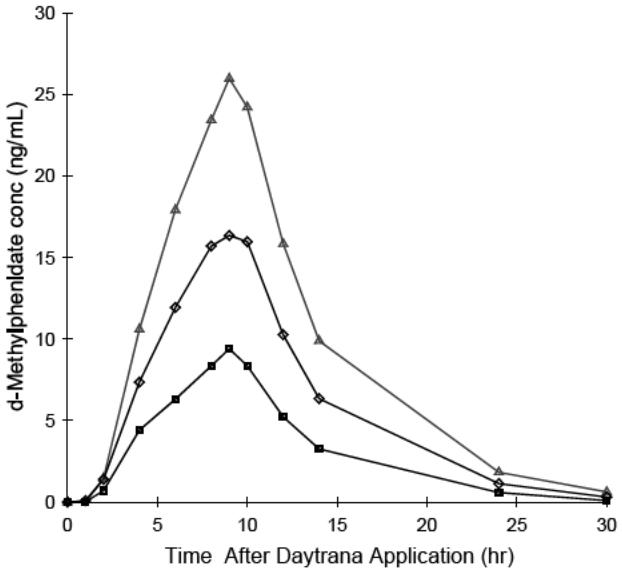
When heat is applied to Daytrana after patch application, both the rate and the extent of absorption are significantly increased. Median T_{lag} occurs 1 hour earlier, T_{max} occurs 0.5 hours earlier, and median C_{max} and AUC are 2-fold and 2.5-fold higher, respectively.

Application sites other than the hip can have different absorption characteristics and have not been adequately studied in safety or efficacy studies.

Dose Proportionality

Following a single 9-hour application of Daytrana patch doses of 10 mg / 9 hours to 30 mg / 9 hours patches to 34 children with ADHD, C_{max} and AUC_{0-t} of *d*-methylphenidate were proportional to the patch dose. Mean plasma concentration-time plots are shown in Figure 1. C_{max} of *l*-methylphenidate was also proportional to the patch dose. AUC_{0-t} of
l-methylphenidate was only slightly greater than proportional to patch dose.

FIGURE 1
Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (△) per 9-Hour Patches



Distribution

Upon removal of Daytrana, methylphenidate plasma concentrations in children with ADHD decline in a biexponential manner. This may be due to continued distribution of MPH from the skin after patch removal.

Metabolism and Excretion

Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity.

Transdermal administration of methylphenidate exhibits much less first pass effect than oral administration. Consequently, a much lower dose of Daytrana on a mg/kg basis, compared to oral dosages, may still produce higher exposures of *d*-MPH with transdermal administration compared to oral administration. In addition, very little, if any, *l*-methylphenidate is systemically available after oral administration due to first pass metabolism, whereas after transdermal administration of racemic methylphenidate, exposure to *l*-methylphenidate is nearly as high as to *d*-methylphenidate.

The mean elimination $t_{1/2}$ from plasma of *d*-methylphenidate after removal of Daytrana in children aged 6 to 12 years and adolescents aged 13-17 years was approximately to 4 to 5 hours. The $t_{1/2}$ of *l*-methylphenidate was shorter than for *d*-methylphenidate and ranged from 1.4 to 2.9 hours, on average.

The C_{max} and AUC of d-methylphenidate were approximately 50% lower in adolescents, compared to children, following either a 1-day or 7-day administration of Daytrana (10mg/9 hr). Multiple-dose administration of Daytrana did not result in significant accumulation of methylphenidate; following 7 days of Daytrana administration (10 mg/ 9 hr) in children and adolescents, the accumulation index of methylphenidate was 1.1 based on the mean steady state area under the plasma concentration-time curve (AUC_{ss}) relative to that anticipated on the basis of single dose pharmacokinetics ($AUC_{0-\infty}$).

Food Effects

The pharmacokinetics or the pharmacodynamic food effect performance after application of Daytrana has not been studied, but because of the transdermal route of administration, no food effect is expected.

Special Populations

Gender

The pharmacokinetics of methylphenidate after single and repeated doses of Daytrana were similar between boys and girls with ADHD, after allowance for differences in body weight.

Race

The influence of race on the pharmacokinetics of methylphenidate after administration of Daytrana has not been defined.

Age

The pharmacokinetics of methylphenidate after administration of Daytrana have not been studied in children less than 6 years of age.

Renal Impairment

There is no experience with the use of Daytrana in patients with renal insufficiency.

Hepatic Impairment

There is no experience with the use of Daytrana in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis/Mutagenesis and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain $p53^{+/-}$, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese hamster ovary cells.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day.

14 CLINICAL STUDIES

Daytrana was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in two (2) randomized double-blind, placebo-controlled studies in children aged 6 to 12 years and one (1) randomized, double-blind, placebo-controlled study in adolescents aged 13 to 17 years who met Diagnostic and Statistical Manual (DSM-IV-TR®) criteria for ADHD. The patch wear time was 9 hours in all three (3) studies.

In Study 1, conducted in a classroom setting, symptoms of ADHD were evaluated by school teachers and observers using the Deportment Subscale from the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale which assesses behavior symptoms in the classroom setting. Daytrana was applied for 9 hours before removal. There was a 5-week open-label Daytrana dose optimization phase using dosages of 10, 15, 20, and 30 mg / 9 hours, followed by a 2-week randomized, double-blind, placebo-controlled crossover treatment phase using the optimal patch dose for each patient or placebo. The mean differences between Daytrana and placebo in change from baseline in SKAMP Deportment Scores were statistically significant in favor of Daytrana beginning at 2 hours and remained statistically significant at all subsequent measured time points through 12 hours after application of the Daytrana patch.

In Study 2, conducted in the outpatient setting, Daytrana or placebo was blindly administered in a flexible-dose design using doses of 10, 15, 20, and 30 mg / 9 hours to achieve an optimal regimen over 5 weeks, followed by a 2-week maintenance period using the optimal patch dose for each patient. Symptoms of ADHD were evaluated by the ADHD-Rating Scale (RS)-IV. Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline for the ADHD-RS-IV total score. Although this study was not designed specifically to evaluate dose response, in general there did not appear to be any additional effectiveness accomplished by increasing the patch dose from 20 mg / 9 hours to 30 mg / 9 hours.

In Study 3, conducted in the outpatient setting, Daytrana or placebo was blindly administered in a flexible-dose design using doses of 10, 15, 20, and 30 mg / 9 hours during a 5-week dose-optimization phase, followed by a

2-week maintenance period using the optimal patch dose for each patient. Symptoms of ADHD were evaluated using the ADHD-Rating Scale (RS)-IV. Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline in the ADHD-RS-IV total score.

15 REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

Daytrana is supplied in a sealed tray or outer pouch containing 30 individually pouched patches. See the chart below for information regarding available strengths.

Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch** (mg)	Patches Per Carton	NDC Number
10	1.1	12.5	27.5	30	54092-552-30
15	1.6	18.75	41.3	30	54092-553-30
20	2.2	25	55	30	54092-554-30
30	3.3	37.5	82.5	30	54092-555-30

*Nominal *in vivo* delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each patch.

Store at 25º C (77º F); excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers.

Once the sealed tray or outer pouch is opened, use contents within 2 months. Apply the patch immediately upon removal from the individual protective pouch. **For transdermal use only**.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Information for Patients

Parents and patients should be informed to apply Daytrana to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The patch should not be applied to the waistline, or where tight clothing may rub it.

If patients or caregivers experience difficulty separating the patch from the release liner or observe tearing and/or other damage to the patch during removal from the liner, the patch should be discarded according to the directions provided in this label, and a new patch should be applied *[see Dosage and Administration (2.3)]*. Patients or caregivers should inspect the release liner to ensure that no adhesive containing medication has transferred to the liner. If adhesive transfer has occurred, the patch should be discarded.

Daytrana should be applied 2 hours before the desired effect. Daytrana should be removed approximately 9 hours after it is applied, although the effects from the patch will last for several more hours. Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal. The Medication Guide included at the end of this insert also includes a timetable to calculate when to remove Daytrana, based on the 9 hour application time.

Patients or caregivers should avoid touching the adhesive side of the patch during application, in order to avoid absorption of methylphenidate. If they do touch the adhesive side of the patch, they should immediately wash their hands after application.

In the event that a patch does not fully adhere to the skin upon application, or is partially or fully detached during wear time, the patch should be discarded according to the directions provided in this label, and a new patch should be applied *(see Dosage and Administration (2.3)]*. If a patch is replaced, the total recommended wear time for that day should remain 9 hours, regardless of the number of patches used.

Patches should not be applied or re-applied with dressings, tape, or other common adhesives.

Exposure to water during bathing, swimming, or showering can affect patch adherence.

Do not cut patches. Only intact patches should be applied.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the patch off earlier may be attempted before decreasing the patch dose.

Skin redness or itching is common with Daytrana and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the patch should not be worn and the patient should be seen by the prescriber. Patients or caregivers should not apply hydrocortisone or other solutions, creams, ointments, or emollients immediately prior to patch application, since the effect on patch adhesion and methylphenidate absorption has not been established. The potential adverse effects of topical corticosteroid use during treatment with Daytrana are unknown.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that Daytrana does not adversely affect their ability to engage in such activities.

Patches should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted that do not exceed 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) *[see How Supplied/Storage and Handling (16).* Patients or caregivers should be advised not to store Daytrana in the refrigerator or freezer.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Daytrana and should counsel them in its appropriate use. A patient Medication Guide is available for Daytrana. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Manufactured for Shire US Inc., Wayne, PA 19087 by Noven Pharmaceuticals, Inc., Miami, FL 33186.

For more information call 1-800-828-2088 or visit www.daytrana.com.

Dot Matrix™ is a trademark of Noven Pharmaceuticals, Inc.
Daytrana® is a registered trademark of Shire Pharmaceuticals Ireland Limited.

This product is covered by US patents including 5,958,446; 6,210,715; 6,348,211.

Last Modified: 06/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 29, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Daytrana (methylphenidate patch) for the treatment of attention deficit hyperactivity disorder (ADHD) in adolescents (ages 13-17).

TO: File NDA 21-514/S-010
[Note: This overview should be filed with the 9-4-09 original submission of this supplemental NDA.]

1.0 BACKGROUND

Daytrana is a patch formulation of methylphenidate that is already approved for the treatment of ADHD in children in a dose range of 10 to 30 mg/day. This supplement was intended to support the treatment of Daytrana in adolescents with ADHD in this same dose range. The studies in support of this application were conducted under IND 54,732.

The primary clinical reviewer for this application was Dr. Christina Burkhart and the primary statistical reviewer was Dr. Yeh-Fong Chen. A secondary review of this application was conducted by Dr. Robert Levin. Part of the review of this application included conversion of the label into PLR format.

2.0 CHEMISTRY

There were no CMC issues that required review as part of this supplement other than the new labeling format and consideration for categorical exclusion. All labeling issues have been resolved and the CMC group recommended approval.

3.0 PHARMACOLOGY

There were no pharm/tox issues that required review as part of this supplement other than the new labeling format. All labeling issues have been resolved and the pharm/tox group also recommended approval.

4.0 BIOPHARMACEUTICS

The biopharmaceutic issues included the new labeling format and a pk study in children and adolescents (SPD485-106). This was a single and multiple-dose study in a dose range of 10 to 30 mg/day (9 hours wear time). Exposures in children were roughly twice those in adolescents, in direct relation to the differences in weights. Accumulation was essentially the same in both age groups. Minor changes were made to the new labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on a single multicenter, randomized, double-blind, parallel group, placebo-controlled trial of Daytrana in adolescents with ADHD (study SPD485-409). This was a flexible dose study in which patients were optimized on Daytrana in a dose range of 10-30 mg/day (9 hours wear time), and then maintained for two weeks on their individualized optimum dose (randomization at the beginning of the 7 week period was to Daytrana or placebo, in a 2:1 ratio). Daytrana was statistically significanctly superior to placebo on mean change from baseline on the ADHD-RS-IV.

DSI found the data generated for this program to be acceptable.

-Efficacy Conclusions: I agree with Drs. Levin, Burkhart, and Chen that the sponsor has demonstrated efficacy for Daytrana in the treatment of adolescent ADHD.

5.2 Safety Data

Daytrana was adequately tolerated in the adolescent population and there were no new or unexpected safety findings.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not to take this application to the PDAC.

7.0 LABELING AND APPROVAL LETTER

7.1 Labeling

As noted, our review of labeling included consideration of the new PLR formatting, and we made a number of modifications to the sponsor's proposed labeling. We have now reached agreement with the sponsor on final labeling.

7.2 Approval Letter

The approval letter includes our agreed upon final labeling. There were no phase 4 commitments or requirements.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that Daytrana is effective and acceptably safe in the treatment of adolescent ADHD. We have reached agreement on final labeling, and I will issue the attached approval letter along with the agreed upon final labeling.

cc:
Orig NDA 21-514/S-010
HFD-130
HFD-130/TLaughren/MMathis/RLevin/CBurkhart/JToure

DOC: Daytrana_Adolescent ADHD_NDA21514_S-010_Laughren_AP Memo.doc

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
06/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

OFFICER/EMPLOYEE LIST

Officer/Employee list
Application: SNDA 021514/S-010

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Dempsey, Mary
Duer, Robin
Laughren, Thomas
Mathis, Mitchell

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

CROSS DISCIPLINE TEAM LEADER REVIEW

Clinical Team Leader Review Memo

Date	June 6, 2010
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA# / Supp #	21514 / S-010
Sponsor	Shire Pharmaceuticals
Proprietary / Established name	DAYTRANA (methylphenidate transdermal system)
Submission date	September 4, 2009
Dosage forms / strengths	10 mg (12.5 cm^2), 15 mg (18.75 cm^2), 20 mg (25 cm^2), and 30 mg (37.5 cm^2) transdermal patches
Proposed Indication	Attention Deficit-Hyperactivity Disorder in Adolescents (ages 13 to 17 years)
Recommendation:	Approval

1. Introduction

Daytrana (methylphenidate transdermal system) is an adhesive-based matrix transdermal system (patch) that is applied to the skin daily for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children (ages 6-12 years). It is the only transdermal system stimulant formulation currently approved for the treatment of ADHD.

2. Background/Regulatory History

Daytrana was approved for the treatment of ADHD in children (ages 6-12) on April 6, 2006. The original NDA was submitted on June 27, 2002, and the Division of Neuropharmacologic Drug Products took a non-approvable action on April 25, 2003, due to concerns about excessive exposures and adverse events. In the studies supporting the original NDA, the daily wear time (12 hours) that had been studied and proposed was longer than the currently approved daily wear time (9 hours) that was used in subsequent studies that supported the approval of Daytrana. In the initial NDA review, the primary adverse reactions of concern were gastrointestinal adverse effects, decreased appetite, weight loss, insomnia, and anxiety.

The sponsor submitted a non-approvable response on June 28, 2005. The studies supporting the resubmission included two new efficacy and safety trials in children (ages 6-12) with ADHD. The doses used were 10 mg (12.5 cm^2), 15 mg (18.75 cm^2), 20 mg (25 cm^2), and 30 mg (37.5 cm^2) transdermal patches with a wear time of 9 hours. Both studies demonstrated the efficacy of Daytrana in ADHD in children. In addition, treatment with Daytrana was reasonably safe and well tolerated. The Division took an approvable action on December 23, 2005; the sponsor submitted an approvable response on February 9, 2006; and the Division took an approval action on April 6, 2006.

In the April 6, 2006 approval letter, the Division requested a Phase 4 postmarketing commitment. Under section 2 of the Pediatric Research Equity Act (PREA), the sponsor would

be required to conduct an adequate and well controlled trial of Daytrana in the treatment of ADHD in pediatric patients (ages 13 to 17 years). The final report submission date would be 3 years form the date of approval of the NDA (April 2009). On October 9, 2006, the sponsor submitted a Proposed Pediatric Study Request for a pivotal study of Daytrana in adolescents with ADHD. The review of the study was filed in November 2006.

3. CMC

There was no new Chemistry, Manufacturing, and Controls information submitted in this application. There are no unresolved CMC issues that would affect an action on this application.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved Pharmacology/Toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

Andre Jackson, Ph.D. conducted the clinical pharmacology/biopharmaceutics review. Dr. Jackson concluded that the clinical pharmacology data submitted for this application are acceptable. The sponsor submitted data from Study SPD485-106, which was a clinical pharmacology study of Daytrana in pediatric subjects between the ages of 6 and 17 years-old with a diagnosis of ADHD. The objective of the study was to evaluate the pharmacokinetics of methylphenidate when Daytrana was administered as fixed single-doses and fixed multiple-doses. The doses used were 10 mg/day (12.5 cm^2 patch) and 30 mg/day (37.5 cm^2 patch), which are the lowest and highest Daytrana strengths, respectively. A specific objective was to evaluate the degree of accumulation of methylphenidate with multiple-dosing of Daytrana.

Compared to children (ages 6-12), the C_{max} and AUC_{inf} of methylphenidate in adolescents treated with single doses of Daytrana 10 mg/9 hours were decreased by 55% and 51%, respectively. After 7 days of dosing with 10 mg/9 hours, the Css_{max} and AUC_{ss} of methylphenidate in adolescents (compared to children) were decreased by 56% and 50%, respectively. Thus, the exposure differences between adolescents and children were comparable following single and multiple doses. Following fixed, multiple doses of Daytrana for 7 and 28 days, the accumulation index (based on AUC_{ss}) in children was 1.12 and 1.64, respectively. Following fixed, multiple doses of Daytrana for 7 and 28 days, the accumulation index in adolescents was 1.14 and 1.75, respectively.

Dr. Jackson also noted that since the efficacy studies of Daytrana in children and adolescents used flexible dosing, one cannot formally assess whether there is a dose/response relationship:

> "The efficacy data presented by the firm for weeks 1-7 for the 13-14 and 15-17 yr olds did not exhibit any dose response. Therefore the decreased exposure in adolescents compared to children does not warrant any adjustment in dose based upon dose response. Due to the study design, a true exposure response could not be assessed. In addition, the label recommends that the dosage be titrated to effect."

Based on his analysis of the PK data, Dr. Jackson has recommended specific additions in labeling for the clinical pharmacology sections.

6. Clinical Microbiology

There are no clinical microbiology issues regarding this application.

7. Clinical/Statistical

The Division and the sponsor prospectively agreed that one adequate and well controlled study of Daytrana in adolescents with ADHD would be adequate to: 1) meet the requirements of the written request, and 2) support the addition of labeling language describing the study results. In addition, the Division and the sponsor prospectively agreed on the specific design of the pivotal study (SPD485-409).

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The flexible doses used in adolescent study SPD485-409 were identical to those used in the controlled ADHD studies in children (ages 6 to 12). The sponsor conducted single-dose and multiple-dose pharmacokinetic studies in children and adolescents with the various Daytrana dose strengths, in order to select the doses in this controlled study. The choice of doses was also based on the controlled efficacy data in children.

7.1.2. Phase 3 clinical studies essential to regulatory decisions, including design, analytic features, and results

7.1.2.1 Study Design

Study SPD485-409 was conducted in 32 U.S. centers between June 28, 2007 and May 19, 2008. This was a randomized, double-blind, placebo-controlled, outpatient, flexible-dose study of methylphenidate transdermal system (Daytrana) in adolescents (ages 13-17) with Attention Deficit-Hyperactivity Disorder. The primary objective was to evaluate the efficacy of Daytrana compared to placebo transdermal patches. The primary endpoint was the change in mean ADHD-RS-IV score at the end of Week 7.

