

## CLINICAL REVIEW

Application Type:	Type 2 NDA Resubmission
Submission Number:	NDA 21-514
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Reviewer Name:	Robert Levin, M.D.
Completion Date:	November 7, 2005
Established Name:	Methylphenidate Transdermal System
Trade Name:	Daytrana (proposed)
Therapeutic Class:	Stimulant
Applicant:	Noven Pharmaceuticals, Inc.
Priority Designation:	P
Formulation:	Transdermal Patch
Dosing Regimen:	12.5, 18.75, 25, 37.5 cm <sup>2</sup> patches
Indication:	Attention Deficit/Hyperactivity Disorder
Intended Population:	Children with ADHD (ages 6 to 12 years)

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## CLINICAL REVIEW

### 1. EXECUTIVE SUMMARY

#### 1.1 Recommendation on Regulatory Action

I recommend that the Division take a not-approvable action for NDA 25-514. Methylphenidate Transdermal System (MTS) treatment in children (ages 6 to 12) with Attention Deficit Hyperactivity Disorder (ADHD) was associated with an adverse event profile and potential risks that could pose clinically important risks to a significant number of pediatric patients who might be exposed to MTS.

Specifically, treatment with MTS was associated with a high incidence of insomnia, anorexia or decreased appetite, headache, and gastrointestinal symptoms including vomiting, nausea, and upper abdominal pain. These adverse events were significantly more common in the MTS group than in the active comparator group (Concerta) and the placebo group. MTS treatment was also associated with decreased weight in these short-term studies.

In addition, treatment with MTS was associated with a relatively high risk of developing tic disorder, compared to the active comparator group (Concerta) and the placebo group. Also, treatment with MTS was associated with a significant degree of dermal signs and symptoms at the patch application site.

In my opinion, the safety and tolerability profile of MTS treatment in these 2 new studies does not appear to be significantly more acceptable than that in the previous MTS submission. Generally, it appears that the identical safety concerns remain.

#### 1.2 Recommendation on Postmarketing Actions

Currently, there are no specific recommendations for postmarketing actions, risk management activities, or Phase 4 commitments, since it is recommended that the Division take a not-approvable action.

#### 1.3 Reason for the Type 2 Resubmission

The sponsor has submitted a Type 2 Resubmission for Methylphenidate Transdermal System (MTS) in the treatment of ADHD. The original NDA (submitted on June 27, 2002) resulted in a not-approvable action taken by the Division of Neuropharmacological Drug Products (April 23, 2003). Although the sponsor had demonstrated the efficacy of MTS in one controlled trial, the Division concluded that subjects experienced excessive drug exposure at inappropriate times of the day (including the evening), and they experienced unacceptable incidences of insomnia, anorexia, and significant weight loss in the short term. Furthermore, these adverse events could possibly result in growth retardation or other serious adverse consequences during more chronic treatment.

Moreover, the potential benefits of MTS relative to other once-a-day products available for this population were not thought to outweigh the risks associated with MTS treatment.

The Division suggested that decreasing the patch wear time (from 12 hours) may decrease the risk of insomnia, anorexia, and significant wear time to acceptable levels. The sponsor would need to conduct a new trial demonstrating that MTS with a decreased wear was both safe and effective in the target population.

The Division recommended a classroom study including pharmacokinetic and pharmacodynamic (using the SKAMP Scale) assessments to define more clearly the time course of effect of treatment. The Division asked the sponsor to prospectively monitor insomnia (using an appropriate, directed assessment), anorexia (assessing weight gain or loss), blood pressure, and pulse. The Division also requested that the sponsor use an active comparator (a long-acting oral formulation of methylphenidate) in the study, in order to compare the adverse events profiles of the two types of methylphenidate formulations.

In addition, agency Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6-week duration would be helpful in investigating this potential signal.

The Division also concluded the MTS posed a significant abuse liability, since it appears that the methylphenidate in MTS may be extracted with common household solvents. This makes it available to be diverted and abused in a non-patch-bound form. Even if the methylphenidate contained in MTS could not be extracted, significant amounts of methylphenidate remain in the patch to be diverted and abused. Additional amounts of methylphenidate would be available for diversion if wear-time were decreased.

## **1.4 Summary of Clinical Findings**

### **1.4.1 Brief Overview of Clinical Program**

The sponsor has submitted data from 2 new clinical studies of Methylphenidate Transdermal System (MTS) in pediatric patients (ages 6 to 12) with Attention-Deficit/Hyperactivity Disorder (ADHD).

Study 201 is a phase 2, multi-center, randomized, double-blind, placebo-controlled dose optimization and analog classroom, crossover study. The main objectives were to assess the time course of treatment effect, and the safety and tolerability of MTS treatment in children with ADHD. The study began with a 5-week open-label dose optimization phase in which all subjects were treated with MTS. Individual subjects' doses were titrated weekly, depending on the subject's clinical response and tolerability. Patch sizes used included 12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup>, and 37.5cm<sup>2</sup>. Immediately after the end of 5 weeks, there was a 2-week double-blind, placebo-controlled crossover phase. In the

controlled crossover phase, each subject had one week of MTS treatment and one week of placebo treatment, in one of two randomized sequences.

Study 302 was a phase 3, multi-center, outpatient, randomized, double-blind, placebo-controlled and active-controlled, parallel group dose optimization study, designed to evaluate the safety and efficacy of Methylphenidate Transdermal System (MTS) (compared to matching placebo transdermal system as well as CONCERTA and matching oral placebo) in pediatric patients (ages 6-12 years) with ADHD. The duration of the dose optimization phase was 5 weeks, and the duration of the maintenance phase was 2 weeks. MTS patch sizes used included 12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup>, and 37.5cm<sup>2</sup>. Matching placebo Transdermal System patches were used. Concerta doses used were

### 1.4.2 Efficacy

In both studies, the sponsor demonstrated the efficacy of MTS in the treatment of children with ADHD.

In Study 201, the primary efficacy endpoint was the change from baseline in the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) department scale, which is an appropriate efficacy measure for a trial in subjects with ADHD. The SKAMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS. Subscale scores for department, attention and quality of work were evaluated at each time point to assess the duration of effect of MTS vs. placebo. Using the ITT data set provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint and he derived the same p-values. The results are depicted in Table 3.1.1.5.

**Table 3.1.1.5 Analysis of Mean SKAMP Department Score during Patch Application (Hours 2.0 – 9.0): ITT Population**

	<b>MTS (N=79)</b>	<b>Placebo (N=79)</b>	<b>p-value</b>
<b>Mean (SD)</b>	3.2 (3.64)	8.0 (6.33)	
<b>LS Mean (SE)</b>	3.2 (0.58)	8.0 (0.58)	<0.0001 <sup>a</sup>
<b>Difference and 95% CI of LS Means (MTS-Placebo)</b>	-4.8 (-5.89, -3.63)	NA	

<sup>a</sup>: The p-value is obtained using the mixed effects model.

In Study 302, the primary efficacy endpoint was the change from baseline in mean clinician-rated ADHD-Rating Scale-IV (ADHD-RS-IV) among treatment groups (MTS, placebo TS, Concerta, and matching placebo). The ADHD-RS-IV is an appropriate efficacy measure for a trial in children with ADHD.

Using both the ITT and PP data sets provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint using both the LOCF and OC data

sets, and he derived the same p-values. The results of ITT population analysis are given in the following table.

**Table 3.1.2.5 Analyses of the Change from Baseline of ADHD-RS-IV Total Score (ITT Population)**

	<b>MTS (N=96)</b>	<b>Concerta (N=89)</b>	<b>Placebo (N=85)</b>
<b>LOCF analysis</b>			
N	96	89	85
Mean (SD)	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
LS Mean (SE)	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
<b>Difference and 95% CI of LS Means (Active-Placebo)</b>	-13.89 (-18.06, -9.72)	-11.32 (-15.58, -7.06)	
<b>p-value</b>	<0.0001	<0.0001	
<b>OC Analysis</b>			
N	70	64	31
Mean (SD)	-29.8 (10.40)	-28.0 (11.13)	-22.4 (13.67)
LS Mean (SE)	-30.1 (1.21)	-27.2 (1.27)	-23.5 (1.83)
<b>Difference and 95% CI of LS Means (Active-Placebo)</b>	-6.58 (-10.91, -2.24)	-3.77 (-8.19, 0.66)	
<b>p-value</b>	0.0032	0.095	

### 1.4.3 Safety

#### **Deaths, Serious Adverse Events, Discontinuations due to AE, and Common AE**

There were no deaths in Study 201 or Study 302. There were no serious adverse events reported in Study 201 or Study 302. In the studies combined, there were a number of discontinuations due to adverse events that were probably related to treatment with MTS and were clinically significant. These included tic (3), anorexia (2), rash at patch application site (4), elevated blood pressure (1), weight loss (1), and mood lability (2). During Study 302 in the Concerta group, there were several discontinuations due to AE that were possibly related to treatment with Concerta. These included syncope, aggression, anger, and headache (1 case each).

The most commonly reported AE attributable to MTS treatment in Study 201 and Study 302 (respectively) were anorexia (29% and 26%), insomnia (16% and 13%), headache (12% and 15%), nausea or vomiting (10% and 22%), abdominal pain (8% and 7%), and weight decreased (2% and 9%). In addition, irritability, lability, or anger was reported for 15% of subjects in Study 201.

In Study 302, irritability and affective lability were reported for 7% and 7% of subjects, respectively. In the cases of tic, insomnia, anorexia, decreased appetite, weight decreased, nausea, vomiting, and affective lability, the proportions of subjects with these AE in the MTS group exceeded those in the Concerta group.

#### **Weight Findings**

In both studies, there was a trend toward weight loss. The mean weight decreased in the MTS groups. Furthermore, there were decreases in the mean z-scores for both weight



and BMI in the MTS groups. The clinical significance of the finding of weight loss is currently unclear. However, during chronic use of MTS, it is possible that exposed patients could experience more pronounced weight loss.

In Study 201, at the end of Week 6, there was a decrease in mean weight of -2.2 lbs and -0.6 lbs in the MTS and PTS groups, respectively. At the end of Week 7, the change in weight was -1.3 lbs and -0.6 lbs in the MTS and PTS groups, respectively. In Study 201, the mean z-score for weight decreased from -0.08 to -0.15. The mean z-score for height increased from -0.06 to -0.03. Mean z-scores for BMI decreased from -0.07 to -0.21.

In Study 302, there was a decrease in mean weight from baseline at all in both the MTS and CONCERTA groups, while subjects in the placebo group had an increase in mean weight from baseline. The maximum mean decrease in weight from baseline was observed at Visit 8 in both the MTS (-2.2lbs) and CONCERTA (-2.1lbs) groups. The maximum mean increase in weight from Baseline in the placebo group was +2.1lbs at Visit 8. In the MTS group, there was a higher proportion of subjects with weight measurements below the normal range, compared to the Concerta and placebo groups, between Baseline and Visit 9 in the MTS group. At Visit 9, three (3.1%) MTS subjects had weight measurements below the normal range. There were no subjects with weight measurements below the normal range in the CONCERTA or placebo groups.

The mean z-score for weight decreased in both the MTS and CONCERTA groups. In the MTS group, the mean z-score decreased from 0.05 to -0.21. In the Concerta group, the mean z-score decreased from 0.28 to 0.04. In the placebo group, the mean z-score increased from 0.15 to 0.24. The mean z-score for height was relatively unchanged from Screening to Visit 9 in all three treatment groups. The mean z-score for BMI decreased from 0.13 to -0.23 in the MTS group, and it decreased from 0.30 to -0.06 in the Concerta group. In the placebo group, the mean z-score for BMI increased from 0.25 to 0.34.

### **Vital Signs Findings**

Generally, MTS treatment had few clinically significant effects on blood pressure, pulse, or temperature. In Study 201, there were no significant changes or differences in mean diastolic blood pressure, systolic blood pressure, or heart rate. The sponsor acknowledges that heart rate often increased in subjects shortly after patch application. In the open-label phase, one subject (1%) had significantly elevated blood pressure. During the placebo-controlled phase, 2.5% of subjects in the MTS group had elevated blood pressure (compared to 0% in the placebo group). Of note, one subject discontinued due to elevated blood pressure.

