Clinical Pharmacology/Biopharmaceutics Review

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

REVIEW OF s-NDA FOR METHYLPHENIDATE TRANSDERMAL SYSTEM

EXECUTIVE SUMMARY

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

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

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

RECOMMENDATION:

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

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INTRODUCTION

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

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

QUESTION BASED REVIEW

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

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

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

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

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

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

Efficacy data presented by the firm was located at:

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

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

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

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

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

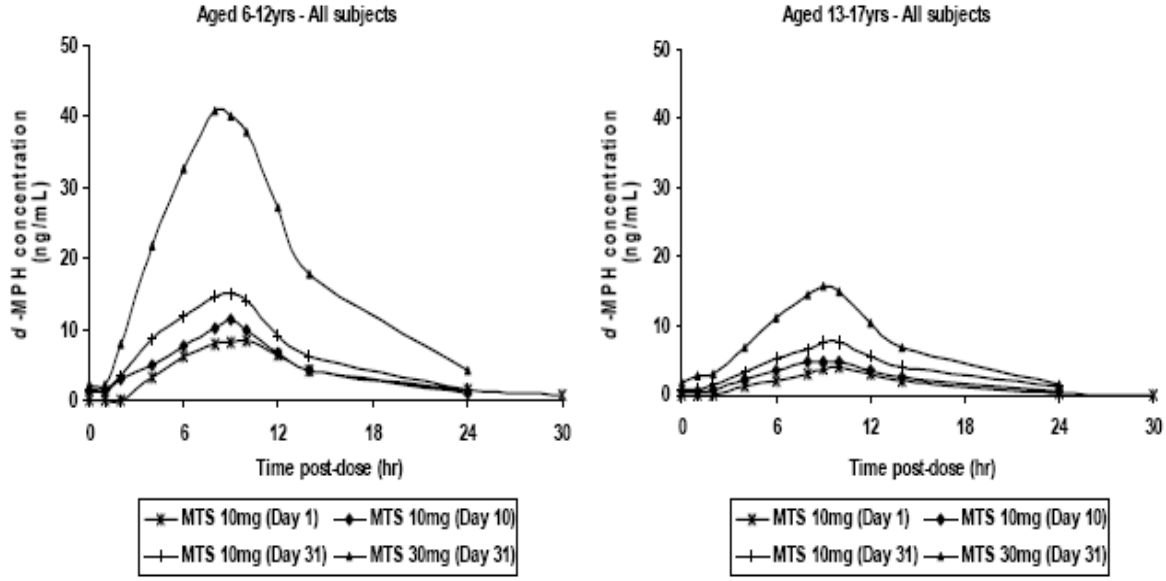

Table 3. **Summary of Pharmacokinetic Parameters of *d*-MPH for All Children (Aged 6-12 Years) and Adolescents (Aged 13-17 Years) in the Pharmacokinetic**

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

Treatment for 28 days

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

* Median value (minimum, maximum)

SD=Standard Deviation; MTS=Methylphenidate Transdermal System

Treatment for 7 days

	MTS (10mg/9h)				CONCERTA® (18mg)			
	Aged 6-12 years		Aged 13-17 years		Aged 6-12 years		Aged 13-17 years	
Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	23	0.00 (0.00, 2.00)	22	0.00 (0.00, 4.05)	10	0.00 (0.00, 0.00)	9	0.00 (0.00, 0.00)
t_{max}* (h)	23	9.00 (2.00, 12.0)	22	10.0 (8.03, 12.0)	10	8.00 (4.00, 10.0)	9	8.00 (4.00, 12.1)
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R_{ss}	19	1.16 (0.423)	16	1.28 (0.340)	9	1.11 (0.145)	9	1.07 (0.303)

Median values (minimum, maximum)

FDA Calculations based upon observed AUCss/AUCinf

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

INSPECTION REPORT

DSI was requested to give the following points special attention:

1.The firm has reported-

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

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

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

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

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

OCP Request

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

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

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

OCP Request

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

OCP COMMENTS ON PRELIMINARY RESPONSE FROM DSI

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

FIRM'S LABEL

(b) (4)

[redacted]