7.1.2.2 Subject Selection Criteria

Subjects were outpatient male and female adolescents between the ages of 13 and 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). Subjects must have had a baseline ADHD-RS-IV total score of > 26. They must have had an IQ score > 80 as measured by the Kaufman Brief Intelligence Test. In addition, subjects had to have normal blood pressure values for their age, gender, and height and must have had no significant comorbid illnesses, significant ECG findings, or history of dermatologic disorders.

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

7.1.2.3 Demographic Features

A total of 217 subjects participated in the study. Subjects were randomized to Daytrana (n= 145) or placebo (n= 72) in a 2:1 ratio. The study population was 75% male and 25% female, which is consistent with the gender distribution of ADHD in the pediatric population. The age subgroups were well represented (52.5% were 13-14 years-old, and 47.5% were 15-17 years-old). The distribution of ethnicities in the study subjects was as follows: Caucasian (77%), African American (18%), Asian (0.5%), Native American (0.5%), and Other (4%). The mean weight, height, and BMI were 130 lbs., 65 inches, and 21.2 kg/m2, respectively. These demographic features were well balanced between treatment groups.

7.1.2.4 Dose Optimization and Maintenance Phases of the Study

After a screening and drug washout period, subjects entered the randomized, double-blind, placebo-controlled treatment phase (7 weeks). Subjects were randomized to treatment with either Daytrana or placebo (in a 2:1 ratio) and began a 5-week dose optimization phase. All subjects in the Daytrana group began treatment with 10 mg/9 hour (12.5 cm^2). After one week, the dose could be increased to 15 mg/9 hour (18.75 cm^2), depending on response and tolerability. At the end of Weeks 2 and 3, the dose could be increased to 20 mg (25 cm^2) and 30 mg (37.5 cm^2), respectively. The dose could be decreased by one dose level during the 5-week dose-optimization phase. During a 2-week double-blind, placebo-controlled maintenance phase, the subjects' doses remained constant. The primary efficacy assessment was conducted at the end of the 2-week maintenance phase (at the end of Week 7).

7.1.2.5 Efficacy findings and Statistical Analysis

Christina Burkhart, M.D. performed the clinical review. As Dr. Burkhart notes, the results of Study 409 demonstrated the efficacy of Daytrana in the treatment of ADHD in an adolescent study population. The primary efficacy results are illustrated in the table below (adapted from the sponsor's Table 19 in the clinical study report). The primary efficacy instrument was the Attention Deficit-Hyperactivity Rating Scale-IV (ADHD-RS-IV), which is a well validated and widely used efficacy measure for assessing ADHD symptoms in children and adolescents with a diagnosis of ADHD.

The primary endpoint was the mean change in ADHD-RS-IV total score at the end of Week 7. The primary statistical analysis was a comparison between the Daytrana and placebo groups in the mean change from baseline in ADHD-RS-IV total score at endpoint using an ANCOVA model with treatment as a factor and baseline ADHD-RS-IV total score as a covariate. The least square mean difference (95% CI) between Daytrana and placebo was -9.96 (-13.39, -6.53). At endpoint, the least square mean change from baseline in ADHD-RS-IV total score

was statistically significantly greater ($p < 0.001$) for the MTS group (-18.8) compared with the placebo group (-8.8). This magnitude of difference in ADHD-RS score is clinically significant.

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

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

The key secondary efficacy endpoint was the change in mean total score on the Conners' Parent Rating Scale-Revised Short Version (CPRS-R) at the end of Week 7. This key secondary endpoint was positive, and it supports the primary efficacy findings. The LS mean difference (95% CI) between the Daytrana and placebo groups in the change from baseline CPRS-R total score was -13.48 (-18.48, -8.47). The difference between groups was statistically significant ($p < 0.001$).

Sponsor's Table 23: Analysis of LS Mean (SE) Change from Baseline CPRS-R 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)	-7.5 (2.08)	-20.9 (1.45) -13.48	(-18.48, -8.47)	<0.001

Yeh-Fong Chen, Ph.D. conducted the statistical review. Essentially, Dr. Chen replicated the sponsor's analysis results for the primary and secondary endpoints, and she concluded that Study 409 demonstrated the efficacy of Daytrana in this study:

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

7.1.3. Discussion of primary and secondary reviewers' comments and conclusions

7.1.3.1. Clinical Review

Dr. Burkhart has concluded that the clinical data demonstrate that Daytrana was efficacious in the treatment of ADHD in adolescents. She concluded that Study 409 was an adequate and well controlled study. I agree with her conclusions.

7.1.3.2. Statistical Review

Dr. Chen replicated the sponsor's efficacy analysis, and she concluded that the results demonstrated the efficacy of treatment with Daytrana in Study 409. I agree with her conclusions.

7.1.4. Pediatric use/PREA waivers/deferrals

In the April 6, 2006 Daytrana approval letter, the Division requested a phase 4 postmarketing commitment for the studies currently under review. Under section 2 of the Pediatric Research Equity Act (PREA), the sponsor would be required to conduct an adequate and well controlled trial of Daytrana in the treatment of ADHD in pediatric patients (ages 13 to 17 years). The final report submission date would be 3 years form the date of approval of the NDA (April 2009). On October 9, 2006, the sponsor submitted a Proposed Pediatric Study Request for a pivotal study of Daytrana in adolescents with ADHD. The review of the study was filed in November 2006. There are no other outstanding commitments under PREA.

7.2. Safety

7.2.1. General safety considerations

The safety database was adequate for this application. The safety monitoring was appropriate and adequate for a study of methylphenidate in pediatric subjects. The number of subjects exposed to Daytrana and the duration of exposure were adequate for assessing the safety parameters. There were 145 subjects exposed to Daytrana for a total exposure of 16.4 subject-years in the short-term, controlled study. The median duration of Daytrana exposure was 48 days. In the open-label extension study (410), the median exposure was 168 days, and the total exposure was 57.6 subject-years.

7.2.2. Safety findings from the clinical studies

There were no new or unexpected safety findings related to treatment with Daytrana, compared to previous experience with Daytrana or other methylphenidate formulations. There were no deaths in the study, and there were two serious adverse events.

One subject treated with Daytrana had two serious adverse events (syncope), which led to discontinuation from the study. The subject recovered from the episodes. Subject (b) (6) had episodes of dizziness followed by syncope on Day 8 and Day 11 after beginning treatment with Daytrana. On Day 13, the subject reported these episodes. Both episodes of syncope occurred approximately 1 hour after removal of the patch and lasted less than 30 seconds. The subject's dose had been 15 mg/d (18.75 cm^2 patch). The subject's screening, baseline, and early termination visit ECGs were reviewed by a pediatric cardiologist. Reportedly, there was no evidence of structural heart disease or aberrant conduction.

There were no other serious adverse events in the study. Drug-related adverse events leading to discontinuation included: decreased appetite, irritability, dizziness, dry mouth, syncope, and

application site dermatitis. In the methylphenidate group, 6% of subjects discontinued due to an adverse event. In the placebo group, 3% of subjects discontinued due to an adverse event. Commonly reported adverse reactions included decreased appetite (26%), weight loss (6%), irritability (11%), insomnia (6%), nausea (10%), abdominal discomfort (5%), vomiting (2%), dizziness (6%), and application site reactions (6%).

The mean change in weight in the Daytrana group was -0.86 kg (-1.9 lbs.). In the placebo group, the mean change in weight was +0.804 kg (+1.77 lbs). There were small increases in pulse rate and blood pressure in the Daytrana. The mean pulse, SBP, and DBP increased by 6.7 bpm, 2 mm Hg, and 1.7 mm Hg, respectively.

7.2.3. Safety update

The sponsor submitted the Four Month Safety Update Report on January 4, 2010. The sponsor reported that during the period of September 4, 2009 to January 4, 2010, no clinical studies with Daytrana had been initiated or ongoing. The sponsor stated that there were no significant safety findings that would change the assessment of the safety profile of Daytrana. Daytrana is not currently marketed in any countries other than the U.S.

The sponsor submitted the results of two non-clinical safety studies in juvenile rats (January 4, 2010) as part of the Four Month Safety Update. As Dr. Burkhart notes, the results of the two studies do not change the interpretation of safety profile of Daytrana.

7.2.4. Discussion of primary reviewer's comments and conclusions

Dr. Burkhart conducted a thorough and thoughtful review of the safety data. She has concluded that treatment with Daytrana in the adolescent ADHD study was generally safe and well tolerated. Dr. Burkhart also concluded that there were no new safety findings in this study, compared to those in previous Daytrana studies or with methylphenidate studies in general. I agree with Dr. Burkhart's conclusions.

8. Advisory Committee Meeting

There was no advisory committee meeting regarding this application, because there were no unique or controversial features of the application. Daytrana is approved for the treatment of ADHD in children (ages 6-12).

9. Financial Disclosure

There are no concerns about the financial disclosure of investigators who participated in the studies supporting this submission.

10. Labeling

10.1 Physician labeling

As part of the review of this submission, the Division converted approved Daytrana labeling into the Physician Labeling Rule labeling format. All relevant disciplines conducted the labeling review.

10.2 Clinical Pharmacology Section - Pharmacokinetics

Dr. Jackson (OCP) recommends adding the following language to the pharmacokinetics section:

> The Cmax and AUC of d-methylphenidate were approximately 50% lower in adolescents, compared to children, following either a 1-day or 7-day administration of Daytrana (10mg/9 hr). Multiple-dose administration of Daytrana did not result in significant accumulation of methylphenidate; following 7 days of Daytrana administration (10 mg/ 9 hr) in children and adolescents, the average accumulation index of methylphenidate was 1.1.

10.3 Clinical Studies Section

The Division has proposed the following additional language to describe the efficacy results of Study 409:

> In Study 3, conducted in the outpatient setting, Daytrana or placebo was blindly administered in a flexible-dose design using doses of 10, 15, 20, and 30 mg / 9 hours during a 5-week dose-optimization phase, followed by a 2-week maintenance period using the optimal patch dose for each patient. Symptoms of ADHD were evaluated using the ADHD-Rating Scale (ADHD-RS-IV). Daytrana was statistically significantly superior to placebo as measured by the mean change from baseline in the ADHD-RS-IV total score.

10.4 Patient labeling/Medication guide

We have proposed substantial changes to the medication guide, in order to make it more consistent with labeling and to use more accessible language for patients and families.

11. DSI Audits

Anthony Orencia, M.D. conducted the DSI review. The Division recommended auditing two U.S. clinical sites which were relatively high enrollers of subjects in Study 409. The investigators are: 1) Robert Findling, M.D. at University Hospitals Case Medical Center, Division of Child and Adolescent Psychiatry, and 2) Keith Saylor, Ph.D. at NeuroScience Inc., Herndon, Virginia. There were no significant concerns about the data from these two sites. Dr. Orencia concluded that the study was conducted adequately at the sites, and he found the data to be acceptable. Dr. Orencia recommended that there was no action indicated for both sites.

12. Conclusions and Recommendations

12. 1 Recommended regulatory action

I recommend approval of this supplemental NDA for Daytrana in the treatment of ADHD in adolescents (ages 13-17). The sponsor conducted an adequate and well controlled trial of Daytrana that clearly demonstrated efficacy in the treatment of ADHD in adolescents. The study demonstrated that treatment with Daytrana was reasonably safe and well tolerated. There were no new or unexpected safety concerns related to treatment, compared to previous experience with Daytrana or other methylphenidate formulations.

12.2 Safety concerns to be followed postmarketing

We and the sponsor will continue routine pharmacovigilance for Daytrana.

12.3 Risk Minimization Action Plan

There is no specific risk minimization action plan for Daytrana.

12.4 Postmarketing studies

Other than the studies under review, there are no outstanding required postmarketing studies.

12.5 Comments to be conveyed to the applicant in the regulatory action letter

There are no specific comments to convey to the sponsor. We have sent our proposed labeling.

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

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/s/

ROBERT L LEVIN
06/06/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

CLINICAL REVIEW(S)

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 29, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Daytrana (methylphenidate patch) for the treatment of attention deficit hyperactivity disorder (ADHD) in adolescents (ages 13-17).

TO: File NDA 21-514/S-010
[Note: This overview should be filed with the 9-4-09 original submission of this supplemental NDA.]

1.0 BACKGROUND

Daytrana is a patch formulation of methylphenidate that is already approved for the treatment of ADHD in children in a dose range of 10 to 30 mg/day. This supplement was intended to support the treatment of Daytrana in adolescents with ADHD in this same dose range. The studies in support of this application were conducted under IND 54,732.

The primary clinical reviewer for this application was Dr. Christina Burkhart and the primary statistical reviewer was Dr. Yeh-Fong Chen. A secondary review of this application was conducted by Dr. Robert Levin. Part of the review of this application included conversion of the label into PLR format.

2.0 CHEMISTRY

There were no CMC issues that required review as part of this supplement other than the new labeling format and consideration for categorical exclusion. All labeling issues have been resolved and the CMC group recommended approval.

3.0 PHARMACOLOGY

There were no pharm/tox issues that required review as part of this supplement other than the new labeling format. All labeling issues have been resolved and the pharm/tox group also recommended approval.

4.0 BIOPHARMACEUTICS

The biopharmaceutic issues included the new labeling format and a pk study in children and adolescents (SPD485-106). This was a single and multiple-dose study in a dose range of 10 to 30 mg/day (9 hours wear time). Exposures in children were roughly twice those in adolescents, in direct relation to the differences in weights. Accumulation was essentially the same in both age groups. Minor changes were made to the new labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on a single multicenter, randomized, double-blind, parallel group, placebo-controlled trial of Daytrana in adolescents with ADHD (study SPD485-409). This was a flexible dose study in which patients were optimized on Daytrana in a dose range of 10-30 mg/day (9 hours wear time), and then maintained for two weeks on their individualized optimum dose (randomization at the beginning of the 7 week period was to Daytrana or placebo, in a 2:1 ratio). Daytrana was statistically significanctly superior to placebo on mean change from baseline on the ADHD-RS-IV.

DSI found the data generated for this program to be acceptable.

-Efficacy Conclusions: I agree with Drs. Levin, Burkhart, and Chen that the sponsor has demonstrated efficacy for Daytrana in the treatment of adolescent ADHD.

5.2 Safety Data

Daytrana was adequately tolerated in the adolescent population and there were no new or unexpected safety findings.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not to take this application to the PDAC.

7.0 LABELING AND APPROVAL LETTER

7.1 Labeling

As noted, our review of labeling included consideration of the new PLR formatting, and we made a number of modifications to the sponsor's proposed labeling. We have now reached agreement with the sponsor on final labeling.

7.2 Approval Letter

The approval letter includes our agreed upon final labeling. There were no phase 4 commitments or requirements.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that Daytrana is effective and acceptably safe in the treatment of adolescent ADHD. We have reached agreement on final labeling, and I will issue the attached approval letter along with the agreed upon final labeling.

cc:
Orig NDA 21-514/S-010
HFD-130
HFD-130/TLaughren/MMathis/RLevin/CBurkhart/JToure

DOC: Daytrana_Adolescent ADHD_NDA21514_S-010_Laughren_AP Memo.doc

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

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/s/

THOMAS P LAUGHREN
06/29/2010

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	021514
Priority or Standard	Standard
Submit Date(s)	4 September 2009
Received Date(s)	4 September 2009
PDUFA Goal Date	4 July 2010
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)

(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 Drs. (b) (6), and (b) (6) have received "significant payments of other sorts" as defined in 21 CFR 54.2(f).

Dr. (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)

(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).

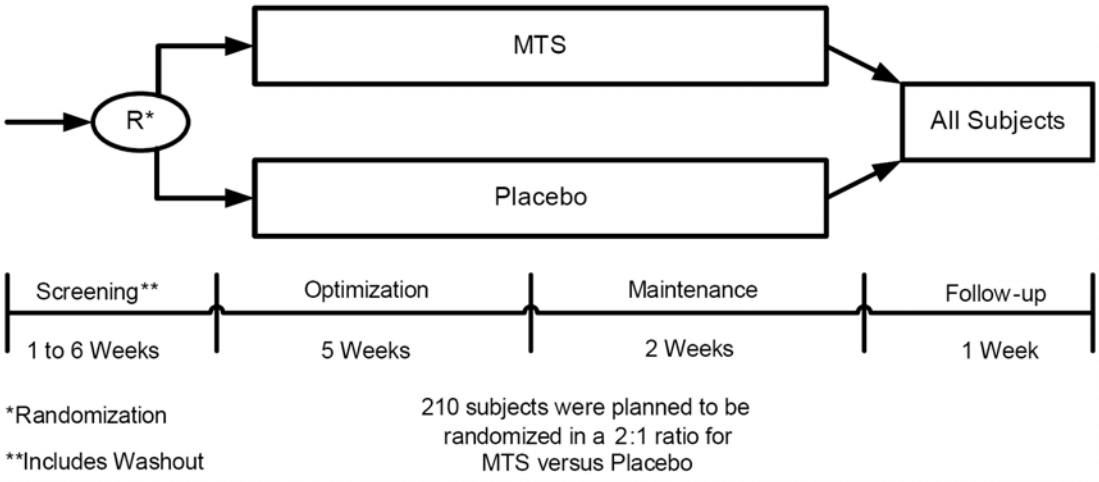
Eligible subjects were outpatient male and female adolescents aged 13-17 years, with a primary diagnosis of ADHD. The diagnosis was based on a structured Kiddie-Schedule for Affective Disorders-Present and Lifetime-Diagnostic Interview (K-SADS-PL). A total score of $\geq$ 26 on the ADHD-RS-IV at baseline, 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.

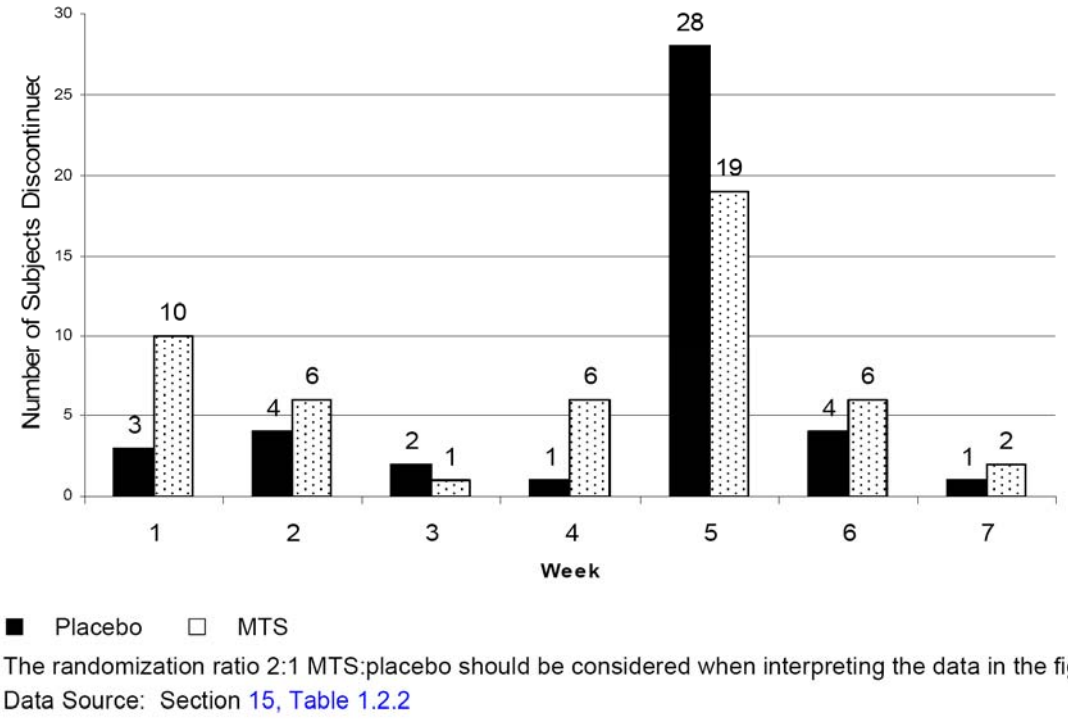
Table 15: Summary of Early Terminations by MTS Final Patch Size (Safety Population)

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.

