* **What is the bioavailability of MethyPatch® relative to orally administered methylphenidate?**

When adjusted for the dose delivered from the MethyPatch® transdermal system the relative exposures are 3.5 fold higher for *d*-methylphenidate (*d*-MPH) and 173 fold higher for *l*-methylphenidate (*l*-MPH) as compared to oral administration with Ritalin®, (see Figure 2).

In addition, the expected mean *l*-MPH Cmax is higher than the mean Cmax of *d*-MPH of around 15 ng/ml normally achieved with oral dosing. In addition, the AUC for *l*-MPH (which is around 50% of the AUC for d-MPH with transdermal administration) is also likely to be relatively high relative to the usual *d*-MPH AUC achieved with oral dosing. Thus these higher exposures to *l*-MPH relative to oral administration raises the question of whether there is adequate historical safety information in patients or subjects to adequately assess the safety of *l*-MPH exposure.

Are there pharmacokinetics differences by gender?

There are no apparent pharmacokinetic differences with MethyPatch by Gender.

Are there pharmacokinetics differences by race or ethnicity?

There are no obvious differences for race or ethnicity for MethyPatch®.

Are there bioavailability differences by application site?

The mean bioavailability of *d,l*-MPH in children from MethyPatch when applied to the scapular area as compared to when applied to the hip was 76%. However, the use of AUC_{0-16} rather than $AUC_{0-\infty}$ would suggest that the true relative bioavailability might be lower.

What are the pharmacokinetic characteristics in children?

Children from 6 years and up were studied. With regards to the concentration time profiles there was an apparent trend to higher exposures with younger ages in children, however there was significant overlap in concentrations with the same dose between age groups.

* **What factors might effect bioavailability and rate of drug delivery?**

Applying MethyPatch to inflamed skin resulted in approximately a 3 fold increase in exposure (both Cmax and AUC) and a much more rapid absorption so that Tlag was 3 hours shorter and Tmax occurred 10 hours earlier.

This raises concerns if the patient or parent should repeatedly apply patches to the same site as inflammation could result and absorption and adverse effects could increase.

Application of heat to the patch while being worn increased both the rate and extent of absorption. Thus, median Tlag and Tmax occurred 1 hour earlier, and median Cmax and AUCs were 2 and 2.5 fold higher respectively.

* **What are the pharmacokinetic / pharmacodynamic characteristics of MethyPatch®?**

For both MethyPatch and subcutaneous methylphenidate the time course of euphoria and dysphoria paralleled the time course of the methylphenidate concentration vs. time profile. However, there was much greater dysphoria relative to euphoria with the Methypatch, whereas there was greater euphoria compared to dysphoria with SC administration. This suggests that although MethyPatch may be abusable via topical administration, it's less likely to be as desirable a method of abuse.

In addition to euphoria and dysphoria, there were clear and substantial elevations in systolic and diastolic blood pressure, and pulse rate. Mean systolic pressures were as much as 35 mmHg higher than with placebo, and pulse rate was as much as 30 bpm higher. However, these elevations occurred with the application of three to eight 25 cm^2 MethyPatches. Thus the degree of elevation in blood pressure and pulse rate that will be seen with clinical dosing is unclear.

There was also a dose related decrease in the number of hours of sleep that subjects had, with subjects receiving 3 x 25 cm^2 patches having an average of less than 3 hours of sleep, and 6 x 25 cm^2 patches having an average of about 1.5 hours of sleep. These results are consistent with the pharmacokinetic profiles observed. However, as these doses were high the degree of insomnia under clinical dosing needs to be assessed.

* **What is the methylphenidate transdermal delivery rate from MethyPatch®?**

The sponsor has proposed a drug delivery rate of approximately [redacted] mg / hour /cm^2. This rate is based upon multiple dose *in vivo* drug delivery rate over 12 hours for the 82.5 mg / 37.5 cm^2 in 6 'children' (primarily adolescents) in study 17-016, with the rates for the other patch sizes assigned in proportion to the patch area.

Inspection of data over shorter and longer time periods from children and adults indicates that the extent of drug depletion is so great that first order kinetics for delivery rate are applicable. Thus the delivery rate will vary with duration of patch application and possibly with the aging of the skin, (e.g. faster in young children or the elderly).

The initial patch application period is [redacted] hours and results in a nominal delivery rate of 0.8 mg / cm^2 over 12 hours which is easy to remember (i.e. 10 mg / 12.5 cm^2 and 30 mg / 37.5 cm^2 over 12 hours). This review suggests that labeling be changed to reflect this with a notation that this is an average rate over [redacted] hours and that the rate of drug delivered will be faster earlier in the application period and slower later.

* **What is the abuse potential of MethyPatch?**

Buccal application resulted in 'rapid' absorption with drug detected in plasma within 15 minutes and concentrations after 2 hours of application approximately 4 fold higher than the Cmaxs achieved with transdermal application.

In addition, skin inflammation could be intentionally induced and heat application could be used for purposes of abuse or misuse. The sponsor did not study the effects of chewing or other manipulations of the patch.

However, most worrisome are the high amounts of methylphenidate that remain in discarded patches that would be available for diversion. After 8 hours of application approximately ⅔'s of the drug content remains in the patch. Thus, for a typical dose of 110 mg / 50 cm^2 approximately 74 mg would remain. Methylphenidate is easily extracted from MethyPatch with a number of readily available solvents. A detailed review of the extractability of methylphenidate with household solvents can be found in the Controlled Substance Staff review for this NDA, N21-514. In addition, the PK of this product make it likely that it would be 'misused' by truckers, students, or others who are not looking for a 'high' but rather want to stay alert and awake for prolonged periods.

* **What are the adhesion characteristics of MethyPatch?**

Although not designed to assess adhesion, adhesiveness and adhesive residue was also assessed in study 17-006 that used 25 cm^2 patches worn for 16 hours daily for 6 days.

Adult subjects were allowed to shower; but were to avoid immersion bathing. Since this was an inpatient study bathing, swimming, and exercise were probably not available, and would be unlikely to reflect childhood activity levels.

Once the system was applied and after removal, the site was not allowed to be rubbed or treated with any soap, lotion, or cream. Study personnel applied the systems rather than subjects and the procedures used were not specified.

Patches remained greater than 90% adhered more than 95% of the time and 75% - 90% adhered less than 5% of the time. There were no detachments. Although the degree of adherence is likely not as good for larger patches, the high adherence reported is consistent with what was expected due to the short patch wear time, (i.e. 16 hours). Unfortunately this study did not assess the degree of adherence under conditions of actual use.

Immediately following the removal of the transdermal system, the amount of adhesive remaining at the application site was examined and graded as none, light, medium, heavy or system not present. Approximately 2% of patch applications resulted in a medium amount of adhesive residue, although light residue was present in up to 30% of applications daily. It should be noted that the amount of residue could be higher with other patch sizes.

What is the dermal tolerability of MethyPatch?

Dermal tolerability and skin irritation was also assessed in study 17-006 that used 25 cm^2 patches worn for 16 hours daily for 6 days.

Skin irritation was assessed by evaluation of 4 parameters: edema, erythema, 'other signs of irritations' (i.e. papules and vesicles), and discomfort in 29 subjects. The duration of the study and the number of subjects were too small to draw firm conclusions however, observations are summarized below.

No edema was reported and approximately 1-2% of subjects reported mild discomfort that always resolved by the following day.

Less than 7% of subjects exhibited papules or vesicles for potentially up to 20 hours on 2 days.

Slight erythema was visible by the end of the first day in a quarter of subjects and by the 5^{th} day some erythema was visible in 50% of subjects. The time course of erythema post patch removal suggests that the erythema persists at least until the following day. It's interesting to note that there appears to be an increase in incidence, duration, severity, and erythema the following day as the week progresses. This might due to erythema persisting from the previous day and / or due to sensitization. Well-defined erythema with slight, definite margins was observed for short periods of time during the second half of the week in <7% of subjects.

Are the proposed dissolution method and acceptance criteria acceptable?

Yes, both the proposed dissolution method and acceptance criteria are acceptable.

3 INFORMATION FOR COMMUNICATION TO SPONSOR

3.1 COMMENTS TO SPONSOR

3.1.1 COMMENTS ALREADY CONVEYED

No comments have been conveyed to the sponsor.

3.1.2 COMMENTS TO BE CONVEYED

3.1.2.1 Dissolution Method and Specifications

Please adopt the following dissolution method and specifications for all strengths of MethyPatch.

Table 3 Dissolution Method and Acceptance Criteria

Apparatus:	USP Drug Release Apparatus 6 (modified cylinder)
Medium:	0.01N HCl
Temperature:	32 ± 0.5°C
Volume:	900 mL
Rotation Speed:	50 rpm
Sampling Times:	0.5 hour 1.5 hour 3.0 hour
Acceptance Criteria:	0.5 hour % to % of Label Claim 1.5 hour % to % of Label Claim 3.0 hour % to % of Label Claim As per USP 26 / NF 21 <724> Drug Release acceptance table 4 for transdermal drug delivery systems

3.1.2.2 General Comments

OCPB has no general comments for the sponsor.

3.2 PHASE IV COMMITMENTS

No phase IV commitments are requested.

3.3 LABELING COMMENTS

Labeling comments in three column format follow:

The following editorial marks are used in the labeling comments to indicate various changes:

Single underline is the reviewer's proposed addition to sponsor's proposed labeling
Single ~~strikethrough~~ is the reviewer's proposed deletion to sponsor's proposed labeling

39 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

Raman Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

4.1 OCPB BRIEFING MEETING:

Date:	Monday, March 31, 2003
Time:	3:00 PM - 4:00 PM
Location:	WOC-2 4th Floor Conference Room E
Level:	Optional Inter-divisional
Attendees:	Paul Andreason, Solomon Sobel, Mehul, Mehta, John Lazor, Chandrahas G. Sahajwalla, Raman K. Baweja, Ronald Kavanagh, Dhruba J. Chatterjee

4.2 CC LIST:

NDA 21-514 (orig., 1 copy)
HFD-120 (HommonayJ, MannheimG, AndreasonP, LaughrenT, KatzR, FisherE)
HFD-860 (KavanaghR, BawejaR, MehtaM, SahajwallaC)
HFD-810 (McLamoreS)
HFD-009 (MaustA, CalderonS, KleinM, LeidermanD)
CDR (Barbara Murphy)

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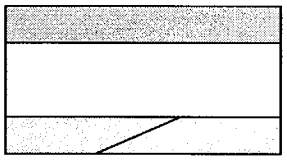
5 CHEMISTRY

5.1 DRUG PRODUCT

The methylphenidate transdermal system (MTS) is a [redacted] nit comprised of three layers as shown below:



Proceeding from the outer surface toward the surface adhering to the skin, the layers are:

1) A polyester/ethylene vinyl acetate laminate film backing
2) A proprietary adhesive formulation incorporating Noven's DOT™ Matrix transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate
3) A fluoropolymer-coated polyester protective liner that is attached to the adhesive surface and must be removed before the system can be used.

5.1.1 QUALITATIVE / QUANTITATIVE FORMULATION

The Qualitative / Quantitative composition of the [redacted] methylphenidate transdermal systems (MTS) are shown in Table 4.

Table 4 Quantitative Composition of Methylphenidate Transdermal System

Adhesive Containing Methylphenidate		% (w/w)	Weight (mg)[a]				
			per cm^2	Patch size (cm^2)			
Code No.	Ingredient			12.5	18.75	25	37.5
[redacted]	Methylphenidate Base	[redacted]	[redacted]	27.5	41.3	55.0	82.5
	Acrylic Adhesive						
	Silicone Adhesive						
Total Weight							

a Amounts reported on a [redacted].
b Previously named [redacted]
c [redacted]

5.1.2 BATCH MANUFACTURING FORMULAE

The 75 and 150 kg batch formulae are representative of those to be used in the manufacture of the drug product and are provided below. In each case the finished laminate is [redacted] to the required dosage size.

Table 5 Batch Formulae for [redacted] Drug Impregnated Adhesive

Noven Code #	Components in Adhesive	Grade	Trade Name	Function	% (w/w) Wet	Theoretical Quantity (kg)	
						75 kg Batch*	150 kg Batch*
[redacted]	Methylphenidate Base			Active	[redacted]	[redacted]	[redacted]
	Silicone Adhesive		[redacted]	Adhesive			
	Acrylic Adhesive		[redacted]	Adhesive			
	[redacted]	FCC or NF		[redacted]			
	[redacted]	NF		[redacted]			
Total							

a The actual quantities added for the inactive ingredients are adjusted based on the actual % solids of the incoming batch of the silicone and acrylic adhesives as shown in the following below:
b [redacted]
c [redacted]

Adjustment for [redacted]

(Theoretical Quantity per batch X Theoretical % Solids) / (Actual % Solids) = (Theoretical Quantity per batch X 60) / (Actual % Solids)

Adjustment for [redacted]

(Theoretical Quantity per batch X Theoretical % Solids) / (Actual % Solids)= (Theoretical Quantity per batch X 37.5) / (Actual % Solids)

Adjustment for [redacted]

Total Batch size Œ Actual Quantity Added for Active and Adhesives

Table 6 Liner Materials

Noven Code #	Component	Trade Name	Function
Backing			
[redacted]	Polyester/ethylene vinyl acetate film laminate	[redacted]	Backing
[redacted]			
Protective Liner (Removed at time of application)			
[redacted]	Fluropolymer Coated Polyester Release Liner	[redacted]	Release Liner

5.1.3 ESTIMATED BATCH YIELDS

Estimated batch yields have been set for each unit size based on laminate produced from 75 and 150 kg of polymer blend. Since all sizes are produced from the same blend/laminate formulation, the actual packaging lot yield may be less than the full lot quantities stated below.

Table 7 Estimated Batch Yield at Primary Packaging

Unit Size	75 kg Polymer Blend Batch	150 kg Polymer Blend Batch
12.5 cm^2		
18.75 cm^2		
25 cm^2		
37.5 cm^2		

5.1.4 MANUFACTURING, PACKAGING AND TEST SITES

The site of all manufacture, packaging and control of the Methylphenidate Transdermal System is:

Noven Pharmaceuticals, Inc.
11960 SW 144 Street, Miami, FL 33186

5.1.5 DISSOLUTION

The sponsor's proposed dissolution method and acceptance criteria are acceptable to OCPB. They are delineated and data to support them are included in the following subsections.

5.1.5.1 Sponsor's Proposed Dissolution Method and Acceptance Criteria

Table 8 Sponsor's Proposed Dissolution Method and Acceptance Criteria

Dosage Form:	Transdermal Systems
Strengths:	27.5 mg / 12.5 cm^2 mg /18.75 cm^2 55.0 mg / 25 cm^2 82.5 mg / 37.5 cm^2
Apparatus:	USP Drug Release Apparatus 6 (modified cylinder)
Medium:	0.01N HCl
Temperature:	32 ± 0.5°C
Volume:	900 mL
Rotation Speed:	50 rpm
Sampling Times:	0.5 hour 1.5 hour 3.0 hour
Brief Description of Dissolution Analytical Method:	HPLC, with UV detection, nm Column: Inertsil ODS-2, 5µm / 10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH_2PO_4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile
Proposed Acceptance Criteria:	% to % % to % % to %

5.1.5.2 Dissolution Data for Pivotal Pediatric Efficacy and Bioavailability Studies

Although not explicitly stated it appears that all dissolution data was generated with n's of 6 patches.

Table 9 Initial Dissolution Means and Ranges for Active MPH Adhesive Batches Used in Pivotal Pediatric Efficacy and Bioavailability Studies

MTS Strength / Size (mg / cm^2)	MPH Impregnated Adhesive Patch lot #	Secondary Packaging Lot #	Sampling Times (Hours)					
			0.5		1.5		3.0	
			Mean	Range	Mean	Range	Mean	Range
13.8 / 6.25	*1F2801-A3*	*C1[a]*	*28*		*50*		*69*	
27.5 / 12.5	*1F2801-A2*	*C1[a]*	*31*		*53*		*72*	
41.3 / 18.75	*1F2801-A1*	*C1[a]*	*30*		*52*		*72*	
13.8 / 6.25	1G1202-A3	C1[b]	30		51		69	
		C2[b]	27		54		68	
41.3 / 18.75	1G1202-A4	C1[b]	29		50		69	
		C2[b]	28		50		69	
55 / 25	*1G1202-A2*	*C1[a,b]*	*29*		*52*		*71*	
		C2[b]	29		52		70	
110 / 50	*1G1202-A[a]*	*C [a,b]*	*32*		*55*		*75*	
		C2[b]	31		55		73	
		C3[b]	30		53		72	
82.5 / 37.5	*1G3001-A1*	*C [a,b]*	*32*		*54*		*73*	
Global Mean & Range	Pivotal Efficacy Study	—	30.3		52.7		72.0	
	Pivotal BA Study	—	29.7		52.6		70.9	
	Both Pivotal BA & Efficacy Studies	—	29.7		52.4		70.9	
Sponsor's Proposed Acceptance Criteria	—	—						

a Pivotal Efficacy Study in Children – Study 17-018
b Pivotal Bioavailability Study Batches in Children – Study 17-016

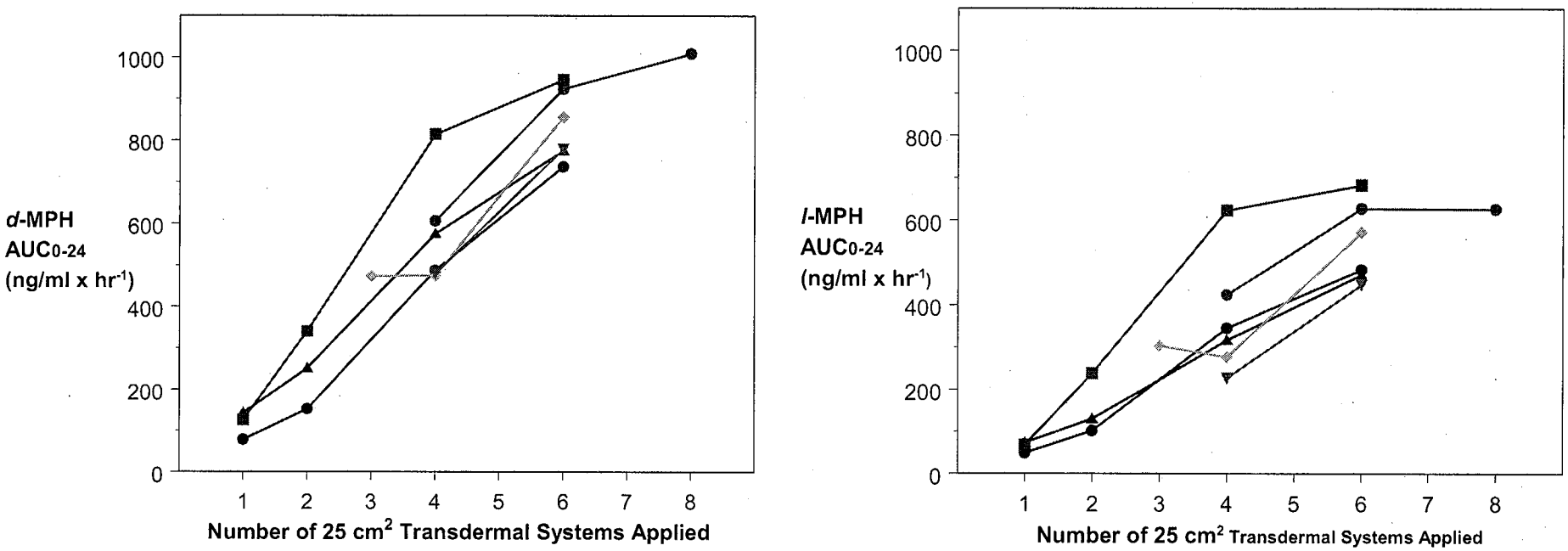
5.1.5.3 Dissolution Data and Methods for Batches Used in Clinical Pharmacology Studies

Table 10 Dissolution Data for MTS Batches used in Pharmacokinetic, Pharmacodynamic, and Clinical Pharmacology Studies[a]

Study No.	Date of Test	Dosage Form and Strength	Lot No.	Dissolution Apparatus	Media / Temperature / Volume	Speed of Rotation	Brief Description of Analytical Method	Collection Times	Units Tested	%DISSOLVED	
										Mean	Range
N17-005, N17-006, N17-007, N17-012 & N17-014	18 May 00	Transdermal 55.0 mg / 25 cm^2	0D2601-A1	USP Drug Release Apparatus 5 with modified Transdermal Holder	0.01N HCl / 32 ± 0.5°C 900 mL	50 rpm	HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile	0.5 hour 1.5 hour 3.0 hour	6 6 6	32 52 70	
N17-016 N17-018	**22 Aug 01**	**Transdermal 82.5 mg / 37.5 cm^2**	**1G3001-A1-C1**	**USP Drug Release Apparatus 6 (modified cylinder)**	**0.01N HCl / 32 ± 0.5°C 900 mL**	**50 rpm**	**HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile**	**0.5 hour 1.5 hour 3.0 hour**	**6 6 6**	**32 54 73**	
N17-016 N17-018	**22 Aug 01**	**Transdermal 110.0 mg / 50 cm^2**	**1G1202-A1-C1**	**USP Drug Release Apparatus 6 (modified cylinder)**	**0.01N HCl / 32 ± 0.5°C 900 mL**	**50 rpm**	**HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile**	**0.5 hour 1.5 hour 3.0 hour**	**6 6 6**	**32 55 75**	
N17-017 N17-018	**20 Aug 01**	**Transdermal 55.0 mg / 25 cm^2**	**1G1202-A2-C1**	**USP Drug Release Apparatus 5 with modified Transdermal Holder**	**0.01N HCl / 32 ± 0.5°C 900 mL**	**50 rpm**	**HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile**	**0.5 hour 1.5 hour 3.0 hour**	**6 6 6**	**29 52 71**	
N17-002	*2 Feb 99*	*Transdermal 27.5 mg / 10 cm^2*	*R901261-A1*	*USP Drug Release Apparatus 5 with modified Transdermal Holder*	*0.01N HCl / 32 ± 0.5°C 900 mL*	*50 rpm*	*HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile*	*1.0 hour 3.0 hour 5.0 hour*	*6 6 6*	*56 81 88*	
N17-004	4 April 00	Transdermal 13.8 mg / 6.25 cm^2	0B0202-A3	USP Drug Release Apparatus 5 with modified Transdermal Holder	0.01N HCl / 32 ± 0.5°C 900 mL	50 rpm	HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile	0.5 hour 1.5 hour 3.0 hour	6 6 6	29 47 63	
N17-004	4 April 00	Transdermal g 27.5 mg / 12.5 cm^2	0B0202-A2	USP Drug Release Apparatus 5 with modified Transdermal Holder	0.01N HCl / 32 ± 0.5°C 900 mL	50 rpm	HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2PO4 buffer & 4mM OSA, pH 3.0 ± 0.1: Acetonitrile	0.5 hour 1.5 hour 3.0 hour	6 6 6	28 47 64	
N17-004	4 April 00	Transdermal 55.0 mg / 25 cm^2	0B0202-A1	USP Drug Release Apparatus 5 with modified Transdermal Holder	0.01N HCl / 32 ± 0.5°C 900 mL	50 rpm	HPLC, UV detection, 210 nm Column : Inertsil ODS-2, 5µm/10 cm x 4.6 mm M.P :70:30 (v:v): 5mM KH2 PO4 buffer & 4mM OSA,	0.5 hour 1.5 hour 3.0 hour	6 6 6	29 49 66	

a Information in bold is for lots used in the pivotal efficacy study 17-018 and pivotal bioavailability study 17-016. Italized information is for the early developmental formulation.

Figure 4 *d*-MPH and *l*-MPH AUC_{0-24} vs. Number of 25 cm^2 MTS Patches for Individual Subjects in Study 17-007



5.2 BIOANALYSIS

The validated assay methods used in Methypatch NDA 21-514 are acceptable to OCPB and are shown in Table 11. Reviews of the validation reports for these assays are included in APPENDIX 1.