In Study 302, there were small increases in mean systolic blood pressure from baseline to Visits 6, 7, 8, and 9 in both the MTS and CONCERTA groups, compared to the placebo group. The maximum mean increases in systolic BP from Baseline were observed at Visit 7 (1.3mmHg) in the MTS group and at Visits 6 and 7 (1.6mmHg) in the CONCERTA group. Similarly, small increases in mean diastolic blood pressure were observed at most visits in the MTS and CONCERTA groups. The maximum mean increases in diastolic BP from Baseline were observed at Visit 7 in the MTS group (1.6mmHg) and at Visit 8

in the CONCERTA group (2.7mmHg). In the MTS group, no subjects had systolic BP or diastolic BP above the normal range compared to baseline. Several subjects in the Concerta group had systolic BP measurement above the normal range.

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

The number of subjects with pulse measurements above the normal range was higher at most visits compared to the number of subjects with above normal pulse values at baseline. However, the incidence of pulse values above the normal range was generally similar between the active treatment groups and placebo. At Visit 8, the incidence of pulse values above the normal range was similar between the two active treatment groups, yet higher than in the placebo group.

### **Sleep Findings**

As noted above, insomnia was a commonly reported adverse event in both pivotal studies (16% and 13% in studies 201 and 302, respectively). In Study 303, insomnia was reported for 8% and 5% in the Concerta and placebo groups, respectively. In my opinion, the proportion of subjects in the MTS group who had insomnia is significant, especially when compared to the proportions in the Concerta and placebo groups.

The sponsor also conducted a prospective, directed assessment of sleep functioning. The instrument used was the Child's Sleep Habits Questionnaire (CSHQ). The CSHQ is a directed assessment of numerous items related to sleep function. It is designed to screen for the most common sleep problems in children aged 4 to 12. It assesses sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The CSHQ has 33 questions, responses range from 1 (rarely occurring) to 3 (usually occurring) with total scores ranging from 33 to 99. The specific CSHQ items are listed in Section. Generally, in both studies, results of the CSHQ assessment suggested that there was no significant effect of MTS treatment on sleep. However, in my opinion, in my opinion, the use of the CSHQ, which uses a number of items, may obscure the extent of the problem with insomnia in these studies, since many of the items do not appear to be directly relevant to the sleep problems specific to stimulant treatment. The most relevant items pertain to initial, middle, and terminal insomnia as well as sleep duration and quality. Use of the CSHQ may dilute possible clinically important adverse events related to insomnia.

### **Clinical Laboratory Findings**

There were few significant clinical laboratory findings. There were no significant differences in mean hematology or chemistry parameters. Two subjects had eosinophilia, and one had a decreased platelet count. Neither abnormality was likely to be related to MTS treatment, and there no apparent clinical symptoms related to these laboratory abnormalities. On e subject was discontinued due to having an abnormal lymphocyte morphology.

There were no significant changes in mean chemistry parameters, and there were no significant differences between groups. Among the few abnormalities in clinical chemistry parameters, non was likely due to MTS treatment.

#### 1.4.4 Dosing Regimen and Administration

##### DOSAGE AND ADMINISTRATION

Four dosage strengths for Methylphenidate Transdermal System (MTS) are available: 12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, 25 cm<sup>2</sup>, and 37.5 cm<sup>2</sup>. The corresponding dosage rates and methylphenidate contents are listed in the table below.

Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch** (mg)
10	1.1	12.5	27.5
16	1.8	18.75	41.3
20	2.2	25	55.0
27	3.0	37.5	82.5

It is recommended that the patch be applied to the hip area in the morning and worn for 9 hours. The sponsor recommends the titration schedule below for patients newly treated with methylphenidate.

Upward Titration, if Response is Not Maximized			
Week 1	Week 2	Week 3	Week 4
10 mg (1.1 mg/hr)* daily	16 mg (1.8 mg/hr)* daily	20 mg (2.2 mg/hr)* daily	27 mg (3.0 mg/hr)* daily

Patients currently treated with methylphenidate extended release (methylphenidate-ER) products should follow the conversion guide below when initiating therapy with MTS.

Previous Methylphenidate-ER Daily Dose	Daily Delivered Dose (Recommended MTS Dosage Rate)
18 - 27 mg q am Methylphenidate-ER	10 mg (1.1 mg/hr)*
36 - 60 mg q am Methylphenidate-ER	16 mg (1.8 mg/hr)*

Conversion from previous daily dosages of methylphenidate-ER less than 18 mg daily to MTS is not recommended.

### **Application**

The adhesive side of MTS 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. Avoid the waistline, since clothing may cause the patch to rub off. When applying the patch the next morning, place on the opposite hip.

MTS should be applied immediately after opening the pouch and removing the protective liner. Do not use if the pouch seal is broken. 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. Bathing, swimming, or showering have not been shown to affect patch adherence. In the unlikely event that a patch should fall off, a new patch may be applied at a different site, but the total recommended wear time should remain 9 hours.

### **Disposal of MTS**

Upon removal of MTS, 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. Each unused patch should be removed from its pouch, separated from the protective liner, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container.

### **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 MTS. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who uses MTS for extended periods in patients with ADHD should periodically evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

### **Dose/Wear Time Reduction and Discontinuation**

MTS 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 to decline when the patch is removed. 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.

### **1.4.5 Drug-Drug Interactions**

MTS should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors (see **CONTRAINDICATIONS-Monoamine Oxidase Inhibitors**).

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

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

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). Downward dose adjustment 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 concomitant methylphenidate.

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.

#### **1.4.6 Special Populations**

##### **Gender**

The pharmacokinetics of methylphenidate after single and repeated doses of MTS 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 MTS has not been defined.

##### **Age**

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

##### **Renal and Hepatic Insufficiency**

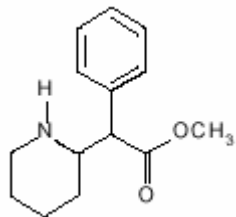
The pharmacokinetics of methylphenidate after administration of MTS has not been studied in patients with renal or hepatic insufficiency.

## **2. INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Methylphenidate Transdermal System is an adhesive-based matrix transdermal patch system (patch) provides continuous systemic delivery of methylphenidate, a central nervous system (CNS) stimulant, during application to intact skin. The chemical name for methylphenidate is *d,l* (racemic) methyl-alpha-phenyl-alpha-(2-piperidyl)-acetate. 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<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>. The structural formula of methylphenidate is:



### Patch Components and Performance

Each once-a-day [TRADEMARK] is designed to release methylphenidate continuously for at least 16 hours when in contact with intact skin. The total dose delivered is dependent on the patch size and wear time. identical.

Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch** (mg)
10	1.1	12.5	27.5
16	1.8	18.75	41.3
20	2.2	25	55.0
27	3.0	37.5	82.5

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

\*\*Methylphenidate content in each patch.

## 2.2 Currently Available Treatments for the Indication (ADHD)

Several immediate release methylphenidate formulations are currently marketed for the treatment of Pediatric ADHD: Methylphenidate HCl, Ritalin, Methylin, and Focalin. There are also various amphetamine formulations (e.g. ADDERALL, ADDERALL XR, etc). Three long acting methylphenidate formulations are currently available and approved for once daily dosing in the treatment of pediatric ADHD: 1) Ritalin LA, 2) Concerta, 3)Metadate CD and 4) Methylin ER. All these formulations combine extended and immediate release (ER, IR) components resulting in different release patterns. Ritalin LA produces greater exposure to MPH and higher MPH concentrations during the first 6 hours post dosing, a time of great importance in the school day [the first peak concentration (C<sub>max</sub>), and time to the first peak (T<sub>max1</sub>) is reached in 1-3 hours]. Concerta peaks after 1-2 hours then increases gradually over the next several hours with a C<sub>max</sub> of 6.8 hours. Metadate has an early peak concentration about 1.5 hours after dose intake, and a second peak concentrations (median) about 4.5 hours after dose intake. Methylin ER has duration of action of approximately 8 hours.

MTS is supposed to have an advantage to current formulations by providing a once daily administration, hence, minimizing problems associated with taking oral MPH immediate release during the school day. There is no other current transdermal formulations.

### **2.3 Important Issues with Pharmacologically Related Products**

Immediate and sustained oral formulations of methylphenidate and other stimulants have been associated with insomnia, anorexia, weight loss, decreased growth, abdominal pain and hypertension.

### **2.4 Presubmission Regulatory Activity & Other Relevant Background Information**

Noven Pharmaceuticals, Inc. (Noven) submitted an Investigational New Drug Application (IND 54,732) for its Methylphenidate Transdermal System (MTS) on December 12, 1997. On June 27, 2002, Noven submitted an original New Drug Application (NDA 21-514) for MTS for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). On April 25, 2003, the Division issued an action letter concluding that the NDA was not approvable. The letter specified the deficiencies and problems in Noven's application. Noven met with the Division on May 15, 2003 to discuss these deficiencies.

On October 10, 2003, Noven submitted to its IND a Request for Special Protocol Assessment, seeking the Division's comment on a proposed clinical study (SPD485-301) designed to address those clinical deficiencies identified in points 1 and 2 of the not approvable letter. On November 26, 2003, the Division provided comments and found that the proposed study did not adequately address FDA's concerns.

On March 1, 2004 Noven requested a Type C meeting to obtain further Division input on its proposed development plan to address the issues raised in the not approvable letter and subsequent correspondence related to that letter. The Type C meeting was held on May 26, 2004. At that meeting, participants from both Noven and its co-development partner, Shire Development Inc. (Shire), gained Division concurrence with the sponsors' proposal to pursue three new Phase II/III studies that would produce data that could address FDA's concerns.

After initiation of these new clinical studies, Noven requested a second Type C meeting with the Division. FDA granted that request on January 5, 2005 and scheduled the meeting for April 5, 2005. At this meeting, the sponsors discussed their plans for a Type 2 Resubmission and gained Division concurrence to proceed with a mid-2005 submission.

### **Non-Approvable Items in Response to the Original MTS NDA Submission**

The Division specified a number of problems and deficiencies in the NDA submission which constituted non-approvable items. The Division had several concerns regarding

safety, tolerability, and drug exposure during treatment with methylphenidate transdermal system. The Division's concerns and comments are specified below:

Actual NA Letter (4/25/03):

Clinical Issues

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 Statistics**

The statistics review was completed by Fanhui Kong, Ph.D. In summary, Dr. Kong concluded that the sponsor demonstrated the efficacy of MTS in Study 201 and Study 302. He duplicated the sponsor's efficacy analyses in both studies. For details, please refer to Dr. Kong's statistics review.

#### **3.2 Biopharmaceutics**

The results of the Biopharmaceutics review are currently not available.

#### **3.3 Controlled Substance Staff-**

The results of the Controlled Substance Staff review are currently not available.

#### **3.4 Dermatology**

The results of the dermatology review are currently not available.

### **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

#### **4.1 Sources of Clinical Data**

For Study 201, sources of clinical data include the 201 Study Report, the Integrated Summary of Safety, including text and data tables, and data from JMP files. Similarly, for Study 302, sources of clinical data include the 302 Study Report, the Integrated Summary of Safety, including text and data tables, and data from JMP files. For Study 303, sources of data included the Safety Update.

#### **4.2 Review Strategy**

The review focused on all of the efficacy and safety data from the pivotal studies in this submission, Study 201 and Study 302. The review also focused on interim safety data from the open-label extension study, Study 303.

#### **4.3 Data Quality and Integrity**

The quality and integrity of the data were acceptable.

#### **4.4 Compliance with Good Clinical Practices**

It appears that the studies were conducted in compliance with Good Clinical Practices.



## 4.5 Financial Disclosures

Financial disclosures were provided for the investigators who participated in the clinical studies. It does not appear that there were any significant financial conflict of interest.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The pharmacokinetics of MTS have been studied in healthy adult subjects and in ADHD patients 6 to 16 years old.

#### Absorption

MTS continuously releases methylphenidate that is transported across intact skin leading to therapeutic circulating levels of *d*- and *l*-methylphenidate during the application period. Residual methylphenidate remains in used patches when worn as recommended. The amount of methylphenidate absorbed systemically is a function of both wear time and the patch surface area.<sup>3</sup> In patients with ADHD, peak plasma levels of methylphenidate are reached at about 9 hours after single <sup>4</sup> and 8 hours after repeat <sup>5</sup> patch applications (12.5 cm<sup>2</sup> to 37.5 cm<sup>2</sup>) of MTS worn up to 9 hours. Plasma concentrations for *d*-methylphenidate increase throughout the wear-time. After first patch application, concentrations at 2, 4, and 6 hours were, on average, 7%, 42%, and 66%, respectively, of C<sub>max</sub>, independent of dose. On repeat dosing, higher concentrations are observed earlier in the profile. Thus at 2, 4.5, and 6 hours after patch application, they were, on average, 29%, 71%, and 78%, respectively, of C<sub>max</sub>, independent of dose. The mean pharmacokinetic parameters of *d*-methylphenidate from a repeated dosing study in ADHD patients (6 to 12 years old) are summarized in Table 1.

