PHARMACOKINETICS/PHARMACODYNAMICS SUMMARY
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

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1. PHARMACOKINETIC SUMMARY

Seven (7) studies with biopharmaceutic/pharmacokinetic components have been conducted in pediatric patients with ADHD (Attention-Deficit/Hyperactivity Disorder) and 6 studies have been conducted in adults as part of the clinical development program for Methylphenidate Transdermal System (MTS). The 4 most recent studies focused on a 9-hour wear time are presented in detail in this PK/PD Summary, 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 (MPH) 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 27.5, 41.3, 55 and 82.5mg *d,l*-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 AUC parameters were 17% lower at 10 hours than for CONCERTA® and 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.

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. PK/PD effects corresponding to an E_{max} or E_{inhib} model for the population were observed, with EC_{50} values of 16 - 17 ng/ml *d*-MPH based on SKAMP deportment (SKAMP-D) or 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 PK/PD 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 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. This is discussed in detail in Section 7 of this summary.

2. INTRODUCTION

MPH is a drug with an intrinsically short half-life of 2-3 hours and as an immediate release formulation (e.g. Ritalin®) has a duration of action of 1 – 4 hours [1], necessitating a divided dose regimen of 2 to 3 times daily. As a consequence, new formulations have been developed to sustain concentrations of *d*-MPH throughout the day, allowing a once daily regimen. Conventional sustained release formulations achieving plateaus in plasma concentrations were perceived as disappointing in the extent to which they prolonged the duration of action, relative to immediate release MPH and it was postulated that concentrations needed to continue to increase to avoid tolerance and hence termination of the effect too early in the day[2]. As a result, more recently, different types of extended release formulations (e.g., the OROS® formulation CONCERTA®) were developed with the goal of generating a plasma concentration - time profile that continued to increase through the major part of the waking day ands thus sustaining its duration of action. Most published pharmacokinetic data on CONCERTA® is in healthy adults, but in 1 well controlled single dose study in 16 children aged 6-12 years with ADHD, doses of 18mg, 36mg and 54mg resulted in C_{max} values of 6, 13.2 and 20.3 ng/mL, respectively, occurring at 7-8 hours after dosing. AUC was only determined up to 11.5 hours after dosing, achieving values of 47.2, 106.4 and 151.2 ng/mL, respectively[3,4].

MTS has been designed as an alternative extended release formulation delivering *d,l*-MPH transdermally instead of orally to allow flexibility of dosing by varying the wear time to suit individual patient requirements.

MPH 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 27.5, 41.3, 55 and 82.5mg *d,l*-MPH.

Seven (7) studies with biopharmaceutic/pharmacokinetic components have been conducted in pediatric subjects (4 Phase I, 2 Phase II, and 1 Phase III) and 6 studies have been conducted in adults (all Phase I) as part of the clinical development program for MTS (Table 1 and Table 2, respectively).

Table 1: Pharmacokinetic/Biopharmaceutic Studies in the MTS Clinical Development Program

Study Type	Study Description	Study Number	Number of Subjects in PK Population
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	23
	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	11
	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	N17-002	9
Phase II, Controlled, Short-Term Studies (with PK/PD modeling)	Placebo-controlled, multiple-dose, crossover safety and efficacy study in pediatric ADHD subjects in the classroom setting	SPD485-201	74
Phase III, Controlled, Short-Term Studies (with sparse sampling for PK/PD assessment)	Placebo- and active-controlled, multiple-dose, parallel-group, dose-titration safety and efficacy study in pediatric ADHD subjects.	SPD485-302	142

Table 2: Pharmacokinetic/Biopharmaceutic Studies in the MTS Clinical Development Program

Study Type	Study Description	Study Number	Number of Subjects in the PK Population
Adult studies			
Pharmacokinetic/ Biopharmaceutic Studies	Single-dose, crossover evaluation of dose proportionality in healthy adult subjects	N17-004	14
	Steady-state, crossover comparison of the pharmacokinetic profiles of MTS and Ritalin in healthy adult subjects	N17-006	29
	Single-dose, crossover evaluation of the pharmacokinetic profile and abuse potential of MTS in adult subjects currently abusing stimulants	N17-007	25
	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	N17-012	6
	Evaluation of the pharmacokinetic profile of MTS following repeated application of the same patch in healthy adult subjects	N17-014	6
	Single-dose, crossover comparison of the pharmacokinetic profile of MTS on application to normal and inflamed skin in healthy adult subjects	N17-017	8

The focus of this PK/PD Summary will be on the key pharmacokinetic studies to define the appropriate wear time for further study by reference to CONCERTA® (study SPD485-101), to establish relative bioavailability to CONCERTA® at the highest patch size and dose proportionality of pharmacokinetics for the full range of patch sizes over the chosen wear time (study SPD485-102) and to explore relationships of efficacy and safety to systemic exposure in studies in which efficacy was demonstrated with a 9-hour MTS wear time (studies SPD485-201 and SPD485-302).

SPD485-101 was a Phase I, open-label, randomized, single-dose, 4 -treatment, 4-period crossover study with the primary objective of determining the relative bioavailability of *d*-MPH from a 25cm^2 MTS patch at 3 different wear times (6-hour, 8-hour, and 10-hour) versus a 36mg dose of CONCERTA® in 24 pediatric patients (aged 6-12 years) with ADHD. SPD485-102 was a randomized, open-label, single-dose, 4-treatment, 4-period, crossover study to assess the relative bioavailability of *d, l (threo)*-methylphenidate after application of MTS 37.5cm^2 size for a 9-hour wear time and the 54mg dose of CONCERTA® in pediatric patients aged 6-12 with ADHD and to assess the dose proportionality of pharmacokinetics of *d, l (threo)*-methylphenidate after application of the MTS 12.5, 25, and 37.5cm^2.

Study SPD485-201 was an Analog Classroom study that consisted of an open-label dose optimization period of 5 weeks where Investigators could increase patch size to optimal effect on ADHD symptoms and for tolerability to methylphenidate and the patch, followed by a 2-week Analog Classroom period. Blood samples for pharmacokinetic assessment were collected throughout the Analog Classroom period at each time of pharmacodynamic testing and data were used to define the pharmacokinetics of *d,l*-MPH on repeat dose MTS application and to evaluate relationships between plasma concentrations of *d*-MPH and relevant efficacy and safety parameters. Study SPD485-302 was a 7-week outpatient study in which eligible subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA®, or matching placebo. The study had a 5-week double blind stepwise 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. Sparse sampling at 3 sampling times around the end of the wear time was conducted in all patients to determine the extent of systemic exposure and explore relationships between systemic exposure and relevant efficacy and safety parameters.

The data from the studies of MTS with a 9-hour wear time are discussed in the context of previous data utilizing different and mostly longer wear times, particularly as relevant to the overall development program of MTS. Additionally, there is focus on the pharmacokinetic basis for the choice of wear time, the implications of the pharmacokinetic profile of MTS for its duration of action and the systemic exposures to *d*-MPH and *l*-MPH after MTS application, relative to those for CONCERTA®. The emphasis is mainly on the pharmacokinetics of the more active enantiomer *d*-MPH, but the pharmacokinetics of the less active enantiomer *l*-MPH were evaluated in the majority of studies, including all those with a 9-hour wear time and the potential relevance of these data are also discussed.

3. 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 (see studies designated with N17- protocol numbers in Table 1 and Table 2). 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 10cm^2 to Ritalin 10 mg tid administered to 11 pediatric patients. The study established that a once daily application of 2 MTS 10cm^2 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 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 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, 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. 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 bur 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 aimed at supporting 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 and significant weight loss) 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 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*-methylphenidate (*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 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 PK/PD 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.

4. PK/PD OF MPH DELIVERED BY MTS

4.1 New studies in Shire/Noven Resubmission

4.1.1 Single dose

4.1.1.1 SPD485-101

Study Design

SPD485-101 was a Phase I, open-label, randomized, single-dose, 4 -treatment, 4-period crossover study with the primary objective of determining the relative bioavailability of *d*-MPH from a 25cm^2 MTS patch at 3 different wear times (6-hour, 8-hour, and 10-hour) versus a 36mg dose of CONCERTA® in 24 pediatric patients (aged 6-12 years) with ADHD. The 4 dosing days were separated by a 7-day washout period.

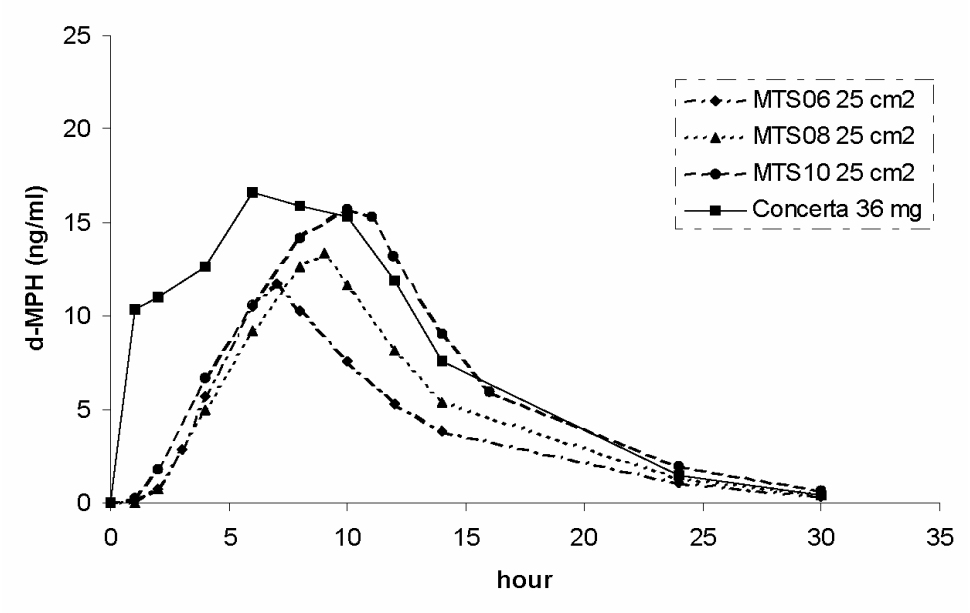
Methods

During each of the 4 test periods, blood draws were performed at pre-dose (hour zero) through 30 hours post-dose for determination of pharmacokinetics. Quantitation of *d*- and *l*-methylphenidate in plasma was performed using a validated chiral liquid chromatography, tandem mass spectrometric detection assay. Non-compartmental methods were used to derive pharmacokinetic parameters.

Results

Plasma concentrations of *d*-MPH across all subjects for the 4 treatments are illustrated in Figure 1 and pharmacokinetic parameters are summarized in Table 3.

Figure 1: Mean Plasma *d*-MPH Concentration-Time Profiles Across Treatments



N = 24 for CONCERTA®; N = 23 for MTS Treatments.

MTS06, MTS08 and MTS10 represent wear times before patch removal at 6, 8 and 10 hours, respectively

Overall, plasma concentrations of *d*-MPH increased more slowly for MTS treatments than for CONCERTA®. Mean C_{max} values increased with wear time such that the value for the 10 hour wear time was very similar to that for CONCERTA®. Area under the plasma concentration-time curve (AUC), also increased with wear time for MTS, with mean $AUC_{0\text{-}inf}$ for the 10 hour wear time achieving approximately 82% of the corresponding value for CONCERTA®. Large intersubject variability (coefficients of variation of 60.1% to 82.5% for C_{max} and AUC parameters) in systemic exposure was observed in the MTS treatment groups, compared to 39.1% to 51.7% for CONCERTA®. Despite the high intersubject variability, intrasubject coefficients of variation for the 3 MTS treatments were much lower, with values for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of 19.1%, 20.5% and 22.7%, respectively.

Table 3: Summary of Pharmacokinetic Parameters for *d*-MPH Across All Subjects

	MTS 6 hr (n = 23)	MTS 8 hr (n = 23)	MTS 10hr (n = 23)	CONCERTA® (n = 24)
C_{max} (ng/mL)	12.3 ± 9.2	13.8 ± 9.2	17.3 ± 13.2	17.7 ± 6.9
t_{max} (hr)	8.1 ± 2.1	9.21 ± 1.53	10.4 ± 2.2	6.69 ± 2.70
$AUC_{0\text{-}t}$ (ng.hr/mL)	112 ± 71	138 ± 85	188 ± 155	229 ± 117
$AUC_{0\text{-}inf}$ (ng.hr/mL)	116 ± 72*	142 ± 85	192 ± 157	233 ± 120
Kel $_{(lambda)}$ (hr^{-1})	0.15 ± 0.03*	0.16 ± 0.03	0.17 ± 0.03	0.19 ± 0.03
$t_{1/2}$(hr)	4.96 ± 1.27*	4.38 ± 0.91	4.29 ± 0.88	3.70 ± 0.67
T_{lag} (hr)	2.2 ± 1.1	2.37 ± 1.20	2.16 ± 1.72	0.00 ± 0.00

*n = 22

Although there was no formal statistical assessment of bioavailability of MTS, relative to that of CONCERTA®, in this study, comparisons made by determining the individual ratios (MTS to CONCERTA®), within-subject, for C_{max} and AUC and deriving summary statistics (Mean ± SD) on the ratios by parameter and wear time are presented in Table 4.