Table 11 Validated Assay Methods Used in Methypatch NDA 21-514

Assay Number	Description
17129-1	Validation of an LC/MS/MS Method for the Quantitation of Methylphenidate in Human Plasma
19261-2	Validation of an LC/MS/MS Method for the Quantitation of Phenteramine in Human Heparinized Plasma
21183-1 Revised	Validation of a [redacted]C/MS/MS Method for the Quantitation of d/l-threo- Methylphenidate in Human EDTA Plasma
21183-1	Validation of a [redacted] LC/MS/MS Method for the Quantitation of d/l-threo-Methylphenidate in Human EDTA Plasma
21183-2	Validation of [redacted] LC/MS/MS Method for the Quantitation of d/l-threo-Ritalinic Acid in Human

The specific assay method used in each pharmacokinetic study and the analyte(s) measured are shown in Table 12.

Table 12 Analytes, Biological Matrices and Assay Methods Used in Pharmacokinetic Studies

Study Number	Analyte	Biological Matrix	Assay
N17-002	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
	d-RA	EDTA Plasma	21183-2
	l-RA		
N17-004	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
N17-005	*d,l*-MPH	EDTA Plasma	17129-1
N17-006	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
N17-007	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
	Phenteramine	Heparinized Plasma	19261-2
N17-012	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
N17-014	*d,l*-MPH	EDTA Plasma	17129-1
N17-016	*d*-MPH	EDTA Plasma	17129-1
	l-MPH		
N17-017	*d,l*-MPH	EDTA Plasma	17129-1

6 PHARMACOKINETICS

6.1 OVERVIEW

Table 13 lists the pharmacokinetic, pharmacodynamic and clinical pharmacology studies submitted to NDA 21-514.

The initial study 17-002 utilized a preliminary development methylphenidate transdermal system (MTS) formulation. All other studies used the to-be-marketed formulation (TBM) and each study addressed a different clinical issue.

Study 17-002 was not reviewed.

Table 13 Summary of Pharmacokinetic, Pharmacodynamic and Clinical Pharmacology Studies Submitted in NDA 21-514

Study Number	Study Title	Date
N17-004	A Study to Evaluate the Linearity of Methylphenidate Pharmacokinetics Using Different Doses of Noven™ Methylphenidate Transdermal System in Healthy Adult Subjects	4/30/00
N17-006	A Multiple Dose Pharmacokinetic Study of a Methylphenidate Transdermal System Compared to Ritalin® in Healthy Adult Subjects	6/21/00
N17-016	A Multiple Dose Pharmacokinetic Study of Methylphenidate with Noven™ Methylphenidate Transdermal System in Pediatric Patients with Attention Deficit Hyperactivity Disorder	12/9/01
N17-005	A Bioavailability Study of Noven Methylphenidate Transdermal System Using Two Different Sites of Application in Pediatric Patients with Attention Deficit Hyperactivity Disorder	7/30/00
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	3/21/99
N17-007	Human Pharmacology and Abuse Potential of Methylphenidate Administered Transdermally	12/17/00
N17-017	A Study to Evaluate the In Vivo Pharmacokinetics of Noven™ Methylphenidate Transdermal System on Normal and Inflamed Skin in Healthy Adult Subjects	11/18/01
N17-014	A Study to Evaluate the Dose Delivery Profile of Repeated Applications of a Noven™ Methylphenidate Transdermal System in Healthy Adult Subjects	4/4/01
N17-012	The Effect of Heat and Transmucosal Application on the Human Pharmacology of a Methylphenidate Transdermal System	4/5/01

Table 14 lists the safety and efficacy studies submitted to NDA 21-514.

Table 14 Summary of Safety and Efficacy Studies Submitted in NDA 21-514

Study	Title	Date
Controlled Clinical Trials		
N17-003	Double Blind, Placebo-Controlled, Dose Ranging Study of Four Doses of a Methylphenidate Transdermal System in Pediatric Patients with Attention Deficit Hyperactivity Disorder	11/2/99 – 11/13/99
N17-009	Double Blind, Placebo-Controlled, Dose Ranging Study of Three Doses of Methylphenidate Transdermal Systems in Patients with Attention Deficit Hyperactivity Disorder in a Summer Treatment Program	6/26/00 – 8/4/00
N17-010	A Multicenter, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Methylphenidate Transdermal System in Pediatric Patients with Attention Deficit Hyperactivity Disorder	9/12/00 – 2/16/01
N17-015	A double-blind, placebo-controlled, dose-ranging study of a once-a-day methylphenidate transdermal system: Efficacy and time course in pediatric patients with ADHD	6/26/01 – 8/17/01
N17-018	A Multicenter, Double-blind, Placebo-Controlled, Safety and Efficacy Study of Methylphenidate Transdermal System in Pediatric Patients with Attention Deficit Hyperactivity Disorder, Data	10/23/01 – 3/5/02
Uncontrolled Clinical Trials		
N17-011	A Long-Term, Open-Label Study of Methylphenidate Transdermal System in Pediatric Patients With Attention Deficit Hyperactivity Disorder	8/17/00 – 12/15/00
N17-008	Skin Irritation and Sensitization Testing of Noven™ Methylphenidate Transdermal System	7/27/00 – 10/01/00

Table 15 summarizes the study designs for the studies reviewed by OCPB.

Table 15 Summary of Study Designs for Pharmacokinetic, Pharmacodynamic, and Clinical Pharmacology Studies in NDA 21-512

Study #	Study Objective	Population	M/F Ratio	Race / Ethnicity	n	Dose	Dose Regimen	Application Site	Application Duration	Analyte(s)
17-004	Dose Linearity	Healthy young adults	Male	White	14	6.25 cm^2 12.5 cm^2 25 cm^2	Rising SD	Hip	16 hours	d-MPH & l-MPH
17-005	BE Hip vs. Scapula	Children with ADHD	~1:1 M/F	mixed races	23	25 cm^2	SD	Hip Scapula	16 hours	d,l-MPH
17-006	BA relative to Ritalin 20 mg tid	Healthy young adults	~1:1 M/F	mixed races	29	25 cm^2	MD x 6	Hip	16 hours	d-MPH & l-MPH & d,l-MPH
17-007	Abuse Potential	Healthy young adults drug abusers?	24/3	1W/24B	3&3&18	1 to 10 x 25 cm^2	Rising SD	Back	24 hours	d-MPH & l-MPH
	Absolute BA vs. SQ administration					25 cm^2 \ vs. 25 mg SQ				
17-012	No Heat	Healthy young adults	5/1 M/F	Black	6	3 x 25 cm^2	SD	Arm	8 hours	d-MPH & l-MPH
	Heat x 6 hours					3 x 25 cm^2				
	Buccal Mucosa					2 x 25 cm^2		Buccal Mucosa	2 hours	
17-014	Drug Delivery	Healthy young adults	4/2 M/F	White/H	6	25 cm^2	MD x 2	Hip	16 hours	d,l-MPH
17-016	Drug Delivery	Children with ADHD	4/8	W11/H1	6	37.5 cm^2	MD x 4	Hip	8 or 12 hours	d-MPH & l-MPH
					6	50 cm^2			8 or 12 hours	
17-017	Inflamed Skin	Healthy young adults	Male	w6/H2	8	25 cm^2	SD	Hip	16 hours	d,l-MPH

6.2 DOSE LINEARITY

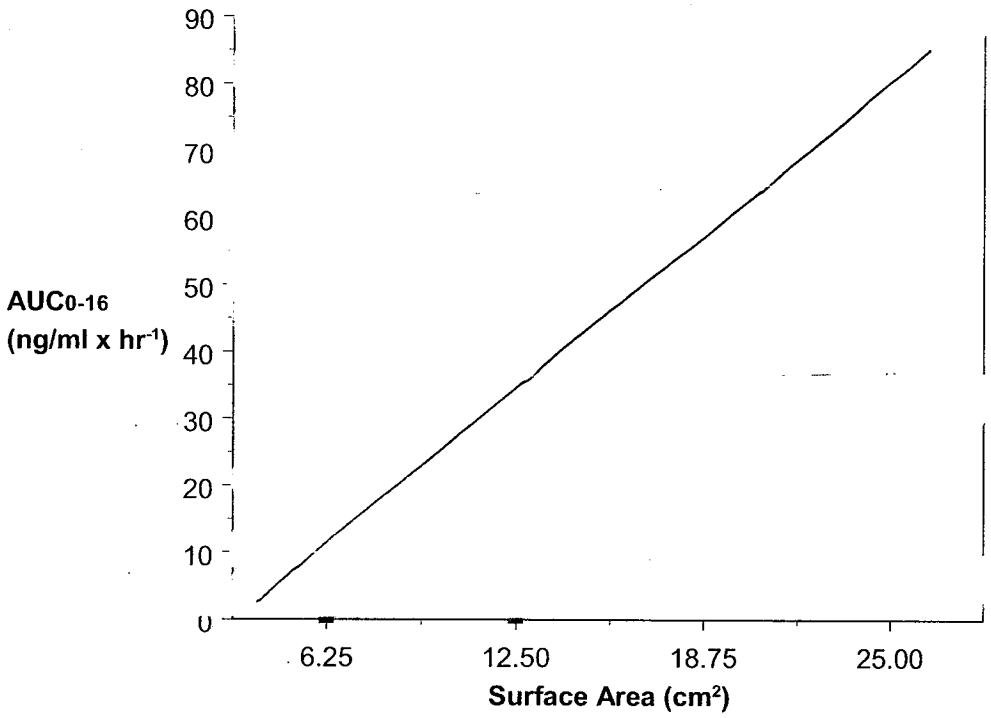
Dose linearity was examined in studies 17-004 and 17-007 in healthy young adults.

6.2.1 STUDY 17-004

Study 17-004 was a single rising dose crossover design study in 14 white adult males. On each treatment day one 6.25 cm^2, 12.5 cm^2, or 25 cm^2 methylphenidate transdermal system (MTS) was applied to the hip for 16 hours.

There was a linear rise in AUC_{0-16} with patch size / strength. Individual study subject's AUC_{0-16}s vs. patch size for study 17-004 are shown in Figure 3.

Figure 3 AUC_{0-16} vs. Patch Size for Individual Subjects in Study 17-004.



6.2.2 STUDY 17-007

Study 17-007 was a 2 part single rising dose double-dummy crossover study with an assessment of absolute bioavailability relative to subcutaneous methylphenidate in young male and female adult stimulant abusers. This study also included a pharmacokinetic/pharmacodynamic assessment.

Part 1 of the study, consisted of 2 groups of 3 subjects.

Group one group received 25 mg MPH subcutaneously (SC) or saline placebo and 0, 1, 2, 4 or 6 x 55 mg/25 cm^2 MTS applied to the back for 24 hours and sufficient placebo patches to qs ad 10 patches total. Treatments were separated by 1 day.

Group two received 50 mg MPH subcutaneously (SC) or saline placebo and 3, 4, 6, or 8 x 55 mg/25 cm^2 MTS applied to the back for 24 hours and sufficient placebo patches to qs ad 10 patches total.

Part 2 was a 6-way crossover study to assess the abuse potential and PK/PD of MTS in 19 stimulant abusers. In two arms of the study subjects received single doses of either 3 or 6 MTS applied to the back. The remainder of the study is discussed in §7.1 Clinical Pharmacology - Pharmacokinetics / Pharmacodynamics.

Results for the dose linearity part of the study are shown in Table 16, Table 17 and Figure 4. It is readily apparent that there is dose linearity up to about six 55 mg / 25 cm^2 patches.

Table 16 Mean (± SD) Pharmacokinetic Parameters for *d*-MPH – Study 17-007

	Treatment	N	Cmax (ng/ml)	Tmax (h)	AUC0-24 (ng/ml x hr^{-1})
Part 1, Group 1	1 MTS	3	7.5 ± 1.9	11 ± 1.73	115.8 ± 33.7
	2 MTS	3	15.4 ± 3.4	12 ± 0	248.0 ± 94.1
	4 MTS	3	42.4 ± 17.9	15 ± 7.94	626.0 ± 169.1
	6 MTS	3	54.1 ± 16.3	10 ± 1.73	819.0 ± 111.5
Part 1, Group 2	3 MTS	1	34.5	12	474.4
	4 MTS	3[a]	35.3 ± 5.2	12.8 ± 1.5	547.9 ± 81.4
	6 MTS	3[b]	60.6 ± 10.1	11.4 ± 1.3	978.1 ± 196.1
	8 MTS	2	82.6 ± 1.1	90 ± 0	1008.4c
Part 2	3 MTS	19	20.3 ± 8.5	11.84 ± 2.54	313.6 ± 146.8
	6 MTS	19	46.9 ± 16.3	11.68 ± 3.59	713.8 ± 269.3

a 3 subjects, 1 of them studied twice
b 3 subjects, 2 of them studied twice
c AUC0-24 determined in only 1 subject.

Table 17 Mean (± SD) Pharmacokinetic Parameters for *l*-MPH – Study 17-007

	Treatment	N	Cmax (ng/ml)	Tmax (h)	AUC0-24 (ng/ml x hr^{-1})
Part 1, Group 1	1 MTS	3	4.4 ± 0.9	7 ± 4.58	63.3 ± 13.0
	2 MTS	3	9.4 ± 2.8	7.33 ± 2.89	156.8 ± 72.1
	4 MTS	3	29.0 ± 10.5	15 ± 7.94	428.6 ± 169.5
	6 MTS	3	41.4 ± 15.7	8 ± 1.73	546.2 ± 118.8
Part 1, Group 2	3 MTS	1	28.6	12	304.1
	4 MTS	3[a]	22.0 ± 5.7	10.5 ± 1.7	327.0 ± 90.6
	6 MTS	3[b]	39.6 ± 9.9	8.4 ± 1.3	619.1 ± 181.1
	8 MTS	2	53.4 ± 17.0	90	627.1[c]
Part 2	3 MTS	19	30.4 ± 6.1	1.05 ± 0.23	66.6 ± 14.2
	6 MTS	19	54.7 ± 16.6	1.05 ± 0.23	124.3 ± 31.9

a 3 subjects, 1 of them studied twice
b 3 subjects, 2 of them studied twice
c AUC0-24 determined in only 1 subject.

6.3 MULTIPLE DOSE PHARMACOKINETICS AND TIME INVARIANCE

Multiple dose pharmacokinetics were examined in the 3 studies shown in Table 18.

Table 18 Multiple Dose Pharmacokinetic Studies in NDA 21-512

Study #	Study Objective	Population	n	Dose	Dose Regimen	Application Site	Application Duration (hours)	Analyte(s)s
17-014	Drug Delivery	Healthy young adults	6	25 cm^2	MD x 2	Hip	16	*d,l*-MPH
17-006	BA relative to Ritalin 20 mg tid	Healthy young adults	29	25 cm^2	MD x 6	Hip	16	*d*-MPH & *l*-MPH
17-016	Drug Delivery	Children with ADHD	6	37.5 cm^2	MD x 4	Hip	8 or 12	*d*-MPH, *l*-MPH & *d,l*-MPH
			6	50 cm^2			8 or 12	

In study 17-014 pharmacokinetics were determined after patch applications on days 1 and 2. Whereas in studies 17-006 and 17-016 pharmacokinetic metrics were determined after either 6 or 4 days of daily dosing respectively, although neither study examined pharmacokinetics on day one for comparison. In addition, differences in study design as to analytes, dose, or dosage interval makes comparisons difficult.

The results of studies 17-006 and 17-016 in adults will be discussed here. Study 17-016 in children will be discussed separately under §6.5.1 Special Populations - Children.

6.3.1 ADULTS

6.3.1.1 Adults - Study 17-006

Study 17-006 was a multiple dose 2-way crossover study comparing the bioavailability of 55 mg / 25 cm^2 MethylPatch® MTS applied to the hip for 16 hours relative to the cumulative exposure from Ritalin 20 mg tid administered at 4 hour intervals.

Immediate release methylphenidate products are known not to exhibit time variant pharmacokinetics on multiple dosing and have a short half-life of approximately 3 hours. Thus each day is pharmacokinetically equivalent to dosing a drug naïve subject. In contrast, the long application time for Methylpatch of 16 hours in this study means that by the time the next patch is applied the next morning there is residual drug remaining in the body and thus there is some accumulation over the first few days of dosing.

In study 17-006 trough concentrations on days 4, 5, 6, and 7 show that steady-state was reached by day 4 (93% of days 6 and 7), (see Table 19). In fact the mean steady-state *d*-MPH 24 hour trough concentrations (approximately 2.5 ng/ml) are sufficiently high such that there may be some residual effect remaining first thing in the morning.

Consequently, the high residual 24 hour trough concentrations seen with the MethyPatch® raises concerns regarding whether this formulation will result in problems with sleep and potentially lower efficacy if there is insufficient recovery from the pharmacodynamic tolerance to methylphenidate.

Table 19 24 Hour Trough Concentrations on Days 4, 5, and 6 in Adult Subjects in Study 17-006

24 Hour Trough Concentration (ng/ml)				
Analyte	***d*-MPH**		***l*-MPH**	
Treatment	**25 cm^2 MTS**	**Ritalin 20 mg TID**	**25 cm^2 MTS**	**Ritalin 20 mg TID**
Day 4	2.337	0.560	0.405	0.000
Day 5	2.453	0.583	0.395	0.000
Day 6	2.505	0.677	0.395	0.000
Day 7	2.509	0.603	0.391	0.000
Mean	2.451	0.606	0.397	0.000

This residual circulating drug also raises questions regarding the plasma drug concentrations present at night and the potential effect on sleep. Methylphenidate concentrations after oral administration of IR and MR formulations typically drop to close to zero during the previous day. In fact, it has been postulated that this overnight 'drug free' period might be necessary to allow the body to recover from the tolerance to the effect of methylphenidate on attention that typically occurs during the course of a day.

Figure 5 through Figure 7 demonstrate the comparative mean and individual plasma concentration profiles of *d*-MPH from the MethyPatch® and from Ritalin 20 mg tid. In contrast to MethyPatch the mean 24 hour *d*-MPH concentration from Ritalin is less than 1 ng/ml. In addition, after hour 12 the plasma concentrations from the MTS formulation are much higher. It should be noted however that the Ritalin was administered 3 times at 7AM, 11 noon, and 3 PM, whereas in practice BID administration would be more likely. Consequently, the plasma concentration profile after the last dose of Ritalin should be shifted 4 hours earlier.

Secondly, the absorption lag is very long, (mean *d*-MPH Tlag = 3 hours, maximum 5 hour), indicating that we can't even expect any effect at all the first several hours after dosing in the morning, (see Table 20). In addition, it takes nearly 8 hours to achieve plasma *d*-MPH concentrations of 6 ng/ml with the MTS formulation, with concentrations of approximately 6 – 8 ng/ml probably necessary for efficacy[1]. As compared to <1 hour with Ritalin. Lastly, the peak plasma concentrations with the MTS are also significantly lower (see Figure 5 through Figure 7).

These observations indicate that to achieve efficacy with the MTS formulation sufficiently early in the day, a much greater strength patch would been needed to drive a higher rate of drug delivery early on. Earlier removal of the patch, (e.g. after 8 hours), would also be required to avoid excessive concentrations at night. This would result in a discarded patch with much, much greater amounts of methylphenidate remaining which could be extracted and abused. Presently, the amounts recoverable from a discarded 25 cm^2 patch, (55 mg methylphenidate), applied for 8 hours are likely on the order of 67% of the initial content, i.e. 37 mg.

6.3.1.2 Adults - Study 17-014

Study 17-014 showed a slightly slower Tlag and Tmax on the first day of dosing as compared to study 17-006, (see Table 20 and Table 21). However, on the second day of dosing the Tlag, and Tmax are significantly longer and the Cmax and AUCs are much lower as compared to day 1, (see Table 21). This suggests there may also be inter-day variability and patients may have even more delayed and less efficacy on some days.[2]

[1] Based upon preliminary data analysis from regulatory research project
[2] although study 17-014 measured the racemate and study 17-006 measured the individual isomers, the Tlag for both isomers in study 17-006 was much shorter than for the racemate.

Figure 5

FIGURE 2. ARITHMETIC MEAN (LINEAR) D-MPH PLASMA CONCENTRATION-TIME PROFILES IN 29 SUBJECTS ON DAY 6 AFTER ADMINISTERING 25CM2 MTS UNITS ONCE DAILY (MTS) FOR 16 H OR 20 MG ORAL RITALIN AT 7 AM, 11 AM AND 3 PM DAILY.

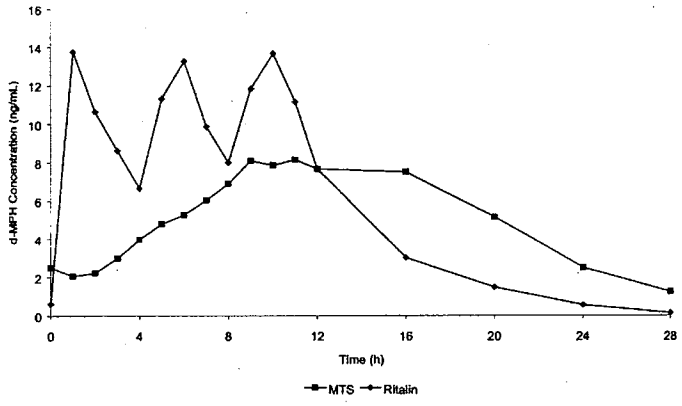


Figure 6

FIGURE 6. INDIVIDUAL PLASMA PROFILES (SPAGHETTI PLOTS) OF *D-THREO*-METHYLPHENIDATE (*D*-MPH) FROM DAY 6 AFTER DOSING WITH 25 CM^2 MTS UNITS ONCE DAILY FOR 16 H (N=29).

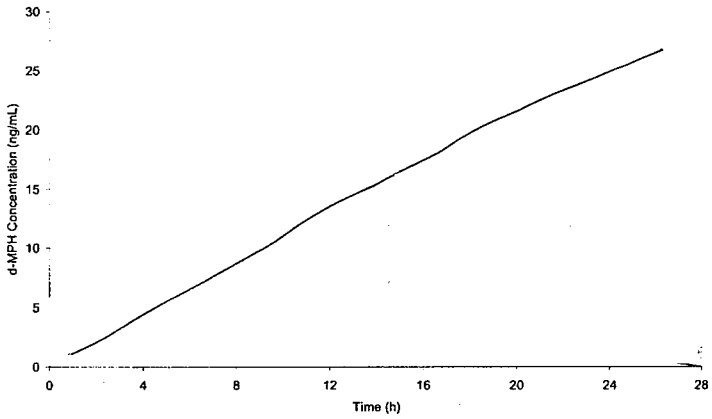


Figure 7

FIGURE 8. INDIVIDUAL PLASMA PROFILES (SPAGHETTI PLOTS) OF D-THREO-METHYLPHENIDATE (D-MPH) FROM DAY 6 AFTER DOSING WITH 20 MG RITALIN 3 TIMES DAILY (N=29).

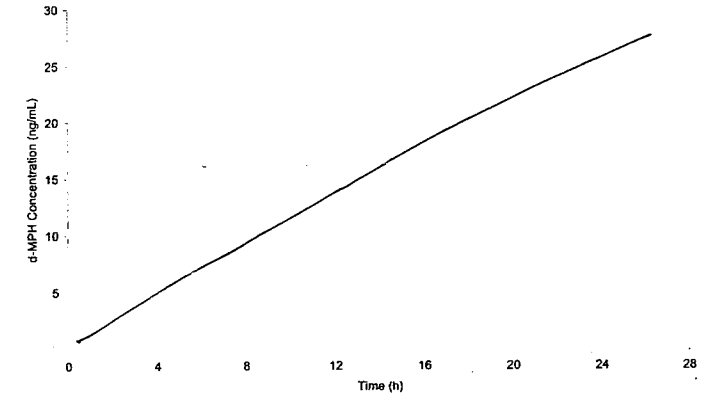


Figure 8

FIGURE 4. ARITHMETIC MEAN (LINEAR) L-MPH PLASMA CONCENTRATION-TIME PROFILES IN 29 SUBJECTS ON DAY 6 AFTER ADMINISTERING 25CM2 MTS UNITS ONCE DAILY (MTS) FOR 16 H OR 20 MG ORAL RITALIN AT 7 AM, 11 AM AND 3 PM DAILY.