7 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

SIGNATURES

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

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

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

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

DETAILED STUDY REPORTS

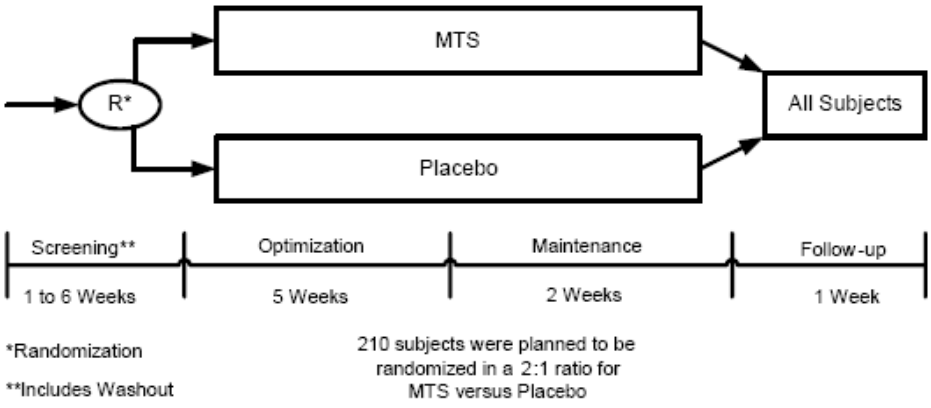
ANALYTICAL SECTION

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

EXPOSURE RESPONSE

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

Figure 1: Study Schematic



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

Drug Concentration and Relationship to Response

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

ACCUMULATION RATIO CALCULATION

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

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

Table 1a. FDA calculations for Accumulation

	Child	Adol
t1/2	5.01	4.35
ke	0.138	0.159

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

STUDY NO: SPD485-106

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

STUDY OBJECTIVES
Primary

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

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

Study Design:

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

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

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

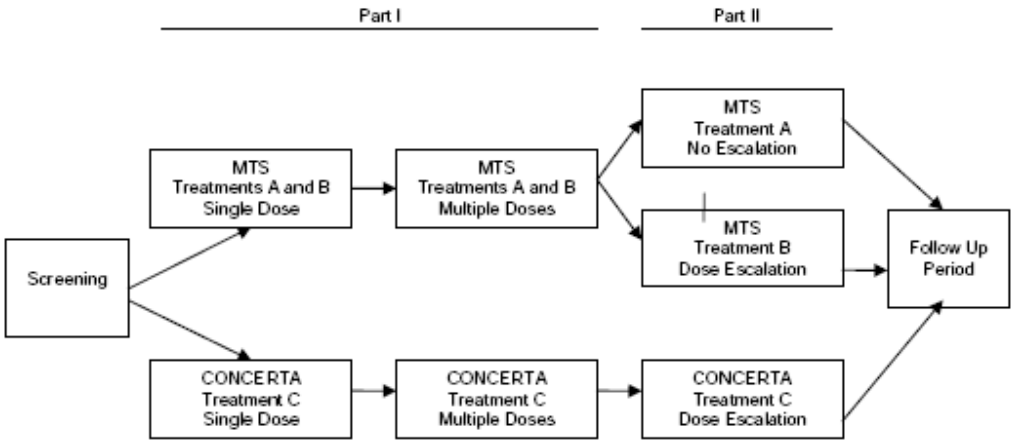


Figure 1: Subject Disposition: Children 6-12 Years of Age

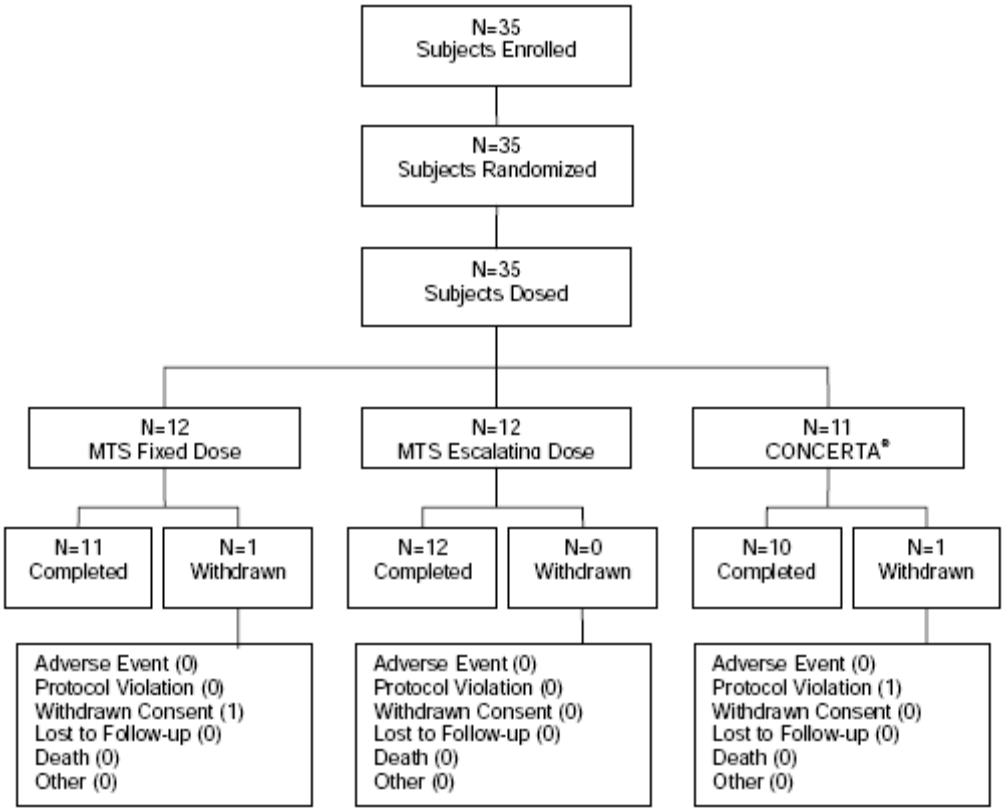
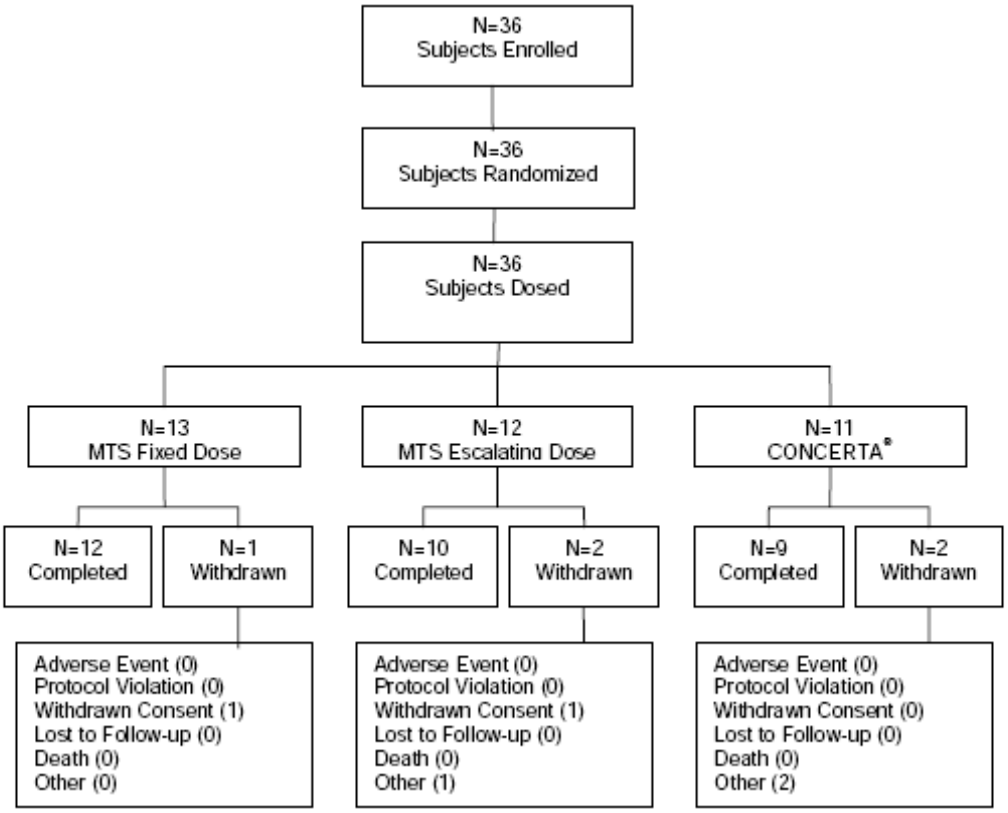