Table 4: Ratios (Test/reference, with CONCERTA® as the Reference Formulation) for C_{max} and AUC of *d*-MPH (Mean ±SD)

	MTS 6hr/ CONCERTA® (n = 23)	MTS 8hr/ CONCERTA® (n = 23)	MTS 10hr / CONCERTA® (n = 23)
C_{max}	0.78 ± 0.56	0.87 ± 0.58	0.98 ± 0.59
AUC_{0-t}	0.58 ± 0.38	0.69 ± 0.42	0.83 ± 0.50
AUC_{0-inf}	0.58 ± 0.37*	0.69 ± 0.41	0.83 ± 0.48

These ratios provided an alternative way of looking at the systemic exposure data for MTS presented in Table 3, relative to that of CONCERTA®, and supported the same conclusions.

In addition, the plasma concentrations most affected by varying the wear time of MTS (i.e., at hours 6, 8, 10, 12, and 14) were expressed as ratios (MTS to CONCERTA®) within subject and are summarized in Table 5.

Table 5: Mean ± SD ratios (MTS / CONCERTA®) for Plasma Concentrations of *d*-MPH at 6-14 Hours *After* Initiation of Dosing, Across All Subjects

Concentrations at 6-14 Hours after Initiation of Dosing (C6-C14)	MTS 6hr/ CONCERTA® (n = 23)	MTS 8hr/ CONCERTA® (n = 23)	MTS 10hr/ CONCERTA® (n = 23)
C6	0.72 ± 0.59	0.63 ± 0.57	0.62 ± 0.57
C8	0.74 ± 0.46	0.90 ± 0.63	0.91 ± 0.68
C10	0.56 ± 0.30	0.84 ± 0.49	1.04 ± 0.64
C12	0.54 ± 0.30	0.81 ± 0.41	1.21 ± 0.65
C14	0.65 ± 0.38*	0.89 ± 0.41*	1.33 ± 0.62*

* n = 22

For the 6- and 8-hour wear times, mean plasma *d*-MPH concentrations for MTS were below those for CONCERTA®. At the 10-hour wear time, mean plasma *d*-MPH concentrations exceeded those for CONCERTA® at 10hrs, 12hrs, and 14hrs after initiation of dosing, as indicated by mean ratios in excess of unity.

Pharmacokinetic parameters of *l*-MPH are summarized in Table 6. Plasma concentrations of *l*-MPH were lower than *d*-MPH concentrations for both MTS and CONCERTA®. However, *l*-MPH levels for MTS were substantially higher than for CONCERTA® (10- to 12-fold for C_{max} and 8- to 15-fold for AUC_{0-t}).

Table 6: Mean Pharmacokinetic Parameters for *l*-MPH Across Treatments

	MTS 6 hr (n = 23) Mean ± SD	MTS 8 hr (n = 23) Mean ± SD	MTS 10hr (n = 23) Mean ± SD	CONCERTA® (n = 24) Mean ± SD
C_{max} (ng/mL)	7.03 ± 5.32	7.66 ± 4.78	9.92 ± 8.51	0.77 ± 1.58[c]
t_{max} (hr)	6.2 ± 1.2	8.1 ± 1.8	9.7 ± 2.0	5.3 ± 4.2[b]
AUC_{0-t} (ng.hr/mL)	40.62 ± 29.60	51.16 ± 35.23	75.42 ± 70.50	5.12 ± 12.83[c]
AUC_{0-inf} (ng.hr/mL)	42.51 ± 29.07	55.74 ± 33.88[a]	77.62 ± 70.14	18.01 ± 19.70[d]
Kel (lambda) (hr^{-1})	0.3029 ± 0.1539	0.3381 ± 0.1806[a]	0.3022 ±0.1398	0.2159 ± 0.1881[d]
$T_{1/2}$(hr)	2.9 ± 1.3	2.64 ± 1.23[a]	2.9 ± 1.5	5.90 ± 4.20[d]
T_{lag} (hr)	2.1 ± 1.1	2.4 ± 1.5	2.3 ± 2.0	2.1 ± 3.7[b]

[a] n = 22, [b] n = 12, [c] n = 24, [d] n = 8

Discussion

The 10-hour wear time resulted in *d*-MPH bioavailability most similar to that of CONCERTA®. The AUC parameters were 17% lower for MTS at 10 hours than for CONCERTA® and C_{max} values were similar across both treatments. Delayed absorption from MTS was reflected by significant T_{lag} values not seen with CONCERTA® and slower absorption was indicated by longer t_{max} values associated with similar or lower C_{max}. However, 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 had slightly higher values.

Analysis focused primarily on the *d*-MPH plasma concentrations, since this is recognized as the psycho-pharmacologically active enantiomer of *d,l*-MPH with respect to inhibition of uptake of dopamine and noradrenaline pertinent to its efficacy in treatment of ADHD. Substantially higher systemic exposure to *l*-MPH (10- to 12-fold for C_{max} and 8- to 15-fold for AUC_{0-t}) was observed for all wear times of MTS than for CONCERTA®, as anticipated, due to the high and selective oral first-pass metabolism of *l*-MPH reported in the literature[1.] Since drug-metabolizing activity in the skin is low, relative to that in the liver, first-pass elimination after transdermal administration is expected to be negligible and hence the large differences between systemic exposure to *d*-MPH and *l*-MPH seen after oral administration of methylphenidate were not expected after transdermal administration.

Despite the much higher plasma concentrations of *l*-MPH after MTS application than after oral CONCERTA®, these are of minimal clinical significance because of the much lower potency of *l*-MPH and the higher circulating concentrations of *d*-MPH. The potency of *l*-MPH in *in vitro* monoamine (dopamine and norepinephrine) reuptake inhibition screens is at least an order of magnitude lower than that of *d*-MPH and this difference in potency appears to be borne out in comparative *in vivo* studies both in animals and in man (see Section 7 for more detail). Moreover, in this study, mean C_{max} for *l*-MPH was only approximately 56% of that for *d*-MPH and mean AUC even lower in proportion, approximately 38%. Thus the combination of lower circulating concentrations of *l*-MPH than of *d*-MPH and the much lower potency of the *l*-enantiomer would lead to a minimal contribution of *l*-MPH to the therapeutic actions of

MPH. The safety impact of the circulating *l*-MPH is also likely to be insignificant. The recognized side effects of methylphenidate (reduced appetite, weight loss and impaired growth; vomiting and abdominal cramps; cardiovascular effects, principally increased blood pressure and heart rate; insomnia and restlessness) are all shared with other psychostimulant drugs e.g. amphetamines, which have a sympathomimetic profile (see Section 7). Hence these adverse effects of *d,l*-MPH are a direct consequence of its psychostimulant pharmacology. Since *d*-MPH is much more active than *l*-MPH, there is no reason to suggest that *l*-MPH can contribute any more significantly to the adverse effects than to the efficacy of *d,l*-MPH in ADHD.

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

4.1.1.2 SPD485-102

Study Design

SPD485-102 was a randomized, open-label, single-dose, 4-treatment, 4-period, crossover study to assess the relative bioavailability of *d, l (threo)*-methylphenidate after application of MTS 37.5cm^2 size for a 9h wear time and the 54mg dose of CONCERTA® in pediatric patients aged 6-12 with ADHD. The major secondary objective was to assess the dose proportionality of pharmacokinetics of *d, l (threo)*-methylphenidate after application of the MTS 12.5, 25, and 37.5cm^2.

Methods

During each of the 4 test periods, blood draws were performed at pre-dose (hour zero) through 30 hours post-dose for determination of pharmacokinetics. Quantitation of *d*- and *l*-methylphenidate in plasma was performed using a validated chiral liquid chromatography, tandem mass spectrometric detection assay. Plasma concentration-time data were subjected to non-compartmental analysis to determine pharmacokinetic parameters: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}medtmax}$, C_{max}, $t_{1/2\ Kel}$, t_{lag}, T_{max}.

Statistical analyses were performed on *d*- and *l*-methylphenidate (MPH) parameters (C_{max} and $AUC_{0\text{-}t}$) organized by patch size, for the PK population. The relative bioavailability of *d,l*-MPH MTS 37.5cm^2 and the 54mg dose of CONCERTA® was assessed, for *d*-MPH and *l*-MPH separately, by analysis of variance (ANOVA). The log transformed C_{max} and $AUC_{0\text{-}t}$ was subjected to ANOVA for a 4 period crossover design with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. For each parameter, the 90% confidence intervals (CIs) were constructed for the ratio (MTS/CONCERTA®).

Based on the same model, the 25cm^2 patch size and the 37.5cm^2 patch size were compared to the 12.5cm^2 patch size. The 90% CIs were constructed for each ratio. In order to conclude dose proportionality, the 90% CI was to lie within the intervals of (1.6 to 2.5) and (2.4 to 3.75) for the doublings and triplings in patch size, respectively. These upper and lower bounds correspond to double and triple the equivalence acceptance limits of 0.80 to 1.25, taking account of the fact that C_{max} and $AUC_{0\text{-}t}$ values were not normalized with respect to patch

size before statistical analysis. To assess dose proportionality of pharmacokinetics with increasing apparent dose, power analyses were performed separately on log transformed *d*-MPH and *l*-MPH parameters (C_{max} and AUC_{0-t}) excluding the CONCERTA® data, with sequence and period as fixed effects, subject-within-sequence as a random effect and including a covariate for logged apparent dose. For each parameter, the 90% CIs were constructed. In order to conclude dose-proportionality for a tripling in dose within the range of the data, the 90% CI was required to lie within the interval of 2.4 to 3.75.

Results

The mean plasma concentrations of *d*-MPH are illustrated in Figure 2 by treatment and mean pharmacokinetic parameters are summarized in Table 7. Medians (ranges) are presented for T_{max} and t_{lag}.

Figure 2: Arithmetic Mean Plasma Concentrations of *d*-MPH After Single Doses of *d,l*-MPH by MTS (12.5, 25 or 37.5 cm^2 with a 9-Hour Wear Time) or Oral CONCERTA® 54mg

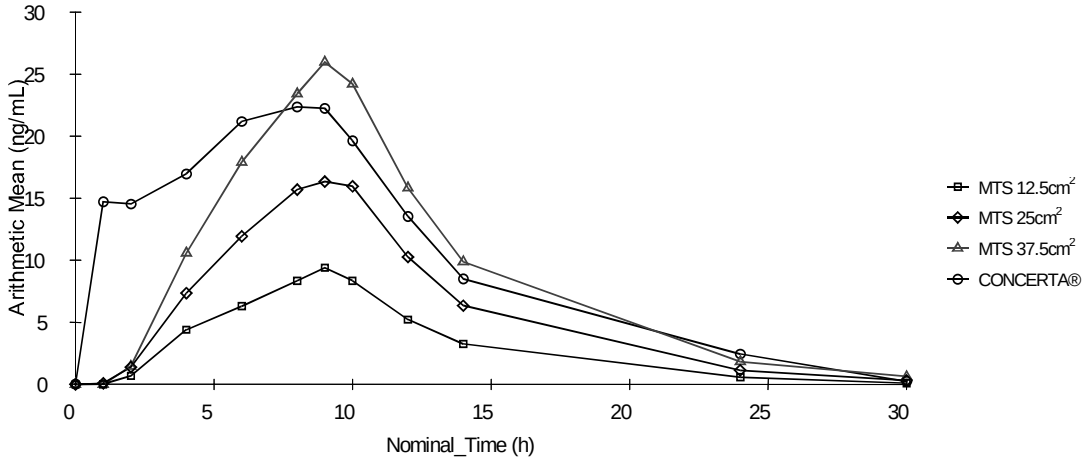


Table 7: Pharmacokinetic Parameters of *d*-MPH After Single Doses of *d,l*-MPH by MTS (12.5, 25 or 37.5 cm^2 With a 9-Hour Wear Time) or Oral CONCERTA® 54mg

Treatment	C_{max} (ng/mL)	T_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2\ Kel}$ (h)
MTS 12.5cm^2	9.78	8.99	1.94	86.3	90.0	3.80
	(49.8)	(5.95-10.2)	(0-4.0)	(54.3)	(52.3)	(19.0)
MTS 25cm^2	17.8	9.93	1.98	164	170	3.81
	(50.2)	(7.97-12.0)	(0-4.0)	(55.5)	(53.6)	(15.4)
MTS 37.5cm^2	27.2	9.00	1.00	251	255	3.87
	(44.7)	(5.95-12.0)	(0-2.03)	(44.8)	(44.5)	(12.2)
54mg CONCERTA®	24.2	7.99	0.00	281	262	3.22
	(43.4)	(2.12-10.0)	(0-0.00)	(60.7)	(44.3)	(18.6)

The mean pharmacokinetic parameters for *l*-MPH are summarized in the Text Table below.