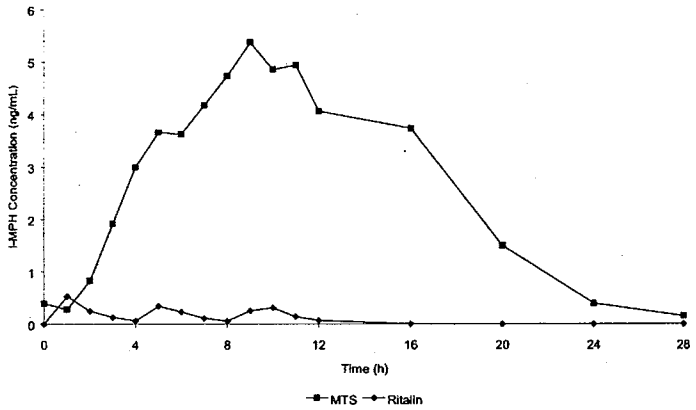


Figure 9

FIGURE 7. INDIVIDUAL PLASMA PROFILES (SPAGHETTI PLOTS) OF *L-THREO*-METHYLPHENIDATE (*L*-MPH) FROM DAY 6 AFTER DOSING WITH 25 CM^2 MTS UNITS ONCE DAILY FOR 16 H (N=29).

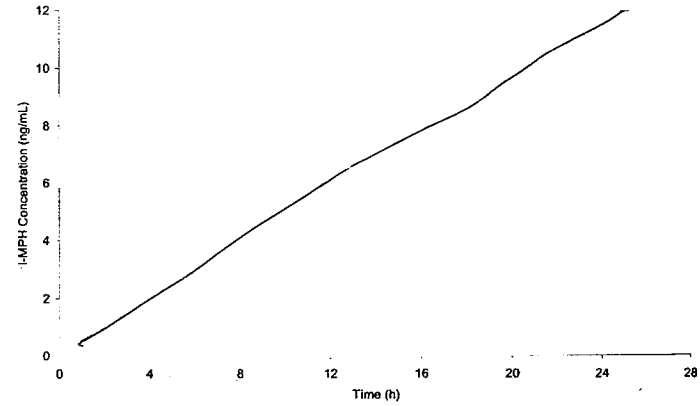


Figure 10

FIGURE 9. INDIVIDUAL PLASMA PROFILES (SPAGHETTI PLOTS) OF L-THREO-METHYLPHENIDATE (L-MPH) FROM DAY 6 AFTER DOSING WITH 20 MG RITALIN 3 TIMES DAILY (N=29).

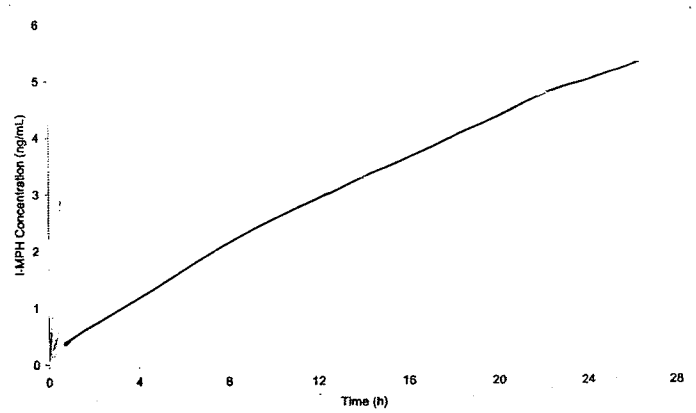


Table 20 Methylphenidate Pharmacokinetic Metrics Following the Six Daily Applications of MethyPatch MTS 55 mg / 25 cm^2 for 16 hours Applied to the Hip– Study 17-006 [a]

Subject Grouping	Age (yrs)	Height (cm)	Weight (kg)	Tlag (hours)		Cmax (ng/ml)		Tmax (hours)		AUCss (ng/ml x hr^{-1})		AUC0-16 (ng/ml x hr^{-1})		Combined d-MPH & l-MPH AUCs		T1/2 (hours)		%Fluc0-16 (%)[b]	
				d-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	AUCss	AUC0-16	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH
All Subjects 29	33.6 ± 5.9 (17.6) 21.0 - 40.0 [36.0]	166.4 ± 10.6 (6.4) 147.3 - 185.4 [165.1]	72.6 ± 11.6 (16.0) 49.1 - 91.8 [72.3]	3.0 ± 1.1 (35.5) 1.0 - 5.0 [3.0]	2.1 ± 0.7 (32.4) 1.0 - 4.0 [2.0]	9.5 ± 3.6 (37.5) 4.2 - 16.8 [8.9]	6.0 ± 2.3 (38.3) 2.8 - 10.9 [5.9]	12.2 ± 2.7 (22.5) 9.0 - 16.0 [11.0]	10.3 ± 2.7 (26.3) 5.0 - 16.0 [9.0]	134.7 ± 43.6 (32.4) 73.2 - 228.6 [125.1]	69.5 ± 24.8 (35.8) 34.0 - 127.8 [64.3]	94.0 ± 35.8 (38.1) 39.9 - 167.8 [90.9]	55.2 ± 23.0 (41.7) 23.9 - 108.0 [49.9]	204.1 ± 67.0 (32.8) 110.6 - 356.3 [192.9]	149.2 ± 57.9 (38.8) 65.1 - 275.8 [145.5]	3.9 ± 0.7 (17.8) 3.0 - 6.5 [3.9]	2.5 ± 0.4 (15.4) 1.7 - 3.2 [2.5]	132.7 ± 28.8 (21.7) 94.5 - 223.0 [121.9]	172.5 ± 31.2 (18.1) 130.6 - 270.1 [165.8]

a Mean ± S.D. (C.V.%), range, [median]
b As calculated by sponsor – Caverage not defined

Table 21 *d,l*-Methylphenidate Pharmacokinetic Metrics Following the First and Second Applications of MethyPatch MTS 55 mg / 25 cm^2 for 16 hours applied to the Hip - Study 17-014[a,b]

Dose Application	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	C_{24} (ng/ml)	AUC_{0-16} (ng/ml x hr^{-1})	AUC_{0-24} (ng/ml x hr^{-1})	$AUC_{0-\infty}$ (ng/ml x hr^{-1})	$t_{1/2}$ (hours)
First	3.7 ± 0.8 (22.3) 2 - 4 [4]	11.1 ± 1.7 (14.9) 8.3 - 13.3 [11.3]	14.3 ± 2.7 (18.6) 10.0 - 16.0 [16.0]	2.4 ± 0.8 (33.5) 1.2 - 3.4 [2.5]	94.8 ± 14.8 (15.6) 79.1 - 114.5 [89.4]	147.1 ± 17.1 (11.6) 123.4 - 169.5 [144.3]	166.5 ± 15.3 (9.2) 148.6 - 189.3 [163.0]	3.7 ± 0.4 (11.9) 3.1 - 4.1 [3.9]
Second	7.0 ± 2.4 (35.0) 4 - 10 [6]	6.2 ± 1.1 (17.2) 4.8 - 8.1 [6.0]	15.7 ± 2.9 (18.7) 10.0 - 18.0 [16.0]	2.2 ± 0.9 (42.0) 1.2 - 3.6 [2.1]	56.8 ± 13.2 (23.3) 45.5 - 81.5 [51.7]	91.1 ± 18.6 (20.4) 72.9 - 122.8 [87.0]	—	—

a Mean ± S.D. (C.V.%), range, [median]
b n = 6

6.3.2 GENDER EFFECTS - STUDY 17-006

Based upon inspection of the summary statistics of the pharmacokinetic metrics for study 17-006 there are no obvious gender differences for MethyPatch® MTS, (see Table 22 and Table 24).

Study 17-006 was the only study in adults with large numbers of males and females dosed in a similar manner, so an analysis of the pharmacokinetic metrics by gender from this study was performed. Although both males and females were included in a number of other studies the total number of subjects per study or group was small thus additional analyses were not performed, (see Table 15).

6.3.3 RACE / ETHNICITY - STUDY 17-006

Based upon inspection of the summary statistics of the pharmacokinetic metrics for study 17-006 there are no obvious differences for race or ethnicity for MethyPatch® MTS, (see Table 23 and Table 24).

Study 17-006 was the only study in adults with large numbers of subjects of various races or ethnicity dosed in a similar manner, so an analysis of the pharmacokinetic metrics by race, ethnicity and gender from this study was performed. Although members of various races and ethnic groups were included in a number of other studies the total number of subjects of various races and ethnicity per study or group that allowed comparisons was small thus additional analyses were not performed, (see Table 15).

Table 22 Multiple Dose Methypatch Pharmacokinetics by Gender in Adults – Study 17-006[a]

Subject Grouping	Age (yrs)	Height (cm)	Weight (kg)	Tlag (hours)		Cmax (ng/ml)		Tmax (hours)		AUCss (ng/ml x hr^{-1})		AUC0-16 (ng/ml x hr^{-1})		Combined d-MPH & l-MPH AUCs		T1/2 (hours)		%Fluct0-16 (%)[b]	
				d-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	AUCss	AUC0-16	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH
Males n = 14	33.1 ± 6.7 (20.2) 21.0 - 40.0 [34.5]	175.4 ± 6.3 (3.6) 165.1 - 185.4 [176.6]	81.3 ± 7.9 (9.8) 68.2 - 91.8 [82.1]	2.7 ± 0.9 (33.7) 2.0 - 5.0 [2.5]	2.0 ± 0.6 (27.7) 1.0 - 3.0 [2.0]	8.9 ± 3.4 (38.3) 4.2 - 16.8 [8.2]	6.1 ± 2.1 (34.7) 3.0 - 9.9 [6.0]	11.9 ± 2.8 (23.4) 9.0 - 16.0 [11.0]	9.4 ± 2.4 (25.9) 5.0 - 16.0 [9.0]	128.7 ± 38.4 (29.9) 73.2 - 216.2 [124.0]	70.4 ± 21.9 (31.1) 38.7 - 110.2 [67.4]	91.1 ± 32.6 (35.8) 41.7 - 160.8 [86.3]	56.3 ± 20.2 (35.8) 26.1 - 92.6 [55.8]	199.1 ± 59.0 (29.6) 111.9 - 321.4 [193.1]	147.4 ± 51.7 (35.1) 67.8 - 248.6 [143.9]	4.0 ± 0.5 (11.4) 3.3 - 4.8 [4.0]	2.5 ± 0.4 (14.4) 1.7 - 3.1 [2.5]	125.5 ± 32.3 (25.7) 96.9 - 223.0 [119.4]	168.3 ± 36.6 (21.8) 130.6 - 270.1 [159.1]
Females n = 15	34.1 ± 5.3 (15.6) 21.0 - 40.0 [36.0]	158.0 ± 5.7 (3.6) 147.3 - 167.6 [157.5]	64.5 ± 8.0 (12.5) 49.1 - 77.3 [61.8]	3.2 ± 1.1 (35.8) 1.0 - 5.0 [3.0]	2.3 ± 0.8 (35.2) 1.0 - 4.0 [2.0]	10.0 ± 3.7 (37.0) 5.5 - 16.5 [9.1]	6.0 ± 2.6 (42.6) 2.8 - 10.9 [5.2]	12.4 ± 2.8 (22.4) 9.0 - 16.0 [11.0]	11.1 ± 2.8 (25.0) 8.0 - 16.0 [10.0]	140.2 ± 48.6 (34.7) 76.6 - 228.6 [138.7]	68.6 ± 28.0 (40.9) 34.0 - 127.8 [62.4]	96.6 ± 39.6 (40.9) 39.9 - 167.8 [94.5]	54.3 ± 26.1 (48.1) 23.9 - 108.0 [46.9]	208.8 ± 75.4 (36.1) 110.6 - 356.3 [191.7]	150.9 ± 65.0 (43.0) 65.1 - 275.8 [145.5]	3.8 ± 0.9 (22.8) 3.0 - 6.5 [3.9]	2.5 ± 0.4 (16.8) 1.8 - 3.2 [2.4]	139.4 ± 24.4 (17.5) 94.5 - 192.3 [140.4]	176.5 ± 25.9 (14.7) 146.5 - 247.1 [170.2]

a Mean ± S.D. (C.V.%), range, [median]
b As calculated by sponsor – Caverage not defined

Table 23 Multiple Dose Methypatch Pharmacokinetics by Race / Ethnicity in Adults – Study 17-006[a]

Subject Grouping	Age (yrs)	Height (cm)	Weight (kg)	Tlag (hours)		Cmax (ng/ml)		Tmax (hours)		AUCss (ng/ml x hr^{-1})		AUC0-16 (ng/ml x hr^{-1})		Combined d-MPH & l-MPH AUCs		T1/2 (hours)		%Fluct0-16 (%)[b]	
				d-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	AUCss	AUC0-16	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH
White n = 15	32.6 ± 6.2 (19.1) 21.0 - 39.0 [35.0]	166.6 ± 9.8 (5.9) 147.3 - 182.9 [167.6]	73.6 ± 12.9 (17.5) 49.1 - 88.6 [77.3]	2.7 ± 1.1 (41.7) 1.0 - 5.0 [2.0]	1.9 ± 0.7 (36.4) 1.0 - 4.0 [2.0]	10.6 ± 3.3 (31.1) 5.7 - 16.8 [9.6]	6.8 ± 2.0 (28.7) 3.6 - 9.9 [6.5]	11.5 ± 2.5 (22.0) 9.0 - 16.0 [11.0]	9.1 ± 1.6 (17.4) 5.0 - 12.0 [9.0]	147.5 ± 33.3 (22.6) 91.8 - 216.2 [146.1]	77.0 ± 18.7 (24.2) 49.2 - 110.2 [74.5]	105.3 ± 27.9 (26.5) 54.7 - 160.8 [106.9]	62.3 ± 17.6 (28.3) 33.9 - 92.6 [59.0]	224.5 ± 48.9 (21.8) 141.0 - 321.4 [220.5]	167.6 ± 43.6 (26.0) 88.6 - 248.6 [160.3]	3.9 ± 0.9 (21.8) 3.0 - 6.5 [3.8]	2.5 ± 0.3 (11.5) 2.1 - 3.1 [2.4]	131.9 ± 32.4 (24.5) 94.5 - 223.0 [121.2]	169.8 ± 34.4 (20.3) 130.6 - 270.1 [165.8]
Non - White n = 14	34.7 ± 5.6 (16.2) 24.0 - 40.0 [37.0]	166.2 ± 11.8 (7.1) 152.4 - 185.4 [161.3]	71.6 ± 10.5 (14.6) 57.3 - 91.8 [69.6]	3.3 ± 0.9 (27.8) 2.0 - 5.0 [3.0]	2.4 ± 0.6 (26.9) 2.0 - 4.0 [2.0]	8.3 ± 3.5 (42.6) 4.2 - 15.8 [7.2]	5.2 ± 2.4 (46.8) 2.8 - 10.9 [4.4]	12.9 ± 2.9 (22.4) 9.0 - 16.0 [11.0]	11.6 ± 3.1 (26.7) 8.0 - 16.0 [10.5]	120.9 ± 50.1 (41.4) 73.2 - 228.6 [111.7]	61.4 ± 28.6 (46.6) 34.0 - 127.8 [55.4]	81.8 ± 40.3 (49.2) 39.9 - 167.8 [70.2]	47.7 ± 26.2 (55.1) 23.9 - 108.0 [42.5]	182.3 ± 78.0 (42.8) 110.6 - 356.3 [165.5]	129.5 ± 66.1 (51.0) 65.1 - 275.8 [110.3]	3.9 ± 0.5 (13.1) 3.0 - 4.6 [4.0]	2.4 ± 0.5 (19.2) 1.7 - 3.2 [2.6]	133.5 ± 25.6 (19.2) 100.6 - 192.3 [126.3]	175.3 ± 28.4 (16.2) 146.5 - 247.1 [163.7]
Black n = 5	35.8 ± 4.4 (12.2) 30.0 - 40.0 [36.0]	172.2 ± 12.6 (7.3) 157.5 - 185.4 [177.8]	77.9 ± 14.3 (18.4) 57.3 - 91.8 [74.6]	3.6 ± 1.1 (31.7) 2.0 - 5.0 [4.0]	2.8 ± 0.8 (29.9) 2.0 - 4.0 [3.0]	7.0 ± 2.9 (41.2) 4.2 - 11.4 [5.7]	4.4 ± 1.3 (28.5) 3.0 - 6.0 [4.0]	13.8 ± 3.0 (22.0) 10.0 - 16.0 [16.0]	12.4 ± 3.5 (28.3) 9.0 - 16.0 [12.0]	99.7 ± 34.1 (34.2) 73.2 - 148.4 [79.0]	50.4 ± 13.9 (27.5) 38.7 - 70.5 [44.5]	65.3 ± 32.7 (50.0) 39.9 - 109.6 [44.3]	37.1 ± 15.7 (42.4) 25.2 - 58.2 [26.2]	150.1 ± 46.3 (30.9) 111.9 - 207.3 [123.5]	102.4 ± 47.6 (46.5) 65.1 - 159.5 [70.5]	4.0 ± 0.6 (14.4) 3.2 - 4.6 [3.9]	2.4 ± 0.4 (17.5) 1.8 - 2.8 [2.7]	142.4 ± 35.4 (24.9) 100.6 - 192.3 [140.4]	190.8 ± 37.2 (19.5) 159.4 - 247.1 [170.2]
Hispanic n = 9	34.1 ± 6.4 (18.6) 24.0 - 40.0 [38.0]	162.9 ± 10.6 (6.5) 152.4 - 177.8 [160.0]	68.0 ± 6.0 (8.9) 61.4 - 79.6 [68.2]	3.1 ± 0.8 (25.1) 2.0 - 4.0 [3.0]	2.1 ± 0.3 (15.8) 2.0 - 3.0 [2.0]	9.0 ± 3.8 (42.2) 5.5 - 15.8 [8.1]	5.7 ± 2.9 (50.7) 2.8 - 10.9 [4.5]	12.3 ± 2.8 (23.0) 9.0 - 16.0 [11.0]	11.1 ± 2.9 (26.4) 8.0 - 16.0 [10.0]	132.7 ± 55.3 (41.7) 76.6 - 228.6 [119.7]	67.5 ± 33.4 (49.5) 34.0 - 127.8 [58.8]	91.0 ± 42.9 (47.1) 46.0 - 167.8 [70.6]	53.5 ± 29.8 (55.7) 23.9 - 108.0 [45.2]	200.2 ± 88.4 (44.1) 110.6 - 356.3 [168.4]	144.5 ± 72.5 (50.2) 69.9 - 275.8 [116.5]	3.8 ± 0.5 (12.8) 3.0 - 4.4 [4.0]	2.4 ± 0.5 (21.1) 1.7 - 3.2 [2.5]	128.5 ± 19.0 (14.8) 107.6 - 164.5 [121.9]	166.8 ± 19.8 (11.9) 146.5 - 201.1 [159.8]

a Mean ± S.D. (C.V.%), range, [median]
b As calculated by sponsor – Caverage not defined

Table 24 Multiple Dose ——— Pharmacokinetics by Race / Ethnicity and Gender in Adults – Study 17-006

