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FDA Psychopharmacologic Drugs Advisory Committee
Briefing Document

Prepared October 24, 2005

Methylphenidate Transdermal System

NDA 21-514

Noven Pharmaceuticals, Inc.
Shire Development Inc.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder – Rating Scale, Version IV
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BMI	Body Mass Index
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CI	Confidence Interval
C_{max}	Maximum Concentration
CPRS-R	Conners' Parent Rating Scale – Revised: Short Form
CTRS-R	Conners' Teacher Rating Scale – Revised: Short Form
d-MPH	dextro-threo-methylphenidate
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th ed. – Text Revision
FDA	Food and Drug Administration
I/O	Inattentive/Overactivity
ITT	Intention-to-Treat
l-MPH	levo-threo-methylphenidate
LS	Least Squares
MPH	Methylphenidate
MTS	Methylphenidate Transdermal System (SPD485)
NA	Not Applicable
NDA	New Drug Application
O/D	Oppositional/Defiant
PERMP	Permanent Product Measure of Performance
PTS	Placebo Transdermal System
RMP	Risk Management Program
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale

STP	Summer Treatment Program
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Maximum Concentration
USP	United States Pharmacopeia

1. BACKGROUND

This briefing document includes a summary description of the methylphenidate transdermal system (MTS), its regulatory history, the supporting clinical studies, risk management plan, and overall benefits and risks. Following the summaries are appendices addressing each of these topics in detail. This briefing document is provided without redaction for public dissemination.

This briefing document includes findings from the pending New Drug Application (NDA) that support the safety and efficacy of MTS. Specifically, in 2 pivotal trials (SPD485-201 and –302) with a 9-hour MTS wear time, MTS demonstrated significant improvements in overall Attention-Deficit Hyperactivity Disorder (ADHD) symptoms compared to placebo. Adverse events (AEs) reported in the MTS clinical development program were generally similar in nature to those reported for other methylphenidate formulations. These 2 studies support the efficacy and safety of MTS worn for 9 hours in the treatment of ADHD in children.

1.1 Background Information

The National Institute of Mental Health estimates that approximately 2 million children or 3-5% of all children suffer from ADHD. ADHD can be a serious impairment to academic, social, and occupational development. Several types of treatment modalities are available and can help many of these children. As with other disorders, however, the needs and preferences of patients and their caregivers vary widely.

Shire Development Inc. (Shire) and Noven Pharmaceuticals, Inc. (Noven) have worked together to develop a new formulation of the widely used and studied medicine, methylphenidate, which has been used for the treatment of ADHD in children and adults for decades. MTS is a transdermal once daily treatment for ADHD. The methylphenidate incorporated in the multi-polymeric adhesive layer of MTS provides controlled transdermal delivery of methylphenidate during the period of patch application. This transdermal system also provides for drug delivery through a prolonged period such that clinical control of symptoms may be achieved without supplemental medication during the critical period of a patient's activity. When the MTS is removed from the skin, plasma methylphenidate levels begin to decline (the terminal elimination half-life of the active isomer is 3 to 4 hours after removal of MTS).

1.2 Clinical Utility of the Transdermal System in the Treatment of ADHD

Methylphenidate has been proven to be safe and efficacious for over 50 years, and as a stimulant, is a first line therapy for children with ADHD. MTS offers a transdermal once daily treatment for ADHD. One group where this technology will be helpful will be for children who are unwilling or unable to swallow oral ADHD medication. In a survey conducted in September 2005 (Moms and Pediatric Prescription Medications Study; Russell Research), it was reported that three-fourths of mothers are enthusiastic about pediatric medications in the form of a patch. Mothers said their children have difficulty fully swallowing pills and, in addition, mothers of children with ADHD were also more likely to report difficulty in getting

their child to take pills every day and that their children simply dislike taking pills. MTS offers additional benefits as it avoids the first pass metabolism process, thus efficacy is not affected by gastrointestinal effects or food intake. The patch can also be removed early if one wishes, for example, to minimize late day side effects (e.g., insomnia, decreased appetite), a flexibility not possible with an oral medication.

2. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

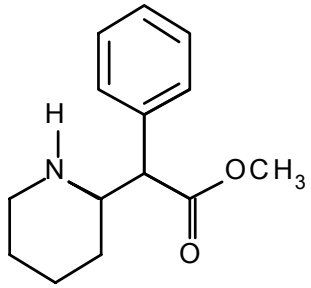
Methylphenidate hydrochloride, United States Pharmacopeia (USP) is converted to the base form by the supplier prior to incorporation into MTS.

2.1 Chemical Name and Physical Properties

Chemical name:	methylphenidate: *d*,*l*- (racemic) methyl-alpha-phenyl-alpha-(2-piperadyl)-acetate
Generic name:	methylphenidate transdermal system
INN:	1) 2-piperidineacetic acid, α-phenyl-, methyl ester 2) α-phenyl-2-piperidineacetic acid methyl ester
CAS Registry Number:	113-45-1
US Adopted name:	methylphenidate
Physical description:	methylphenidate is a white to off-white powder
Chirality:	methylphenidate is a racemic mixture
Solubility:	methylphenidate is soluble in alcohol, ethyl acetate, and ether, and practically insoluble in water and petrol ether

2.2 Chemical Structure

Figure 1: Structural Formula of Methylphenidate



Molecular formula: $C_{14}H_{19}NO_2$

Molecular weight: 233.31

2.3 Formulation Details

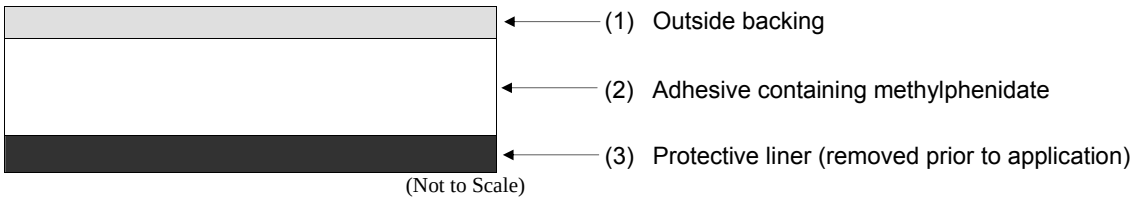
MTS contains methylphenidate base in a multi-polymeric adhesive matrix. Each once-a-day MTS is designed to release methylphenidate continuously throughout the day upon application to intact skin. Four (4) patch systems are available; the composition per unit area of all systems is identical.

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

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

**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.

The patch consists of 3 layers, as seen in the figure below (cross-section of the patch).



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

The active component of the system is methylphenidate base. The remaining components of the methylphenidate adhesive layer (2) include silicone and acrylic-based adhesives. The main constituent of the backing and protective liner (1, 3) is polyester. These remaining components are pharmacologically inactive. The finished product does not contain material of animal origin.

