

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-514**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**NEW DRUG APPLICATION – RESUBMISSION – REVIEW**  
**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**

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<b>NDA:</b>	21-514
<b>Amendment</b>	AZ – Major Amendment Multiple Disciplines
<b>Submission Date(s):</b>	June 28, 2005
<b>Brand Name</b>	Daytrana®
<b>Generic Name</b>	Methylphenidate Transdermal System
<b>Reviewer</b>	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
<b>Team Leader</b>	Raman Baweja, Ph.D.
<b>OCPB Division</b>	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
<b>ORM division</b>	Division of Neuropharmacological Drug Products (DNBP) HFD-120
<b>Relevant IND(s)</b>	54,732
<b>Sponsor</b>	Noven Pharmaceuticals Inc. Miami, Florida
<b>Submission Type; Code</b>	N – New Drug Application
<b>Formulation(s); Strength(s)</b>	Adhesive Transdermal System (Patch); 27.5 mg / 12.5 cm <sup>2</sup> 10 mg delivered over 9 hours (1.1 mg / hr) — mg / 18.75 cm <sup>2</sup> 15 mg delivered over 9 hours (— mg / hr) 55.0 mg / 25 cm <sup>2</sup> 20 mg delivered over 9 hours (2.2 mg / hr) 82.5 mg / 37.5 cm <sup>2</sup> 30 mg delivered over 9 hours (3.3 mg / hr)
<b>Route(s) of Administration</b>	Transdermal
<b>Indication(s)</b>	Attention Deficit Hyperactivity Disorder

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## 1 EXECUTIVE SUMMARY

### 1.1 Background

#### Formulation Description

Daytrana® (methylphenidate transdermal system - MTS) is an adhesive-based matrix transdermal patch. The formulation method is proprietary as methylphenidate is first dispersed in an acrylic adhesive which is then secondarily dispersed in a silicone adhesive. This results in acrylate adhesive containing methylphenidate droplets being dispersed in a non-methylphenidate containing silicone adhesive carrier, (see §7.1 APPENDIX 1 –DOT Matrix Formulation Used for MTS).

#### Indication

The proposed indication for Daytrana® is 'for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)'.

#### Regulatory History

The original NDA for Daytrana® was submitted on June 27, 2002 with a proposed indication of "In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication", and a proposed trade name of MethyPatch®.

After review of the application a non-approvable letter was issued on April 25, 2003. To paraphrase, the reasons for non-approval given in the letter included the following:

1. Over-medication and excessive drug exposure resulting in an unacceptable incidence of significant adverse events, specifically insomnia, anorexia, and significant weight loss compared to the rates produced by methylphenidate products approved for once daily dosing.
2. A significant amount of methylphenidate remains in the patch after use and can be easily extracted and diverted as there is no easy method of accountability to prevent diversion.
3. A possible signal for skin sensitization.

In addition, in a follow-up meeting with the sponsor held on May 13, 2003, the sponsor was asked to address the time of onset as PK data indicated a 2-3 hour lag time before any drug would begin to be absorbed. In contrast other recently approved once a day products have a 0.5 hour lag time and a documented onset of effect at 1 hour. The sponsor was also asked to address the long term safety of exposure to the *l*-isomer and diversion issues including drug remaining in used patches.

Other significant issues identified in the original OCPB NDA review included the following:

- Applying Daytrana® to inflamed skin resulted in approximately a 3 fold increase in exposure (both Cmax and AUC) and a much more rapid absorption. This raised concerns about increased absorption with repeated applications.
- Application of heat to the patch while being worn increased both the rate and extent of absorption.

### **Advisory Committee**

On December 2, 2005 the Methylphenidate Transdermal System was presented to the Psychiatry Advisory Committee. The committee made the following recommendations:

1. Advise practitioners that MTS should be reserved for children who:
  - a. Cannot swallow tablets
  - b. Compliance with oral formulations is a particularly important issue in that patient
  - c. Has a medical condition that limits the administration of oral formulations
2. Advise practitioners that the reason that MTS should be reserved is because it may induce sensitivity to methylphenidate, which would preclude future administration of any methylphenidate formulation.
3. This information should be placed at the beginning of the indication section and that adequate warnings and descriptions of indicators of contact sensitization should be placed in the patient package insert.
4. The sponsor should commit to post-marketing monitoring or other methods to further investigate the risks from contact sensitization.

## **1.2 Recommendations**

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-514 submitted June 28, 2005.

OCPB finds this application acceptable. However, the biopharmaceutics and clinical pharmacology of methylphenidate transdermal system raises concern whether this formulation should be reserved for patients for whom therapy with oral methylphenidate is not an appropriate option regardless of whether it induces contact sensitization or not. This should be assessed by the medical review team.

Comments should be communicated to the sponsor as appropriate:  
(See Section 3.1 on page 7).

Labeling comments should also be communicated to the sponsor as appropriate:  
(See Section 3.3 Labeling Comments on page 7).

## 2 OCPB FINDINGS

### What new studies were included in this resubmission?

Six new clinical studies were included in the present submission, of these 4 are covered in this review in whole or in part. These 4 studies include:

- A 4 way biocomparison study of MTS 25 cm<sup>2</sup> applied for 6, 8, or 10 hours to Concerta® 36 mg po to examine various durations of application.
- A single-dose, dose-linearity study of MTS 12.5 cm<sup>2</sup>, 25 cm<sup>2</sup> and 37.5 cm<sup>2</sup> applied for 9 hours and biocomparison to Concerta® 54 mg.
- A phase II classroom PK-PD study examining the time course of effect.
- Sparse sampling in the phase III pivotal efficacy study

The other two studies included a skin sensitization study that was consulted to the dermatology division, and a phase III long term open label extension study.

### \*\* What is the single dose pharmacokinetics?

After single dose 9 hour application of the highest strength patch (37.5 cm<sup>2</sup>) the C<sub>max</sub> and AUC were comparable to a 54 mg Concerta® tablet, (methylphenidate OROS ER tablet), with C<sub>max</sub> approximately 10-15% higher with the MTS. T<sub>max</sub> for the 9 hour wear time averaged around 9 hours however they range from 6 hours to possibly greater than 14 hours. Lag time, (i.e. the time to detect any drug in the circulation), with single dosing was greater than 2 hours in 50% in subjects in 1 study, and greater than 3 hours in 60% of subjects in the other study.

### Is there dose linearity?

With single dosing there is dose proportionality over patch sizes from 12.5 cm<sup>2</sup> to 37.5 cm<sup>2</sup>.

### \*\* What are the multiple dose pharmacokinetics and the exposure on clinical dosing?

In the pivotal phase III efficacy study after dosing for at least 5 weeks geometric mean *d*-MPH 9 hour plasma concentrations for MTS were about 1.9 fold the concentrations for comparable doses of Concerta®. Even when only the peak concentrations are compared the MTS peak concentrations are still 1.7 fold higher than the peak concentrations for Concerta®. Similar peak concentrations for MTS were also seen in the phase II study after dosing of MTS for at least 6 weeks. These MTS peak concentrations are much greater than previously observed after 4 days of dosing, although 4 days is not considered adequate time to assess time invariant pharmacokinetics. The Concerta® concentrations in this phase III study were similar to what is expected based upon other submissions. In addition only one subject out of 82 taking Concerta had a C<sub>max</sub> greater than 60 ng/ml, whereas 15 of the 80 subjects taking MTS had a C<sub>max</sub> > 60 ng/ml. These high concentrations cannot be due to superpositioning as in the 12 subjects with C<sub>max</sub> > 40 ng/ml the effect of superpositioning contributed to less than 1% of C<sub>max</sub> in 10 cases and in the other two cases the contribution was 2.4% of C<sub>max</sub>.

### \*\* What factors might produce these higher exposures?

A variety of factors were examined that might have produced these higher exposures with MTS.

The effect of sampling time was ruled out based upon the similar phase II data, and the fact that samples were collected at 7.5, 9, and 10.5 hours, therefore the 7.5 hour and 9 hour samples should provide a good estimate of Concerta's (C<sub>max</sub>) and that the difference remained when observed C<sub>max</sub>s were compared.

Differences by age were ruled out as differences were present in subjects at each year of age and at each year of age Cmax distributions were similar within each treatment group but were different between treatments.

There was no obvious difference in dosage titration patterns by clinicians at any age. If anything at most ages more subjects received the highest dose of Concerta® compared to the number who received the highest dose of MTS.

Neither were there any obvious differences in dosing patterns between treatments by weight, gender, or race.

The effect of skin irritation with the particular patch application on the day of the PK-PD assessment showed varying effects. There was no additional effect of erythema alone, papules formed in only 2 subjects and thus there were insufficient numbers of subjects to assess an effect. Although the presence of edema is expected to result in increased absorption there were no subjects who developed edema so this could not be assessed, whereas in the single subject in whom vesicles formed there was a dramatic increase in exposure.

Other possible factors include:

- Variations in manufacture of the formulation resulting in varying sizes and distributions of the drug containing acrylate beads in the silicone adhesive matrix.
- temperature effect from clothing, (this might also be problematic with children sitting close together on buses or in car pools)
- physical effects of restrictive clothing
- greater physical activity in these studies
- Time of year or location where studies are conducted (was air dry?, e.g. winter, high or low humidity area, and use of moisturizers)
- changes in skin vascularization or the changes in the epidermal barrier layers over time due to repeated short term irritation from the patch, itching, or from repeated application and removals.

**\*\* What are the clinical implications of these higher exposures?**

Examination of population PK-PD relationships with weight changes, heart rate, blood pressure and SKAMP score all revealed similar patterns with maximal effect being achieved around 40 ng/ml, and an EC50 in the teens. Although changes in heart rate, or blood pressure, or weight might be slightly higher on average than achieved with the Cmaxs of Concerta, (low 20 ng/ml range), this might be more of a long term issue. The PK-PD relationships observed in the present studies are also similar to those seen previously although the present study better anchors the Emax. The issue of insomnia and appetite suppression is probably also effected by the duration of higher exposures in the evening and the shorter wear time has obviously decreased these exposure durations. The higher concentrations may proscribe switching directly from another methylphenidate product.

**\*\* What is the time of onset for effect?**

Although there is a statistically significant difference in effect from placebo at 2 hours this appears to be driven by a minority of the patients. Concentrations needed for a minimum measurable response appear to be around 5 ng/ml, which is similar but slightly lower than predicted from previous NDAs. Although the slower rate of absorption with the present formulation makes our ability to determine the MEC more accurate.

Even with the increased absorption over time with ongoing treatment, at 6 weeks 2/3's of subjects had a 2 hour concentration less than 5 ng/ml, although 25% had a 2 hour concentration >10 ng/ml. At 3 hours 40% of subjects still had concentrations of less than 5 ng/ml. In contrast oral formulations with an immediate release component are rapidly absorbed with peak concentrations at around 1 – 1.5 hours.

### **Can the dosage be decreased to minimize peak exposures?**

Possibly, although the individuals with high peak exposures also have the higher concentrations at 2 hours and some super positioning may be needed for efficacy at 2 hours in some individuals. Preliminary analysis suggests that a dosage around 0.75 cm<sup>2</sup>/kg may produce acceptable effects at 2 hours without excessive peak concentrations, although further analysis and clinical phase II studies would be needed to confirm this.

### **What are the effects of race and gender?**

Some exploratory data analysis suggested apparent longer Tlag in blacks compared to whites and higher exposures in females. When this was examined in greater detail in multiple studies, looking at the effects of other factors such as dosing by weight, etc., it appeared that the previous observed patterns were likely by chance.

### **\*\* What are the dermal tolerance and adherence characteristics?**

Dermal tolerance and adhesive characteristics were assessed in the original NDA. Although new data was available from the PK/PD study in the present submission, this was not reviewed except to evaluate the relationship of the degree of dermal irritation with drug exposure on a particular day at 6 or 7 weeks.

Of these observations 17% of subjects had no irritation, 79% exhibited erythema, 2 of 78 had developed papules, and 1 of 78 had vesicle formation. The vesicle formation is of most interest as it might represent sensitization, and this is different from the case in the phase III study that redeveloped on re-challenge with oral methylphenidate. In the original submission vesicles were coded in combination with papules with a result of <7% of subjects having either.

### **\*\* What is the drug delivery rate from the MTS formulation?**

Drug delivery rate with patch formulations is not constant. With the present formulation we expect that there is a lag until delivery begins, then it should increase rapidly, followed by a diminishing rate. Averaged over the 9 hours of patch application the average rate was roughly proportional to patch size but was about 10% higher in some cases. The sponsor has proposed labeling with the actual delivery rates; however, the 10% difference in average rates is small for a patch. Thus to simplify prescribing it is recommended that a strictly proportional delivery rate be used.

Labeling of the delivery rate and drug content will obviously make it very easy for individuals to calculate the amount of drug remaining in the patch and may serve to notify individuals who are interested in diversion that there is excess drug available for extraction and diversion post-removal.

### **What other clinical pharmacology issues are there?**

Exposure to *l*-MPH from the MTS has been addressed by the original animal studies racemic methylphenidate as they do absorb *l*-MPH in contrast to humans and by the long term safety study with MTS in humans.

Although insomnia was decreased in the present submission by shortening the application duration there is still going to be intrasubject variability, thus the sponsor's rating system that scores 1 case of insomnia per week the same as 0 cases might have minimized differences in the incidence rate between MTS and Concerta®.

As younger children had higher concentrations with MTS, the time until concentrations fall low enough so that the effects wear off is expected to be longer. Thus insomnia may be a more frequent occurrence in younger children. If MTS is reserved for children who cannot take oral therapy then the frequency of insomnia in the relevant population in clinical practice may be higher than in the clinical trials.

**What are the overall clinical pharmacology conclusions?**

In addition to the issue of skin sensitization this formulation has other limitations including the following:

- Diversion by other students removing and stealing the patch, or patients or caregivers extracting and diverting the excess drug.
- The prolonged lag in time to onset in a large percentage of patients
- The higher and prolonged concentrations that result in a slightly greater degree of appetite suppression and insomnia.
- The possibility of a greater risk of long term complications due to higher average heart rates, and blood pressure.
- Forgetting to remove the patch.

However, when these risks are considered against the complications of not treating the illness at all, the greater good appears to be in having the MTS available as a treatment option. Although, these additional issues also suggest that the MTS should be reserved for patients for whom oral treatment is not a realistic option. This might also mitigate stealing of patches, as younger children would be the most likely candidates for MTS and are potentially less likely to experience this particular problem.

**APPEARS THIS WAY  
ON ORIGINAL**

### 3 INFORMATION FOR COMMUNICATION TO SPONSOR

#### 3.1 Comments to the Sponsor – If NDA is Approved

##### 3.1.1 Dissolution Method and Specifications

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

**Table 1 Dissolution Method and Acceptance Criteria**

<b>Apparatus:</b>	USP Drug Release Apparatus 6 (modified cylinder)		
<b>Medium:</b>	0.01N HCl		
<b>Temperature:</b>	32 ± 0.5°C		
<b>Volume:</b>	900 mL		
<b>Rotation Speed:</b>	50 rpm		
<b>Sampling Times:</b>	0.5 hour 1.5 hour 3.0 hour		
<b>Acceptance Criteria:</b>	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 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

41 Page(s) Withheld

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

✓  
       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 4 SIGNATURES

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**Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.**

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**Date**

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

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**Raman Baweja, Ph.D.**

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**Date**

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

### 4.1 CC List:

DFS            NDA 21-514 AZ 6-28-2005  
HFD-120      (TaylorR, LevinR, MannheimG, AndreasonP, LaughrenT, OliverT)  
HFD-860      (KavanaghR, BawejaR, MehtaM, SahajwallaC)

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## 6 REVIEW

### 6.1 Submitted Studies

The sponsor has submitted 6 new clinical studies. These include 2 exploratory phase I PK studies for estimation of application duration, a phase II, PK-PD study, a phase II skin sensitization study, a phase III efficacy study and a phase III, long term efficacy study. An overview of the studies, their designs and what was covered in this OCPB review is shown in Table 2.