**TABLE 1<sup>7</sup>**  
**Mean ± SD Plasma *d*-Methylphenidate**  
**Pharmacokinetic Parameters After Repeated 9-Hour**  
**Applications of [TRADEMARK] for 7 Days**

Parameters	12.5 cm <sup>2</sup> (N = 7)	18.75 cm <sup>2</sup> (N = 32)	25 cm <sup>2</sup> (N = 27)	37.5 cm <sup>2</sup> (N = 8)
C <sub>max</sub> (ng/mL)	20.0 ± 11.1	23.9 ± 8.9	30.5 ± 16.0	46.5 ± 27.3
T <sub>max</sub> (hrs) <sup>a</sup>	7.1 (4.3 – 8.8)	8.0 (5.7 – 11.8)	8.8 (5.8 – 11.7)	8.8 (7.3 – 10.3)
AUC <sub>0-4</sub> (ng·hr/mL)	139 ± 95.2	171 ± 78.1	225 ± 139.0	332 ± 254.0

<sup>a</sup>Median (range)

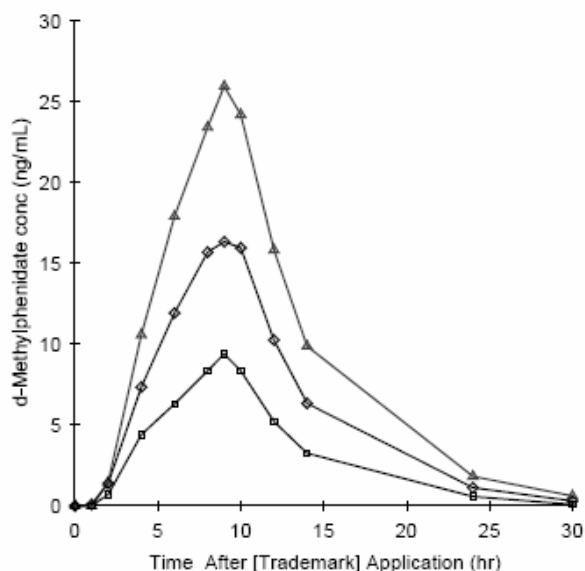
Comparable values for *l*-methylphenidate were 27% to 45% lower, on average, than for *d*-methylphenidate on multiple dosing. The terminal elimination half-life (t<sub>1/2</sub>) of *d*-methylphenidate from plasma was approximately 3 to 4 hours after removal of the patch (after wear times of 8 to 10 hours), and was independent of patch size. Comparisons

of  $C_{max}$  values after single and repeated doses of MTS indicate 71 to 104 % accumulation of d-methylphenidate with repeated dosing.

### Dose Proportionality

Following a single 9-hour application of MTS patch sizes of 12.5 cm<sup>2</sup> to 37.5 cm<sup>2</sup> to 34 children with ADHD,  $C_{max}$  and  $AUC_{0-t}$  of d-methylphenidate were proportional both to the patch surface area and to the apparent dose.<sup>11</sup> Mean plasma concentration-time plots are shown in Figure 1.  $C_{max}$  of l-methylphenidate was also proportional both to the patch surface area and to the apparent dose.  $AUC_{0-t}$  of l-methylphenidate was only slightly greater than proportional both to patch surface area and to apparent 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 [TRADEMARK] 12.5 (□), 25 (◇) and 37.5 (△) cm<sup>2</sup> Patch Sizes**



### Distribution

Methylphenidate plasma concentrations in children with ADHD decline in a multiphasic manner upon removal of MTS.

### Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity. In children, the metabolism of methylphenidate after once-daily administration of MTS, as evaluated by metabolism to ritalinic acid, is similar to that of oral methylphenidate given three times per day.

The mean elimination  $t_{1/2}$  from plasma of *d*-methylphenidate after removal of MTS in both children and adults was approximately 3 to 4 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.

### **Food Effects**

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

### **Adhesion**

In multiple clinical trials, the majority of patches remained on patients throughout treatment days with an average of =90% of the patch surface remaining on the skin.<sup>17</sup> No patients discontinued therapy during clinical trials due to adhesion failure.

### **Special Populations**

#### **Gender**

The pharmacokinetics of methylphenidate after single and repeated doses of MTS 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 MTS has not been defined.

#### **Age**

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

#### **Renal and Hepatic Insufficiency**

The pharmacokinetics of methylphenidate after administration of MTS has not been studied in patients with renal or hepatic insufficiency.

## **5.2 Pharmacodynamics**

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 monoamines into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space.

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

## **6 INTEGRATED REVIEW OF EFFICACY for STUDY 201**

### **6.1 Indication**

The proposed indication for Methylphenidate Transdermal System (MTS) is the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (ages 6 to 12 years).

### **6.2 Study Design**

#### **SPD485-201: Phase II Analog Classroom Study**

##### **Description of Study Design**

Study SPD484-201 (201) was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, analog classroom, crossover efficacy and safety study of Methylphenidate Transdermal System (MTS) in pediatric subjects (age 6- 12) with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD). The study began with a 5-week, open-label dose optimization study, followed by a 2-week double-blind, placebo-controlled crossover phase. In the controlled crossover phase, each subject had one week of MTS treatment and one week of placebo treatment. Patch sizes used throughout all phases of the study included 12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup> , and 37.5cm<sup>2</sup> patch sizes).

##### **Primary Study Objective**

The primary objective of was to evaluate, under controlled conditions at multiple time points throughout the day, the behavioral effects of treatment (MTS compared to placebo) as measured by the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) department scale in children (aged 6-12) diagnosed with ADHD (as per DSM-IV-TR criteria.

##### **Secondary Objectives**

The main secondary objective was to assess the duration of efficacy of MTS compared to placebo in children with ADHD using the Permanent Product Measure of Performance; age-adjusted math test (PERMP) administered at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application/dosing in a controlled environment.

##### **Safety Objectives included:**

- Evaluation of treatment on adverse events, blood pressure, heart rate, weight, physical examination, ECG parameters, clinical laboratory parameters
- Assessment of sleep parameters using the Child's Sleep Habits Questionnaire (CSHQ)
- Assessment of skin tolerance to MTS using the Dermal Evaluation and Response Scale.

##### **Pharmacokinetic/Pharmacodynamic Objectives:**

- To evaluate the pharmacokinetic parameters of MTS by measurement of plasma *d*-MPH and *l*-MPH concentrations and analysis by non-compartmental methods.

- To assess the relationship between the pharmacokinetics of *d*-MPH and the response measures (e.g. SKAMP and PERMP) during the Analog Classroom day.
- To evaluate the relationship between plasma *d*-MPH concentrations and measurements of vital signs (blood pressure and heart rate).
- To assess the potential relationship between adverse events and MPH plasma exposure.

### **Screening and Washout Period**

Subjects were screened for approximately 2 weeks prior to washout (up to a maximum of 28 days). The washout schedule for prior prohibited medications is in Appendix....

### **Open-Label Dose Optimization Period:**

The objective of this 5-week period was to ensure subjects were titrated to an optimal dose of MTS, using 12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup>, and 37.5cm<sup>2</sup> patch sizes. The decisions regarding dose titrations were based upon the investigator's review of parent rating forms, adverse event reporting, and clinical judgment (using the ADHD-RS-IV). All subjects were initiated on the MTS 12.5cm<sup>2</sup> size patch (1/day) and were evaluated after one week (7 ± 3 days) for tolerability and effectiveness. The approximate duration of MTS patch wear was 9 hours per day; a new patch was applied each morning upon awakening. Subjects were titrated to the next patch size after a minimum of one week on the previous patch size. Subjects may have been titrated back down to the previous patch size to optimize tolerability. Subject response was categorized by the investigator into one of the following three conditions:

1. **Intolerable condition:** (unacceptable safety profile): Subject had their dose decreased to a smaller MTS patch size (if available). If the lower patch size was not tolerable, the subject was discontinued from the study.
2. **Ineffective condition:** (< 25% change in ADHD-RS score with acceptable safety profile): The MTS patch size was increased to the next available dose strength followed by weekly evaluation.
3. **Acceptable condition:** Significant reduction in ADHD symptoms with minimal adverse effects.

Subjects who had not reached an acceptable patch size by Visit 7 were withdrawn from the study.

During the last visit of the Dose Optimization period, Visit 7, there was a half-day practice Analog Classroom to allow subjects to become acquainted with each other, with study staff, and with the specific schedule and procedures of the classroom. It was recommended that the practice Analog Classroom consist of a minimum of two cycles, starting with the 0615 check-in planned according to Text Table 3. This visit also involved practice dosing with the subject's acceptable MTS patch.

**Double-Blind, Crossover, Analog Classroom Period:**

Following completion of the Dose Optimization period, subjects were randomized (in a 1:1 ratio) to a sequence of one week of treatment with each of MTS and PTS. The total duration of this period was 2 weeks. Each end of week assessment included measurement of behavioral effects and plasma collection, and occurred in the controlled environment of the Analog Classroom. During scheduled classroom visits, subjects arrived at the study site at approximately 6:15 A.M and were dismissed at approximately 7:30 P.M.

The first Analog Classroom session, Visit 8, was held on the Saturday following the first week of double-blind treatment. The second Analog Classroom session, Visit 9, was held 1 week later. Subjects and their parent/legal guardian's were reminded to bring their double-blind treatment to the visit, as site staff would be supervising the MTS/PTS application during the visit.

**Follow-up Period:**

At the End of Study/Early Termination Visit (Visit 9), eligible subjects had the option to enroll into an open-label extension study (protocol SPD485-303). Subjects who did not enroll into the open-label extension study (protocol SPD485-303) at the End of Study/Early Termination Visit (Visit 9) were followed for 30 days (+2 days) after their last dose of study drug.

Subjects who did not enroll into the extension were followed to monitor safety post-discontinuation. A telephone contact occurred at approximately 30 days ( $\pm 2$  days) following the last dose of investigational product to collect information on ongoing AEs and serious adverse events (SAEs) and to collect any new related AEs and any new onset SAEs. This information was documented in the source, and the clinical and safety databases were updated prior to database lock, if necessary.

**Test product, dose and mode of administration:**

MTS was provided as 27.5mg/12.5cm<sup>2</sup>, 41.3mg/18.75cm<sup>2</sup>, 55mg/25cm<sup>2</sup>, and 82.5mg/37.5cm<sup>2</sup> patch sizes, to deliver *d,l* (*threo*)-methylphenidate transdermally at a continuous rate upon application to intact skin. MTS was applied to a clean, dry, non-oily and non-irritated site on the hip of each subject. Initial placement on the left or right side was up to the subject or caregiver. Subsequent applications were alternated to the opposite side so that the same site was not used for two consecutive applications.

**Selection of doses in the study**

The MTS patch sizes in this study, 27.5mg/12.5cm<sup>2</sup>, 41.3mg/18.75cm<sup>2</sup>, 55mg/25cm<sup>2</sup>, and 82.5mg/37.5cm<sup>2</sup> MPH/patch size), were designed to deliver *d,l* (*threo*)-MPH transdermally at a continuous rate upon application to intact skin. Selection of these MTS patch sizes was based on two pharmacokinetic (N17-005, N17-006), one proof-of-concept with a PK component (N17-002), and two double-blind, placebo-controlled phase III studies (N17-010, N17-018) previously conducted in pediatric subjects with ADHD.

### Key Subject Selection Criteria

Eligible subjects were male or female children aged 6 to 12 years, who met the DSM-IV-TR criteria for a primary diagnosis of ADHD. All eligible subjects had blood pressure measurements within the 95th percentile, had no comorbid illness that could affect safety or tolerability, and had no comorbid psychiatric diagnosis except Oppositional Defiant Disorder (ODD).

