INTEGRATED SUMMARY OF RISKS AND BENEFITS

NDA NO: 21-514

Generic Name:	SPD485, *d,l (threo)*-methylphenidate, Methylphenidate Transdermal System (MTS)
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Noven Pharmaceuticals, Inc. 11960 Southwest 144th Street Miami, FL 33186
Agent of Sponsor:	Shire Development Inc. 725 Chesterbrook Boulevard Wayne, PA 19087, USA

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1. INTEGRATED SUMMARY OF RISKS AND BENEFITS

1.1 Introduction

Attention Deficit Hyperactivity Disorder (ADHD), the most prevalent psychiatric disorder of childhood[1], is estimated to occur in 2-9% of school-aged children.[2,3,4,5,6] The principal characteristics of ADHD consist of distractibility, short attention span, disorganization, impulsivity, and hyperactivity[7]. Stimulant medications with or without concomitant behavioral therapy are the standard of care for treating children with ADHD[9]. Ritalin® brand methylphenidate (MPH) was the first commonly prescribed pharmacotherapy; however, it has an inconvenient dosing schedule that necessitates twice or 3 times daily administration, including at least 1 dose administered during school hours. The development of once-a-day sustained-release (SR) preparations of methylphenidate, overcome these problems associated with multiple-dose administration. The currently available methylphenidate formulations include CONCERTA®, Focalin™, Focalin™ XR, Metadate®CD, Metadate ER, Methylin®, Methylin ER, Ritalin, Ritalin LA, and Ritalin-SR. All formulations provide reliable, effective pharmacotherapy for ADHD.

Methylphenidate Transdermal System (MTS), a matrix transdermal delivery system in which the matrix acts as both the drug reservoir and adhesive layer, was developed by Noven Pharmaceuticals, Inc. (Noven) as a means of delivering systemic methylphenidate with once-daily application of the patch.

The benefits and risks associated with MTS pharmacotherapy for ADHD in pediatric patients are summarized below.

2. BENEFITS AND RISKS

The clinical benefits of MTS include delivery of a recognized effective treatment for ADHD, and once-daily dosing with titration-to-effect based on a recommended patch size and wear time for the individual patient. MTS may also have a potentially lower abuse profile and decreased risk of accidental poisoning compared to oral methylphenidate formulations. The transdermal route of administration provides sustained levels of active drug and may be advantageous in particular patient populations (e.g., those unable to swallow pills). The risks of MTS are primarily those associated with methylphenidate. The risks attributable to the delivery system are predominantly local irritation and a potential for sensitization. The benefits and risks to be discussed are summarized in Text Table 1. Noven conducted the initial clinical program, designated in this document as Phase III-1. On 27 June 2002, the original New Drug Application (NDA 21-514) for MTS was submitted to FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). On 25 April 2003, the Agency issued an action letter regarding the application. As a result of this action letter, Shire Development Inc., acting as agent for Noven, conducted a second phase of clinical development. This phase is designated as Phase III-2 in this document.

Table 1: Summary of Benefits and Risks of MTS

Benefits	Risks

• Methylphenidate is an effective treatment for ADHD
• MTS is efficacious in the treatment of ADHD
• Once-daily dosing with sustained efficacy
  • Response to behavioral symptoms: within 1-2 hours of application
  • Efficacy persists after patch is removed: duration of effect ~12.5 hours with 9-hour patch wear time
• Efficacy observed by clinicians, parents and teachers
• Transdermal route of administration: - no oral dosing
• Pharmacokinetics
  • MTS provides sufficient exposure to methylphenidate to support efficacy conclusions
  • Similar systemic exposure in all races studied
  • Clinical effects noted in all races studied
  • Drug delivery stops upon patch removal
  • Ability to individualize drug delivery: patch size (drug content) and application time
• Decreased risk of accidental poisoning
  • Low potential for inadvertent overdose
  • Lower potential for diversion and abuse
  • Easy to dispose of used patches
	• Drug-related adverse events associated with methylphenidate
	• Adverse events related to longer exposures (> 9 hours)
	  • Longer wear times may lead to overmedication and additional adverse effects
	• Effects on growth and weight are similar to other stimulants
	• Risks of MTS related to the delivery system: potential for skin irritation and sensitization
	• Residual methylphenidate in patches and potential for abuse or diversion

2.1 Methylphenidate is an effective treatment for ADHD

Methylphenidate is an enantiomeric mixture of *d,l*-methylphenidate. In animal models of behavior, the apparent therapeutic effect of the *d-,l-* racemate appears to be entirely due to the *d*-MPH isomer. In humans, administered *d-,l*-MPH via the oral route, the *l*-MPH isomer is selectively removed by first pass metabolism in the liver. Stimulant medications such as methylphenidate have been used for over 60 years to treat children with ADHD. In 1994, it

was estimated that about 80 percent of all diagnosed cases of ADHD were treated with methylphenidate, and positive effects on behavior and academic productivity are well-established for this stimulant medication.[8,9,10,11] Studies have shown that methylphenidate improves classroom functioning and teacher ratings of children with ADHD by decreasing disruptive behavior and increasing academic productivity and accuracy.[12,13,14,15] In addition, methylphenidate has been shown to improve performance in children on a number of cognitive tasks, such as measures of attention, learning, and memory[16].

The national ADHD organization, Children and Adults with Attention Deficit Disorders (CHADD), notes that between 70-80% of children with ADHD respond positively to psychostimulants, the most widely used medications for the management of ADHD-related symptoms[17]. Methylphenidate has widespread acceptance as one of the most effective ADHD pharmacotherapies. Methylphenidate benefits are recognized by clinicians, parents and patients.