Table 8: Pharmacokinetic Parameters of *l*-MPH After Single Doses of *d,l*-MPH by MTS (12.5, 25 or 37.5 cm^2 With a 9-Hour Wear Time) or Oral CONCERTA® 54mg

Treatment	C_{max} (ng/mL)	T_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2\ Kel}$ (h)
MTS 12.5cm^2	6.03	8.98	1.48	37.6	40.4	1.35
	(52.0)	(4.0-10.2)	(0-4.0)	(62.1)	(58.6)	(21.5)
MTS 25cm^2	10.5	8.96	1.98	73.0	80.7	2.04
	(50.9)	(3.93-10.0)	(0-4.0)	(59.2)	(57.5)	(56.5)
MTS 37.5cm^2	17.4	8.91	1.00	114	105	2.35
	(45.5)	(4.0-10.0)	(0-2.03)	(47.2)	(49.1)	(50.5)
54mg CONCERTA®	0.812	7.00	0.00	5.06	9.46	1.86
	(62.0)	(1.0-24.0)	(0-6.0)	(106)	(59.6)	(49.9)

Least squares geometric means and ratios of geometric means (37.5 cm^2 MTS/CONCERTA®) with 90% CI for *d*-MPH are provided in Table 9.

Table 9: Least Squares Geometric Means and Ratios of Geometric Means (37.5 cm^2 MTS/CONCERTA®) With 90% CI for *d*-MPH

	Geometric Least Squares Means		Ratio of Geometric Least Squares Means (MTS/CONCERTA®)	
Parameter	MTS 37.5cm^2	54mg CONCERTA®	Estimate	90 % Confidence Interval
C_{max}	24.7	22.0	1.12	(0.97, 1.30)
AUC_{0-t}	228	243	0.94	(0.80, 1.10)

Systemic exposure to *d*-MPH (AUC_{0-t} and C_{max}) from MTS over 37.5cm^2 was not appreciably different from that of CONCERTA®.

Based on AUC_{0-t}, the relative bioavailability of *d*-MPH following administration of *d,l*-MPH MTS over 37.5cm^2 was, on average, 6% lower (90% CI: 20% lower to 10% greater) than that following oral administration of 54mg CONCERTA®. The relative bioavailability of *d*-MPH, based on C_{max}, following administration of *d,l*-MPH MTS over 37.5cm^2 was, on average, 12% greater (90% CI: 3% lower to 30% greater) than that following oral administration of 54mg CONCERTA®.

The CIs for AUC_{0-t} and C_{max} included unity and, therefore, apparent differences in relative bioavailability were not statistically significant.

Least squares geometric means and ratios of geometric means (37.5 cm^2 MTS/CONCERTA®) with 90% CI for *d*-MPH are provided in Table 10.

Table 10: Least Squares Geometric Means and Ratios of Geometric Means (MTS 37.5cm^2/CONCERTA®) with 90% CI for *l*-MPH

	Geometric Least Squares Means		Ratio of Geometric Least Squares Means (MTS/CONCERTA®)	
Parameter	MTS 37.5cm^2	CONCERTA®	Estimate	90% Confidence Interval
C_{max}	15.9	0.625	25.38	(20.39, 31.58)
AUC_{0-t}	101	2.41	42.05	(29.66, 59.63)

C_{max} (an indirect measure of rate of bioavailability) of *l*-MPH following administration of *d,l*-MPH MTS over 37.5cm^2 was, on average, 25-fold greater (90% CI: 20-fold to 32-fold greater) than following oral administration of 54mg CONCERTA®.

Based on AUC_{0-t}, the relative bioavailability of *l*-MPH following administration of *d,l*-MPH MTS over 37.5cm^2 was, on average, 42-fold greater (90% CI: 30-fold to 60-fold greater) than following oral administration of 54mg CONCERTA®).

Statistical assessment of the relationship between AUC_{0-t} and C_{max} values and patch size of *d*-MPH following administration of MTS are given in Table 11.

Table 11: Least Squares Geometric Means and Ratios of Geometric Means for Comparison of *d*-MPH C_{max} and AUC_{0-t} at Different MTS Patch Sizes

Patch Size		Geometric Least Squares Means		Ratio of Geometric Least Squares Means (MTS 25cm^2 / MTS 12.5cm^2)	
Range (cm^2)	Parameter	MTS 25cm^2	MTS 12.5cm^2	Estimate	90 % Confidence Interval
12.5-25	C_{max}	15.7	8.65	1.82	(1.57, 2.11)
	AUC_{0-t}	143	75.7	1.89	(1.62, 2.22)

Patch Size		Geometric Least Squares Means		Ratio of Geometric Least Squares Means (MTS 37.5cm^2 / MTS 12.5cm^2)	
Range (cm^2)	Parameter	MTS 37.5cm^2	MTS 12.5cm^2	Estimate	90 % Confidence Interval
12.5-37.5	C_{max}	24.7	8.65	2.86	(2.47, 3.30)
	AUC_{0-t}	228	75.7	3.01	(2.58, 3.51)

There was no statistical evidence to indicate that the extent of systemic exposure increased in a non-proportional manner from 12.5 to 25cm^2 and from 12.5 to 37.5cm^2. The 90% CIs for a doubling (12.5 to 25cm^2) and tripling (12.5 to 37.5cm^2) in patch size were within the prescribed limits of 1.6 to 2.5 and 2.4 to 3.75, respectively.

The exponents of the power model and 90% CIs were also used to determine the expected fold-increase in exposure for a tripling in dose. Given that the 90% CI for the expected fold increases were within the prescribed limits of 2.4 to 3.75, there was no evidence for a non-dose proportional increase in exposure to *d*-MPH based on apparent dose.

Statistical assessment of the relationship between AUC_{0-t} and C_{max} values and patch size of *d*-MPH following administration of MTS are given in Table 12.

Table 12 : Statistical Assessment of the Relationship Between AUC_{0-t} and C_{max} Values and Patch Size of *l*-MPH Following Administration of MTS

Patch Size		Geometric Least Squares Means		Ratio of Geometric Least Squares Means (MTS 25cm^2 / MTS 12.5cm^2)	
Range (cm^2)	Parameter	MTS 25cm^2	MTS 12.5cm^2	Estimate	90% Confidence Interval
12.5-25	C_{max}	9.16	5.26	1.74	(1.48,2.04)
	AUC_{0-t}	61.1	31.6	1.94	(1.50,2.51)*

There was no statistical evidence to indicate that C_{max} increased in a non-proportional manner from 12.5 to 25cm^2 or from 12.5 to 37.5cm^2. However, there was evidence to indicate a slightly greater than proportional increase in exposure to *l*-MPH AUC_{0-t} from 12.5 to 25cm^2 and from 12.5 to 37.5cm^2.

The 90% CIs for a doubling (12.5 to 25cm^2) and tripling (12.5 to 37.5cm^2) in patch size were entirely within the limits 1.6 to 2.5 and 2.4 to 3.75, respectively, for C_{max} but not for AUC_{0-t}.

For AUC_{0-t}, the 90% CI for a doubling in patch size was wide and straddled the prescribed limits for concluding dose-proportionality. For a tripling in patch size, the upper 90% CI were outside the prescribed limits for concluding dose-proportionality.

As observed in the primary analysis based on patch size, there was no statistical evidence to indicate that the extent of systemic exposure increased in a non-proportional manner over the dose range studied based on C_{max} (90% CI were within the prescribed limits 2.4 to 3.75). However, for AUC_{0-t} there was evidence to indicate a slightly greater than proportional increase in exposure to *l*-MPH.

For AUC_{0-t}, the upper 90% CIs were outside the prescribed limits for concluding dose-proportionality.

Discussion

The primary objective of this study was to assess the relative bioavailability *d, l*-MPH after application of MTS 37.5cm^2 size for a 9-hour wear time and the 54mg dose of CONCERTA® in pediatric patients (aged 6-12) with ADHD. Overall, the relative bioavailability of *d*-MPH from MTS was not dissimilar from that of CONCERTA®, after single doses at these strengths, with C_{max} averaging 12% greater (90% CI: 3% lower to 30% greater) and AUC_{0-t} 6% lower (90% CI: 20% lower to 10% greater, respectively, but encompassed unity; hence differences between MTS and CONCERTA® were not statistically significant.

In contrast, as observed previously (Study SPD485-101), the bioavailability of *l*-MPH from MTS 37.5cm^2 was substantially higher than that of the corresponding CONCERTA® dose. For *l*-MPH, C_{max} values were, on average, 25-fold greater (90% CI: 20-fold to 32-fold) and AUC_{0-t}, on average, 42-fold greater (90% CI: 30-fold to 60-fold) for MTS 37.5cm^2 than for CONCERTA®. This difference is attributable to the well documented more extensive first-pass elimination of *l*-MPH than of *d*-MPH after oral administration not expected after transdermal administration. It is believed to be of minimal clinical significance because of the much lower potency (at least an order of magnitude) and the lower circulating concentrations of *l*-MPH than of *d*-MPH.

A secondary objective was to assess the dose proportionality of pharmacokinetics of *d, l*-MPH after application of the MTS 12.5, 25, and 37.5cm^2. Increases in pharmacokinetics of *d*-MPH were found not to deviate significantly from dose proportionality over a 3-fold increase in patch size. Similarly, proportional results were obtained for *d*-MPH with respect to apparent dose. Although *l*-MPH pharmacokinetics could not be claimed to be dose proportional, the deviation from dose proportionality over this 3-fold increase in patch size was quite small, with an average increase of 3.21 for AUC_{0-t} (90% CI: 2.50 to 4.14), with the upper confidence interval overlapping the prescribed upper boundary of 3.75. Similarly, with respect to apparent dose, there was only a slightly greater than proportional increase in AUC_{0-t}, with an average 3.59 fold increase (90% CI: 3.33 to 3.87).

Consistent with results of study SPD485-101, inter-subject variability in pharmacokinetics in this study was high, with between-subject CVs for AUC_{0-t} ranging from 45%-62% for MTS. In this study the comparable values for CONCERTA® were higher (61% to 106%). The much lower within-subject variability (CVs of 15%-23%) confirmed the view that MTS delivers *d, l*-MPH consistently from occasion to occasion within the same individual.

In summary, 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®. By contrast, the relative bioavailability of *l*-MPH was substantially greater (on average 42-fold greater based on AUC_{0-t}) following administration of MTS 37.5cm^2 compared to 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}. The systemic availability of *l*-MPH appeared to be dose-proportional over the dose range/patch size studied based on C_{max}; however, there was a tendency towards a slightly greater than proportional increase in exposure based on AUC_{0-t}.

4.1.2 Repeat dose

4.1.2.1 SPD485-201

Study Design

SPD485-201 was a Phase II, randomized, double-blind, multi-center, placebo-controlled, Analog Classroom, crossover study, with an open-label optimization phase, designed to assess the time course of treatment effect, tolerability and safety of MTS in pediatric subjects diagnosed with ADHD.

The main pharmacokinetic objectives were

- To evaluate the pharmacokinetic parameters of MTS by measurement of plasma *d*-MPH and *l*-MPH concentrations and analysis by non-compartmental methods.
- To assess the relationship between the pharmacokinetics of *d*-MPH and the response measures (e.g., SKAMP and PERMP) during the Analog Classroom day.
- To evaluate the relationship between plasma *d*-MPH concentrations and measurements of vital signs (e.g., blood pressure and heart rate).

Methods

Patients underwent an initial 5-week dose optimization to ensure they were titrated to an optimal dose of MTS (using 12.5cm^2, 18.75cm^2, 25cm^2, and 37.5cm^2 patch sizes) based upon investigator review of parent rating forms, Treatment Emergent Adverse Events (TEAEs), and clinical judgment (using the ADHD Rating Scale-IV) (ADHD-RS-IV). All subjects were initiated on the MTS 12.5cm^2 size patch (1/day) and were evaluated after 1 week (7 $\pm$ 3 days) for tolerability and effectiveness.The approximate duration of MTS patch wear was 9 hours per day; a new patch was applied each morning upon awakening. Subjects were titrated to the next patch size after a minimum of 1 week on the previous size. Subjects may have been titrated back down to the previous patch size to optimize tolerability. An acceptable condiditon was defined as a significant reduction in ADHD symptoms with minimal side effects. Subjects who had not reached an acceptable patch size by Visit 7 were withdrawn from the study.