Figure 2: Subject Disposition: Adolescents 13-17 Years of Age



Demographics:

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

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

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

PHARMACOKINETIC METHODS:

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

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

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

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

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

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

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

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

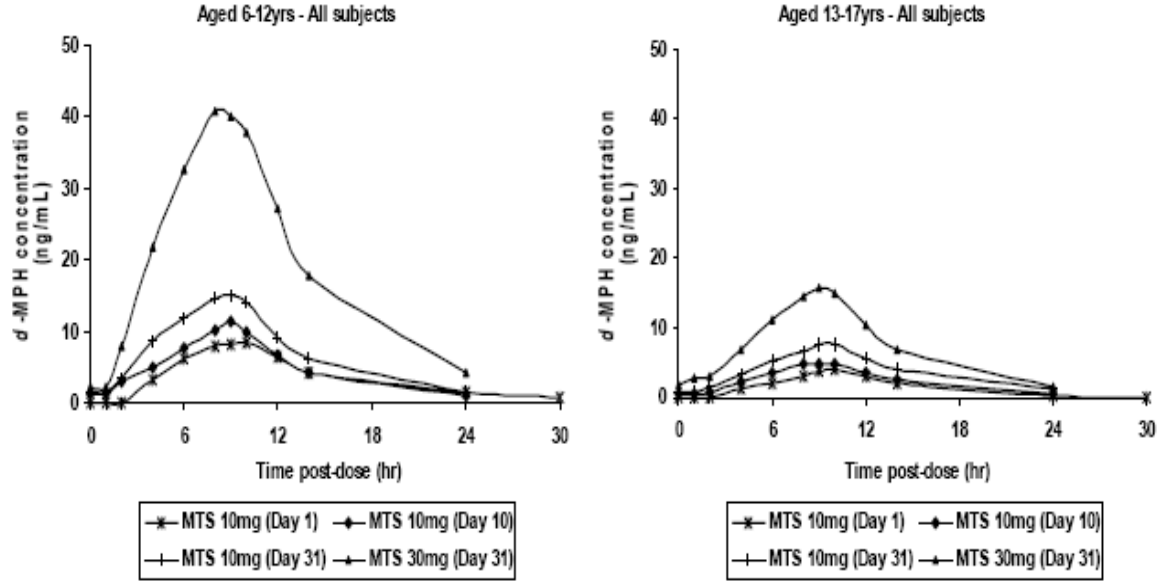
ANALYTICAL METHOD:
There was minimal <0.25% of interconversion of the isomers.