2.2 MTS is efficacious in the treatment of ADHD

In the initial MTS clinical development program (Phase III-1), 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 majority of the patch wear times in these studies were 12 hours. All 6 studies demonstrated evidence of superiority of MTS over placebo transdermal system (PTS) in improving behavior of pediatric patients with ADHD assessed by laboratory or community teachers, camp counselors, or parents. In Phase III-1 Study N17-018, which employed a parallel group design and a large range of doses, MTS was found to be superior to PTS at a statistically significant level ($p<0.0001$) 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, Phase III-1 clinical studies demonstrated benefits on behavioral symptoms, the 12-hour patch wear time was associated with a higher incidence of methylphenidate-related adverse effects. Two (2) additional clinical studies in Phase III-2 were conducted to support the efficacy of MTS using a shorter patch wear time. Subsequently, the patch wear time of 9 hours was chosen based on the pharmacokinetics of *d*-MPH administered by MTS as compared to a dose of CONCERTA. The pharmacokinetic profile of CONCERTA shows a T_{max} of 7 hours followed by a plateau in *d*-MPH concentrations up to 9 hours when elimination becomes apparent. A 9-hour wear time for MTS was slightly longer than the T_{max} for CONCERTA and approximates the plateau and elimination of orally administered CONCERTA. It was postulated that if the adverse events were due to prolonged elevations in plasma methylphenidate levels a reduced wear time should reduce the adverse effects observed to a similar rate as observed with other oral methylphenidate products. An additional consideration for the 9-hour wear time selection was the duration of the school

day. Application of MTS around 07:00 AM would allow for removal around 4:00 PM daily after the school day is completed.

The 9-hour wear time was studied in an Analog Laboratory Classroom protocol, Study SPD485-201. The results of the Analog Laboratory Classroom study demonstrated an overall effect on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) deportment score during the period of patch wear (0-9 hours). In the pivotal clinical study, using the clinician rated ADHD-RS-IV, MTS demonstrated significant improvements in overall ADHD symptoms compared to placebo. In this study, CONCERTA was used as a reference treatment. CONCERTA also significantly improved ADHD symptoms compared to placebo. The magnitude of the effect for MTS and CONCERTA was comparable between the 2 active treatments. This study was not powered nor designed to test MTS and CONCERTA.

These 2 studies support the efficacy of MTS worn for 9 hours in the treatment of ADHD in children.

2.3 Once-daily dosing with sustained efficacy

Studies in the MTS clinical development program demonstrated that once-daily MTS provides sustained plasma methylphenidate levels for the entire duration of patch wear, with clinical efficacy maintained over the entire wear period.

Study N17-002 showed that once daily application of MTS worn for 24 hours provided 24-hour plasma AUC values for total methylphenidate and metabolite comparable to those obtained following oral TID Ritalin. Study N17-006 demonstrated that once-daily application of MTS for a period of 16 hours for 6 days provided comparable total methylphenidate AUC values for MTS and immediate release (IR) methylphenidate. Both of these studies clearly showed that the transdermal route was not associated with the peak and trough fluctuations in plasma methylphenidate levels typical of multiple daily doses of IR methylphenidate. Efficacy measures in Study N17-002 for the TID Ritalin condition showed the "scalloping" effect associated with multiple daily doses of methylphenidate[16], whereas MTS treatment was not associated with fluctuations in efficacy.

In a summer-treatment laboratory classroom setting, onset of clinical effects with MTS began about 2 hours following patch application, and effects were sustained for as long as the patch remained on the skin. Effects waned over a 4-hour period after patch removal and appeared to be dose related. In the initial study with MTS (N17-002), wear time was set at 24 hours. Subsequent to this trial, wear time was reduced to no more than 16 hours for the remaining studies in the MTS program. In the Phase II, 6-week, dose response daily cross-over study (N17-015) in which patch sizes of 12.5 to 37.5 cm^2 were studied, MTS was effective compared to placebo TS for the majority of efficacy variables, as measured by teachers, counselors and parents with a wear time of 8.5 hours.

The results from the laboratory classroom study (SPD485-201) that compared MTS versus PTS after an open-label dose optimization period demonstrated that the onset of action of MTS on behavioral symptoms was evident approximately 1-2 hours after patch application. This was demonstrated by a significant improvement in SKAMP deportment scores as observed in the classroom setting. The duration of effect persisted after patch removal until

the last observation at 12 hours. Thus, the duration of effect was defined as at least 12.5 hours. These results are supported by the results of the secondary endpoint, the PERMP where significant effects were noted at the 3-hour session and continued through the last class session at 12 hours.

These results support the previous findings that once daily administration of MTS and removal at 9 hours provides ADHD symptom improvements from 1-2 hours after application through the remainder of the typical waking day for children.

The data from the clinical efficacy studies suggest that MTS is an effective method of delivering once-daily methylphenidate for the treatment of ADHD, with the added benefit versus oral methylphenidate of offering the clinician a means to modulate drug exposure during the day by adjusting patch size and/or wear time, which may have implications for the management of the side effect profile and daily activities.

2.4 Efficacy observed by clinicians, parents and teachers

The clinical evidence suggests that MTS may be an effective alternative to oral methylphenidate in treating children with ADHD.

In study SPD485-201, secondary efficacy measures included the clinician-rated ADHD-Rating Scale (RS)-IV scale, Clinical Global Impressions (CGI), Parents Global Assessment (PGA) and the Connor's Parent rating scale (CPRS). MTS showed significant improvement on all 3 scales when compared to placebo. The CPRS was rated during both the morning and the afternoon by parents. The beneficial effects of MTS were noted at both times supporting the SKAMP deportment observations, which were obtained in the laboratory classroom sessions.