Subject Grouping	Age (yrs)	Height (cm)	Weight (kg)	Tlag (hours)		Cmax (ng/ml)		Tmax (hours)		AUCss (ng/ml x hr^{-1})		AUC0-16 (ng/ml x hr^{-1})		Combined d-MPH & l-MPH AUCs		T1/2 (hours)		%Fluct0-16 (%)	
				d-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH	AUCss	AUC0-16	*d*-MPH	*l*-MPH	*d*-MPH	*l*-MPH
White Male n = 8	31.4 ± 6.4 (20.5) 21.0 - 39.0 [31.0]	173.0 ± 6.9 (4.0) 165.1 - 182.9 [172.7]	82.8 ± 6.1 (7.4) 70.9 - 88.6 [84.6]	2.4 ± 0.5 (21.8) 2.0 - 3.0 [2.0]	1.8 ± 0.5 (26.5) 1.0 - 2.0 [2.0]	10.6 ± 3.3 (31.5) 7.0 - 16.8 [9.9]	7.2 ± 1.9 (27.0) 4.1 - 9.9 [6.9]	11.1 ± 2.2 (19.5) 9.0 - 16.0 [10.5]	8.5 ± 1.6 (18.9) 5.0 - 10.0 [9.0]	149.2 ± 33.2 (22.3) 112.3 - 216.2 [148.5]	81.8 ± 19.9 (24.3) 60.4 - 110.2 [80.3]	107.4 ± 28.5 (26.5) 76.6 - 160.8 [108.2]	66.4 ± 17.9 (27.0) 46.7 - 92.6 [63.3]	230.9 ± 50.4 (21.8) 172.8 - 321.4 [227.3]	173.8 ± 44.3 (25.5) 123.7 - 248.6 [173.5]	3.9 ± 0.5 (12.1) 3.3 - 4.8 [3.9]	2.5 ± 0.3 (12.9) 2.1 - 3.1 [2.5]	128.7 ± 39.8 (30.9) 96.9 - 223.0 [119.5]	169.0 ± 46.3 (27.4) 130.6 - 270.1 [155.6]
White Female n = 7	34.0 ± 6.2 (18.1) 21.0 - 39.0 [36.0]	159.3 ± 7.3 (4.6) 147.3 - 167.6 [157.5]	63.1 ± 10.1 (16.1) 49.1 - 77.3 [60.9]	3.0 ± 1.5 (50.9) 1.0 - 5.0 [3.0]	2.1 ± 0.9 (42.0) 1.0 - 4.0 [2.0]	10.6 ± 3.5 (33.2) 5.7 - 16.5 [9.6]	6.4 ± 2.1 (32.0) 3.6 - 9.4 [6.5]	12.0 ± 3.0 (25.0) 9.0 - 16.0 [12.0]	9.7 ± 1.4 (14.2) 8.0 - 12.0 [9.0]	145.6 ± 35.9 (24.7) 91.8 - 205.7 [142.4]	71.5 ± 16.9 (23.6) 49.2 - 92.3 [69.1]	102.8 ± 29.2 (28.4) 54.7 - 146.5 [98.6]	57.7 ± 17.4 (30.2) 33.9 - 79.8 [58.0]	217.2 ± 50.0 (23.0) 141.0 - 296.7 [220.5]	160.5 ± 45.2 (28.2) 88.6 - 221.6 [146.7]	3.9 ± 1.2 (30.6) 3.0 - 6.5 [3.4]	2.5 ± 0.3 (10.7) 2.3 - 3.1 [2.4]	135.7 ± 23.9 (17.6) 94.5 - 157.6 [143.0]	170.9 ± 16.1 (9.4) 149.0 - 197.4 [168.7]
NonWhite male n = 6	35.5 ± 6.9 (19.3) 24.0 - 40.0 [39.5]	178.7 ± 3.8 (2.1) 175.3 - 185.4 [177.8]	79.4 ± 10.2 (12.8) 68.2 - 91.8 [77.1]	3.2 ± 1.2 (36.9) 2.0 - 5.0 [3.0]	2.3 ± 0.5 (22.1) 2.0 - 3.0 [2.0]	6.6 ± 1.9 (29.2) 4.2 - 9.5 [6.2]	4.6 ± 1.3 (28.5) 3.0 - 6.3 [4.3]	13.0 ± 3.3 (25.7) 9.0 - 16.0 [13.5]	10.7 ± 2.9 (27.6) 8.0 - 16.0 [9.5]	101.4 ± 27.1 (26.7) 73.2 - 141.6 [97.9]	55.3 ± 14.7 (26.6) 38.7 - 72.5 [55.4]	69.3 ± 25.2 (36.4) 41.7 - 105.2 [66.9]	42.7 ± 14.9 (34.9) 26.1 - 60.1 [42.9]	156.7 ± 41.6 (26.5) 111.9 - 214.1 [153.2]	112.0 ± 40.0 (35.7) 67.8 - 165.3 [109.8]	4.1 ± 0.4 (10.7) 3.5 - 4.6 [4.2]	2.4 ± 0.4 (17.3) 1.7 - 2.8 [2.6]	121.3 ± 21.2 (17.5) 100.6 - 159.0 [115.0]	167.3 ± 21.9 (13.1) 148.1 - 210.2 [160.0]
NonWhite Female n = 9	33.7 ± 4.8 (14.2) 25.0 - 40.0 [33.0]	159.2 ± 7.9 (5.0) 152.4 - 177.8 [157.5]	68.6 ± 10.4 (15.2) 57.3 - 91.8 [68.2]	3.4 ± 0.7 (21.1) 2.0 - 4.0 [4.0]	2.4 ± 0.7 (29.7) 2.0 - 4.0 [2.0]	9.0 ± 4.0 (44.6) 5.3 - 15.8 [8.1]	5.5 ± 2.9 (53.8) 2.8 - 10.9 [4.4]	13.1 ± 2.8 (21.1) 10.0 - 16.0 [11.0]	12.7 ± 3.2 (25.6) 9.0 - 16.0 [11.0]	128.8 ± 59.4 (46.1) 75.0 - 228.6 [119.7]	63.0 ± 35.0 (55.5) 34.0 - 127.8 [48.7]	85.7 ± 48.0 (56.1) 39.9 - 167.8 [69.9]	48.6 ± 31.9 (65.7) 23.9 - 108.0 [34.1]	191.8 ± 93.8 (48.9) 110.6 - 356.3 [168.4]	134.2 ± 79.5 (59.2) 65.1 - 275.8 [104.0]	3.7 ± 0.5 (12.7) 3.0 - 4.4 [3.9]	2.5 ± 0.5 (20.5) 1.8 - 3.2 [2.7]	144.4 ± 24.9 (17.2) 116.9 - 192.3 [140.4]	184.6 ± 32.0 (17.3) 146.5 - 247.1 [173.8]
Black Male n = 3	36.7 ± 5.8 (15.7) 30.0 - 40.0 [40.0]	181.2 ± 3.9 (2.1) 177.8 - 185.4 [180.3]	85.9 ± 9.8 (11.4) 74.6 - 91.8 [91.4]	3.7 ± 1.5 (41.7) 2.0 - 5.0 [4.0]	2.7 ± 0.6 (21.7) 2.0 - 3.0 [3.0]	5.9 ± 2.1 (35.4) 4.2 - 8.3 [5.3]	4.2 ± 1.6 (37.5) 3.0 - 6.0 [3.6]	14.0 ± 3.5 (24.7) 10.0 - 16.0 [16.0]	12.3 ± 3.5 (28.5) 9.0 - 16.0 [12.0]	90.4 ± 28.2 (31.2) 73.2 - 122.9 [75.0]	49.5 ± 18.2 (36.7) 38.7 - 70.5 [39.4]	59.0 ± 27.7 (47.0) 41.7 - 90.9 [44.3]	36.8 ± 18.5 (50.3) 26.1 - 58.2 [26.2]	139.9 ± 46.3 (33.1) 111.9 - 193.4 [114.4]	95.8 ± 46.2 (48.3) 67.8 - 149.1 [70.5]	4.3 ± 0.4 (10.3) 3.8 - 4.6 [4.6]	2.7 ± 0.1 (2.9) 2.7 - 2.8 [2.7]	126.5 ± 29.7 (23.5) 100.6 - 159.0 [119.8]	178.9 ± 27.4 (15.3) 159.4 - 210.2 [167.0]
Black female n = 2	34.5 ± 2.1 (6.1) 33.0 - 36.0 [34.5]	158.8 ± 1.8 (1.1) 157.5 - 160.0 [158.8]	66.0 ± 12.2 (18.5) 57.3 - 74.6 [66.0]	3.59 ± 0.7 (20.2) 3.0 - 4.0 [3.5]	3.0 ± 1.4 (47.1) 2.0 - 4.0 [3.0]	8.5 ± 4.0 (46.6) 5.7 - 11.4 [8.5]	4.7 ± 1.0 (21.5) 4.0 - 5.4 [4.7]	13.5 ± 3.5 (26.2) 11.0 - 16.0 [13.5]	12.5 ± 4.9 (39.6) 9.0 - 16.0 [12.5]	113.7 ± 49.1 (43.2) 79.0 - 148.4 [113.7]	51.7 ± 10.2 (19.7) 44.5 - 58.9 [51.7]	74.7 ± 49.3 (66.0) 39.9 - 109.6 [74.7]	37.6 ± 17.5 (46.5) 25.2 - 49.9 [37.6]	165.4 ± 59.2 (35.8) 123.5 - 207.3 [165.4]	112.3 ± 66.8 (59.4) 65.1 - 159.5 [112.3]	3.6 ± 0.5 (13.5) 3.2 - 3.9 [3.6]	2.0 ± 0.4 (18.8) 1.8 - 2.3 [2.0]	166.3 ± 36.7 (22.1) 140.4 - 192.3 [166.3]	208.7 ± 54.4 (26.1) 170.2 - 247.1 [208.7]
White Hispanic n = 7	35.0 ± 5.8 (16.5) 25.0 - 40.0 [38.0]	162.2 ± 9.7 (6.0) 152.4 - 175.3 [160.0]	67.3 ± 4.4 (6.5) 61.4 - 72.7 [68.2]	3.3 ± 0.8 (23.0) 2.0 - 4.0 [3.0]	2.1 ± 0.4 (17.6) 2.0 - 3.0 [2.0]	9.1 ± 4.4 (48.2) 5.5 - 15.8 [6.3]	5.8 ± 3.3 (56.7) 2.8 - 10.9 [4.5]	13.0 ± 2.8 (21.8) 10.0 - 16.0 [11.0]	11.6 ± 3.1 (26.9) 9.0 - 16.0 [10.0]	132.6 ± 63.7 (48.0) 76.6 - 228.6 [103.8]	67.5 ± 38.5 (57.0) 34.0 - 127.8 [51.9]	90.6 ± 48.9 (54.0) 46.0 - 167.8 [69.9]	53.8 ± 34.1 (63.5) 23.9 - 108.0 [39.9]	200.2 ± 101.7 (50.8) 110.6 - 356.3 [162.7]	144.4 ± 82.9 (57.4) 69.9 - 275.8 [104.0]	3.9 ± 0.4 (10.8) 3.2 - 4.4 [4.0]	2.6 ± 0.5 (20.8) 1.7 - 3.2 [2.7]	130.3 ± 20.4 (15.6) 107.6 - 164.5 [121.9]	170.6 ± 20.7 (12.2) 148.1 - 201.1 [159.8]
Black Hispanic M/F n = 2 M higherPK	31.0 ± 9.9 (31.9) 24.0 - 38.0 [31.0]	165.1 ± 18.0 (10.9) 152.4 - 177.8 [165.1]	70.7 ± 12.6 (17.8) 61.8 - 79.6 [70.7]	2.5 ± 0.7 (28.3) 2.0 - 3.0 [2.5]	2.0 ± 0.0 (0.0) 2.0 - 2.0 [2.0]	8.8 ± 0.9 (10.7) 8.1 - 9.5 [8.8]	5.3 ± 1.3 (24.9) 4.4 - 6.3 [5.3]	10.0 ± 1.4 (14.1) 9.0 - 11.0 [10.0]	9.5 ± 2.1 (22.3) 8.0 - 11.0 [9.5]	132.8 ± 12.5 (9.4) 124.0 - 141.6 [132.8]	67.5 ± 7.1 (10.5) 62.4 - 72.5 [67.5]	92.2 ± 18.3 (19.9) 79.2 - 105.2 [92.2]	52.7 ± 10.5 (20.0) 45.2 - 60.1 [52.7]	200.3 ± 19.6 (9.8) 186.4 - 214.1 [200.3]	144.9 ± 28.9 (19.9) 124.4 - 165.3 [144.9]	3.6 ± 0.8 (22.8) 3.0 - 4.1 [3.6]	2.1 ± 0.3 (14.7) 1.9 - 2.3 [2.1]	122.3 ± 17.1 (14.0) 110.1 - 134.4 [122.3]	153.5 ± 9.9 (6.4) 146.5 - 160.5 [153.5]
White Hispanic Female n = 5	33.2 ± 6.0 (18.0) 25.0 - 40.0 [32.0]	157.0 ± 4.6 (2.9) 152.4 - 162.6 [157.5]	66.4 ± 4.9 (7.4) 61.4 - 72.7 [68.2]	3.4 ± 0.9 (26.3) 2.0 - 4.0 [4.0]	2.2 ± 0.4 (20.3) 2.0 - 3.0 [2.0]	10.2 ± 4.8 (47.1) 5.5 - 15.8 [9.1]	6.3 ± 3.8 (60.2) 2.8 - 10.9 [4.5]	12.8 ± 3.0 (23.2) 10.0 - 16.0 [11.0]	12.4 ± 3.4 (27.2) 9.0 - 16.0 [11.0]	146.5 ± 72.2 (49.3) 76.6 - 228.6 [119.7]	72.4 ± 45.9 (63.5) 34.0 - 127.8 [48.7]	100.1 ± 56.5 (56.4) 46.0 - 167.8 [69.9]	58.1 ± 40.7 (70.1) 23.9 - 108.0 [34.1]	218.9 ± 118.0 (53.9) 110.6 - 356.3 [168.4]	158.2 ± 97.1 (61.4) 69.9 - 275.8 [104.0]	3.9 ± 0.4 (11.1) 3.2 - 4.4 [4.0]	2.8 ± 0.4 (15.1) 2.1 - 3.2 [2.8]	134.8 ± 21.6 (16.1) 116.9 - 164.5 [121.9]	177.4 ± 20.6 (11.6) 156.0 - 201.1 [173.8]
White Hispanic Male n = 2	39.5 ± 0.7 (1.8) 39.0 - 40.0 [39.5]	175.3 ± 0.0 (0.0) 175.3 - 175.3 [175.3]	69.6 ± 1.9 (2.7) 68.2 - 70.9 [69.6]	3.0 ± 0.0 (0.0) 3.0 - 3.0 [3.0]	2.0 ± 0.0 (0.0) 2.0 - 2.0 [2.0]	6.2 ± 0.0 (0.6) 6.2 - 6.3 [6.2]	4.3 ± 0.3 (6.2) 4.1 - 4.5 [4.3]	13.5 ± 3.5 (26.2) 11.0 - 16.0 [13.5]	9.5 ± 0.7 (7.4) 9.0 - 10.0 [9.5]	97.9 ± 8.4 (8.6) 91.9 - 103.8 [97.9]	55.4 ± 4.9 (8.9) 51.9 - 58.8 [55.4]	66.9 ± 5.1 (7.7) 63.3 - 70.6 [66.9]	42.9 ± 4.3 (9.9) 39.9 - 45.9 [42.9]	153.2 ± 13.3 (8.7) 143.8 - 162.7 [153.2]	109.8 ± 9.4 (8.6) 103.2 - 116.5 [109.8]	3.8 ± 0.5 (14.2) 3.5 - 4.2 [3.8]	2.1 ± 0.6 (27.7) 1.7 - 2.5 [2.1]	119.2 ± 16.3 (13.7) 107.6 - 130.7 [119.2]	153.4 ± 7.6 (4.9) 148.1 - 158.8 [153.4]

6.4 BIOAVAILABILITY

6.4.1 ABSOLUTE BIOAVAILABILITY

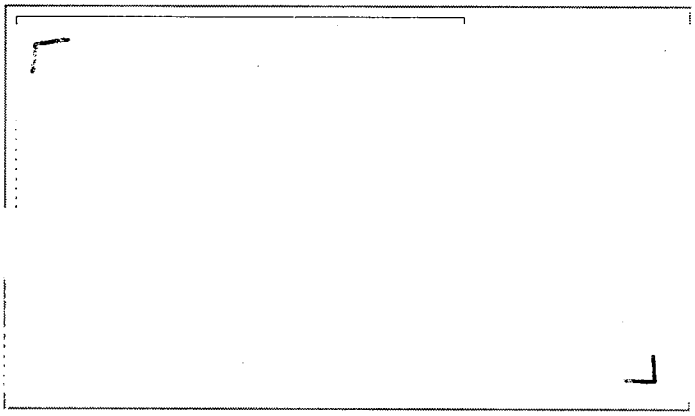
The absolute bioavailability of a single application of Methypatch applied to the back relative to subcutaneous methylphenidate was assessed in a single dose crossover design in 19 subjects in study 17-007. To assess absolute bioavailability the single dose AUCs of *d,l*-MPH after application of 3 or 6 MTS adjusted for the dose of drug delivered from the patches was compared to the AUCs achieved from 25 mcg or 50 mcg of methylphenidate administered subcutaneously. The mean bioavailability was 90% and summary statistics and the frequency distribution for individual subject bioavailabilities are shown in Table 25 and Figure 11 respectively.

Table 25 Summary Statistics for *d,l*-MPH Absolute Bioavailability for Methylpatch (F)

Absolute Bioavailability of Methypatch (F) Relative to Subcutaneous Administration[a]	
n	19
Mean ± SD **(%CV)** **Range** **[Median]**	0.90 ± 0.19 (21.4) 0.67 - 1.34 [0.86]
95% CI for Mean	0.808 – 0.994

a Mean ± S.D. (C.V.%), range, [median]

Figure 11 Frequency Distribution of Methypatch Absolute Bioavailability (F) – Study 17-007



6.4.2 RELATIVE BIOAVAILABILITY

6.4.2.1 Methypatch vs. Ritalin – Study 17-006

The relative bioavailability of a 16 hour application of Methypatch at steady-state applied to the hip was assessed in healthy adults in study 17-006. To assess relative bioavailability the steady-state AUCs of *d*-MPH and *l*-MPH after application of a 25 cm^2 MTS adjusted for the dose delivered from the patch was compared to the steady-state AUCs achieved from 60 mg of orally administered Ritalin, (20 mg po TID in 4 hour intervals). The mean bioavailability was 353% for *d*-MPH and 17330% for *l*-MPH. That is, the relative exposures are 3.5 fold higher for *d*-MPH and 173 fold higher for *l*-MPH for equal doses of methylphenidate administered transdermally as compared with oral administration. Summary statistics and frequency distributions are shown in Table 26 and Figure 12 respectively.

The much higher ratios for *l*-MPH as compared with *d*-MPH may be due to either greater absorption or less first pass effect for the *l*-isomer via the transdermal route.

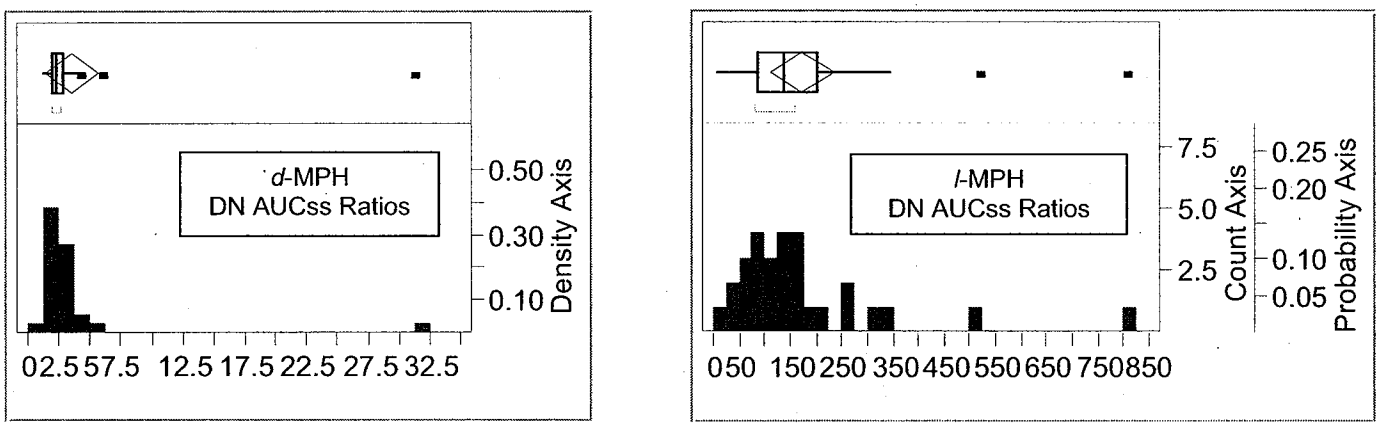
The relative much higher exposures to *l*-MPH upon transdermal administration as compared to oral administration raises the question of whether there is adequate historical safety information in patients or subjects for to determine the safety to the expected clinical *l*-MPH exposures with MethyPatch®.

Table 26 Summary Statistics for *d*-MPH & *l*-MPH Dose Normalized MTS:Ritalin AUCss Ratios[a]

Dose Normalized MTS:Ritalin AUCss Ratios[b] ($F_{relative}$)		
	***d*-MPH**	***l*-MPH**
n	29	29
Mean ± SD **(%CV)** **Range** **[Median]**	3.53 ± 5.45 (154.5) 1.21 - 31.42 [2.38]	173.3 ± 162.1 (93.5) 7.25 - 809.14 [136.08]
95% CI for Mean	1.46 – 5.60	112 - 235

a 1 x MTS 55 mg / 2 cm^2 for 16 hours compared with Ritalin 20 mg po x 3.
b Mean ± S.D. (C.V.%), range, [median]

Figure 12 Frequency Distributions of *d*-MPH & *l*-MPH Dose Normalized (DN) Methypatch:Ritalin AUCss Ratios ($F_{relative}$)[a]



a 1 x MTS 55 mg / 2 cm^2 for 16 hours compared with Ritalin 20 mg po x 3.

6.4.3 APPLICATION SITE AND OTHER FACTORS EFFECTING DRUG ABSORPTION

The effect of dermal application site and several other factors including: application to inflamed skin, application of heat to the patch, and application to buccal mucosa were assess in 3 single dose crossover studies. These included studies 17-005, 17-017, and 17-012. Details as to subject population, number of patches applied, duration of patch application, and analytes varied between studies and are described in Table 15.

Results of these studies follow:

6.4.3.1 Scapula vs. Hip – Study 17-005

The results of study 17-005 are shown in Table 27. As can be seen the mean bioavailability in children when applied to the scapula as compared to when applied to the hip is 76%. However, there are two caveats. First the relative bioavailability was assessed by comparing AUC_{0-16} rather than $AUC_{0-\infty}$. Consequently, the treatment arm with higher concentrations would be expected to have an even greater proportion of the total $AUC_{0-\infty}$ as $AUC_{16-\infty}$. Thus we would expect that the true relative bioavailability when applied to the scapula would be even lower than reported. Secondly, the pharmacokinetic metrics are for *d,l*-MPH, whereas the active isomer is *d*-MPH. As *d*-MPH tends to have higher exposures and longer half-life than *l*-MPH, if *d*-MPH alone were assessed the relative bioavailability might be even less as the fraction of the total AUC attributable to $AUC_{16-\infty}$ for *d*-MPH is likely greater than for *l*-MPH.

Table 27 Relative Bioavailability of 1 x 55 mg / 25 cm^2 MTS Applied to the Scapula as compared to the Hip for 16 hours in Children

Metrics	Test	Reference	Log Transformed LS Means		Ratio (%)	90% Confidence Interval
	Scapula	Hip	Scapula	Hip		
Tlag (hours)	2.1 ± 0.7 (35.1) 0.0 – 4.0 [2.0]	2.1 ± 0.4 (20.8) 2.0 – 4.0 [2.0]	—	—	—	—
Cmax (ng/ml)	26.6 ± 11.2 (42.5) 13.9 – 52.3 [24.7]	33.8 ± 10.2 (30.1) 13.4 – 57.8 [33.2]	3.2 (24.5)	3.5 (33.1)	76.2	67.8 – 85.5
Tmax (hours)	8.6 ± 2.5 (29.4) 6.0 – 16.1 [8.0]	9.8 ± 1.6 (15.9) 7.9 – 12.0 [10.0]	—	—	—	—
AUC_{0-16} (ng/ml x hr^{-1})	264.4 ± 115.2 (43.6) 111.1 – 510.1 [246.0]	333.2 ± 113.5 (34.1) 110.8 – 647.0 [312.1]	5.5 (244.7)	5.75 (314.2)	76.4	66.8 – 87.6
DOSE DELIVERED (MG)	23.0 ± 6.5 (28.2) 1.8 - 31.6 [23.4]	28.2 ± 7.2 (25.5) 10.8 - 43.3 [27.1]	—	—	—	—
Mean % of Patch Drug Content Delivered	42%	51%	—	—	—	—

a Mean ± S.D. (C.V.%), range, [median]

Figure 13 and Figure 14 demonstrate that the ages and weights of the 23 children in study 17-005 were adequately distributed.

Figure 13 Frequency Histogram of Subject Ages in Years in Study 17-005

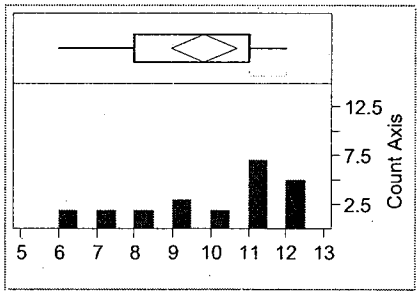
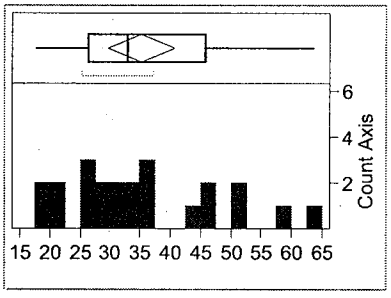


Figure 14 Frequency Histogram of Subject Weights in Kg in Study 17-005



6.4.3.2 Inflamed Skin – Study 17-017

Study 17-017 is a single dose crossover design study in 8 healthy young adult males of the relative bioavailability of a 55 mg / 25 cm^2 MTS applied to the hip for 16 hours in the presence of intact and inflamed skin. Skin inflammation was induced by a controlled pre-exposure to 1% sodium lauryl sulfate (SLS) to produce erythema that was clearly present.

As shown in Table 28 in the presence of inflamed skin both the rate and extent of absorption are significantly increased as compared with intact skin. With median Tmax occurring 10 hours earlier and median exposures 3 fold higher.

Table 28 Relative Bioavailability of 1 x 55 mg / 25 cm^2 MTS Applied to Inflamed as compared to Intact Skin for 16 hours

Metrics	Inflamed Skin	Intact Skin	Time Difference or Ratio
Tlag (hours)	1.0 ± 0.0 (0.0) 1.0 - 1.0 [1.0]	3.8 ± 0.7 (18.9) 2.0 - 4.0 [4.0]	-2.8 ± 0.7 (25.7) -3.0 - -1.0 [-3.0]
Tmax (hours)	4.4 ± 2.0 (45.0) 1.0 - 8.0 [4.0]	14.8 ± 1.9 (12.60 12.0 - 18.1 [14.0]	-10.4 ± 2.5 (-24.0) -14.1 - -6.1 [-10.5]
Cmax (ng/ml)	46.4 ± 10.5 (22.6) 32.4 - 62.9 [43.9]	15.0 ± 6.3 (42.2) 7.9 - 24.2 [14.2]	3.4 ± 1.1 (31.7) 1.7 - 5.2 [3.4]
AUC0-∞ (ng/ml x hr^{-1})	493.9 ± 76.5 (15.5) 383.3 - 591.8 [494.3]	193.2 ± 89.0 (46.1) 100.8 - 363.5 [177.8]	2.9 ± 1.0 (33.1) 1.6 - 4.3 [2.9]
AUC0-16 (ng/ml x hr^{-1})	442.5 ± 69.9 (15.8) 334.3 - 536.2 [437.1]	123.0 ± 67.4 (54.8) 47.8 - 249.7 [101.3]	4.4 ± 1.8 (40.8) 2.1 - 7.0 [4.0]
AUC0-t (ng/ml x hr^{-1})	490.7 ± 75.8 (15.4) 380.3 - 587.9 [491.0]	187.6 ± 86.2 (45.9) 97.3 - 351.1 [172.4]	3.0 ± 1.0 (33.2) 1.7 - 4.5 [2.9]
t1/2 (hour)	3.6 ± 0.4 (11.1) 2.8 - 4.2 [3.6]	3.9 ± 0.2 (5.9) 3.5 - 4.3 [3.9]	0.9 ± 0.1 (9.8) 0.8 - 1.0 [0.9]
Apparent Dose (mg)	46.3 ± 2.7 (5.8) 41.3 - 49.7 [46.7]	20.5 ± 3.6 (17.5) 16.0 - 25.8 [21.2]	2.3 ± 0.5 (19.9) 1.6 - 2.9 [2.2]
Delivery Rate (mg/hour)	2.9 ± 0.2 (5.7) 2.6 - 3.1 [2.9]	1.3 ± 0.2 (16.9) 1.0 - 1.6 [1.3]	2.4 ± 0.5 (19.1) 1.6 - 2.9 [2.2]
Dose Delivered (%)*	85.5 ± 4.9 (5.8) 76.3 - 91.9 [86.3]	37.9 ± 6.6 (17.4) 29.6 - 47.7 [39.1]	2.3 ± 0.5 (19.9) 1.6 - 2.9 [2.2]

a Mean ± S.D. (C.V.%), range, [median]

This raises concerns if the patient or parent should repeatedly apply patches to the same site as inflammation could result and absorption and adverse effects could increase.