Following completion of the Dose Optimization period, subjects were randomized to a sequence of 1 week of treatment with each of MTS and PTS (Placebo Transdermal System). The duration of this period was 2 weeks and each end-of-week assessment, included both

measurement of behavioral effects and plasma collection, and occurred in the controlled environment of the Analog Classroom.

The primary outcome measure was the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) rating scale, which provided an assessment of subject behavior as evaluated by trained evaluators. The SKAMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS; subscale scores for deportment, attention and quality of work were evaluated at each time point to assess the duration of effect of MTS vs. placebo.

The main secondary outcome measure of the study was the Permanent Product Measure of Performance (PERMP). The PERMP is an age-adjusted math test that provides an objective measure of math productivity that is time-sensitive, ADHD medication-sensitive, and well documented as an effective measure to evaluate ADHD subjects across the day. The PERMP was measured at pre-dose, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours post application of MTS, and was used to assess the duration of effect of MTS as compared to placebo. The number of math problems answered correctly and the number of math problems attempted were evaluated.

Blood samples for the analysis of plasma concentration of *d*-MPH and *l*-MPH over time were collected pre-dose and at 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours after patch application during each Analog Classroom day. Quantitation of *d*- and *l*-methylphenidate in plasma was performed using a validated chiral liquid chromatography, tandem mass spectrometric detection assay.

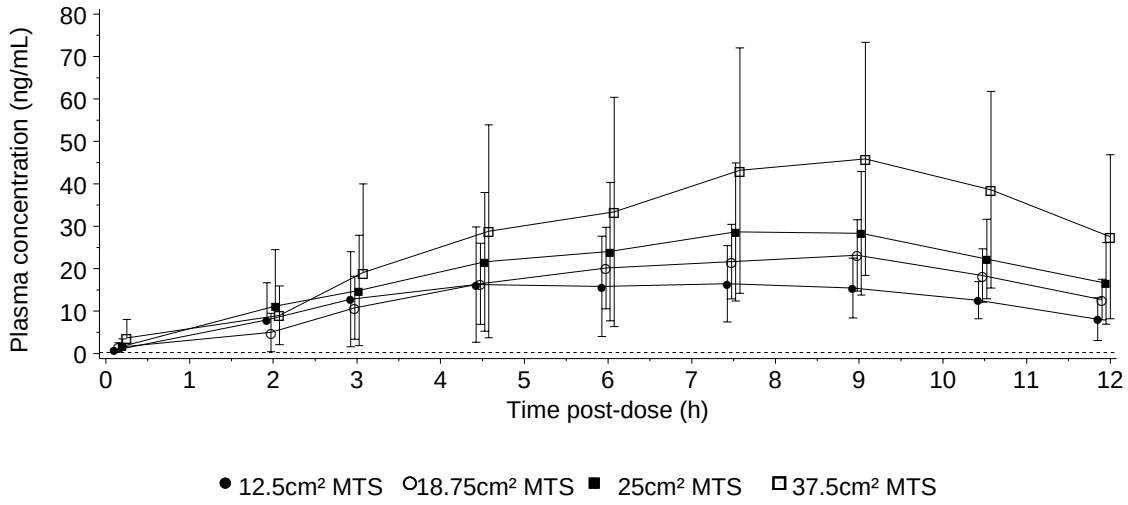
Both plasma *d*-MPH and *l*-MPH concentrations were analyzed by non-compartmental methods to calculate the pharmacokinetic parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, K_{el}, $t_{1/2kel}$, C_{max}, t_{lag}, and t_{max}. Relationships were also explored between plasma concentrations of *d*-MPH, and SKAMP deportment (SKAMP-D), PERMP, blood pressure and heart rate.

Pharmacokinetic Results

The mean proportion of *d,l*-MPH delivered during from the different patch sizes over a 9-hour wear time in this study 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%.

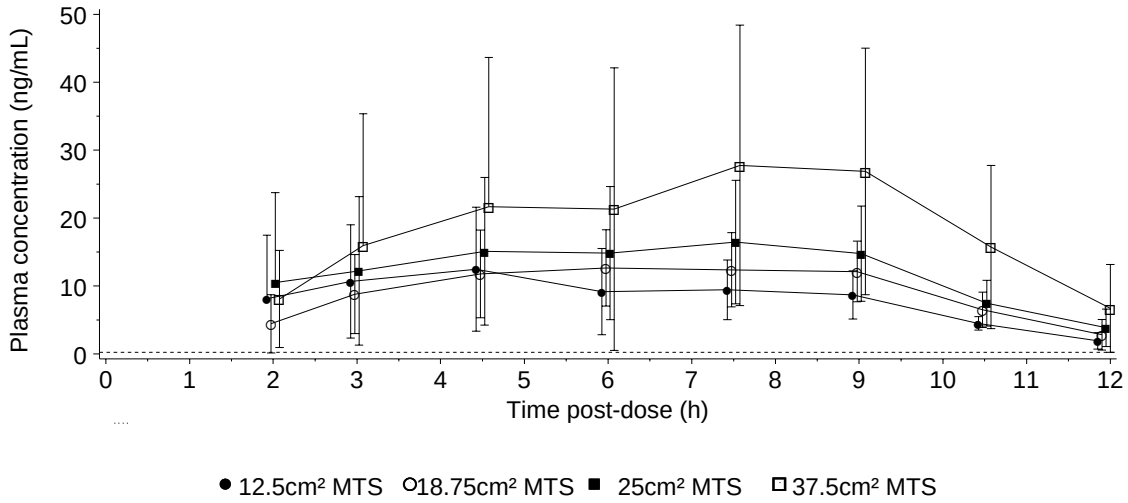
Plasma concentrations of *d*- and *l*-MPH during the Analog Classroom Day after daily dosing for 7 days illustrated in Figure 3 and Figure 4.

Figure 3: Arithmetic Mean (+/- SD) Plasma Concentration Profiles of *d*-MPH After Repeat Doses of *d,l*-MPH by MTS (12.5, 18.75, 25 or 37.5 cm^2 with a 9-Hour Wear Time)



- - - Lower limit of quantification (0.25 ng/mL)

Figure 4: Arithmetic Mean (+/- SD) Plasma Concentration Profiles of *l*-MPH After Repeat Doses of *d,l*-MPH by MTS (12.5, 18.75, 25 or 37.5 cm^2 with a 9-Hour Wear Time)



- - - Lower limit of quantification (0.25 ng/mL)

The pharmacokinetic parameters of *d*-MPH and *l*-MPH are summarized in Table 13 and Table 14.

Table 13: Mean (± SD) Pharmacokinetic Parameters of *d*-MPH After Single Doses of *d,l*-MPH by MTS (12.5, 18.75, 25 or 37.5 cm^2 With a 9-Hour Wear Time) on an Analog Classroom Day

Parameter of *d*-MPH	MTS Treatment (mean apparent dose of *d*-MPH)			
	12.5cm^2 (6.2mg) (n = 7)	18.75cm^2 (8.0mg) (n = 32)	25cm^2 (11.1mg) (n = 27)	37.5cm^2 (15.6mg) (n = 8)
$AUC_{0\text{-}12\ h}$ (ng.h/mL)	145[a] (103)	181[b] (79.9)	229[c] (144)	378[a] (281)
$AUC_{0\text{-}t}$ (ng.h/mL)	139 (95.2)	171 (78.1)	225 (139)	332 (254)
C_{max} (ng/mL)	20.0 (11.1)	23.9 (8.89)	30.5 (16.0)	46.5 (27.3)
T_{max} (h)	7.12 (4.28–8.75)	8.04 (5.73–11.8)	8.75 (5.77–11.7)	8.78 (7.25–10.3)
T_{lag} (h)	0 (0–0)	0 (0–4.10)	0 (0–1.92)	0 (0–0)

Arithmetic mean (SD) data presented, except median (min-max) for T_{max} and T_{lag}
$t_{½kel}$ was not calculable for *d*-MPH
[a] n = 6; [b] n = 27; [c] n = 25

Table 14: Mean (± SD) Pharmacokinetic Parameters of *l*-MPH After Single Doses of *d,l*-MPH by MTS (12.5, 18.75, 25 or 37.5 cm^2 With a 9-Hour Wear Time) on an Analog Classroom Day

Parameter of *l*-MPH	MTS Treatment (mean apparent dose of *l*-MPH)			
	12.5cm^2 (6.2mg) (n = 7)	18.75cm^2 (8.0mg) (n = 32)	25cm^2 (11.1mg) (n = 27)	37.5cm^2 (15.6mg) (n = 8)
$AUC_{0\text{-}12\ h}$ (ng.h/mL)	86.2[a] (58.1)	100[b] (44.2)	129[c] (83.5)	229[a] (209)
$AUC_{0\text{-}t}$ (ng.h/mL)	83.9 (53.4)	96.6 (41.8)	127 (80.7)	202 (184)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	72.5[d] (47.8)	112[e] (37.6)	136[e] (62.4)	286[f] (224)
C_{max} (ng/mL)	14.6 (7.66)	15.0 (5.93)	18.4 (10.0)	29.5 (19.6)
T_{max} (h)	7.12 (4.28–8.75)	7.20 (2.92–8.92)	7.33 (1.90–8.98)	7.34 (4.23–8.87)
T_{lag} (h)	0 (0-1.53)	0 (0–4.10)	0 (0–2.90)	0 (0–0)
$t_{½kel}$ (h)	1.77[d] (1.02)	1.16[e] (0.167)	1.27[e] (0.228)	1.46[f] (0.228)

Arithmetic mean (SD) data presented, except median (min-max) for T_{max} and T_{lag}
[a] n = 6; [b] n = 27; [c] n = 25; [d] n = 4; [e] n = 18; [f] n = 5

Prior to application of MTS in patch sizes of 12.5, 18.75, 25 and 37.5cm^2, mean (SD) on the Analog Classroom Day, plasma concentrations of *d*-MPH were 0.79 (0.23), 1.50 (1.05), 1.71 (1.71) and 3.65 (4.40) ng/mL, respectively, representing minimum concentrations remaining from application on the previous day. Following patch application of MTS, *d*-MPH was steadily absorbed into the systemic circulation with maximum plasma concentrations of *d*-MPH occurring at a median T_{max} of 7.1 to 8.8 hours after patch application. Lag times, if observed, were generally shorter than the time to the first post-application sampling time, i.e., <2.0 hours. The rate of absorption appeared to show some slight dose dependency, with median T_{max} occurring approximately 1.7 hours later with application of the 37.5cm^2 patch compared to the 12.5cm^2 patch.

Following removal of the MTS patch after approximately 9.0 hours, plasma concentrations of *d*-MPH appeared to decline in a generally monophasic manner. It was not possible to determine the terminal elimination half-life of *d*-MPH for any of the subjects following the removal of the patch. However, mean plasma concentrations at 12.0 hours after patch application (3.0 hours after patch removal) were approximately 41% to 59% of C_{max}, which is indicative of an elimination half-life of approximately 3.0 hours. Furthermore, mean plasma levels at 12.0 hours post-dose, were approximately 8- to 10–fold higher than pre-dose values (taken approximately 15.0 hours after removal of the preceding day's patch), which is consistent with an elimination half-life of 3.0 to 4.0 hours.

There were no gross deviations from dose-proportionality based on changes in $AUC_{0\text{-}12\ h}$ and C_{max} over the entire range of patch sizes and the entire range of apparent doses of *d*-MPH.

Similarly, *l*-MPH maximum plasma concentrations occurred at a median T_{max} of 7.1 to 7.3 hours after patch application and lag times, if observed, were generally shorter than the time to the first post-application sampling time, i.e., <2.0 hours.

Following removal of the MTS monophasic decline resulted in terminal elimination half-lives, where calculable, for individual subjects ranging from approximately 0.83 to 3.30 hours with mean values of between 1.16 to 1.77 hours. There appeared to be no trends in half-life with increasing patch size. Mean plasma concentrations at 12.0 hours after patch application were approximately 13.1% to 22.7% of C_{max}.

As for *d*-MPH, there were no gross deviations from dose-proportionality based on changes in $AUC_{0\text{-}12\ h}$ and C_{max} over the entire range of patch sizes and the entire range of apparent doses of *l*-MPH.

Exposure to *l*-MPH, based on mean $AUC_{0\text{-}12h}$ and C_{max} values, was notably lower than *d*-MPH for all patch sizes. The ratios between the *l* and *d*-enantiomers appeared relatively constant across the 4 dose levels (0.59 to 0.63 across both $AUC_{0\text{-}12h}$ and C_{max}), except for C_{max} at the lowest patch strength (0.73).