2.4 Storage and Handling

Storage and handling recommendations for MTS in commercial use will be the following:

MTS should not be stored unpouched. MTS should be stored at 25º C (77º F) with excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature].

MTS is supplied in sealed trays containing either 10 or 30 individually pouched systems and a desiccant. Once the tray is opened, the contents should be used within 2 months. The patch is to be applied immediately upon removal from the protective pouch. **For transdermal use only**.

3. NONCLINICAL SUMMARY

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

The toxicological profile of MTS has been found to be similar to that of oral methylphenidate. The predominant toxicities associated with oral methylphenidate, observed in acute, subchronic and chronic studies, consisted of exaggerated pharmacologic effect of the drug (e.g., hyperactivity, hyperexcitability, mydriasis, etc.) induced by the high doses administered. In general, only the very high multiples of the intended human doses, used in toxicity studies in animals, were associated with reduction in body weight.

Methylphenidate was not mutagenic in the Ames reverse mutation assay or in the mouse lymphoma cell forward mutation assay. The results of the Chinese Hamster Ovary chromosomal aberration assay and the sister chromatid exchange assay were not consistent between laboratories. Positive results, whenever they occurred, were associated with either exposure to very high concentrations and/or longer than standard times of incubation. Shire and Noven further characterized the genotoxic potential of methylphenidate in an *in vivo* mouse micronucleus assay. Dose levels up to 400 mg/kg did not induce a positive effect.

Although a complete set of studies to assess the reproductive toxicity of methylphenidate in animals has not been done, studies conducted in mice, rats, and rabbits by the sponsors and others demonstrated that methylphenidate had no effect on reproductive function, embryo-fetal viability and development, or maturation of the offspring.

The potential for MTS to induce dermal toxicity has been investigated in rabbits. MTS application sites were evaluated for erythema and edema immediately prior to removal and up to 48 hours after removal. Both the active and placebo patches produced well defined to moderate-to-severe erythema and very slight-to-moderate edema in intact and abraded skin, thought to be due to the mechanical trauma resulting from patch removal. Both active and placebo patches were therefore considered to be moderate irritants. Histopathologic evaluation indicated that the active test material was generally well-tolerated but was slightly more irritating than the placebo material. No evidence of necrosis was found.

A further study investigated the relative level of irritation in intact and abraded sites and demonstrated that abrading the skin did not affect the results. MTS was not found to act as a dermal sensitizer in the standard occluded patch guinea pig model.

4. OVERVIEW OF CLINICAL STUDIES

Sixteen studies have been conducted in pediatric subjects (4 Phase I, 5 Phase II, 3 Phase III and 4 Long-Term), and 8 studies have been conducted in adults (all Phase I) as part of the clinical development program for MTS (Table 1).

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

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

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

Study Type	Study Description	Study Number	Number of Subjects
Uncontrolled, Long-Term Studies	Open-label, long-term safety studies in pediatric ADHD subjects (9-hour wear time for SPD485-303 and 12-hour wear time for N17-011, -013, and –021)	N17-011	118
		N17-013	20*
		N17-021	191
		SPD485-303	289**
Adult Studies			
Pharmacokinetic/ Biopharmaceutic Studies	Single-dose, crossover evaluation of dose proportionality in healthy adult subjects (16-hour wear time)	N17-004	14
	Steady-state, crossover comparison of the pharmacokinetic profiles of MTS and Ritalin in healthy adult subjects (16-hour wear time)	N17-006	30
	Single-dose, crossover evaluation of the pharmacokinetic profile and abuse potential of MTS in adult subjects currently abusing stimulants (24-hour wear time)	N17-007	27
	Single-dose, crossover evaluation of 1) the effect of heat on methylphenidate release from MTS and 2) the buccal absorption of methylphenidate from MTS in adult subjects currently abusing stimulants (2, 6, and 8-hour wear times)	N17-012	6
	Evaluation of the pharmacokinetic profile of MTS following repeated application of the same patch in healthy adult subjects (16-hour wear time)	N17-014	6
	Single-dose, crossover comparison of the pharmacokinetic profile of MTS on application to normal and inflamed skin in healthy adult subjects (16-hour wear time)	N17-017	8
Special Safety Studies	Evaluation of skin irritation and sensitization of MTS after repeated applications in healthy adult subjects (24-hour wear time)	N17-008	122
	Evaluation of skin sensitization potential of MTS after repeated applications in healthy adult subjects (24-hour wear time)	N17-020	194

- *Patients from studies N17-011 and N17-015.
- **Patients from studies SPD485-102, -201, -302, and N17-021.

The focus of this Briefing Document will be on the pivotal studies (studies SPD485-201 and –302) in which efficacy was demonstrated with a 9-hour MTS wear time. Study SPD485-201 was an Analog Classroom study consisting of an open-label dose optimization period of 5 weeks, followed by a 2-week Analog Classroom period for efficacy evaluation. During dose optimization, investigators could adjust patch size for optimal effect and tolerability. Study SPD485-302 was a 7-week parallel-group study in which subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA®, or matching placebo. The study had a 5-week double-blind dose optimization period to titrate to at least an acceptable dose of MTS (using 12.5cm^2, 18.75cm^2, 25cm^2, and 37.5cm^2 patch sizes) or CONCERTA® (using 18mg, 27mg, 36mg, and 54mg dosage strengths). Subjects remained on the optimized dose for 2 weeks for efficacy evaluation.

5. OVERVIEW OF BRIEFING DOCUMENT

5.1 Pharmacokinetics/Pharmacodynamics Summary

Seven (7) studies with biopharmaceutic/pharmacokinetic components have been conducted in pediatric patients with ADHD and 6 studies have been conducted in adults as part of the clinical development program for MTS. The 4 most recent studies focused on a 9-hour wear time are presented in detail below, with mention of the earlier data as appropriate. Pharmacokinetic data were generally consistent across all the studies, taking account of different patch sizes and wear times evaluated.

Methylphenidate is administered as a racemic mixture with equal amounts of the *d*- and *l*-enantiomers (50:50) being delivered via MTS patch sizes of 12.5, 18.75, 25 and 37.5cm^2 which are equivalent to nominal doses of 27.5mg, 41.3mg, 55.0mg and 82.5mg *d,l*-methylphenidate (MPH).

In a single dose comparison of 6-, 8- and 10-hour wear times in pediatric ADHD patients, the 10-hour wear time for MTS 25cm^2 resulted in *d*-MPH bioavailability most similar to that of 36mg CONCERTA®. The area under the curve (AUC) parameters were 17% lower at 10 hours than for CONCERTA® and maximum concentration (C_{max}) values were similar across both treatments. The terminal portion of the profiles over the 6- to 14-hour period from the end of the shortest wear time until a typical end of the active day demonstrated similar or higher exposures for MTS at the longer wear times. The 8-hour wear time resulted in slightly lower concentrations than CONCERTA® at the end of the day while the 10-hour wear time had slightly higher values. The mean terminal elimination half-life for *d*-MPH from MTS was 4.3 to 5.0 hours. A 9-hour wear time was selected for further studies (see Section 5.2, below).