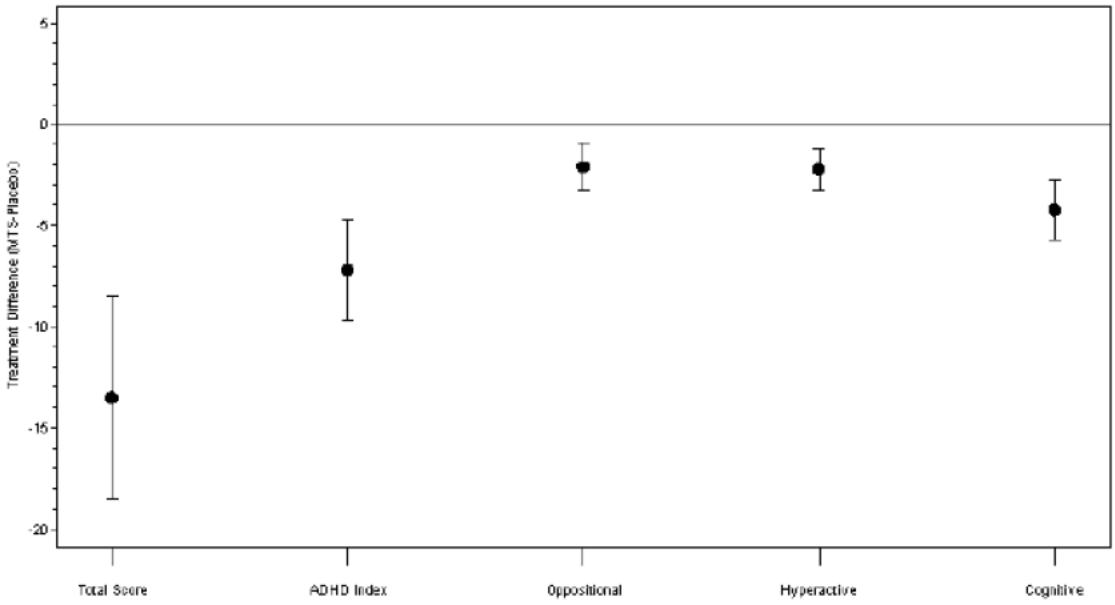
Table 23: Analysis of LS Mean (SE) Change from Baseline CPRS-R Total Score (ANCOVA model)-ITT Population

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 $\leq$ 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 (b) (6)	Study Treatment	Patch Size at Onset	SAE (PT)	Relationship	Subject Disposition
	MTS	18.75 cm^2 18.75 cm^2	syncope syncope	related related	discontinued discontinued
	Placebo	37.5 cm^2	negativism	not related	discontinued

(Clinical Report, p. 85)

Subject (b) (6) was randomized to MTS and started study treatment on (b) (6). On (b) (6), the subject reported that he had experienced two episodes of dizziness followed by syncope on (b) (6) and (b) (6). 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
(b) (6)	MTS	37.5 cm^2	application site erythema	related	N	moderate
	MTS	25 cm^2	decreased appetite	related	N	moderate
	MTS	25 cm^2	dry mouth	related	N	moderate
			anorexia	related	N	moderate
			sedation	related	N	mild
	MTS	18.75 cm^2	dizziness	related	N	moderate
			syncope	related	Y	moderate
			syncope	related	Y	moderate
	MTS	18.75 cm^2	psoriasis	not related	N	moderate
			folliculitis	not related	N	moderate
	MTS	18.75 cm^2	somnolence	related	N	moderate
			fatigue	related	N	moderate
	MTS	18.75 cm^2	application site dermatitis	related	N	moderate
	MTS	25 cm^2	application site dermatitis	related	N	severe
	Placebo	37.5 cm^2	negativism	not related	Y	severe
	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 (b) (6) 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 (b) (6)

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 (b) (6) was a 16-year-old female who discontinued secondary to decreased appetite. Her course is summarized in Table 34.

Table 34: Subject (b) (6)

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 (b) (6) 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 (b) (6)

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 (b) (6) 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 (b) (6) 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 (b) (6) 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 (b) (6)

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 (b) (6) 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 (b) (6)

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 ([(b) (6)]) 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 ((b) (6)) experienced a decreased appetite and a 6% decrease in weight from baseline to Day 41 and therefore was discontinued from the study. Another subject (b) (6) 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 ((b) (6)) 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 (b) (6) 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 (b) (6) 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 (≥ 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 ([b) (6)]) 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 [(b) (6)] exhibited PCI high pulse rate of 109bpm at Week 4 and Subject [(b) (6)] 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 ([redacted]) 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 ≥ 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 (b) (6) 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 (b) (6) 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 (b) (6) 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 (b) (6) 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					
(b) (6)	25cm^2	Social avoidant behavior	Y	N	moderate
	25cm^2	Application site reaction	Y	N	moderate
	18.75cm^2	Decreased appetite[c]	Y	N	moderate
		Weight decreased[c]	Y	N	moderate
		Compulsions	Y	N	moderate
	37.5cm^2	Affect lability	Y	N	moderate
		Irritability	Y	N	moderate
	25cm^2	Clonic convulsion	N	Y	mild
	37.5cm^2	Application site burning	Y	N	severe
	37.5cm^2	Nausea	Y	N	moderate
	12.5cm^2	Anxiety	Y	N	moderate
	18.75cm^2	Affect lability	Y	N	moderate
	37.5cm^2	Hallucination, auditory	Y	Y	moderate
		Hallucination, visual	Y	Y	moderate
	37.5cm^2	Application site erythema	Y	N	moderate
		Application site oedema	Y	N	moderate
		Application site pruritus	Y	N	moderate
	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 ((b) (6) 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 (b) (6) 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 (b) (6) 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 (b) (6) 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
(b) (6)	MTS 25cm^2	M/13	Clonic convulsion	N	Y
	MTS 37.5 cm^2	F/13	Hallucination, auditory Hallucination, visual	Y Y	Y Y
	None (event occurred after completion of study)	M/13	Grand mal convulsion	N	N
	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 (b) (6)) 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA P BURKHART
04/07/2010

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

PRODUCT QUALITY REVIEW(S)

DIVISION OF POST-MARKETING VALUATION
Review of Chemistry, Manufacturing, and Controls

NDA # 21-514 **SUPPLEMENT**: SE5-010 REVIEW DATE: 03-Jun-2010

SUPPLEMENT(S) PROVIDE(S) FOR: treatment of ADHD in Adolescents (13-17 years old).

TYPE of SUPPLEMENT:
☐ SUPAC ☐ CBE-0 ☐ CBE-30 ☒ Prior Approval ☐ Bundled Review ☐ Expedited Review

THE USER FEE GOAL DATE: 04-Jul-2010

SUBMISSION DATE	**SUB. TYPE**	**DOC. DATE**	**CDER DATE**	**ASSIGNED DATE**
04-Sep-2010	electronic	04-Sep-2010	04-Sep-2010	20-Oct-2010

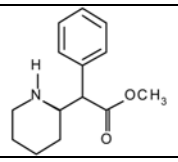
NAME & ADDRESS OF APPLICANT: James Ewing, Manager, Global Regulatory Affairs.
Shire Development Inc.
725 Chesterbrook Blvd, Wayne, PA 19087
(b) (6) F: 484-595-8156

DRUG PRODUCT NAME:

Proprietary:	Daytrana™
Nonproprietary/Established/USAN:	Methylphenidate Transdermal System
Code Name/#:	N/A
Chem. Type/Therapeutic Class:	23/S

PHARMACOL. CATEGORY/INDICATION: Treatment of Attention Deficit Hyperactivity Disorder
DOSAGE FORM: Transdermal
STRENGTHS: 1.1, 1.6, 2.2, 3.3 mg/hr
ROUTE OF ADMINISTRATION: percutaneous.
DISPENSED: xx Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

methylphenidate is alpha-phenyl-2-piperidineacetic acid methyl ester. Its molecular weight is 233.31. Its empirical formula is $C_{14}H_{19}NO_2$.	

SUPPORTING DOCUMENTS: N/A
RELATED DOCUMENTS (if applicable): N/A
CONSULTS: N/A

REMARKS/COMMENTS: (see review notes as well)

No significant change is proposed.
Otherwise, from a CMC standpoint, this supplement is approved.

CONCLUSIONS & RECOMMENDATIONS: **Approval**

Li-Shan Hsieh, Ph.D., Review Chemist,

James Vidra, Ph.D., Chief of Branch VII

Review Notes

This official efficacy supplement provides for treatment of ADHD in Adolescents (13 to 17 years old).

Package insert

Description: No description changes are proposed, see attached e-mail below:

From: Levin, Robert
Sent: Wednesday, May 05, 2010 2:27 PM
To: Chidambaram, Nallaperum; Toure, Juliette T
Cc: Burkhart, Christina; Duffy, Eric P; Vidra, James D; Hsieh, Li Shan
Subject: RE: Wrap up Mtg - NDA 21-514/S-010 Daytrana; Adolescent Pt Pop

Dear All,

Juliette and I discussed this point. We should probably not propose any change for the established name: methylphenidate transdermal system.
Thanks.

Bob

From: Chidambaram, Nallaperum
Sent: Wednesday, May 05, 2010 1:36 PM
To: Toure, Juliette T
Cc: Levin, Robert; Burkhart, Christina; Duffy, Eric P; Vidra, James D; Hsieh, Li Shan
Subject: RE: Wrap up Mtg - NDA 21-514/S-010 Daytrana; Adolescent Pt Pop

Juliette,

We need some more time to discuss the issue internally regarding proposed change in established name described below:

Change from “Daytrana® (methylphenidate transdermal system)” to (b) (4)

(b) (4)

We hope to get back by end of this week. Let us know if this time frame will work for you.

Thanks,
Chid

16 HOW SUPPLIED/STORAGE AND HANDLING

Daytrana is supplied in a sealed tray or outer pouch containing 30 individually pouched patches. See the chart below for information regarding available strengths.

Nominal Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm^2)	Methylphenidate Content per Patch** (mg)	Patches Per Carton	NDC Number
10	1.1	12.5	27.5	30	54092-552-30
15	1.6	18.75	41.3	30	54092-553-30

20	2.2	25	55	30	54092-554-30
30	3.3	37.5	82.5	30	54092-555-30

*Nominal *in vivo* delivery rate in (b) (4) children and adolescents (b) (4) when applied to the hip, based on a 9-hour wear period.
**Methylphenidate content in each patch.

Store at 25º C (77º F); excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]. Do not store patches unpouched. Do not store patches in refrigerators or freezers.

Once the sealed tray or outer pouch is opened, use contents within 2 months. Apply the patch immediately upon removal from the individual protective pouch. **For transdermal use only**.

Evaluation and Comment: ***Adequate***

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI SHAN HSIEH
06/17/2010

JAMES D VIDRA
06/17/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21-514
Supporting document/s:	Supporting Document 0026, (Efficacy Supplement S-10)
Applicant's letter date:	09-04-2009
CDER stamp date:	09-04-2009
Product:	Daytrana (methylphenidate transdermal system)
Indication:	Attention Deficit Hyperactivity Disorder
Applicant:	Shire
Review Division:	Division of Psychiatry Drug Products
Reviewer:	Ikram Elayan, Ph.D.
Supervisor/Team Leader:	Linda Fossom, Ph.D.
Division Director:	Tom Laughren, M.D.
Project Manager:	Juliette Toure, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21514 are owned by Shire or are data for which Shire has obtained a written right of reference.

Any information or data necessary for approval of NDA 21514 that Shire does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Shire does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21514

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

See comments under Labeling, below.

1.1.1 Approvability

Approvable (See comments under Labeling, below.)

1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

The original labeling for Daytrana is being converted to PLR format. No changes should be made to the content of the original labeling from a preclinical point of view based on the studies submitted. A statement that was added by the sponsor (b) (4) (b) (4) (b) (4) The section that was added by the Sponsor is presented (underlined, in blue) here:

(b) (4)

The labeling of Daytrana describes the results of the juvenile rat study and other preclinical studies that were performed with oral methylphenidate; however, it should be pointed out that the animal doses used were expressed in the labeling as mg/kg/day with no safety factors calculated based on the doses used in the animal studies and the MRHD. The reason for this is that the juvenile animal studies were conducted using the oral route while Daytrana is a transdermal formulation. A sentence can be added to the description of these studies in the labeling to clarify that.

The following is the labeling for Daytrana that pertains to the results of the juvenile animal studies:

> Pediatric Use
>
> The safety and efficacy of Daytrana™ in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).
>
> In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

For clarity, the description of the oral studies in juvenile rats can be preceded by the following sentence:

> Studies with the transdermal patch were not conducted in animals.

1.2 Brief Discussion of Nonclinical Findings:

Background: Daytrana (methylphenidate transdermal system) has been approved for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 to 12 years (under this NDA on 4/6/2006). The current submission is an efficacy supplement for treatment of ADHD in adolescents (13 to 17 years old), conducted as a postmarketing commitment; the Sponsor is requesting revisions to the US Prescribing Information (i.e., labeling), based on 3 efficacy studies completed in the adolescent patient population. Additionally, the Sponsor submitted a Prior Approval Supplement (6/30/2009), providing for the conversion of the current/original labeling to PLR format; action on this supplement is being combined with this efficacy supplement.

In the current submission, the Sponsor has provided reports for 3 non-clinical studies conducted in spontaneously hypertensive rats (SHR):

1) comparing the effects of d- and l-methylphenidate on extracellular levels of dopamine in the striatum and noradrenaline in the prefrontal cortex;
2) determining the effects of racemic (d,l-) methylphenidate (MPH) on extracellular levels of dopamine in the striatum and noradrenaline in the prefrontal cortex ; and
3) comparing the effects of d- and l-methylphenidate on behavioral parameters in SHR (and wild-type (WKY) rats).

The Sponsor proposed [redacted] The reviewer has reservations about this implication (see discussion).

The data in these studies demonstrated that d,l-MPH increased both DA (in striatum) and NE (in PFC) at doses of 10 and 20 mg/kg in SHR. The isomers were only tested up to 10 mg/kg, at which dose d-MPH increased both DA and NE; however, l-MPH only increased DA, not NE. Based on this limited data it is not possible to assess the relative potencies of the isomers to increase DA and NE in SHR rats.

Regarding the behavioral assessments of the isomers, there was evidence that d-MPH decreased "hyperactivity" and "impulsiveness" in SHR rats at doses up to 6 mg/kg; at that dose, l-MPH did not appear to decrease these parameters. Although higher doses of both d- and l-MPH might have provided more compelling results, [redacted]

Additionally, [redacted]

2 Drug Information

2.1 **Drug**: Daytrana (methylphenidate) Transdermal System.

2.1.1 CAS Registry Number (Optional)

2.1.2 **Generic Name:** Methylphenidate (base).

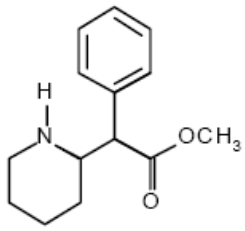
2.1.3 Code Name: Not applicable.

2.1.4 Chemical Name: α-phenyl-2-piperidineacetic acid methyl ester.

2.1.5 Molecular Formula/Molecular Weight:

$C_{14}H_{19}NO_2$, MW 233.3

2.1.6 Structure



Methylphenidate has 2 chiral centers (resulting in 2 stereoisomers and their optical isomers); however, the methylphenidate used here consists of the racemic pair of d,l-*threo* enantiomers; (b) (4)

2.1.7 Pharmacologic class:

CNS stimulant.

2.2 Relevant IND/s, NDA/s, and DMF/s

2.3 Clinical Formulation

Transdermal patch.

2.3.1 Drug Formulation

2.3.2 Comments on Novel Excipients

2.3.3 Comments on Impurities/Degradants of Concern

2.4 Proposed Clinical Population and Dosing Regimen

2.5 Regulatory Background

3 Studies Submitted

3.1 Studies Reviewed: see above.

3.2 Studies Not Reviewed: none

3.3 Previous Reviews Referenced: original NDA review (2002).

4 Pharmacology

4.1 Primary Pharmacology

(b) (4)

These studies are entitled:

1) Effects of the d- and l-threo-methylphenidate on extracellular levels of dopamine in the striatum and noradrenaline in the frontal cortex of spontaneously hypertensive rats,

2) Effects of dl-threo-methylphenidate on extracellular levels of dopamine in the striatum and noradrenaline in the frontal cortex of spontaneously hypertensive rats, and

3) Behavioral study of effects of d- and l-methylphenidate in a rat model of attention-deficit hyperactivity disorder.

The submitted studies are briefly summarized below. (b) (4) (b) (4) It should be noted that although methylphenidate has 2 chiral centers (resulting in 2 stereoisomers and their optical isomers), the methylphenidate used in Daytrana consists of the racemic pair of d,l-*threo* enantiomers; these enantiomers will also be referred to as d-MPH and l-MPH in this review.