**Table 2 Summary of Studies Included in Present Submission, Study Designs, and Items Reviewed by OCPB**

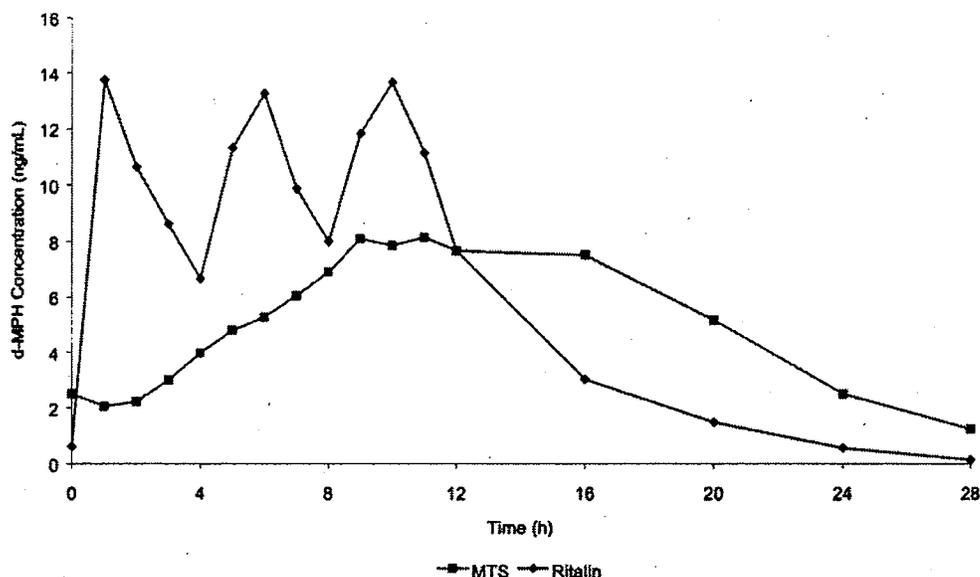
Study No.	Type of Study	Study Design	Age Range (years)	N	MTS			Concerta		Reviewed by OCPB
					Dose (cm <sup>2</sup> )	Regimen	Duration of Application	Dose (mg)	Regimen	
<b>Phase I</b>										
101	Biocomparison Study	4 period, 4 Rx, 4-way XO	6-12	23	25	SD	6, 8, 10	36	SD	Yes
102	Biocomparison Study	4-way XO	6-12		12.5 25 37.5	SD	9	54		Yes
<b>Phase II</b>										
201	MD PK/PD	Rand, DB, PBO-Controlled, XO, Dose Optimization, Classroom PK/PD Study	6-12		12.5 18.75 25 37.5	MD	9			Yes
17-020	Skin Sensitization Testing					MD				No. Reviewed by Dermatology.
<b>Phase III</b>										
302	MD Efficacy Safety	Rand, DB, Parallel Grp, PBO- Controlled, Flexible Dose Efficacy Study	6-12		12.5 18.75 25 37.5	MD	9	18 27 36 54	QD	Only PK, PK/PD of weight loss, & flexible dosing relative to Concerta
N17-021	OL Long Term Safety Extension Study		6-12			MD				No.

## 6.2 Review of Major PK Findings from Original Application

Figure 1 shows a comparison of mean *d*-MPH plasma concentration vs. time profiles from a 25 cm<sup>2</sup> dose of MethyPatch after 4 days of dosing compared to a 60 mg daily dose (20 mg tid) in adults from the original submission. However this is not an appropriate comparison as a low dose of MethyPatch®, (25 cm<sup>2</sup>), is being compared to the maximal dose of Ritalin, (20 mg TID).

**Figure 1 Sponsor's Comparison of a Maximal Daily Dose of Ritalin (20 mg TID) to a Low Dose of MethyPatch (25 cm<sup>2</sup>) in Adults<sup>a</sup>**

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



a Maximal dose of MethyPatch would be twice as much i.e. 50 cm<sup>2</sup>

In contrast figure 2 shows a simulated comparison base on the expected dosing in a typical twelve year old, as explained below:

A) The red line shows the expected *d*-MPH vs. time profile in a twelve year old patient when an expected MTS dose of 50 cm<sup>2</sup> per day is applied for 12 hours.

i.) First the average 12 yo male weighs 43 kg compared if a 70 kg adult, thus the average C<sub>max</sub> of 8.5 ng/ml in an adult with a 25 cm<sup>2</sup> patch would instead result in a C<sub>max</sub> of about 13.8 ng/ml in a 12 year old male.

ii. Secondly, based upon actual usage date from the sponsor's phase III study the typical 12 year old will receive a dose of 50 cm<sup>2</sup>, thus doubling the above estimated C<sub>max</sub> will result in a C<sub>max</sub> of approximately 27.6 ng/ml strength

iii. Lastly, the higher C<sub>min</sub> must be accounted for resulting in a C<sub>max</sub> of approximately 30 ng/ml.

B) In contrast the blue line shows the expected d-MPH vs. time profile in an adult patient when an expected Ritalin dose of 20 mg BID is administered. n.b. from Figure 1 shows that a 3<sup>rd</sup> dose resulting in a maximal daily dose of 60 mg a day does not appreciably increase the C<sub>max</sub>, instead it simply prolongs the duration of exposure.

i. N.B. weight adjustments appear to have been forgotten. However numerous other PK profiles in children would indicate that the blue line is what is truly expected.

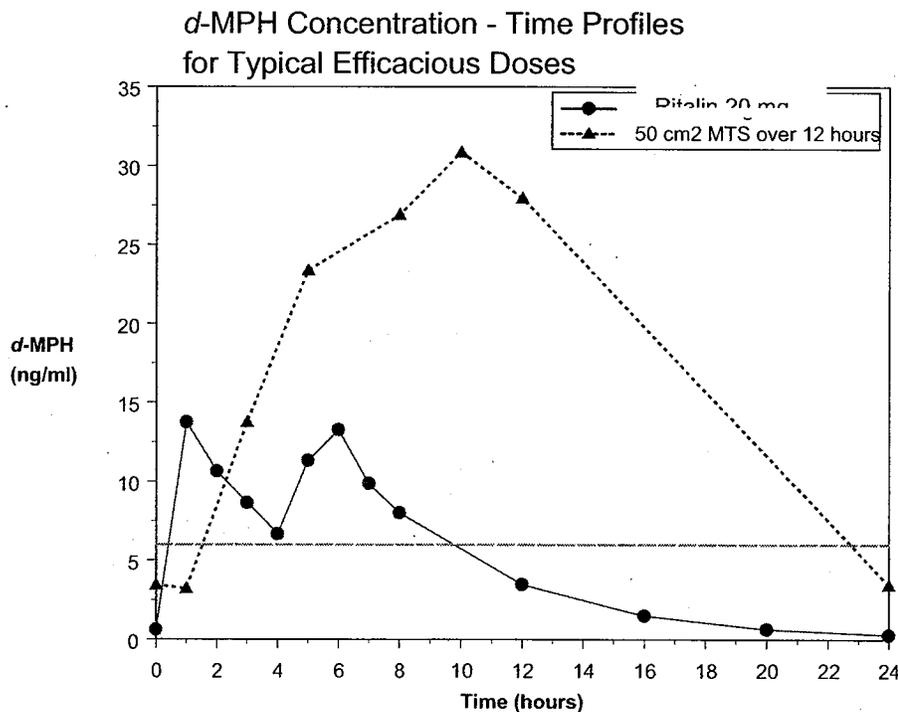
ii. Even if we do adjust for weight the difference in C<sub>max</sub> would decrease but would not disappear entirely, i.e. adjusting for weight would give an approximate Ritalin C<sub>max</sub> of 22.5 ng/ml.

C) For young children dosing would be proportional to weight and similar quantitative concentration vs. time profiles are expected.

However, even with adjusting for weight we still have the following problems:

- Based on previous PK-PD studies the average minimum concentration producing a measurable response is around 6 ng/ml.
- Thus it is questionable whether there will be clinical effect at 2 hours after patch application for any but a minority of patients.
- Concentrations that are expected to produce clinical effects are sustained for well into the night for MTS compared to oral formulations thus appetite suppression is expected well into the night as well as insomnia. These side effects are not expected to be nearly as troublesome with oral formulation because effects would wear off much earlier in the evening and patients would be more likely to eat before bedtime.

**Figure 2 Comparison of Expected d-MPH Concentration vs. Time Profiles with Therapeutic Dosing in Children**



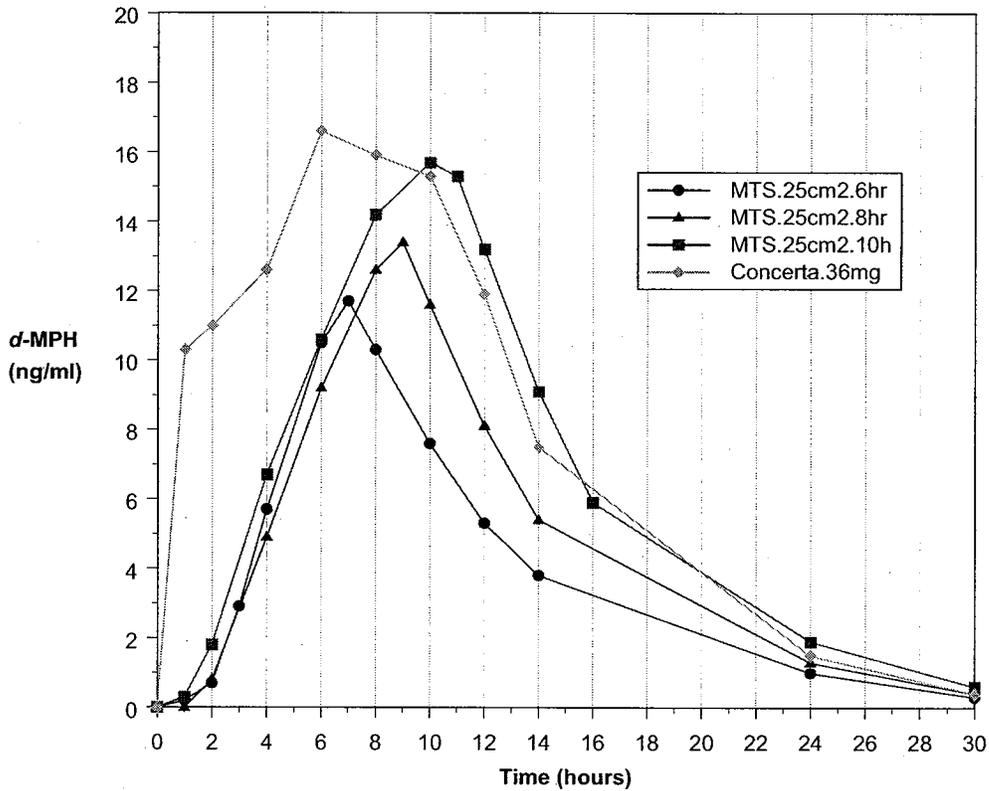
### 6.3 Exploration of Dosing Regimens

In response the sponsor has conducted 2 single dose studies, studies 101 and 102, to explore the appropriate duration of application and the maximal dosage.

#### 6.3.1 Exploration of Duration of Patch Application

Study 101 compared exposures after application of a 25 cm<sup>2</sup> patch to the hips of 6 – 12 year olds of application durations of 6, 8, or 10 hours with a single 36 mg dose of Concerta. Comparative plots of naïve pooled mean concentration vs. time plots are shown in Figure 3. Based on this data the sponsor chose an application duration of 9 hours in order to avoid prolonged evening and nighttime exposures and minimize adverse event in the evening and at night.

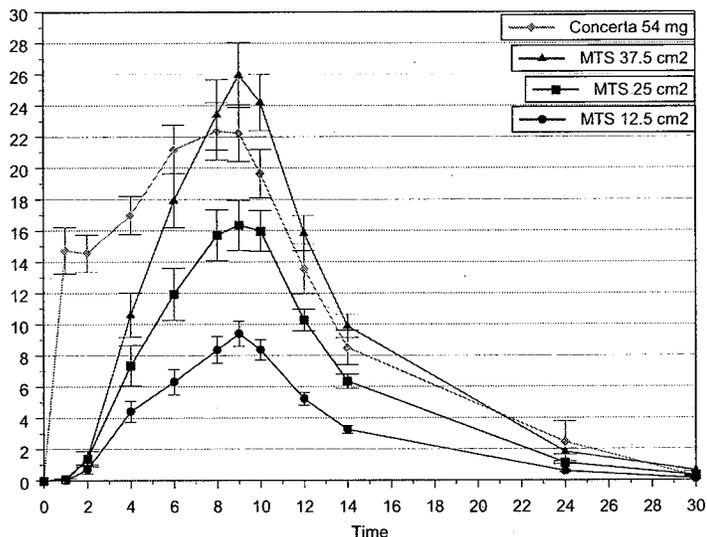
**Figure 3 Single Dose Naïve Pooled Mean Concentration vs. Time Plots of MTS applied for 6, 8, or 10 hours and Concerta 36 mg po in 6 – 12 year olds - Study 101**



#### 6.3.2 Exploration of Maximal Dose

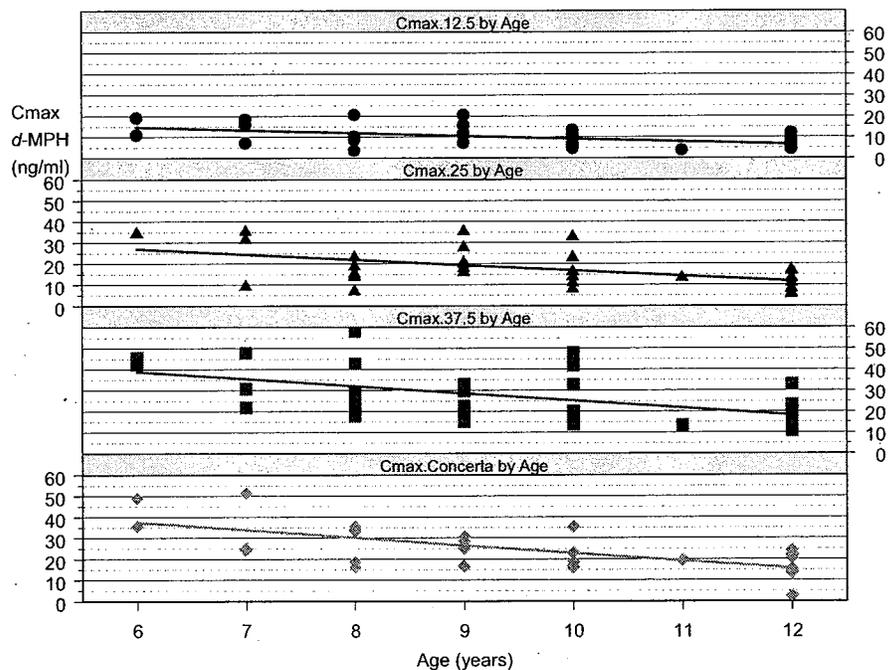
Study 102 was single dose study that compared exposures after application of 37.5 cm<sup>2</sup> patch to the hips of 6 – 12 year olds for 9 hours with a single 54 mg dose of Concerta. Figure 4 shows mean (±SE) concentration vs. time profiles for methylphenidate transdermal systems applied for 9 hours compared to a 54 mg Concerta in Children 6 – 12 years of Age. This study indicated that peak concentrations with a single dose of MTS are only slightly higher than with a comparable single dose of Concerta.