In addition, skin inflammation could be intentionally induced for purposes of abuse or misuse.

6.4.3.3 Heat Application – Study 17-012

Study 17-012 is a single dose crossover design study in 6 healthy young adult males of the relative bioavailability of three 55 mg / 25 cm^2 MTS applied to the Arm for 8 hours in the presence and absence of the application of heat for the first 6 hours.

As shown in Table 29 in the presence of heat both the rate and extent of absorption are significantly increased. With median Tlag and Tmax occurring 1 hour earlier, and median Cmax 2 fold higher, and median exposures more than 2.5 fold higher.

Table 29 Relative Bioavailability of 3 x 55 mg / 25 cm^2 MTS Applied to the Arm in the Presence and Absence of Heat[a]

Metric	*d*-MPH			*l*-MPH		
	Heat	No Heat	Time Difference or Ratio	Heat	No Heat	Time Difference or Ratio
Tlag (hours)	1.75 ± 0.61 (34.99) 0.50 - 2.00 [2.00]	2.83 ± 0.75 (26.57) 2.00 - 4.00 [3.00]	1.08 ± 1.02 (94.21) 0.00 - 2.50 [1.00]	1.08 ± 0.49 (45.38) 0.50 - 2.00 [1.00]	1.42 ± 1.07 (75.42) 0.50 - 3.00 [1.25]	0.33 ± 1.37 (409.88) -1.50 - 2.00 [0.25]
Cmax (ng/ml)	26.54 ± 7.74 (29.16) 17.58 - 38.72 [26.08]	14.60 ± 3.59 (24.59) 9.45 - 20.50 [14.50]	1.91 ± 0.74 (38.80) 1.26 - 3.06 [1.62]	18.20 ± 5.03 (27.67) 12.87 - 25.12 [16.23]	9.58 ± 3.15 (32.87) 6.76 - 14.91 [9.06]	1.97 ± 0.47 (23.93) 1.38 - 2.50 [1.97]
Tmax (hours)	6.83 ± 1.33 (19.45) 5.00 - 8.00 [7.00]	7.33 ± 0.82 (11.13) 6.00 - 8.00 [7.50]	0.50 ± 1.76 (352.14) -2.00 - 2.00 [1.00]	5.67 ± 1.37 (24.11) 4.00 - 8.00 [5.50]	7.00 ± 0.89 (12.78) 6.00 - 8.00 [7.00]	1.33 ± 1.86 (139.64) -1.00 - 4.00 [1.00]
AUC_{0-8} (ng/ml x hr^{-1})	120.0 ± 39.9 (33.28) 85.0 - 192.7 [108.90]	49.8 ± 20.0 (40.20) 27.8 - 86.4 [46.09]	2.64 ± 1.10 (41.72) 1.56 - 4.17 [2.30]	88.9 ± 31.3 (35.20) 62.6 - 140.5 [77.44]	37.5 ± 16.6 (44.42) 23.0 - 66.0 [30.70]	2.58 ± 0.97 (37.50) 1.58 - 4.04 [2.36]

a Mean ± S.D. (C.V.%), range, [median]

Table 30 Mean Drug Delivery from a 55 mg / 25 cm^2 MTS Applied to the Arm in the Presence and Absence of Heat[a]

mg Delivered		Ratio	% Delivered	
Heat	No Heat	Heat :No Heat	Heat	No Heat
48.9 ± 7.9 (16.1) 37.8 - 58.1 [50.6]	32 ± 4.6 (14.4) 25.6 - 38.2 [32.1]	1.55 ± 0.31 (19.88) 1.18 - 1.90 [1.53]	29.2 ± 5.2 (17.6) 23 - 35.4 [30.85]	19.3 ± 3.1 (16) 15.6 - 23.3 [19.55]

a Mean ± S.D. (C.V.%), range, [median] Buccal Mucosa – Study 17-012

In the second part of study 17-012, the bioavailability of 2 x 55 mg / 25 cm^2 MTS was evaluated when applied to the buccal mucosa for 2 hours.

Table 31 shows the dose normalized pharmacokinetic metrics after a 2 hour buccal application as compared to application of a similar dose to the arm for 8 hours. It's apparent that upon buccal application that Tlag is essentially eliminated and the rate of absorption is significantly increased such that Cmax and Drug delivery is 3 fold higher even when only applied for 2 hours as compared to 8 hours of application, (see Table 32).

The rapid drug absorption and high peak concentrations achieved on buccal administration raises the possibility of use of buccal application for drug abuse.

Table 31 Relative Dose Normalized Bioavailability of MTS when Applied Bucally as Compared with Application to the Arm[a,b]

Metric	*d*-MPH			*l*-MPH		
	Buccal	Arm (No Heat)	Time Difference or Ratio	Buccal	Arm (No Heat)	Time Difference or Ratio
Tlag (hours)	0.25 ± 0.0 (0.00) 0.25 - 0.25 [0.25]	2.83 ± 0.75 (26.57) 2.0 - 4.0 [3.0]	2.58 ± 0.75 (29.14) 1.75 - 3.75 [2.75]	0.13 ± 0.14 (109.54) 0.0 - 0.25 [0.13]	1.42 ± 1.07 (75.42) 0.50 - 3.0 [1.25]	1.29 ± 1.20 (92.76) 0.25 - 3.00 [1.13]
Cmax (ng/ml)	59.2 ± 25.7 (43.46) 36.6 - 107.6 [55.26]	14.60 ± 3.59 (24.59) 9.45 - 20.50 [14.50]	4.08 ± 1.38 (33.95) 2.63 - 6.18 [3.72]	49.5 ± 20.7 (41.79) 33.2 - 84.8 [39.14]	9.6 ± 3.2 (32.87) 6.8 - 14.9 [9.06]	5.14 ± 1.00 (19.40) 3.50 - 6.16 [5.25]
Tmax (hours)	1.71 ± 0.40 (23.45) 1.0 - 2.0 [1.88]	7.33 ± 0.82 (11.13) 6.0 – 8.0 [7.5]	5.63 ± 1.05 (18.59) 4.25 - 7.00 [5.50]	1.83 ± 0.20 (11.13) 1.50 - 2.0 [1.88]	7.0 ± 0.9 (12.78) 6.0 - 8.0 [7.0]	5.17 ± 0.92 (17.76) 4.00 - 6.25 [5.25]
$AUC_{partial}$[c] (ng/ml x hr^{-1})	58.1 ± 19.2 (33.09) 35.3 - 82.6 [51.53]	49.8 ± 20.0 (40.20) 27.8 - 86.4 [46.09]	—	53.2 ± 19.4 (36.49) 33.0 - 79.7 [46.44]	37.5 ± 16.6 (44.42) 23.0 - 66.0 [30.70]	—

a Mean ± S.D. (C.V.%), range, [median]
b 2 MTS to dose corrected 3 MTS for comparison purposes
c AUCpartial = AUC_{0-2} for buccal administration and AUC_{0-8} for application to the arm

Table 32 Relative Dose Normalized Methylphenidate Drug Delivery from MTS when Applied Buccal as Compared with Application to the Arm[a,b]

mg delivered			Ratio	% Delivered	
Arm (No Heat)	Buccal 2 MTS	Buccal Delivery Dose Normalized to 3 MTS	Buccal : Arm	Arm (No Heat)	Buccal MTS
32 ± 4.6 (14.4) 25.6 - 38.2 [32.1]	61.4 ± 6.3 (10.2) 50.8 - 69.9 [61.8]	92.2 ± 9.4 (10.21) 76.2 - 104.8 [92.7]	2.91 ± 0.41 (14.20) 2.46 - 3.65 [2.85]	19.3 ± 3.1 (16) 15.6 - 23.3 [19.55]	56.4 ± 6.4 (11.3) 46.4 - 63.9 [56.5]

a Mean ± S.D. (C.V.%), range, [median]
b 2 MTS to dose corrected 3 MTS for comparison purposes

6.5 SPECIAL POPULATIONS

6.5.1 CHILDREN

Two pharmacokinetic studies were conducted in children with ADHD.

Study 17-016 was a 4 day multiple dose crossover study comparing the bioavailability of *d*-MPH, *l*-MPH and *d,l*-MPH from an 82.5 mg / 37.5 cm^2 patch and a 110 mg / 50 cm^2 MTS patch when applied to the hip for 8 or 12 hours.

There were two groups of 6 children examined in study 17-016. The first had MTS patches applied for 8 hours, and the second group had patches applied for 12 hours.

Figure 15 and Figure 16 show the ages of the subjects studied, and indicate that this pivotal multiple dose bioavailability study does not adequately cover the age range of 6 – 12 years old that the sponsor wishes to market the drug for.

Figure 15 Frequency Histogram of Subject Ages in Years in Study 17-016 - 8 Hour Wear Group

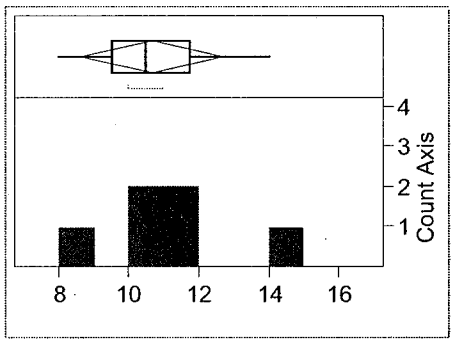


Figure 16 Frequency Histogram of Subject Ages in Years in Study 17-016 - 12 Hour Wear Group

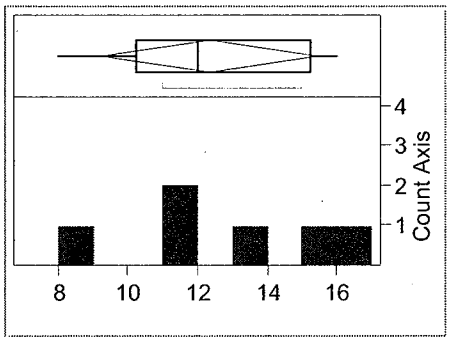


Figure 17 shows the mean steady-state plasma concentration time profiles for the 4 treatment groups in study 17-016 for *d*-MPH and *l*-MPH.

Based upon these profiles a 50 cm^2 patch would need to be applied for a total of 4 hours in this age group in order to rapidly achieve likely therapeutic concentrations, (i.e. > 5 ng/ml), in the morning without having excessive peak concentrations, and an adequate drug free period overnight. Although the summary statistics indicate that the Tlag in many individuals may be so long that even applying a higher strength patch for a shorter time would not be adequate to achieve therapeutic effects sufficiently rapidly in the morning. The data also indicate that the pharmacokinetics are linear and that drug delivery tends to slow down over time as the drug content of the patch is depleted. (see Table 33 to Table 35).

Study 17-005 was a single-dose crossover bioavailability study, comparing *d,l*-MPH bioavailability after application to the scapula as compared to the hip when applied for 16 hours. It was discussed previously in §6.4.3.1 and the hip data is included here only for comparison purposes to study 17-016.

Inspection of concentration vs. time profiles by age in children does tend to show an inverse trend of exposure with age, although the there is too there is a great deal of overlap, (see Figure 18).

Dose normalized pharmacokinetic metrics indicate that a dose of approximately 0.33 mg/kg may be appropriate assuming that there were not so many problems with the time course of exposures, (see Table 36).

Figure 17 Mean Steady-State *d*- & *l*-MPH Plasma Concentration Time Profiles after 8 and 12 hour Applications of 37.5 cm^2 and 50 cm^2 MethyPatches® to the Hip in Children

FIGURE 14.4.3
Mean d-Methylphenidate Plasma Concentrations After MTS Application for 8 or 12 Hours on Day 4 of Treatment

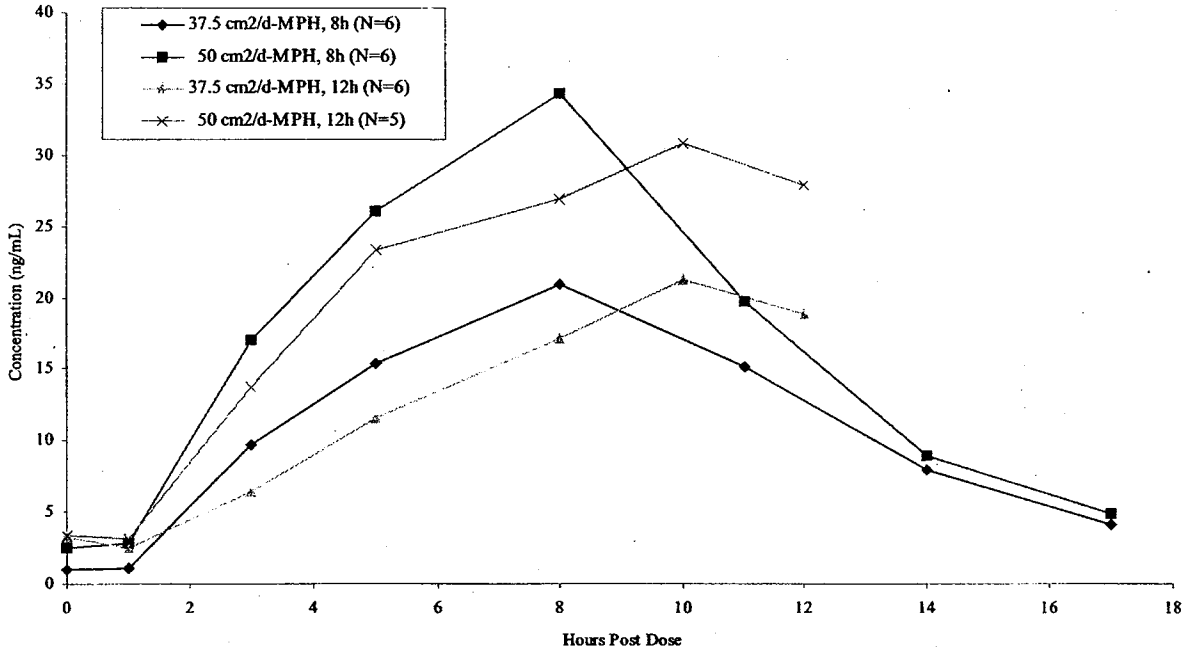


FIGURE 14.4.4
Mean l-Methylphenidate Plasma Concentrations After MTS Application for 8 or 12 Hours on Day 4 of Treatment

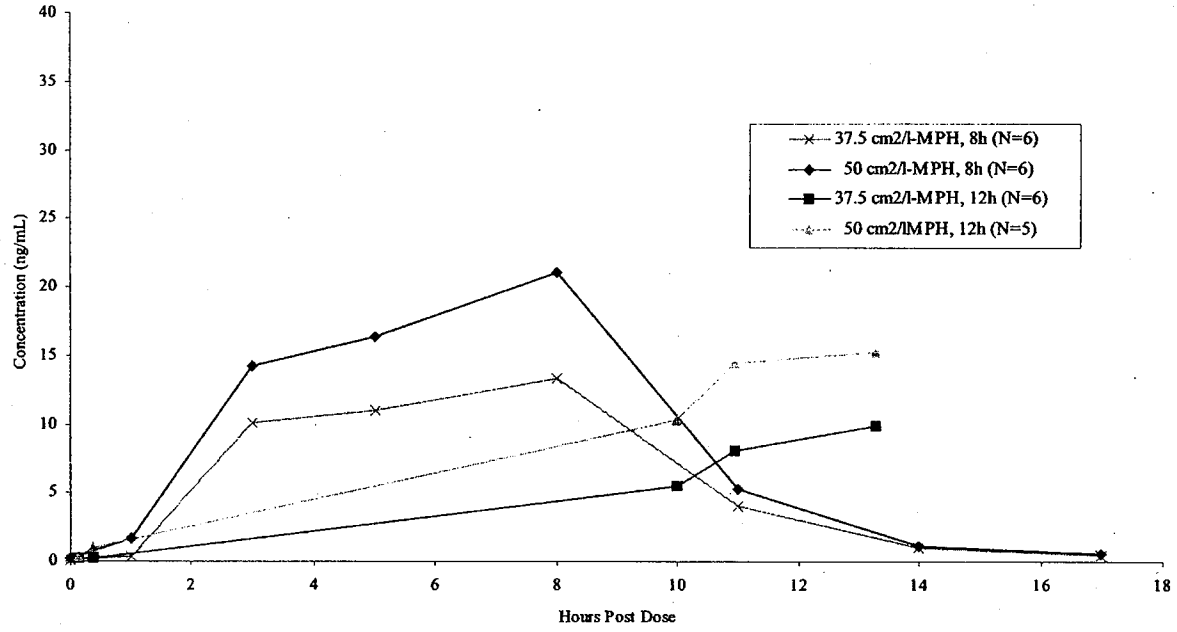


Figure 18 Individual MethyPatch Concentration vs. Time Profiles Grouped by Age

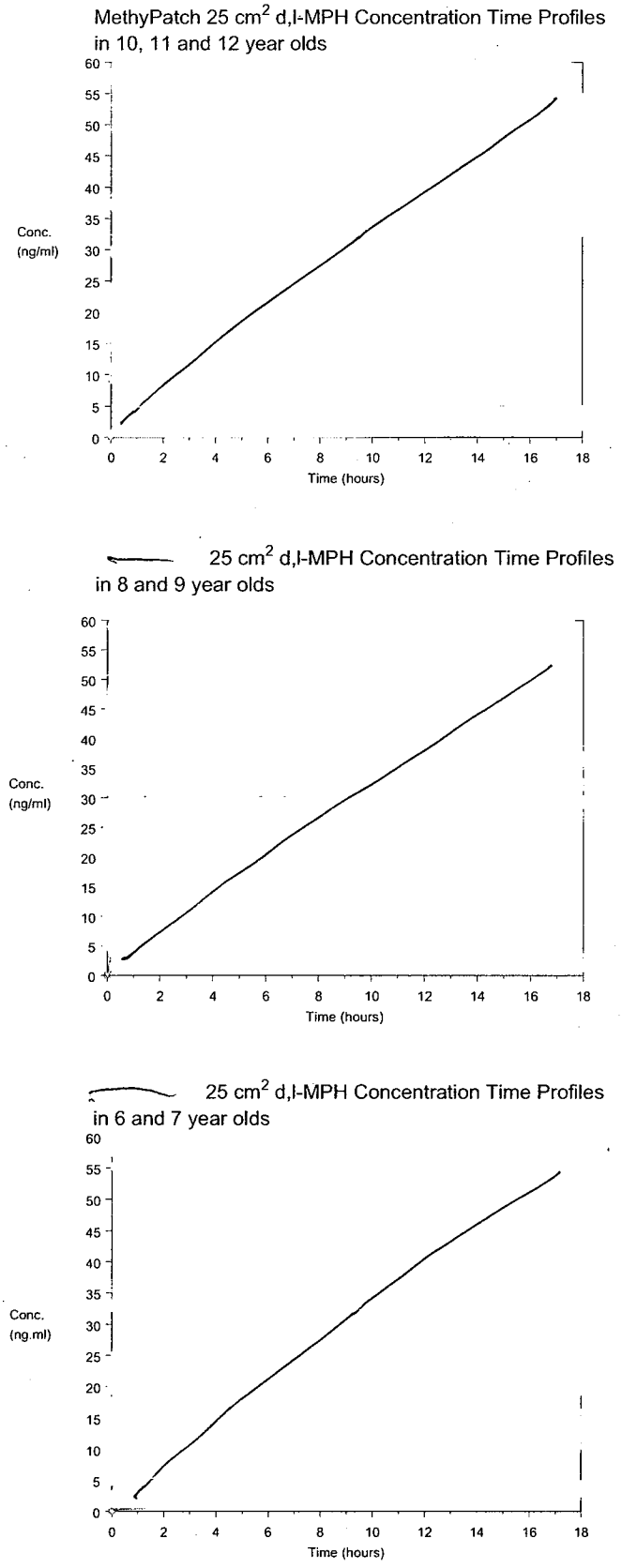


Table 33 *d*-MPH & *l*-MPH Pharmacokinetic Metrics Following Multiple 8 hour Applications (4 days) of ——— ,® MTS to Children[a]

Analyte	Treatment or Comparison	C0 (ng/ml)	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC0-8 (ng/ml x hr^{-1})	AUC0-t (ng/ml x hr^{-1})	AUC0-∞ (ng/ml x hr^{-1})	t1/2 (hours)
d-MPH	37.5 cm^2 MTS for 8 Hours	1.02 ± 0.66 (64.7) 0 - 2.02 [1.04]	2.3 ± 1.0 (44.3) 1.0 - 3.0 [3.0]	22.34 ± 8.62 (38.58) 14.72 - 37.96 [19.7]	7.5 ± 1.22 (16.33) 5.00 - 8.00 [8.0]	91.29 ± 30.56 (33.48) 56.80 - 137.60 [82.3]	197.87 ± 73.96 (37.38) 128.8 - 330.4 [169.0]	217.22 ± 78.38 (36.08) 140.6 - 358.8 [188.9]	3.26 ± 0.52 (15.98) 2.93 - 4.31 [3.1]
	50 cm^2 MTS for 8 Hours	2.5 ± 1.6 (61.4) 0.6 - 5.1 [2.5]	2.3 ± 1.0 (44.3) 1.0 - 3.0 [3.0]	34.53 ± 9.67 (28.00) 17.68 - 44.38 [36.6]	7.5 ± 1.22 (16.33) 5.00 - 8.00 [8.0]	156.28 ± 59.49 (38.07) 58.05 - 236.10 [169.6]	301.30 ± 84.58 (28.07) 151.3 - 385.6 [314.1]	324.09 ± 89.60 (27.65) 167.6 - 407.0 [339.7]	3.04 ± 0.63 (20.68) 2.41 - 4.04 [3.0]
	Ratio of 50:37.5 cm^2 MTS	2.2 ± 1.0 (45.7) 0.8 - 3.6 [2.1][b]	1.2 ± 0.9 (74.5) 0.3 - 3.0 [1.0]	1.7 ± 0.63 (37.79) 1.10 - 2.59 [1.4]	1.0 ± 0.31 (30.24) 0.63 - 1.60 [1.0]	1.8 ± 0.73 (41.19) 1.02 - 2.90 [1.5]	1.6 ± 0.49 (30.69) 1.12 - 2.40 [1.5]	1.5 ± 0.42 (27.13) 1.13 - 2.29 [1.5]	1.0 ± 0.28 (29.47) 0.56 - 1.38 [1.0]
l-MPH	37.5 cm^2 MTS for 8 Hours	0.12 ± 0.09 (73.76) 0 - 0.24 [0.11]	1.7 ± 1.0 (62.0) 1.0 - 3.0 [1.0]	15.02 ± 7.80 (51.95) 8.64 - 29.38 [13.5]	6.2 ± 2.14 (34.65) 3.00 - 8.00 [6.5]	67.94 ± 33.83 (49.80) 37.13 - 121.60 [56.1]	103.86 ± 52.52 (50.57) 57.08 - 194.48 [81.8]	105.12 ± 52.29 (49.75) 57.77 - 195.30 [83.5]	1.87 ± 0.30 (16.21) 1.43 - 2.12 [2.0]
	50 cm^2 MTS for 8 Hours	0.3 ± 0.2 (60.1) 0.1 - 0.6 [0.2]	2.0 ± 1.1 (54.8) 1.0 - 3.0 [2.0]	20.95 ± 7.04 (33.58) 9.15 - 28.98 [20.9]	8.0 ± 0.00 (0.00) 8.00 - 8.00 [8.0]	103.27 ± 44.67 (43.25) 34.89 - 164.60 [104.7]	154.58 ± 57.30 (37.07) 65.46 - 223.43 [156.9]	156.09 ± 57.43 (36.79) 66.03 - 224.16 [158.4]	1.69 ± 0.17 (10.00) 1.44 - 1.84 [1.7]
	Ratio of 50:37.5 cm^2 MTS	2.6 ± 2.1 (79.8) 1.0 - 5.1 [1.2][b]	1.3 ± 0.8 (61.2) 1.0 - 3.0 [1.0]	1.6 ± 0.68 (43.81) 0.91 - 2.64 [1.3]	1.5 ± 0.65 (44.15) 1.00 - 2.67 [1.3]	1.7 ± 0.91 (54.12) 0.94 - 3.30 [1.3]	1.6 ± 0.79 (47.86) 1.01 - 3.15 [1.4]	1.6 ± 0.76 (46.70) 1.02 - 3.09 [1.4]	1.0 ± 0.27 (27.23) 0.71 - 1.29 [1.0]

a Mean ± S.D. (C.V.%), range, [median]; n = 6

Table 34 *d*-MPH & *l*-MPH Pharmacokinetic Metrics Following Multiple 12 hour Applications (4 days) of ——— ® MTS to Children