In study SPD485-302, the main secondary outcome was the change in the Connor's Teacher rating scale (CTRS) score. Teachers evaluated subjects on 2 days and 2 times on those days. The CTRS-R, Endpoint analysis in the ITT population showed statistically significant differences in change scores between MTS and placebo and also between CONCERTA and placebo for the CTRS-total score, ADHD index score, hyperactivity score, and cognitive score. There were no statistically significant differences between MTS and CONCERTA on the CTRS.

Other secondary measures in SPD485-302 included the clinician-rated CGI, the parent-rated CPRS and the parent-rated PGA. MTS demonstrated statistically significant improvements on each of these scales compared to placebo.

The 3 groups most affected by the behavior of children with ADHD are parents, teachers and the clinician who follows these patients. MTS demonstrated that effects on ADHD symptoms were evident not only to trained observers, but also to parents and teachers.

In addition to conferring direct therapeutic benefits on the patient, MTS may be beneficial in helping prevent the stigma and loss of privacy associated with school administration of methylphenidate, a well-documented reason for methylphenidate non-compliance.[18,19] Patch application each morning and removal at home each evening by a parent/guardian is discreet and helps assure parental control over treatment compliance. When asked whether

removing the patch and discontinuing treatment at any time afforded them control over their child's treatment, 73% and 82% of parents in Studies N17-010 and N17-018, respectively, strongly agreed. In addition, the use of MTS vs. immediate-release methylphenidate circumvents the need for supervision and storage of Schedule II drugs at school. Across the 7 clinical safety and efficacy studies completed in pediatric patients at the time of the original NDA filing (N17-002, N17-003, N17-009, N17-010, N17-011, N17-015, and N17-018), 1 of which was long-term (N17-011), no euphoria or dysphoria was reported and no instances of MTS abuse or diversion were reported.

2.5 Transdermal route of administration: - no oral dosing

Some school-aged children, including a few older children and adolescents, have not acquired the ability to swallow pills, creating an impediment to drug treatment with products available only in pill form. Counseling and training-based interventions addressing this problem have been reported, most often in the setting of serious or life-threatening chronic illnesses requiring oral therapy.[20] The use of MTS may prevent inadvertent repeated doses, as the patch will be a visible reminder to parents or patients who may not remember if their pill was taken on a particular day.

Despite the high levels of physical activity in which children typically engage, there was a high degree of patch adherence to the skin. Patients in the Phase III-1 controlled studies reported ≥90% patch adherence across all visits. In the 2 Summer Treatment Program studies in a camp setting (N17-009 and N17-015), the fall-off rate for patches was 8% and 1%, respectively, despite high levels of physical activity (swimming, sports, changing clothes, etc.). The majority of patches in Study N17-015 (85-100% across all treatment groups) were greater than 75% adhered at 2 evaluations (at lunch and prior to removal at 12 hours).

In study SPD485-302, an outpatient study conducted during the school year, observations for the dermal evaluation were made at each clinic visit. The majority of patients (97.6%) demonstrated acceptable patch adherence (Text Table 2).

Table 2: Dermal Adherence Scores in Study SPD485-302 (9-hour Wear Time)

	MTS		PTS	
*Score	N obs.= 443	(%)	N obs. = 713	(%)
0	360	(81.3)	628	(88.1)
1	72	(16.3)	72	(10.1)
2	8	(1.8)	5	(0.7)
3	0	0	3	(0.4)
4	3	(0.7)	5	(0.7)

*Score: 0: ≥90%; 1: 75-90%; 2: 50-75%; 3: <50% and 4: detached

Overall the rate of patch adherence indicated that the patch can withstand the normal daily activities of children 6-12 years old.

2.6 Pharmacokinetics

2.6.1 MTS provides sufficient exposure to methylphenidate to support efficacy conclusions.

The evidence presented supports the linear dose proportionality of MTS and suggests similar bioavailabilities of *d*-MPH from MTS patch sizes of 25 cm^2 and 37.5 cm^2 to the equivalent doses of orally administered CONCERTA (36 and 54 mg respectively).

MTS delivers racemic *d*- and *l*-methylphenidate transdermally, which avoids the first pass elimination of the *l*-methylphenidate isomer by the liver. In all the studies during Phase III-2 where methylphenidate levels were measured, the levels of *l*-MPH were easily detectable. The *l*-isomer is not believed to be pharmacologically active in animals[21] or in man and no correlations between the *l*-isomer and pharmacodynamic or adverse events were observed.

The evidence presented in reports of the 2 Phase-I studies supports the linear dose proportionality of pharmacokinetics for single doses of MTS. Data from these 2 studies indicate similar bioavailabilities for *d*-MPH delivered from MTS patch sizes 25 and 37.5 cm^2 to those achieved after oral administration of the equivalent CONCERTA doses (36 and 54 mg, respectively).

In study SPD485-101, across all subjects, the 10-hour wear-time for MTS 25 cm^2 resulted in *d*-MPH bioavailability similar to that of 36 mg CONCERTA. The AUC parameters were only 18% lower at 10 hours for MTS than for CONCERTA and C_{max} values were similar across both treatments. The terminal portion of the profiles, between the 6-14 hour period from the end of the shortest wear-time until a typical end of the active day demonstrated similar or slightly 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. Based on this and the logistics of a school day a patch wear time of 9 hours was chosen as optimal.