### Number of subjects (total and for each treatment arm):

As shown in Table I below, ninety-three subjects were enrolled into the Open-Label Dose Optimization period. Following completion of the dose-optimization period, 80 subjects were randomized, in a 1:1 sequence ratio (MTS/PTS:PTS/MTS), into the double-blind crossover Analog Classroom period.

### Disposition of Subjects in Study 201

Parameter	Treatment Sequence		Total
	MTS/PTS	PTS/MTS	
Enrolled (O-L)	NA	NA	93
DC before random.	NA	NA	13
Randomized (D-B)	42	38	80
Discontinued D-B)	1	0	1
Completed	41	38	79
ITT	41	38	79
PP	31	25	56
PK	NA	NA	74
Safety Population	NA	NA	93

### 6.3 Efficacy Results and Conclusions- Study 201

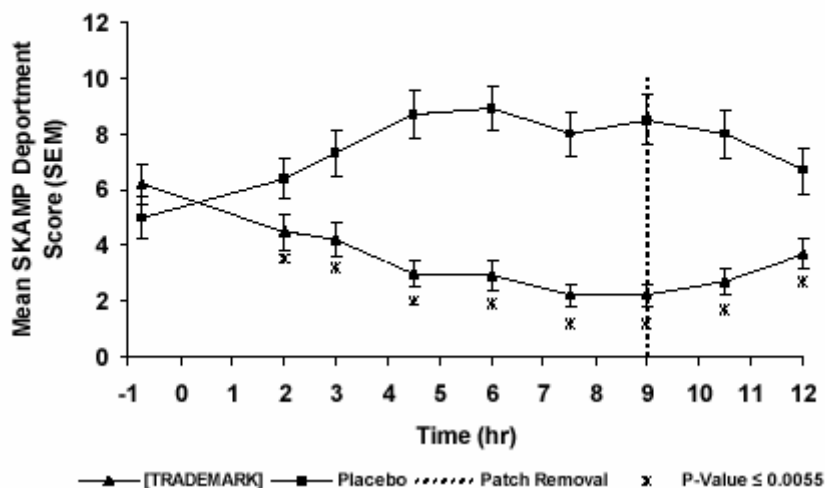
In Study 201, the primary efficacy endpoint was the change from baseline in the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) department scale, which is an appropriate efficacy measure for a trial in subjects with ADHD. The SKAMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS. Subscale scores for department, attention and quality of work were evaluated at each time point to assess the duration of effect of MTS vs. placebo. Using the ITT data set provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint and he derived the same p-values. The results are depicted in Table 3.1.1.5.

**Table 3.1.1.5 Analysis of Mean SKAMP Department Score during Patch Application (Hours 2.0 – 9.0): ITT Population**

	MTS (N=79)	Placebo (N=79)	p-value
Mean (SD)	3.2 (3.64)	8.0 (6.33)	
LS Mean (SE)	3.2 (0.58)	8.0 (0.58)	<0.0001 <sup>a</sup>
Difference and 95% CI of LS Means (MTS-Placebo)	-4.8 (-5.89, -3.63)	NA	

<sup>a</sup>: The p-value is obtained using the mixed effects model.

**FIGURE 2<sup>22</sup>**  
**Mean SKAMP Department Score by Timepoint After Administration of [TRADEMARK]**



## 7 INTEGRATED REVIEW OF SAFETY- STUDY 201

### 7.1 Deaths

There were no deaths in Study 201 in the open-label or the controlled phases.

### 7.2 Serious Adverse Events

There were no serious adverse events reported in Study 201 for either the open-label or controlled phases of the study.

### 7.3 Discontinuations Due to Adverse Events

Eight subjects were discontinued from the study early due to adverse events. Seven subjects discontinued during the open-label dose optimization phase, and one subject discontinued during the placebo-controlled phase. Reasons for discontinuation included tic (2 cases), rash at application site (2 cases), decreased appetite (2 cases), elevated blood pressure, weight loss, and mood lability (all in a single subject) and prolonged QT interval.



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

Tic was the reason for discontinuation in 2 cases and was attributed to MTS treatment. Neither subject had a history of tic disorder. A seven-year-old boy (01-012) developed a vocal tic after 7 days of open-label treatment. He had not received previous treatment with stimulant medication. The tics were considered due to MTS treatment, and treatment was discontinued. During a 30-day follow-up call, the subject’s vocal tics had reportedly resolved. A six-year-old girl (02-007), without a history of tic disorder, developed a tic (involuntary eye movement) after 2 days of MTS treatment. The tic was thought to be due to MTS treatment, and treatment was discontinued after 5 days of treatment. At the 30-day follow-up, the tic had not resolved, but the AE apparently resolved within 2- 3 months of onset.

In the 2 cases of rash (at application site), the rash was attributed to MTS treatment. In one case, the subject (02-015) was treated with hydrocortisone on the 12<sup>th</sup> day of MTS treatment. On the 15<sup>th</sup> day, the subject developed erythema, papules, and edema at 2 different patch application sites. The subject was discontinued on the 16<sup>th</sup> day of treatment. Reportedly, the rash had resolved approximately 3 weeks after study discontinuation.

Subject 02-023 developed a rash at the application site 15 days after beginning MTS treatment. Six days later, the subject was treated with hydrocortisone and diphenhydramine. At the end of the study, the subject continued to have a considerable reaction spreading beyond the patch sites bilaterally.

Subject 05-007 reported the AE, decreased appetite on Day 7 of MTS treatment. The AE was attributed to MTS treatment. The decreased appetite resolved approximately 4 days after discontinuing treatment. The subject’s weight decreased from 62.5 kg at baseline to 61 kg at week 2. Subject 05-012 experienced decreased appetite on Day 4 of treatment. The decreased appetite was attributed to MMTS treatment, and treatment was discontinued on Day 9. The subject did not experience significant weight loss, and the decreased appetite resolved.

Subject 02-024 was discontinued due to an elevated QTc interval. This 7-year-old girl had QTc values and heart rate as illustrated in the table below. She did not have a history of cardiac or cardiovascular disease.

Study Visit	QTcB (msec)	QTcF (msec)	Heart Rate (bpm)
Screening	438	425	72
Baseline	466	430	97
EOS-ET	474	434	102

At baseline, the subject had a prolonged QTc value (QTcB= 466 msec and QTcF= 430 msec) thought to be unrelated to study drug treatment. At the end of study, the QTcB interval was 474msec and the QTcF was 434 msec. The investigator decided to discontinue study drug treatment due to the elevated QTc values. The length of exposure was 10 days. No further adverse events were reported at the 30-day follow-up call. An additional follow-up call confirmed that the adverse event of elevated QTc value was resolved. During a follow-up contact in, the parents reported that a follow-up ECG with another physician in January 2005 was completely normal.

Subject 01-014 discontinued from the study due to elevated blood pressure, affective lability, and weight loss. Elevated blood pressure (146/83) was reported on Day 39. The baseline blood pressure was 100/62. The table below presents the subject's blood pressure measurements throughout the study. From the pattern of blood pressure measurements, it appears that the elevated blood pressure may be related to study drug treatment.

Moodiness was also reported on Day 39. The investigator concluded that the elevated blood pressure was possibly related to MTS treatment. The moodiness was thought to be possibly related to MTS treatment. The decreased weight was attributed to treatment with MTS. The subject's weight at baseline was 66 lbs. and 63.6 lbs. at the end of the study. At the 30-day follow-up call, it was reported that the weight loss and increased moodiness had resolved. The elevated blood pressure was unresolved at end of study and at the 30-day follow-up call.

#### 7.4 Common Adverse Events

Generally, in the open-label phase, the most commonly reported AE with short-term MTS treatment for all subjects (regardless of patch size titration) were the type that would be expected with methylphenidate. However, the finding of tic disorder (2%) during short-term stimulant treatment was somewhat unexpected. In addition, the commonly reported AE occurred in a relatively high proportion of subjects. Anorexia was reported for 29%, insomnia was reported for 16 %, headache was reported for 12%, nausea or vomiting was reported for 10%, and abdominal pain was reported for 8% of subjects. Irritability, anger, or lability was reported for 15% of subjects. In addition, significant rash at the application site was reported for 3% of subjects. Although there was no placebo group for comparison in this phase, it is reasonable to conclude that the majority of these commonly reported AE were related to treatment with MTS, since such AE were commonly reported in previous MTS studies, and these AE are commonly reported with stimulant treatment in general. In this reviewer's opinion, the type and degree of these common adverse events are clinically significant, and they could pose a significant safety risk in children treated with MTS. In seven cases, these AE resulted in the subject's discontinuation from the study. There were 2 discontinuations due to tics, 2

discontinuations due to anorexia, 2 discontinuations due to rash at application site, one discontinuation due to elevated blood pressure.

**Most Commonly Reported AE in Open-label MTS Phase**

Adverse Event	All subjects in O-L Phase N= 93
Anorexia/decreased appetite	27 (29)
Insomnia	15 (16)
Headache	11 (12)
Nausea/vomiting	9 (10)
Abdominal pain	7 (8)
Irritability/anger/lability	14 (15)
Tic	2 (2)
Weight loss	2 (2)
Tremor	2 (2)
Rash, application site	3 (3)
Blood pressure elevated	1 (1)
Tachycardia	1 (1)
QT interval prolongation	1 (1)

**Commonly Reported AE During the Placebo-controlled Crossover Phase**

The most commonly reported AE that were expected included nausea (3.8%), anorexia (2.5%), elevated blood pressure (2.5%), and headache (3.8%). The proportions of subjects reporting these AE were relatively low, compared to the open-label phase. This was probably due, in part, to the fact that some subjects had discontinued due to adverse events before the controlled phase. In addition, some subjects may have become tolerant to the adverse effects of MTS. The importance of the finding of lymphadenopathy in MTS-treated subjects is currently unclear.

**Table 28: Most Commonly Reported TEAEs (≥2% of Subjects)- Analog Classroom Period, Safety Population**

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

## 7.5 Weight Findings

From the beginning of the open-label MTS phase to the end of the placebo-controlled crossover phase (over a total of 7 weeks), both treatment groups (MTS/PTS and PTS/MTS) had a decrease in mean weight. Through the end of week 1 (Visit 8) of the analog classroom phase, the change in mean weight was -2.2 lbs (-8.9, 2.0) for the MTS group and -0.6 lbs (-7.5, 3.5) for the PTS group. At the end of the analog classroom period (Visit 9), the change in mean weight was -1.3 lbs (-11.6, 4.0) for the MTS group, and -0.6 lbs (-5.5, 6.0) for the PTS group. Thus, there was a consistent mean weight loss during the short-term study. The clinical significance of this finding is unclear. During chronic use of MTS, it is possible that exposed patients could experience more pronounced weight loss.

Z-scores for height, weight and BMI at Screening and at Visit 9 are presented in the table below. The mean z-score for weight did not change appreciably between the visits. The mean z-score for height was higher at Visit 9 than Screening in the PTS/MTS group. Mean z-scores for BMI appeared to be higher at Visit 9 than Screening for both treatment sequence groups.