Analyte	Treatment or Comparison	C_0 (ng/ml)	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC_{0-8} (ng/ml x hr^{-1})	AUC_{0-t} (ng/ml x hr^{-1})
		5	6	6	6	6	6
d-MPH	37.5 cm^2 MTS for 12 Hours	3.2 ± 0.4 (13.4) 2.4 - 3.7 [3.3]	3.0 ± 0.0 (0.0) 3.0 - 3.0 [3.0]	22.28 ± 5.16 (23.16) 14.13 - 28.88 [22.4]	10.0 ± 1.26 (12.65) 8.0 - 12.0 [10.0]	72.76 ± 23.20 (31.89) 49.00 - 106.40 [64.4]	151.33 ± 38.67 (25.55) 109.58 - 202.21 [135.8]
	50 cm^2 MTS for 12 Hours [b]	3.4 ± 1.0 (29.4) 1.6 - 4.1 [3.8][a]	2.2 ± 1.1 (49.8) 1.0 - 3.0 [3.0] [a]	31.37 ± 8.90 (28.37) 22.21 - 42.21 [31.8]	10.8 ± 1.10 (10.14) 10.0 - 12.0 [10.0]	132.74 ± 54.04 (40.71) 81.22 - 194.80 [117.3]	249.27 ± 85.04 (34.11) 167.29 - 344.98 [199.9]
	Ratio of 50:37.5 cm^2 MTS [b]	1.0 ± 0.2 (20.3) 0.7 - 1.2 [1.1]	0.7 ± 0.4 (49.8) 0.3 - 1.0 [1.0] [a]	1.5 ± 0.42 (27.34) 0.98 - 2.15 [1.5]	1.1 ± 0.12 (11.42) 1.0 - 1.3 [1.0]	2.0 ± 0.64 (32.37) 1.28 - 2.98 [1.8]	1.8 ± 0.55 (30.81) 1.31 - 2.67 [1.7]
l-MPH	37.5 cm^2 MTS for 12 Hours	0.3 ± 0.1 (36.7) 0.2 - 0.4 [0.2]	2.3 ± 1.0 (44.3) 1.0 - 3.0 [3.0]	11.67 ± 3.88 33.23 6.10 - 16.10 [12.4]	9.3 ± 1.03 11.07 8.0 - 10.0 [10.0]	46.27 ± 19.59 42.34 30.01 - 71.80 [36.4]	86.48 ± 30.99 35.83 54.28 - 130.56 [75.7]
	50 cm^2 MTS for 12 Hours [b]	0.3 ± 0.2 (57.6) 0.1 - 0.5 [0.3]	1.8 ± 1.1 (60.9) 1.0 - 3.0 [1.0][a]	18.08 ± 3.45 (19.07) 13.26 - 21.05 [19.9]	7.6 ± 2.51 (33.03) 5.0 - 10.0 [8.0]	81.1 ± 27.96 (34.47) 48.68 - 112.00 [68.2]	140.53 ± 40.09 (28.53) 99.58 - 181.48 [137.0]
	Ratio of 50:37.5 cm^2 MTS [b]	1.1 ± 0.4 (34.5) 0.7 - 1.6 [1.2]	1.0 ± 1.2 (115.5) 0.3 - 3.0 [0.3] [a]	1.8 ± 0.57 (31.49) 1.25 - 2.60 [1.6]	0.8 ± 0.24 (29.54) 0.5 - 1.0 [1.0]	2.1 ± 0.75 (36.36) 1.56 - 3.36 [1.7]	1.9 ± 0.56 (30.08) 1.44 - 2.84 [1.7]

a Mean ± S.D. (C.V.%), range, [median]
b n = 5; One subject's MTS was not removed 12 hours prior to dose on Day 4 of treatment

Table 35 *d,l*-MPH Pharmacokinetic Metrics Following Single or Multiple (4 days) Applications of [redacted]® MTS to Children[a]

Study	Treatment or Comparison	C0 (ng/ml)	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC0-8 (ng/ml x hr^{-1})	AUC0-t (ng/ml x hr^{-1})	AUC0-∞ (ng/ml x hr^{-1})	t1/2 (hours)
n		6		6	6	6	6	6	6
MD (4 days) Study 17-016	37.5 cm^2 MTS for 8 Hours	1.14 ± 0.72 (63.02) 0 - 2.14 [1.16]	1.7 ± 1.0 (62.0) 1.0 - 3.0 [1.0]	36.87 ± 16.64 (45.14) 23.53 - 67.33 [31.9]	7.0 ± 1.55 (22.13) 5.0 - 8.0 [8.0]	159.24 ± 64.19 (40.31) 93.93 - 259.2 [138.4]	301.7 ± 126.3 (41.87) 185.9 - 524.9 [250.4]	321.0 ± 129.8 (40.42) 198.0 - 551.3 [270.5]	2.95 ± 0.36 (12.2) 2.65 - 3.62 [2.9]
	50 cm^2 MTS for 8 Hours	2.8 ± 1.7 (60.8) 0.8 - 5.7 [2.7]	2.0 ± 1.1 (54.8) 1.0 - 3.0 [2.0]	55.32 ± 16.23 (29.34) 26.82 - 71.23 [57.3]	8.0 ± 0.00 (0.00) 8.0 - 8.0 [8.0]	259.6 ± 103.1 (39.74) 92.9 - 400.8 [277.8]	455.9 ± 140.8 (30.89) 216.8 - 609.1 [468.7]	478.2 ± 145.7 (30.46) 231.5 - 621.3 [494.0]	2.72 ± 0.42 (15.47) 2.21 - 3.38 [2.6]
	37.5cm^2 MTS for 12 Hours	3.5 ± 0.5 (13.8) 2.7 - 3.9 [3.6]	3.0 ± 0.0 (0.0) 3.0 - 3.0 [3.0]	33.66 ± 9.38 (27.88) 19.25 - 44.99 [34.8]	9.7 ± 1.51 (15.57) 8.0 - 12.0 [10.0]	119.04 ± 42.60 (35.78) 79.01 - 178.20 [100.4]	237.8 ± 69.4 (29.16) 163.9 - 327.1 [211.0]	—	—
	50 cm^2 MTS for 12 Hours[b]	3.7 ± 1.1 (30.0) 1.8 - 4.7 [4.2][a]	1.8 ± 1.1 (60.9) 1.0 - 3.0 [1.0][a]	47.83 ± 11.56 (24.16) 33.89 - 60.41 [51.7]	9.0 ± 2.24 (24.85) 5.0 - 10.0 [10.0]	213.9 ± 81.5 (38.09) 129.9 - 306.9 [185.1]	389.8 ± 123.4 (31.67) 270.5 - 526.4 [333.5]	—	—
SD Study 17-005	25 cm^2 MTS for 16 hours	—	2.1 ± 0.4 (20.8) 2.0 - 4.0 [2.0]	33.8 ± 10.2 (30.1) 13.4 – 57.8 [33.2]	9.8 ± 1.6 (15.9) 7.9 – 12.0 [10.0]	—	333.2 ± 113.5 (34.1) 110.8 – 647.0 [312.1][c]	—	—

a Mean ± S.D. (C.V.%), range, [median]
b n = 5
c AUC0-t = AUC0-16

Table 36 ***d*-MPH, *l*-MPH, and *d,l*-MPH Dose Normalized Pharmacokinetic Metrics Following Multiple 8 and 12 hour Applications (4 days) of MethyPatch® MTS to Children[a,b]**

MTS Strength (mg / cm^2)	Analyte	8 hour Applications x 4 days			12 hour Applications x 4 days		
		Cmax (ng/ml / mg/kg)	AUC0-8 (ng/ml x hr^{-1} / mg/kg)	AUC0-∞ (ng/ml x hr^{-1} / mg/kg)	Cmax (ng/ml / mg/kg)	AUC0-8 (ng/ml x hr^{-1} / mg/kg)	AUC0-t (ng/ml x hr^{-1} / mg/kg)
82.5 / 37.5	n	6.0	6.0	6.0	6.0	6.0	6.0
	d-MPH	66.2 ± 8.4 (12.7) 56.2 - 78.4 [66.5]	271.7 ± 24.1 (8.9) 246.4 - 311.2 [270.1]	649.1 ± 98.8 (15.2) 531.9 - 810.1 [653.1]	58.5 ± 10.0 (17.1) 52.0 - 77.3 [53.7]	193.6 ± 63.9 (33.0) 131.8 - 314.6 [172.5]	401.1 ± 98.9 (24.7) 342.1 - 597.9 [359.3]
	l-MPH	43.1 ± 9.0 (20.8) 33.6 - 55.3 [40.5]	192.9 ± 26.0 (13.5) 152.7 - 217.8 [196.7]	300.7 ± 44.5 (14.8) 222.1 - 349.8 [313.6]	30.4 ± 8.3 (27.4) 21.5 - 44.2 [30.2]	121.7 ± 48.5 (39.9) 80.7 - 212.3 [110.4]	225.5 ± 65.9 (29.2) 169.0 - 351.2 [199.5]
	d,l-MPH	107.7 ± 18.0 (16.7) 81.2 - 126.9 [112.2]	464.7 ± 33.9 (7.3) 402.3 - 495.6 [471.0]	945.4 ± 123.8 (13.1) 753.6 - 1119.5 [972.4]	87.9 ± 18.9 (21.5) 70.8 - 121.5 [83.9]	315.3 ± 111.6 (35.4) 212.5 - 526.9 [287.2]	626.6 ± 162.2 (25.9) 511.1 - 949.1 [578.7]
110 / 50	n	6.0	6.0	6.0	5.0	5.0	5.0
	d-MPH	75.8 ± 14.1 (18.6) 58.8 - 101.2 [72.2]	332.1 ± 77.8 (23.4) 259.7 - 448.3 [299.6]	706.0 ± 71.5 (10.1) 619.9 - 822.2 [693.9]	67.3 ± 8.9 (13.2) 55.5 - 78.1 [70.4]	282.9 ± 83.6 (29.6) 189.6 - 402.1 [293.3]	532.6 ± 108.1 (20.3) 435.4 - 697.0 [499.8]
	l-MPH	44.8 ± 5.1 (11.4) 37.7 - 50.4 [44.7]	213.9 ± 43.5 (20.3) 156.1 - 286.1 [204.3]	329.6 ± 34.0 (10.3) 295.3 - 389.7 [319.3]	39.4 ± 4.8 (12.2) 33.2 - 44.1 [42.0]	173.3 ± 37.9 (21.9) 130.9 - 231.2 [169.6]	302.0 ± 46.6 (15.4) 249.0 - 374.6 [303.6]
	d,l-MPH	120.3 ± 17.7 (14.7) 96.4 - 151.4 [118.8]	546.0 ± 115.8 (21.2) 415.7 - 696.7 [499.6]	1031.1 ± 86.8 (8.4) 918.7 - 1168.5 [1023.3]	103.4 ± 12.4 (12.0) 84.7 - 114.8 [101.7]	456.2 ± 120.2 (26.3) 340.6 - 633.4 [462.8]	834.6 ± 147.4 (17.7) 727.4 - 1071.6 [748.7]

a Mean ± S.D. (C.V.%), range, [median]
Values calculated by taking reported pharmacokinetic metrics and dividing by mg/kg dose actually administered. Amount of dose obtained from amount of drug depleted from patches.

6.6 DRUG DELIVERY RATE

The sponsor's claimed drug delivery rate in mg/hr for various size patches are shown in Table 37.

Table 37 Sponsor's Claimed Methypatch Steady-State Drug Delivery Rate[a]

Methypatch Strength (mg / cm^2)	Sponsor's Claimed Drug Delivery Rate (mg/hr)	Approximate Total Methylphenidate Delivered over — Hours to Children	Approximate Total Methylphenidate Delivered over — Hours to Older Children

6.6.1 IN VIVO – DRUG DELIVERY RATE

6.6.1.1 Children – Study 17-016

Table 38 Mean Drug Delivery Rates via the Hip on Day 4 of Treatment from Multiple Dose Study 17-006 in Children[a]

Patient Group[b]	Patch Size	Application Duration	n	Dose Delivered (mg)	Delivery Rate (mg/hour)	Delivery Rate (mg/hr/cm^2)	Dose Delivered (%)
1	37.5 cm^2	8 Hours	6	26.1 ± 5.8 (22.2) 18.5 - 33.5	3.3 ± 0.7 (22.2) 2.3 - 4.2	0.087 ± 0.019 (22.2) 0.062 - 0.112	32.9 ± 7.3 (22.2) 23.3 - 42.2
1	50 cm^2	8 Hours	6	35.7 ± 6.8 (19.2) 25.8 - 43.3	4.5 ± 0.9 (19.2) 3.2 - 5.4	0.089 ± 0.017 (19.2) 0.065 - 0.108	34.3 ± 6.6 (19.2) 24.8 - 41.6
2	37.5 cm^2	12 Hours	6	32.8 ± 5.3 (16.1) 26.7 - 39.3	**2.7 ± 0.4** **(16.1)** **2.2 - 3.3**	0.073 ± 0.012 (16.1) 0.059 - 0.087	41.3 ± 6.6 (16.1) 33.6 - 49.5
2	50 cm^2	12 Hours	6	44.0 ± 10.0 (22.8) 26.7 - 56.3	3.7 ± 0.8 (22.8) 2.2 - 4.7	0.073 ± 0.017 (22.8) 0.045 - 0.094	42.3 ± 9.7 (22.8) 25.7 - 54.1

a Mean ± S.D. (%C.V.) Minimum - Maximum
b Group 1: Subjects 101, 102, 104, 108, 109, 112; Group 2: Subjects 103, 105, 106, 107, 110, 111

6.6.1.2 Adults – Study 17-014

Table 39 Calculation of Transdermal Drug Delivery Rates via application of a 25 cm^2 MTS to the Hip for 16 hours in Adults – Data from Study 17-014

mg Delivered / 32 hours (2 applications)	Mean mg/hr over 2 applications over 32 hours	AUC_{0-16}			% AUC		mg delivered		mg/hr		mg/hr/cm^2	
		Day 1	Day 2	Day 1+2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
27.4 ± 4.6 (16.8) 22.6 - 34.8 [25.45]	0.86 ± 0.14 (16.8) 0.71 - 1.09 [0.80]	94.82 ± 14.78 (15.6) 79.15 - 114.47 [89.4]	44.29 ± 11.19 (25.3) 35.64 - 66.05 [40.93]	139.11 ± 14.42 (10.4) 122.22 - 156.02 [138.40]	68.1 ± 7.0 (10.2) 57.7 - 75.9 [67.5]	31.9 ± 7.0 (21.8) 24.1 - 42.3 [32.5]	18.6 ± 3.2 (17.0) 14.6 - 23.7 [18.4]	8.8 ± 3.0 (34.0) 6.2 - 14.7 [7.9]	**1.2 ± 0.2** **(17.0)** **0.9 - 1.5** **[1.2]**	**0.6 ± 0.2** **(34.0)** **0.4 - 0.9** **[0.5]**	0.047 ± 0.008 (17.0) 0.037 - 0.059 [0.046]	0.022 ± 0.008 34.0 0.016 - 0.037 [0.02]

a Mean ± S.D. (C.V.%), range, [median]

6.6.2 *IN VITRO – DRUG DELIVERY RATE*

According to the sponsor approximately 7.5 mg of methylphenidate was released from a 27.4 mg / 10.0 cm^2 system over 24 hours in a human cadaver skin model. Details were not provided as to age, sex, site or thickness of skin, nor were *in vitro - in vivo* correlations performed. The *in vitro* delivery period was 24 hours which is at least twice as long as the *in vivo* application time. The degree of drug depletion from the Methypatch system is so great *in vivo* that even after only 12 hours that drug delivery follows first-order kinetics rather than the desired pseudo-zero order kinetics. Due to all of these factors, the *in vitro* data cannot be used as a surrogate for the *in vivo* delivery rate. In fact the sponsor's *in vitro* delivery rate is less than half the claimed *in vivo* rate in children, although it is similar to the mean *in vivo* rate in adults, (see Table 40). This may be due partially due to the more similar application periods.

Table 40 Comparison of Sponsor's Claimed *In Vitro* and *In Vivo* Delivery Rates

	In Vitro	*In Vivo in Adults*	*In Vivo in Children*		
			Actual	*Nominal*	
Amount Delivered (mg)	7.5	27.5	32.8	10	30
Patch Size (cm^2)	10	25	37.5	12.5	37.5
Delivery Period (hours)	24	32	12	12	
Delivery Rate (mg / hr / cm^2)	**0.03125**	**0.0345**	**0.073**	**0.067**	

7 CLINICAL PHARMACOLOGY

7.1 PHARMACOKINETICS / PHARMACODYNAMICS

7.1.1 EUPHORIA AND DYSPHORIA

In study 17-007 the sponsor evaluated possible pharmacokinetic-pharmacodynamic relationships between plasma levels of MPH feelings of dysphoria and euphoria by correlation analysis of the AUC for *d*-MPH, the more active entaniomer, vs. the area under the effect curves, (AUEC), for euphoria and dysphoria. Pharmacodynamic effects for euphoria and dysphoria were measured by the Drug Rating Questionnaire Subject (DRQS) pre-dose and then at 1, 2, 3, 4, 5, 6, 9, 12, 15, and 24 hours after study drug administration.

Methylphenidate was administered to drug addicts as single doses of 3 or 6 MTS applied to the back and 25 mg or 50 mg of methylphenidate administered subcutaneously.

The relationship between Cmax for *d*-MPH and *l*–MPH and euphoria and dysphoria was evaluated for both MTS and subcutaneous methylphenidate by comparing mean Cmaxs by dose and method of administration with the presence or absence of euphoria and dysphoria.

There was no correlation between AUEC for euphoria or dysphoria and *d*-MPH AUC (see Figure 19 and Figure 20). This is not totally unexpected as we would expect euphoria and dysphoria would be better correlated with peak concentrations and rate of rise in concentration.

In contrast there are higher mean Cmaxs for both *d*-MPH and *l*–MPH in subjects administered MPH via MTS who experience euphoria and dysphoria as compared with those who didn't experience euphoria or dysphoria. Although, there is a great deal of overlap in the range of Cmaxs observed in those who did and didn't experience euphoria or dysphoria, (see Figure 21 and Figure 22).

When we look at mean Cmaxs for both *d*-MPH and *l*–MPH in subjects administered MPH subcutaneously it's not readily apparent at first glance that there's any relationship between Cmax and euphoria or dysphoria. However, upon close inspection we see that no subject had dysphoria with the 25 mg dose, whereas 7/19 (58%) of subjects had dysphoria with the 50 mg SC dose. In addition a greater percentage of subjects had euphoria with the 50 mg SC dose (14/19; 73%) as compared with the lower 25 mg SC dose (8/19; 42%), (see Figure 23 and Figure 24).

The high degree of overlap in Cmaxs seen in subjects who experienced euphoria and those who experienced dysphoria with MTS application might be partially due to using subjects who were stimulant abusers, as tolerance can develop, and the degree of tolerance can be related to the degree of prior abuse. Thus the concentration effect relationships can be quite different between different stimulant abusers. In addition, intermittent (i.e. binge) abusers might be more susceptible to the euphoric as well as other effects at similar or even lower concentrations. These results indicate that stimulant abusers can use transdermal administration as another route of abuse, possibly for a prolonged high.

However, when the time courses of euphoria and dysphoria are examined, they tend to follow the plasma concentration profiles no matter the route of administration.

Note that the number of subjects experiencing (or degree of – MBG Score) euphoria is greater with subcutaneous administration, and the number of subjects (or degree of - LSD score) experiencing dysphoria is greater with the transdermal formulation. Indicating that although the transdermal formulation has a potential for direct abuse, the risk may be less with direct application of the patch itself and instead extraction of drug from the patch is likely to be preferred. Especially as extraction is likely to be easy and should only take a couple of hours, (see Figure 25 to Figure 27)

Differences in apathetic sleepiness (PCAG Score) are statistically significant, however as the method as to how this score is derived was not available to the reviewer, the clinical significance can not be assessed for this review, (see Figure 26).

It should be noted however that since stimulant abusers were used in this study lower methylphenidate doses might result in a similar or greater degree of euphoria and/or dysphoria in non-abusers.

Figure 19 AUEC for Euphoria vs. *d*-MPH AUC for MTS and SC Methylphenidate

FIGURE 11. RELATIONSHIP BETWEEN AREA UNDER THE EUPHORIA CURVE AND AREA UNDER THE PLASMA CONCENTRATION VS. TIME CURVE FOR *D*-MPH FOR 3 AND 6 MTS (N=12)

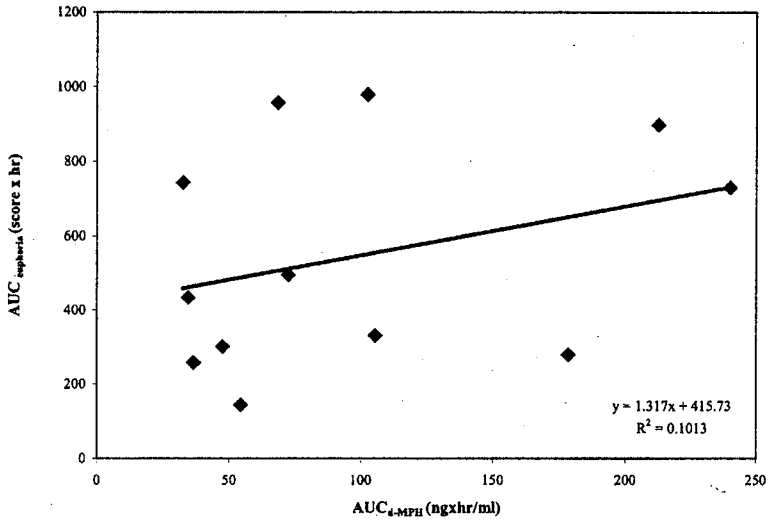


FIGURE 12. RELATIONSHIP BETWEEN AREA UNDER THE EUPHORIA CURVE AND AREA UNDER THE PLASMA CONCENTRATION VS. TIME CURVE FOR *D*-MPH FOR 25 AND 50 MG SC MPH (N=22)

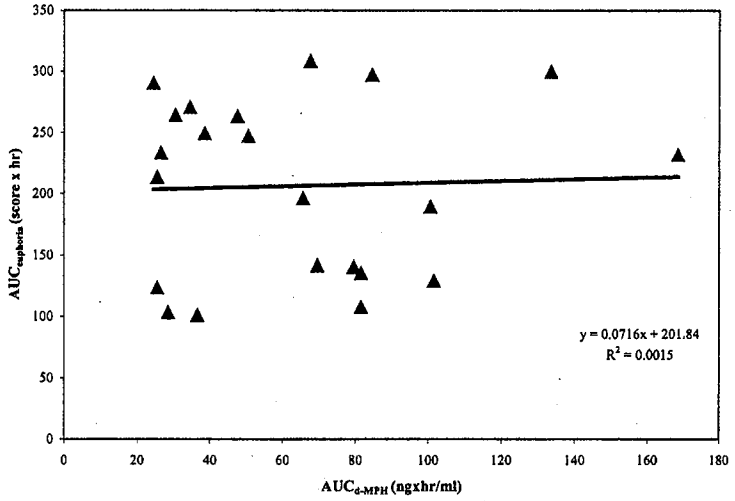


Figure 20 AUEC for Dysphoria vs. *d*-MPH AUC for MTS and SC Methylphenidate

FIGURE 19. RELATIONSHIP BETWEEN AREA UNDER THE DYSPHORIA CURVE AND AREA UNDER THE PLASMA CONCENTRATION VS. TIME CURVE FOR *D*-MPH FOR 3 AND 6 MTS (N=14)