In a further single dose study in pediatric ADHD patients, the relative bioavailability of *d*-MPH following administration of MTS 37.5cm^2 was not dissimilar to that observed following oral administration of 54mg CONCERTA®. The systemic availability of *d*-MPH appeared to be dose-proportional over the dose range/patch size studied based on C_{max} and AUC_{0-t}, although *l*-MPH AUC_{0-t} increased slightly more than dose proportionately. The mean terminal elimination half-life for *d*-MPH from MTS was 3.2 to 3.9 hours.

During repeat dosing in an Analog Classroom study in pediatric ADHD patients, the mean proportion of *d,l*-MPH delivered from the different patch sizes over a 9-hour wear time ranged from 38% - 45%, although the inter-subject variability was high for each patch size; individual amounts of *d,l*-MPH delivered ranging from 15% - 72%. MPH was steadily absorbed into the systemic circulation, with maximum plasma concentrations of *d*-MPH and *l*-MPH occurring at median times of approximately 7 to 9 hours after application of the MTS patch. The terminal elimination phase could not be fully defined for *d*-MPH, although the half-life was estimated to be approximately 3.0 hours. AUC_{0-12h} and C_{max} for *d*-MPH and *l*-MPH increased in a generally dose proportional manner over the entire range of patch sizes and apparent delivered doses of *d,l*-MPH. Pharmacokinetic/pharmacodynamic effects corresponding to an E_{max} or E_{inhib} model for the population were observed, with EC50 values of 16-17 ng/ml *d*-MPH based on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP)

deportment or Permanent Product Measure of Performance (PERMP). The duration of action of MTS was determined as 11.5 hours based on the protocol-defined endpoints. Activity may have persisted longer in some individuals, based on the decay in plasma concentrations after patch removal and the related efficacy predicted from the pharmacokinetic/pharmacodynamic models, but had declined to insignificant levels by the time of the next patch application. No robust model represented changes in blood pressure or heart rate with plasma *d*-MPH concentration and no clear relationship could be established between changes in vital signs and plasma *d*-MPH concentration.

Results of sparse sampling around the time of patch removal in a repeat dose Naturalistic study demonstrated higher concentrations after 9 hours of wear time for MTS versus 9 hours after administration of CONCERTA®, suggesting that the systemic exposure after MTS is greater than after CONCERTA® at nominally equivalent doses.

In all these studies, the plasma concentrations of *l*-MPH for MTS were lower than those of *d*-MPH (approximately one-half to two-thirds, on average). However, *l*-MPH levels for MTS were substantially higher than for CONCERTA® (e.g., 10- to 12-fold for C_{max} and 8- to 15-fold for AUC_{0-t} after a single application of MTS 25cm^2 for periods of 6-10 hours) as expected, due to high and selective oral first-pass metabolism of *l*-MPH in CONCERTA® as previously reported in the literature. The higher circulating concentrations of *l*-MPH for MTS than for CONCERTA® are not considered clinically significant because of the much lower potency (at least an order of magnitude) and the lower circulating concentrations of *l*-MPH than of *d*-MPH.

5.2 Rationale for Choice of Wear Time

In the clinical program instigated by Noven to develop MTS, pharmacokinetics and pharmacodynamics were investigated in 6 clinical pharmacology studies in adult volunteers and 3 in pediatric patients. The tolerability and wear characteristics were investigated following single and repeat doses for various wear times and various factors potentially affecting absorption (application of heat, buccal administration, and application on inflamed compared to normal skin) were also studied. Results of studies pertinent to choice of wear time are briefly summarized below.

The first exploratory study in the MTS development program (N17-002) was a placebo-controlled, crossover bioavailability/efficacy study comparing 2 MTS 10 cm^2 patches to Ritalin 10 mg tid administered to 11 pediatric patients. The study established that a once daily application of 2 MTS 10 cm^2 patches worn for 24 hours provided similar peak plasma concentrations (C_{max}) to Ritalin 10 mg tid and areas under the plasma concentration-time curves (AUC) approximately 2.5 times higher than obtained from Ritalin. Subsequent to this study, the MTS formulation was modified to improve patch adherence.

Study N17-004 was a single-dose, 3-way crossover study in 14 adult male subjects which evaluated the dose proportionality of MPH pharmacokinetics from MTS 6.25cm^2, 12.5cm^2 and 25cm^2 patches following a 16 hour wear time. Results showed that the pharmacokinetics of MPH was linear over the dose range tested and that the wear characteristics (and notably adherence) of the modified patch were favorable.

In study N17-006, the steady-state pharmacokinetics of *d*-MPH and *d*-MPH following 16 hour application of MTS 25cm^2 patches for 6 days were compared with the pharmacokinetic profile of Ritalin 20mg tid for the same duration in an open-label, 2-way crossover design. Results demonstrated that steady state exposure (AUC_{ss}) to *d*-MPH delivered by MTS was similar but not bioequivalent to that of Ritalin at these doses. Although plasma concentrations of *l*-MPH delivered by MTS were higher than those delivered by oral Ritalin, the increased concentrations did not appear to be associated with any increased adverse events.

In study N17-016, the pharmacokinetics and safety of higher doses of MTS were evaluated following repeat dosing with different wear times. In an open label design in pediatric ADHD patients, MTS 37.5cm^2 and 50cm^2 patches, each worn for either 8 or 12 hours for 4 consecutive days were investigated. Overall, application of MTS (up to 50cm^2) was safe and generally well tolerated. The exposure to *d*-MPH (C_{max} and AUC_{0-t}) was greater (40-60%) for both wear times after application of 50cm^2 than after 37.5cm^2 patches. Time to maximum concentration (t_{max}) was independent of dose within a given wear time. Similar results were obtained with *l*-MPH. The percentage of methylphenidate delivered from MTS was independent of dose but dependent on wear time.

Based on the outcomes of these clinical pharmacology studies, a dose ranging study (N17-003) with wear times of 13-16 hours and then 2 well-controlled classroom studies with wear times of around 12 hours (N17-010 and N17-018) were performed to definitively evaluate efficacy and safety.

The culmination of the Noven clinical program was the submission of NDA 21-514 that was designed to support a recommended wear time of 12 hours in clinical practice. However, in reviewing this NDA, the Agency found an unacceptable incidence of adverse events (insomnia, anorexia, significant weight loss, and the potential for skin sensitization) with the proposed dosage regimen/wear time and believed that decreasing the wear time might reduce the incidence of these adverse events. In pursuing a program of work to address the Food and Drug Administration's (FDA's) action letter for NDA 21-514, Shire/Noven sought to define in a pediatric pharmacokinetic study the wear time which would most closely match the pharmacokinetic profile of the major active enantiomer, *d*-MPH, to that delivered from the approved oral extended release methylphenidate product CONCERTA® and then to utilize the chosen wear time in the 3 new Phase II/III studies agreed with FDA to address their concerns.