In study SPD485-102, using the wear time of 9 hours, the bioavailability of *d*-MPH following administration of MTS 37.5 cm^2 was not appreciably different to that following oral administration of 54 mg CONCERTA.

In study SPD485-201, exposure to methylphenidate after MTS administration increased over time, indicative of accumulation. Comparisons of C_{max} values after single and repeated doses of MTS indicate 71% to 104% accumulation of methylphenidate with repeated dosing.

In study SPD485-302, plasma concentrations at the end of wear-time (9 hours) for MTS were higher (on average 1-5 to 2-fold) than those for the comparable doses of CONCERTA. For each patch size, these C_{max} concentrations were very similar to those seen in study SPD485-201, indicating that steady state concentrations had been achieved some time within the first week of dosing (as expected for a drug with a 3-4 hour half-life) and had not accumulated further.

PK/PD modelling in study SPD485-201 indicated a concentration required to obtain 50% of the maximum effect (EC_{50}) value of 17ng/mL for the relationship between placebo-adjusted SKAMP deportment scores and plasma concentration. The predicted line of best fit indicates additional benefit may be seen at concentrations up to at least 40 ng/mL, the order of magnitude of the mean 9-hour concentration for the 37.5cm^2 patch at steady-state. Similar findings came from the modelling of baseline-adjusted PERMP.

2.6.2 Similar systemic exposure in all races studied

In Study SPD485-101, there were differences noted in the pharmacokinetics profile between Black and White subjects. The analysis by race indicated a significant decrease in *d*-MPH exposure from MTS among the Black subgroup. Systemic exposure (both AUC and C_{max}) was lower for MTS than for CONCERTA in this group and was approximately half that of the White group receiving the MTS treatments.

In Study SPD485-102, using a 9-hour wear time the differences between Black and White were not as evident. Pharmacokinetic parameters from this study are presented in Text Table 3. There were no appreciable differences among races with respect to any pharmacokinetics parameter measured. The t_{lag} tended to be shorter in the Other races than in Black or White subjects, and T_{max} tended to be slightly longer in Black subjects than Other races although these differences were small compared to the standard deviations.

In the clinical studies SPD485-201 and SPD485-302, plasma MPH levels were obtained either during the classroom day or as sparse samples around T_{max}. In these studies, with small numbers of non-White subjects, there were no obvious differences in exposure or plasma concentrations between White and Black subjects.

Table 3: Mean Pharmacokinetic Parameters by Race in Study SPD485-102

Patch Size (cm^2)	Cmax (ng/mL)			Tmax (h)			t_{lag} (h)			AUC 0-t (ng*hr/mL)		
	W	B	O	W	B	O	W	B	O	W	B	O
12.5	9.33	9.98	11.9	8.57	8.95	8.99	1.49	1.77	1.31	81.8	92.0	91.4
25.0	17.5	17.5	20.3	9.42	9.73	8.98	1.65	2.08	1.34	157	170	184
37.5	27.4	27.5	24.8	8.89	9.42	8.32	1.08	1.58	0.98	251	257	231

W= White subjects (n = 19); B= Black subjects (n = 12); O= All other races (n = 3)
Source: SPD485-102 PK Report, Section 6.6

2.6.3 Clinical effects noted in all races studied

The evidence supports the conclusion that there may be small differences in the pharmacokinetics parameters among children of various races exposed to MTS. However,

MTS improves symptoms of ADHD in Black and Other races when evaluated by trained observers in the laboratory classroom, school setting (teachers), clinicians and parents.

Because of the potential differences in pharmacokinetics parameters noted in study SPD485-101, efficacy parameters were examined in SPD485-201 and SPD485-302 with regard to race. In these analyses, the numbers of subjects were too small to do formal statistical testing; however, the trends observed are important indicators of any potential differences in MTS response by race. In Study SPD485-201, the laboratory classroom study, the only differences noted when results were categorized by race was that Black subjects tended to have higher baseline scores on the SKAMP deportment scale. When examined by classroom session, an effect was noted at the second post-dose classroom assessment (3 hours) compared to White and Other race subjects. These results were also observed on the PERMP.

In the Pivotal study SPD485-302, the results for the primary endpoint, the clinician-rated ADHD-RS-IV scale were similar in all races.

2.6.4 Drug delivery stops upon patch removal

One of the advantages of MTS is that drug absorption through the skin stops with the removal of the patch. This is demonstrated in the clinical pharmacology studies conducted with MTS. When patches are removed at 9 hours, the mean values for *d*-MPH observed at the first post removal blood samples are lower than the 9-hour value for all patch sizes. The implications for this are that if adverse events are noted to occur at specific times post patch application (i.e., apparently related to plasma drug concentration), the patch may be removed before or at the time of the adverse events to prevent or limit the duration of the adverse effect. In study N17-018, the target patch wear time was 12 hours, but reduction of wear time to about 8 hours was allowed if patients developed late-day side effects. The advantage of reducing wear time was most evident in those patients who developed insomnia during this study. A wear time reduction alleviated insomnia in approximately 65% of the cases.