Summary of Z-Scores: All Enrolled Subjects in Study 201						
Z-Score	Statistic		Treatment Sequence			Overall (N=93)
			TPR (N=13)	MTS/PTS (N=42)	PTS/MTS (N=38)	
<b>Weight</b>	Screening	N	10	41	38	89
		Mean (SD)	-0.41 (1.277)	-0.11 (0.995)	0.04 (0.751)	-0.08 (0.935)
		Median	0.05	-0.08	-0.03	-0.06
	Visit 9 (Wk7)/ EOS /ET	Min, Max	-2.5, 1.5	-2.2, 2.2	-1.7, 2.2	-2.5, 2.2
		N	10	41	38	89
		Mean (SD)	-0.39 (1.315)	-0.16 (0.998)	-0.07 (0.765)	-0.15 (0.941)
	Median	0.01	-0.13	-0.15	-0.14	
	Min, Max	-2.6, 1.6	-2.1, 2.0	-1.5, 2.0	-2.6, 2.0	
<b>Height</b>	Screening	N	10	41	38	89
		Mean (SD)	-0.07 (1.048)	-0.14 (0.914)	0.03 (0.810)	-0.06 (0.880)
		Median	-0.13	-0.14	0.06	-0.06
	Visit 9 (Wk 7)/ EOS /ET	Min, Max	-1.6, 1.5	-2.0, 1.4	-1.5, 2.6	-2.0, 2.6
		N	10	41	38	89
		Mean (SD)	-0.08 (1.077)	-0.14 (0.927)	0.11 (0.980)	-0.03 (0.963)
	Median	-0.23	-0.26	-0.02	-0.07	
	Min, Max	-1.7, 1.4	-1.9, 1.5	-1.4, 3.3	-1.9, 3.3	
<b>BMI</b>	Screening	N	10	41	38	89
		Mean (SD)	-0.56 (1.236)	-0.04 (1.077)	0.04 (0.854)	-0.07 (1.011)
		Median	-0.65	0.06	0.08	0.06
	Visit 9 (Wk 7)/ EOS /ET	Min, Max	-2.4, 1.5	-2.6, 2.2	-1.7, 2.1	-2.6, 2.2
		N	10	41	38	89
		Mean (SD)	-0.50 (1.260)	-0.12 (1.076)	-0.23 (1.077)	-0.21 (1.091)
	Median	-0.40	0.05	-0.10	-0.17	
	Min, Max	-2.4, 1.4	-2.3, 2.1	-3.4, 1.9	-3.4, 2.1	

## 7.6 Vital Signs Findings

There were few significant effects of MTS treatment on vital sign parameters in this study. There were no significant differences in mean diastolic blood pressure, systolic blood pressure, or heart rate. The sponsor acknowledges that heart rate often increased in subjects shortly after patch application. In the open-label phase, one subject (1%) had significantly elevated blood pressure. During the placebo-controlled phase, 2.5% of subjects in the MTS group had elevated blood pressure (compared to 0% in the placebo group). Of note, one subject discontinued due to elevated blood pressure. The elevations were thought to be due to MTS treatment.

## 7.7 Sleep Findings

In the open-label phase of MTS treatment, 16% had the AE, insomnia reported. In addition to AE reporting, the sponsor conducted a prospective, directed assessment of sleep functioning. The instrument used was the Child's Sleep Habits Questionnaire (CSHQ). The CSHQ is a directed assessment of numerous items related to sleep function. It is designed to screen for the most common sleep problems in children aged 4 to 12. It assesses sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The CSHQ has 33 questions, responses range from 1 (rarely occurring) to 3 (usually occurring) with total scores ranging from 33 to 99. The specific CSHQ items are listed below.

1. Child goes to bed at the same time at night
2. Child falls asleep within 20 minutes after going to bed
3. Child falls asleep alone in own bed
4. Child falls asleep in parent's or sibling's bed
5. Child needs parent in the room to fall asleep
6. Child struggles at bedtime (cries, refuses to stay in bed)
7. Child is afraid of sleep in the dark
8. Child is afraid of sleeping alone
9. Child sleeps too little
10. Child sleeps the right amount
11. Child sleeps about the same amount each day
12. Child wets the bed at night
13. Child talks during sleep
14. Child is restless and moves a lot during sleep
15. Child sleepwalks during the night
16. Child moves to someone else's bed during the night (parent, brother, sister, etc)
17. Child grinds teeth during sleep
18. Child snores loudly
19. Child seems to stop breathing during sleep
20. Child snorts and/or gasps during sleep
21. Child has trouble sleeping away from home (visiting relatives, vacation)
22. Child awakens during night screaming, sweating and inconsolable
23. Child awakens alarmed by a frightening dream
24. Child awakes once during the night
25. Child awakes more than once during the night
26. Child wakes up by him/herself (r)
27. Child wakes up in negative mood
28. Adults or siblings wake up child
29. Child has difficulty getting out of bed in the morning
30. Child takes a long time to become alert in the morning
31. Child seems tired
32. Watching TV
33. Riding in a car

The results of CSHQ assessments at the end of the open-label Dose Optimization Period, with the exception of the subjects who discontinued before randomization to the double-blind Analog Classroom Periods, are presented in the table below. A higher score represents a greater degree of sleep problems. By Week 5, the CSHQ mean total score and the number of items identified as problems had decreased in most dosing groups. However, the analysis did not take into account those subjects who discontinued during this open-label phase. Furthermore, in my opinion, the use of the CSHQ, which uses a number of items, may obscure the extent of the problem with insomnia in these studies,

since many of the items do not appear to be directly relevant to the sleep problems specific to stimulant treatment. The most relevant items pertain to initial, middle, and terminal insomnia as well as sleep duration and quality. Use of the CSHQ may dilute possible clinically important adverse events related to insomnia.

Parameter	Baseline (Week 0)	Visit 7 (Week 5)			
	Pre-dose	Patch Size			
	n=92	12.5cm <sup>2</sup> n=9	18.75cm <sup>2</sup> n=35	25.0cm <sup>2</sup> n=28	37.5cm <sup>2</sup> n=9
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
CSHQ Score	45.9 (9.81)	N/A			
Items Identified as a Problem	3.0 (4.28)	N/A			
Change from Baseline		1.0 (9.99)	-0.9 (8.93)	-1.0 (6.14)	-4.0 (4.92)
Change in Items Identified as a Problem	N/A	-1.4 (3.71)	-1.6 (3.42)	-0.8 (4.24)	-1.8 (3.23)

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

During the Analog Classroom Period, CSHQ analysis indicated small decreases in the mean CSHQ, as well as the mean number of sleep problems identified.

## 7.8 Laboratory Findings

### Hematology

Three subjects had treatment-emergent abnormal hematology values. Two subjects had eosinophil values greater than 10%, and one subject had a platelet count less than 75.0GI/L. Apparently, none of these subjects had clinical symptoms related to these abnormalities. Three subjects had abnormal hematology results reported as AEs. One subject (01-012), who was discontinued prior to randomization (MTS 12.5cm<sup>2</sup> treatment) had an abnormal lymphocyte morphology, assessed by the Investigator as mild in intensity and unrelated to study drug. Subject 01-014 had an increased lymphocyte count at screening that was reported as resolved. This subject was subsequently randomized to the PTS/MTS (18.75cm<sup>2</sup>) treatment sequence and had no subsequent

laboratory abnormalities reported. Subject 01-015 (MTS/PTS, 12.5cm<sup>2</sup>) had a decreased neutrophil count at screening, and increased creatinine, eosinophil, and lymphocyte counts at Visit 8.

### Serum Chemistry

Three subjects had treatment-emergent abnormal chemistry values. Two subjects had serum potassium values greater than 5.5mmol/L, and one subject had a serum potassium value of less than 3.0mmol/L. One subject had a calcium value of less than 2.10mmol/L, and one subject had a serum sodium value of greater than 150mmol/L. Six subjects had abnormal chemistry results reported as AEs. The most common abnormalities were reported for calcium and glucose levels. Increased calcium levels of mild intensity and possibly related to study drug were reported for subjects 01-002 (Visit 8, MTS/PTS, 37.5cm<sup>2</sup>) and 01-010 (Visit 9, MTS/PTS, 18.75cm<sup>2</sup>). Increased glucose levels of mild intensity were reported for subjects 01-005 (Baseline, PTS/MTS, 12.5cm<sup>2</sup>, unrelated to study drug) and 01-009 (Visit 8, PTS/MTS, 12.5cm<sup>2</sup>, possibly related to study drug). Elevated transaminase and hypoglycemia, both of mild intensity and unrelated to study drug, were reported for subject 02-024 at screening. This subject was terminated prior to randomization at Visit 3 due to QTc prolongation. Elevated TSH (mild intensity, possibly related to study drug) was reported for subject 01-013 (Visit 8, PTS/MTS, 18.75cm<sup>2</sup>).

### 7.9 Dermatology Findings

At the end of the Dose Optimization Period (Visit 7), a significant proportion of subjects had evidence of erythema or irritation. Similarly, a significant proportion of subjects discomfort or pruritus at application sites. The table below presents the findings.

Table 21: Dermal Evaluations: Dose Optimization Period – Visit 7* (Study SPD485-201)				
Dermal Evaluation*	Patch Size			
	12.5cm <sup>2</sup> n (%)	18.75cm <sup>2</sup> n (%)	25.0cm <sup>2</sup> n (%)	37.5cm <sup>2</sup> n (%)
<b>Dermal Response Scale</b>				
Total Number of Application Sites Assessed	N=18	N=72	N=55	N=18
Application Sites With More Than Minimal Erythema (> 1 on Dermal Response Scale)	4 (22)	3 (4)	8 (15)	3 (17)
<b>Experience of Discomfort and Pruritus</b>				
Total Number of Application Sites Assessed	N=18	N=72	N=55	N=18
Application Sites With More Than Mild Discomfort (> 1 on Experience of Discomfort and Pruritus Scale)	4 (22)	1 (1)	4 (7)	0

During the Analog Classroom Period, a significant proportion of subjects had evidence of erythema or irritation at the application site. In the MTS group, 30% and 24% of subjects (at Week 8 and Week 9, respectively) had positive dermal findings, compared to the placebo group (3% and 6% at Weeks 8 and 9, respectively).



Dermal Evaluation	Visit 8		Visit 9	
	MTS n (%)	PTS n (%)	MTS n (%)	PTS n (%)
<b>Dermal Response Scale</b>				
Total Number of Application Sites Assessed	N=82	N=74	N=75	N=80
Application Sites With More Than Minimal Erythema (> 1 on Dermal Response Scale)	25 (30)	2 (3)	18 (24)	5 (6)
<b>Experience of Discomfort and Pruritus</b>				
Total Number of Application Sites Assessed	N=79	N=72	N=75	N=80
Application Sites With More Than Mild Discomfort (> 1 on Experience of Discomfort and Pruritus Scale)	0	0	2 (3)	0

These results indicate that patches containing MPH pose a significant risk of irritation. Several subjects were discontinued from the study due to rash as the application site.

### 7.10 Overdose Experience

There were no apparent cases of MTS overdose in the studies.

### Signs and Symptoms of Overdosage

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, coma, euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

### Recommended Treatment of MTS Overdosage

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 treatment may be required in order to maintain adequate circulation and respiratory exchange. External cooling procedures may be required for hyperpyrexia. The efficacy of peritoneal dialysis or extracorporeal hemodialysis for MTS overdosage has not been established.

### 7.11 Exposure- Populations Exposed and Extent of Exposure (201)

A summary of subject drug exposure for the Safety population is presented in the table below. During the Dose-Optimization and Analog Classroom periods of this study, the mean (SD) duration of MTS patch wear was 36.0 (9.85) days, with a range of 5.0 to 45.0 days. Percentages are based on the number of subjects in the Safety population. Please refer to Section 8.1.3 for details regarding apparent dose delivered.

## Length of Exposure in Study 201

Parameter	Statistic	MTS (N=93)
		Length of Exposure (days)*
Length of Exposure Category (days)		n (%)
≤ 7		5 (5.4)
8 - ≤ 14		2 (2.2)
15 - ≤ 21		3 (3.2)
22 - ≤ 28		1 (1.1)
29 - ≤ 35		6 (6.5)
36 - ≤ 42		58 (62.4)
43 - ≤ 49		18 (19.4)

The apparent dose of *d,l*-MPH and *d*-MPH administered via the MTS patch, based on the residual dose after patch removal, is summarized below in the table below.

Parameter	MTS Treatment			
	12.5cm <sup>2</sup> (N=7)	18.75cm <sup>2</sup> (N=36)	25cm <sup>2</sup> (N=28)	37.5cm <sup>2</sup> (N=8)
Nominal dose of <i>d,l</i> -MPH	27.5mg	41.3mg	55mg	82.5mg
Mean (range) apparent dose of <i>d,l</i> -MPH	12.3mg (6.6-19.8mg)	16.0mg (6.4-26.9mg)	22.1mg (9.1-39.3mg)	31.3mg (21.3-51.0mg)
Percentage of <i>d,l</i> -MPH delivered	45% (24-72%)	39% (15-65%)	40% (17-71%)	38% (26-62%)
Mean (range) apparent dose of <i>d</i> -MPH	6.2mg (3.3-9.9mg)	8.0mg (3.2-13.5mg)	11.1mg (4.6-19.7mg)	15.6mg (10.7-25.5mg)
Mean (range) apparent dose of <i>l</i> -MPH	6.2mg (3.3-9.9mg)	8.0mg (3.2-13.5mg)	11.1mg (4.6-19.7mg)	15.6mg (10.7-25.5mg)

The mean percentage of *d,l*-MPH delivered over the 9-hour dosing period was generally similar for all four patch sizes, ranging from 38% to 45% of the total nominal dose of *d,l*-MPH, although the inter-subject variability was high for each patch size. For each treatment, total apparent MPH dose (administered as a racemic mixture) comprised equal proportions of both *d*- and *l*-MPH.