In study SPD485-101, the bioavailability and pharmacokinetics of *d*- and *l*-methylphenidate after single administrations of MTS 25cm^2 patches worn for 6, 8 or 10 hours were compared to those observed after a single oral dose of 36mg CONCERTA®. Data show that the bioavailability of *d*-MPH from MTS was slightly lower than from CONCERTA® when worn for 8 hours and slightly higher when worn for 10 hours. A wear time of 9 hours was based on the PK profile of MTS related to CONCERTA® and on the basis of the logistics of a typical school day for a child with ADHD. Dose proportionality of *d*-MPH and *l*-MPH across the range of 12.5 to 37.5cm^2 patch sizes was studied in the SPD485-102 Phase I study.

Low intra-subject variability in pharmacokinetic data demonstrated consistent delivery of *d*-MPH from MTS within subjects, though inter-subject variability was high. The 8- or 10-hour wear times for MTS produced the most similar exposure to that of CONCERTA®. The

pharmacokinetic/pharmacodynamic data summarized in this document are those from the additional Shire/Noven studies filed in the 28 June 2005 Resubmission, all subsequent to SPD485-101 and utilizing a 9-hour wear time.

5.3 Efficacy Summary

The clinical evidence demonstrates that MTS is an effective and well-tolerated once daily medication for treating children with ADHD.

In the initial MTS clinical development program (original NDA submission), a total of 287 pediatric patients between 6 and 13 years of age with ADHD were treated in 6 controlled efficacy studies (N17-002, N17-003, N17-009, N17-010, N17-015, and N17-018) with patch sizes of MTS ranging from 2.5 cm^2 to 50 cm^2. The patch wear time in these studies was 12 hours. All 6 studies demonstrated evidence of the clinical utility of MTS over placebo transdermal system (PTS) in improving behavior of pediatric patients with ADHD as assessed by laboratory or community teachers, camp counselors, or parents. In Study N17-018, which employed a parallel group design and a large range of doses, MTS was found to be more effective than PTS ($p<0.0001$) on all primary and secondary efficacy measures, including the teacher and parent scores on the Inattention/Overactivity (I/O) and Oppositional/Defiant (O/D) factors of the IOWA Conners Rating Scale, the Abbreviated Conners Rating Scale, the Peer Relations Rating Scale; teacher scores on the Effectiveness Normalization Scale; and Clinical Global Impressions-Improvement (CGI-I) scores. MTS effects in Study N17-018 were independent of gender, race, age, and prior ADHD medication use.

While the initial clinical studies demonstrated benefits on behavioral symptoms, the 12-hour-long patch wear time was associated with a higher incidence of methylphenidate-related adverse effects (such as anorexia and insomnia). It was postulated that if the adverse events were due to overexposure to methylphenidate, a reduced wear time should result in an overall rate of adverse effects similar to those observed with other oral methylphenidate products. In the subsequent development program, 2 additional clinical studies (SPD485-201 and -302) were conducted to support the efficacy of MTS using a shorter patch wear time. A patch wear time of 9 hours was chosen based on the pharmacokinetics of *d*-MPH administered by MTS and the logistics of a typical day for an ADHD child. The 9-hour wear time was slightly longer than the T_{max} of CONCERTA® (approximately 7 hours). Examination of the *d*-MPH plasma concentration-time curve for CONCERTA® showed that after T_{max} was reached, there was a plateau in *d*-MPH concentrations until around 9 hours when elimination became apparent by a reduction in plasma concentrations.

The purpose of study SPD485-201 was to evaluate the safety and efficacy of MTS and to characterize the duration of efficacy of MTS in pediatric subjects aged 6-12 compared to placebo. The primary objective of this study was to evaluate, under controlled conditions at multiple time points throughout the day, the behavioral effects (measured by SKAMP deportment scale) of MTS compared to placebo in children (aged 6-12) diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders, 4th ed. – Text Revision (DSM-IV-TR) criteria. The main secondary objective was to assess the duration of efficacy of MTS compared to placebo in children with ADHD using the 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. Additional secondary objectives included: Attention Deficit Hyperactivity Disorder-Rating Scale-IV (ADHD-RS-IV), Clinical Global Impressions – Severity of Illness (CGI-S), CGI-I, Parent's Global Assessment, and Conners' Parent Rating Scale – Revised: Short Form (CPRS-R).

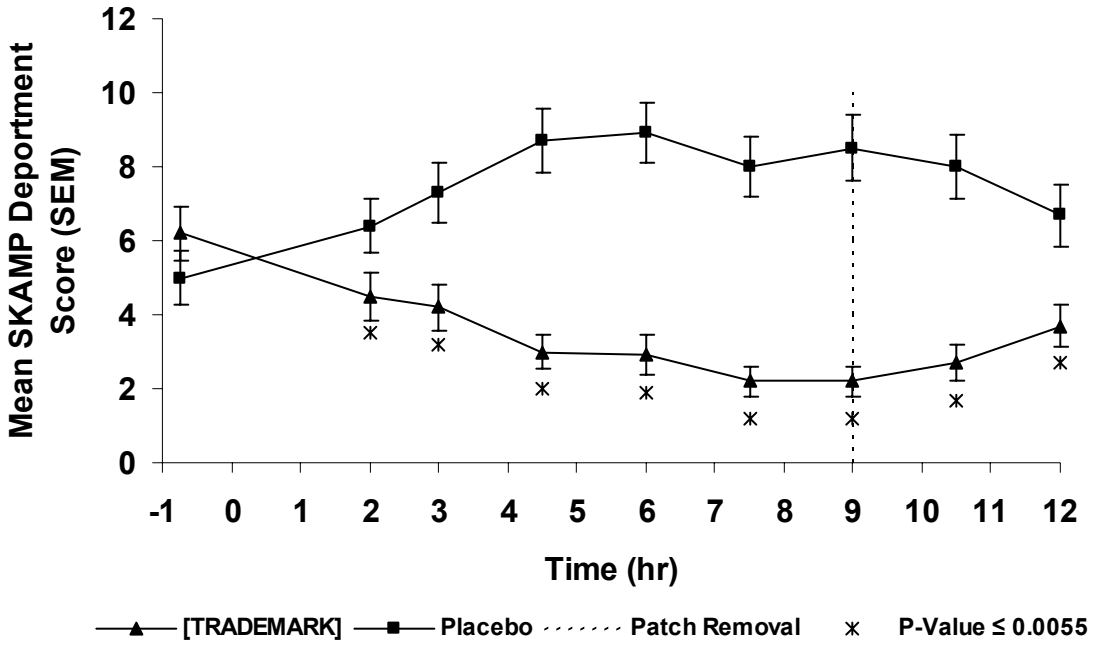
The primary endpoint was the mean SKAMP deportment score during the 9 hours of patch application. When examined at each time interval, the difference was statistically significant from placebo at the first post-baseline evaluation (2 hours) and statistically significant at all timepoints up to and including 12.0 hours post dose. Mean SKAMP deportment scores were significantly lower for MTS compared to placebo at all post-dose timepoints. This difference was statistically significant (see the Text Table and Text Figure below).