Study 1: In freely moving spontaneously hypertensive rats (SHR) using in vivo microdialysis, d-threo-methylphenidate (1, 3, and 10 mg/kg, ip) dose dependently increased striatal extracellular dopamine (DA) levels up to 957% compared to control at 10 mg/kg (these were the Sponsor's calculation, the reviewer's calculations were slightly different in which the baseline values were used instead of comparing the increase to the control, and the changes were ~9 fold). l-Threo-methylphenidate (10 mg/kg, ip) also increased DA level up to 183% compared to control in the striatum (again these are the Sponsor's calculations and the reviewer's calculations based on expressing the increase relative to the baseline levels were ~2 fold increase). The total increase in extracellular DA produced by the same dose of d-threo-MP was ~3.6-fold greater than those produced by l-threo-MP (based on AUC). Extracellular levels of NA in the cortex were increased with d-threo-MP (up to 493% compared to control at 10 mg/kg according to the Sponsor's calculations and an ~4 fold increase was obtained based on expressing the increase relative to the baseline levels) but not by l-threo-MP. The sponsor's conclusion from this study was: "the effects of d-threo and l-threo-MP on DA efflux are probably mediated predominantly via release through an interaction at 'cocaine binding sites' on the DA reuptake transporter as well as through classical reuptake inhibition. In contrast, the effects of d-threo-MP on NA function may be predominantly mediated by classical uptake inhibition". The results from the study are summarized in this table as extracted from the Sponsor's submission:

Table 1. Effect of d- and l-threo methylphenidate on extracellular DA in the striatum in SHR

Table 3: Effects of d- and l-threo methylphenidate on extracellular levels of dopamine in the striatum of spontaneous hypertensive rats

Treatment	*d*-methylphenidate (mg/kg ip)				*l*-methylphenidate (mg/kg ip)
	0[¥] (n = 11)	1 (n = 10)	3 (n = 8)	10 (n = 9)	10 (n = 10)
Sampling Time	Dopamine efflux from rat striatum (% baseline)				
-45 min	108.9	96.4	100.8	111.9	99.1
-30 min	103.1	100.2	102.6	107.6	106.2
-15 min	98.2	102.0	96.7	99.5	99.3
0 min	96.0	107.3	105.6	88.2	101.4
15 min	96.7	211.1***	377.7***	478.1***	159.1*
30 min	108.8	336.9***	513.2***	1042.4***	200.1**
45 min	111.8	256.0***	420.0***	912.8***	162.4*
60 min	113.3	209.0***	327.2***	851.9***	134.4
75 min	98.5	165.8**	284.1***	736.9***	124.4
90 min	102.0	143.1	209.8***	557.0***	117.9
105 min	110.6	139.6	212.4***	443.8***	109.3
120 min	105.6	127.8	181.8**	367.5***	119.8
135 min	105.7	124.5	177.4**	298.7***	117.4
150 min	111.9	124.3	167.1	227.7**	99.1
165 min	105.2	124.6	159.1*	187.7**	98.7
180 min	96.7	109.4	142.4	162.6*	95.0
195 min	104.7	91.9	152.3	155.2	101.3
210 min	111.5	117.2	153.1*	170.9**	100.4
225 min	102.4	126.3	153.3*	145.6*	98.9
240 min	97.2	107.3	139.4	126.6	91.9

[¥] Saline
* p<0.05, ** p<0.01, *** p<0.001 – significant differences from saline treated animals (Williams' test)

Table 2. Effect of d- and l-threo methylphenidate on extracellular NE levels in the prefrontal cortex in SHR

Table 4: Effects of d- and l-threo methylphenidate on extracellular levels of norepinephrine in the prefrontal cortex of spontaneous hypertensive rats					
Treatment	Saline	*d*-methylphenidate (mg/kg ip)			*l*-methylphenidate (mg/kg ip)
	0[¥] (n = 13)	1 (n = 9)	3 (n = 10)	10 (n = 9)	10 (n = 9)
Time	Norepinephrine efflux from rat prefrontal cortex (% baseline)				
-45 min	92.5	94.5	101.9	101.7	99.0
-30 min	109.9	104.7	88.8	115.2	104.5
-15 min	105.8	111.2	114.0	100.1	97.1
0 min	92.0	92.3	99.6	85.0	99.2
15 min	86.4	129.1*	153.7**	189.2***	117.2
30 min	96.1	179.2**	257.7***	378.9***	116.8
45 min	89.7	161.7**	272.1***	384.8***	114.0
60 min	91.0	154.5*	275.7***	449.2***	91.1
75 min	93.6	161.3**	247.7***	440.9***	103.7
90 min	96.2	123.4	238.3***	441.4***	95.9
105 min	86.0	139.1*	191.6***	409.7***	96.3
120 min	83.1	117.1	176.4***	367.3***	95.6
135 min	89.3	112.9	153.5**	352.1***	91.5
150 min	86.9	116.6	112.2	323.5***	99.3
165 min	86.0	105.9	116.0	317.3***	91.6
180 min	116.9	100.7	110.9	286.7***	68.4
195 min	86.8	75.1	94.1	268.6***	80.7
210 min	106.6	99.1	95.6	253.0***	80.5
225 min	90.8	92.5	86.1	205.7***	87.0
240 min	99.5	86.5	90.8	202.6***	70.5
[¥] Saline * p<0.05, ** p<0.01, *** p<0.001 – significant differences from saline treated animals (Williams' test)					

Study 2: In freely moving SHR (rats) using in vivo microdialysis, dl-threo-methylphenidate (10 and 20 mg/kg, ip) increased striatal extracellular DA levels up to 598% compared to control at 20 mg/kg (this was the Sponsor calculation, according to the reviewer's calculation and based on the increase relative to the baseline there was a ~7 fold increase) and increased cortical extracellular NA levels up to 532% compared to control at the same dose (this is also the Sponsor's calculation while the reivewer's calculation based on the increase relative to baseline, the fold increase was ~4.6). The sponsor's conclusion from this study is: "dl-threo-MP may enhance dopaminergic function via dual mechanisms: release through an interaction at 'cocaine binding sites' on the DA reuptake transporter and classical uptake inhibition. In contrast, the effects of dl-threo-MP on NA function appear to be predominantly mediated by classical uptake inhibition". The results of this study are summarized in the following tables as extracted from the sponsor's submission:

Table 3. Effect of dl-threo methylphenidate on extracellular levels of DA in the striatum of SHR

Table 1: Effects of dl-threo methylphenidate on extracellular levels of dopamine in the striatum of spontaneous hypertensive rats			
Treatment	*dl*-methylphenidate (mg/kg ip)		
	0[¥] (n = 8)	10 (n = 8)	20 (n = 9)
Sampling Time	Dopamine efflux from rat striatum (% baseline)		
-45 min	103.5	120.3	96.1
-30 min	99.5	111.7	113.5
-15 min	104.9	86.6	96.5
0 min	97.8	91.4	101.3
15 min	92.1	245.1	303.1*
30 min	124.4	369.6*	618.9**
45 min	121.9	387.6*	729.4***
60 min	111.5	389.4**	641.3***
75 min	119.9	346.6**	589.7***
90 min	93.8	283.7**	504.9***
105 min	87.9	250.5**	355.9**
120 min	96.8	275.4**	304.9**
135 min	86.5	270.9**	219.9**
150 min	118.9	323.2**	258.8**
165 min	94.4	201.3**	229.9**
180 min	90.4	229.2*	196.8*
195 min	100.9	168.0*	188.2*
210 min	93.0	171.1*	168.1*
225 min	90.8	142.2	118.0
240 min	77.3	129.9	99.7
[¥] saline * p<0.05, ** p<0.01, *** p<0.001 – significant differences from saline treated animals (Williams' test)			

Table 4. Effect of dl-threo methylphenidate on extracellular levels of NE in the prefrontal cortex of SHR

Table 2: Effects of dl-threo methylphenidate on extracellular levels of norepinephrine in the prefrontal cortex of spontaneous hypertensive rats			
Treatment	*dl*-methylphenidate (mg/kg ip)		
	0[¥] (n = 13)	10 (n = 10)	20 (n = 10)
Sampling Time	Norepinephrine efflux from rat prefrontal cortex (% baseline)		
-45 min	109.3	92.8	120.4
-30 min	93.1	102.8	91.8
-15 min	93.8	119.4	106.3
0 min	106.3	87.2	85.9
15 min	88.2	146.2	203.9**
30 min	89.7	271.8***	447.7***
45 min	90.2	376.3***	462.2***
60 min	93.4	335.0***	468.9***
75 min	97.1	364.8***	414.3***
90 min	113.6	326.1***	432.8***
105 min	88.1	300.8***	469.0***
120 min	91.3	339.0***	328.7***
135 min	101.6	318.8***	315.4***
150 min	93.4	244.4**	302.6***
165 min	98.8	265.0***	310.8***
180 min	116.8	265.2*	233.0**
195 min	97.5	204.1**	269.9***
210 min	113.6	176.8	241.9**
225 min	108.6	190.8*	219.9**
240 min	91.0	166.3*	274.4***
[¥] Saline * p<0.05, ** p<0.01, *** p<0.001 – significant differences from saline treated animals (Williams' test)			

Study 3: Using SHR (16 male rats, 4 weeks of age) as a model for ADHD, the sponsor tested the effect of treatment with d-threo-MP (doses of 0.75, 1.5, 3, and 6 mg/kg, ip, every 3rd day for 15 days) and l-threo-MP (only a 6 mg/kg dose was used) on activity and impulsive behavior of these animals compared to those of their control counterparts, Wistar Kyoto rats (WKY, 16 males, 4 weeks of age). The sponsor stated that there was reproducible reduction of hyperactivity in SHR rats treated with the d-isomer; however, the hyperactivity was not reduced to non-dosed WKY levels. Additionally, decreased impulsiveness was seen with the d-isomer in both SHR and WKY rats, with the effect more pronounced in SHR rats (even though the drug levels in plasma were lower than in the WKY controls). The effect on sustained attention in this study was not interpretable. The l-isomer appeared to be without an effect at the single dose tested in this study. The results of this study are summarized in the following figures as extracted from the sponsor's submission:

Figure 1. Effect of methylphenidate on activity in SHR and WKY controls

Figure 1: Effect of methylphenidate on activity in SHR and WKY controls

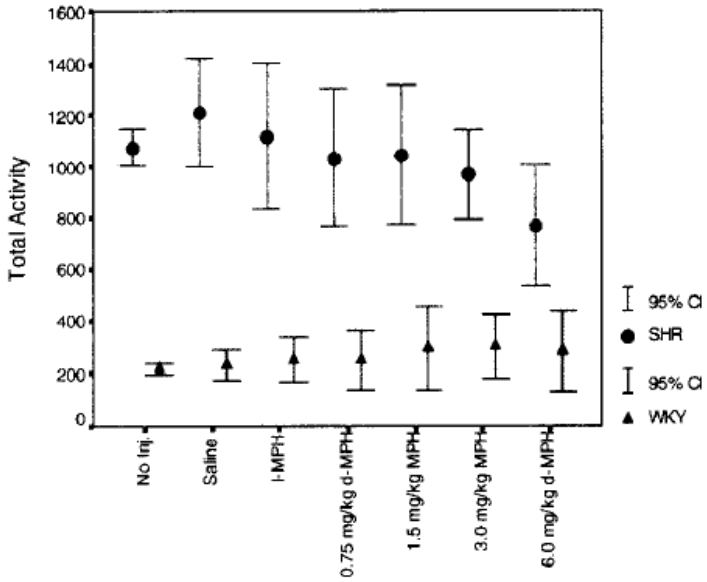
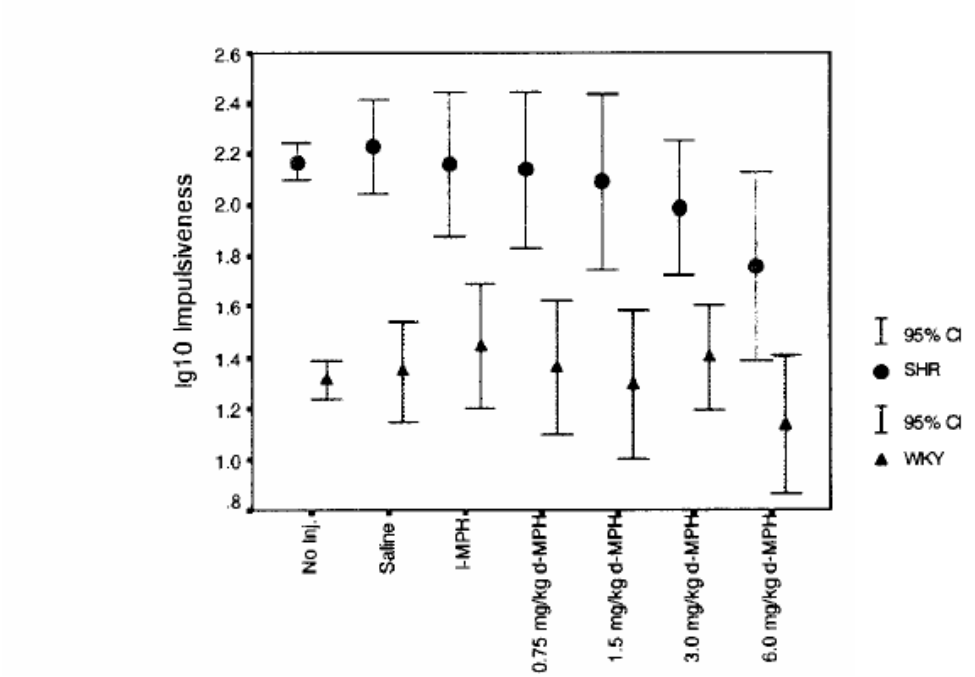


Figure 2. Effect of methylphenidate on impulsiveness in SHR and WKY controls

Figure 2: Effect of methylphenidate on impulsiveness (log10 transformed) in SHR and WKY controls.



11 Integrated Summary and Safety Evaluation

The results of these studies indicate that:

1) racemic methylphenidate (MPH) increased DA in striatum to ~4-fold baseline and NE in PFC to ~4-fold baseline at 10 mg/kg; and increased DA to ~7-fold and NE to ~4.5-fold at 20 mg/kg in SHR rats;
2) d-MPH increased DA to ~10-fold and NE to ~4.5-fold at 10 mg/kg in SHR rats;
3) l-MPH increased DA to ~4-fold and did not increase NE at 10 mg/kg (the highest dose tested) in SHR rats;
4) d-MPH appeared to decrease total activity at 6 mg/kg in SHR rats, but l-MPH did not decrease total activity at this dose;
5) d-MPH decreased "impulsiveness" at 6 mg/kg in SHR rats, but l-MPH did not decrease "impulsiveness" at this dose;
6) there was no clear effect of d- or l-MPH on total activity or "impulsiveness" in wild-type (WKY) rats at 6 mg/kg;
7) SHR rats exhibited much higher baselines for total activity and "impulsiveness" than wild-type (WKY) rats (i.e., without MPH); d- and l-MPH increased the variability for both behavioral measures in both strains of rats.

The Sponsor proposed (b) (4)

(b) (4)

The data in the neurochemistry studies demonstrated that d,l-MPH increased both DA (in striatum) and NE (in PFC) at doses of 10 and 20 mg/kg in SHR. The isomers were only tested up to 10 mg/kg, at which dose d-MPH increased both DA and NE; however, l-MPH only increased DA, not NE. Based on this limited data it is not possible to assess the relative potencies of the isomers to increase DA and NE in SHR rats.

Regarding the behavioral assessments of the isomers, there was evidence that d-MPH decreased "hyperactivity" and "impulsiveness" in SHR rats at doses up to 6 mg/kg; at that dose, l-MPH did not appear to decrease these parameters. Although higher doses of both d- and l-MPH might have provided more compelling results (b) (4)

(b) (4)

12 Appendix/Attachments

Davids E, Zhang K, Tarazi FI, Baldessarini RJ. Animal models of attention-deficit hyperactivity disorder. Brain Res Rev 2003; 42:1-21.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IKRAM M ELAYAN
06/29/2010

LINDA H FOSSOM
06/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-514 (S-10)
Drug Name:	DAYTRANA® (Methylphenidate Transdermal System)
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Applicant:	Shire
Dates:	Date of Document: 9/4/2009
	PDUFA Due Date: 7/4/2010
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D. (HFD-710)
Concurring	Peiling Yang, Ph.D. (HFD-710)
Reviewers:	James Hung, Ph.D. (HFD-710)
Medical Division:	Division of Psychiatry Products, HFD-120
Clinical Team:	Christina Burkhart, M.D. (HFD-130)
	Robert Levin, M.D. (HFD-130)
	Mitchell Mathis, M.D. (HFD-130)
	Thomas Laughren, M.D. (HFD-130)
Project Manager:	Juliette Toure (HFD-130)

Table of Contents

1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

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

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

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

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

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

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

1.3 STATISTICAL ISSUES AND FINDINGS

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

2. INTRODUCTION

2.1 OVERVIEW

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

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

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

2.2 DATA SOURCES

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

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study SPD485-409

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

3.1.1.1 Study Objectives

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

The secondary objectives of this study were:

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

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

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

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

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

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

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

3.1.1.2 Study Design

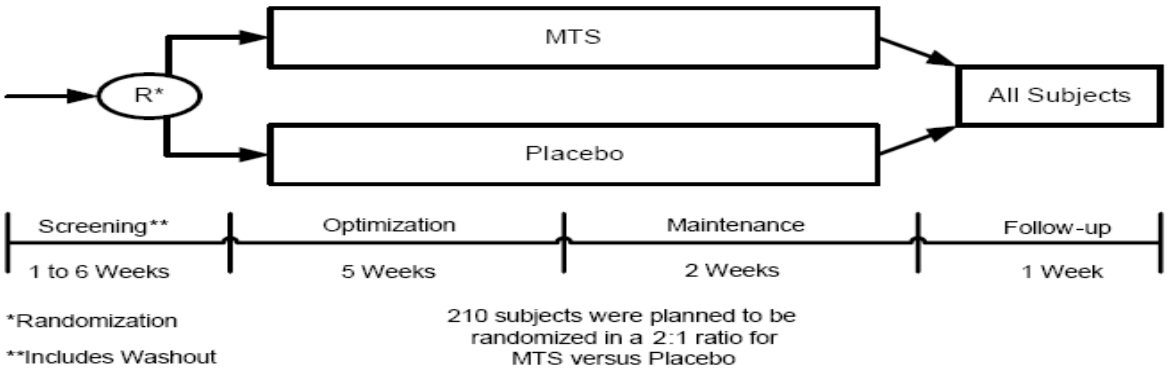
This was a Phase IIIb, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the efficacy and safety of MTS (10, 15, 20, and 30 mg/9 hour doses) compared with placebo in adolescent subjects (aged 13-17 years) with ADHD. Note that the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

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

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

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

Figure 1. Study Schematic



Source: Sponsor's Figure 1 of CSR

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

3.1.1.3 Efficacy Endpoints and Analyses

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

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

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

3.1.2 Sponsor's Efficacy Analysis Results

3.1.2.1 Disposition of Subjects and Baseline Characteristics

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

Table 3.1 Subject Disposition for Study SPD 485-409

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

Source: Sponsor's Table 7 of CSR

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

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

Source: Sponsor's Table 8 of CSR

3.1.2.2 Results for Primary and Secondary Endpoints

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

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

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

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

Table 3.4 Sponsor's Analysis Results for Secondary Endpoints

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

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

3.1.3 Statistical Reviewer's Findings and Comments

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

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

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

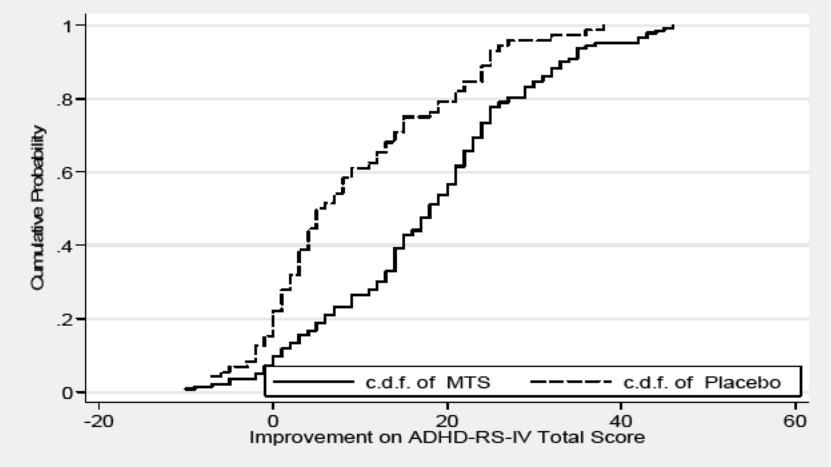
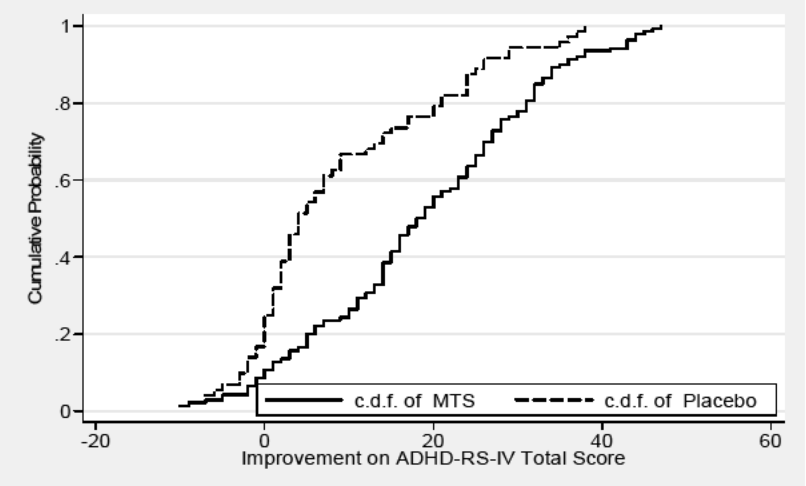