In general, as assessed from the arithmetic coefficient of variation (CV%), high inter-subject variability was noted for $AUC_{0\text{-}12\ h}$ and C_{max} of both enantiomers, with values ranging from 44% to 74.3% and 37% to 59%, respectively, for *d*-MPH; and from 44% to 91% and 40% to 66.4%, respectively, for *l*-MPH.

Exposure to *l*-MPH, based on mean AUC_{0-12h} and C_{max} values, was notably lower than *d*-MPH for all patch sizes. The ratios between the *l*- and *d*-enantiomers for both parameters appeared relatively constant across the 4 dose levels, except for C_{max} at the lowest patch strength.

Pharmcokinetic/Pharmcodynamic Results

From an examination of individual subject observed PD results as a function of time, as a function of *d*-MPH concentration, and as adjusted for baseline, the following observations were apparent:

- No hysteresis patterns (clockwise or anti-clockwise trends in response to the same plasma concentrations, dependent on whether concentrations are increasing or decreasing) indicative of tolerance (clockwise) or a delayed response (anti-clockwise) were observed.
- No consistent patterns showing definitive concentration-response relationship were observed.
- All PD response data were highly variable. When specific patterns were observed, particularly for SKAMP-D and PERMP, they tended to coincide with an E_{max} model.

In order to reduce the impact of the individual subject concentration-response variability, 2 additional modeling alternatives were examined. The first involved pooling all the individual subjects' responses for each PD marker and modeling the resulting data. The second approach involved computing the average response and the average plasma concentration for each time point by treatment (patch size/dose). As a result, pharmacodynamic models were developed and evaluated for each of the pharmacodynamic marker variations, namely original data, baseline adjusted, mean placebo adjusted, and individual placebo adjusted pharmacodynamic marker.

Average change from baseline and average change from mean placebo (mean placebo adjusted) were plotted against mean *d*-MPH concentration (pooled) at each scheduled time point for the 5 pharmacodynamic endpoints.

Examination of the pooled mean treatment concentration-response data demonstrated that the average response data (especially for SKAMP-D, PERMP and heart rate (HR) tended to follow an E_{max} pharmacodynamic model. As the plasma concentrations increased during the initial portions of the concentration-time profile the responses tended to increase asymptotically up to a maximum effect (plateau) then stopped responding to increasing concentrations. There were no indications of hysteresis. SKAMP-D showed a pattern consistent with an inhibitory E_{max} model, while PERMP and HR showed patterns consistent with a classic E_{max} model. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed no consistent patterns.

For SKAMP-D, the inhibitory E_{max} model suggests improved deportment (to a plateau) with increasing drug concentrations; for PERMP, increased performance (to a plateau) with increasing drug concentrations. The data also suggest a potential association between *d*-MPH plasma concentrations and increased heart rate.

A pattern of change throughout the placebo Analog Classroom session was observed for SKAMP-D, PERMP, DBP, SBP and HR. This finding suggested that any response observed while on study drug may also represent population variability. As an example, the placebo subject's HR presented a pattern of increase, though not consistent throughout the observation period. The average HR for the placebo subjects in general increased over the entire classroom session.

Based upon these findings model evaluation was also performed using mean (and individual) placebo response adjusted data (response adjusted for the average- and individual-placebo observations at the corresponding time points for subjects administered the placebo treatment).

Based upon the patterns observed for SKAMP-D and PERMP, the models evaluated included E_{max} (classic and inhibitory), E_{max} with baseline adjustment (intercept), and linear regression. Model specific PD parameters, i.e., the maximum effect (E_{max}), concentration associated with 50% maximal effect (EC_{50}), baseline (E0), slope (A) and intercept (B) were estimated. The pharmacodynamic models were developed and evaluated for each of the pharmacodynamic marker variations, namely original data, baseline adjusted, mean placebo adjusted, and individual placebo adjusted pharmacodynamic marker.

Table 15 shows the chosen models, based on visual inspection, accuracy of model prediction and best fit to goodness-of-fit criteria, for both SKAMP-D and PERMP with their parameter estimates, CV%, and 90% confidence intervals.

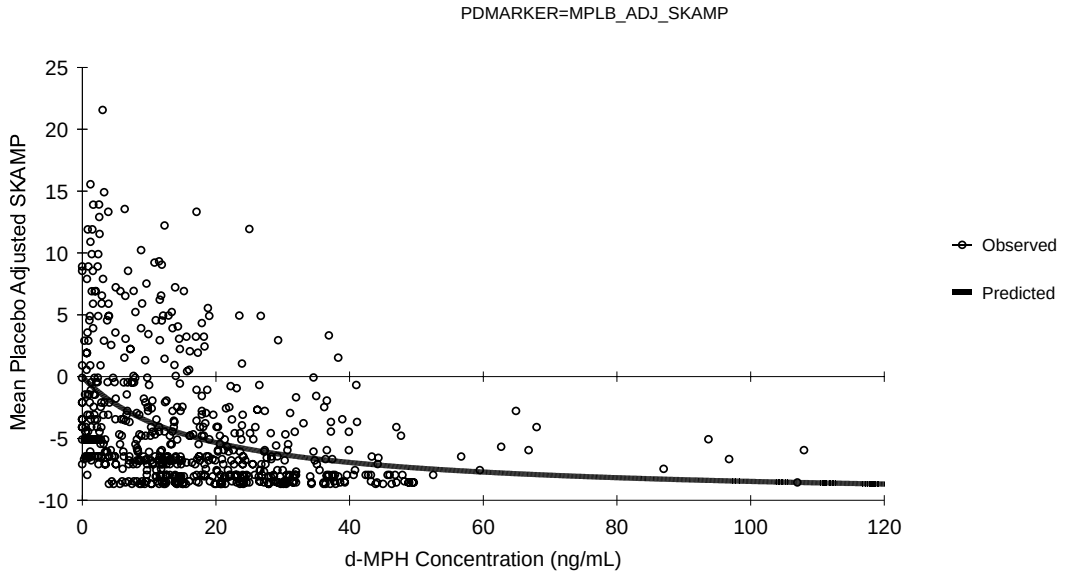
Table 15: PK/PD Models Relating SKAMP-D and PERMP Scores to Plasma Concentrations of *d*-MPH

Model	PD Marker	Treatment	E_{max}			EC_{50}		
			Estimate (Score)	CV%	CI%	Estimate (ng/mL)	CV%	CI%
1	MPLB_SKAMP	Pooled Indv	-9.93	13.45	-12.56, -7.31	17.26	30.30	6.99, 27.54
2	ADJ_PERMP	Pooled Indv	136.7	12.55	103.0, 170.41	15.50	29.56	6.50, 24.49

MPLB_SKAMP: mean placebo adjusted SKAMP. ADJ_PERMP: Baseline adjusted PERMP.
Pooled Indv: pooled PD response data for all the individuals.

Figure 5 shows the observed mean placebo adjusted SKAMP-D values for each measured *d*-MPH concentration of each subject (pooled) plotted with the inhibitory E_{max} model prediction for the change in SKAMP-D scores.

Figure 5: Inhibitory Emax Goodness-of-Fit: Model Prediction and Observed Data of Mean Placebo Adjusted SKAMP Versus *d*-MPH Concentration



The model prediction generally followed the observed data. The slope of the first portion of the MPLB_SKAMP versus concentration curve can be expressed as $(-)E_{max}/EC_{50}$ (when concentration is much less than EC_{50}). This slope was determined to be -0.58, and indicates that for each 10ng/mL *d*-MPH concentration there was an average 5.8-unit decrease in SKAMP-D test scores, i.e. improved deportment.

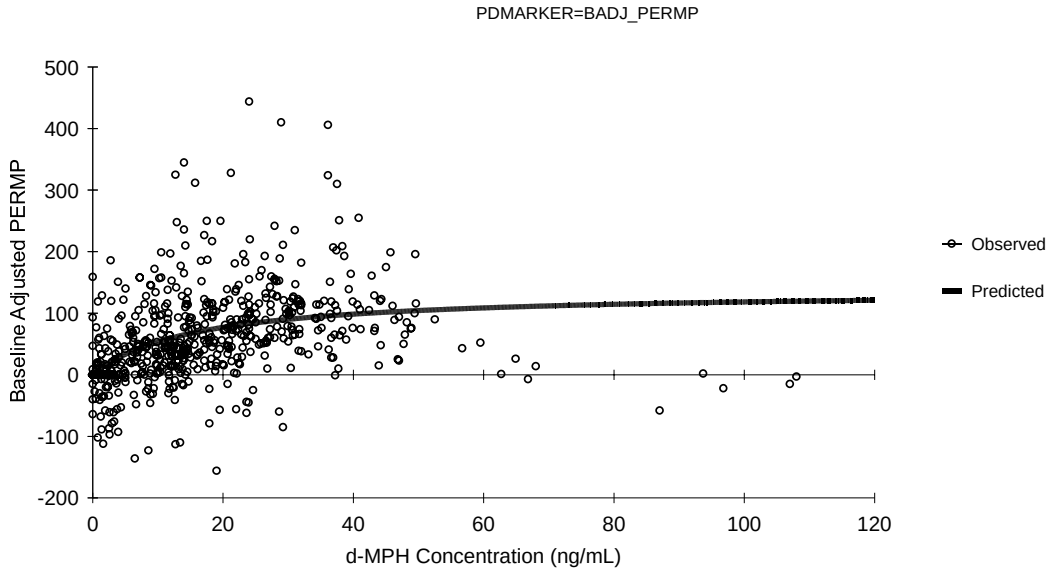
Figure 6 shows the baseline adjusted PERMP (ADJ_PERMP) scores and the generated E_{max} model predictions illustrating the relationship between the adjusted PERMP scores and *d*-MPH plasma concentrations.

The model prediction generally followed the observed data. The ratio of E_{max}/EC_{50} (slope) of the initial portion of the curve was 8.82 indicating that for each 10ng/mL *d*-MPH concentration there was 88-unit increase in PERMP score.

SBP and DBP data were found to have large variability in both the placebo and active treatment groups and no clear pattern was observed when plotted against *d*-MPH concentration. Nevertheless, E_{max}, E_{max} with intercept, and linear models were applied to the blood pressure data but no specific model was found applicable for these data.

An E_{max} model was fitted for heart rate using individual-pooled baseline-adjusted HR (ADJ HR) versus concentration of *d*-MPH. The correlation between heart rate and plasma drug concentration, however, was considered an artifact since similar changes in HR were observed in placebo treated subjects. The observed HR for all subjects, active and placebo, followed the same profile through the analog classroom session.

Figure 6: Emax Goodness-of-Fit: Model Prediction and Observed Data of Baseline Adjusted PERMP Versus *d*-MPH Concentration



Discussion

Following application of MTS in patch sizes of 12.5, 18.75, 25 and 37.5cm^2, the *d*- and *l*-enantiomers of MPH were steadily absorbed over the 9-hour period that the patches were applied, as demonstrated by median T_{max} values of 7 to 9 hours. This steady rate of absorption following MTS application is consistent with that found previously in pediatric subjects.

Although the terminal elimination phase of *d*-MPH could not be defined over the 12-hour blood sampling period because the post-patch removal period of 3 hours was not long enough to clearly delineate the terminal elimination phase, a rough estimate of the half-life of *d*-MPH gave values of 3 to 4 hours. This is also consistent with the elimination rate reported previously in pediatrics. *l*-MPH was eliminated more rapidly than the *d*-enantiomer, giving a mean terminal elimination half-life of approximately 1.2 to 1.8 hours across the 4 patch sizes.

Following administration of a racemic mixture of *d,l*-MPH, the systemic exposure was notably lower for the *l*-enantiomer of MPH compared to the *d*-enantiomer, with mean $AUC_{0\text{-}12h}$ and C_{max} values generally being 37% to 45% lower across the 4 patch sizes. In addition, the elimination half-life of *d*-MPH was longer than that of *l*-MPH. In a previous study conducted in healthy adult subjects, it was suggested that the difference in the pharmacokinetics of the 2 enantiomers was due to enantioselectivity in presystemic metabolism, with *l*-MPH being preferentially converted into 1-ritalinic acid[5], which accounted for the lower C_{max} values observed for *l*-MPH in the present study. In addition, current literature suggests that MPH also undergoes stereoselective clearance[1], which would explain the lower AUC values and shorter half-life for *l*-MPH in the present study.

Visual examination of the pharmacokinetic parameters of *d*-MPH and *l*-MPH indicated that overall systemic exposure and maximum plasma concentrations of both enantiomers increased in a generally dose proportional manner over the entire range of patch sizes (12.5 to 37.5cm^2) and over the entire range of apparent doses delivered for each enantiomer (6.2 to 15.6mg). However, it should be noted that the inter-subject variability in the pharmacokinetics of *d*-MPH and *l*-MPH was high, although this was expected since the apparent dose delivered from each patch size was also highly variable. These differences may reflect differences in skin type and thicknesses between subjects.