Table 2: Summary and Analysis of Mean SKAMP Deportment Score During Patch Application (Hours 2.0 – 9.0) – ITT Population

Statistic	MTS	PTS
N	79	79
Mean (SD)	3.2 (3.64)	8.0 (6.33)
Median	2.2	7.3
Min, Max	0, 17	0, 29
LS Mean (SE)	3.2 (0.58)	8.0 (0.58)
Difference and 95% CI of LS Means (MTS-PTS)	-4.8 (-5.89, -3.64)	
P-value	<0.0001	

CI = Confidence Interval; ITT = Intention to Treat; LS = Least Squares; SD = Standard Deviation; SE = Standard Error.

Figure 2: Plot of SKAMP Deportment Score by Timepoint – Analog Classroom Period – ITT Population – Means and One Standard Error



This study showed significant differences in all primary and secondary efficacy variables in MTS-treated subjects when compared to placebo-treated subjects. The MTS group demonstrated significant improvements in subjective measurements of behavior as rated by teachers, clinicians and parents. In addition, the PERMP, an objective assessment of math productivity in the classroom, also showed significant improvements. The onset of effect was apparent by the 2.0 hour timepoint and persisted for the duration of the classroom observation period as measured by the SKAMP deportment scale. Therefore, treatment with MTS in this study was successful in reducing ADHD symptoms as measured by a wide assortment of both subjective and objective standard measurements.

Study SPD485-302 was a Phase III, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study designed to evaluate the safety and efficacy of MTS (12.5cm^2, 18.75cm^2, 25cm^2, and 37.5cm^2 patch sizes) compared to placebo with reference to CONCERTA® in pediatric subjects diagnosed with ADHD.

The primary efficacy measurement was the ADHD-RS-IV total scores. The Baseline consisted of the ADHD-RS-IV total score obtained at Baseline (Visit 2) prior to treatment. The endpoint of the primary efficacy measurement was defined as the last post-Baseline assessment for which a valid ADHD-RS-IV score was obtained. The primary efficacy variable was the ADHD-RS-IV change score at the Endpoint from Baseline.

The study met its primary objective. MTS demonstrated significant improvements in ADHD-RS-IV total scores compared with placebo (Table 3). The decrease in the adjusted mean ADHD-RS-IV total score at Endpoint from Baseline in subjects in the ITT population treated with MTS was statistically significantly different from that in subjects treated with placebo. Separate comparisons showed a statistically significant difference between CONCERTA® and placebo, as well, but not between MTS and CONCERTA®.

Table 3: Primary Efficacy Outcome – Change from Baseline in ADHD-RS-IV Total Score at Endpoint - ITT Population

Variable	Treatment		
	MTS (N=96)	CONCERTA® (N=89)	Placebo (N=85)
Baseline ADHD-RS-IV Total Score			
n	96	89	85
Mean (SD)	43.0 (7.45)	43.8 (6.65)	41.9 (7.43)
Change from Baseline			
n	96	89	85
Mean (SD)	-24.2 (14.55)	-22.0 (14.91)	-9.9 (14.06)
Median	-26.0	-23.0	-5.0
Minimum, Maximum	-54, 10	-45, 13	-48, 17
LS mean (SE)	-24.2 (1.45)	-21.6 (1.51)	-10.3 (1.54)
Difference (95% CI of LS means*) Active - Placebo	-13.893 (-18.062, -9.724)	-11.319 (-15.579, -7.059)	NA
P-value (Active - Placebo)	<0.0001	<0.0001	NA
Difference (95% CI of LS means) MTS - CONCERTA®	-2.574 (-6.690, 1.541)		NA
P-value (MTS - CONCERTA®)	0.2192		NA

* LS means from ANCOVA model with term for treatment as a factor and Baseline score as a covariate
ANCOVA = Analysis of Covariance; NA = Not Applicable

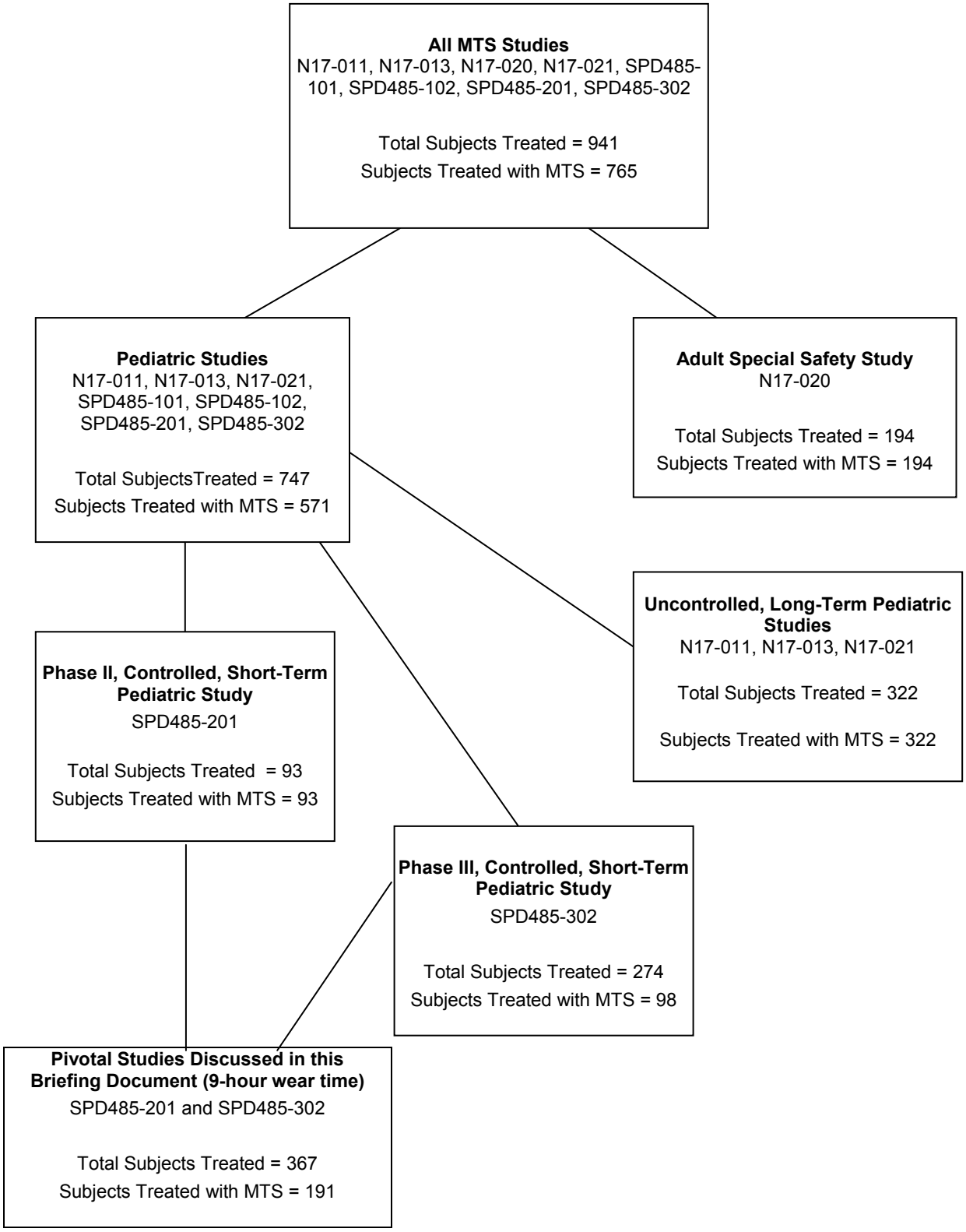
MTS also demonstrated significant improvements in scores for the ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscales. The change in ADHD-RS-IV total score and subscale scores for the CONCERTA® group were also significantly improved compared with placebo. There were no significant differences in ADHD-RS-IV total or subscale scores at endpoint between MTS and CONCERTA® groups. The study also met its main secondary objectives by demonstrating efficacy in the Conners' Teacher Rating Scale – Revised: Short Form (CTRS-R), CPRS-R, CGI-I, and PGA.