**Figure 4 Mean Concentration ( $\pm$ SE) vs. Time Profiles for Methylphenidate Transdermal Systems Applied for 9 hours Compared to Concerta 54 mg in Children 6 – 12 years of Age - (Study 102)**



Although, this study indicates that peak concentrations and evening concentrations should not be much different than a comparable dose of Concerta in children, these plasma concentration profiles are not quantitatively representative of concentrations that would be seen with therapeutic dosing as some children are either under-dosed or overdosed on a mg/kg basis in each treatment arm. This is illustrated by Figure 5.

**Figure 5 d-MPH Cmax vs. Patient Age by MTS Dose - Study 102**



Summary statistics for pharmacokinetic metrics from these studies are shown in Table 3.

Table 3 Summary Statistics for Pharmacokinetic Metrics from Phase I Studies

Study	Rx Arm	Dose	Duration of Application	N	Tlag <sup>a</sup> (h)	Tmax <sup>a</sup> (h)	Cmax <sup>a,b</sup> (ng/mL)	AUClast <sup>a</sup> (ng <sup>h</sup> /mL)	AUCinl <sup>p</sup> (ng <sup>h</sup> /mL)	t1/2 <sup>b</sup> (h)
101	A	MTS 25 cm <sup>2</sup>	6 hrs	23	3.3 ± 1.5 (44.2) 1 - 6 [3]	8.1 ± 2.1 (25.3) 6.0 - 14.0 [7.0]	12.3 ± 9.2 (75.2) 1.7 - 45.3 [11.8]	112.3 ± 70.7 (63.0) 22.0 - 343.2 [99.9]	116.3 ± 71.8 (61.7) 28.2 - 344.7 [103.4]	5.0 ± 1.3 (25.6) 3.4 - 8.3 [4.6]
	B	MTS 25 cm <sup>2</sup>	8 hrs	23	4.2 ± 1.4 (33.2) 2 - 8 [4]	9.2 ± 1.5 (16.6) 7.9 - 14.0 [9.0]	13.8 ± 9.2 (66.1) 2.0 - 39.8 [11.7]	138.2 ± 85.1 (61.6) 28.0 - 379.1 [122.8]	141.7 ± 85.2 (60.1) 31.6 - 381.3 [126.7]	4.4 ± 0.9 (20.7) 3.1 - 6.8 [4.25]
	C	MTS 25 cm <sup>2</sup>	10 hrs	23	3.9 ± 2.3 (58.1) 1 - 10 [4]	10.4 ± 2.2 (21.1) 4.0 - 14.0 [10.1]	17.3 ± 13.2 (76.4) 2.2 - 55.5 [13.7]	187.5 ± 154.7 (82.5) 31.9 - 683.4 [145.7]	192.3 ± 156.6 (81.4) 35.7 - 699.8 [148.7]	4.3 ± 0.9 (20.6) 2.8 - 6.4 [4.06]
	D	Concerta 36 mg	—	24	1 ± 0 (0) 1 - 1 [1]	6.7 ± 2.7 (40.4) 1.0 - 10.1 [6.0]	17.7 ± 6.9 (39.1) 8.1 - 39.6 [15.9]	228.6 ± 117.2 (51.25) 101.6 - 599.5 [197.8]	232.8 ± 120.5 (51.7) 102.9 - 618.7 [200.1]	3.7 ± 0.7 (18.1) 2.8 - 5.5 [3.7]
102	A	MTS 12.5 cm <sup>2</sup>	9 hrs	34	3.3 ± 1.3 (38.5) 1.0 - 6.0 [4.0]	8.8 ± 1.2 (13.8) 6.0 - 10.0 [9.0]	9.8 ± 4.9 (49.8) 3.7 - 20.6 [8.9]	91.7 ± 48.5 (52.9) 36.0 - 222.1 [79.8]	90.0 ± 47.1 (52.3) 35.2 - 215 [78.6]	3.8 ± 0.7 (19) 2.2 - 5.4 [3.6]
	B	MTS 25 cm <sup>2</sup>	9 hrs	34	3.4 ± 1.5 (43.1) 1.0 - 6.0 [4.0]	9.5 ± 0.8 (8.9) 8.0 - 12.0 [10.0]	17.8 ± 8.9 (50.2) 5.7 - 35.8 [16.0]	173.4 ± 94.1 (54.3) 62.6 - 394.2 [155.8]	170 ± 91.2 (53.6) 62 - 383 [150]	3.8 ± 0.6 (15.4) 3.0 - 5.0 [3.7]
	C	MTS 37.5 cm <sup>2</sup>	9 hrs	34	2.6 ± 1.0 (35.9) 2.0 - 4.0 [2.0]	9.0 ± 1.0 (11.1) 6.0 - 12.0 [9.0]	27.2 ± 12.2 (44.7) 10.8 - 58.4 [23.4]	265.9 ± 115.9 (43.6) 97.0 - 522.1 [259.1]	255 ± 114 (44.5) 94.4 - 502 [230]	3.9 ± 0.5 (12.2) 3.1 - 5.0 [3.9]
	D	Concerta 54 mg	—	33	1.0 ± 0.2 (18.2) 0.0 - 1.0 [1.0]	7.5 ± 1.0 (19.3) 4.0 - 10.0 [8.0]	24.2 ± 10.3 (42.6) 2.6 - 51.2 [22.1]	295.2 ± 180.4 (61.1) 21.1 - 1045.1 [268.9]	262 ± 116 (44.3) 20.4 - 669 [259]	3.2 ± 0.6 (18.6) 1.8 - 4.7 [3.3]

a As calculated by OCPB Reviewer  
b As Calculated by Sponsor

The study does however indicate that the different strengths are likely dose proportional, and the sponsor's statistical assessment is shown in Table 4 and Table 5.

**Table 4 Sponsor's Statistical Assessment of the Relationship between AUC0-t and Cmax Values and Patch Size of d-MPH Following Administration of MTS**

Parameter	Geometric Means			Geometric Mean Ratio (90% Confidence Interval)	
	MTS 12.5cm <sup>2</sup>	MTS 25cm <sup>2</sup>	MTS 37.5cm <sup>2</sup>	25 cm <sup>2</sup> : 12.5 cm <sup>2</sup>	37.5 cm <sup>2</sup> : 12.5 cm <sup>2</sup>
<b>Cmax</b>	8.65	15.7	24.7	1.82 (1.57, 2.11)	2.86 (2.47, 3.30)
<b>AUC0-t</b>	75.7	143	228	1.89 (1.62, 2.22)	3.01 (2.58, 3.51)

### 6.3.2.1 l-MPH exposures

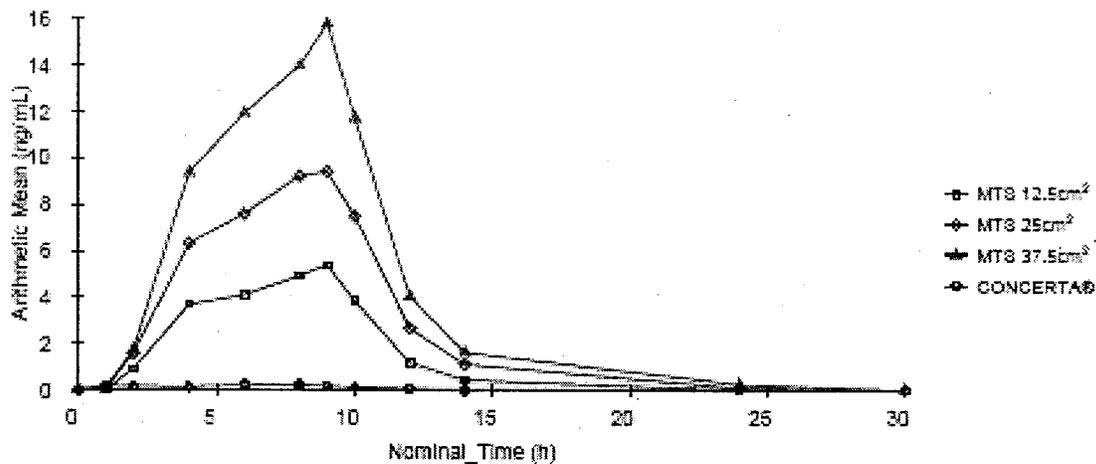
l-MPH exposures are high compared to oral dosing as seen in the original submission. Additional information can be found in the OCPB review of the original submission.

**Table 5 Sponsor's Statistical Assessment of the Relationship between AUC0-t and Cmax Values and Patch Size of l-MPH Following Administration of MTS**

Parameter	Geometric Means			Geometric Mean Ratio (90% Confidence Interval)	
	MTS 12.5cm <sup>2</sup>	MTS 25cm <sup>2</sup>	MTS 37.5cm <sup>2</sup>	25 cm <sup>2</sup> : 12.5 cm <sup>2</sup>	37.5 cm <sup>2</sup> : 12.5 cm <sup>2</sup>
<b>Cmax</b>	5.26	9.16	15.9	1.74 (1.48, 2.04)	3.01 (2.58, 3.52)
<b>AUC0-t</b>	31.6	61.1	101	1.94 (1.50, 2.51)*	3.21 (2.50, 4.14)**

\*\*Upper 90% CI lies outside the prescribed limits of 2.4 to 3.75.

**Figure 6 Mean l-MPH Concentration vs. Time Profiles for Methylphenidate Transdermal Systems Applied for 9 hours Compared to Concerta 54 mg in Children 6 – 12 years of Age - (Study 102)**

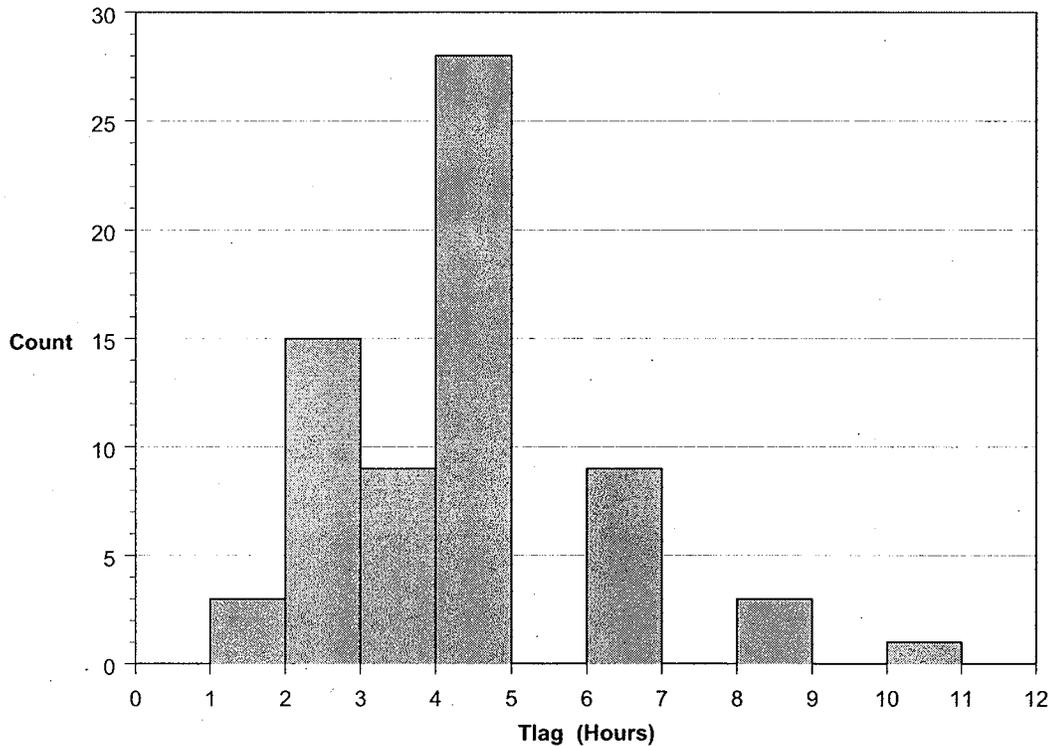


### 6.3.3 Absorption Lag Time

These studies however continue to raise concerns regarding the time until the onset of effect is seen.

Assuming a minimum effective concentration of 5 ng/ml and that Figure 3 likely shows typical clinical concentration profiles, adjusting for accumulation we would expect an average time of onset of around 3 hours. Although 3 hours is an expected average time of onset lag times indicate some patients would have earlier and some would have later times of onset. This is represented graphically by Figure 7.

**Figure 7 Histogram of Absorption Lag Times for MTS 25 cm<sup>2</sup> Patches in Study 101**



It may be noted that the lag times as calculated by this reviewer are longer than those calculated by the sponsor, (see Table 3). This reviewer's calculations are correct as the lag time is the time when drug is first observed in the body, whereas the sponsor utilized the last time that no drug was observed. The sponsor's method is inappropriate as it is too dependent on sampling time. For example if the true lag time is 1.75 hour with sampling times at 1 hour and 2 hours, the one method will give 1 hour and the other 2 hours. However if the first sample is at 5 minutes one method would give a lag time of 5 minutes whereas the other would never give a lag time less than the true lag time.

It should be remembered that time of onset will be later than the lag time as the lag time is simply when drug is first observed in the body, and it will take additional time until drug concentrations rise high enough to cause a clinical effect.

Although Figure 7 combines lag times for all MTS treatments this is appropriate as the MTS treatments differ only in their application duration and this will not effect lag time. Table 6 shows the same data as % and cumulative percent of patients by lag time.

**Table 6 Lag Times by Percent and Cumulative Percent of Subjects in Study 101**

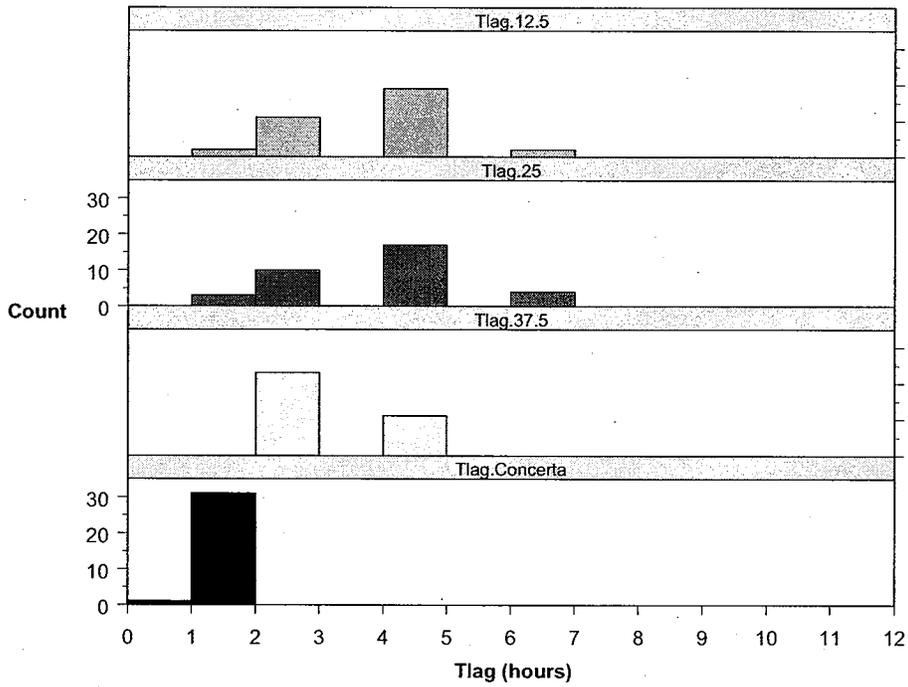
Lag Time (hours)	0	1	2	3	4	6	8	10	—
Count	0	3	15	9	33	9	3	1	73
% of Patients	0	4.1	20.6	12.3	45.2	12.3	4.1	1.4	—
Cumulative Percent	0	4.1	24.7	37.0	82.2	94.5	98.6	100	100

Histograms of lag times from study 102 are shown in Figure 8. Again we can see that lag times are much longer than for Concerta. In fact all MPH formulations with an immediate release component such as Concerta and Ritalin LA have an even shorter lag time of around ½ hour. In the present study the lag time for Concerta is 1 hour as there was no sampling performed earlier.