The study was designed so that all subjects were at steady-state prior to pharmacodynamic assessments, and therefore clinical findings were likely influenced by existing *d*-MPH plasma concentrations. Furthermore, the placebo group showed large variability in the primary PD markers, SKAMP-D and PERMP, and for the modeled vital signs. Therefore, PD models were also evaluated for mean placebo adjusted- and individual placebo adjusted-endpoints. The changes in the pharmacodynamic endpoints when modeled against *d*-MPH plasma concentrations showed no indication of any type of hysteresis. Hence, indirect-effect and/or tolerance models were not included in the data modeling. The modeling approach included E_{max} (classic and inhibitory), E_{max} with intercept, and linear models for assessing changes in the pharmacodynamic endpoints.

When modeling either pooled individual data (data pooled across all subjects) or pooled mean data (data from mean plasma *d*-MPH concentrations and mean PD endpoint at each nominal time point) a relationship between plasma *d*-MPH concentrations and clinical endpoints were observed. After adjustment for placebo observations no relationship between plasma *d*-MPH concentrations and SBP, DBP or HR were observed.

For the primary endpoint SKAMP deportment (SKAMP-D), an inhibitory E_{max} pharmacodynamic model was developed. The parameter estimates were E_{max}=-9.93 and EC_{50}=17.26ng/mL. The model met the selection criteria but showed high inter-individual variability. Nevertheless, improved deportment as a function of increasing *d*-MPH concentrations (to a plateau) was seen when pooled (individual and means of all treatments) data were used for pharmacodynamic modeling.

For the secondary performance marker, PERMP, an E_{max} model was developed. The parameter estimates were E_{max}=136.70 and EC_{50}=15.50ng/mL. The model met the model selection criteria but showed high inter-individual variability. The model showed however, improved performance as a function of increasing *d*-MPH concentrations (to a plateau) when pooled (individual and means of all treatments) data were used for pharmacodynamic modeling.

There was no robust model developed to represent changes in systolic and diastolic blood pressure or heart rate with plasma *d*-MPH concentration and no clear relationship could be established between change in vital signs and *d*-MPH plasma concentration.

In summary, MPH was steadily absorbed into the systemic circulation, with maximum median plasma concentrations of *d*-MPH and *l*-MPH occurring at approximately 7 to 9 hours after application of the MTS patch. There were frequently quantifiable plasma concentrations of *d*-MPH prior to MTS patch application, and there was minimal evidence of significant lag times.

The terminal elimination phase could not be fully defined for *d*-MPH, although the half-life was estimated to be approximately 3.0 hours. The terminal elimination half-life of *l*-MPH was approximately 1.2 to 1.8 hours across the 4 patch sizes studied. $AUC_{0\text{-}12\ h}$ 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. The inter-subject variability was high for both these pharmacokinetic parameters with arithmetic CV% values ranging from 37% to 91%. The systemic exposure, based on $AUC_{0\text{-}12\ h}$ and C_{max}, was approximately 37% to 45% lower for *l*-MPH compared to *d*-MPH. PK/PD effects corresponding to an E_{max} or E_{inhib} model for the population were observed, with EC_{50} values of 16-17 ng/mL based on either SKAMP deportment (SKAMP-D) or PERMP.

4.1.2.2 SPD485-302

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 pharmacokinetic objective was to assess the relationship between plasma exposure and the safety and efficacy measures of MTS and CONCERTA via sparse sampling.

Eligible subjects were randomized in a 1:1:1 ratio to MTS, CONCERTA®, or matching placebo and entered the double-blind stepwise dose optimization period. The objective of this period was to ensure subjects were titrated to at least an acceptable dose of MTS (using $12.5cm^2$, $18.75cm^2$, $25cm^2$, and $37.5cm^2$ patch sizes) or CONCERTA® (using 18mg, 27mg, 36mg, and 54mg dosage strengths) based upon investigator review of parent and teacher rating forms,TEAEs, and clinical judgment (using the ADHD-RS-IV). During 1 of the last 3 visits, Visit 7, 8 or 9, 3 venous blood samples were drawn at 7.5 hr, 9.0 hr, and 10.5 hr post dosing for Pharmacokinetic (PK) evaluation. The duration of this period was 5 weeks to allow for titration up to the highest dose and 1 titration down to a prior dose level, if necessary. No further titration up or down was permitted once subjects had been titrated down.

The duration of MTS/PTS (Placebo Transdermal System) patch wear was 9 hours per day; a new patch was applied each morning at approximately 0700 hours. All subjects were initiated on the MTS/PTS $12.5cm^2$ size patch (1/day) and the CONCERTA®/matching placebo 18mg dose (1/day), and were evaluated after 1 week (7±2 days) for tolerability and effectiveness. Titration to the next patch size/dosage strength was allowed after a minimum of 1 week on the previous size/dose based on the overall response of the subject. Additionally, subjects may have been titrated back down to the previous patch size/dosage strength (once) to optimize tolerability and effectiveness. A response was defined as acceptable if a subject showed at least a 25% reduction in ADHD symptoms with minimal side effects. Subjects who did not reach at least an acceptable dose (i.e., “Acceptable condition”) by Visit 7, were withdrawn from the study. Subjects completing Visit 7 (Week 5) were permitted to enroll in the SPD485-303 open-label study. Following successful titration to at least an acceptable dose of MTS/CONCERTA®/Placebo by Visit 7, subjects maintained the dose through the maintenance period. Double-blind assessment of the safety and efficacy of MTS/CONCERTA®/Placebo proceeded for 2 weeks.

The primary outcome measure of the study was the ADHD-RS-IV. The ADHD-RS consists of

18 items designed to reflect current symptomatology of ADHD. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0 to 54. The scale may be sub-divided into 2 sub-scales of 9 items each: hyperactivity/impulsivity and inattentiveness. Secondary efficacy measures were the Connors' Teacher Rating Scale – Revised: Short Form (CTRS-R), the Connors' Parent Rating Scale – Revised: Short Form (CPRS-R), Clinical Global Impressions – Improvement (CGI-I), and Parent Global Assessment (PGA).

Safety and tolerability assessments included AEs, laboratory tests, vital signs, physical examinations, electro-cardiograms (ECGs), Children's Sleep Habits Questionnaire (CSHQ), Dermal Evaluations (Dermal Response, Dermal Discomfort and Transdermal System Adherence), and weight.

Pharmacokinetic evaluations were conducted on subjects at visit 7, 8 or 9. Three (3) venous blood samples were drawn at 7.5 hr, 9.0 hr, and 10.5 hr after patch application. Quantitation of *d*- and *l*-methylphenidate in plasma was performed using a validated chiral liquid chromatography, tandem mass spectrometric detection assay.

The primary efficacy assessment was defined as the ADHD-RS-IV total scores. The Baseline consisted of the ADHD-RS-IV total score obtained at Visit 2. The endpoint of the primary efficacy assessment 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 from Baseline score at the endpoint. Secondary efficacy assessments were the CTRS-R total scores and CPRS-R, CGI-I and PGA scores. The endpoint of these secondary efficacy assessments was defined as the last post-Baseline assessment for which a valid value was obtained.

Retrospective analyses of data from 2 previous Phase I studies were conducted to select the best of the 3 sample times (7.5, 9.0, and 10.5 hours) to serve as surrogate for systemic exposure with which to explore relationships with efficacy and safety measures. Exploratory plots and regression analyses were conducted to assess potential relationships with efficacy measures (ADHD-RS-IV, CTRS-R, CPRS-R, CGI, and PGA ratings) and safety measures (e.g., change in systolic BP, diastolic BP, heart rate, pulse, and respiratory rate, and the following TEAEs: weight loss or sleep changes [CSHQ ratings]).

Results

The plasma concentration at patch removal time, 9 hours after application, was selected, on the basis of regression analyses of data from 2 previous studies (SPD 485-101 and N17-016), as the optimum surrogate for systemic exposure with which to explore relationships with efficacy and safety measures.

For each of the comparable patch sizes and capsule strengths, concentrations for *d*- and *l*-MPH at the 9-hour time point appear to be higher for MTS, as shown in Table 16.

Table 16: Mean (SD) 9-Hour Plasma *d*- and *l*-MPH Concentrations (ng/mL) for MTS and CONCERTA®

Patch Size	*d*-MPH	*l*-MPH	Capsule Strength	*d*-MPH	*l*-MPH
12.5cm^2 (n = 5)	12.7 (7.42)	6.87 (4.09)	18mg (n = 3)	8.65 (1.75)	0.00 (0.00)
18.75cm^2 (n = 14)	20.1 (15.3)	10.0 (7.08)	27mg (n = 13)	11.0 (9.48)	0.852 (2.31)
25cm^2 (n = 20)	38.6 (17.0)	20.2 (8.64)	36mg (n = 23)	20.1 (9.77)	0.178 (0.322)
37.5cm^2 (n = 33)	47.0 (27.1)	28.6 (20.6)	54mg (n = 41)	23.2 (13.2)	0.337 (0.618)

Based on the regression analysis, a relationship was observed between body weight and *d*-MPH concentration (P=0.0002). No relationship was observed between any of the relevant efficacy or any of the other safety parameters and exposure. Table 17 presents a summary of the regression analysis results.

Table 17: Summary of Exposure-Response Regression Analysis on Safety and Efficacy Variables

Efficacy and Safety Variables	N	Slope	Intercept	R^2	Significance F
ADHD Rating Scale - Change From Baseline	72	-0.0196	18.9812	0.001052	0.7853
CGI-I Results	72	-0.0021	1.9969	0.002362	0.6831
CGI-S Result	72	0.0057	4.4083	0.03872	0.0952
CSHQ - Change From Baseline	72	-0.0035	-3.5274	0.000175	0.9109
CPRS - Change From Baseline	65	-0.1267	-23.4790	0.02456	0.2089
CTRS - Change From Baseline	72	-0.0870	-13.8115	0.01011	0.4292
Systolic Blood Pressure - Change From Baseline	72	0.0403	0.4878	0.01307	0.3355
Diastolic Blood Pressure - Change From Baseline	72	0.0592	-0.0022	0.03108	0.1357
PGA Result	72	-0.0044	2.3955	0.008765	0.4308
Heart Rate - Change From Baseline	70	0.1266	5.9196	0.04718	0.0688
Pulse - Change From Baseline	72	0.0519	4.1030	0.008138	0.4479
Respiratory Rate - Change From Baseline	72	0.0024	0.5691	0.0003736	0.8711
Weight - Change From Baseline	72	-0.0471	0.0264	0.1761	0.0002197

Discussion

Based on the results of a retrospective regression analysis of 2 previous studies (SPD 485-101 and N17-016), it was determined that the *d*-MPH concentration at patch removal time, 9 hours in this study, was the most appropriate surrogate for exposure.

The relationships between *d*-MPH plasma concentrations at the 9-hour time point to safety- and efficacy-related observations were explored graphically. In addition, regression analyses were performed for the safety and efficacy observations with the concentration of *d*-MPH at the 9-hour time point. regression analyses between *d*-MPH plasma concentrations at the 9-hour time point and weight loss revealed a significant relationship. Similar analyses did not reveal any other relationships between efficacy or safety endpoints and exposure.

For each of the respective patch sizes and capsule strengths, concentrations for *d*- and *l*-MPH at the 9-hour time point appear to be higher for MTS.

In summary, a relationship was observed between weight loss and exposure based on graphical evaluations and regression analyses. No such relationship was observed with respect to any other efficacy or safety endpoint. Higher concentrations after 9 hours of wear time for MTS versus 9 hours after dosing for CONCERTA® suggest that the systemic exposure after MTS is greater than after CONCERTA®.

4.2 New data in context of data in Noven NDA 21-514

In the Noven NDA 21-514, data from 3 pharmacokinetic studies in pediatric patients were submitted:

- N17-016: A multiple dose pharmacokinetic study of methylphenidate with Noven™ Methylphenidate Transdermal System in pediatric patients with Attention Deficit Hyperactivity Disorder
- N17-005: A bioavailability study of Noven Methylphenidate Transdermal System using 2 different sites of application in pediatric patients with Attention Deficit Hyperactivity Disorder
- N17-002: A double-blind, placebo-controlled, steady-state pharmacokinetic and efficacy study of a Methylphenidate Transdermal System compared to Ritalin-IR in pediatric patients with Attention Deficit Hyperactivity Disorder.

Data from pharmacokinetic studies submitted in NDA 21-514 (designated with N17- protocol numbers) and those in the subsequent Shire/Noven resubmission (designated with SPD485 protocol numbers) were generally consistent, taking account of the various wear times investigated.

Across all studies combined, systemic exposure (mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) increased generally dose proportionately with patch size. When normalized for patch size, mean AUC_{0-t} and $AUC_{0-\infty}$ increased approximately proportionately with wear time, whereas the normalized C_{max} did not change markedly with wear time.