In summary, the clinical studies of MTS demonstrated statistically significant reductions in symptoms of ADHD in both primary and secondary endpoints in children aged 6-12 utilizing once-daily dosing with a 9-hour wear time.

5.4 Safety Summary

In this Safety Summary, a total of 941 unique subjects evaluable for safety analysis (i.e., who received at least 1 dose of study treatment) contributed data, including 765 who received MTS. A total of 571 pediatric subjects received MTS: 93 in Phase II studies, 98 in Phase III studies and 322 in Long-Term studies. The 941 unique subjects evaluable for safety analysis are shown in the Text Figure below.

Figure 3: Overall Disposition of Subjects Included in the MTS Clinical Program



12-hour Wear Time (Original NDA Filing)

In the original NDA filing (in which studies were conducted with a 12-hour wear time) a total of 620 unique subjects/patients received at least 1 application of MTS (2.5 cm^2, 5 cm^2, 6.25 cm^2, 10 cm^2, 12.5 cm^2, 20 cm^2, 18.75 cm^2, 25 cm^2, 37.5 cm^2, or 50 cm^2); 202 subjects/patients received only placebo. Of these 620 subjects/patients receiving MTS, 414 were pediatric patients and 206 were adult subjects. Subject/patient exposure to MTS ranged from 1-6 days to >84 days. For the Phase III Controlled Pediatric Population, most of the patients (78%) received MTS for 21-42 days. The largest number of patients in the Pediatric Population (42%) also received between 21-42 days of MTS. However, more patients received MTS for > 42 days in this population than the Phase III Controlled Pediatric Population because of the 118 patients who were enrolled in the long-term Study N17-011.

The most frequently reported AEs (≥ 10 %) during MTS treatment in the original Phase III Controlled Pediatric Population included application site reaction, anorexia, insomnia, headache, and abdominal pain (listed in order of decreasing frequency). With the exception of application site reaction, the AE profile in MTS-treated subjects/patients consisted of well-described events commonly encountered with administration of stimulant medications, although the incidence for some (anorexia, insomnia, headache, and abdominal pain) was generally higher than that reported in commercial methylphenidate product labeling.

No deaths occurred in the initial 12-hour MTS studies submitted in the original NDA. No AEs associated with MTS treatment were considered serious. One (1) serious adverse event (SAE; constipation) was reported in a patient receiving placebo. No IND Safety Reports were submitted to FDA. Adverse events in 3.6% of subjects/patients led to discontinuation of study drug in the original NDA filing.

Application site reaction was reported by 69% of subjects/patients during MTS treatment (all subjects population) in the original NDA; however, only 4 patients discontinued due to application site reaction. In the Phase III Controlled Pediatric Population, the majority of ratings of discomfort and dermal irritation (≥90% and ≥71%, respectively) were mild or non-existent. In a special study examining the sensitization potential of MTS in a laboratory setting (N17-008), 1 patient out of 116 had confirmed sensitization. An additional patient was suspected of being sensitized to MTS but the observation could not be confirmed due to the lack of follow-up.

Misuse or diversion of MTS was not observed during the development program. Approximately 73-82% of parents from the Phase III studies strongly agreed that MTS afforded them control over their child's treatment and peace of mind over potential misuse.

12-hour Wear Time and Long-Term Pediatric Population

In the Long-Term Pediatric Population (12-hour wear time), no deaths occurred. Three (3) SAEs occurred (all in MTS patients; none of the SAEs were considered by the investigators to be related to study treatment). Two (2) SAEs involved hospitalization for outbursts of hostility and one SAE was for dehydration following an elective outpatient procedure.

There was some association between increases in the rates of occurrence of anorexia and increases in most common patch size and cumulative patch size. Decreasing patch size was

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

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

9-hour Wear Time

On 25 April 2003, the Agency issued an action letter for NDA 21-514. The Agency stated there was an unacceptable incidence of insomnia and anorexia, significant weight loss in the short term, and the potential for skin sensitization, and expressed concerns that these adverse events could result in possible growth retardation or other serious adverse consequences with more chronic treatment with MTS due to methylphenidate overexposure. The Agency suggested that decreasing the wear time of the MTS patch might decrease the incidences of insomnia, anorexia, and significant weight loss to acceptable levels. In meetings (26 May 2004 and 05 April 2005) and correspondence with the Agency, Shire and Noven gained FDA concurrence to pursue 3 new Phase II/III studies to address FDA's concerns (Study SPD485-201, an analog laboratory classroom study; Study SPD485-302, a 7-week outpatient naturalistic study with a CONCERTA® reference arm; and Study SPD485-303, an ongoing open-label extension study). These new studies utilized a 9-hour MTS wear time in tested subjects. On 28 June 2005, an NDA Resubmission was made to the FDA detailing the results of these 9-hour wear time studies (additionally, data on the long-term pediatric population with a 12-hour MTS wear time was also submitted, as discussed previously in the preceding section).