2.6.5 Ability to individualize drug delivery: patch size (drug content) and application time

The pharmacokinetics of MTS allow for the manipulation of 2 independent parameters to allow clinicians to modify treatment to optimize individual response. The total exposure to methylphenidate is determined by the size of the patch and the wear time. The patch is capable of delivering drug for up to 24 hours. Clinical studies with patch wear times of greater than 9 hours have shown that MTS improves ADHD symptoms but at the cost of increased adverse events. However there may be some circumstances when increased symptom control may be needed based on individual needs and responses to therapy, even at the expense of potential insomnia or decreased appetite. Thus, there is the potential to individualize treatment on an as needed basis without new prescriptions or an office visit being required. Wear times shorter than 9 hours have not been tested; however, given the results observed in the laboratory classroom study that onset of action is by 1-2 hours and persists for up to 12.5 hours, shorter patch application times may also give ADHD symptom

control. The patch size can also be changed to increase the dose under conditions of the recommended wear time of 9 hours. The recommended wear time was determined by comparison of the pharmacokinetics parameters between CONCERTA and MTS as well as the logistics of the school day. Under normal circumstances it is recommended that MTS wear time is fixed at 9 hours and the dose nominally increased by increasing patch size until symptoms are controlled. Four (4) MTS patch sizes will be available. The dose of methylphenidate delivered with these patches will cover the usual effective dose range offered by long-acting oral methylphenidate products.

2.7 Decreased risk of accidental poisoning

Methylphenidate is a potential source of medication poisoning in children[22,23]. The pediatric methylphenidate overdoses described in summaries from poison control centers involve mistaken doses given to patients by care providers (often an inadvertent repeated dose), deliberate self-administration of medication above the prescribed dose (most often by older children who supervise their own medications), and exposures in children not prescribed methylphenidate (commonly in younger siblings of the patient). Nearly all reported overdose episodes involve ingestion of an oral formulation and may occur in conjunction with another substance. Serious medical outcomes are rare. During the MTS development program, there were no reports of MTS-related methylphenidate overdoses (patients receiving more than the protocol-specified dose) among patients or subjects.

Accidental drug overdoses related to chewing or swallowing of transdermal patches by young children have been reported, although these events are uncommon[24,25]. Accidental oral exposure of young children may be less common for medication patches than pills because of the individual childproof protective coverings, the offensive taste, and the unpleasantness of the adhesive.

2.8 Lower potential for diversion and abuse

MTS may have a lower potential for abuse or diversion than oral formulations of methylphenidate. MTS produces a slower rate of rise in blood drug levels and has a slower onset of action than immediate-release preparations, factors that are important determinants of abuse potential.[28] Also, since MTS is administered in the morning by the parent and removed by the parent after the child returns home from school, the potential for abuse and diversion related to school storage and dispensing of oral formulations[26,27] is mitigated. When asked whether MTS afforded them peace of mind over potential misuse, 79% and 81% of parents in Studies N17-010 and N17-018, respectively, strongly agreed.

Study N17-007 examined the abuse potential of MTS in adult stimulant-abusing volunteers. The degree of euphoria from six 25cm^2 MTS patches was comparable to that of 30mg oral phentermine, a Schedule IV drug. On average, the peak euphoric effects occurred much later (6-12 hours) after patch application; thus, the delayed onset of these feelings would not satisfy the immediate needs of the stimulant abuser. Also, fewer than half of the subjects reported liking the MTS drug effect (reported as euphoria) at either patch dose tested (3 or six 25cm^2 MTS patches). In contrast to subcutaneous methylphenidate, fewer patients reported euphoria as MTS dose increased. The high dose of MTS was associated with

greater numbers of subjects reporting dysphoria. Thus, increasing doses of MTS decreased the likelihood of experiencing euphoria and increased the likelihood of disliking the drug effect, a pattern that may not lend itself to the dose progression associated with recreational stimulant use.

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. Directions for safe storage and disposal of unused and used patches are included in the patient and physician labeling.

3. RISKS

MTS is associated with some risks, including those typically associated with stimulant drugs (e.g., anorexia, weight loss, nervousness, insomnia, headache, abdominal pain, emotional lability, abuse potential). The risks associated with the method of delivery are primarily those of skin irritation and discomfort as well as the potential for sensitization to methylphenidate.

3.1 Drug-related adverse events associated with methylphenidate

Adverse events 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, as well as the frequency of skin reactions (a category of adverse events related to the transdermal route of administration, the details of which are discussed in Section 3.3). With shorter patch wear times the incidence of skin reactions was less because of both the shorter exposure time and the fact that a separate dermal evaluation system was used to evaluate the skin reactions rather than recording as an adverse event.

The most common adverse events (≥5% frequency) in MTS-treated pediatric patients in the Phase III-1 controlled studies (N17-010 and N17-018) with application times of 12 hours, were application site reaction (88.1%), anorexia (33.7%), insomnia (23.3%), headache (14.4%), abdominal pain (13.4%), nervousness (7.9%), emotional lability (6.9%), viral infection (6.9%), rhinitis (5.4%), weight loss (5.4%), cough increased (5.4%), vomiting (5.0%) and twitching (5.0%). The majority of these events (anorexia, insomnia, nervousness, headache, abdominal pain, emotional lability, and twitching) are associated with stimulant medications. Most adverse events were considered mild or moderate in severity, and only 7 of 202 MTS-treated patients (3.5%) in the Phase III-1 controlled studies (N17-010 and N17-018) discontinued prematurely due to adverse events. The adverse events that most commonly (≥ 1%) led to discontinuation in the controlled pediatric studies (N17-010 and N17-018) included anorexia (1.5%) and insomnia (1.5%). No deaths occurred during any of the studies in the MTS clinical development program. There were 4 serious adverse events reported in the pediatric studies (constipation in a patient receiving PTS and 2 cases of hostility in males receiving MTS and dehydration secondary to vomiting in an 8-year old female on MTS; (none of the SAEs were considered by the investigators to be related to study treatment). There were an additional 2 SAEs in adults participating in the dermal sensitization study. One event was chest pain and gastroenteritis considered related to methylphenidate and an event of abdominal pain considered unrelated to study medication.