Figure 2 Empirical Distribution Function of Change in ADHD-RS-IV Total score (By Week 7 LOCF data)



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

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

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

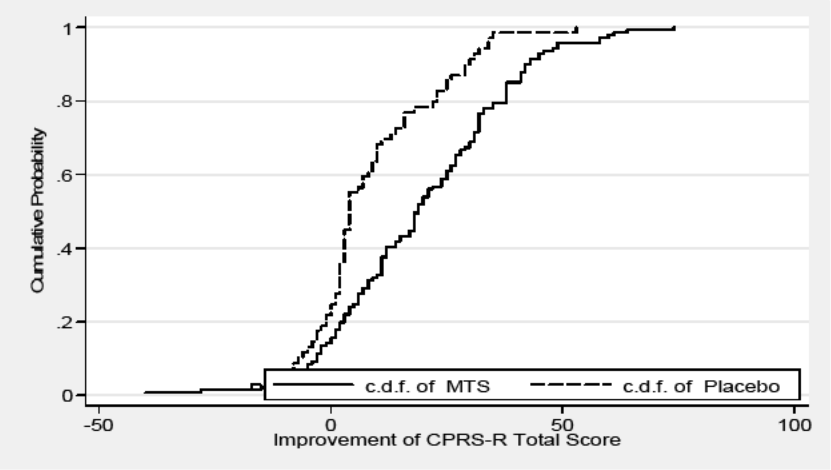
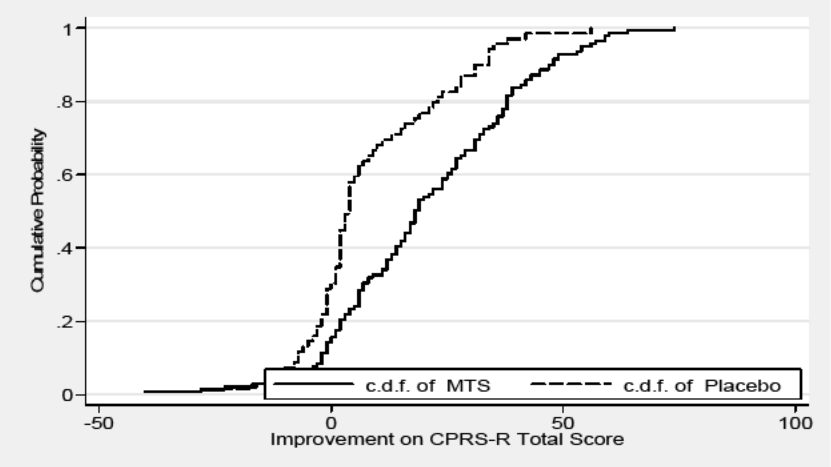


Figure 4 Empirical Distribution Function of Change in CPRS-R Total score (By Week 7 LOCF data)



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

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

3.2 EVALUATION OF SAFETY

Please refer to the medical review for the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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

4.1 GENDER, RACE and AGE

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

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

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

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

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

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

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

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

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

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

5.2 CONCLUSIONS AND RECOMMENDATIONS

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

_____

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-514
HFD-130/Dr. Laughren
HFD-130/Dr. Mathis
HFD-130/Dr. Levin
HFD-130/Dr. Burkhart
HFD-130/Ms. Toure
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang
HFD-710/Dr. Chen

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YEH FONG CHEN
05/28/2010

PEILING YANG
05/28/2010

HSIEN MING J J HUNG
05/28/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Methylphenidate Transdermal System
PRODUCT (Brand Name):	Daytrana
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTHS: PATCH SIZE:	10mg/9 hrs-12.5cm^2 patch 15mg/9 hrs- 18.75 cm^2 patch 20mg/9 hrs- 25 cm^2 patch 30mg/9 hrs -37.5 cm^2 patch
NDA:	21514
NDA TYPE:	Supplement 0010
SUBMISSION DATE:	September 9, 2009
SPONSOR:	Shire Pharmaceuticals
REVIEWER	Andre Jackson

REVIEW OF s-NDA FOR METHYLPHENIDATE TRANSDERMAL SYSTEM

EXECUTIVE SUMMARY

The transdermal system (MTS) for methylphenidate has been approved for a 9 hr application in children 6-12 yrs old. Study SPD485-106 which was conducted in ages 6-12 yrs and 13-17 yrs by the firm to investigate the pharmacokinetics and determine the degree of accumulation following fixed single/multiple dosing using the 12.5 cm^2 and 37.5 cm^2 size patches.

Cmax and AUCinf of d-methylphenidate were decreased by 55% and 51% respectively in adolescents compared to children following the application of the 10mg/9h transdermal patch for methylphenidate.

Following multiple fixed doses of 10mg/9 h for 7 days the accumulation index based upon AUCss was 1.1 while at day 28 the value was 1.6.

RECOMMENDATION:

This sNDA for Methyphenidate transdermal system for adolescents has been found to be acceptable to OCP based on the Clinical Pharmacology study submitted.

TABLE OF CONTENTS

INTRODUCTION

Methylphenidate transdermal system (MTS) is an adhesive-based matrix transdermal patch that provides continuous systemic delivery of MPH during application to intact skin. Methylphenidate transdermal system was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of ADHD in children aged 6-12 years on 06 April 2006. The effectiveness of MTS in treating ADHD in children was demonstrated in two randomized, double-blinded, placebo-controlled studies (SPD485-201 and SPD485-302) in children aged 6-12 years. The patch wear time was 9 hours in both studies.

The current NDA is for ADHD following a 9 hr wear time in adolescents.

QUESTION BASED REVIEW

1. Are there differences in exposure for children and adolescents following a single dose and multiple dose administration for 7 days of 10mg/9hr MTS?

Table 1: Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Single Doses of MTS (10mg/9h; Treatments A and B) or CONCERTA® (18mg; Treatment C)

	MTS (10mg/9h)				**CONCERTA® (18mg)**			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	24	2.00 (0.95, 2.08)	24	2.00 (1.00, 9.00)	11	0.00 (0.00, 1.00)	11	0.00 (0.00, 0.00)
t_{max}* (h)	24	10.0 (8.00, 12.0)	24	10.0 (6.00, 12.0)	11	6.02 (4.00, 10.0)	11	8.00 (1.00, 10.0)
C_{max} (ng/mL)	24	9.30 (3.60)	24	4.15 (2.59)	11	7.80 (3.35)	11	4.95 (1.42)
AUC_{0-t} (ng•h/mL)	24	101 (48.0)	24	36.9 (24.9)	11	85.1 (44.4)	11	57.3 (17.7)
$AUC_{0-\infty}$ (ng•h/mL)	21	99.2 (42.9)	18	48.7 (21.9)	10	94.2 (43.8)	10	60.1 (16.3)
K_{el} (h^{-1})	21	0.144 (0.0302)	18	0.169 (0.0303)	10	0.176 (0.0577)	10	0.169 (0.0392)
$t_{1/2}$ (h)	21	5.01 (1.02)	16	4.35 (0.788)	10	4.26 (1.20)	7	4.74 (1.05)

Table 2. Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Fixed Doses of MTS (10mg/9h Daily for 7 Days; Treatments A and B) or CONCERTA® (18mg Daily for 7 Days; Treatment C)

	MTS (10mg/9h)				CONCERTA® (18mg)			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	23	0.00 (0.00, 2.00)	22	0.00 (0.00, 4.05)	10	0.00 (0.00, 0.00)	9	0.00 (0.00, 0.00)
t_{max}* (h)	23	9.00 (2.00, 12.0)	22	10.0 (8.03, 12.0)	10	8.00 (4.00, 10.0)	9	8.00 (4.00, 12.1)
C_{ssmax} (ng/mL)	23	12.4 (7.84)	22	5.45 (2.99)	10	8.37 (4.14)	9	5.23 (1.72)
C_{ssmin} (ng/mL)	23	0.773 (0.700)	22	0.288 (0.238)	10	0.708 (1.08)	9	0.360 (0.478)
Degree of fluctuation	22	2.53 (0.730)	20	2.27 (0.427)	10	2.07 (0.391)	9	1.97 (0.204)
AUC_{ss} (ng•h/mL)	22	112 (64.8)	20	55.7 (28.2)	10	97.7 (67.0)	9	59.7 (19.1)
R_{obsAUC}	22	1.21 (0.462)	18	1.57 (0.957)	9	1.16 (0.176)	9	1.13 (0.323)
$R_{obsCmax}$	23	1.34 (0.694)	22	1.57 (1.09)	10	1.13 (0.223)	9	1.19 (0.369)
R_{ss}	19	1.16 (0.423)	16	1.28 (0.340)	9	1.11 (0.145)	9	1.07 (0.303)

Cmax and AUC0-∞ of d-methylphenidate were decreased by 55% and 51% respectively in adolescents compared to children after a single application of the 10mg/9h transdermal patch. Cssmax and AUCss were decreased by 56% and 50% respectively in adolescents compared to children following the daily single application of the 10mg/9h transdermal patch for methylphenidate for 7 days. Therefore the decrease is comparable following single and multiple dosing.

Efficacy data presented by the firm was located at:

\\Cdsesub1\evsprod\NDA021514\0026\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\spd485-409\spd485-409-report-body.pdf

The efficacy data presented by the firm for weeks 1-7 for the 13-14 and 15-17 yr olds did not exhibit any dose response. Therefore the decreased exposure in adolescents compared to children does not warrant any adjustment in dose based upon dose response. Due to the study design a true exposure response could not be assessed. In addition, the label recommends that the dosage be titrated to effect.

2. What is the comparative accumulation for transdermal Daytrana following multiple dosing at a constant level of dose administration-between (Day1-Day 7 compared to (Day 1-Day 28)?

Study SPD485-106 conducted by the firm was done in male and female children (6-12 years of age) and adolescents (13-17 years of age) with ADHD. There were three treatments A and B were MTS-10mg/9hr (methylphenidate transdermal system) while treatment C was a single daily dose of Concerta 18 mg.

Figure 1. Arithmetic Mean Plasma Concentration-Time Profiles from Day 1 to Day 31 for *d*-MPH Following Single and Multiple Doses of MTS to Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population .

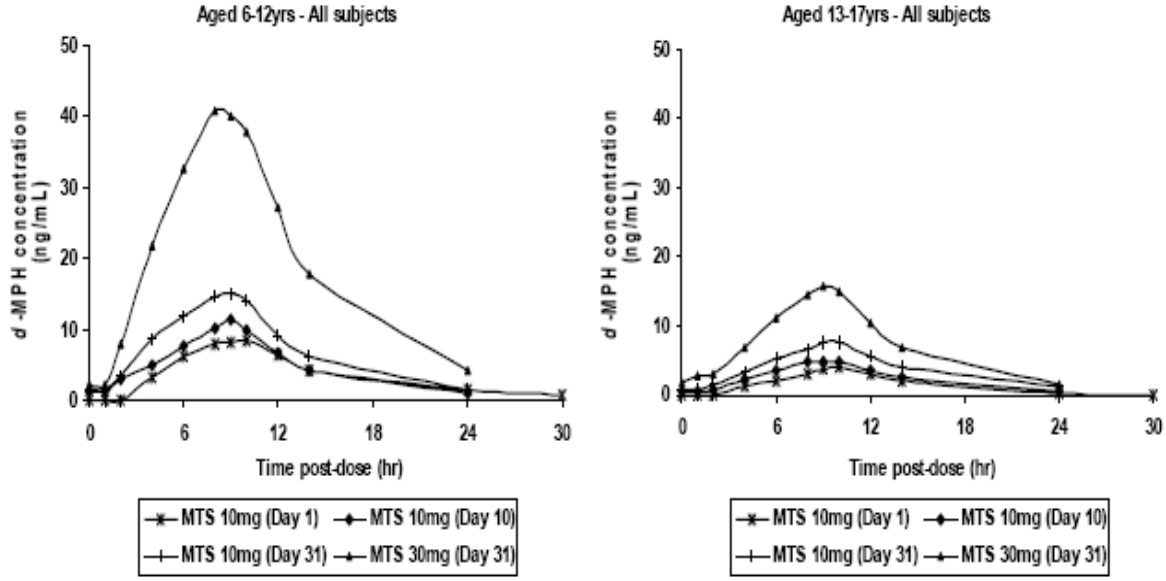


Table 3. **Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic**

Population Following Multiple Fixed Doses of MTS (10mg/9h Daily for 28 Days or 7 Days; Treatment A).

Treatment for 28 days

	MTS Fixed Dose (10mg/9h)			
	Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	11	0.00 (0.00, 2.00)	12	0.00 (0.00, 2.00)
t_{max}* (h)	11	9.00 (8.00, 10.0)	12	10.0 (6.00, 24.0)
C_{ssmax} (ng/mL)	11	15.7 (9.39)	12	8.32 (4.60)
C_{ssmin} (ng/mL)	11	1.04 (1.17)	12	0.544 (0.383)
Degree of fluctuation	11	2.20 (0.391)	12	2.31 (0.572)
AUC_{ss} (ng•h/mL)	11	163 (101)	12	85.7 (50.0)
R_{obsAUC}	11	1.70 (0.896)	10	1.94 (1.00)
$R_{obsCmax}$	11	1.76 (1.05)	12	1.79 (0.955)
R_{ss}	11	1.53 (0.805)	10	1.83 (0.915)

* Median value (minimum, maximum)

SD=Standard Deviation; MTS=Methylphenidate Transdermal System

Treatment for 7 days

	MTS (10mg/9h)				CONCERTA® (18mg)			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	23	0.00 (0.00, 2.00)	22	0.00 (0.00, 4.05)	10	0.00 (0.00, 0.00)	9	0.00 (0.00, 0.00)
t_{max}* (h)	23	9.00 (2.00, 12.0)	22	10.0 (8.03, 12.0)	10	8.00 (4.00, 10.0)	9	8.00 (4.00, 12.1)
C_{ssmax} (ng/mL)	23	12.4 (7.84)	22	5.45 (2.99)	10	8.37 (4.14)	9	5.23 (1.72)
C_{ssmin} (ng/mL)	23	0.773 (0.700)	22	0.288 (0.238)	10	0.708 (1.08)	9	0.360 (0.478)
Degree of fluctuation	22	2.53 (0.730)	20	2.27 (0.427)	10	2.07 (0.391)	9	1.97 (0.204)
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R_{obsAUC}	22	1.21 (0.462)	18	1.57 (0.957)	9	1.16 (0.176)	9	1.13 (0.323)
$R_{obsCmax}$	23	1.34 (0.694)	22	1.57 (1.09)	10	1.13 (0.223)	9	1.19 (0.369)
R_{ss}	19	1.16 (0.423)	16	1.28 (0.340)	9	1.11 (0.145)	9	1.07 (0.303)

Median values (minimum, maximum)

FDA Calculations based upon observed AUCss/AUCinf

Treatment Comparison	Accumulation Children	Accumulation Adolescents
Day 7/Day1	112/99.2=1.12	55.7/48.7=1.14
Day 28/Day1	163/99.2=1.64	85.7/48.7=1.75

INSPECTION REPORT

DSI was requested to give the following points special attention:

1.The firm has reported-

There were more than expected batch failures for either one or both analytes over the course of this study. Most of the batches failed due to known issues as outlined below. No data was reported from these failed batches. All samples were re-assayed and data was reported from acceptable batches. Reasons given by the firm were:

Suspected Contamination. Ten batches failed due to methylphenidate peaks in the blanks, especially in blanks injected after other blanks which showed no carryover. Batches 027, 029, 034, 046, 047, 048, 050, 063, 064, and 066 were rejected for this reason. Initially, these appeared to be random and not associated with a particular chemist or equipment. However, later batches were extracted by a particular chemist. After this discovery, the chemist was observed by operations management during the

extractions. As a result, some techniques were modified that may have contributed to potential contamination in the batches.

OCP Request
Please verify that the reason for the contamination was satisfactorily identified and that a more appropriate methodology has been instituted.

2. The firm has reported-
QC Pool Bias. Batches 002 and 005 failed for d-*threo*-methylphenidate, while batch 003 failed for both analytes. Investigations showed that the QCs used in batches 001-007 were biased. Therefore a new set of QCs were prepared for use. Batch 036 failed for d-*threo*-methylphenidate and batches 037-041 failed for both d-*threo*-methylphenidate and l-*threo*-methylphenidate due to an issue with QCs being biased low versus the freshly prepared standards. This was the second set of QCs that were prepared low. The chemist involved in the preparation of the biased QCs is being retrained.

OCP Request

Please confirm exactly how this occurred and were there violations of their SOP's. Was the chemist properly trained to follow SOP's and what actions have been taken to prevent such an occurrence in the future?

3. The firm has reported-
Batch Acceptance Failures: Batches 008, 061, 062, 067, 070, and 081 failed for d-*threo*-methyphenidate due to insufficient acceptable QCs. Batch 065 failed for both analytes due to insufficient acceptable fresh standards. In addition, we had two instances (batches 010 and 043) where the data for the batches were lost. The data collected for the instruments is collected on the network. There is a buffer on the systems as a backup. In cases where a batch is started on one instrument but is moved to another due to sensitivity issues or instrument issues the Covance procedure requires that the data file be renamed otherwise there is the potential for the older file, if kept in the buffer for some reason, to upload to the network at a later time and overwrite a file already on the network. Batch 043 was known to have been lost as the procedure requiring renaming of the data files was not followed by the operator when the batch was moved to another instrument. Batch 010 appears to have been lost for the same reason. To prevent this issue in the future, the file name procedure has been changed to include the name of the instrument to prevent this error.
As indicated above, most of the failed batches could be attributed to known issues. Because the sample through-put was emphasized, the problems were not found or corrected until more than expected batches failed. Some of the batch failures, due to the issues listed above, could have been avoided. However, Covance believes that the bioanalytical method and the laboratory operations in general were reliable. For example, many samples in the study were re-assayed and the majority of the re-assayed results were consistent with the original results.
Therefore, although there were more than expected batch failures, Covance is confident that the final bioanalytical results reported are accurate. In this study, some of the study samples were re-assayed in error or with incorrect dilution factors. Covance realizes this problem and is seeking measures to improve the re-assay procedure to prevent this from happening in the future. The data from these re-assays were reported according to Shire SOP BC-104 ver. 2. The re-assays mentioned do not have any negative impact on the quality of the data. As indicated above, the majority of the re-assayed

results were consistent with the original results. Covance acknowledges that a number of the issues resulting in a higher than expected batch failure rate were associated with chemist training and less than optimal methodology. Training and laboratory process improvements have been implemented and in the future management supervision will be improved to minimize these problems.

OCP Request

There are numerous issues with batch failure. These batch failures and the reasons need to be validated and determined if SOP were followed or were ad hoc changes made to accommodate the many assay problems. Further, it is important to determine if these failures indeed had no impact on the final data reported. What actions have been taken to prevent such an occurrence in the future?

OCP COMMENTS ON PRELIMINARY RESPONSE FROM DSI

a. Based upon preliminary comments from DSI the problems which the firm had with the assay were all corrected. The problems occurred during early stages of the assay and the values in the final study report were all based upon repeats of problematic assays with updated procedures. No data were deleted. Based upon preliminary discussions with DSI the analytical will be acceptable.