## 8 INTEGRATED REVIEW OF EFFICACY- STUDY 302

### 8.1 Indication

The sponsor proposes the indication of Methylphenidate Transdermal System (MTS) in the treatment of children with Attention Deficit Disorder.

## 8.2 Study Design

Study SPD485-302 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, and active-comparator (Concerta) dose optimization study designed to evaluate the safety and efficacy of MTS (12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup>, and 37.5cm<sup>2</sup> patch sizes) compared to placebo and CONCERTA® in pediatric subjects diagnosed with ADHD. Subjects visited the study site nine times during the course of approximately 14 weeks.

The study consisted of three periods detailed below:

**Screening & Washout Period** – Subjects were screened for approximately 2 weeks prior to washout. Washout (if applicable) was up to 28 days depending upon the half-life of the subject's medication requiring washout.

### **Double-Blind Dose Optimization/Maintenance Period:**

Eligible subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA, or matching placebo (placebo patch or placebo capsule) and entered the double-blind dose optimization period. The objective of this period was to ensure subjects were titrated to at least an acceptable dose of MTS (using 12.5cm<sup>2</sup>, 18.75cm<sup>2</sup>, 25cm<sup>2</sup>, and 37.5cm<sup>2</sup> patch sizes) or CONCERTA (using 18mg, 27mg, 36mg, and 54mg dosage strengths) based upon investigator review of parent and teacher rating forms, adverse event reporting, and clinical judgment (using the ADHD-RS-IV). During one of the last three visits, Visit 7, 8 or 9, three venous blood samples were drawn at 7.5 hr, 9.0 hr, and 10.5 hr post dosing for Pharmacokinetic (PK) evaluation. The duration of this period was five weeks to allow for titration up to the highest dose and one titration down to a prior dose level, if necessary. No further titration up or down was permitted once subjects had been titrated down.

The duration of MTS or PTS (Placebo Transdermal System) patch wear was nine hours per day. A new patch was applied each morning at approximately 0700 hours. All subjects were initiated on the MTS/PTS 12.5cm<sup>2</sup> size patch (1/day) and the CONCERTA/matching placebo 18mg dose (1/day), and were evaluated after 1 week for tolerability and effectiveness. Titration to the next patch size/dosage strength was allowed after a minimum of 1 week on the previous size/dose based on the overall response of the subject. Additionally, subjects may have been titrated back down to the previous patch size/dosage strength (once) to optimize tolerability and effectiveness. Subject response was categorized by the investigator into 1 of 3 conditions and associated actions:

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

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

**Acceptable condition:** A response was defined as acceptable if a subject showed at least a 25% reduction in ADHD symptoms with minimal side effects. Investigators were to refer to the subject’s Baseline ADHD-RS-IV score to aid in dose adjustments. Subjects categorized as “acceptable” may have been maintained at their current dose for the remainder of the study (through Visit 7). Alternatively, the subject’s dose could have been increased to the next larger patch size/dosage size, if the current dose was well tolerated, and in the Investigator’s opinion the subject would potentially receive further symptom reduction through titration to the next patch size/dosage size. Visit 6 was the last visit at which titration could occur. No further titration was permitted after Visit 6. Subjects who did not reach at least an acceptable dose (i.e. “Acceptable condition”) by Visit 7, were withdrawn from the study.

Following successful titration to at least an acceptable dose of MTS or CONCERTA or Placebo by Visit 7, subjects maintained the dose through the 2-week maintenance period. Double-blind assessment of the safety and efficacy of MTS/PTS and CONCERTA/matching placebo occurred for two weeks.

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

### 8.3 Efficacy Findings and Conclusions

In Study 302, the primary efficacy endpoint was the change from baseline in mean clinician-rated ADHD-Rating Scale-IV (ADHD-RS-IV) among treatment groups (MTS, placebo TS, Concerta, and matching placebo). The ADHD-RS-IV is an appropriate efficacy measure for a trial in children with ADHD.

Using both the ITT and PP data sets provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint using both the LOCF and OC data sets, and he derived the same p-values. The results of ITT population analysis are given in the following table.

**Table 3.1.2.5 Analyses of the Change from Baseline of ADHD-RS-IV Total Score (ITT Population)**

	<b>MTS (N=96)</b>	<b>Concerta (N=89)</b>	<b>Placebo (N=85)</b>
<b>LOCF analysis</b>			
<b>N</b>	96	89	85
<b>Mean (SD)</b>	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
<b>LS Mean (SE)</b>	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
<b>Difference and 95% CI of LS Means (Active-Placebo)</b>	-13.89 (-18.06, -9.72)	-11.32 (-15.58, -7.06)	
<b>p-value</b>	<0.0001	<0.0001	

<b>OC Analysis</b>			
<b>N</b>	70	64	31
<b>Mean (SD)</b>	-29.8 (10.40)	-28.0 (11.13)	-22.4 (13.67)
<b>LS Mean (SE)</b>	-30.1 (1.21)	-27.2 (1.27)	-23.5 (1.83)
<b>Difference and 95% CI of</b>	-6.58	-3.77	
<b>LS Means (Active-Placebo)</b>	(-10.91, -2.24)	(-8.19, 0.66)	
<b>p-value</b>	0.0032	0.095	

## 9 INTEGRATED REVIEW OF SAFETY- STUDY 302

### 9.1 Deaths

There were no deaths reported in Study 302

### 9.2 Serious Adverse Events

There were no serious adverse events reported in Study 302.

### 9.3 Discontinuations Due to Adverse Events

Eleven subjects experienced AEs that led to study discontinuation. Seven subjects (7.1%) in the MTS group, three subjects (3.3%) in the CONCERTA group, and one subject (1.2%) in the placebo group discontinued due to an AE. The AE leading to discontinuation are listed in the table below.

One subject in the MTS group discontinued due to tic. The AE was attributed to MTS treatment, and the tic was unresolved at the time of a 6-month follow-up call. Two subjects in the MTS group discontinued due to application site reactions. One of the subjects was treated with hydrocortisone. Other AE leading to discontinuation in the MTS group included headache, irritability, crying, confusional state, viral infection, and infectious mononucleosis.

Table 29: Summary of Adverse Events Leading to Discontinuation – Safety population (Study SPD485-302)				
Treatment	Subject ID	Gender/Age/Race	TEAE	Relationship
MTS	12-002	M/6/W	Tics	Probably
	15-002 <sup>†</sup>	M/9/W	Application site reaction	Probably
	19-003 <sup>†</sup>	F/9/W	Application site erythema	Probably
	28-019 <sup>†</sup>	M/7/W	Headaches	Possibly
	29-010 <sup>†</sup>	M/10/W	Irritability	Possibly
			Crying	Possibly
			Confusional state	Possibly
	45-013 <sup>†</sup>	F/6/H	Viral infection	Unrelated
	65-012	F/7/W	Infectious mononucleosis	Unrelated
CONCERTA <sup>®</sup>	31-004	M/11/W	Syncope	Possibly
	39-007 <sup>††</sup>	M/12/W	Abdominal pain	Unrelated
	41-008	M/6/W	Aggression	Possibly
			Anger	Possibly
			Headache	Possibly
Placebo	11-003 <sup>‡</sup>	M/9/W	Worsening ADHD symptoms	Unrelated

#### 9.4 Common Adverse Events

The most commonly reported AE in Study 302 are presented in the table below. The most common AE reported in the MTSS group were those that would be expected with MTS or stimulant treatment. These included decreased appetite (26%), headache (15%), insomnia (13%), nausea (12%), vomiting (10%), decreased weight (9%), tic (7%), abdominal pain (7%), irritability (7%), affective lability (7%), and decreased appetite (5%). In the cases of tic, insomnia, anorexia, decreased appetite, weight decreased, nausea, vomiting, and affective lability, the proportion of subjects with these AE exceeded the proportion of subjects with these AE in the Concerta group. These AE are likely to be clinically significant. Tic was an unexpected finding in this short-term study.

<b>Table 27: Most Commonly Reported Treatment-Emergent Adverse Events (≥5%; all Causalities) – Safety population (Study SPD485-302)</b>					
System Organ Class Preferred Term*	Number (%) of subjects reporting TEAE				
	MTS (N=98)		CONCERTA® (N=91)		Placebo (N=85)
No. subjects with ≥1 TEAE	74	(76)	63	(69)	49 (58)
<b>Gastrointestinal Disorders</b>					
Abdominal pain upper	7	(7)	9	(10)	5 (6)
Nausea	12	(12)	7	(8)	2 (2)
Vomiting	10	(10)	9	(10)	4 (5)
<b>General Disorders and Administrative Site Conditions</b>					
Pyrexia	2	(2)	4	(4)	8 (9)
<b>Infections and Infestations</b>					
Nasopharyngitis	5	(5)	4	(4)	2 (2)
<b>Investigations</b>					
Weight decreased	9	(9)	7	(8)	0
<b>Metabolism and Nutrition Disorders</b>					
Anorexia	5	(5)	3	(3)	1 (1)
Decreased appetite	25	(26)	17	(19)	4 (5)
<b>Nervous System Disorders</b>					
Headache	15	(15)	18	(20)	10 (12)
<b>Psychiatric Disorders</b>					
Affect lability	6	(6)	3	(3)	0
Insomnia	13	(13)	7	(8)	4 (5)
Irritability	7	(7)	7	(8)	4 (5)
Tic	7	(7)	1	(1)	0
<b>Respiratory</b>					
Cough	7	(7)	5	(6)	4 (5)
Nasal congestion	6	(6)	3	(3)	1 (1)
Pharyngolaryngeal pain	6	(6)	3	(3)	5 (6)

## 9.5 Weight Findings

There was a decrease in mean weight from Baseline at all post-Baseline visits (3-9) in both the MTS and CONCERTA groups, while subjects in the placebo group had an increase in mean weight from Baseline. The maximum mean decrease in weight from Baseline was observed at Visit 8 in both the MTS (-2.2lbs) and CONCERTA (-2.1lbs) groups. The maximum mean increase in weight from Baseline in the placebo group was +2.1lbs at Visit 8. In the MTS group, there was a higher proportion of subjects with weight measurements below the normal range, compared to the Concerta and placebo groups. between Baseline and Visit 9 in the MTS group. At Visit 9, three (3.1%) MTS subjects had weight measurements below the normal range. There were no subjects with weight measurements below the normal range in the CONCERTA or placebo groups.

A summary of z-scores for height, weight, and BMI at Screening and at Visit 9/EOS/ET for all subjects is presented in the table below. The mean z-score for weight was lower at

Visit 9 compared to Screening in the MTS and CONCERTA groups. The mean z-score for height was relatively unchanged from Screening to Visit 9 in all three treatment groups. Mean z-scores for BMI were lower at Visit 9 compared to Screening in the MTS and CONCERTA groups.