An Interim Safety Report was submitted to the Agency on 25 August 2005. This update presented data from SPD485-303, the only study with active, participating subjects at the time of data collection. This study utilizes the target 9-hour MTS wear time. As of 03 June 2005, the mean (SD) length of exposure in the ongoing long-term open label SPD485-303 study was 132.0 (56.20) days with a range of 7 to 229 days. In this study, forty-seven subjects have received MTS for over 7 months and 10 subjects have received MTS for over 8 months.

The safety assessments for the studies conducted with a 9-hour wear time indicate that the overall safety profile of MTS is consistent with the published results of other approved methylphenidate products. The majority of adverse events were mild to moderate in intensity, transient, and typically resolved with continued dosing. Commonly encountered treatment-emergent adverse events (TEAEs) were those expected to be associated with use of stimulant medication, (insomnia, anorexia, and headache). The adverse events in MTS-treated subjects were similar to those in the CONCERTA® group.

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

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

Summary of Differential AE Profile With 9-Hour vs. 12-Hour Wear Times

AEs reported in the MTS clinical development program were generally similar in nature to those reported for other methylphenidate formulations. However, the incidences of anorexia and insomnia with a patch application time of 12 hours or longer were noteworthy, and may be due to overexposure of methylphenidate. With shorter patch wear times the incidence of these AEs was reduced.

In summary, the AE and clinical evaluations conducted during the clinical development program with an average 9-hour wear time indicate an acceptable safety profile for MTS. No other unexpected safety risks beyond those commonly associated with stimulant medications were identified.

5.5 Potential for Abuse and Overdose

Two (2) studies (N17-007, N17-012) evaluated potential for abuse in standard laboratory settings for such evaluations. Study N17-014 examined the pharmacokinetics of previously used MTS patches to provide information relevant to assessing their potential attractiveness for abuse.

Study N17-007 examined the abuse potential of MTS in adult stimulant-abusing volunteers according to a standardized protocol and by a leading investigator in abuse liability assessment. The study compared 2 doses of MTS to 2 doses of subcutaneously administered methylphenidate and a dose of oral phentermine (a Schedule IV stimulant). The main findings bearing on abuse potential were as follows: (1) Application of 3 or 6 MTS 25cm^2 patches produced subjective stimulant effects (e.g., mild euphoria) that were comparable to those produced by oral administration of phentermine and lower than those produced by subcutaneous methylphenidate. (2) Time to onset of the subjective stimulant effects was relatively slow compared to phentermine and subcutaneous methylphenidate, occurring an average of 2 or more hours after patch application. (3) Less than one-half of all subjects experienced euphoria and the higher dose was increasingly associated with mild dysphoria (42%). Taken together, these results indicate that the MTS does have stimulant-like abuse potential but that it would be predicted to be less attractive to abusers than prototypic stimulants of abuse (such as readily available methamphetamine and cocaine),

which many studies have demonstrated produce stronger, more reliable, and faster onsetting effects.

Study N17-012 examined the abuse potential of MTS by heating the patch or applying the patch to the buccal mucosa. This was a 2-part study that was conducted on an in-patient basis with 6 adult stimulant abusers. Part 1 was a double-blind, single-dose, randomized, crossover study of active or placebo MTS applied to the arm for 8 hours, with heat or no heat for 6 hours. Part 2 was a double-blind, placebo-controlled, single-dose, randomized, crossover study of active or placebo MTS applied to buccal mucosa for 2 hours. There was a 24-hour washout period between each treatment period.

Application of heat to MTS doubled the exposure to *d*-methylphenidate and *l*-methylphenidate, and slightly reduced the lag time of these enantiomers' appearance in plasma. The higher plasma levels of methylphenidate were associated with most subjects feeling the drug effect and liking it for up to 12 hours post application. Both of these responses were greater with heat than without, and were reported by both subject and observer. Dysphoric feelings were prominent up to 12 hours in 2 of 6 subjects during the period when heat was applied to the patches during the 24-hour period of observation. For blood pressure, there were larger mean increases (6 to 12 mmHg) in supine systolic and diastolic blood pressures from 4 - 6 hours to 12 hours after patch application with heat compared to the no heat condition. This finding is consistent with the greater systemic exposure of *d*-MPH with heat. However, it is unlikely that these effects (subjective and hemodynamic) would be readily apparent when the drug is used to treat ADHD since 3 x 25 cm^2 patches clearly exceeds the recommended MTS dose range and heating the patch is not expected to occur under normal conditions of use.

Although MTS is meant to be applied to the skin, if one applies it to the buccal mucosa, plasma concentrations of *d*-methylphenidate and *l*-methylphenidate would be detectable at 15 minutes and increase progressively up to 2 hours or beyond. Approximately 56% of the dose of methylphenidate was delivered from MTS after only a 2-hour exposure to the buccal mucosa. All subjects developed euphoria, as indicated by both the subject and observer. Dysphoric feelings of varying degrees in most subjects were noted, but did not reach statistical significance compared to placebo treatment. It is noteworthy that subjects could not eat, drink, talk, or smoke during this 2-hour period.

Study N17-014 examined the pharmacokinetics of MTS patches that had previously been used. This was an open-label study of MTS methylphenidate pharmacokinetics following two 16-hour applications of the same 25 cm^2 patch. The subjects were 6 healthy adult volunteers. The purpose of the study was to evaluate methylphenidate pharmacokinetics in plasma during and after application of a used patch, which is a potential source of abuse and diversion. Mean methylphenidate concentrations, C_{max}, and AUC were lower in plasma after application of a used patch compared with the unused patch. The mean apparent dose of methylphenidate delivered during the total 32-hour wear time was 27.4 mg. Based on mean AUC_{0-24} values, approximately 60% of this methylphenidate dose was delivered during the first 16-hour wear period with the remainder delivered during the second wear period.

In conclusion, the potential for abuse with MTS is no greater (and may prove to be less) than expected for oral methylphenidate and other products in this drug class.

5.6 Risk Management Program

The impact of MTS availability on national trends in stimulant abuse and diversion is expected to be very low. It is not expected to increase abuse and diversion because it is not a preferred form for abuse, and because less expensive preferred forms (such as methylphenidate pills) are readily available.

The approach to risk management for MTS flows from the following core observations and conclusions:

1. Methylphenidate is a Schedule II controlled substance for which there is a potential for abuse and diversion.

2. The most common forms of current methylphenidate abuse are the swallowing of intact pills and "snorting" or injection of crushed pills.

3. Methylphenidate is relatively inexpensive and readily available in easily abusable pill form via the Internet and "street" dealers.

4. MTS, whether new or used, is not expected to be attractive to abusers or diverters because applying a system (new or used) will not produce the stimulant euphoria of pills (swallowed or "snorted"), and because extraction from a transdermal patch to obtain an abusable form of methylphenidate requires several chemical processes and relies upon a relatively expensive and limited supply as compared to presently available pills.

5. Although there have been reports of methylphenidate diversion (oral dosage forms) from patients to friends, most abuse appears to rely on methylphenidate obtained illicitly and through "doctor shopping".