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

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

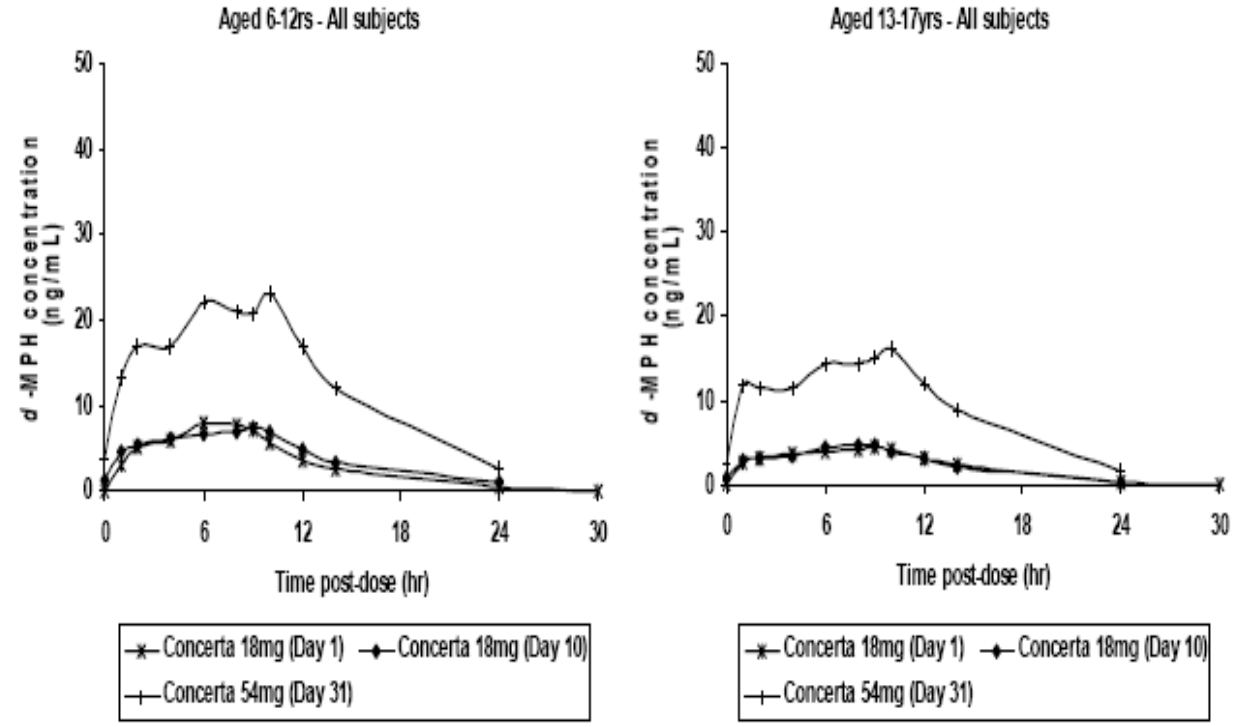
RESULTS

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



Source: Section 14, Table 2.1 to Table 2.6

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



Source: Section 14, Table 2.1 to Table 2.6

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

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

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

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

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

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

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

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

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

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

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

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

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

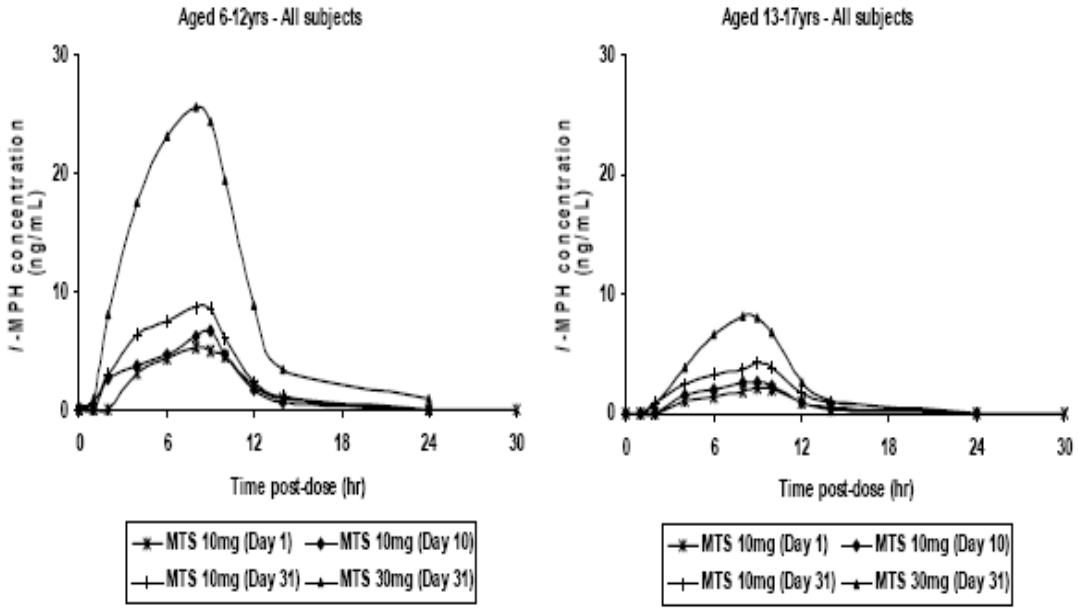
		MTS Fixed Doses (10mg/9h)			
		Aged 6-12 years		Aged 13-17 years	
Parameter	Sex	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
t_{lag}* (h)	F	4	0.00 (0.00, 0.00)	5	0.00 (0.00, 2.00)
	M	7	0.00 (0.00, 2.00)	7	0.00 (0.00, 0.00)
t_{max}* (h)	F	4	9.00 (8.00, 10.0)	5	10.0 (8.08, 10.0)
	M	7	9.00 (8.00, 10.0)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