Table 30: Summary of Z-Scores - All Enrolled Subjects (Study SPD485-302)						
Z-Score		Statistic	MTS (N=100)	CONCERTA <sup>®</sup> (N=94)	Placebo (N=88)	Overall (N=282)
Weight	Screening	n	92	89	77	258
		Mean (SD)	0.05 (1.075)	0.28 (0.933)	0.15 (0.927)	0.16 (0.985)
		Median	0.04	0.21	0.13	0.11
		Min, Max	-2.7, 2.5	-2.1, 2.2	-2.1, 2.8	-2.7, 2.8
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.21 (1.168)	0.04 (0.926)	0.24 (0.937)	0.01 (1.034)
		Median	-0.24	-0.10	0.24	-0.08
		Min, Max	-2.9, 2.4	-2.3, 1.9	-1.8, 2.8	-2.9, 2.8
Height	Screening	n	92	89	77	258
		Mean (SD)	-0.05 (1.025)	0.12 (0.906)	-0.00 (1.078)	0.02 (1.001)
		Median	0.08	0.13	-0.03	0.07
		Min, Max	-2.8, 2.1	-1.8, 2.2	-4.0, 2.6	-4.0, 2.6
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.08 (1.053)	0.11 (0.972)	0.02 (1.007)	0.01 (1.011)
		Median	-0.03	0.07	0.03	0.04
		Min, Max	-2.9, 2.2	-1.7, 4.0	-2.7, 2.6	-2.9, 4.0
BMI	Screening	n	92	89	77	258
		Mean (SD)	0.13 (1.027)	0.30 (1.091)	0.25 (0.954)	0.22 (1.028)
		Median	0.12	0.38	0.22	0.22
		Min, Max	-2.4, 2.3	-4.2, 2.2	-3.1, 2.3	-4.2, 2.3
	Visit 9/EOS /ET	n	92	89	77	258
		Mean (SD)	-0.23 (1.170)	-0.06 (1.232)	0.34 (0.984)	0.00 (1.160)
		Median	-0.27	0.02	0.32	0.03
		Min, Max	-2.9, 2.2	-6.0, 2.0	-3.0, 2.4	-6.0, 2.4

## 9.6 Vital Signs Findings

There were small increases in mean systolic blood pressure from baseline to Visits 6, 7, 8, and 9 in both the MTS and CONCERTA groups, compared to the placebo group. The maximum mean increases in systolic BP from Baseline were observed at Visit 7 (1.3mmHg) in the MTS group and at Visits 6 and 7 (1.6mmHg) in the CONCERTA group. Similarly, small increases in mean diastolic blood pressure were observed at most visits in the MTS and CONCERTA groups. The maximum mean increases in diastolic BP from Baseline were observed at Visit 7 in the MTS group (1.6mmHg) and at Visit 8 in the CONCERTA group (2.7mmHg). In the MTS group, no subjects had systolic BP or



diastolic BP above the normal range compared to baseline. Several subjects in the Concerta group had systolic BP measurement above the normal range.

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

The number of subjects with pulse measurements above the normal range was higher at most visits compared to the number of subjects with above normal pulse values at baseline. However, the incidence of pulse values above the normal range was generally similar between the active treatment groups and placebo. At Visit 8, the incidence of pulse values above the normal range was similar between the two active treatment groups, yet higher than in the placebo group.

### **9.7 Sleep Findings**

Through adverse events reporting, MTS appeared to have a significantly negative effect on sleep. In the MTS group, 13% of subjects reported insomnia, compared to

The impact of MTS on sleep (compared with placebo and CONCERTA) was also assessed using data collected via the Children's Sleep Habits Questionnaire (CSHQ). The mean total CSHQ score was lower at each visit compared to Baseline in all three treatment groups. The reduction in mean total CSHQ score appeared to be larger in the MTS group compared to the CONCERTA or placebo group; however the differences were small. Similarly, there was a reduction at all visits in the mean total number of problems reported in all treatment groups. There appeared to be little difference in the magnitude of mean reduction in the number of problems among the three treatment groups. Data for the total CSHQ scores are presented in the table below.

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

The tables below present summaries of CSHQ subscale scores for bedtime resistance, sleep onset delay, and sleep duration, respectively. As with the total CSHQ score, a reduction in mean change from Baseline and number of problems was seen in each subscale.

Visit	MTS (N=98)	CONCERTA® (N=91)	Placebo (N=85)
Baseline - Total Score	8.4 (2.88)	8.2 (2.80)	8.4 (2.79)
Visit 3	-0.2 (1.67)	-0.3 (1.68)	-0.3 (1.57)
Visit 4	-0.1 (1.67)	-0.1 (2.03)	-0.1 (1.91)
Visit 5	-0.2 (1.96)	-0.2 (2.14)	-0.3 (2.16)
Visit 6	-0.3 (1.80)	+0.1 (2.28)	-0.1 (2.11)
Visit 7	-0.5 (1.92)	-0.5 (2.04)	-1.2 (2.16)
Visit 8	-0.5 (1.89)	-0.3 (2.02)	-1.4 (2.23)
Visit 9/EOS/ET	-0.5 (2.10)	-0.3 (2.18)	-0.6 (2.16)
Baseline – No. of Problems	1.1 (1.58)	1.0 (1.30)	0.9 (1.53)
Visit 3	-0.2 (1.00)	-0.2 (0.89)	-0.2 (0.88)
Visit 4	-0.2 (1.17)	-0.3 (1.23)	-0.2 (1.23)
Visit 5	-0.3 (1.15)	-0.3 (1.21)	-0.3 (1.31)
Visit 6	-0.4 (1.10)	-0.3 (1.45)	-0.2 (1.37)
Visit 7	-0.5 (1.14)	-0.5 (1.25)	-0.8 (1.55)
Visit 8	-0.5 (1.07)	-0.4 (1.37)	-1.0 (1.47)
Visit 9/EOS/ET	-0.4 (1.27)	-0.5 (1.30)	-0.3 (1.45)

Source: SPD485-302 CSR, Section 12.1, Table 3.9.9

Visit	MTS (N=98)	CONCERTA® (N=91)	Placebo (N=85)
Baseline - Total Score	1.9 (0.82)	1.8 (0.83)	1.6 (0.77)
Visit 3	-0.1 (0.78)	-0.2 (0.66)	0.0 (0.58)
Visit 4	-0.1 (0.82)	-0.2 (0.76)	-0.1 (0.57)
Visit 5	-0.1 (0.84)	-0.1 (0.84)	-0.1 (0.71)
Visit 6	-0.2 (0.85)	-0.1 (0.75)	-0.1 (0.75)
Visit 7	-0.2 (0.92)	-0.2 (0.90)	-0.4 (0.65)
Visit 8	-0.2 (0.92)	-0.1 (0.80)	-0.4 (0.80)
Visit 9/EOS/ET	-0.3 (0.94)	-0.1 (0.92)	-0.2 (0.68)
Baseline – No. of Problems	0.3 (0.46)	0.3 (0.46)	0.3 (0.46)
Visit 3	0.0 (0.43)	-0.1 (0.44)	-0.1 (0.41)
Visit 4	-0.1 (0.53)	-0.2 (0.48)	-0.1 (0.49)
Visit 5	0.0 (0.50)	-0.2 (0.52)	-0.2 (0.47)
Visit 6	-0.1 (0.52)	-0.1 (0.55)	-0.2 (0.49)
Visit 7	-0.1 (0.49)	-0.1 (0.57)	-0.3 (0.51)
Visit 8	-0.1 (0.48)	-0.1 (0.53)	-0.3 (0.55)
Visit 9/EOS/ET	-0.1 (0.50)	-0.2 (0.51)	-0.1 (0.46)

Visit	MTS (N=98)	CONCERTA® (N=91)	Placebo (N=85)
Baseline - Total Score	4.4 (1.94)	4.2 (1.69)	4.3 (1.74)
Visit 3	-0.3 (1.40)	0.0 (1.40)	-0.2 (1.10)
Visit 4	-0.1 (1.31)	-0.3 (1.51)	-0.2 (1.50)
Visit 5	-0.3 (1.52)	+0.1 (1.73)	-0.4 (1.30)
Visit 6	-0.1 (1.66)	0.0 (2.04)	-0.5 (1.54)
Visit 7	-0.3 (1.68)	-0.2 (1.77)	-0.5 (1.42)
Visit 8	-0.4 (1.59)	0.0 (1.76)	-0.6 (1.72)
Visit 9/EOS/ET	0.0 (1.54)	0.0 (1.56)	-0.4 (1.36)
Baseline – No. of Problems	0.6 (1.02)	0.4 (0.72)	0.4 (0.79)
Visit 3	-0.1 (0.94)	-0.2 (0.64)	-0.1 (0.64)
Visit 4	-0.1 (0.70)	-0.2 (0.82)	-0.1 (0.82)
Visit 5	-0.1 (0.87)	-0.1 (0.93)	-0.1 (0.87)
Visit 6	-0.2 (0.91)	0.0 (1.01)	-0.2 (0.85)
Visit 7	-0.1 (0.96)	-0.1 (0.87)	-0.2 (1.02)
Visit 8	-0.2 (0.73)	-0.2 (0.82)	-0.4 (0.80)
Visit 9/EOS/ET	-0.1 (0.82)	-0.2 (0.73)	-0.1 (1.03)

Source: Study SPD485-302 CSR Section 13.1 Table 3.9.4

## 9.8 Laboratory Findings

For hematology parameters, there were no clinically meaningful changes in mean parameters from Screening to Visit 9, and there were no significant differences among treatment groups. There was no apparent pattern between treatment groups in the

occurrence of abnormal hematology values. No subject had a treatment-emergent abnormal hematology value that was considered by the investigator to be clinically significant.

### **Serum Chemistry**

For clinical chemistry parameters, there were no clinically significant changes in mean parameters from Screening to Visit 9, and there were no significant changes between treatment groups or in the pattern in the occurrence of abnormal values. However, two subjects had treatment-emergent laboratory values that were considered by the investigator to be clinically significant. Subject 11-001 had Visit 9 values of 300U/L and 162U/L for ALT and AST, respectively, while receiving Concerta. Subject 54-001 had a Visit 9 value for ALT of 102U/L while receiving PTS. Screening values for each of these parameters was normal for both subjects. All three of these abnormal clinically significant chemistry values were reported as AEs and considered unrelated to study drug.

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

## **9.9 Dermatology Findings**

### **Skin Irritation**

The investigator examined both the current and the prior application sites for the presence or absence of primary skin reactions and other signs of skin irritation in the areas of patch-wear. Findings of erythema, edema, papules and vesicles were graded on a dermal response score scale ranging from 0 (no irritation) to 7 (strong reaction).

The mean dermal response score was higher in the MTS group at all visits compared to the CONCERTA and placebo groups. The mean dermal response scores across all visits in the MTS group ranged +0.5 to +1.0. Mean dermal response scores across all visits in the CONCERTA and placebo groups ranged 0.0 to +0.3. The maximum dermal response score obtained was 4 (definite edema) in the MTS group, 5 (erythema, edema, and papules) in the CONCERTA group, and 3 (erythema and papules) in the placebo group. At all visits, the majority of subjects in the MTS group reported either no irritation or minimal erythema, while the majority of subjects in the CONCERTA and placebo groups reported no evidence of irritation.

### **Skin Discomfort**

Other skin evaluations performed at each MTS/PTS application site included experience of discomfort and pruritus. The evaluator asked the subject, "Are you experiencing any

discomfort (as it relates to the MTS/PTS)?" The overall level of discomfort was rated from 0, for no discomfort to 3, for severe, intolerable discomfort. If the discomfort was Mild, Moderate, or Severe, the evaluator asked the subject, "What kind of overall discomfort did you experience?" and collected discomfort information specific to the symptoms (itching, burning, or other).

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

## 10 ADDITIONAL CLINICAL ISSUES

### 10.1 Dosing Regimen and Administration

#### DOSAGE AND ADMINISTRATION

Four dosage strengths for Methylphenidate Transdermal System (MTS) are available: 12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, 25 cm<sup>2</sup>, and 37.5 cm<sup>2</sup>. The corresponding dosage rates and methylphenidate contents are listed in the table below.

Dose Delivered (mg) Over 9 Hours	Dosage Rate* (mg/hr)	Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch** (mg)
10	1.1	12.5	27.5
16	1.8	18.75	41.3
20	2.2	25	55.0
27	3.0	37.5	82.5

It is recommended that the patch be applied to the hip area in the morning and worn for 9 hours. The sponsor recommends the titration schedule below for patients newly treated with methylphenidate.

Upward Titration, if Response is Not Maximized			
Week 1	Week 2	Week 3	Week 4
10 mg (1.1 mg/hr)* daily	16 mg (1.8 mg/hr)* daily	20 mg (2.2 mg/hr)* daily	27 mg (3.0 mg/hr)* daily

Patients currently treated with methylphenidate extended release (methylphenidate-ER) products should follow the conversion guide below when initiating therapy with MTS.

Previous Methylphenidate-ER Daily Dose	Daily Delivered Dose (Recommended <b>MTS</b> Dosage Rate)
18 - 27 mg q am Methylphenidate-ER	10 mg (1.1 mg/hr)*
36 - 60 mg q am Methylphenidate-ER	16 mg (1.8 mg/hr)*

Conversion from previous daily dosages of methylphenidate-ER less than 18 mg daily to **MTS** is not recommended.

### **Application**

The adhesive side of MTS 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. Avoid the waistline, since clothing may cause the patch to rub off. When applying the patch the next morning, place on the opposite hip.

MTS should be applied immediately after opening the pouch and removing the protective liner. Do not use if the pouch seal is broken. 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. Bathing, swimming, or showering have not been shown to affect patch adherence. In the unlikely event that a patch should fall off, a new patch may be applied at a different site, but the total recommended wear time should remain 9 hours.