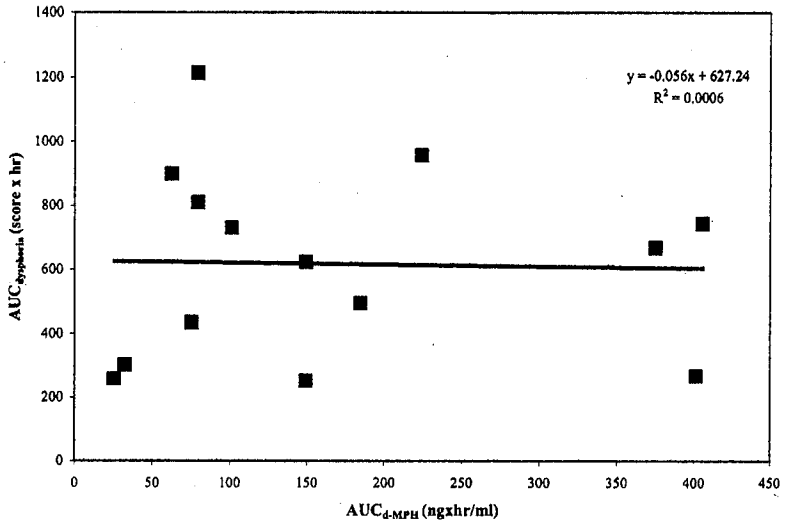


FIGURE 20. RELATIONSHIP BETWEEN AREA UNDER THE DYSPHORIA CURVE AND AREA UNDER THE PLASMA CONCENTRATION VS. TIME CURVE FOR *D*-MPH FOR 25 AND 50 SC MPH (N=7)

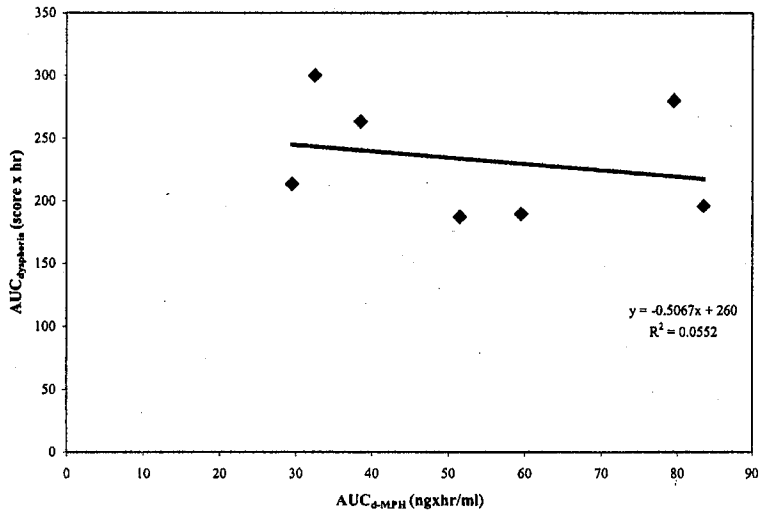


Figure 21 *d*-MPH & *l*-MPH Cmax vs. Euphoria for MTS

FIGURE 14. RELATIONSHIP BETWEEN EUPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH DURING 24-HOUR APPLICATION OF 3 MTS (N=19)

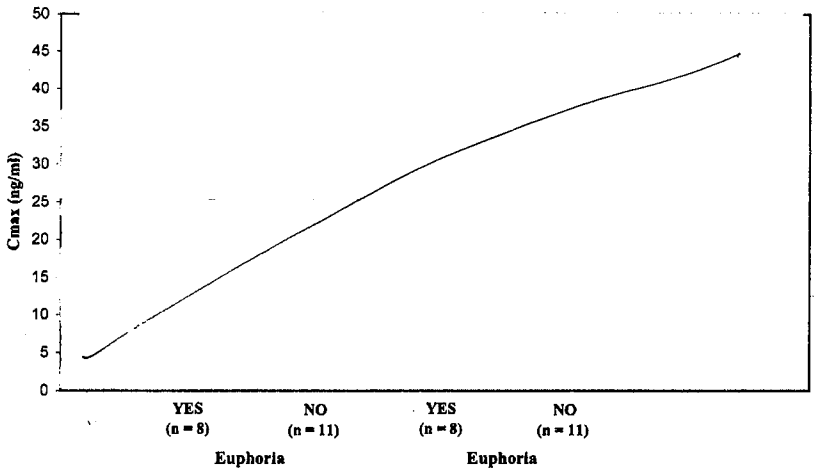


FIGURE 15. RELATIONSHIP BETWEEN EUPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH DURING 24-HOUR APPLICATION OF 6 MTS (N=19)

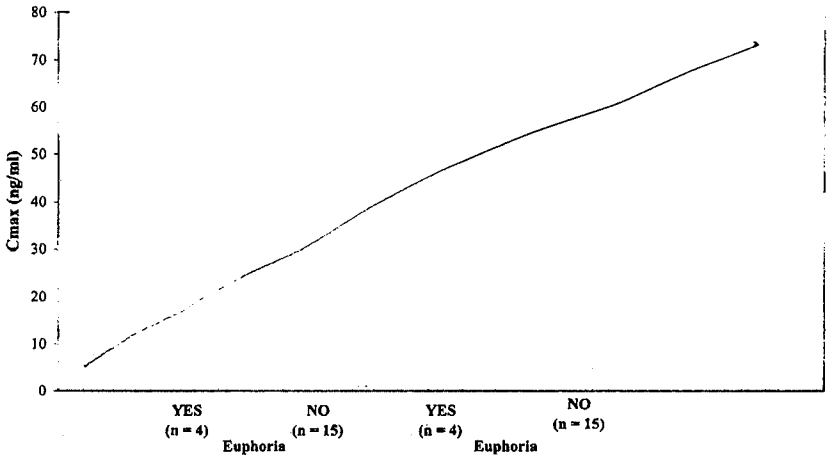


Figure 22 *d*-MPH & *l*-MPH Cmax Vs Dysphoria for MTS

FIGURE 21. RELATIONSHIP BETWEEN DYSPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH DURING 24-HOUR APPLICATION OF 3 MTS (N=19)

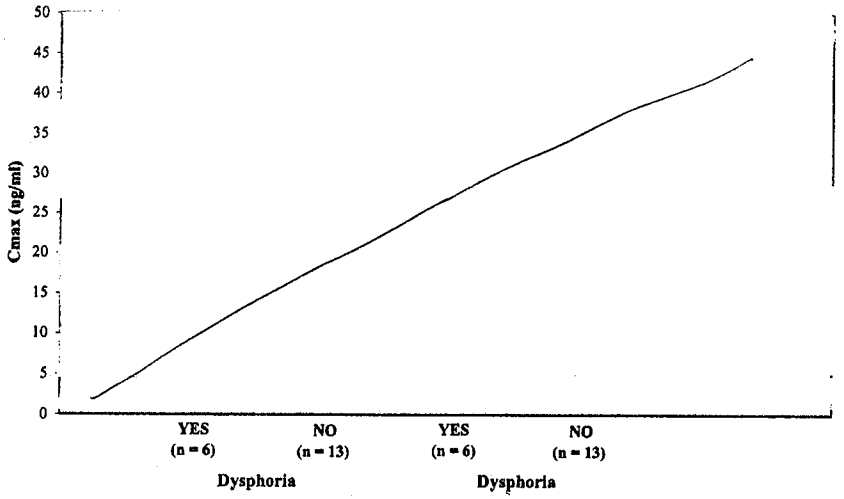


FIGURE 22. RELATIONSHIP BETWEEN DYSPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH DURING 24-HOUR APPLICATION OF 6 MTS (N=19)

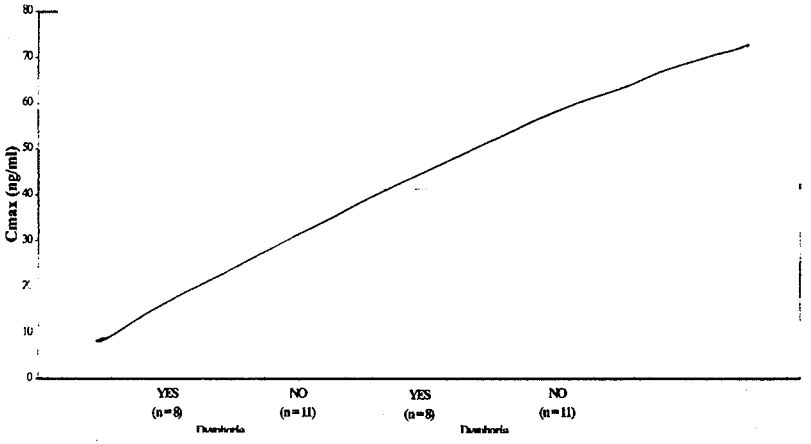


Figure 23 *d*-MPH & *l*-MPH Cmax Vs Euphoria for SC Methylphenidate

FIGURE 16. RELATIONSHIP BETWEEN EUPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH AFTER SC ADMINISTRATION OF 25 MG METHYLPHENIDATE (N=19)

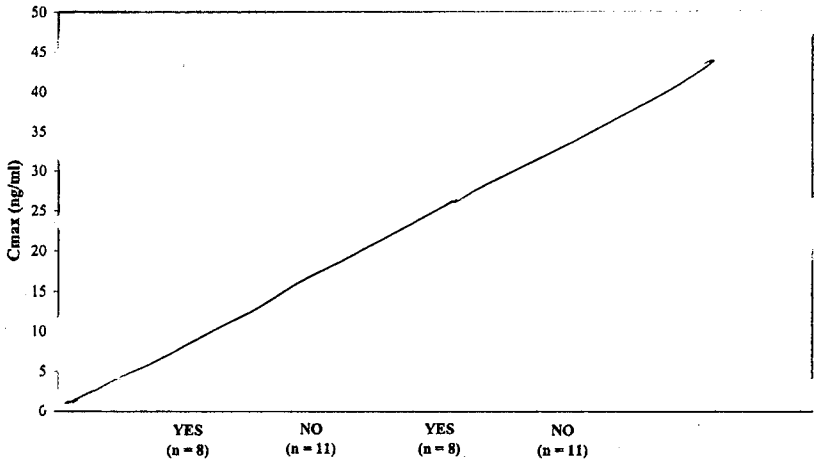


FIGURE 17. RELATIONSHIP BETWEEN EUPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH AFTER SC ADMINISTRATION OF 50 MG METHYLPHENIDATE (N=19)

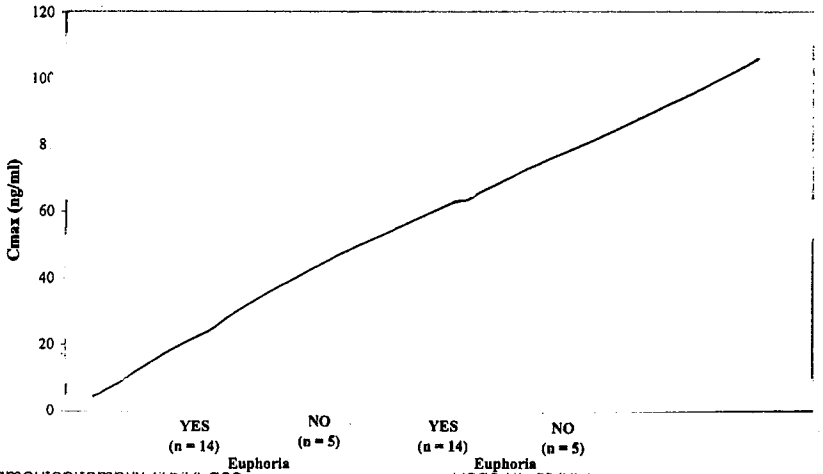


Figure 24 *d*-MPH & *l*-MPH Cmax vs. Dysphoria for SC Methylphenidate

FIGURE 23. RELATIONSHIP BETWEEN DYSPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH AFTER SC ADMINISTRATION OF 25 MG METHYLPHENIDATE (N=19)

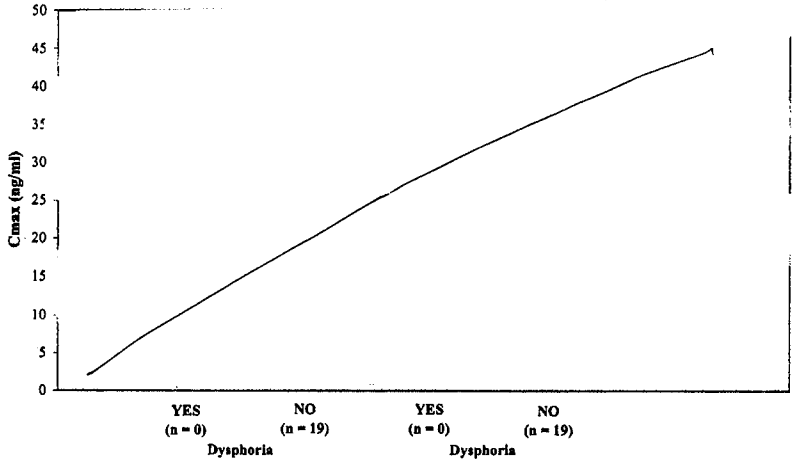


FIGURE 24. RELATIONSHIP BETWEEN DYSPHORIA AND INDIVIDUAL AND MEAN CMAX VALUES OF *D*-MPH AND *L*-MPH AFTER SC ADMINISTRATION OF 50 MG METHYLPHENIDATE (N=19)

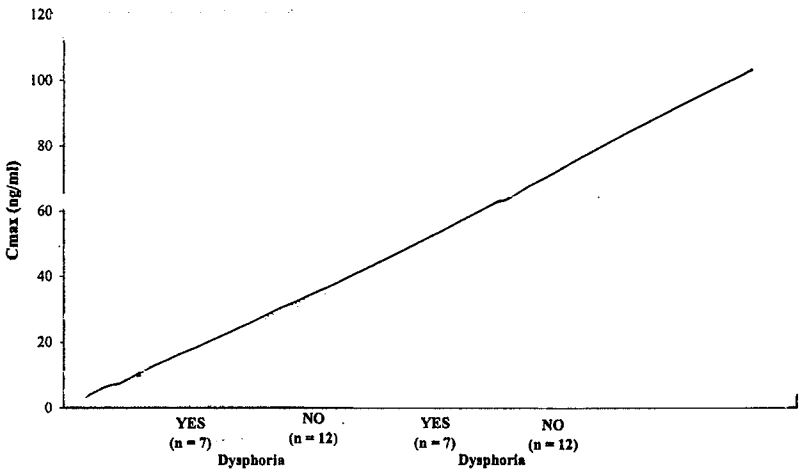


Figure 25 **Drug Response Questionnaire Subject (DRQS) Question Mean Response vs. Time for Subcutaneous and Transdermal Methylphenidate, Oral Phenteramine and Placebo**

NOVEN PROTOCOL 017-007, PART 2
DRUG RESPONSE QUESTIONAIRE SUBJECTS
MEAN RESPONSE OVER TIME

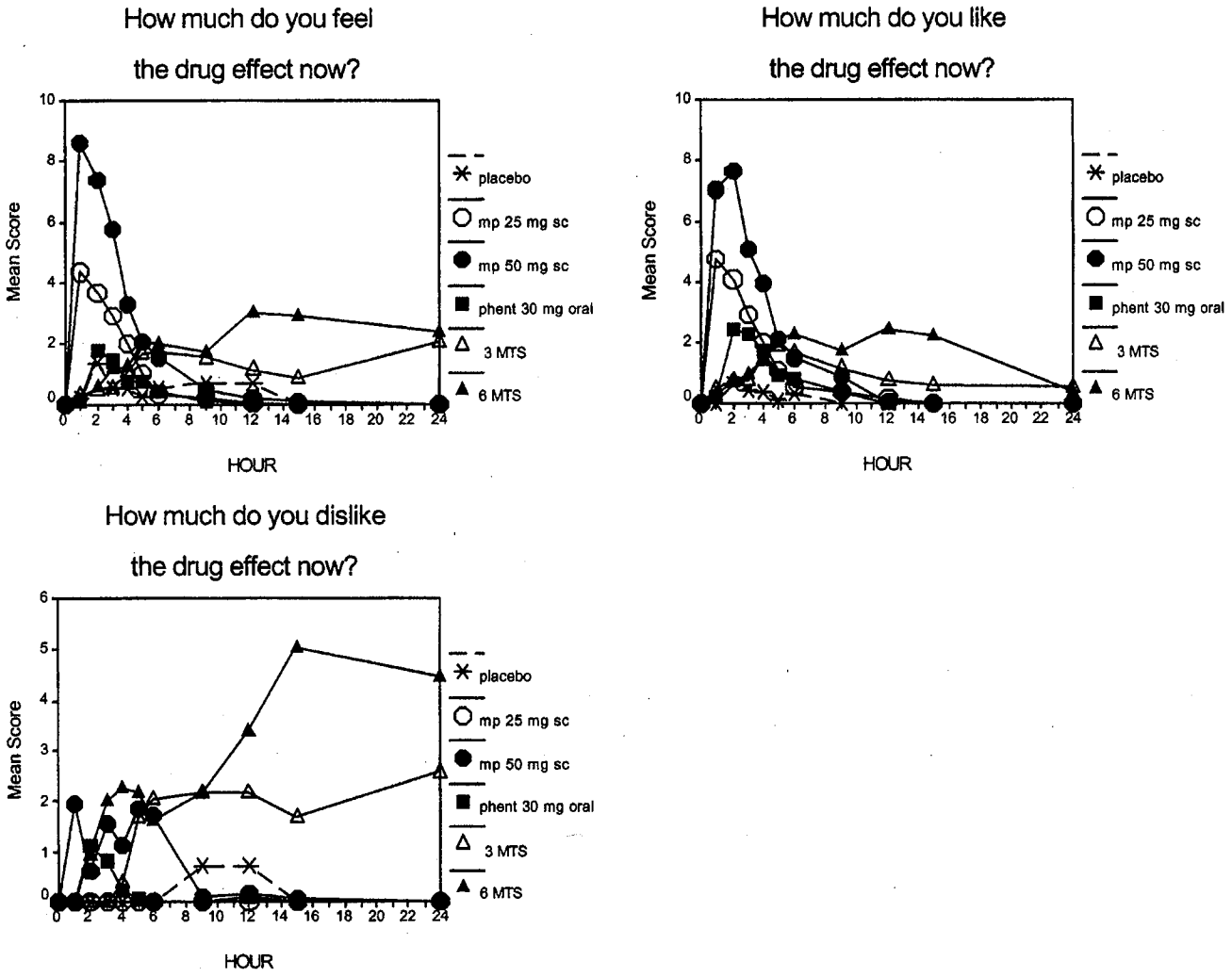


Figure 26 Addiction Research Center (ARCI) Scales Mean Response vs. Time for Subcutaneous and Transdermal Methylphenidate, Oral Phenteramine and Placebo

NOVEN PROTOCOL 017-007, PART 2

ADDICTION RESEARCH CENTER (ARCI) SCALES

MEAN RESPONSE OVER TIME

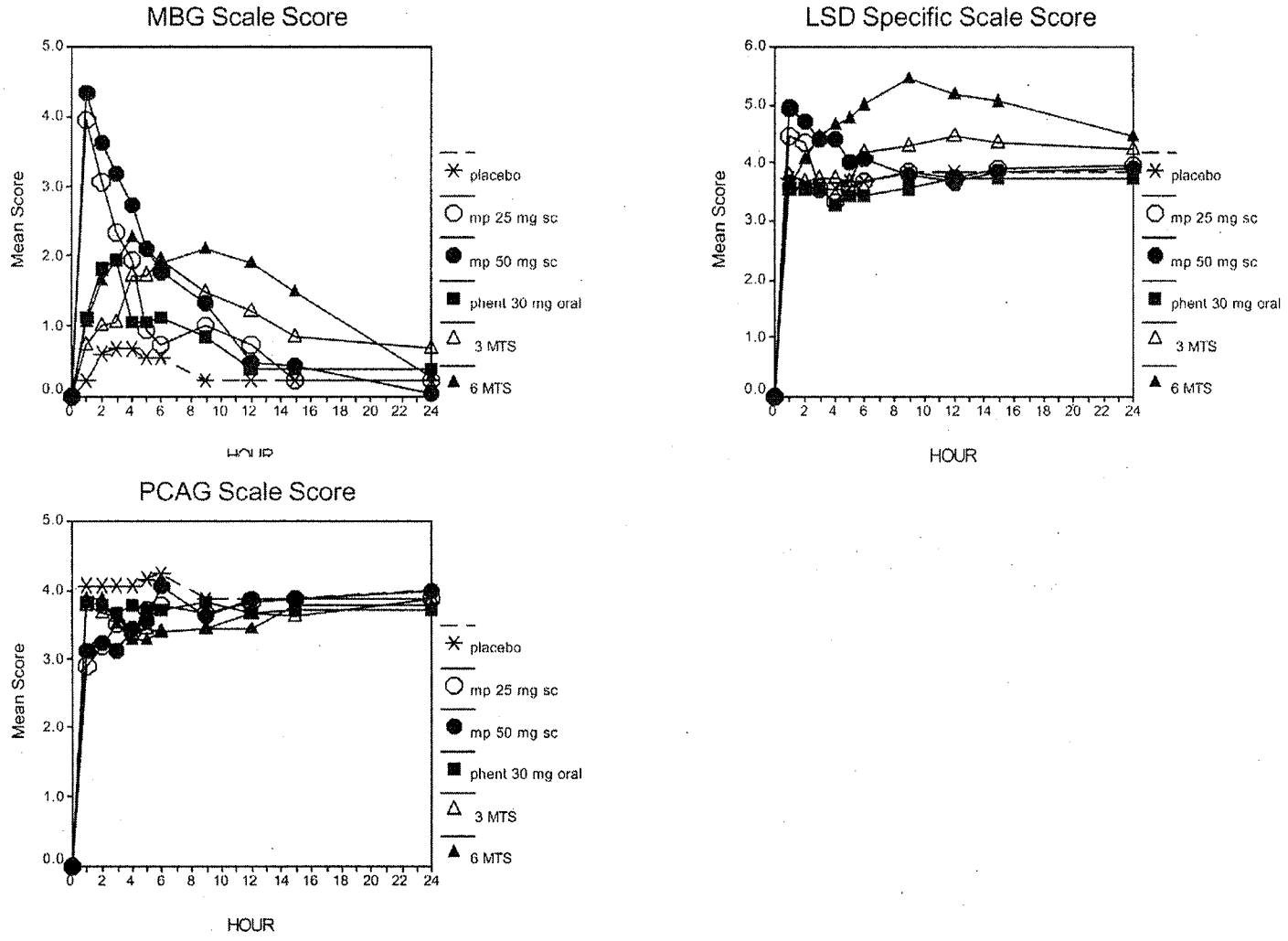
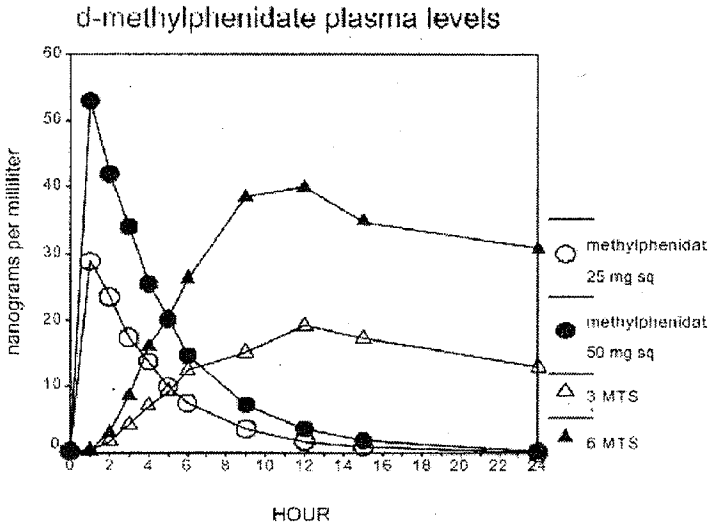
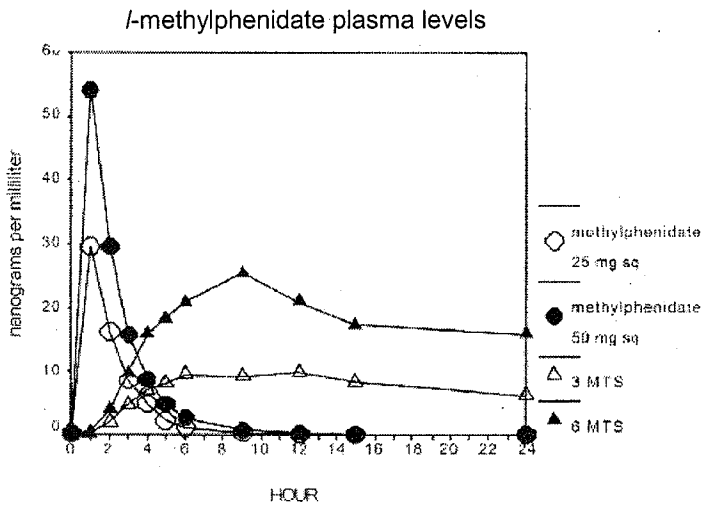
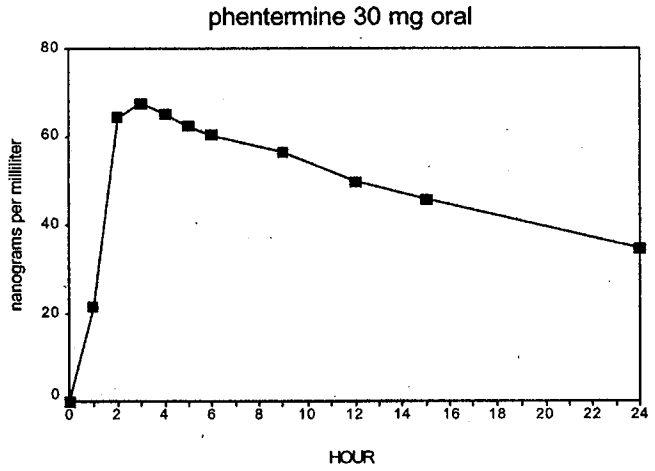


Figure 27 Mean *d*-MPH, *l*-MPH and Phenteramine Plasma Concentrations vs. Time Profiles for PK/PD study 17-007







7.1.2 BLOOD PRESSURE AND PULSE RATE

In study 17-007, in addition to evaluating the PK-PD relationship with euphoria and dysphoria in adult drug abusers, the sponsor also evaluated the pharmacodynamic effect on blood pressure.