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

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

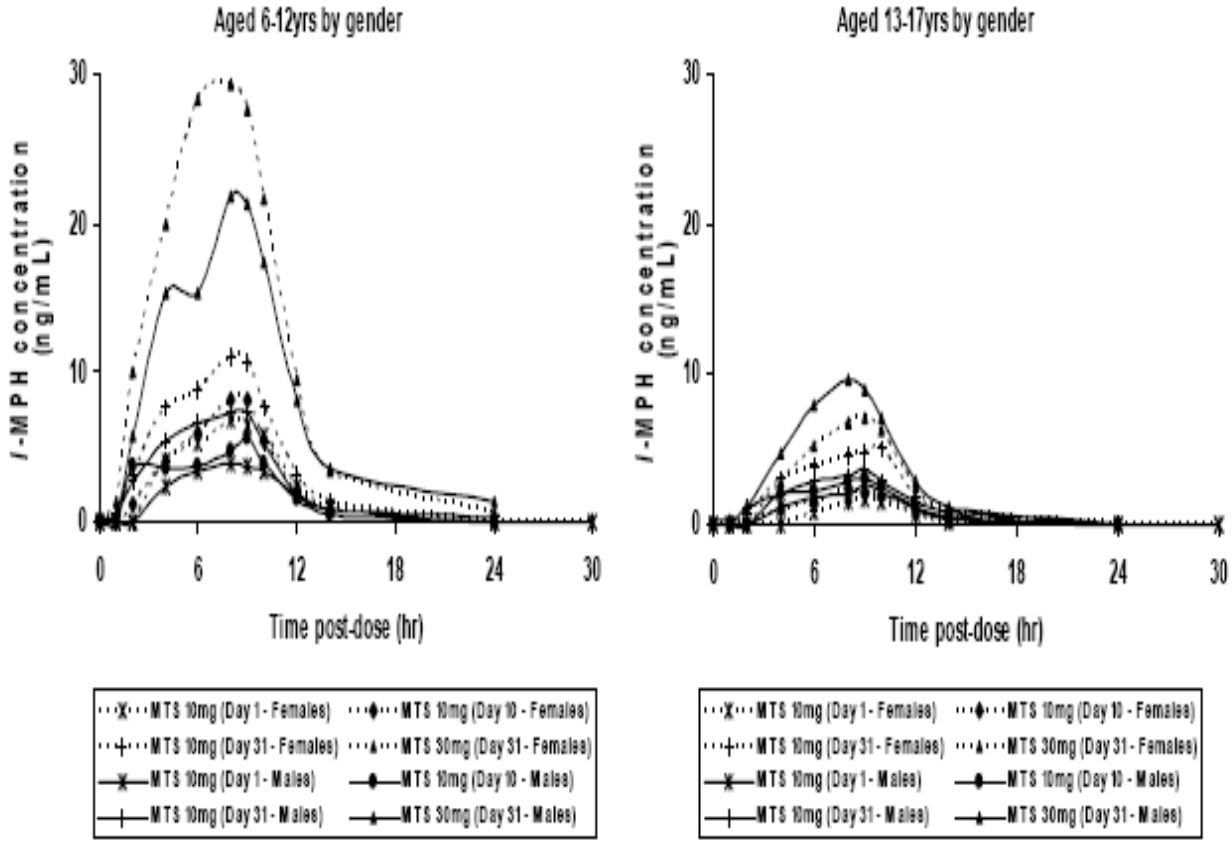
Since the d-isomer has been reported to be more active than the l-isomer only the graphical results for the l-isomer will be presented.

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



Source: Section 14, Table 2.13 to Table 2.18

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



- **Pharmacokinetic Conclusions**

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

- A lag in the absorption of *d*- and *l*-MPH, followed by slow absorption, was apparent across both age groups and sexes, following MTS single doses. In general, this lag-time was not apparent after multiple doses-Tables 3 page 29 and Table 4 page 30.

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

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

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

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

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

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

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

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

- Systemic exposure to *l*-MPH was consistently approximately half that of *d*-MPH, across age groups and sexes, following single and multiple doses of MTS. By comparison, systemic exposure to *l*-MPH was negligible after single and multiple doses of CONCERTA®.

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

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/s/

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05/13/2010

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05/13/2010