Results from the single dose study N17- 005 demonstrated that systemic exposure was higher (approximately 31%) when MTS 25 cm^2 was applied for 16 hours to the hip, compared to when applied for the same length of time to the scapular region. Hence subsequent studies, including all the SPD485-numbered studies, were conducted employing hip application of MTS.

Results from the repeat dose study N17-002 showed that once daily application of MTS 10cm^2 to the buttocks for 24 hours provided similar peak plasma concentrations to an approved immediate release oral formulation of methylphenidate (Ritalin 10mg) administered 3 times daily and AUC values approximately 2.5 times higher.

Results from another repeat dose study, N17-016, provided estimates of systemic exposure after 8 or 12 hour applications of MTS 37.5cm^2 or 50cm^2 to the hip. The exposure to *d*-MPH was greater (40 –60%) after the application of 50cm^2 MTS compared to 37.5cm^2 and T_{max} was independent of dose within a given wear-period. Similar findings were noted for *l*-MPH. The percentage MPH delivered from MTS was independent of dose but dependent on wear time. The drug delivery rate was about 20% higher with a shorter wear time and, as expected, the overall percentage of dose delivered increased with wear time.

In summary, the pharmacokinetic data in pediatric patients submitted in NDA 21-514 provided fundamental pharmacokinetic data in this population which facilitated design of the subsequent Phase I studies in the Noven/Shire program supporting the Resubmission. Data summarized across the 2 parts of the MTS development program were generally consistent.

5. DURATION OF ACTION OF MTS

The duration of action of MTS has been elucidated principally from the results of study SPD485-201, a Phase II, randomized, double-blind, multi-center, placebo-controlled, Analog Classroom, crossover study, with an open-label optimization phase, designed to assess the time course of treatment effect, tolerability and safety of MTS in pediatric subjects diagnosed with ADHD. The design and results of this study are summarized in section 3.2.1 of this PK/PD Summary and given in more detail in the Efficacy Summary. In study SPD485-201, the last sampling time for pharmacodynamic and pharmacokinetic measures occurred at 12 hours after patch application. The protocol-defined estimate of duration of action, as limited by this sampling period, is discussed in the context of additional information about the decline in the plasma concentrations of *d*-MPH after patch removal and the relationship of efficacy measures to plasma concentrations observed in this study, supported by information about the terminal phase half-life of *d*-MPH across studies.

Pharmacodynamic data from study SPD485-201 (SKAMP and PERMP scores representing the primary and main secondary endpoints, respectively) demonstrated that, at steady state after dose optimization, MTS achieved a duration of action of 11.5 hours, based on protocol-defined onset and offset of efficacy. The onset of efficacy was defined as one-half of the time between the first assessment time showing significance and the previous assessment. Likewise, the loss of efficacy was defined as one-half of the time between the last assessment time showing significance and the subsequent time that failed to show significance. If no loss of efficacy were found then the loss of efficacy would be assigned at 12.5 hours. The onset of efficacy observed in this study is thus defined as occurring at 1 hour and the loss of efficacy at 12.5 hours. Therefore, the 9-hour period of patch wear resulted in an 11.5-hour duration of effect.

Notwithstanding the proven duration of efficacy based on the protocol-defined onset and offset of efficacy, the pharmacokinetic/pharmacodynamic data suggest that efficacy would be declining but not necessarily terminated by 12.5 hours. At 12 hours after application, the mean plasma concentration of *d*-MPH ranged from approximately 8 - 28 ng/mL, depending on the patch size to which the patient was optimized. Decline in plasma concentrations subsequently was consistent with a half-life of approximately 3 hours, consistent with values more accurately defined in other studies (e.g., SPD485-101 and SPD485-102). Hence it would be anticipated that concentrations would have fallen to 4 -14 ng/mL by 15 hours after patch application, corresponding approximately to the end of the waking day. These concentrations are below the EC_{50} values found for the inhibitory E_{max} model relating placebo-adjusted SKAMP-D (deportment) scores to plasma *d*-MPH concentration (17 ng/mL) and for the E_{max} model relating baseline-adjusted PERMP scores to the plasma *d*-MPH concentration (16 ng/mL) across the whole study population. According to these models, they would correspond, on average, to predicted reductions in placebo-adjusted SKAMP-D score of between 2 and 4 (19% - 45% of E_{max}), and predicted reductions in baseline-adjusted PERMP score of 28-65 (20% - 48% of E_{max}), on average. By 24 hours after MTS application i.e. immediately before the next application, mean plasma concentrations of *d*-MPH had fallen to 0.79-3.65 ng/mL, corresponding to reductions in scores of between 4% and 19% across the range of patch sizes. In the primary efficacy analysis, differences in SKAMP-D and PERMP data immediately before the next patch application were not

statistically significant and hence reduction in scores of <20% of E_{max} can be regarded as negligible.

Overall then, it may be concluded that MTS rapidly achieves plasma concentrations of the active moiety *d*-MPH on application and maintains active circulating concentrations up to and beyond patch removal at 9 hours after application, resulting in a protocol-defined duration of action of 11.5 hours. Plasma *d*-MPH concentrations decline on patch removal but activity may be retained in some individuals for longer than 11.5 hours. However, the time-course suggests that activity during the nighttime is likely to be low. By the following morning, prior to the next MTS application, plasma *d*-MPH concentrations have generally declined to insignificant levels.

6. BIOAVAILABILITY OF MPH FROM MTS RELATIVE TO THAT FROM CONCERTA®

The bioavailabilities and pharmacokinetics of *d*-MPH and *l*-MPH from MTS, compared to that from the oral extended release product CONCERTA® have been investigated in 3 studies in pediatric patients:

- SPD476-101: A Phase I study to assess the pharmacokinetics of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in pediatric patients aged 6-12 with Attention - Deficit/Hyperactivity Disorder (ADHD).
- SPD476-102: A Phase I study to assess the relative bioavailability and the pharmacokinetics of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in pediatric patients aged 6-12 with Attention Deficit/Hyperactivity Disorder (ADHD).
- SPD476- 302: A Phase III, randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose optimization study, designed to evaluate the safety and efficacy of Methylphenidate Transdermal System (MTS) vs. CONCERTA® in pediatric patients aged 6-12 with Attention -Deficit/Hyperactivity Disorder (ADHD).

Results demonstrated that plasma concentrations of *d*-MPH after single applications of MTS 25cm^2 worn for 8 or 10 hours were closest to those for CONCERTA® 36mg and at the higher patch size of MTS (37.5cm^2) worn for 9 hours were not dissimilar from those for CONCERTA® 54mg. On repeat dosing, plasma concentrations at the end of the 9-hour wear time for MTS (across the recommended dose range: 12.5, 18.75, 25 or 37.5cm^2) were between 1.5-fold and 2-fold higher than those for the equivalent incremental doses of CONCERTA® (18, 27, 36 and 54mg. Plasma concentrations of *l*-MPH were substantially higher for MTS (all patch sizes) than those found after equivalent single or repeat doses of CONCERTA®, in accordance with the known much higher oral first-pass metabolism of *l*-MPH than of *d*-MPH, a phenomenon not observed or expected after transdermal administration of *d,l*-MPH.

In study SPD485-101, the relative bioavailabilities of *d*-MPH and *l*-MPH from a single dose of MTS 25 cm^2 applied for different wear times (6, 8 or 10 hours) were compared with those from a single oral dose of CONCERTA® 36mg.

Plasma concentrations of *d*-MPH delivered from a single dose of MTS increased somewhat more slowly than from CONCERTA®, achieving C_{max} at the end of each wear time. The

systemic exposure after the 10 hour wear time was closest to that for CONCERTA®, with mean C_{max} being essentially equal to that for CONCERTA® and AUC being only 17% lower. With the shorter wear times (8 hours and 6 hours), overall systemic exposure to *d*-MPH from MTS was lower, mean C_{max} being, on average, 13% and 22% less than for CONCERTA®, respectively, and AUC 31% and 42% less, respectively.

When concentrations over the 6 -14 hour period most affected by varying the wear time were compared with those from CONCERTA®, mean plasma concentrations of *d*-MPH from MTS worn for 10 hours approached those for CONCERTA® by 8 hours and exceeded them, by 1% increasing to 33%, over the period 10-14 hours after application. For MTS worn for 8 hours, mean *d*-MPH plasma concentrations were maximal at 8 hours but remained between 10% and 19% lower than for CONCERTA® over the period 8 -14 hours after application. The shorter 6 hour wear time for MTS resulted in lower concentrations over the whole 6-14 hour period, being maximally 28% lower than for CONCERTA® at 8 hours after application.

Hence the 8-hour wear time for MTS (25cm^2) resulted in slightly lower *d*-MPH concentrations than did CONCERTA® (36mg) and the 10-hour wear time slightly higher.

Plasma concentrations of *l*-MPH were lower than those of *d*-MPH for both MTS (at all wear times) and for CONCERTA®. However, *l*-MPH levels for MTS were substantially higher than for CONCERTA® (10-to 12-fold for C_{max} and 8- to 15-fold for AUC_{0-t}).

In study SPD485-102, the relative bioavailabilities of *d*-MPH and *l*-MPH from a single dose of MTS 37.5 cm^2 applied for 9 hours were compared with those from a single oral dose of CONCERTA® 54mg.

Overall, the relative bioavailability of *d*-MPH from MTS was not dissimilar from that of CONCERTA®, with C_{max} averaging 12% greater (90% CI: 3% lower to 30% greater) and AUC_{0-t} 6% lower (90% CI: 20% lower to 10% greater, respectively, but encompassed unity; hence differences between MTS and CONCERTA® were not statistically significant.

In contrast, the bioavailability of *l*-MPH from MTS 37.5cm^2 was substantially higher than that of the corresponding CONCERTA® dose. C_{max} values were, on average, 25-fold greater (90% CI: 20-fold to 32-fold) and AUC_{0-t}, on average, 42-fold greater (90% CI: 30-fold to 60-fold) for MTS 37.5cm^2 than for CONCERTA®.

In study SPD485-302, a Phase III study to evaluate safety and efficacy of MTS after dose optimization to repeat doses of MTS (12.5cm^2, 18.75cm^2, 25cm^2 or 37.5cm^2 daily) or of CONCERTA® (18mg, 27mg, 36mg or 54mg daily), sparse sampling was conducted at times around the end of the wear time for MTS (7.5, 9.0 or 10.5 hours after MTS application) and at the same sampling times after CONCERTA® administration. Plasma concentrations at the end of the wear time, 9 hours after application, were selected on the basis of retrospective regression analysis of data from 2 prior studies as being the best surrogates of systemic exposure to MTS for assessment of correlation with safety and efficacy parameters and concentrations at this time were also summarized for comparison with those from the corresponding CONCERTA® doses.

Mean 9-hour plasma concentrations of *d*-MPH for MTS (12.5cm^2, 18.75cm^2, 25cm^2 or 37.5cm^2 daily) , relative to those of CONCERTA® (18mg, 27mg, 36mg or 54mg daily), were 1.5-fold, 1.8-fold, 1.9-fold and 2.0-fold higher, respectively.

Mean 9-hour plasma concentrations of *l*-MPH were consistently lower than for *d*-MPH but were higher for MTS than for CONCERTA®. For the 12.5cm^2 patch size, mean 9-hour plasma concentrations of *l*-MPH were measurable whereas they were below the limit of quantification for CONCERTA® (18mg). At the higher patch sizes, compared to corresponding dose of CONCERTA®, values were 12-fold, 113-fold and 85-fold higher in order of increasing patch size.

Across studies, plasma concentrations of *d*-MPH from single applications of MTS worn for approximately 9 hours were similar to those from equivalent doses of CONCERTA®, but after repeat doses of MTS, 9-hour plasma concentrations were approximately double those for the corresponding dose of CONCERTA®.

7. THE RELATIVE ROLES OF *d*- AND *l*-MPH PHARMACOLOGY IN RESPECT OF THE EFFICACY/SAFETY PROFILE OF MTS

7.1 Pharmacokinetics of *d*- and *l*-MPH in man after clinically relevant doses of *d*-MPH by MTS

Ten (10) biopharmaceutics studies of MTS have been conducted in which plasma concentrations of *d*- and *l*-MPH have been separately determined: 2 in healthy adult subjects (N17-004 and N17-006), 6 in pediatric ADHD patients (N17-016, N17-002, SPD485-101, SPD485-102, SPD485-201 and SPD485-302) and 2 in adult stimulant abusers (N17-007 and N17-012).

Data from these studies shows that under all circumstances investigated, plasma concentrations of *l*-MPH are consistently lower than those of *d*-MPH (approximately one-half to two-thirds, on average).