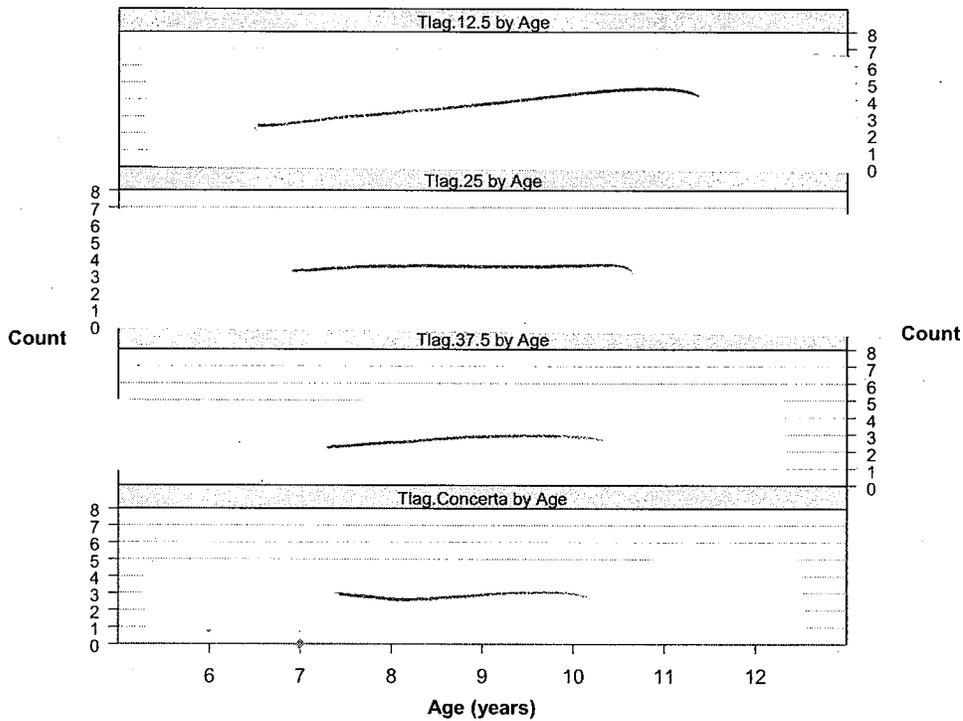
The apparent shift to the left for lag times seen with increasing dose in Figure 8 was expected for this study as an artifact of the study design, however, Figure 9, indicates that this is not the reason. In clinical practice with appropriate dosing the distribution of lag times are expected to be similar to those seen with the 25 cm<sup>2</sup> patches in both studies 101 and 102.

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ON ORIGINAL**

**Figure 8 Histograms of Lag Times for MTS 12.5 cm<sup>2</sup>, 25 cm<sup>2</sup>, 37.5 cm<sup>2</sup> Patches and Concerta 36 mg in Study 102**



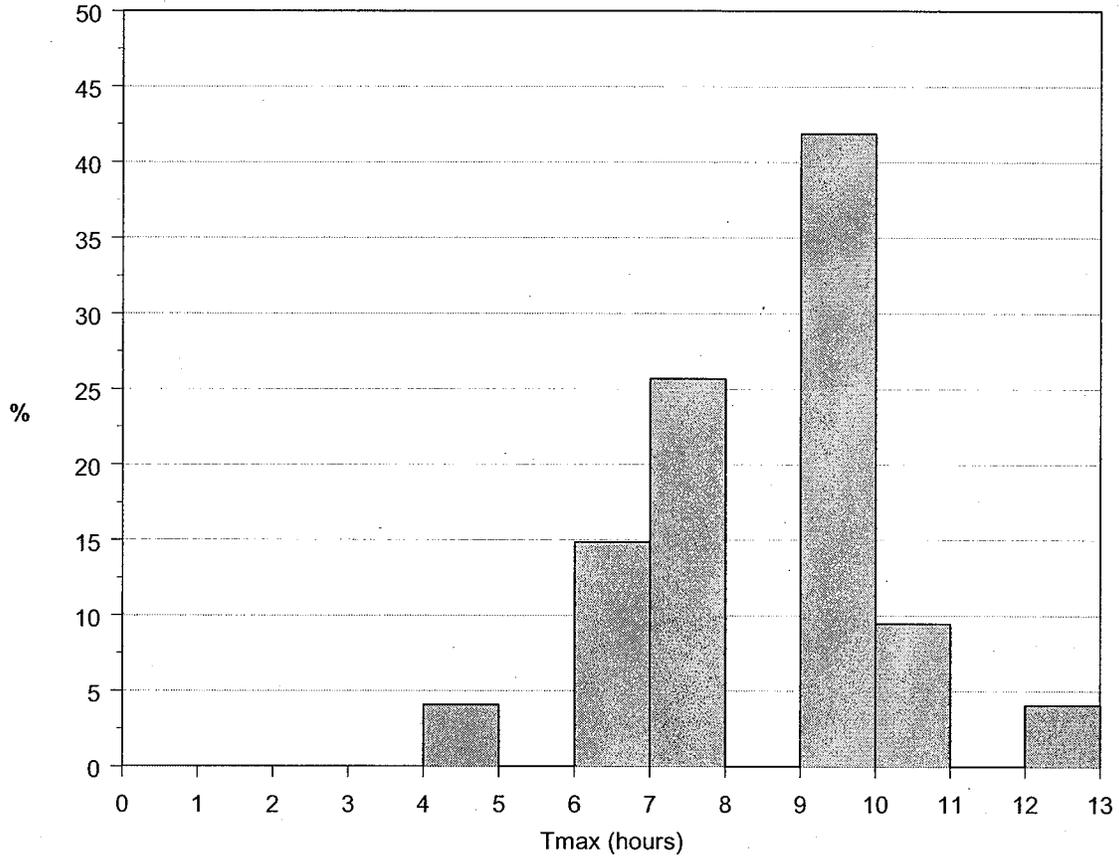
**Figure 9 Lag Times by Treatment and Subject Age in Study 102**



### 6.3.4 Tmax

Due to the design of the biocomparison estimates where subjects of all ages (6 - 12 yo) received each dose extrapolation of Tmax to the clinical situation is difficult. Consequently, the only measurements of Tmax in the present submission are from the PK data from the chronic clinically titrated dosing in the phase II PK-PD study, study 201. A histogram of Tmaxs from this study is shown in Figure 10.

**Figure 10 Frequency Histograms of MTS Tmaxs after Week 6-7 weeks of Clinical Dosing in the Phase II PK/PD Study - Study 201**



## 6.4 d-MPH Exposures with Therapeutic Dosing

In the phase III efficacy studies PK blood samples were obtained after one of the 3 visits after dose optimization for both Concerta and MTS at 7.5, 9, and 11.5 hours after dosing.

### 6.4.1 Comparison of 9 hour Concentrations

Table 7 the shows results reported by the sponsor in the study synopsis for the 9 hour concentrations. It's readily apparent that 9 hour concentrations for MTS are nearly double those for Concerta at every dose level.

**Table 7 Sponsor's Mean (SD) 9 hour Plasma d- MPH Concentrations (ng/ml) by Dose for MTS and Concerta from the Pivotal Phase III Efficacy Study – Study 302**

MTS		Concerta		Ratio of Means
Patch Size	d-MPH Conc. at 9 hours (ng/ml)	Capsule Strength	d-MPH Conc. (ng/ml)	
12.5cm <sup>2</sup> (N=5)	12.7 (7.42)	18mg (N=3)	8.65 (1.75)	1.47
18.75cm <sup>2</sup> (N=14)	20.1 (15.3)	27mg (N=13)	11.0 (9.48)	1.83
25cm <sup>2</sup> (N=20)	38.6 (17.0)	36mg (N=23)	20.1 (9.77)	1.92
37.5cm <sup>2</sup> (N=33)	47.0 (27.1)	54 mg (n=41)	23.2 (13.2)	2.03

**Table 8 Summary Statistics for 9 hour Plasma d-MPH Concentrations for MTS and Concerta from the Pivotal Phase III Efficacy Study for all Subjects – Study 302**

MTS d-MPH Conc. at 9 hours (ng/ml)		Concerta d-MPH Conc. <sup>a</sup> (ng/ml)		Ratio of Means <sup>b</sup>
All Strengths N = 73	36.8 ± 24.4 (66.2) 0 - 114 [36.6]	All Strengths N = 79	20.0 ± 12.2 (60.8) 0 - 66.6 [18.7]	1.84
				1.90

a The total number of subjects is for Concerta inconsistent with the sponsor's numbers in Table 7. The OCPB numbers are correct.

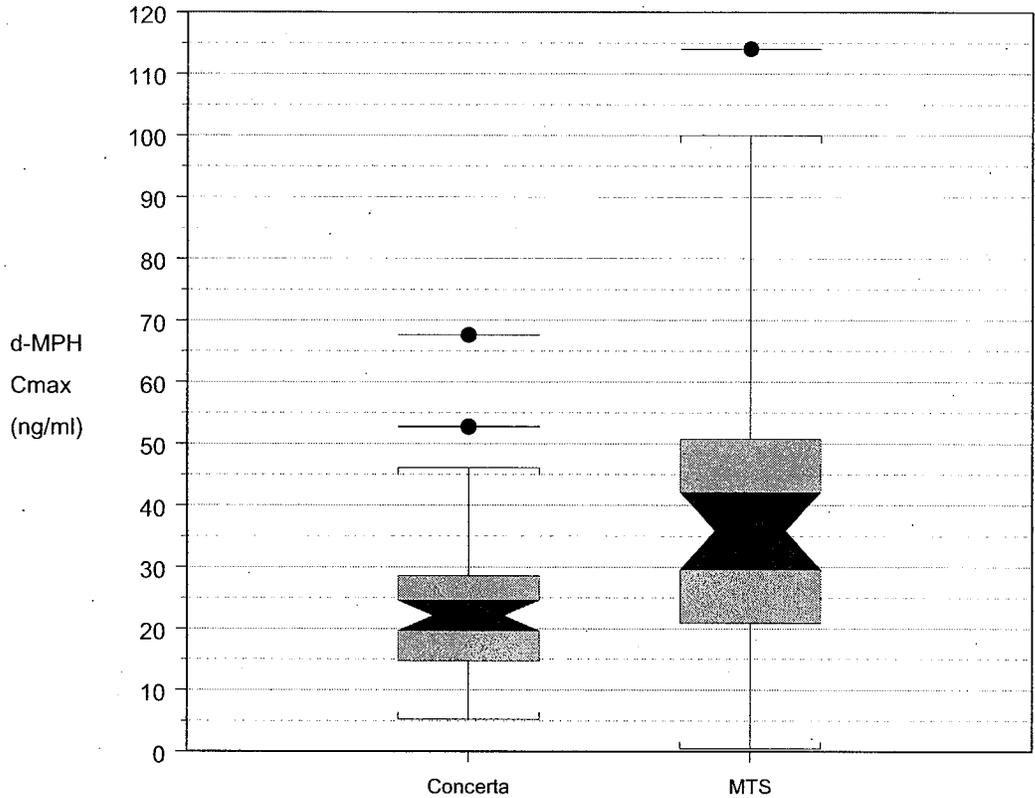
### 6.4.2 Examination of Potential Causes

A variety of factors that might have spuriously produced this result were investigated.

#### 6.4.2.1 Effect of Sampling Time

The first potential complicating factor was the use of only the 9 hour sample for comparison. However, as 7.5, 9, and 10.5 hour samples were obtained and as the 7.5 hour sample would be around the expected T<sub>max</sub> for Concerta, (see Table 3). When the actual C<sub>max</sub>s are compared the ratio was similar. Figure 11 shows a comparison of the absolute C<sub>max</sub>s seen with each treatment.

**Figure 11 Comparative Box Plots of the Absolute Cmax Observed by Treatment Arm in the Pivotal Phase III Study – Study 302**



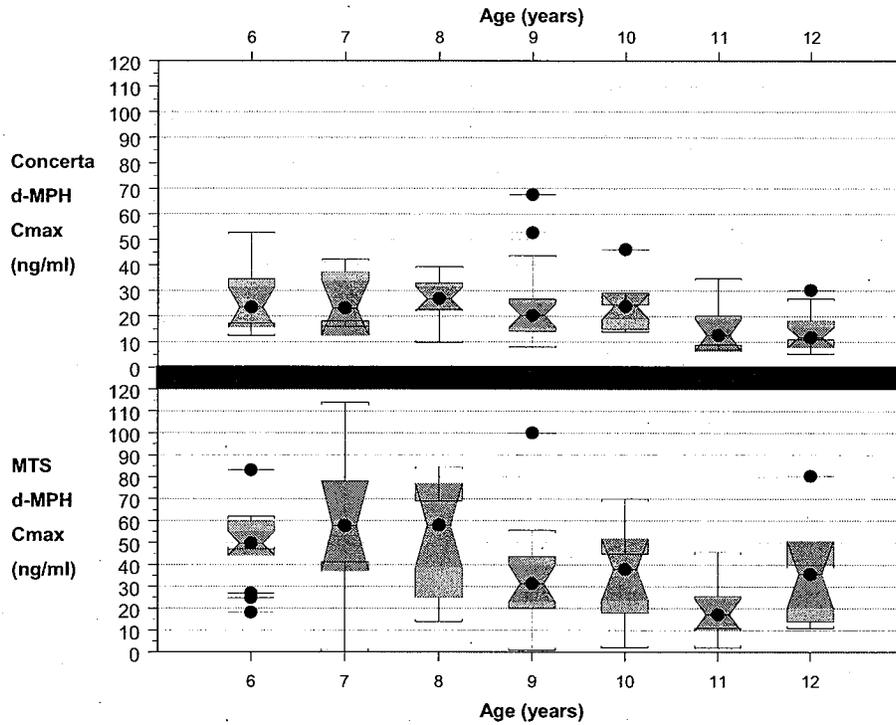
N.B. Figure 11 shows medians, along with the CI around the mean, quartiles, 1.5x the quartile range, and outliers.

(Table 9). Although, Cmax for Concerta may occur slightly earlier in some patients a 7.5 hour sample is expected to be adequate for most subjects receiving Concerta and although the Cmax ratio is expected to decrease slightly it would be expected to change so much as to alter the conclusions.