FIRM'S LABEL

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

SIGNATURES

Andre Jackson_____
Reviewer, Psychiatry Drug Products, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Products, DCP I
Office of Clinical Pharmacology

cc: NDA 21514, HFD-860(Mehta, Baweja, Jackson)
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APPENDIX

DETAILED STUDY REPORTS

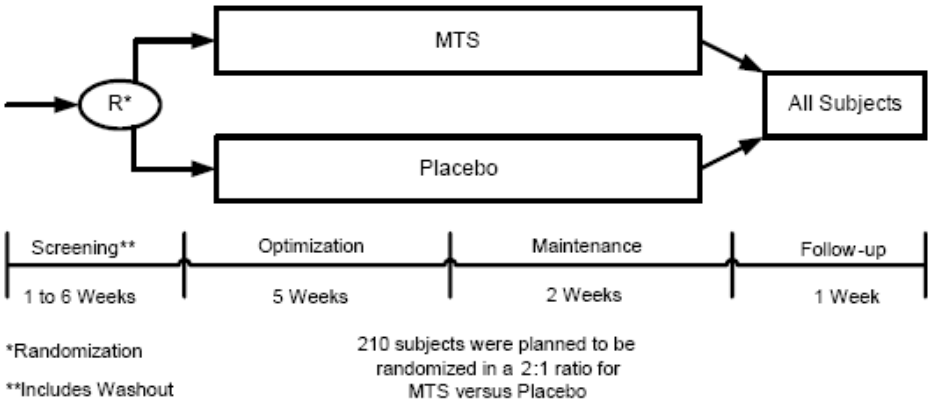
ANALYTICAL SECTION

Parameter	***l-threo*-methylphenidate**	***d-threo*-methylphenidate**
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	6 Cycles QC's 0.75 ng/ml 7.5 ng/ml 35.0 ng/ml	6 Cycles QC's 0.75 ng/ml 7.5 ng/ml 35.0 ng/ml
Benchtop Stability at RT	50hrs	50hrs
Long term at –20° C	783 days	783 days
Extraction Recovery Low Med High	 49% @ 0.75 ng/ml 32% @ 7.5 ng/ml 43% @ 35 ng/ml	 48% @ 0.75 ng/ml 32% @ 7.5 ng/ml 48% @ 35 ng/ml

EXPOSURE RESPONSE

The firm's design of their efficacy study is presented in Figure 1

Figure 1: Study Schematic



During the optimization period, one downward titration to the previous dosage strength/patch size was permitted (Visits 4, 5, and 6) to optimize tolerability and effectiveness. During one of the last three visits, Visit 7, 8, or 9 (Week 5, 6, or 7), a blood sample was collected at approximately 4:00 pm.

Drug Concentration and Relationship to Response

The firm did an exploratory exposure response analysis for selected efficacy parameters (ADHD-RS-IV Total Score, CPRS-R Total Score, YQOL-R, CGI-I, and PGA) and *d*-MPH plasma concentrations after 9-hour wear time and found no correlation. Of the secondary efficacy parameters explored, only YQOL-R total perceptual score showed a significant correlation to plasma concentrations of *d*-MPH (r=0.357; 95% CI 0.133, 0.581; p=0.002). However the data is confounded by the fact that the study was done with escalating doses so it is difficult to make any meaningful interpretation of the results which only showed a relationship to exposure for a secondary endpoint.

ACCUMULATION RATIO CALCULATION

The sponsor calculated accumulation as theoretical AUCss/AUCinf which should have been AUCss/AUC0-24. However the sponsor collected to time t not 24 hrs.
Final estimation of accumulation was based upon the difference between the theoretical value =1 and the observed value of AUCss/AUCinf.

The FDA used the equation $R=1/(1-exp^{-ktau})$ for theoretical and the observed value of AUCss/AUCinf same as the firm. Therefore the firms estimated accumulation ratios differed with the calculated FDA value being consistently lower. FDA calculations will be used for all reported accumulation values.

Table 1a. FDA calculations for Accumulation

	Child	Adol
t1/2	5.01	4.35
ke	0.138	0.159

Accum theory	1.03	1.02
Aucinf (ng/ml*h)	99.2	48.7
aucss7(ng/ml*h)	112	55.7
aucss7/aucinf	1.12	1.14
aucss28(ng/ml*h)	163	85.7
auc28/aucinf	1.64	1.76
Cmax day1 ng/ml	9.3	4.15
Cmax day 28 ng/ml	15.7	8.32
Cmax(d28)/Cmax(d1)	1.68	2.00

STUDY NO: SPD485-106

Study Title: An Open-label, Randomized Study of the Pharmacokinetics of *d*-Methylphenidate and *l*-Methylphenidate After Single and Multiple Doses of Methylphenidate Transdermal System (MTS) or CONCERTA® Administered to Children and Adolescents Ages 6 to 17 Years with Attention-Deficit Hyperactivity Disorder (ADHD)

STUDY OBJECTIVES
Primary

The primary objective of this study was to describe the pharmacokinetics of *d*-MPH and *l*-MPH in children and adolescents ages 6-17 years with ADHD after single and multiple escalating doses of MTS when worn for 9 hours and to determine the extent of accumulation of *d*-MPH and *l*-MPH after multiple escalating doses of MTS when worn for 9 hours.

The secondary objectives of this study were:
• To describe the pharmacokinetics of *d*-MPH and *l*-MPH in children and adolescents ages 6-17 years with ADHD after single and multiple escalating doses of CONCERTA®
• To determine the extent of accumulation of *d*-MPH and *l*-MPH after multiple escalating doses of CONCERTA®.

Study Design:

Methylphenidate Transdermal System was provided as 10, 15, 20, and 30mg/9h patches designed to deliver *d,l (threo)*-MPH transdermally at a continuous rate upon application to intact skin. The target wear time for MTS was 9 hours.

This was an open-label, randomized, multi-center study evaluating the pharmacokinetics of *d*-MPH and *l*-MPH after single and multiple doses of MTS or CONCERTA® in male

and female children (6-12 years of age) and adolescents (13-17 years of age) with ADHD. The study consisted of a single dose/fixed multiple dose period (Part I) followed by a dose escalation phase (Part II).

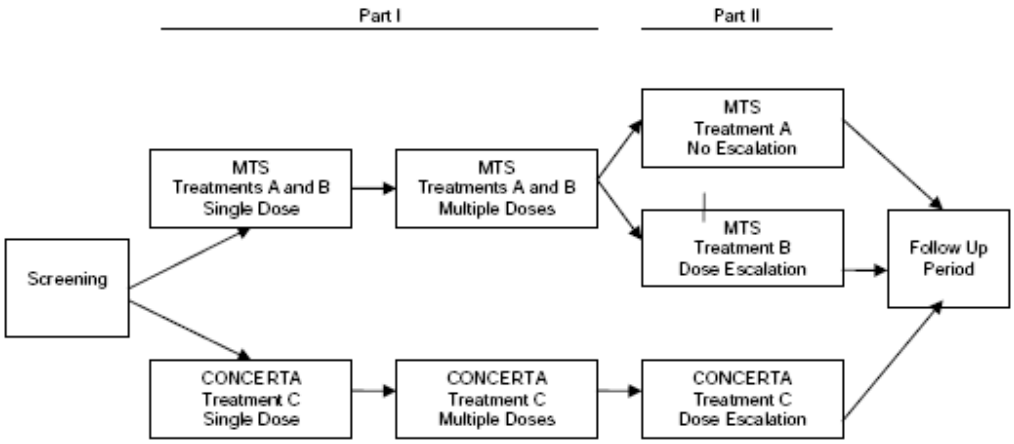


Figure 1: Subject Disposition: Children 6-12 Years of Age

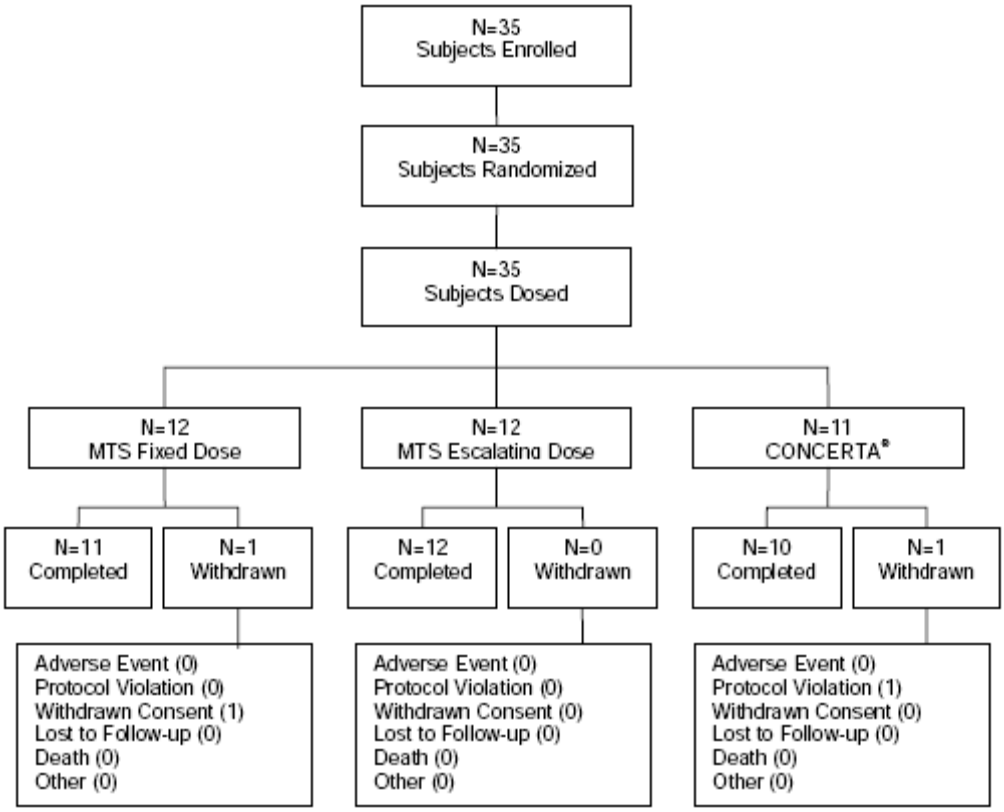
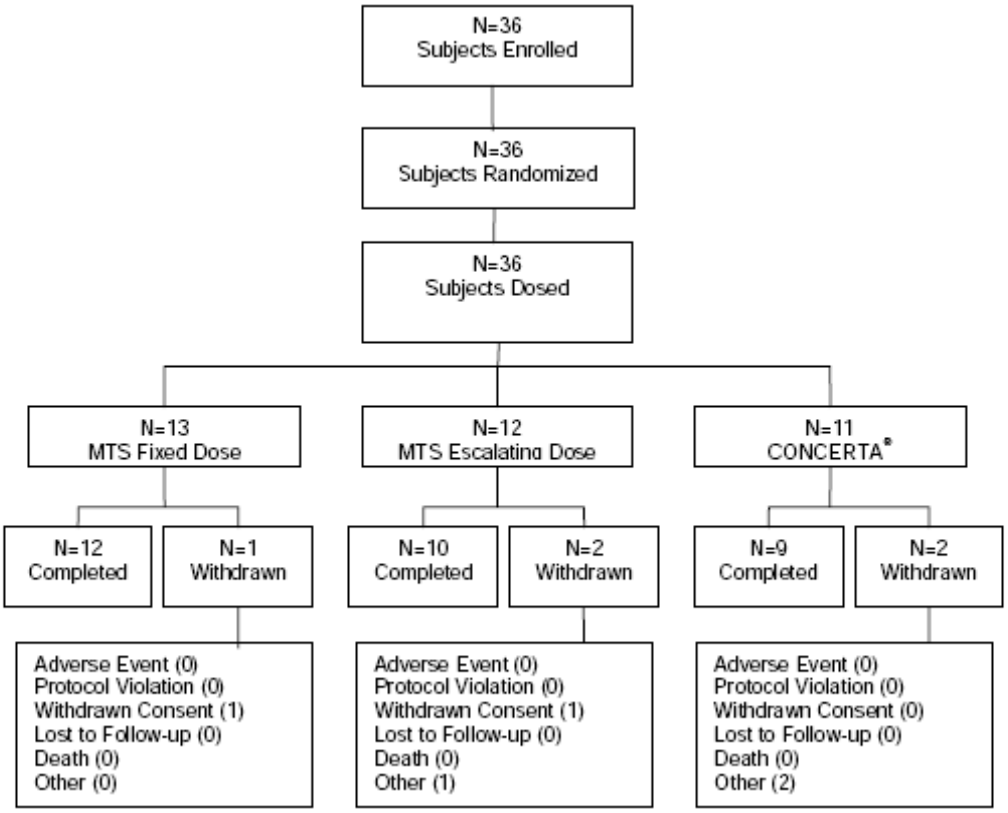


Figure 2: Subject Disposition: Adolescents 13-17 Years of Age



Demographics:

Table 2: Subject Demographics and Baseline Characteristics (Safety Population)

Characteristic	Category/Parameter	MTS Fixed Dose	MTS Escalating Dose	CONCERTA®	Total
Children 6-12 years of age					
		N=12	N=12	N=11	N=35
Age (years)	Mean	9.0	9.3	10.3	9.5
	SD	1.65	2.56	1.35	1.96
	Median	9.5	8.5	11.0	10.0
	Minimum-Maximum	6-11	6-12	8-12	6-12
Gender n (%)	Male	7 (58.3)	6 (50.0)	6 (54.5)	19 (54.3)
	Female	5 (41.7)	6 (50.0)	5 (45.5)	16 (45.7)
Ethnicity n (%)	Hispanic/Latino	3 (25.0)	2 (16.7)	3 (27.3)	8 (22.9)
	Not Hispanic/Latino	9 (75.0)	10 (83.3)	8 (72.7)	27 (77.1)
Race n (%)	White	4 (33.3)	2 (16.7)	3 (27.3)	9 (25.7)
	Black/African American	8 (66.7)	10 (83.3)	8 (72.7)	26 (74.3)
	Native Hawaiian/ Other Pacific Islander	0	0	0	0
	Asian	0	0	0	0
	American Indian/ Alaska Native	0	0	0	0
	Other	0	0	0	0
Weight (kg)	Mean	33.02	34.34	39.59	35.54
	SD	8.512	10.663	7.752	9.272
	Median	31.00	30.95	38.10	35.50
	Minimum-Maximum	22.3-50.8	22.2-50.0	24.9-55.0	22.2-55.0
Height (cm)	Mean	136.7	139.5	144.5	140.1
	SD	9.32	15.91	9.95	12.24
	Median	140.5	138.0	142.0	141.0
	Minimum-Maximum	119-147	116-160	132-159	116-160
BMI (kg/m^2)	Mean	17.51	17.11	18.72	17.76
	SD	2.943	2.312	2.726	2.681
	Median	16.34	16.90	18.82	17.30
	Minimum-Maximum	14.8-24.2	13.8-20.7	13.5-23.2	13.5-24.2

Adolescents 13-17 years of age					
		N=13	N=12	N=11	N=36
Age (years)	Mean	13.8	14.7	13.9	14.1
	SD	1.17	1.44	1.04	1.26
	Median	13.0	14.5	14.0	14.0
	Minimum-Maximum	13-17	13-17	13-16	13-17
Gender n (%)	Male	7 (53.8)	6 (50.0)	6 (54.5)	19 (52.8)
	Female	6 (46.2)	6 (50.0)	5 (45.5)	17 (47.2)
Ethnicity n (%)	Hispanic/Latino	5 (38.5)	3 (25.0)	3 (27.3)	11 (30.6)
	Not Hispanic/Latino	7 (53.8)	8 (66.7)	8 (72.7)	23 (63.9)
Race n (%)	White	7 (53.8)	6 (50.0)	4 (36.4)	17 (47.2)
	Black/African American	6 (46.2)	6 (50.0)	7 (63.6)	19 (52.8)
	Native Hawaiian/ Other Pacific Islander	0	0	0	0
	Asian	0	0	0	0
	American Indian/ Alaska Native	0	0	0	0
	Other	0	0	0	0
Weight (kg)	Mean	56.47	58.73	54.39	56.59
	SD	10.870	10.867	10.744	10.663
	Median	51.70	55.95	55.00	55.60
	Minimum-Maximum	43.2-75.5	45.9-83.1	40.6-80.0	40.6-83.1
Height (cm)	Mean	164.9	168.4	165.7	166.3
	SD	11.27	10.50	5.53	9.45
	Median	167.0	165.0	165.0	165.0
	Minimum-Maximum	146-188	155-193	158-175	146-193
BMI (kg/m^2)	Mean	20.50	20.62	19.69	20.29
	SD	2.699	2.189	2.706	2.502
	Median	20.36	20.90	19.84	20.45
	Minimum-Maximum	16.6-26.4	16.9-24.2	16.3-26.2	16.3-26.4

PHARMACOKINETIC METHODS:

On Day 1, all subjects randomized to Treatments A and B received a single dose of MTS (10mg/9h). Subjects randomized to Treatment C received a single oral dose of CONCERTA® (18mg). Serial blood samples (3mL/sample) for pharmacokinetic evaluation were drawn pre-dose and at 1, 2, 4, 6, 8, 9, 10, 12, 14, 24, and 30 hours post-dose on Day 1. Subjects were discharged from the CRC after completing all assessments on Day 2.

The parent/caregiver was allowed to begin the multiple dose portion of the study (Day 4) 3-9 days following dose administration on Day 1 in order to allow flexibility on the overnight visits. Although the start date of Day 4 could be flexible, the dates for remaining visits were not flexible. On Day 4, subjects received either MTS (10mg/9h; Treatments A and B) or CONCERTA® (18mg; Treatment C) daily for 7 days. Subjects returned to the CRC on the evening of Day 9 and remained housed until completion of all study procedures on Day 11. Serial blood samples (3mL/sample) for pharmacokinetic

evaluation were drawn pre-dose and at 1, 2, 4, 6, 8, 9, 10, 12, 14, and 24 hours following the dose administration on Day 10.

On the morning of Day 11, subjects continued with their treatment regimens as follows:
MTS:
• Treatment A: Subjects continued to receive MTS (10mg/9h) daily for an additional 3 weeks.
• Treatment B: Subjects received escalating doses of 15, 20, and 30mg/9h of MTS at weekly intervals and were maintained on daily doses at each dose level for 7 days.
CONCERTA®:
• Treatment C: Subjects received escalating doses of 27, 36, and 54mg at weekly intervals and were maintained on daily doses at each dose level for 7 days.

Pre-dose samples were taken on the last day of dosing of the first and second weeks (Day 17 and Day 24) of continuous dosing for each treatment regimen. Subjects returned to the CRC on the evening of Day 30. On the morning of Day 31, serial blood samples (3mL/sample) for pharmacokinetic evaluation were drawn pre-dose and at 1, 2, 4, 6, 8, 9, 10, 12, 14, and 24 hours post-dose. Subjects were discharged from the CRC after completing all assessments on Day 32.

Period of estimation and goodness of fit
The apparent terminal phase rate constant (Kel) and apparent terminal half-life (t1/2) values were only calculated when a reliable estimate could be obtained, with the minimum requirement of the inclusion of at least three consecutive plasma concentrations above the LLOQ, with at least one of these concentrations following Cmax. Elimination half-lives were calculated, where possible, over at least two half-lives. Special consideration was given to where Kel and t1/2 were estimated over less than two half-lives, and if they were only calculated over a period less than 1.5 half-lives, the estimate was excluded from the summary statistics. When assessing terminal elimination phases, the coefficient of determination (R2) adjusted value was used, as opposed to the R2 value, as a measure of the goodness of fit of the data to the determined regression, assessed on a case-by-case basis. Where values of the extrapolated portion of the area under the curve (%extrap) were >20%, these values are noted in the report text and where the %extrap was 40%, the $AUC_{0-\infty}$ was not reported.