6. There are several populations of potential concern for abuse including patients, friends, and drug abusers.

7. There are several potential avenues for diversion, including occasional diversion of individual new or used MTS "locally" to friends, and diversion of new or used MTS to illicit drug dealers.

Specific elements of the Risk management Program (RMP) are detailed below.

Packaging And The Charting System: It is proposed that as each MTS is used, a chart (included with the packaging) will be initialed, dated, and the time of administration noted. The time of removal will also be indicated on the chart. The chart will also include space for comments such as the initials of the person who applied the patch, the site of patch application, and the disposal method used. Thus, the chart system will help achieve the dual goal of encouraging appropriate and regular use and also providing a means of detecting diverted product.

Disposal Methods: Proper disposal is a key element of risk management, and was of concern to the Division because of the residual drug contained in and potential diversion of used systems. It is believed that used and folded patches will not be an attractive target for

abusers. Once folded, they cannot readily be reopened without destruction. Thus, re-administration by reapplication would be difficult. Extraction of methylphenidate would require steps to physically alter the MTS and then to chemically extract the methylphenidate. Although this is theoretically possible, the burden would not make this attractive for "friend-to-friend" diversion and appears unlikely to be attractive to illicit drug marketers who can already obtain methylphenidate in more readily abusable forms.

School/Community Monitoring: School/Community Monitoring such as was used to monitor potential student use and diversion of nicotine replacement products upon their switch from prescription to OTC marketing will help enable identification of instances of abuse and diversion that may signal recent and wider abuse ("sentinel" abuse or diversion). An existing infrastructure (i.e., Drug-Free Communities) will serve as the base population.

Internet Monitoring: The objective of Internet Monitoring is to identify potential sentinel occurrences of diversion, tampering, abuse, or misuse of MTS across the broad population that relays such information via the Internet.

News/Media Monitoring: News/Media Monitoring of print and broadcast outlets provides an opportunity to monitor potential instances of abuse and misuse in "real time", complementing the evidence available through analysis of federal surveys.

Federal Surveys Monitoring: The objective of Federal Surveys Monitoring is to detect potential regional issues and track trends. Although the Community and Internet monitoring approaches are expected to yield signs of diversion and abuse more rapidly than the Federal Surveys, the Federal Surveys are validated standards for drug use and abuse assessment, allow monitoring of trends across time, demography, and geography, and, in most cases, provide rates of drug use in the target population.

Supply Chain Monitoring: An education system will be instituted to enhance the ability of critical elements within the distribution/supply chain to detect potential diversion of MTS. Education brochures will be developed for wholesalers to potentially enhance their capability to detect unusual order patterns, and for pharmacists and doctors to enhance their awareness of tactics used for diversion purposes.

Supplementary Educational Materials: Supplementary educational materials provide information and reinforce key messages to relevant populations (i.e., parents, teachers, school nurses, pharmacists, and prescribers).

Sales Representative Training: The objective of sales representative training is to enable representatives to educate health care professionals on the possibility and nature of potential diversion and abuse, and to reinforce compliance messages that reduce that potential.

It is important to note that each component of risk management is part of a comprehensive approach towards reducing and detecting abuse and diversion, and no single component would be expected to fully address the various issues raised by the potential channels of abuse and diversion.

5.7 Risks and Benefits

The clinical benefits of MTS include delivery of an effective treatment for ADHD and once-daily dosing with titration-to-effect based on dose and a recommended wear time for the patient. Patch application and removal at home each morning and afternoon by a parent/guardian helps assure parental control over treatment compliance and may lower the abuse potential and risk of accidental poisoning. Additionally, the transdermal route of administration provides sustained levels of active drug and may be an advantage in certain patient populations (e.g., those unable to swallow pills).

MTS is associated with these risks, typically associated with stimulant drugs (e.g., anorexia, weight loss, nervousness, insomnia, headache, abdominal pain, tics, emotional lability and abuse potential), that are similar to those reported for orally administered methylphenidate products. If the patch is not removed after the prescribed time of 9 hours, adverse effects seen are those related to prolonged exposure to methylphenidate, namely, an increase in anorexia, insomnia and headache. Risks associated with wearing the patch are skin irritation and the potential for sensitization to methylphenidate. While there is residual methylphenidate in the patch, the relative difficulty in extracting methylphenidate from the patch and the time required for transdermal delivery should reduce the incidence of abuse of the MTS product.

Overall, the benefits of MTS use outweigh the risks to pediatric patients with ADHD, and demonstrate that MTS, with its sustained-release characteristics and novel mode of administration, constitutes an effective tool in the treatment of ADHD.

5.8 Regulatory History and Executive Summary

NDA 21-514 was submitted to the FDA by Noven on 27 June 2002 for MTS for the treatment of ADHD in pediatric patients. On 25 April 2003, the Agency issued an action letter for NDA 21-514. The FDA acknowledged the clinical data demonstrating that MTS was efficacious, but noted unacceptable levels of insomnia and anorexia, significant weight loss in the short term, and the potential for skin sensitization, and expressed concerns that these adverse events could result in possible growth retardation or other serious adverse consequences with more chronic treatment with MTS due to overexposure of methylphenidate consequent to longer wear time. The Agency suggested that decreasing the wear time of the MTS patch might decrease the incidences of insomnia, anorexia, and significant weight loss to acceptable levels. In order to demonstrate such decreases in these adverse events, the Agency required evidence that a shorter MTS patch wear time was both safe and effective. The Agency also indicated the need for a comprehensive risk management program.

Shire and Noven have been co-partners for the clinical development of MTS. In meetings and correspondence with the Agency, Shire and Noven gained FDA concurrence to pursue 3 new Phase II/III studies to address FDA's concerns (Study SPD485-201, an analog laboratory classroom study; Study SPD485-302, a 7-week outpatient naturalistic study with a CONCERTA® reference arm; and Study SPD485-303, an ongoing open-label extension study). In addition, 2 MTS pediatric pharmacokinetic studies were conducted (Studies

SPD485-101 and SPD485-102). An NDA Resubmission was made to FDA on 28 June 2005, addressing the concerns stated in the action letter.

In brief, the data from these studies demonstrate that MTS, worn for 9 hours, offers benefit in the treatment of ADHD in patients aged 6-12 and was associated with reduced insomnia, anorexia, and weight loss. A comprehensive Risk Management Program was developed and discussed with the Agency in a meeting on 26 May 2004 and in subsequent meetings and other communications.

Shire and Noven believe that MTS represents an important addition to the range of medications available for treating the diverse needs of children with ADHD.

5.9 Appendices

Appendix 1: Pharmacokinetics/Pharmacodynamics Summary

Appendix 2: Efficacy Summary

Appendix 3: Safety Summary

Appendix 4: Integrated Summary of Risks and Benefits