#### 6.4.2.2 Effect of Age and Dose Titration

Another possibility that was considered was that since this was new formulation physicians might have to titrate to a higher comparative dose with the patch in order to obtain a reasonable effect in the morning. If so, then due to the limited strengths available the high Cmax ratio would be driven by exceptionally high Cmax ratios in the younger patients with little difference in the ratios in the older patients. Comparison of Cmax for each treatment by age failed to show such a pattern, (see Figure 12 and Figure 13).

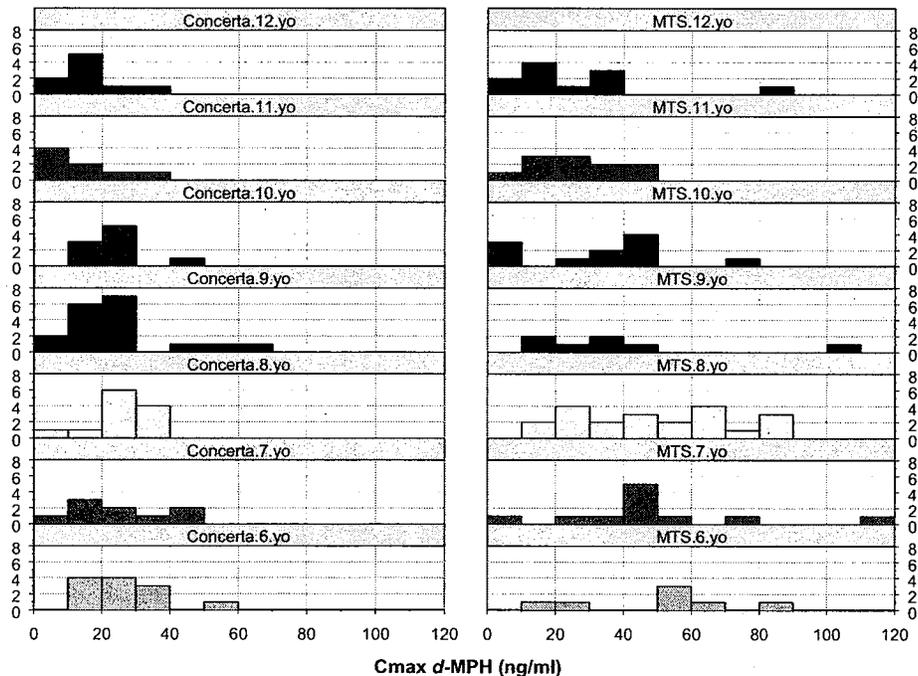
**Figure 12 Comparative Boxplots of Cmaxs for MTS and Concerta by Age for the Pivotal Phase III Study – Study 302**



In fact Figure 12 clearly shows that only a single subject on Concerta had a Cmax greater than 60 ng/ml. Whereas with MTS administration subjects at nearly every age had Cmaxs greater than 60 ng/ml. There's also a clear shift to the right in the distributions thus it is not just some subjects at each age who are driving this observation.

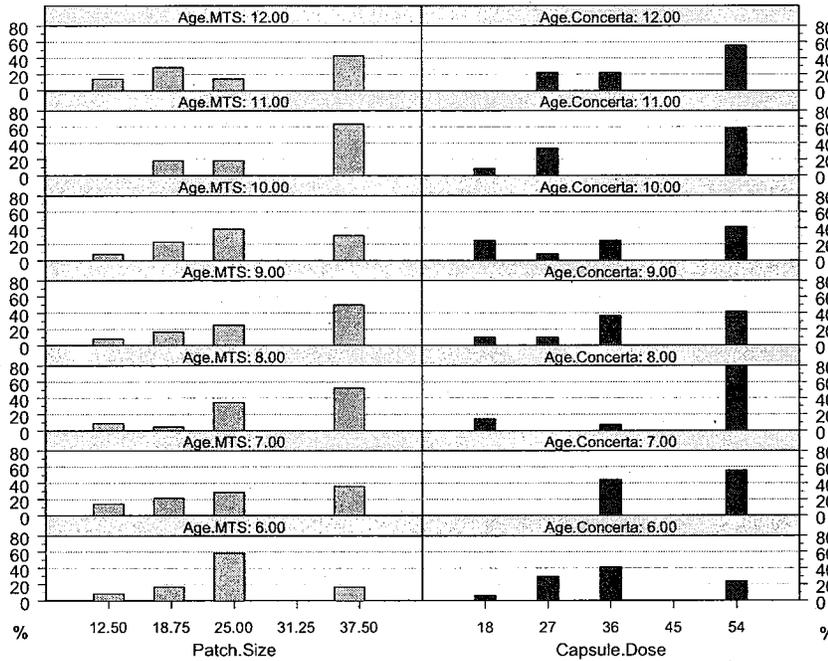
Figure also shows the distribution of Cmaxs achieved with Concerta, although there is a slight shift to right with younger subjects. Based on past experience I would expect only about 1 out of 15 subjects to have a Cmax above 30 ng/ml, whereas about 25% of subjects in the present study have a Cmax of greater than 30 ng/ml. This may be due to recent trends to start at higher doses rather than titrate the dose up, and then even when titrating to titrate to a maximal tolerated dose in order to maximize the effect.

**Figure 13 Histograms of Cmaxs for MTS and Concerta by Age for the Pivotal Phase III Study – Study 302**



Next the distribution of dosages by age was examined. As shown by Figure 14 distribution of dose strengths used are similar for both MTS and Concerta at every age. Thus titration appears to be comparable between groups, and the higher Cmax with MTS are not spurious. Rather Cmax with MTS twice as high as with other formulations are to be expected in clinical practice.

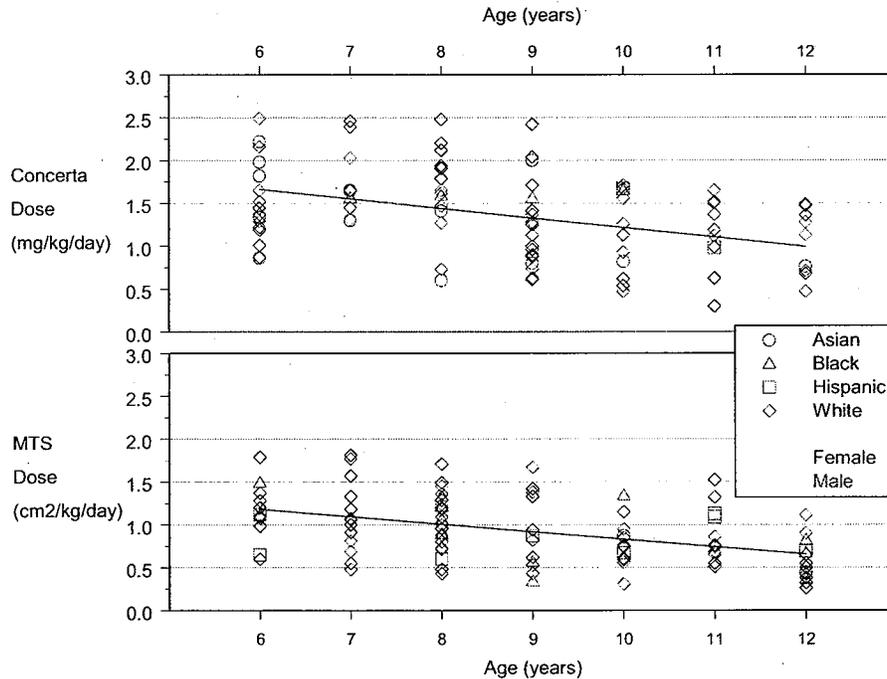
Figure 14 Comparative Histograms of Dosage Strength by Age for both MTS and Concerta in the Pivotal Efficacy Study – Study 302



### 6.4.2.3 Effect of Race and Sex

Plots of weight normalized dosage vs. age also fail to show an obvious pattern by race and sex, (see Figure 15).

Figure 15 MTS and Concerta Weight Normalized Dosage vs. Age by Race and Sex in the Pivotal Phase III Efficacy Study – Study 302



Summary statistics for Cmax and weight normalized dosages for the pivotal phase III efficacy study, (study 302), are shown in Table 9.

Table 9 Comparison of Actual Cmaxs and Dosing for Concerta and MTS by Age from the Pivotal Phase III Efficacy Study – Study 302

Metric	Rx	Age (years)											
		6 – 12 yo	6	7	8	9	10	11	12				
dMPH Cmax (ng/ml)	Concerta	N	82	13	9	13	19	9	23.1 ± 16.1 (69.8) 0 - 67.6 [20.3]	23.7 ± 10.0 (42.2) 13.9 - 46.1 [23.9]	12.5 ± 10.7 [85.8] 0 - 34.8 [9.6]	10	14.9 ± 8.0 (54.1) 5.2 - 30.2 [11.8]
			21.6 ± 12.9 (60.0) 0 - 67.6 [21.2]	24.7 ± 13.5 (54.9) 0 - 52.8 [22.6]	23.9 ± 13.3 (55.7) 0 - 42.3 [22.3]	24.4 ± 10.7 (44.0) 0 - 39.4 [26.1]	23.1 ± 16.1 (69.8) 0 - 67.6 [20.3]	23.7 ± 10.0 (42.2) 13.9 - 46.1 [23.9]	12.5 ± 10.7 [85.8] 0 - 34.8 [9.6]	10	14.9 ± 8.0 (54.1) 5.2 - 30.2 [11.8]		
	MTS	N	80	7	12	21	7	11	11	31.0 ± 21.9 (70.7) 1.0 - 70.0 [33.7]	26.0 ± 13.8 [53.1] 7.6 - 46.5 [22.6]	11	25.4 ± 22.2 (87.5) 2.1 - 80.4 [16.1]
			39.0 ± 25.0 (64.3) 0 - 114 [35.9]	52.6 ± 22.4 (42.5) 18.2 - 83.1 [59.7]	44.8 ± 30.2 (67.3) 0.0 - 114.0 [47.8]	49.4 ± 23.5 (47.6) 14.0 - 84.9 [46.3]	38.5 ± 29.8 (77.3) 10.5 - 100.0 [32.0]	31.0 ± 21.9 (70.7) 1.0 - 70.0 [33.7]	26.0 ± 13.8 [53.1] 7.6 - 46.5 [22.6]	11	25.4 ± 22.2 (87.5) 2.1 - 80.4 [16.1]		
	Ratio	1.8											
Apparent Dose	Concerta (mg/kg)	N	—	13	9	13	19	9	1.3 ± 0.50 (39.8) 0.6 - 2.4 [1.25]	1.4 ± 0.4 (25.5) 0.8 - 1.7 [1.6]	1.1 ± 0.4 [33.4] 0.6 - 1.5 [1.1]	10	1.0 ± 0.4 (35.1) 0.5 - 1.5 [1.1]
			—	1.6 ± 0.4 (28.4) 0.9 - 2.5 [1.4]	1.8 ± 0.4 (25.0) 1.3 - 2.5 [1.7]	1.7 ± 0.4 (26.3) 0.7 - 2.5 [1.7]	1.3 ± 0.50 (39.8) 0.6 - 2.4 [1.25]	1.4 ± 0.4 (25.5) 0.8 - 1.7 [1.6]	1.1 ± 0.4 [33.4] 0.6 - 1.5 [1.1]	10	1.0 ± 0.4 (35.1) 0.5 - 1.5 [1.1]		
	MTS (cm <sup>2</sup> /kg)	N	—	7	12	21	7	11	11	0.8 ± 0.2 (29.6) 0.6 - 1.3 [0.8]	0.9 ± 0.3 [36.8] 0.5 - 1.5 [0.8]	11	0.6 ± 0.3 (44.4) 0.3 - 1.1 [0.5]
			—	1.2 ± 0.4 (29.9) 0.6 - 1.8 [1.2]	1.1 ± 0.4 (36.7) 0.5 - 1.8 [1.0]	1.0 ± 0.3 (32.2) 0.4 - 1.7 [1.1]	0.9 ± 0.5 (50.1) 0.4 - 1.7 [0.8]	0.8 ± 0.2 (29.6) 0.6 - 1.3 [0.8]	0.9 ± 0.3 [36.8] 0.5 - 1.5 [0.8]	11	0.6 ± 0.3 (44.4) 0.3 - 1.1 [0.5]		

## 6.5 Clinical Implications

Potential clinical implications of these high Cmaxs were investigated by exploration of PK-PD relationships in both the phase III and phase II studies.

Although this might be criticized as drop outs might skew the data, or as dose titration prevents a true dose finding study. PK-PD is still a reasonable approach for the following reasons:

Subject disposition and dosing are similar in the phase III study for both MTS and Concerta in spite of differences in Cmaxs, see (Table 10).

MTS dosing and Cmax exposures in the phase II and phase III studies are similar indicating that the phase II data may be extrapolated to the phase III data, (see Table 9 and Figure 16).

There were essentially no drop-outs in the phase II study, (see Table 11).

The phase II study collected PK-PD information over virtually the entire concentration achieved in each subject. Therefore even though this is not a concentration controlled trial and a complete concentration effect curve is not possible for every subject it can still provide a good estimate of the population mean values and the variability.

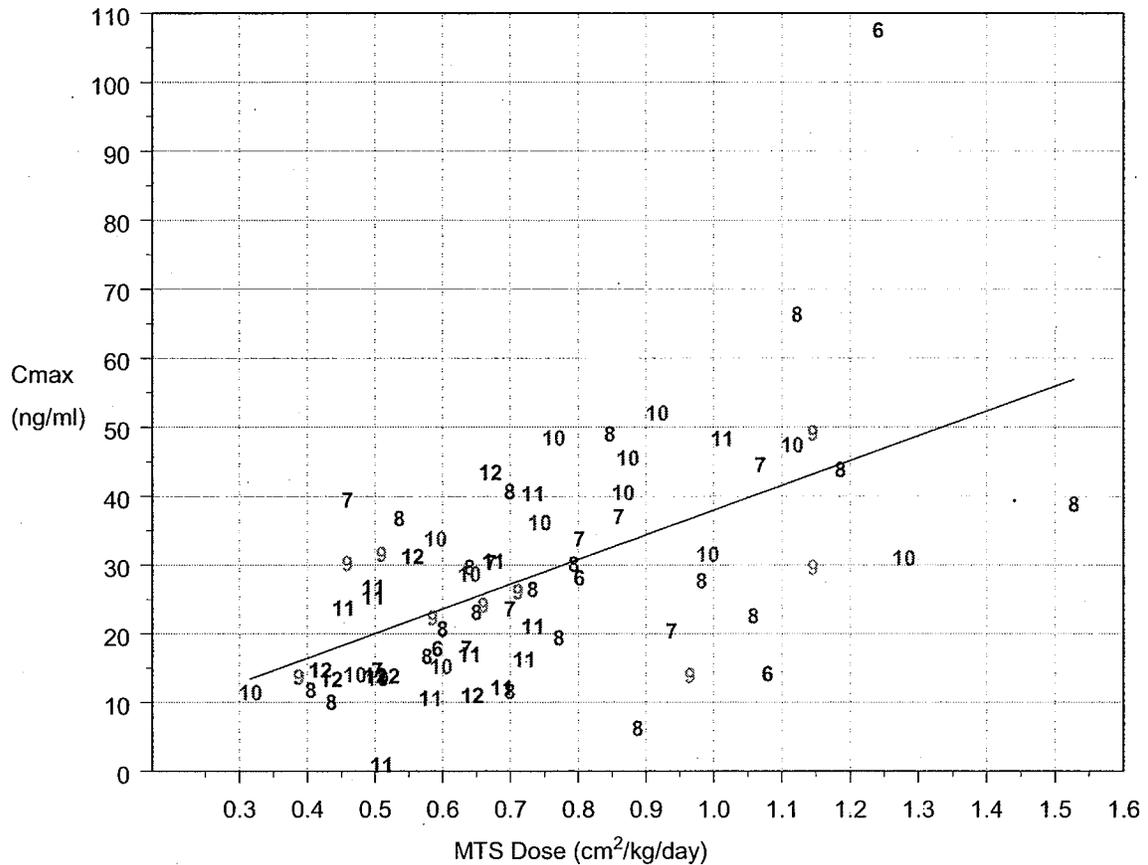
**Table 10 Subject Disposition by Active Treatment in the Pivotal Phase III Study – Study 302**

Group	MTS		CONCERTA	
	N	%	N	%
Enrolled	100	—	94	—
Randomized	100	—	94	—
ITT	96	—	89	—
Completed‡	71	74	66	74
Per Protocol	60	62.5	55	61.7
PK population	72	75	70	78.6
Safety population	98	NA	91	NA

**Table 11 Subject Disposition in the Phase II PK-PD Study – Study 201**

Group	n	%
Enrolled	93	—
Terminated prior to Randomization	13	14
Randomized	80	100.0
Discontinued Post-Randomization	1	1.3
Completed	79	98.8
<b>Primary Reason for Discontinuation Post-Randomization:</b>		
Adverse Event(s)	0	0
Protocol Violation	1	1.3
<b>Analysis Populations:</b>		
Safety	93	NA
ITT	79	98.8
Per Protocol	56	70.0
PK – with Cmax and AUC	74	92.5
PK/PD - with any PK/PD Data	78	<b>97.5</b>

**Figure 16** d-MPH Cmax vs. Normalized MTS Dose (cm<sup>2</sup>/kg/day) by Age in Phase II PK-PD study - Study 201



Pharmacometric summary statistics calculated by OCPB for study 201 are shown in Table 12.