In the Phase III-2 studies, similar types of adverse events were reported with MTS, but the frequencies were overall decreased.

In SPD485-302, the most commonly reported treatment-emergent AEs in the MTS treatment groups were decreased appetite, headache, insomnia, nausea, upper abdominal pain and vomiting.

In the reference arm of the study where subjects were blindly treated with CONCERTA, the most commonly reported treatment emergent adverse events were decreased appetite, headache, insomnia and nausea. The percentage of subjects reporting treatment-emergent insomnia and nausea was higher in the MTS group compared to CONCERTA. The percentage of subjects reporting treatment-emergent upper abdominal pain was higher in the CONCERTA group compared to MTS. The percentage of subjects reporting vomiting was similar between the 2 active treatment groups. The frequencies of these adverse events in the clinical trials are summarized in Text Table 4.

Table 4: Study SPD485-302 Most Commonly Reported Treatment-Emergent Adverse Events (≥5% in MTS and >2X Placebo) – Safety Population (9-hour Wear Time)

Adverse Event (Preferred Term)	MTS (N=98)		CONCERTA® (N=91)		Placebo (N=85)	
	n	(%)	n	(%)	n	(%)
No. Subjects with ≥1 AE	74	(75.5)	63	(69.2)	49	(57.6)
Decreased appetite	25	(25.5)	17	(18.7)	4	(4.7)
Insomnia	13	(13.3)	7	(7.7)	4	(4.7)
Nausea	12	(12.2)	7	(7.7)	2	(2.4)
Vomiting	10	(10.2)	9	(9.9)	4	(4.7)
Weight decreased	9	(9.2)	7	(7.7)	0	(0.0)
Tic	7	(7.1)	1	(1.1)	0	(0.0)
Affect lability	6	(6.1)	3	(3.3)	0	(0.0)
Nasal congestion	6	(6.1)	3	(3.3)	1	(1.2)
Anorexia	5	(5.1)	3	(3.3)	1	(1.2)
Nasopharyngitis	5	(5.1)	4	(4.4)	2	(2.4)

Other AEs of interest include anorexia, decreased weight and events related to the skin. The number of subjects reporting treatment-emergent anorexia and decreased weight was slightly higher in the MTS group (5 subjects, 5.1% and 9 subjects, 9.2%, respectively) compared to CONCERTA (3 subjects, 3.3% and 7 subjects, 7.7%, respectively). The number of subjects in the MTS, CONCERTA, and placebo groups with treatment-emergent AEs related to the skin was (7 (7.1%), 1 (1.1%), and 3 (3.5%), respectively).

The adverse event of tic reported in the MTS group in the SPD485-302 study requires further discussion. In this large clinical study the numbers and percentage of adverse events

reported as tics was higher in the MTS group than in the CONCERTA and placebo arms. This finding is different from previous studies conducted in Phase III-1 and the SPD485-201 study. The incidence of events classified as tics is variable across the Noven and Shire studies due in part to a difference in coding dictionaries employed in the studies as well as the variability in the incidence of tic and dyskinesia in the population. The incidence of tic in the various MTS studies ranged from 0% to 7.1% (Text Table 5). The incidence of tic and dyskinesia reported in the literature (Text Table 6) ranges from 1.3% to 19.6% with the overall average of approximately 5.8% (~148/2540).

Table 5: Summary of Emergent Tics in Clinical Studies of MTS

Study Number	Type of Study	MTS n/N (%)	CONCERTA n/N (%)	Placebo n/N (%)
SPD485-302	DB, PC	7/98 (7.1)	1/91 (1.1)	0/85 (0)
SPD485-201	OL	2/93 (2.2)	NA	NA
SPD485-201	DB	0/80 (0)	NA	NA
SPD485-101	SD, OL, PK	NA	1/24 (4.2)	NA
SPD485-102	SD, OL, PK	0/34 (0)	0/33 (0)	NA
N17-021	OL	2/191 (1.0)	NA	NA

DB: Double-blind; PC: Placebo-controlled; SD: single dose; PK: Pharmacokinetic; OL: Open-label

Table 6: Literature References for Tics and Dyskinesia

Palumbo[26]	DB, PC	Placebo: 8/219 (4.0%) IR MPH tid: 5/226 (2.3%) CONCERTA: 9/224* (4.0%)
Palumbo[26]	OL	5%/month-24 months
Palumbo[26]	OL	39/643 (6.1%) (aged 6-12)
Law[27]	DB, PC	2/12 (16.7%) Oral MPH: 10/51 (19.6%)
Varley[28]	Chart Review	MPH: 31/374 (8.3%%)
Lipkin[29]	Retro CS	IR MPH: 9/122 (7.3%)
CONCERTA Package Insert	PI, OL	1. Concerta: 39/432 (9.0%) 2. Concerta: 9/682 (1.3%)

DB: Double-blind; PC: Placebo-controlled; OL: Open-label; Retro CS: Retrospective Clinical Series; PI: Package Insert
* 224 Unique Patients

The events reported as tic in the MTS studies encompassed a variety of repetitive movements of the face and eyes. Only 1 subject in the MTS group discontinued due to tic, which was classified as moderate in intensity. The event was related to MTS since the subject had no history of tic or previous stimulant medication prior to this event. Of the other subjects, 6 had intermittent events lasting around 7 days with no effect on dosing. The remaining events were mild in intensity, did not interfere with daily activities and typically responded to a reduction in dose. Thus, even though there was an increase in tic events

compared to CONCERTA, these events were typical for methylphenidate-related tic and dyskinesia. The incidence and resolution were within the ranges reported in the recent literature. Tics and dyskinesia are further well known events associated with ADHD either with or without stimulant treatment[30]. An algorithm for managing tics is included in the consensus expert report on the use of methylphenidate in children with ADHD[30]. None of the subjects in this study with MTS required any additional treatment for tic other than ceasing medication or dose reduction. Thus, MTS, while associated with a comparative increase in tics relative to CONCERTA and Placebo, is not associated with an increase beyond that expected for children with ADHD with or without stimulant treatment.