Calculation of AUC_{0-t}
As a minimum, the calculation of area under the plasma-concentration curve (AUC) included at least three consecutive plasma concentrations above the LLOQ, with at least one of these concentrations following C_{max}. AUC values were calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

R_{obsAUC}	Observed accumulation ratio, determined as AUC_{ss}/AUC_{0-24}, single dose, where AUC_{0-24} is the area under the plasma concentration vs. time curve from 0-24 hours
$R_{obsCmax}$	Observed accumulation ratio, determined as C_{ssmax}/C_{max}, single dose

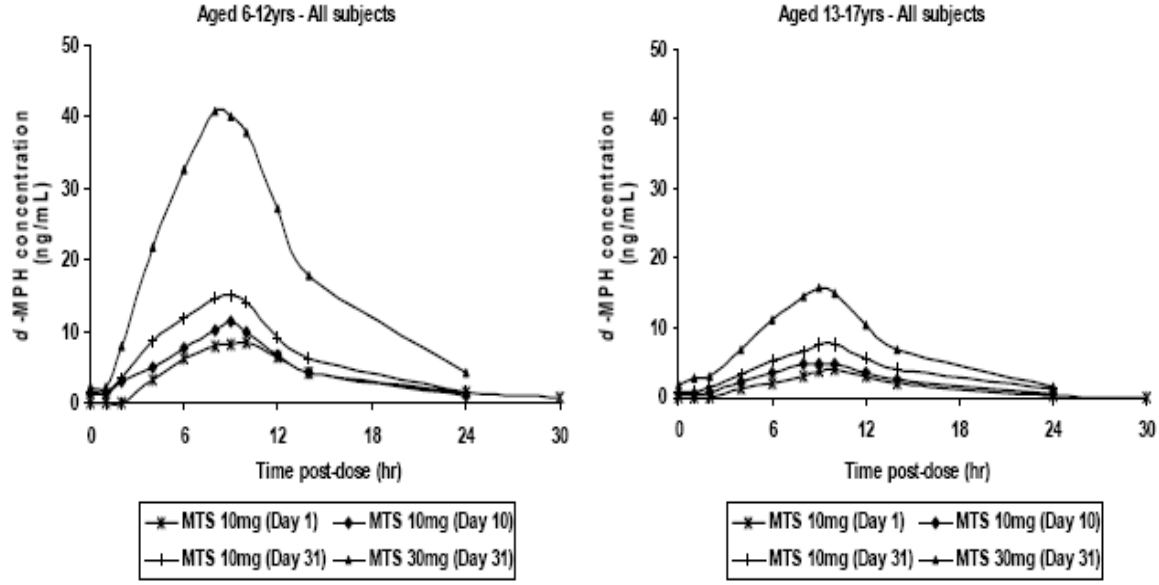
ANALYTICAL METHOD:
There was minimal <0.25% of interconversion of the isomers.

Study Initiation Date**:** 14 November 2007
Date of first sample received: 14-Dec-2007
Date of last batch of assay: 27-Jul-2008
Longest Possible Storage- 9 months~270 days

Parameter	***l-threo*-methylphenidate**	***d-threo*-methylphenidate**
Method	LC-MS/MS	
Sensitivity/LOQ	0.25 ng/mL	0.25 ng/mL
Linearity (Standard curve samples)	0.5ng/ml-50 ng/ml	0.5ng/ml-50 ng/ml
Quality Control (QC) Samples	0.75 ng/mL 7.5 ng/ml 35 ng/ml	0.75 ng/mL 7.5 ng/ml 35 ng/ml
Precision of Standards (%CV)	%@0.25 ng/ml %@ 50 ng/ml	1.2 %@0.25 ng/ml 0.6 %@ 50 ng/ml
Precision of QC Samples (%CV)	7% @ 0.75 ng/ml 5%@7.5 ng/ml 4%@ 35 ng/ml	7% @ 0.75 ng/ml 5%@7.5 ng/ml 4%@ 35 ng/ml
Accuracy of Standards (%)	94 %@0.25 ng/ml 100 %@ 50 ng/ml	89.2 %@0.25 ng/ml 99.7 %@ 50 ng/ml
Accuracy of QC Samples (%)	101%@0.75 ng/ml 98%@7.5 ng/ml 99 %@ 35 ng/ml	101%@0.75 ng/ml 98%@7.5 ng/ml 99 %@ 35 ng/ml

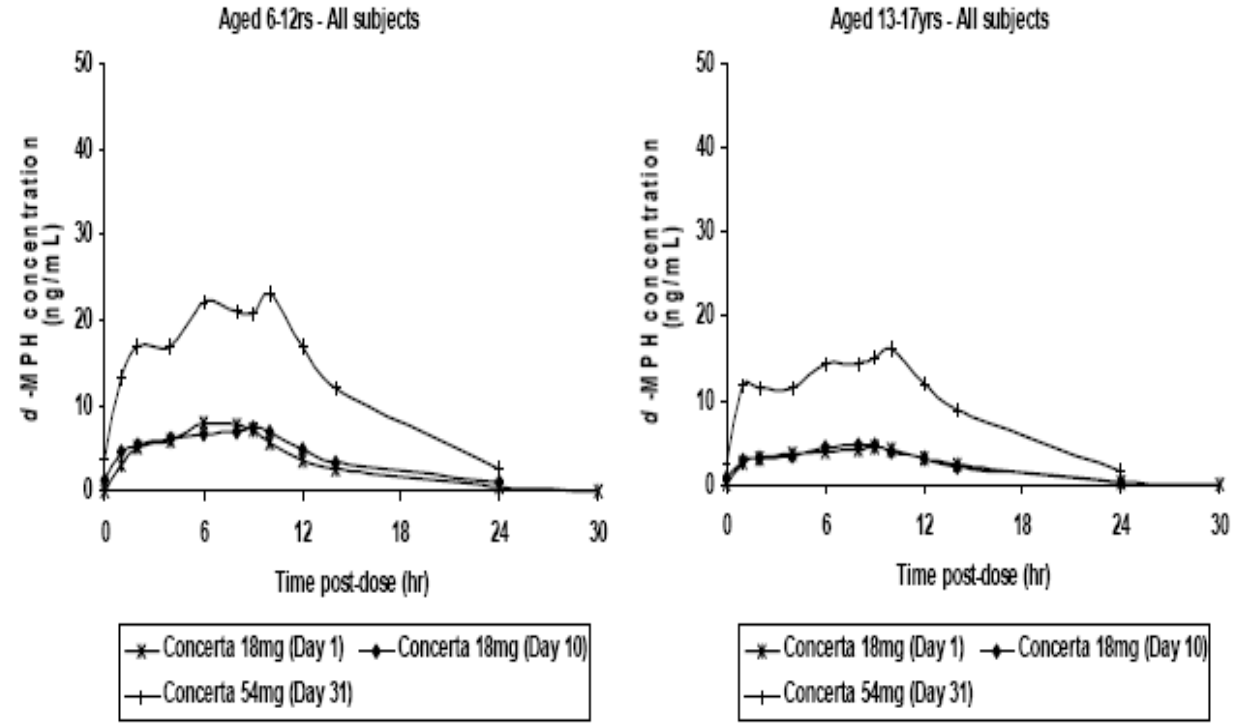
RESULTS

Figure 3: Arithmetic Mean Plasma Concentration-Time Profiles from Day 1 to Day 31 for *d*-MPH Following Single and Multiple Doses of MTS to Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population (Linear).



Source: Section 14, Table 2.1 to Table 2.6

Figure 4: Arithmetic Mean Plasma Concentration-Time Profiles from Day 1 to Day 31 for *d*-MPH Following Single and Multiple Doses of CONCERTA® to Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population (Linear)



Source: Section 14, Table 2.1 to Table 2.6

Table 3: Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Single Doses of MTS (10mg/9h; Treatments A and B) or CONCERTA® (18mg; Treatment C)

	MTS (10mg/9h)				**CONCERTA® (18mg)**			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	24	2.00 (0.95, 2.08)	24	2.00 (1.00, 9.00)	11	0.00 (0.00, 1.00)	11	0.00 (0.00, 0.00)
t_{max}* (h)	24	10.0 (8.00, 12.0)	24	10.0 (6.00, 12.0)	11	6.02 (4.00, 10.0)	11	8.00 (1.00, 10.0)
C_{max} (ng/mL)	24	9.30 (3.60)	24	4.15 (2.59)	11	7.80 (3.35)	11	4.95 (1.42)
AUC_{0-t} (ng•h/mL)	24	101 (48.0)	24	36.9 (24.9)	11	85.1 (44.4)	11	57.3 (17.7)
$AUC_{0-\infty}$ (ng•h/mL)	21	99.2 (42.9)	18	48.7 (21.9)	10	94.2 (43.8)	10	60.1 (16.3)
K_{el} (h^{-1})	21	0.144 (0.0302)	18	0.169 (0.0303)	10	0.176 (0.0577)	10	0.169 (0.0392)
$t_{1/2}$ (h)	21	5.01 (1.02)	16	4.35 (0.788)	10	4.26 (1.20)	7	4.74 (1.05)

Table 4: Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Fixed Doses of MTS (10mg/9h Daily for 7 Days; Treatments A and B) or CONCERTA® (18mg Daily for 7 Days; Treatment C)

	MTS (10mg/9h)				**CONCERTA® (18mg)**			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	23	0.00 (0.00, 2.00)	22	0.00 (0.00, 4.05)	10	0.00 (0.00, 0.00)	9	0.00 (0.00, 0.00)
t_{max}* (h)	23	9.00 (2.00, 12.0)	22	10.0 (8.03, 12.0)	10	8.00 (4.00, 10.0)	9	8.00 (4.00, 12.1)
C_{ssmax} (ng/mL)	23	12.4 (7.84)	22	5.45 (2.99)	10	8.37 (4.14)	9	5.23 (1.72)
C_{ssmin} (ng/mL)	23	0.773 (0.700)	22	0.288 (0.238)	10	0.708 (1.08)	9	0.360 (0.478)
Degree of fluctuation	22	2.53 (0.730)	20	2.27 (0.427)	10	2.07 (0.391)	9	1.97 (0.204)
AUC_{ss} (ng•h/mL)	22	112 (64.8)	20	55.7 (28.2)	10	97.7 (67.0)	9	59.7 (19.1)
R_{obsAUC}	22	1.21 (0.462)	18	1.57 (0.957)	9	1.16 (0.176)	9	1.13 (0.323)
$R_{obsCmax}$	23	1.34 (0.694)	22	1.57 (1.09)	10	1.13 (0.223)	9	1.19 (0.369)
R_{ss}	19	1.16 (0.423)	16	1.28 (0.340)	9	1.11 (0.145)	9	1.07 (0.303)

Table 5: Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Fixed Doses of MTS (10mg/9h Daily for 28 Days; Treatment A)

	MTS Fixed Dose (10mg/9h)			
	Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	11	0.00 (0.00, 2.00)	12	0.00 (0.00, 2.00)
t_{max}* (h)	11	9.00 (8.00, 10.0)	12	10.0 (6.00, 24.0)
C_{ssmax} (ng/mL)	11	15.7 (9.39)	12	8.32 (4.60)
C_{ssmin} (ng/mL)	11	1.04 (1.17)	12	0.544 (0.383)
Degree of fluctuation	11	2.20 (0.391)	12	2.31 (0.572)
AUC_{ss} (ng•h/mL)	11	163 (101)	12	85.7 (50.0)
R_{obsAUC}	11	1.70 (0.896)	10	1.94 (1.00)
$R_{obsCmax}$	11	1.76 (1.05)	12	1.79 (0.955)
R_{ss}	11	1.53 (0.805)	10	1.83 (0.915)

Table 6: Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Escalating Doses of MTS (15, 20, and 30mg/9h Daily for 7 Days Each; Treatment B) or CONCERTA® (27, 36, and 54mg Daily for 7 Days Each; Treatment C).

	MTS Escalating Doses (30mg/9h)				**CONCERTA® Escalating Doses (54mg)**			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	12	0.00 (0.00, 1.00)	10	0.00 (0.00, 2.00)	10	0.00 (0.00, 0.00)	9	0.00 (0.00, 0.00)
t_{max}* (h)	12	8.00 (8.00, 12.0)	10	9.00 (1.00, 10.0)	10	8.50 (6.00, 10.0)	9	8.00 (1.00, 10.0)
C_{ssmax} (ng/mL)	12	42.9 (22.4)	10	16.5 (6.94)	10	26.1 (11.2)	9	18.0 (6.97)
C_{ssmin} (ng/mL)	12	1.96 (1.73)	10	1.02 (0.629)	10	1.19 (1.54)	9	1.50 (0.937)
Degree of fluctuation	12	2.19 (0.309)	10	2.19 (0.377)	10	1.95 (0.412)	9	1.85 (0.312)
AUC_{ss} (ng•h/mL)	12	447 (230)	10	167 (66.0)	10	317 (160)	9	216 (80.8)
R_{obsAUC}	12	5.20 (1.79)	9	6.18 (3.07)	9	3.92 (0.690)	9	3.98 (0.951)
$R_{obsCmax}$	12	4.60 (1.09)	10	7.73 (7.85)	10	3.59 (0.795)	9	4.00 (1.09)

Table 7: Summary of Pharmacokinetic Parameters of *d*-MPH in Male and Female Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Single Doses of MTS (10mg/9h; Treatments A and B) or CONCERTA® (18mg; Treatment C)

		MTS (10mg/9h)				**CONCERTA® (18mg)**			
		Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	Sex	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	F	11	2.00 (1.00, 2.08)	11	4.00 (2.00, 9.00)	5	0.00 (0.00, 1.00)	5	0.00 (0.00, 0.00)
	M	13	2.00 (0.95, 2.00)	13	2.00 (1.00, 6.00)	6	0.00 (0.00, 0.00)	6	0.00 (0.00, 0.00)
t_{max}* (h)	F	11	10.0 (8.00, 10.0)	11	10.0 (6.00, 12.0)	5	8.00 (4.00, 10.0)	5	8.00 (6.00, 10.0)
	M	13	10.0 (8.00, 12.0)	13	9.95 (8.00, 12.0)	6	6.01 (6.00, 8.00)	6	5.99 (1.00, 8.00)
C_{max} (ng/mL)	F	11	11.6 (3.62)	11	3.35 (3.07)	5	7.57 (3.37)	5	5.70 (1.52)
	M	13	7.37 (2.26)	13	4.83 (1.98)	6	7.99 (3.65)	6	4.32 (1.08)
AUC_{0-t} (ng•h/mL)	F	11	125 (58.7)	11	30.0 (28.8)	5	79.6 (37.9)	5	63.9 (21.4)
	M	13	79.8 (22.6)	13	42.8 (20.4)	6	89.8 (52.3)	6	51.8 (13.3)
$AUC_{0-\infty}$ (ng•h/mL)	F	10	119 (51.0)	6	48.3 (30.3)	4	95.6 (28.9)	4	67.4 (20.9)
	M	11	81.5 (24.7)	12	48.9 (17.9)	6	93.3 (54.4)	6	55.2 (11.9)
K_{el} (h-1)	F	10	0.150 (0.0354)	6	0.155 (0.0318)	4	0.175 (0.0226)	4	0.183 (0.0414)
	M	11	0.139 (0.0251)	12	0.176 (0.0280)	6	0.177 (0.0754)	6	0.159 (0.0381)
$t_{1/2}$ (h)	F	10	4.83 (0.991)	6	4.65 (0.980)	4	4.02 (0.574)	2	ND (ND)
	M	11	5.17 (1.06)	10	4.17 (0.638)	6	4.41 (1.53)	5	4.78 (1.09)

Table 8: Summary of Pharmacokinetic Parameters of *d*-MPH in Male and Female Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Fixed Doses of MTS (10mg/9h Daily for 7 Days; Treatments A and B) or CONCERTA® (18mg Daily for 7 Days; Treatment C)

		MTS (10mg/9h)				**CONCERTA® (18mg)**			
		Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	Sex	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	F	10	0.00 (0.00, 2.00)	10	0.00 (0.00, 4.05)	4	0.00 (0.00, 0.00)	3	0.00 (0.00, 0.00)
	M	13	0.00 (0.00, 2.00)	12	0.00 (0.00, 1.07)	6	0.00 (0.00, 0.00)	6	0.00 (0.00, 0.00)
t_{max}* (h)	F	10	9.00 (7.98, 10.0)	10	10.0 (8.07, 12.0)	4	8.00 (6.00, 10.0)	3	8.00 (8.00, 12.1)
	M	13	9.00 (2.00, 12.0)	12	10.0 (8.03, 12.0)	6	8.50 (4.00, 10.0)	6	7.04 (4.00, 9.07)
C_{ssmax} (ng/mL)	F	10	14.0 (8.57)	10	4.87 (3.28)	4	6.58 (2.93)	3	5.40 (0.430)
	M	13	11.2 (7.33)	12	5.93 (2.77)	6	9.57 (4.62)	6	5.15 (2.16)
C_{ssmin} (ng/mL)	F	10	0.855 (0.876)	10	0.188 (0.199)	4	0.439 (0.344)	3	0.618 (0.768)
	M	13	0.710 (0.599)	12	0.371 (0.242)	6	0.887 (1.38)	6	0.231 (0.265)
Degree of fluctuation	F	10	2.42 (0.441)	9	2.28 (0.477)	4	2.01 (0.300)	3	1.97 (0.239)
	M	12	2.62 (0.917)	11	2.26 (0.406)	6	2.11 (0.465)	6	1.98 (0.209)
AUC_{ss} (ng•h/mL)	F	10	133 (84.3)	9	51.2 (27.8)	4	76.6 (39.6)	3	58.3 (1.77)
	M	12	95.1 (38.6)	11	59.3 (29.3)	6	112 (80.9)	6	60.4 (24.1)
R_{obsAUC}	F	10	1.11 (0.530)	8	1.86 (1.41)	3	1.08 (0.194)	3	1.08 (0.300)
	M	12	1.28 (0.404)	10	1.35 (0.219)	6	1.19 (0.172)	6	1.15 (0.359)
$R_{obsCmax}$	F	10	1.12 (0.529)	10	1.94 (1.53)	4	1.02 (0.172)	3	1.14 (0.415)
	M	13	1.51 (0.775)	12	1.26 (0.367)	6	1.20 (0.236)	6	1.21 (0.383)
R_{ss}	F	9	1.10 (0.460)	6	1.27 (0.523)	3	1.04 (0.177)	3	1.04 (0.319)
	M	10	1.21 (0.403)	10	1.28 (0.202)	6	1.14 (0.131)	6	1.09 (0.324)

Table 9: Summary of Pharmacokinetic Parameters of *d*-MPH in Male and Female Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Fixed Doses of MTS(10mg/9h for 28 Days; Treatment A)