**Table 12** Pharmacometric Summary Statistics for the Phase II PK-PD Study – Study 201

Tmax (hours)	Cmax (ng/ml)	AUCt (ng/ml x hr <sup>-1</sup> )
N = 73	N = 75	N = 75
8.2 ± 1.8 (22.2)	28.1 ± 16.2 (57.9)	209.2 ± 140.5 (67.1)
2.0 - 12.0 [9.0]	1.3 - 108.0 [26.6]	5.8 - 942.4 [179.1]

### 6.5.1 Safety 6.5.1.1 Weight Change

Figure 17 and figure 17 show that the percent weight change reaches a population average  $E_{max}$  of around 5% at 40 ng/ml, and that the percent weight loss is independent of age. Therefore even if  $C_{max}$  concentrations are higher with MTS, the expected average percent weight loss might be 4% with MTS vs. 2.5% with Concerta. Whether a 4% weight loss is acceptable in this population should be considered by the medical review team.

Figure 17 % Weight Change with MTS in the Pivotal Phase III Efficacy Trial vs. d-MPH Concentrations by Age

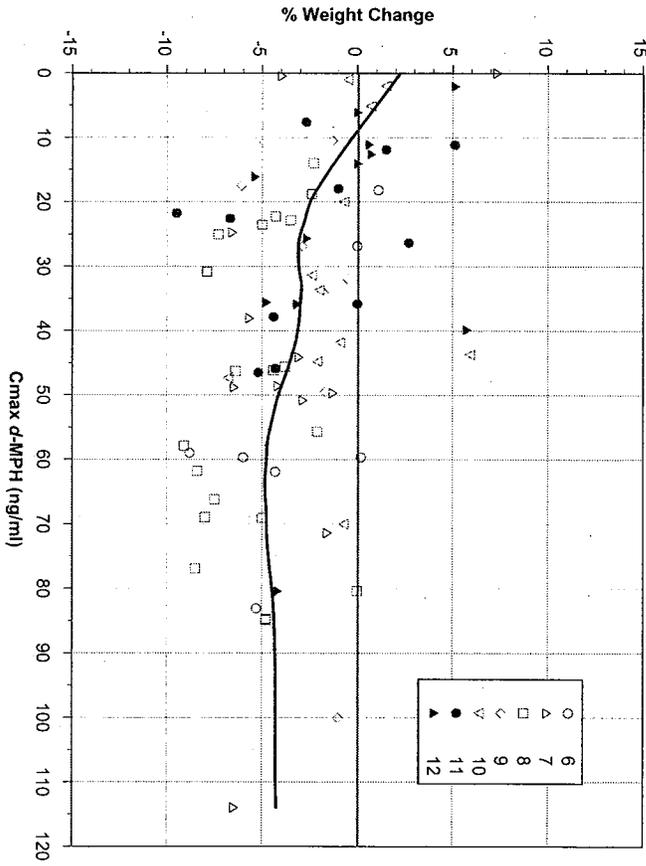
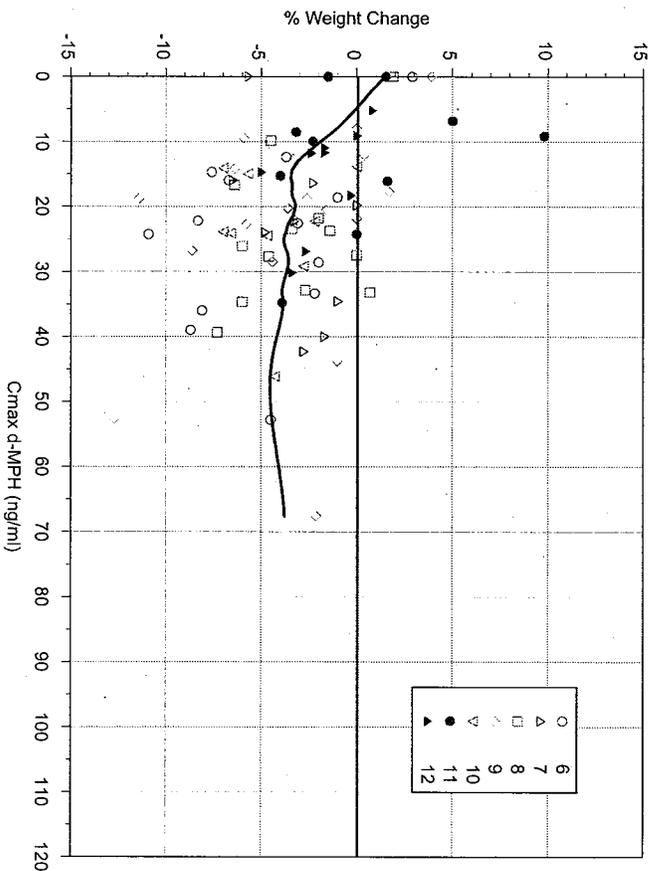


Figure 18 % Weight Change with Concerta in the Pivotal Phase III Efficacy Trial vs. d-MPH Concentrations by Age



### 6.5.1.2 Heart Rate

A similar quantitative effect profile is seen with heart rate, thus a slightly higher maximum change in heart rate of a few bpm's is expected with MTS but the effect in the subjects with higher Cmaxs with MTS will have reached a maximum, (see Figure 19 and Figure 20).

Figure 19 Sponsor's Emax Goodness-of-Fit: Model Prediction and Observed Data of Baseline Adjusted HR versus d-MPH Concentration – Study 201

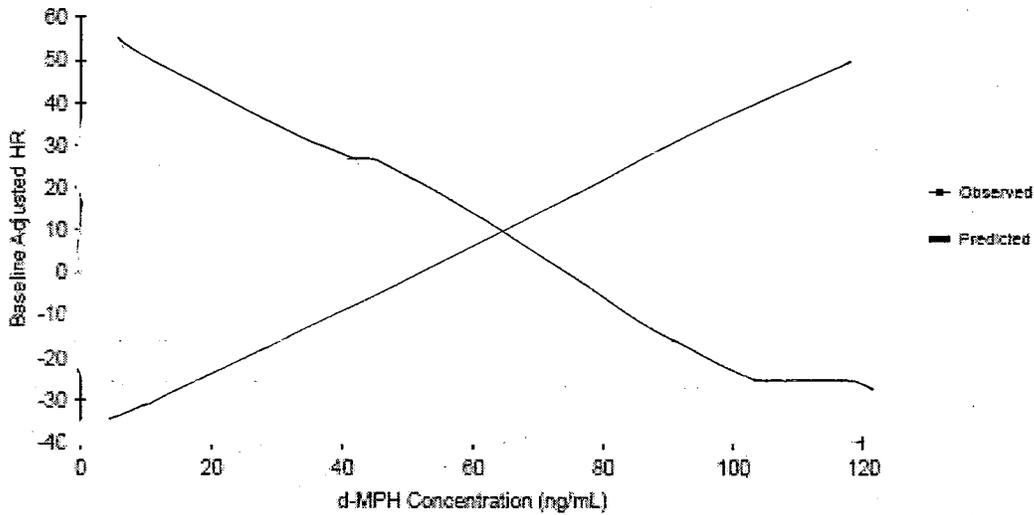
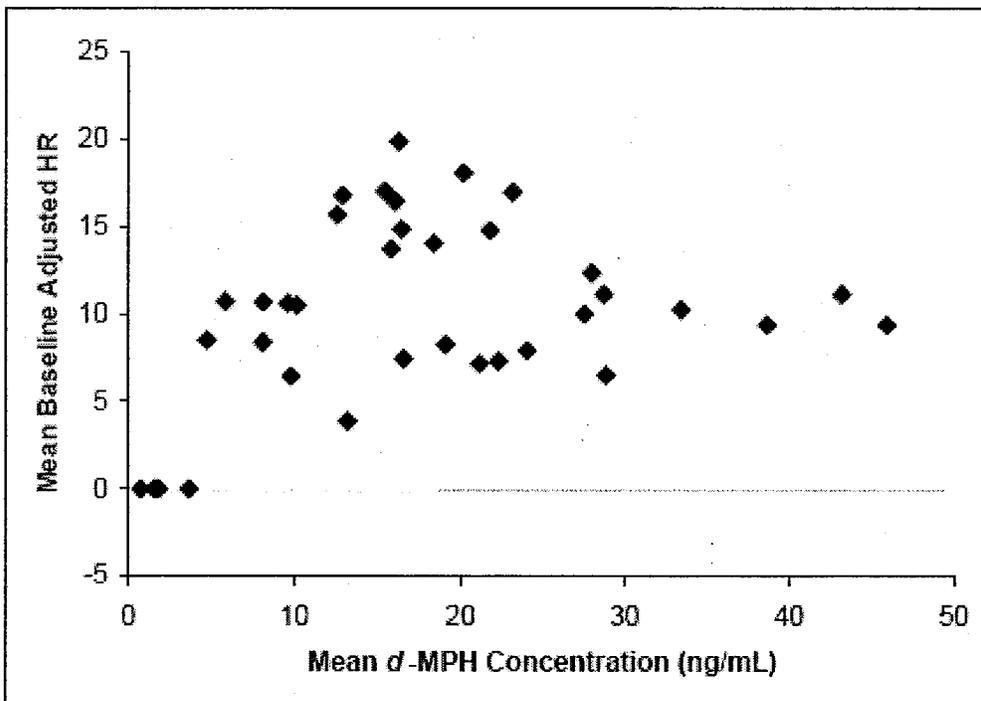


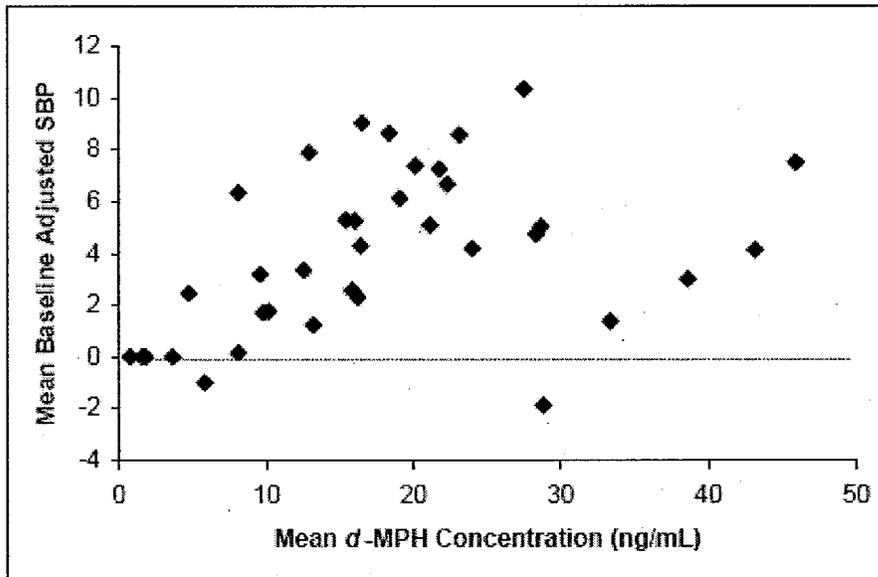
Figure 20 Mean Baseline Adjusted HR vs. Mean d-MPH Concentration



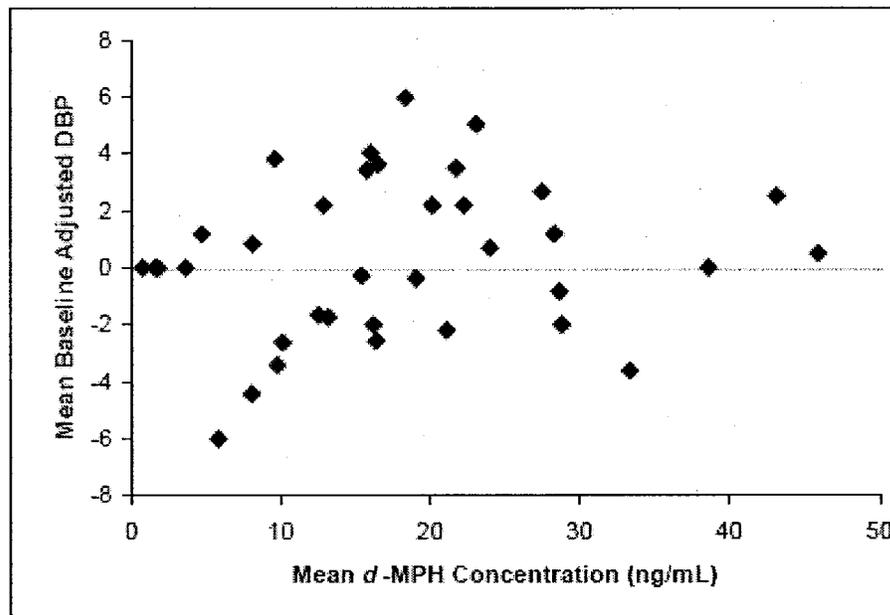
### 6.5.1.3 Blood Pressure

A similar situation with exists with systolic blood pressure, (see Figure 21), although no clear effect on diastolic blood pressure is evident, (see Figure 22). This is not entirely surprising as systolic BP is affected by cardiac output, whereas increases in DBP with age are thought to be due a loss of vascular elasticity, and children likely have adequate vascular elasticity to compensate.

**Figure 21 Mean Baseline Adjusted SBP versus Mean *d*-MPH Concentration – Study 201**



**Figure 22 Mean Baseline Adjusted DBP versus Mean *d*-MPH Concentration – Study 201**



Although, these effects on heart rate and blood pressure raise questions about their long-term implications, any long term complications must also be balanced against the long term effects of not treating ADHD.

## 6.5.2 Efficacy

Another issue is whether lowering the dose to lower Cmax would alter efficacy, both in terms of maximal effect and in terms of the time of onset and duration.