In a long-term study of MTS in children with ADHD, the adverse events of interest were similar to those described in the short-term studies. In study N17-021, which followed patients for a mean of 390 days, the patch sizes and wear times of MTS were higher (up to 50cm^2 and 12 hours) than in the Phase III-2 studies. Thus, the results in this study can be considered as a worst case for subjects who may inadvertently forget to remove the patch after 9 hours. While the overall incidence of certain adverse events in study N17-021 such as anorexia and insomnia was higher than those reported in Study SPD485-302, most of these events occurred during the first month of treatment. Weight loss and anorexia tended to occur throughout MTS treatment similar to oral MPH products.

Overall, AEs with MTS are those expected following treatment with methylphenidate. The incidence of AEs is related to the daily exposure to MTS (both wear time and patch size). In clinical practice, the patch size and wear time can be adjusted to balance efficacy with tolerability. If subjects do not remove the MTS by 9 hours the only effects evident are a slightly higher incidence of adverse events such as anorexia and insomnia.

3.2 Effects on growth and weight are similar to other stimulants

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.

In both the Phase III-1 controlled studies (N17-010 and N17-018) and in the long-term study (N17-011), a mean decrease in weight was observed in the MTS-treated patients with an MTS wear time of 12 hours. In Study N17-011, 34% of patients had clinically significant (≥5%) weight decreases from Baseline to the final study evaluation. Additional analyses of the BMI for these patients indicated that >70% of N17-011 patients were above the national median for BMI. The high incidence of weight loss in Study N17-011 is consistent with the reported correlation of BMI with early weight loss during stimulant therapy (i.e., heavier patients experience greater weight losses). Weight loss was not considered a severe event for any patient in this study, and there were no study discontinuations due to weight loss, suggesting that the managing physician and parents did not judge the weight loss a clinically significant event in these patients.

In the Phase III-2 studies of MTS, the duration of treatment was too short to demonstrate significant long-term effects on growth parameters. However, an analysis of the effects of long-term treatment of MTS on growth parameters was conducted on the available data from the N17-021 study. This study employed patch sizes up to 50 cm^2 and patch wear times of

12 hours. Thus, this study represents the worst-case presentation of the effects of MTS on growth parameters. These results are presented in the Safety Update for this resubmission. The absolute deficits for subjects participating for up to 2 years in this study, were approximately 2.0cm for height, 3.9kg for weight and 1.5 units for BMI. The mean deficit rates per year were 0.68cm for height 1.3kg for weight and 0.49 units for BMI. These results are similar to those reported for other stimulants including Adderall XR[31] and orally administered *d,l*-methylphenidate.[32]

Physicians should monitor growth, as they do for other stimulant formulations. These results suggest that deficits in growth are not a major clinical concern for most children treated with MTS, especially given the range of strategies available to manage these deficits.

3.3 Risks of MTS related to the delivery system: potential for skin irritation and sensitization

Each clinical study in the MTS development program assessed skin reactions to dermal patch application. The use of MTS was associated with some degree of application site skin discomfort (itching, burning), irritation, and sensitization; however, it is important to note that frequent protocol-specified inspection of application sites may have inflated reporting of skin reactions associated with MTS.

In the Phase III-1 controlled pediatric studies with MTS wear times of 12 hours (Studies N17-010 and N17-018), as patch size (dose) increased, the percentage of patients reporting discomfort ratings of “none” decreased. The percentage of patients experiencing moderate or severe discomfort was highest in patients receiving 50 cm^2 MTS; however, even at this highest patch size, 78% of the patients reported no skin discomfort. Likewise, for the Phase III-1 controlled pediatric studies (Studies N17-010 and N17-018), although there was a general tendency for erythema rates to increase with increasing doses of MTS, at least half of the treated subjects reported no or minimal erythema, even at the highest dose tested (50 cm^2). Only 4 patients discontinued treatment due to application site skin reactions across all pediatric studies (none from the Phase III-1 controlled pediatric studies). No serious adverse events were noted involving application site reactions.

In a study examining methylphenidate pharmacokinetics during patch application to irritated skin (for 16 hours) in adult volunteers (Study N17-017), MTS administered to subjects with inflamed skin was associated with more discomfort compared to subjects with intact skin. Therefore, the proposed labeling of MTS includes language to discourage application of the MTS to irritated or inflamed skin.

Contact sensitization following repeated exposure to MTS was specifically addressed in Study N17-008, in which healthy adults were exposed to MTS vs placebo TS and a positive and negative control. Three (3) of the 116 subjects completing the challenge application exhibited reactions suggestive of sensitization to MTS. Based on re-challenge in 2 subjects, reactions confirmed sensitization in 1 subject and did not confirm sensitization in another. The third subject declined to be re-challenged. Given that the patch was applied in a regimen not intended to reflect clinical use (repeated applications to the same site for 24-hour wear periods for up to 21 days), the incidence of topical sensitization is estimated to be no greater than 3%.