7.2 Pharmacology and therapeutic activity of *d*-, *l*- and *d,l*-MPH in ADHD

7.2.1 Studies in animals

In vitro and *in vivo* animal pharmacology studies have provided a variety of information about interactions with the dopamine transporter (DAT) and norepinephrine transporter (NET) and their behavioural *sequelae* which all strongly suggests that the pharmacological properties of *dl*-MPH pertinent to its role in treatment of ADHD are almost, if not entirely, vested in the *d*-enantiomer:

- In *in vitro* studies of monoamine reuptake inhibition, *d-MPH* showed similar or greater potency (based on Ki or IC_{50} values) to that of cocaine, whereas *l*-MPH was 8-41 times less potent against dopamine reuptake and 8 -12 times less potent against norepinephrine reuptake. As ligands for the cocaine binding site on

DAT, *dl*- or *d-MPH* were twice as potent as cocaine itself, and approximately 14 times more potent than *l*- MPH[6].

- In brains of rats[7], baboons and humans[8,9], *d*-MPH bound to DAT sites in the basal ganglia and striatum, whereas the *l*-isomer showed no such specificity of action. Positron Emission Tomography (PET) and MicroPET studies using orally delivered C^{11}-labeled *d*- and *l*-MPH indicated high global uptake of carbon-11 in both baboon and rat brain for both *d*- and *l*-MPH. However, whereas for *d*-MPH this material represented predominantly unchanged tracer, for *l*-MPH it was mainly a labelled metabolite[10].

- When given at identical doses, in a microdialysis study of striatal dopamine efflux, the *d*-isomer was more effective than the racemic mixture at potentiating dopamine efflux, whereas the *l*-isomer was almost without effect[9].

- In rats, *d*-MPH was more potent than *dl*- MPH in inducing locomotor activity, whereas the *l*-isomer was almost totally inactive[11,12]. Increased locomotor activity correlated with increased extracellular striatal dopamine concentrations, up to increases of 150%, and these were also greater for *d*-MPH than for the *l*-isomer. Greater increases in striatal dopamine were associated with stereotypy, which occurred at doses of 2.5 mg/kg iv of *d*-MPH and 5-10 mg/kg *dl*-MPH [12],implying no contribution from the *l*-enantiomer. When *l*-MPH was administered ip to mice at a dose of 3 mg/kg, it neither stimulated locomotor activity nor inhibited the increased locomotor activity die to cocaine administration[10].

- In hyperactive neonatal rats with catecholaminergic lesioned brain pathways as a result of 6-hydroxydopamine treatment (an animal model for ADHD), *d*-MPH and the racemate reversed the hyperactivity[11,13,14], with *d-MPH* showing 3 times the potency of the racemate, whereas *l-threo*-MPH did not affect locomotion in this model[14].

- In functional observation battery (FOB) tests and rota-rod tests in male and female rats administered various doses of *dl-, d- or l*-MPH, Teo et al[15] found that whilst all treatments produced significantly different FOB responses in some dose/sex groups, fewer significant FOBs were seen with equimolar doses of *d- or l*-MPH alone than with *dl*-MPH but *l*-MPH was the least potent in producing FOBs. Similar findings were obtained in the rota-rod studies.

7.2.2 Studies in man

Evidence from studies in man is entirely consistent with that in animals and supports a predominant role for the *d*-enantiomer:

- In a placebo-controlled study of attention, monitored by a battery of computer tests, in 8 pediatric ADHD patients, 5 mg *d*-MPH was equi-efficaceous with 10 mg *dl*-MPH in sustaining attention, whereas 5 mg *l*- MPH did not differentiate from placebo[16]. Hence, improvement in sustained attention was entirely attributable to

the *d*-isomer. Moreover, in this study, the pharmacokinetics of the *d*-isomer were not affected by the presence of the *l*-isomer.

- Volkow et al[17] reported a correlation between DAT blockade and MP-induced changes in heart rate and in systolic but not in diastolic blood pressure, suggesting that cardiovascular effects of MPH are in part mediated by central effects due to dopamine. These authors cited observations[18] that cardiovascular effects of cocaine and amphetamine can be antagonized by dopamine D_2-receptor blockers. Failure to observe any effects on diastolic blood pressure in either study may imply involvement of other factors such as noradrenergic blockade.

- Volkow et al[19]used PET to investigate the mechanism of action of MPH in the human brain and showed that *d*-MPH, but not *l*-MPH, bound to the DAT.

- In a double-blind, placebo-controlled trial of *d*-MPH and *dl*-MPH in children with ADHD, utilising change from baseline to last study visit on teacher-completed Swanson, Nolan and Pelham (Teacher SNAP) rating scale as primary endpoint, an average titrated dose of 18.25mg/kg *d*-MPH was as safe and effective as an average titrated dose of 32.14mg/kg *dl*-MPH[20]

- In a double-blind, placebo-controlled, crossover study in 32 children with ADHD, using a computerised maths test as objective measure and teacher rating on the Connors, Loney and Milich (CLAM) scale in a laboratory classroom setting as subjective measure, the efficacy of a single dose of *d*-MPH (2.5, 5 or 10mg) was equivalent to that of *dl*-MPH (5, 10 or 20mg). Clinical efficacy was highly correlated with plasma concentrations of *d*-MPH. Thus, the elimination of the l-enantiomer did not diminish the efficacy of an acute dose of methylphenidate and it was concluded that efficacy resided in the *d*-enantiomer[21].

7.3 Pharmacology of *d*-, *l*- and *d,l*-MPH in relation to adverse events

The recognized side-effects of methylphenidate include reduced appetite, weight loss and impaired growth; nausea, vomiting and abdominal cramps, probably associated with the reduced food consumption; cardiovascular effects, principally increases in blood pressure and heart rate; insomnia and restlessness[6].

These effects are all shared with other psychostimulant drugs e.g. amphetamines, which have a sympathomimetic profile responsible for the drugs' appetite suppressant and cardiovascular properties (the result of elevated sympathetic tone) and for increased irritability and sleep disturbance which are expected consequences of enhanced stimulation[6,22].

It follows that the adverse effects of *dl*-MPH are a direct consequence of its pharmacological actions. As previously elucidated, these appear to be mediated by its effects on dopamine and norepinephrine reuptake and release. In this respect, all the evidence points to *d*-MPH being the active isomer, with little, if any, contribution from *l*-MPH. Therefore, there is nothing to suggest that *l*-MPH can contribute any more significantly to the adverse effects than to the efficacy of *dl*-MPH in ADHD.

7.4 Discussion

The potency of *l*-MPH in *in vitro* monoamine (dopamine and norepinephrine) reuptake inhibition screens is at least an order of magnitude lower than that of *d*-MPH and this difference in potency appears to be borne out in comparative *in vivo* studies both in animals and in man. Moreover, circulating plasma concentrations of *l*-MPH in man at clinically relevant MTS doses are, on average, approximately one-half to two-thirds of those of *d*-MPH. Thus differences in potency and pharmacokinetics of the 2 enantiomers both favor *d*-MPH. Overall, any contribution by the *l*-isomer to the activity of *dl*-MPH seems likely to be minimal, despite the higher circulating concentrations of this isomer after MTS than after oral administration. Evaluation of the risk/benefit of MTS with the chosen 9-hour wear time has been made on the basis of completed clinical studies that included monitoring of vital signs (including blood pressure and heart rate) and the usual adverse event reporting, as well as evaluation of efficacy by means of the approved clinical outcomes endpoints for ADHD. These studies have shown an adverse event profile similar to those of the approved oral products and give no cause for specific concern about the higher systemic exposure to *l*-MPH associated with MTS than with these approved products.

7.5 Conclusions

- Circulating plasma concentrations of *l*-MPH are, on average, approximately one-half to two-thirds those of *d*-MPH.

- *d,l*-MPH binds to the “cocaine binding sites” on monoamine reuptake transporters DAT and NET. Moreover, the pharmacological actions of methylphenidate in humans are mediated entirely by *d-MPH* in a manner which is consistent with the known *in vitro* and *in vivo* animal pharmacology of *dl*- and *d*-MPH.

- Overall, it has not been proven that *d-MPH* offers any clinical advantage over the racemic product in the treatment of ADHD. The corollary of this conclusion is that the presence of *l*-MPH confers no disadvantage.

8. REFERENCES

1 Kimko HC, Cross JT and Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinet 1999; 37:457-470.

2 Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, Lindemulder E and Wigal S. Development of a new ince-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder. Arch Gen Psychiatr 2003; 60: 204-211.

3 Baren M, Swanson JM, Wigal SB et al. Lack of effect of breakfast conditions on the pharmacokinetics and efficacy of OROS® methylphenidate HCl extended-release tablets in children with ADHD [poster]. The Pediatric Academic Societies and American Academy of Pediatrics Joint Meeting; 2000 May 12-16; Boston (MA).

4 Keating GM, McClellan K and Jarvis B. Methylphenidate (OROS® formulation). CNS Drugs 2001; 15:495-500.

5 Srinivas NR, Hubbard JW, Korchinski ED and Midha KK. Enantioselective pharmacokinetics of *dl-threo*-methylphenidate in humans. Pharm Res 1993; 10: 14-21.

6 Report RSC039 for Shire Pharmaceuticals, A strategic review of methylphenidate and its enantiomers. Renasci, Nottingham, UK. December 2003.

7 Aoyama T, Kotaki H, Sawada Y and Iga T. Stereospecific distribution of methylphenidate enantiomers in rat brain: Specific binding to dopamine reuptake sites. Pharm Res 1994;11:407-411.

8 Ding Y-S, Fowler JS, Volkow ND, Logan J, Gatley SJ and Sugano, Y. Carbon-11-d-threo-methylphenidate binding to dopamine transporter in baboon brain. J. Nucl. Med. 1995; 36:2298-2305.

9 Ding Y-S, Fowler JS, Volkow ND, Dewey SL, Wang G-J, Logan J, et al. Chiral drugs: Comparison of the pharmacokinetics of [^{11}C]d-*threo* and l-*threo*-methylphenidate in the human and baboon brain. Psychopharmacol 1997;131:71-78.

10 Ding Y-S, Gatley SJ, Thanos PK, Shea C, Garza V, Xu Y et al. Brain kinetics of methylphenidate (Ritalin) enantiomers after oral administration. Synapse 2004; 53:168-175.

11 Patrick KS, Caldwell RW, Ferris RM and Breese GR. Pharmacology of the enantiomers of *threo*-methylphenidate. J Pharmacol Exp Ther 1987;241:152-158.

12 Aoyama T, Kotaki H, Sawada Y and Iga T. Pharmacokinetics and pharmacodynamics of methylphenidate enantiomers in rats. Psychopharmacol 1996;127:117-122.

13 Luthman J, Fredriksson A, Lewander T, Jonsson G and Archer T. Effects of d-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment. Psychopharmacol 1989;99:550-557.

14 Davids E, Zhang K, Tarazi FI and Baldessarini RJ. Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning. Psychopharmacol 2002;160:92-98.

15 Teo S. Stirling DI, Thomas, SD and Khetani, VD. Neurobehavioural effects of racemic *threo*-methylphenidate and its D and L enantiomers in rats. Pharmacol Biochem Behav 2003; 74: 747-754.

16 Srinivas NR, Hubbard JW, Quinn D and Midha KK. Enantioselective pharmacokinetics and pharmacodynamics of dl-*threo*-methylphenidate in children with Attention Deficit Hyperactivity Disorder. Clin Pharmacol Ther 1992;52:561-568

17 Volkow ND, Wang G-J, Fowler JS, Gatley SJ, Logan J, Ding Y-S et al. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of "High". J Pharmacol Exp Ther 1999;288:14-20.

18 Tella SR. Possible novel pharmacodynamic action of cocaine: Cardiovascular and behavioural evidence. Pharmacol Biochem Behav 1996; 54:343-354.

19 Volkow ND, Fowler JS, Wang G-J and Gatley SJ. Mechanism of action of methylphenidate: insights from PET imaging studies. J Atten Disord 2002; 6 Suppl 1: S31-43.

20 Wigal S, Swanson JW, Feifel D, Sangal RB, Elia J, Casat CD et al. A double-blind placebo-controlled trial of dexmethylphenidate hydrochloride and *d,l-threo*-methylphenidate hydrochloride in children with Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2004; 43:1406-1414.

21 Quinn D, Wigal S, Swanson J, Hirsch S, Ottolini Y, Dariani M et al. Comparative pharmacodynamics and plasma concentrations of *d-threo*-methylphenidate hydrochloride after single doses of *d,l-threo*-methylphenidate hydrochloride in a double-blind placebo-controlled crossover laboratory school study in children with Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2004; 43:1422-1429.

22 Renasci Report No. RSAC038 for Shire Pharmaceuticals. A strategic review of the enantiomers of amphetamine. November, 2003.