These questions were addressed by examination of the Phase II PK-PD study data from study 201.

Subjects included children an adequate distribution of children 6-12 yo with ADHD with a minimum baseline ADHD-RS-IV score of 26 and an IQ of at least 80.

The study employed a 5 week titration phase with 3 dose escalations at weekly intervals followed by a week to allow dosage decrease if necessary. Dosages were 12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, 25 cm<sup>2</sup>, and 37.5 cm<sup>2</sup> patches applied daily to alternating hips for 9 hours each day. This is similar to the titration procedure used in the phase III efficacy study. At the end of the titration phase, (end of week 5), the subjects were given a practice classroom session, followed by a 2 week crossover phase with MTS and placebo patches with classroom sessions at the end of each of the weeks. PK blood samples were obtained, and SKAMP-D assessments and PERMP tests performed pre-dose, and 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours post patch application.

The statistical analysis of mean efficacy compared to placebo at each time point was reviewed by the medical and statistical reviewer, whereas this review focuses on the PK-PD and clinical pharmacology implications.

### 6.5.2.1 Measurement of Efficacy

Although symptoms of ADHD on average become worse as the day progresses never-the-less they are highly variable within an individual patient, which raises difficulties with respect to the appropriate measures to used for PK-PD analysis as well as data visualization. Thus various methods of data correction were first explored, and this exploration is shown in the next several figures.

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Figure 23 shows the raw SKAMP scores by time after MTS patch application.

**Figure 23 SKAMP Score vs. Time after Patch Application – Study 201**

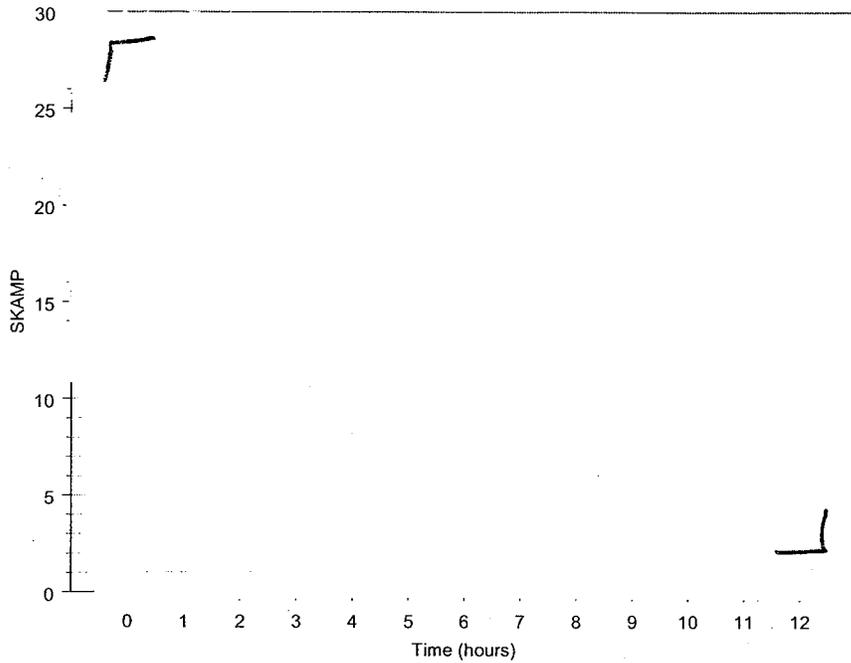


Figure 24 shows the baseline adjusted SKAMP scores by time after MTS patch application. This was explored to adjust for inter-individual differences in baseline severity, (i.e. time 0 score)

**Figure 24 Baseline Adjusted SKAMP Score vs. Time after Patch Application – Study 201**

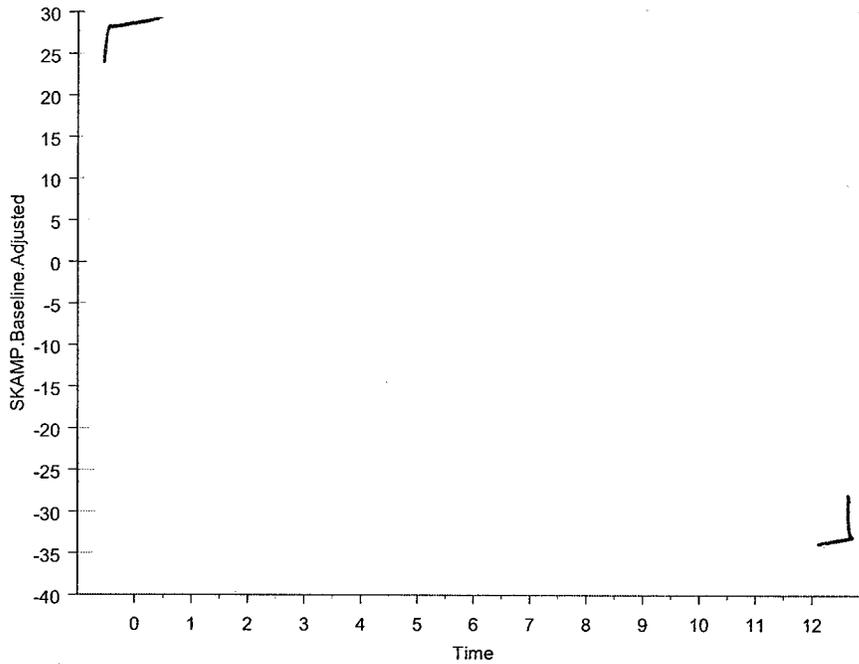


Figure 25 and Figure 26 show adjustments for the expected worsening in symptoms over the course of a day by adjusting for placebo scores at each time point. Figure 25 shows adjustments based on the patients own scores on placebo and Figure 26 scores adjustments based on mean placebo score. Both should probably be examined due to intra-subject variability on different days.

Figure 25 Individual Placebo Corrected SKAMP Score vs. Time after Patch Application – Study 201

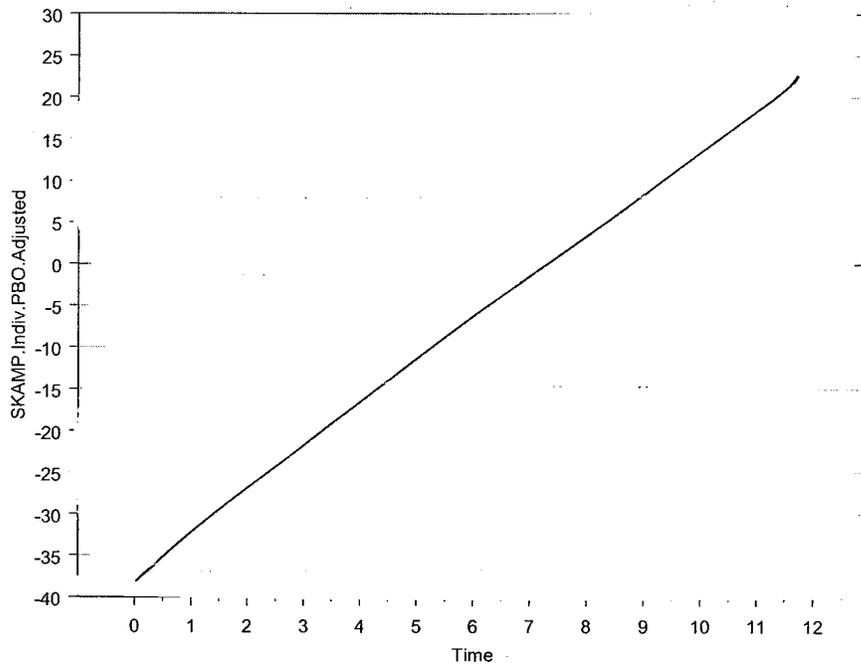


Figure 26 Mean Placebo Corrected SKAMP Score vs. Time after Patch Application – Study 201

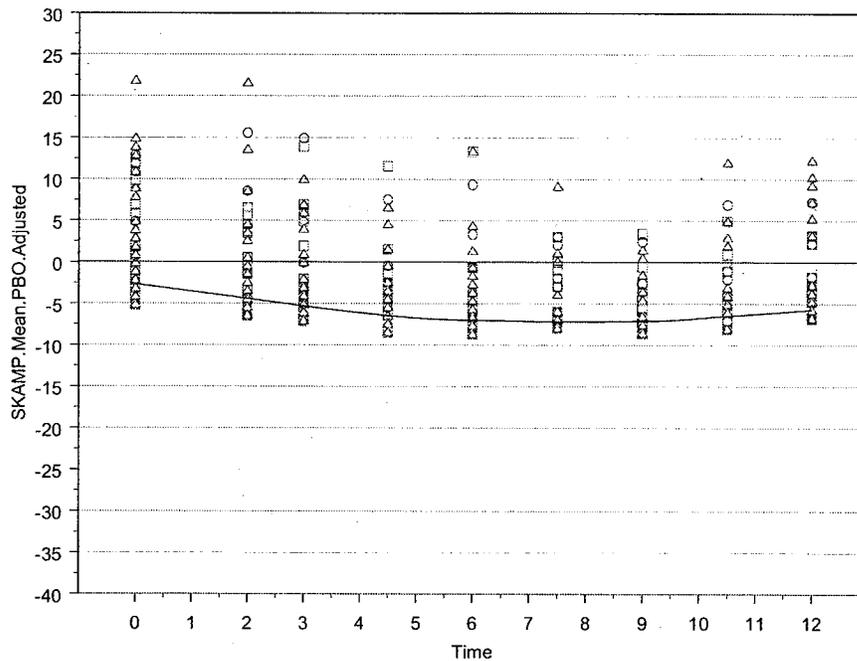
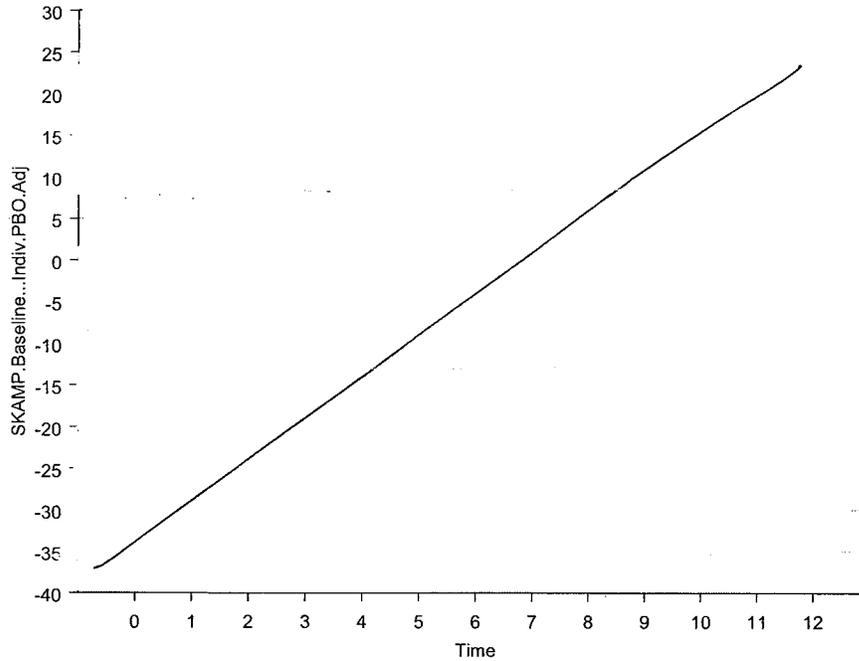


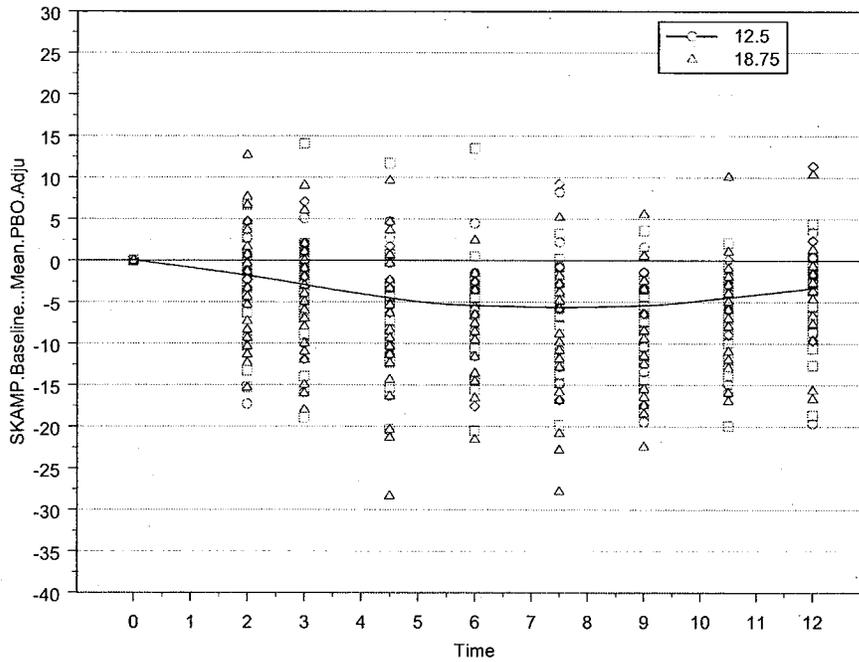
Figure 27 and Figure 28 show the individual and mean placebo corrected scores vs. time adjusted for the baseline score at time 0. Both of these show that the average maximum change in score is about 5 point

and that efficacy probably extends beyond 12 hours. They also show that a large percentage of the patients do not have any efficacy at 2 or 3 hours. In addition, Figure 28 shows dosage is possibly reasonably distributed. Although further analysis is necessary beyond this figure.

**Figure 27 Baseline Adjusted and Individual Placebo Corrected SKAMP Score vs. Time after Patch Application – Study 201**



**Figure 28 Baseline Adjusted and Mean Placebo Corrected SKAMP Score vs. Time after Patch Application – Study 201**



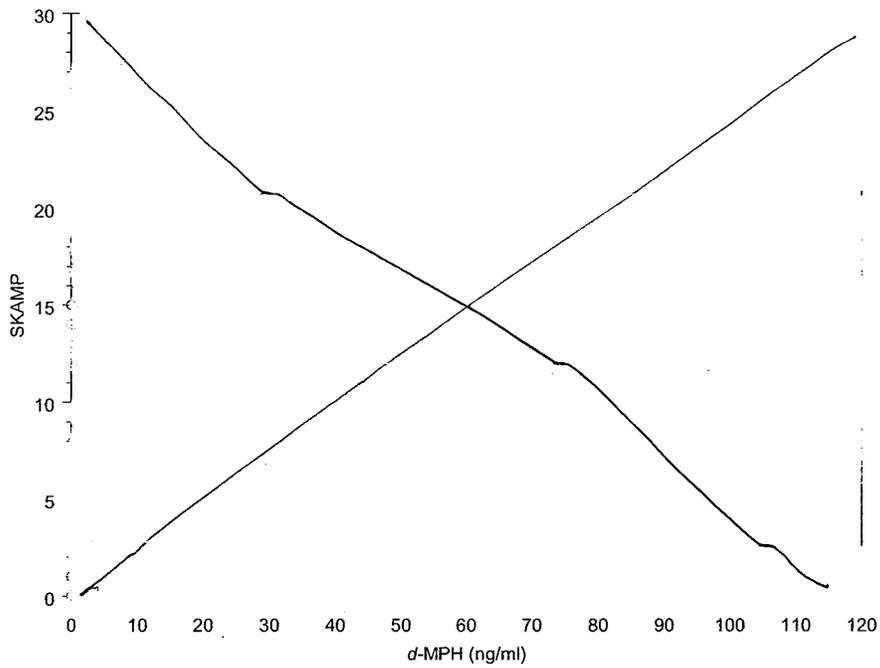
## 6.5.2.2 Measurements of Efficacy (SKAMP-D) vs. Concentration

### 6.5.2.2.1 Population PK-PD

Population PK-PD relationships were explored using the various measurements of efficacy.