A second study (N17-020) was also conducted to assess the potential for sensitization following repeated exposure to methylphenidate. This was a single-center, randomized, evaluator-blind study, utilizing the Jordan-King modification of the Draize procedure. The induction applications were repetitive and continuous (all day) patch applications of test articles to the same site on the skin for 21 days (3 weeks). The 9 applications made during these 3 weeks were termed Induction Days No. 1 through 9. Patches applied on Mondays and Wednesdays were worn for 48 (± 4) hours and patches applied on Fridays were worn for 72 (± 8) hours. Application sites were evaluated for irritation 30 minutes to 1-hour post-removal. Following the induction period, the subjects did not receive application of test articles for approximately 2 weeks. At challenge, one 48-hour patch application of test articles was made to naïve sites to test for reactions indicative of contact sensitization. The sites were scored 48 (± 4) and 96 (± 8) hours after patch application. Because erythema was so common during the challenge phase, it was not possible to state whether this was an irritation or sensitization reaction. As a result, subjects with erythema were invited to participate in a rechallenge approximately 8 weeks after the challenge period. There was a single 48-hour application of test article(s) to a naïve site to further define reactions suggestive of sensitization, with sites scored at 48 (± 4) and 96 (± 8) hours after patch application.

In this study, 133 subjects participated in the challenge period. One (1) subject was clearly sensitized to MTS, and another subject had classical signs of sensitization (strong erythema plus edema) at 48 hours in the challenge phase, but did not have an evaluation at 96 hours. Because of the significant amount of erythema noted during induction and challenge periods, about a third of the subjects were requested to participate in a rechallenge to the test articles. Of the 36 who underwent rechallenge about 8 weeks after the challenge phase, a total of 17 had reactions that were indicative of sensitization, 3 others had reactions that were suggestive of sensitization, and 16 subjects had reactions indicative of irritation. Eight (8) other subjects were classified as having an irritation response, but some may have been sensitized to MTS because rechallenge reactions were not conducted in these subjects. Thus, under the conditions of the study, sensitization, with rechallenge, occurred in 17/133 subjects (12.8%) and could have been as high as 29/133 (21.8%).

In the Phase III-2 clinical studies, there were no reports of potential skin sensitization when the patch was worn as prescribed with alternating sites and a wear time of 9 hours daily. The major finding was mild dermal irritation and discomfort in some subjects

These studies indicate that MTS is associated with skin discomfort, irritation, and the potential for sensitization. The discontinuation rate for application site reactions was low (overall, <2% of MTS-treated patients/subjects in the Phase III-2 program), suggesting that the therapeutic benefit to the patient is greater than the potential risk of sensitization. A review of the literature confirms the low incidence of sensitization to methylphenidate.[33,34,35] Only 3 cases in the literature implicate methylphenidate as a causative agent of allergic reactions to methylphenidate. The sensitization studies employ conditions not usually encountered in the clinical use of the product. Thus, while sensitization to methylphenidate is possible the overall incidence appears to be low in when the product is used as directed in long-term clinical studies.

3.4 Residual methylphenidate in patches and potential for abuse or diversion.

There is a potential for misuse and diversion of MTS. However, the abuse potential of MTS is no greater (and may prove to be less) than that expected for oral methylphenidate or other products in this drug class.

Methylphenidate is structurally similar to amphetamine[36] and shares the abuse liability potential seen with other CNS stimulants.[37,38] Three (3) Phase I clinical pharmacology studies and 2 chemical extraction studies conducted during the MTS development program were designed to address the abuse potential of MTS. Patch application at doses above those relevant to clinical use induced euphoria in some experienced stimulant abusers in Studies N17-007 and N17-012, and the addition of heat to the patch and MTS application to the buccal mucosa resulted in reports of euphoria in adult stimulant abusers in Study N17-012. Repeat application of a used patch will still deliver a substantial amount of drug (approximately 60% of the amount delivered during the first application; Study N17-014), with C_{max} for the second application occurring at approximately 16 hours post-application. Extraction and purification of the active compound from the patch for subsequent ingestion or injection was possible in the chemical extraction studies. However, MTS, whether new or used, is not expected to be attractive to abusers or diverters 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 of drug as compared to presently available pills. Currently, methylphenidate is inexpensive and readily available in an easily abusable pill form via the Internet and “street” dealers. Data suggests that the most common forms of methylphenidate abuse are the swallowing of intact pills and “snorting” or injection of crushed pills. Misuse and abuse occurs with all currently marketed formulations of methylphenidate, both immediate release and extended release.

3.5 Proper Disposal of Patches

Despite the limited risk of abuse and diversion of used patches, it is important that this risk be reduced to every extent possible by educating caregivers directly, as well as through healthcare professionals, on the proper disposal techniques.

Residual methylphenidate remains in MTS patches following use. In Study N17-014, plasma methylphenidate levels were measured following 2 sequential 16-hour applications of the same 25 cm^2 patch. Used patches retain significant amounts of active drug and still deliver approximately half of what the first application provided and therefore should be handled and disposed of with the same care as unused patches. The Sponsors recommend that patients store MTS in the protective pouch and apply the patch immediately upon removal from the pouch. Upon removal of MTS from skin, the adhesive side should be folded over on itself and the folded patch should be flushed down the toilet.

Proper disposal is a key element of risk management, this is because of the residual drug contained in and potential diversion of used systems. Used and folded patches are unlikely to be an attractive target for abusers. Once folded, patches 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 readily abusable forms.

4. CONCLUSIONS

The clinical benefits of MTS include delivery of an effective treatment for ADHD and once-daily dosing with titration-to-effect based on patch size 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 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 demonstrates that MTS, with its sustained-release characteristics and novel mode of administration, may constitute an effective tool in the treatment of ADHD.

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