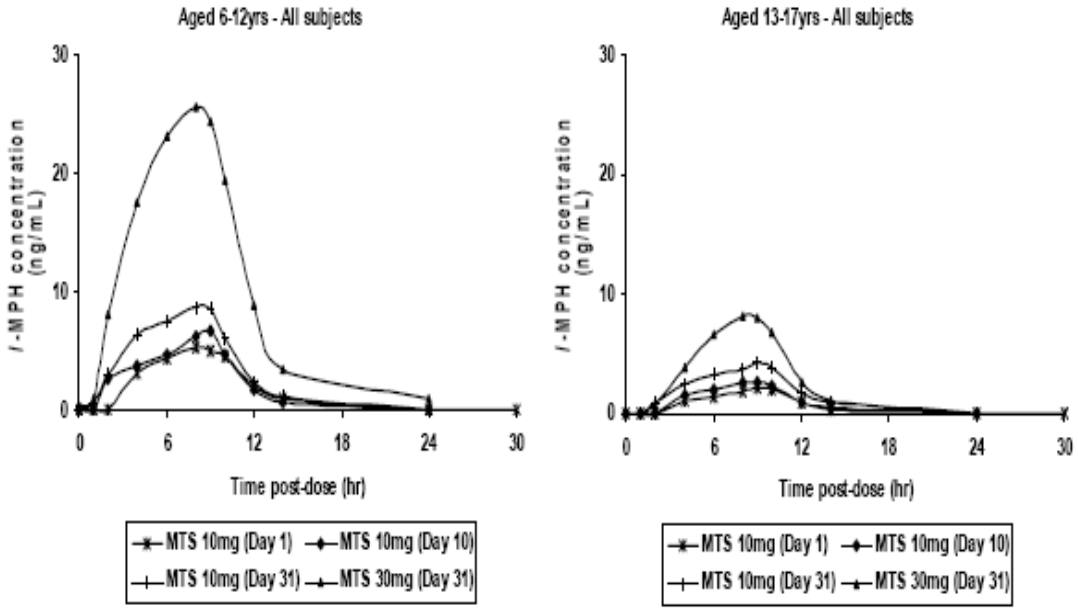
		MTS Fixed Doses (10mg/9h)			
		Aged 6-12 years		Aged 13-17 years	
Parameter	Sex	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	F	4	0.00 (0.00, 0.00)	5	0.00 (0.00, 2.00)
	M	7	0.00 (0.00, 2.00)	7	0.00 (0.00, 0.00)
t_{max}* (h)	F	4	9.00 (8.00, 10.0)	5	10.0 (8.08, 10.0)
	M	7	9.00 (8.00, 10.0)	7	10.0 (6.00, 24.0)
C_{ssmax} (ng/mL)	F	4	20.5 (13.1)	5	10.6 (4.98)
	M	7	13.0 (6.11)	7	6.72 (3.89)
C_{ssmin} (ng/mL)	F	4	1.45 (1.78)	5	0.514 (0.315)
	M	7	0.804 (0.717)	7	0.565 (0.449)
Degree of fluctuation	F	4	2.20 (0.152)	5	2.60 (0.630)
	M	7	2.21 (0.493)	7	2.10 (0.459)
AUC_{ss} (ng•h/mL)	F	4	215 (146)	5	102 (56.2)
	M	7	134 (59.9)	7	74.2 (46.0)
R_{obsAUC}	F	4	1.42 (0.876)	4	2.52 (1.32)
	M	7	1.86 (0.933)	6	1.56 (0.558)
$R_{obsCmax}$	F	4	1.51 (0.973)	5	2.33 (1.26)
	M	7	1.91 (1.14)	7	1.42 (0.465)
R_{ss}	F	4	1.26 (0.751)	4	2.35 (1.19)
	M	7	1.68 (0.851)	6	1.48 (0.540)

Table 10: Summary of Pharmacokinetic Parameters of *d*-MPH in Male and Female Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population Following Multiple Escalating Doses of MTS (15, 20, and 30mg/9h Daily for 7 Days Each; Treatment B) or CONCERTA®(27, 36, and 54mg Daily for 7 Days Each; Treatment C)

		MTS Escalating Doses (30mg/9h)				CONCERTA® Escalating Doses (54mg)			
		Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	Sex	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	F	6	0.00 (0.00, 0.00)	5	0.00 (0.00, 2.00)	4	0.00 (0.00, 0.00)	3	0.00 (0.00, 0.00)
	M	6	0.00 (0.00, 1.00)	5	0.00 (0.00, 0.00)	6	0.00 (0.00, 0.00)	6	0.00 (0.00, 0.00)
t_{max}* (h)	F	6	8.00 (8.00, 10.0)	5	9.00 (1.00, 10.0)	4	9.50 (6.00, 10.0)	3	8.00 (6.00, 9.00)
	M	6	8.50 (8.00, 12.0)	5	9.00 (8.00, 10.0)	6	7.00 (6.00, 10.0)	6	4.50 (1.00, 10.0)
C_{ssmax} (ng/mL)	F	6	48.3 (28.6)	5	14.8 (3.12)	4	21.8 (7.18)	3	16.2 (5.91)
	M	6	37.5 (14.8)	5	18.1 (9.59)	6	28.9 (13.0)	6	18.9 (7.80)
C_{ssmin} (ng/mL)	F	6	2.20 (1.94)	5	1.02 (0.870)	4	1.16 (0.624)	3	1.44 (0.823)
	M	6	1.72 (1.64)	5	1.02 (0.365)	6	1.21 (2.01)	6	1.53 (1.06)
Degree of fluctuation	F	6	2.25 (0.252)	5	2.19 (0.407)	4	1.75 (0.101)	3	1.81 (0.270)
	M	6	2.13 (0.372)	5	2.19 (0.393)	6	2.08 (0.497)	6	1.87 (0.353)
AUC_{ss} (ng•h/mL)	F	6	498 (298)	5	154 (40.4)	4	283 (97.4)	3	200 (84.3)
	M	6	397 (146)	5	180 (88.2)	6	339 (197)	6	224 (85.9)
R_{obsAUC}	F	6	5.11 (2.07)	4	8.34 (2.92)	3	4.11 (0.850)	3	3.48 (0.760)
	M	6	5.28 (1.65)	5	4.46 (2.00)	6	3.83 (0.664)	6	4.24 (0.993)
$R_{obsCmax}$	F	6	4.31 (1.46)	5	11.7 (9.82)	4	3.49 (0.563)	3	3.35 (1.23)
	M	6	4.90 (0.549)	5	3.80 (1.85)	6	3.65 (0.966)	6	4.32 (0.963)

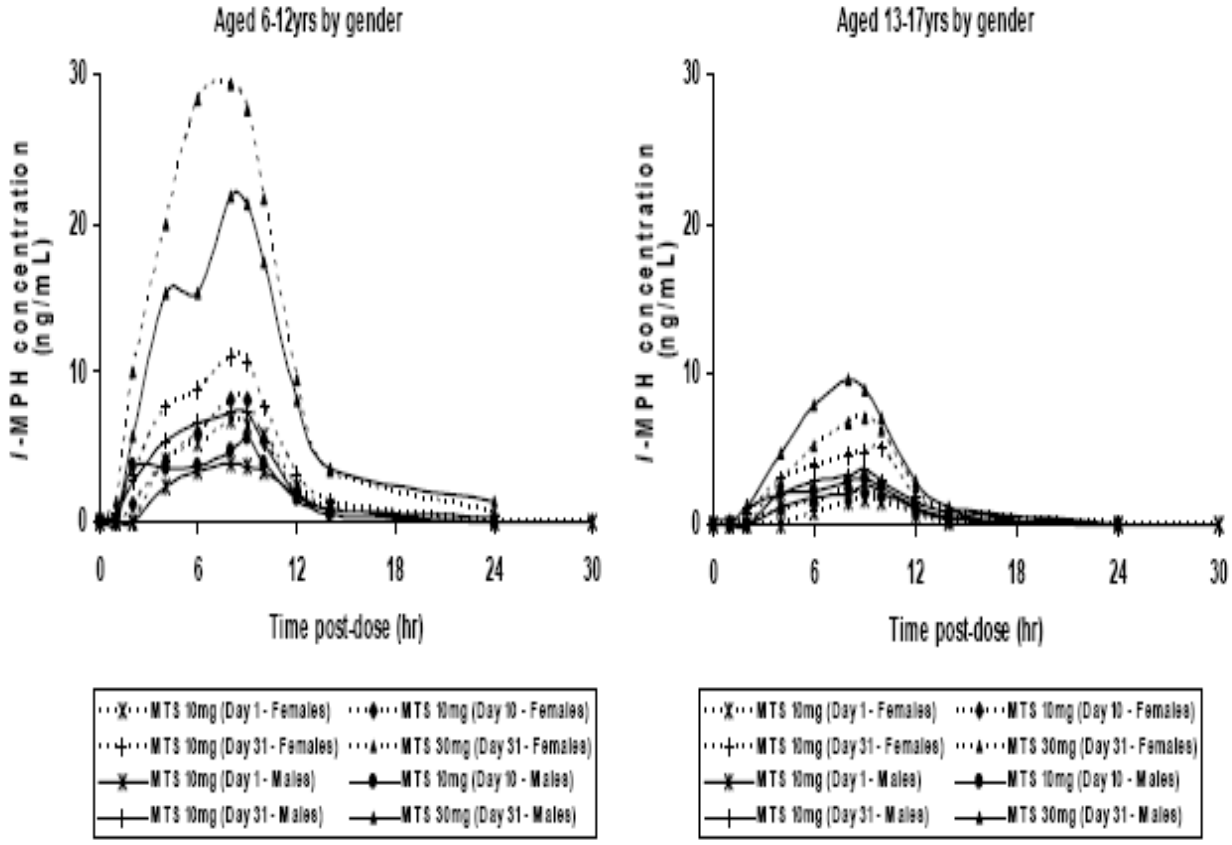
Since the d-isomer has been reported to be more active than the l-isomer only the graphical results for the l-isomer will be presented.

Figure 5: Arithmetic Mean Plasma Concentration-Time Profiles from Day 1 to Day 31 for *l*-MPH Following Single and Multiple Doses of MTS to Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic Population (Linear)



Source: Section 14, Table 2.13 to Table 2.18

Figure 6: Arithmetic Mean Plasma Concentration-Time Profiles from Day 1 to Day 31 for *l*-MPH Following Single and Multiple Doses of MTS to Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic based upon gender Population (Linear)



- **Pharmacokinetic Conclusions**

- Systemic exposure to *d*-MPH (based on estimates of AUC and Cmax) both following single and multiple dosing was consistently lower by approximately 50% in adolescents compared with children across all treatments of MTS. Table 3 page 29 and Table 4 page 30.

- 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-Tables 3 page 29 and Table 4 page 30.

- Given the t1/2 estimates d-MPH(4.8h-children and 4.1h-adolescents), accumulation to steady state of *d*-MPH would have been reached within 2 days and for *l*-MPH (~1.5h) within a 24h dosing interval, respectively, with repeat once-daily dosing either by MTS or CONCERTA®-Table 7 page 33.

- Accumulation from Day 1 to Day 7 for AUCss with fixed dosing was 1.12 and 1.14 for children and adolescents, respectively- Table 1a. page 19

- Accumulation from Day 1 to Day 28 with fixed Dosing was 1.64 for children and 1.76 for adolescents-Table 1a page 19

- Increases in systemic exposure following multiple escalating doses was attributed to dose escalation rather than further accumulation.

- In children, systemic exposure i.e., AUCinf and Cmax to *d*-MPH for a single dose of MTS (10mg/9h) was similar to that for 18mg CONCERTA®. –Table 3 page 29

- In adolescents following a single dose, MTS AUCinf ng/mlxh was 19% lower (MTS/Concerta=48.7/60.1) than for Concerta. Table 3 page 29.

- Systemic exposure to *d*-MPH after multiple fixed doses (10mg/9h daily) was similar to that for CONCERTA® (18mg daily) for up to 7 days in children and adolescents. Table 4 page 30.

- Although some trends were observed, there appeared not to be a consistent sex-related difference in the kinetics of *d*- and *l*-MPH across age groups, treatments and study days.

- 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. By comparison, systemic exposure to *l*-MPH was negligible after single and multiple doses of CONCERTA®.

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

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/s/

ANDRE J JACKSON
05/13/2010

RAMAN K BAWEJA
05/13/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021514Orig1s010

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: May 21, 2010

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products (DPP)

Through: Mary Willy, Ph D, Deputy Director
Division of Risk Management (DRISK)

LaShawn Griffiths, RN, MSHS-PH, BSN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Robin Duer, RN, BSN, MBA
Patient Product Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide, Patient Instructions for Use)

Drug Name(s): DAYTRANA (methylphenidate transdermal system)

NDA # 21-514

Submission Numbers: S-025, S-026

Applicant/sponsor: Shire Pharmaceuticals, Inc.

OSE RCM #: 2009-1672

1 INTRODUCTION

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Patient Instructions for Use (IFU) for DAYTRANA (methylphenidate transdermal system).

Shire Pharmaceuticals submitted a Prior Approval Labeling Supplement (S-025) on June 30, 2009 to provide for the conversion of the current professional labeling to Physician's Labeling Rule (PLR) format. Additionally, an Efficacy Supplement (S-026) was submitted for DAYTRANA on September 4, 2009. DAYTRANA is currently approved for the treatment of ADHD in children ages 6 to 12 years old. Supplement 026 provided for a post marketing commitment to expand the use of DAYTRANA in children ages 13 to 17 years old. This review incorporates all of the proposed patient labeling changes contained in both S-025 and S-026.

Please let us know if DPP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft DAYTRANA (methylphenidate transdermal system) Prescribing Information (PI) submitted on September 4, 2009, revised by the Review Division throughout the current review cycle and received by DRISK on May 18, 2010
- Draft DAYTRANA (methylphenidate transdermal system) Medication Guide (MG) and Patient Instructions for Use (IFU) submitted on September 4, 2009 and received by DRISK on May 7, 2010.

3 RESULTS OF REVIEW

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- rearranged information due to conversion of the PI to PLR format

Our annotated versions of the MG and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the MG and IFU.

Please let us know if you have any questions.

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21514	SUPPL-9	SHIRE DEVELOPMENT INC	Daytrana System
NDA-21514	SUPPL-10	SHIRE DEVELOPMENT INC	Daytrana System

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/s/

ROBIN E DUER
05/21/2010

MARY E WILLY
05/21/2010
I concur

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: May 14, 2010

To: Juliette Toure, Pharm.D.
Regulatory Health Project Manager
DPP

From: Amy Toscano, Pharm.D., CPA
Regulatory Review Officer
DDMAC

Susannah Hubert, MPH
Regulatory Review Officer
DDMAC

Subject: DDMAC comments on DAYTRANA® (methylphenidate transdermal system) PI and Medication Guide
NDA 21-514

DDMAC has reviewed the proposed revised labeling, including the PI and Medication Guide, for Daytrana, which includes the following two labeling supplements:

- 21-514/S-009 Labeling supplement for conversion to PLR format
- 21-514/S-010 Efficacy supplement to add information regarding 3 adolescent studies

DDMAC reviewed the labeling provided by DPP on May 5th, and offers the following comments, which are provided directly on the marked up version of the label attached below.

Thank you for the opportunity to comment on this proposed labeling.

If you have any questions or concerns regarding these comments, please contact us.

39 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21514	SUPPL-9	SHIRE DEVELOPMENT INC	Daytrana System
NDA-21514	SUPPL-10	SHIRE DEVELOPMENT INC	Daytrana System

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/s/

AMY TOSCANO
05/14/2010

SUSANNAH HUBERT
05/14/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 27, 2010

TO: Juliette Touré, PharmD, Regulatory Project Manager
Christina Burkhart, MD, Medical Officer
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orencia, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-514/S-10

APPLICANT: Shire Pharmaceuticals

DRUG: methylphenidate transdermal system (Daytrana)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: treatment of adolescents with Attention Deficit/Hyperactivity Disorder

CONSULTATION REQUEST DATE: October 19, 2009

DIVISION ACTION GOAL DATE: July 4, 2010

PDUFA DATE: July 4, 2010

I. **BACKGROUND**:

Longitudinal and cross-sectional studies provide evidence that majority of adolescents with ADHD continue to show significant ADHD-associated impairment as adults. Persistence of ADHD-associated behavior into adulthood carries a high risk of anxiety disorders, oppositional and antisocial personality disorders, and continued high incidence of substance abuse.

Treatment options for ADHD have included stimulant or non-stimulant medications, and nonpharmacologic interventions. Stimulant medications, such as amphetamine and methylphenidate products, have been used successfully since the 1950s to treat hyperactivity, impulsivity, and attention deficit in ADHD, and remain the most frequently prescribed drug class used to treat children, adolescents, and adults. MTS, marketed as DAYTRANA®, was approved based on clinical studies of safety and efficacy in children (aged 6-12 years) with ADHD. Potential advantages of Methylphenidate Transdermal System (MTS) are the ability to control effect over time by varying patch size (dose) and the duration of patch application (wear time).

Protocol SPD485-409 was a phase IIIb, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the efficacy and safety of MTS (10, 15, 20, and 30mg/9 hour doses) compared with placebo in adolescent subjects (aged 13-17 years) diagnosed with ADHD. This multi-center study was conducted in the United States with 32 centers involved. The first study subject consented on June 28, 2007 and the last subject follow-up visit was conducted on May 14, 2008.

The primary objective of this study was to evaluate the efficacy of Methylphenidate Transdermal System (MTS) compared with placebo, as determined by the change in the clinician-completed ADHD Rating Scale – Version 4th Edition (ADHD-RS-IV), in the symptomatic treatment of adolescents (aged 13-17 years) diagnosed with ADHD (DSM-IV-TR criteria). Eligible subjects were male or female adolescents, aged 13-17 years, at the time of signed informed consent with a primary diagnosis of ADHD, a total score of ≥26 on the ADHD-RS-IV at baseline, and an intelligence quotient score of 80 or above. Primary efficacy was the change in the ADHD RS-IV from baseline to week 7 or at designated endpoint.

The sites selected for inspection were: Dr. Findling (Site 13) and Dr. Saylor (Site 29). In the consult as outlined by the Medical Officers and review team, and discussions with DPP, these sites were selected as they would potentially drive the primary efficacy endpoint results because they were large enrollment sites. Protocol SPD 485-409 was audited for these clinical study sites.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Robert Findling, M.D., /Site #13	Cleveland, OH	SPD485-409	December 2-11, ,2009,	December 17, 2010	No Action Indicated (NAI)
Keith Saylor, Ph.D./ Site 17	Herndon, VA	SPD485-409	November 19-20, 2009	December 7, 2009	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.
Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

PROTOCOL SPD485-409

1. Robert Findling, M.D., /Site #13

10524 Euclid Ave., Suite 1155A
Cleveland, OH 44106

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 2 to 11, 2009. A total of 12 subjects who consented were screened; 4 were enrolled and randomized; 3 subjects completed the study. There were no deaths or SAEs reported. An audit of 4 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

2. Keith Saylor, Ph.D./Site 17
106 Elden Street, Suite 17
Herndon, VA 20170

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from November 19 to 20, 2009. There were 10 subjects screened, and 9 subjects completed the study. No deaths or SAEs were reported. An audit of the 10 enrolled subjects was conducted.

b. Limitations of inspection
None.

c. General observations/commentary:

Verification of source data for efficacy endpoints, subject eligibility, informed consent, test article accountability, monitoring record completions, and protocol-specified procedures for blinding and randomization were assessed. There were no issues related to under-reporting of adverse event data.

d. Data acceptability/reliability for consideration in the NDA review decision:
Study appears to have been conducted adequately, and in compliance with Good Clinical Practices (GCP). Data appear reliable to support the ADHD indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two U.S. clinical investigator sites were inspected in support of this application, for the proposed indication of symptomatic treatment of adolescents with Attention Deficit/Hyperactivity Disorder. No discrepancies were noted with the data listings provided in the NDA and source documents. Inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Data appear acceptable for the proposed indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

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/s/

ANTHONY J ORENCIA
04/28/2010

TEJASHRI S PUROHIT-SHETH
04/28/2010