### **Disposal of MTS**

Upon removal of MTS, 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. Each unused patch should be removed from its pouch, separated from the protective liner, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container.

### **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 MTS. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who uses MTS for extended periods in patients with ADHD should periodically evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

### **Dose/Wear Time Reduction and Discontinuation**

MTS 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 to decline when the patch is removed. 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.

### **10.2 Drug-Drug Interactions**

Please refer to the Drug-Drug Interactions section in the Executive Summary (Section 1).

### **10.3 Special Populations**

Please refer to the Special Populations section in the Executive Summary (Section 1).

### **10.4 Pediatrics**

Please refer to the Pediatrics section in the Executive Summary (Section 1).

## **11. OVERALL ASSESSMENT**

### **11.1 Conclusions**

#### **11.1.2 Efficacy**

In both studies, the sponsor demonstrated the efficacy of MTS in the treatment of children with ADHD.

In Study 201, the primary efficacy endpoint was the change from baseline in the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) department scale, which is an appropriate efficacy measure for a trial in subjects with ADHD. The SKAMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS. Subscale scores for department, attention and quality of work were evaluated at each time point to assess the duration of effect of MTS vs. placebo. Using the ITT data set provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint and he derived the same p-values. The results are depicted in Table 3.1.1.5.

**Table 3.1.1.5 Analysis of Mean SKAMP Department Score during Patch Application (Hours 2.0 – 9.0): ITT Population**

	<b>MTS (N=79)</b>	<b>Placebo (N=79)</b>	<b>p-value</b>
<b>Mean (SD)</b>	3.2 (3.64)	8.0 (6.33)	
<b>LS Mean (SE)</b>	3.2 (0.58)	8.0 (0.58)	<0.0001 <sup>a</sup>
<b>Difference and 95% CI of</b>			

<b>LS Means (MTS-Placebo)</b>	-4.8 (-5.89, -3.63)	NA
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<sup>a</sup>: The p-value is obtained using the mixed effects model.

In Study 302, the primary efficacy endpoint was the change from baseline in mean clinician-rated ADHD-Rating Scale-IV (ADHD-RS-IV) among treatment groups (MTS, placebo TS, Concerta, and matching placebo). The ADHD-RS-IV is an appropriate efficacy measure for a trial in children with ADHD.

Using both the ITT and PP data sets provided by the sponsor, the statistics reviewer duplicated the efficacy results for the primary endpoint using both the LOCF and OC data sets, and he derived the same p-values. The results of ITT population analysis are given in the following table.

**Table 3.1.2.5 Analyses of the Change from Baseline of ADHD-RS-IV Total Score (ITT Population)**

	<b>MTS (N=96)</b>	<b>Concerta (N=89)</b>	<b>Placebo (N=85)</b>
<b>LOCF analysis</b>			
<b>N</b>	96	89	85
<b>Mean (SD)</b>	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
<b>LS Mean (SE)</b>	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
<b>Difference and 95% CI of LS Means (Active-Placebo)</b>	-13.89 (-18.06, -9.72)	-11.32 (-15.58, -7.06)	
<b>p-value</b>	<0.0001	<0.0001	
<b>OC Analysis</b>			
<b>N</b>	70	64	31
<b>Mean (SD)</b>	-29.8 (10.40)	-28.0 (11.13)	-22.4 (13.67)
<b>LS Mean (SE)</b>	-30.1 (1.21)	-27.2 (1.27)	-23.5 (1.83)
<b>Difference and 95% CI of LS Means (Active-Placebo)</b>	-6.58 (-10.91, -2.24)	-3.77 (-8.19, 0.66)	
<b>p-value</b>	0.0032	0.095	

### 11.1.3 Safety Conclusions

#### Deaths, Serious Adverse Events, Discontinuations due to AE, and Common AE

There were no deaths in Study 201 or Study 302. There were no serious adverse events reported in Study 201 or Study 302. In the studies combined, there were a number of discontinuations due to adverse events that were probably related to treatment with MTS and were clinically significant. These included tic (3), anorexia (2), rash at patch application site (4), elevated blood pressure (1), weight loss (1), and mood lability (2). During Study 302 in the Concerta group, there were several discontinuations due to AE that were possibly related to treatment with Concerta. These included syncope, aggression, anger, and headache (1 case each).

The most commonly reported AE attributable to MTS treatment in Study 201 and Study 302 (respectively) were anorexia (29% and 26%), insomnia (16% and 13%), headache



(12% and 15%), nausea or vomiting (10% and 22%), abdominal pain (8% and 7%), and weight decreased (2% and 9%). In addition, irritability, lability, or anger was reported for 15% of subjects in Study 201.

In Study 302, irritability and affective lability were reported for 7% and 7% of subjects, respectively. In the cases of tic, insomnia, anorexia, decreased appetite, weight decreased, nausea, vomiting, and affective lability, the proportions of subjects with these AE in the MTS group exceeded those in the Concerta group.

### **Weight Findings**

In both studies, there was a trend toward weight loss. The mean weight decreased in the MTS groups. Furthermore, there were decreases in the mean z-scores for both weight and BMI in the MTS groups. The clinical significance of the finding of weight loss is currently unclear. However, during chronic use of MTS, it is possible that exposed patients could experience more pronounced weight loss.

In Study 201, at the end of Week 6, there was a decrease in mean weight of -2.2 lbs and -0.6 lbs in the MTS and PTS groups, respectively. At the end of Week 7, the change in weight was -1.3 lbs and -0.6 lbs in the MTS and PTS groups, respectively. In Study 201, the mean z-score for weight decreased from -0.08 to -0.15. The mean z-score for height increased from -0.06 to -0.03. Mean z-scores for BMI decreased from -0.07 to -0.21.

In Study 302, there was a decrease in mean weight from baseline at all in both the MTS and CONCERTA groups, while subjects in the placebo group had an increase in mean weight from baseline. The maximum mean decrease in weight from baseline was observed at Visit 8 in both the MTS (-2.2lbs) and CONCERTA (-2.1lbs) groups. The maximum mean increase in weight from Baseline in the placebo group was +2.1lbs at Visit 8. In the MTS group, there was a higher proportion of subjects with weight measurements below the normal range, compared to the Concerta and placebo groups. between Baseline and Visit 9 in the MTS group. At Visit 9, three (3.1%) MTS subjects had weight measurements below the normal range. There were no subjects with weight measurements below the normal range in the CONCERTA or placebo groups.

The mean z-score for weight decreased in both the MTS and CONCERTA groups. In the MTS group, the mean z-score decreased from 0.05 to -0.21. In the Concerta group, the mean z-score decreased from 0.28 to 0.04. In the placebo group, the mean z-score increased from 0.15 to 0.24. The mean z-score for height was relatively unchanged from Screening to Visit 9 in all three treatment groups. The mean z-score for BMI decreased from 0.13 to -0.23 in the MTS group, and it decreased from 0.30 to -0.06 in the Concerta group. In the placebo group, the mean z-score for BMI increased from 0.25 to 0.34.

### **Vital Signs Findings**

Generally, MTS treatment had few clinically significant effects on blood pressure, pulse, or temperature. In Study 201, there were no significant changes or differences in mean diastolic blood pressure, systolic blood pressure, or heart rate. The sponsor acknowledges that heart rate often increased in subjects shortly after patch application.

In the open-label phase, one subject (1%) had significantly elevated blood pressure. During the placebo-controlled phase, 2.5% of subjects in the MTS group had elevated blood pressure (compared to 0% in the placebo group). Of note, one subject discontinued due to elevated blood pressure.

In Study 302, there were small increases in mean systolic blood pressure from baseline to Visits 6, 7, 8, and 9 in both the MTS and CONCERTA groups, compared to the placebo group. The maximum mean increases in systolic BP from Baseline were observed at Visit 7 (1.3mmHg) in the MTS group and at Visits 6 and 7 (1.6mmHg) in the CONCERTA group. Similarly, small increases in mean diastolic blood pressure were observed at most visits in the MTS and CONCERTA groups. The maximum mean increases in diastolic BP from Baseline were observed at Visit 7 in the MTS group (1.6mmHg) and at Visit 8 in the CONCERTA group (2.7mmHg). In the MTS group, no subjects had systolic BP or diastolic BP above the normal range compared to baseline. Several subjects in the Concerta group had systolic BP measurement above the normal range.

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

The number of subjects with pulse measurements above the normal range was higher at most visits compared to the number of subjects with above normal pulse values at baseline. However, the incidence of pulse values above the normal range was generally similar between the active treatment groups and placebo. At Visit 8, the incidence of pulse values above the normal range was similar between the two active treatment groups, yet higher than in the placebo group.

### **Sleep Findings**

As noted above, insomnia was a commonly reported adverse event in both pivotal studies (16% and 13% in studies 201 and 302, respectively). In Study 303, insomnia was reported for 8% and 5% in the Concerta and placebo groups, respectively. In my opinion, the proportion of subjects in the MTS group who had insomnia is significant, especially when compared to the proportions in the Concerta and placebo groups.

The sponsor also conducted a prospective, directed assessment of sleep functioning. The instrument used was the Child's Sleep Habits Questionnaire (CSHQ). The CSHQ is a directed assessment of numerous items related to sleep function. It is designed to screen for the most common sleep problems in children aged 4 to 12. It assesses sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The CSHQ has 33 questions, responses range from 1 (rarely occurring) to 3 (usually occurring) with total scores ranging from 33 to 99. The specific CSHQ items are listed in Section. Generally, in both studies, results of the CSHQ assessment suggested that there was no significant effect of MTS treatment on sleep. However, in my opinion, in my opinion, the use of the CSHQ, which uses a number of items, may obscure the extent of the problem with insomnia in these studies, since many of the items do not appear to be directly relevant to the sleep problems specific to stimulant treatment. The

most relevant items pertain to initial, middle, and terminal insomnia as well as sleep duration and quality. Use of the CSHQ may dilute possible clinically important adverse events related to insomnia.

### **Clinical Laboratory Findings**

There were few significant clinical laboratory findings. There were no significant differences in mean hematology or chemistry parameters. Two subjects had eosinophilia, and one had a decreased platelet count. Neither abnormality was likely to be related to MTS treatment, and there no apparent clinical symptoms related to these laboratory abnormalities. One subject was discontinued due to having an abnormal lymphocyte morphology.

There were no significant changes in mean chemistry parameters, and there were no significant differences between groups. Among the few abnormalities in clinical chemistry parameters, none was likely due to MTS treatment.

## **11.2 Recommendation on Regulatory Action**

### **Recommendation on Regulatory Action**

I recommend that the Division take a not-approvable action for NDA 25-514. Methylphenidate Transdermal System (MTS) treatment in children (ages 6 to 12) with Attention Deficit Hyperactivity Disorder (ADHD) was associated with an adverse event profile and potential risks that could pose clinically important risks to a significant number of pediatric patients who might be exposed to MTS.

Specifically, treatment with MTS was associated with a high incidence of insomnia, anorexia or decreased appetite, headache, and gastrointestinal symptoms including vomiting, nausea, and upper abdominal pain. These adverse events were significantly more common in the MTS group than in the active comparator group (Concerta) and the placebo group. MTS treatment was also associated with decreased weight in these short-term studies.

In addition, treatment with MTS was associated with a relatively high risk of developing tic disorder, compared to the active comparator group (Concerta) and the placebo group. Also, treatment with MTS was associated with a significant degree of dermal reactions and symptoms at the patch application site.

In my opinion, the safety and tolerability profile of MTS treatment in these 2 new studies does not appear to be significantly more acceptable than in the previous MTS submission. Generally, it appears that the identical safety concerns remain.

### **11.3 Recommendation on Postmarketing Actions, Risk Management Activity, and Phase 4 Commitments**

Currently, there are no specific recommendations for postmarketing actions, risk management activities, or Phase 4 commitments, since it is recommended that the Division take a not-approvable action.

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Robert Levin, M.D., November 7, 2005  
FDA, CDER, ODE1, DPP, HFD-130

Cc: NDA  
T Laughren  
P Andreason  
R Taylor

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Robert Levin  
11/7/2005 05:10:39 PM  
MEDICAL OFFICER

Paul Andreason  
11/8/2005 07:58:44 AM  
MEDICAL OFFICER

We are taking this sNDA application to the Psychiatric  
Drug Advisory Committee on December 2, 2005.