Supine and standing BP and HR were monitored pre-dose (within 30 minutes of study drug administration) and then at 1, 2, 3, 4, 5, 6, 9, 12, 15, and 24 hours after study drug administration. Respiratory rate and tympanic temperature were also monitored at these times but only in the supine position.

All blood pressure (BP) measurements were taken on the same arm each time, using the same calibrated, automated, non-invasive BP monitor (if the circumference of the arm is above 32 cm, a large cuff was used). Systolic and diastolic pressures were determined from the phase I and V Korotkoff sounds. At screening BP, heart rate (HR), respiratory rate (RR), and tympanic temperature were obtained after the subject had been in the supine position for 5 minutes. BP and HR measurements were repeated after the subject had been standing for 2.5 minutes.

There were clear and substantial elevations in systolic and diastolic blood pressure, and pulse rate. Mean systolic pressures were as much as 35 mmHg higher than with placebo, and pulse rate was as much as 30 bpm higher. However, these elevations occurred with the application of eight 25 cm^2 MTS and the lowest dose was three MTS, (see Figure 28, Figure 29 and Figure 30). Thus the degree of elevation in blood pressure and pulse rate that will be seen with clinical dosing is unclear.

7.1.3 SLEEP

On the days during both parts of the study when study medication was given, an observer recorded each subjects sleep every half-hour between 1800 hours and 0600 hours (6 p.m. to 6 a.m.) on a sleep log form. The subjects were also asked to estimate the number of hours they slept.

The number of hours the subjects slept as judged by the subject and an observer are shown in Table 41.

Table 41 Mean (± SE) Hours of Slept as Judged by Subject and Observer

Rater	Placebo	MPH 25 SC	MPH 50 SC	3 MTS	6 MTS	Phenteramine
Subject	5.3 ± 0.4	4.9 ± 0.4	4.5 ± 0.4	2.8 ± 0.4*	1.6 ± 0.4*	4.2 ± 0.4*
Observer	5.8 ± 0.4	5.6 ± 0.4	5.1 ± 0.4	2.9 ± 0.4*	1.1 ± 0.4*	4.8 ± 0.4*

* $p < 0.05$ vs. placebo

These results are consistent with the pharmacokinetic profiles observed, and raise questions as to if other adverse effects such as appetite suppression might exhibit a higher incidence with this formulation due to sustained plasma concentrations.

Figure 28 Change in Systolic BP with MTS and SC Methylphenidate

FIGURE 26. AVERAGE CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE AFTER MTS

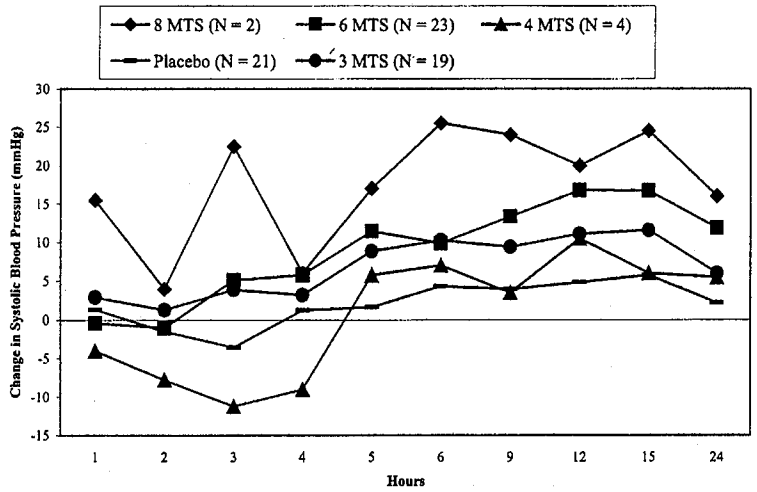


FIGURE 27. AVERAGE CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE AFTER MPH AND PHENTERMINE

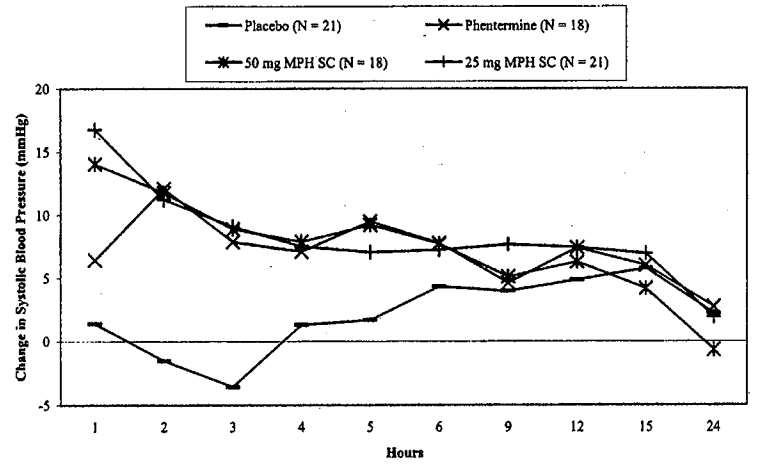


Figure 29 Change in Diastolic BP with MTS and SC Methylphenidate

FIGURE 28. AVERAGE CHANGE FROM BASELINE IN DIASTOLIC BLOOD PRESSURE AFTER MTS

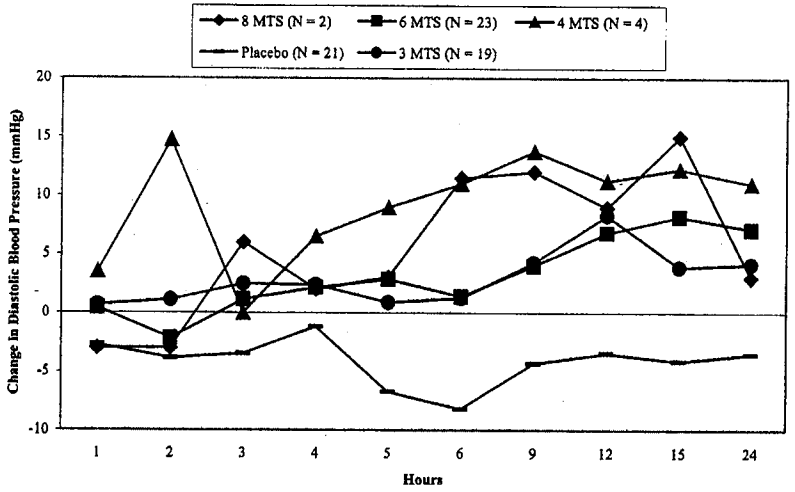


FIGURE 29. AVERAGE CHANGE FROM BASELINE IN DIASTOLIC BLOOD PRESSURE AFTER MPH AND PHENTERMINE

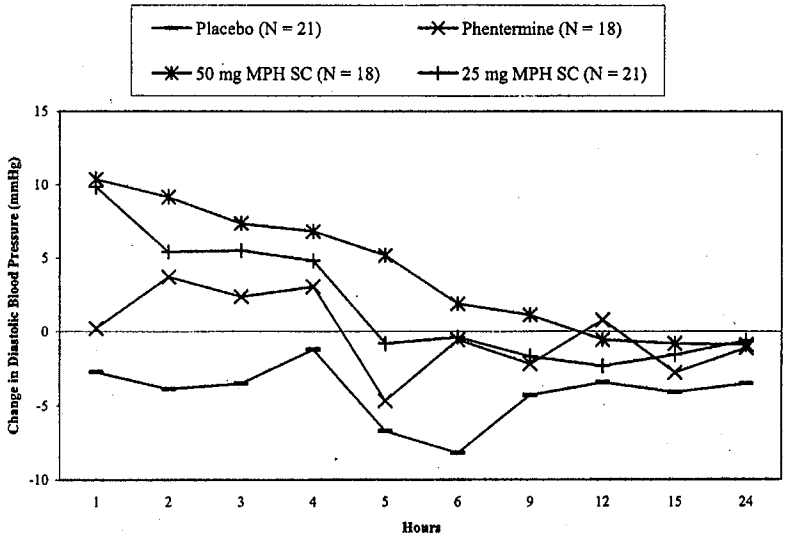


Figure 30 Change in Pulse Rate after MTS and Subcutaneous Methylphenidate

FIGURE 30. AVERAGE CHANGE FROM BASELINE IN PULSE RATE AFTER MTS

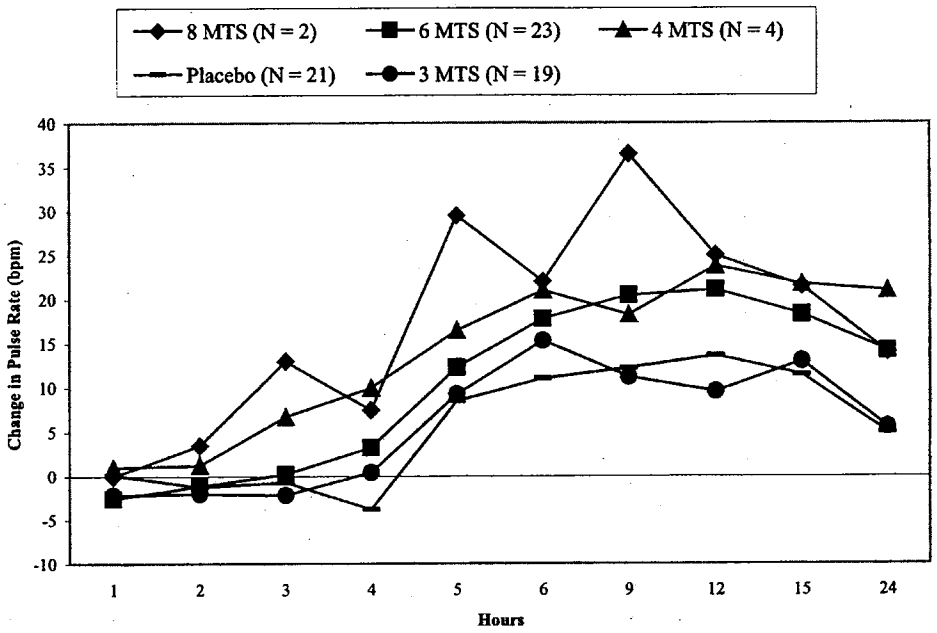
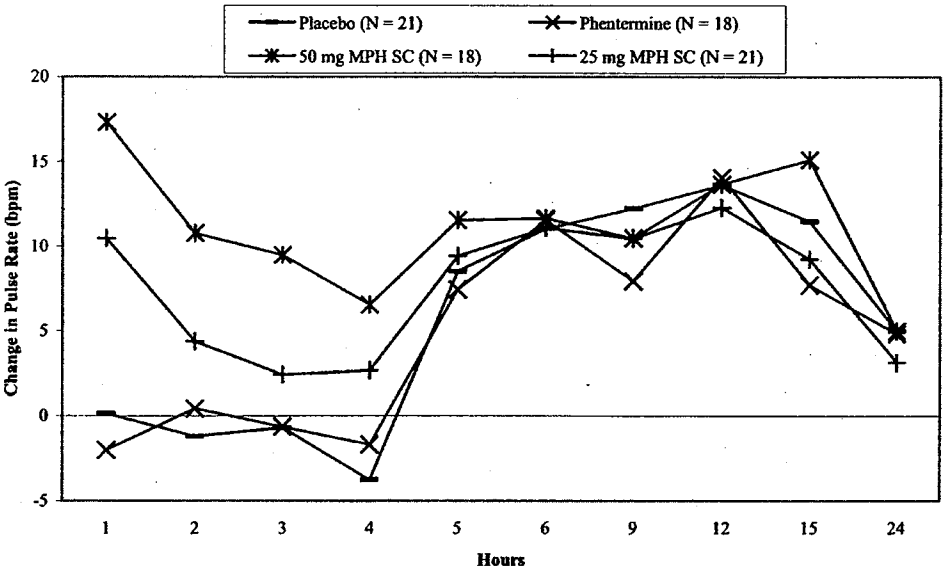


FIGURE 31. AVERAGE CHANGE FROM BASELINE IN PULSE RATE AFTER MPH AND PHENTERMINE



7.2 DERMAL EFFECTS

Skin irritation, adhesiveness, and adhesive residue was assessed in multiple dose study 17-006. This study had the largest number of subjects (n = 29) for the greatest number of days (6 days).

7.2.1 SKIN IRRITATION

Skin irritation was assessed by evaluation of 4 parameters: edema, erythema, 'other signs of irritations' (i.e. papules and vesicles), and discomfort.

In the event that more than one evaluator was required to follow the subject through the trial, then every precaution was taken to limit the number of evaluators to two.

Each day, study personnel examined the application sites for the presence or absence of primary skin reactions and other signs of skin irritations in the area surrounding the transdermal systems at 0 (pre-dose), and at 2, 4, 8, 12 and 16 hours post-application. At 17, 24 and 28 hours post-application, both the area surrounding and the area under the systems were evaluated.

It should be noted that the incidence of skin irritation under clinical use is likely higher as patients will be wearing patches for longer than 6 days, and patches larger than the 25 cm^2 used in this study will be used in practice.

7.2.1.1 Edema

Edema was graded using the following scale:

Score	Definitions
0	No edema (swelling)
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area well-defined by definite raising)
3	Moderate edema (raised approximately 1 mm)
4	Severe edema (raised more than 1 mm and extended beyond the area of exposure)
9	System not present

No edema was observed in study 17-006.

7.2.1.2 Erythema

Erythema was graded using the following scale:

Score	Definitions
0	No erythema (redness)
1	Very slight erythema (barely perceptible)
2	Well-defined erythema (slight, definite margins)
3	Moderate erythema (obliteration of margins)
4	Severe erythema (beet redness spreading beyond margins) to slight eschar formation (injuries in depth)
9	System not present

Erythema was the most common dermal adverse event.

As shown in Table 42 well defined erythema was only observed in less than 7% of subjects. However, very slight erythema was visible by the end of the first day in a quarter of subjects and by the 5th day

some erythema was visible in 50% of subjects. The time course of erythema post removal suggests that the erythema persists at least until the following day. It's interesting to note that there appears to be a trend for erythema to be present earlier in the day and in a greater number of subjects as the study progresses. This might due to erythema persisting from the previous day and / or due to sensitization.

Table 42 Percent of Subjects vs. Time Exhibiting Erythema with 25 cm^2 MTS Applied Daily to the Hips for 16 Hours for 6 Days – Study 17-006

Day	Erythema Scale	% of Subjects (or Time) Reporting								
Hour		0	2	4	8	12	16	17	24	28
1	0	100.0	100.0	100.0	100.0	100.0	76.7	76.7	86.7	96.7
	1	0.0	0.0	0.0	0.0	0.0	**23.3**	**23.3**	**13.3**	**3.3**
2	0	100.0	96.7	93.3	93.3	80.0	76.7	86.7	96.7	93.3
	1	0.0	**3.3**	**6.7**	**6.7**	**20.0**	**23.3**	**13.3**	**3.3**	**6.7**
3	0	100.0	100.0	100.0	100.0	100.0	93.3	93.3	80.0	90.0
	1	0.0	0.0	0.0	0.0	0.0	**6.7**	**6.7**	**20.0**	**10.0**
4	0	100.0	100.0	100.0	86.7	90.0	96.7	66.7	93.3	93.3
	1	0.0	0.0	0.0	**13.3**	**10.0**	**3.3**	**26.7**	**6.7**	**6.7**
	2	0.0	0.0	0.0	0.0	0.0	0.0	**6.7**	0.0	0.0
5	0	83.3	80.0	66.7	60.0	70.0	46.7	46.7	70.0	80.0
	1	**16.7**	**20.0**	**33.3**	**36.7**	**30.0**	**50.0**	**50.0**	**30.0**	**20.0**
	2	0.0	0.0	0.0	**3.3**	0.0	**3.3**	**3.3**	0.0	0.0
6	0	73.3	80.0	86.7	96.7	100.0	56.7	66.7	86.7	90.0
	1	**23.3**	**16.7**	**13.3**	**3.3**	**0.0**	**43.3**	**33.3**	**13.3**	**10.0**
	2	**3.3**	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0

APPEARS THIS WAY
ON ORIGINAL

7.2.1.3 Other Signs of Irritation

Other signs of irritation included the presence of papules or vesicles and they were rated as follows.

Papules (pimples) 0 = No 1 = Yes 9 = System not present
Vesicles (blisters) 0 = No 1 = Yes 9 = System not present

As shown by Table 43 the incidence of papules or vesicles was less than 3% per day.

Table 43 Percent of Subjects Exhibiting Papules or Vesicles for 25 cm^2 MTS Applied Daily to the Hips for 16 Hours for 6 Days – Study 17-006

Day	Irritation Scale	% of Subjects (or Time) Reporting								
Hour		0	2	4	8	12	16	17	24	28
1	0	100	100	100	100	100	100	100	100	100
	1	0	0	0	0	0	0	0	0	0
2	0	100	100	100	100	100	100	100	100	100
	1	0	0	0	0	0	0	0	0	0
3	0	100	100	100	100	100	100	100	96.7	96.7
	1	0	0	0	0	0	0	0	**3.3**	**3.3**
4	0	100	100	100	100	100	100	100	100	100
	1	0	0	0	0	0	0	0	0	0
5	0	100	100	100	100	100	100	100	100	100
	1	0	0	0	0	0	0	0	0	0
6	0	100	100	100	96.7	93.3	96.7	96.7	100	100
	1	0	0	0	**3.3**	**6.7**	**3.3**	**3.3**	0	0

APPEARS THIS WAY
ON ORIGINAL

7.2.1.4 Discomfort

Another skin evaluation was performed at each application site to assess the experience of discomfort.

This evaluation was performed pre-dose (0-hour), and at 2, 4, 8, 12, 16, 17, 24 and 28 hours post-application. The evaluator asked the subject, "Are you experiencing any discomfort related to the transdermal systems?" If no, the overall level of discomfort was rated as 0. If yes, the evaluator then asked, "What kind of overall discomfort did you experience?"

Any discomfort mentioned was recorded and rated as follows:

Score	Definitions
0	No discomfort
1	Mild
2	Moderate but tolerable
3	Severe, intolerable
9	System not present

Only mild discomfort was felt and it was present for less than 2% of the time, and in each case the discomfort was gone by the following morning, (see Table 44).

Table 44 Percent of Subjects vs. Time Reporting Discomfort with 25 cm^2 MTS Applied Daily to the Hips for 16 Hours for 6 Days – Study 17-006

		Mean % of Subjects (or Time) Reporting								
Hour		0	2	4	8	12	16	17	24	28
Discomfort Scale	0	0	98.9	98.3	97.8	99.4	98.9	99.4	100.0	100.0
	1	0	1.1	1.7	2.2	0.6	1.1	0.6	0	0
	2	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0

7.2.2 ADHESION

An examiner evaluated system adherence during each period at 2, 4, 8, 12, and 16 hours post-application. As shown in Table 45 the patches were greater than 90% adhered more than 95% of the time and more 75% - 90% adhered less than 5% of the time, with no detachments. Although the degree of adherence is likely not as good for larger patches, the high adherence is consistent with what was expected due to the short patch wear time, (i.e. 16 hours).

Table 45 Adhesion Score Summary for 25 cm^2 MTS Applied Daily to the Hips for 16 Hours for 6 Days – Study 17-006

Time of Measurement (hours post application)			2	4	8	12	16	Totals
Δ Hours			2	2	4	4	4	
Adhesion Score[a]	0	# observations	173	172	173	168	179	865
		# subject hours	346	344	692	672	716	2770
		% of time	96.1	95.6	96.1	93.3	99.4	96.2
	1	# observations	7	8	7	12	1	35
		# subject hours	14	16	28	48	4	110
		% of time	3.9	4.4	3.9	6.7	0.6	3.8%
	2	# observations	0	0	0	0	0	
		# subject hours	0	0	0	0	0	
		% of time	0	0	0	0	0	0.0%
	3	# observations	0	0	0	0	0	
		# subject hours	0	0	0	0	0	
		% of time	0	0	0	0	0	0.0%
	4	# observations	0	0	0	0	0	
		# subject hours	0	0	0	0	0	
		% of time	0	0	0	0	0	0.0%
	9	# observations	0	0	0	0	0	
		# subject hours	0	0	0	0	0	
		% of time	0	0	0	0	0	0.0%
Total # Subject Hours[b]			360	360	720	720	720	2880

a System Adherence Scores:
0= System adhered> 90%,
1= System adhered 75%- 90%,
2= System adhered 50%- 74%,
3= System adhered <50%
4= System completely detached and was reapplied,
9= System not present on skin

b Total # Subject Hours = # subjects (30) * # MTS applications per subject (6) * Δ Hours

Adhesiveness and the presence of adhesive residue as reported in study 17-006 was conducted in such a manner as to probably over-predict adhesiveness.

Adult subjects were allowed to shower during transdermal system application; but were requested to avoid immersion bathing. Since this was an inpatient study bathing, swimming, and exercise were probably not available, and would be unlikely to reflect childhood activity levels.

Once the system was applied and after removal, the site was not allowed to be rubbed or treated with any soap, lotion, or cream. Study personnel applied the systems rather than subjects and the procedures used were not specified.

7.2.3 ADHESIVE RESIDUE

Immediately following the removal of the transdermal system, the amount of adhesive remaining at the application site was examined and graded as none, light, medium, heavy or system not present. Approximately 2% of patch applications resulted in a medium amount of adhesive residue, although light residue was present in up to 30% of applications daily. It should be noted that the amount of residue could be higher with other patch sizes.

Table 46 Adhesive Residue Summary for 25 cm^2 MTS Applied 16 Daily to the Hips for 16 Hours for 6 Days – Study 17-006

	Residue Adhesion Score	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Total
Number of Patches	Total Number of MTS	30	30	30	30	30	30	180
	None	21	23	24	18	26	24	136
	Light	9	7	6	9	4	6	41
	Medium	0	0	0	3	0	0	3
	Heavy	0	0	0	0	0	0	0
	System Not Present	0	0	0	0	0	0	0
% of Patches	None	70	76.7	80.0	60.0	86.7	80.0	75.6
	Light	30	23.3	20.0	30.0	13.3	20.0	22.8
	Medium	0	0	0	10.0	0	0	1.7
	Heavy	0	0	0	0	0	0	0
	System Not Present	0	0	0	0	0	0	0

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