Figure 29 shows the raw SKAMP-D scores vs. *d*-MPH concentration.

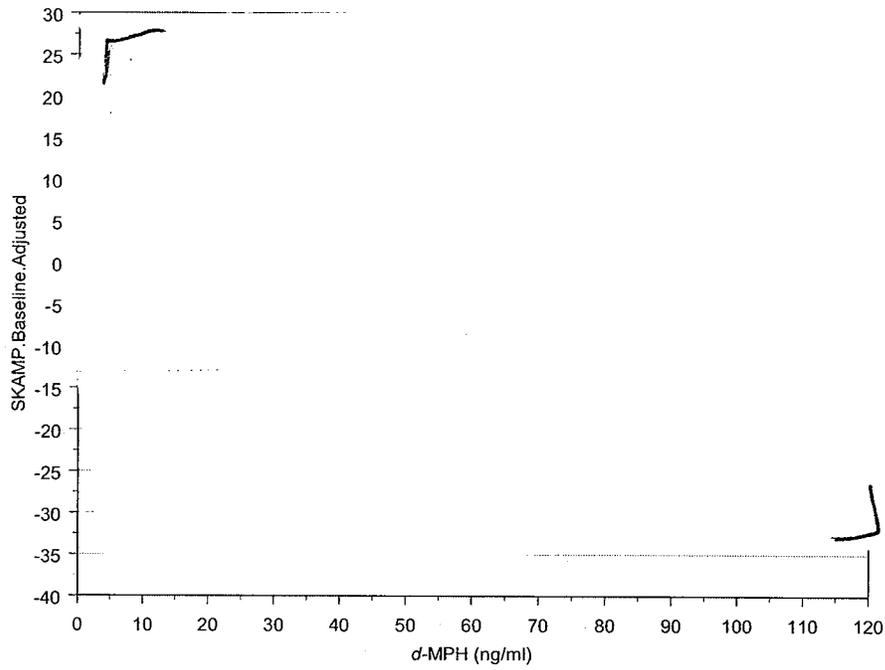
**Figure 29 SKAMP-D Score vs. *d*-MPH Concentration – Study 201**



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Figure 30 shows the baseline corrected SKAMP-D scores vs. d-MPH concentration.

**Figure 30 Baseline Adjusted SKAMP-D Score vs. d-MPH Concentration – Study 201**

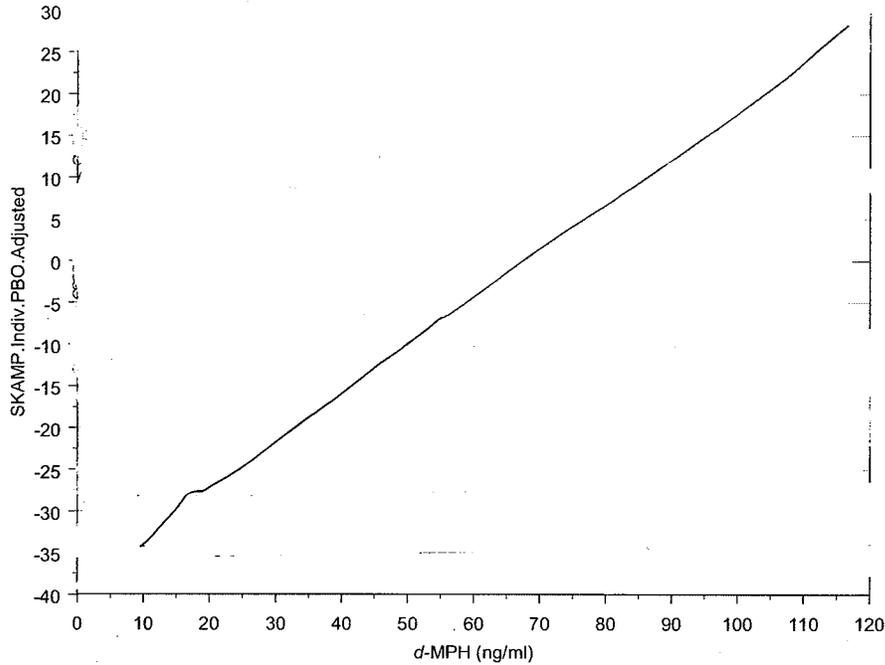


The apparent lack of efficacy at high concentrations is spurious due to the worsening of the underlying disease as the day progresses. As shown in the following placebo adjusted PK-PD profiles.

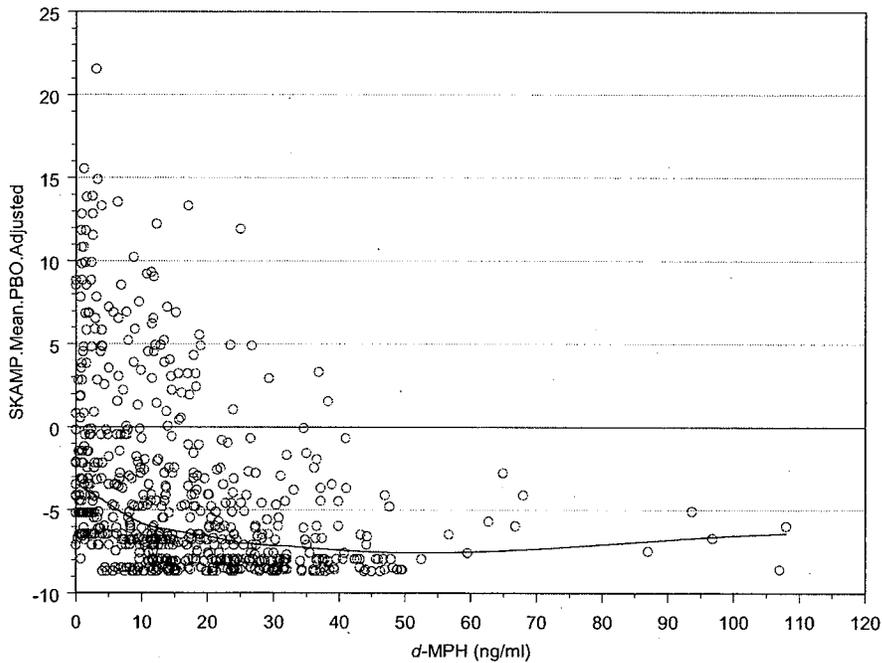
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Figure 31 and Figure 32 show the individual and mean placebo corrected SKAMP-D scores vs. *d*-MPH concentration respectively.

**Figure 31 Individual Placebo Corrected SKAMP-D Score vs. *d*-MPH Concentration – Study 201**

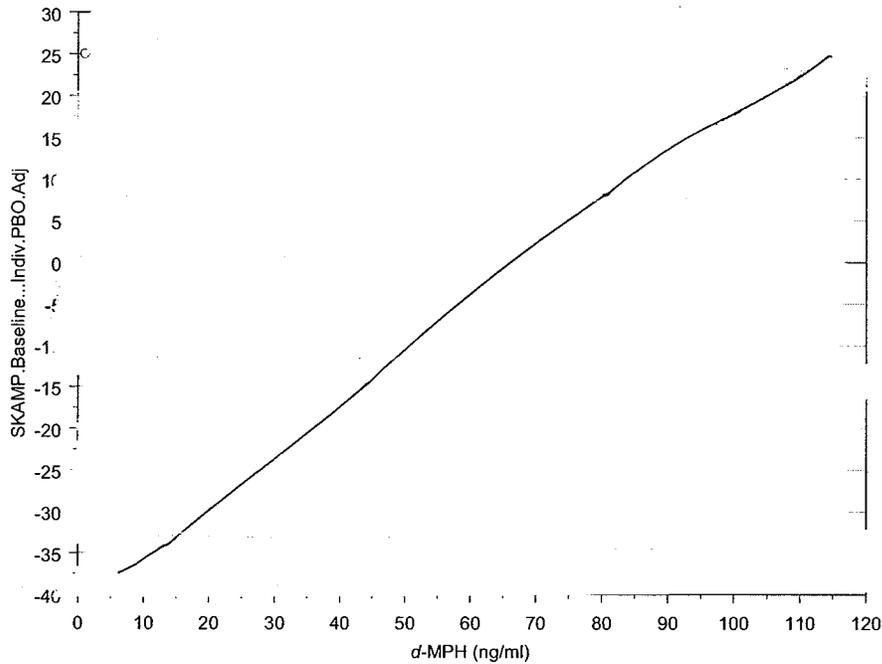


**Figure 32 Mean Placebo Corrected SKAMP-D Score vs. *d*-MPH Concentration – Study 201**

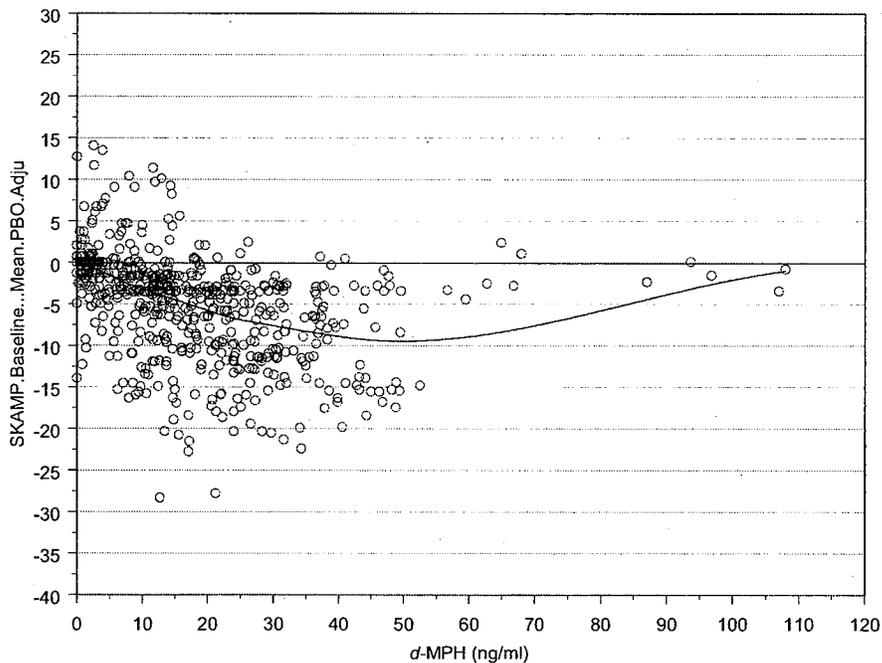


Whereas Figure 33 and Figure 34 show the individual and mean placebo corrected SKAMP-D scores adjusted for baseline vs. *d*-MPH concentration.

**Figure 33 Baseline and Individual Placebo Corrected SKAMP-D Score vs. *d*-MPH Concentration – Study 201**



**Figure 34 Baseline and Mean Placebo Corrected SKAMP-D Score vs. *d*-MPH Concentration – Study 201**



These plots indicated that individual placebo and baseline corrected plots might be the most useful.

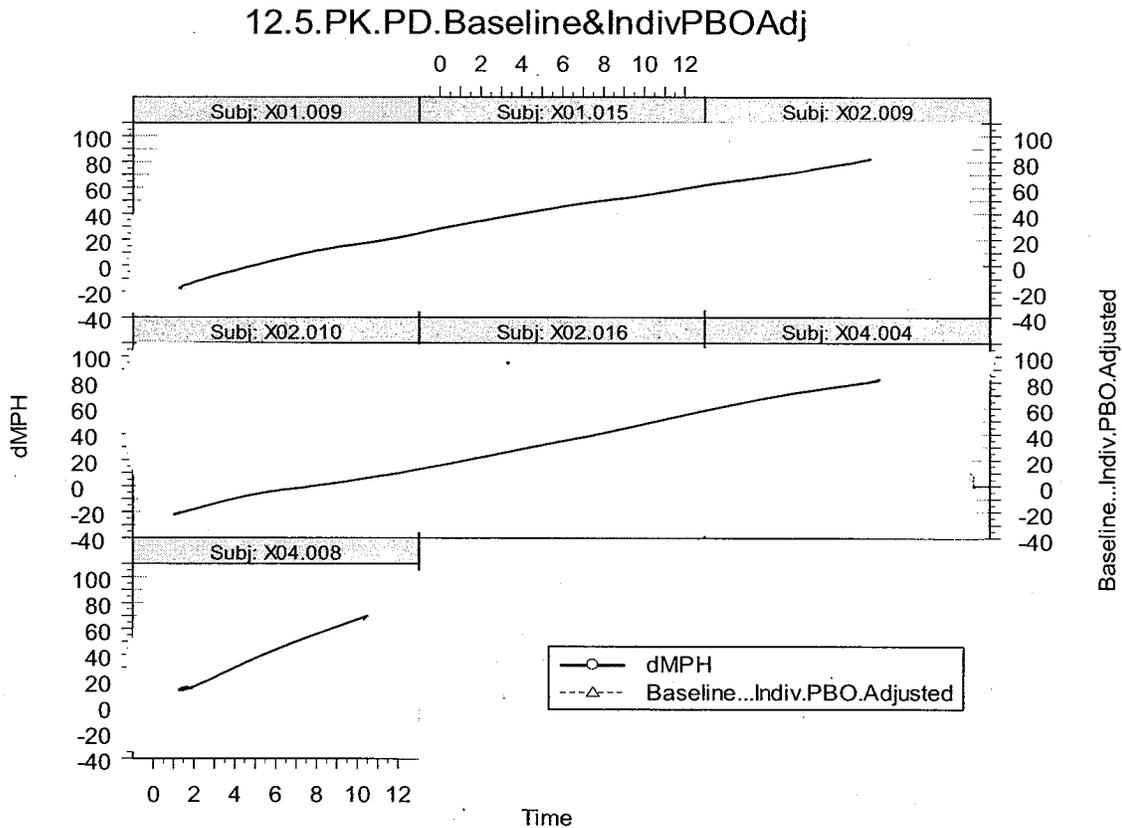
### 6.5.2.2.2 Individual PK-PD Relationships

Individual placebo adjusted and baseline corrected SKAMP-D scores vs. time profiles were plotted side-by-side with *d*-MPH concentration vs. time profiles, and are reproduced on a smaller scale by dose on the next several pages in Figure 35 to Figure 38.

What was most striking is that those individuals with high C<sub>max</sub>s also had very high early concentrations and many but not all of these subjects had a greater response in SKAMP-D scores at early time points.

This led to the question of whether these particular subjects were driving the 2 hour efficacy scores. It also reinforced the original question of whether there was clinical adequate efficacy early in the day and also introduced the question whether patients who may or may not have high exposures and efficacy early in the day could be predicted *a priori*.

**Figure 35 Baseline and Individual Placebo Corrected SKAMP Scores vs. *d*-MPH Concentration by Subject for Subjects receiving the 12.5 cm<sup>2</sup> MTS – Study 201**



**Figure 36 Baseline and Individual Placebo Corrected SKAMP Scores vs. d-MPH Concentration by Subject for Subjects receiving the 18.75 cm<sup>2</sup> MTS – Study 201**

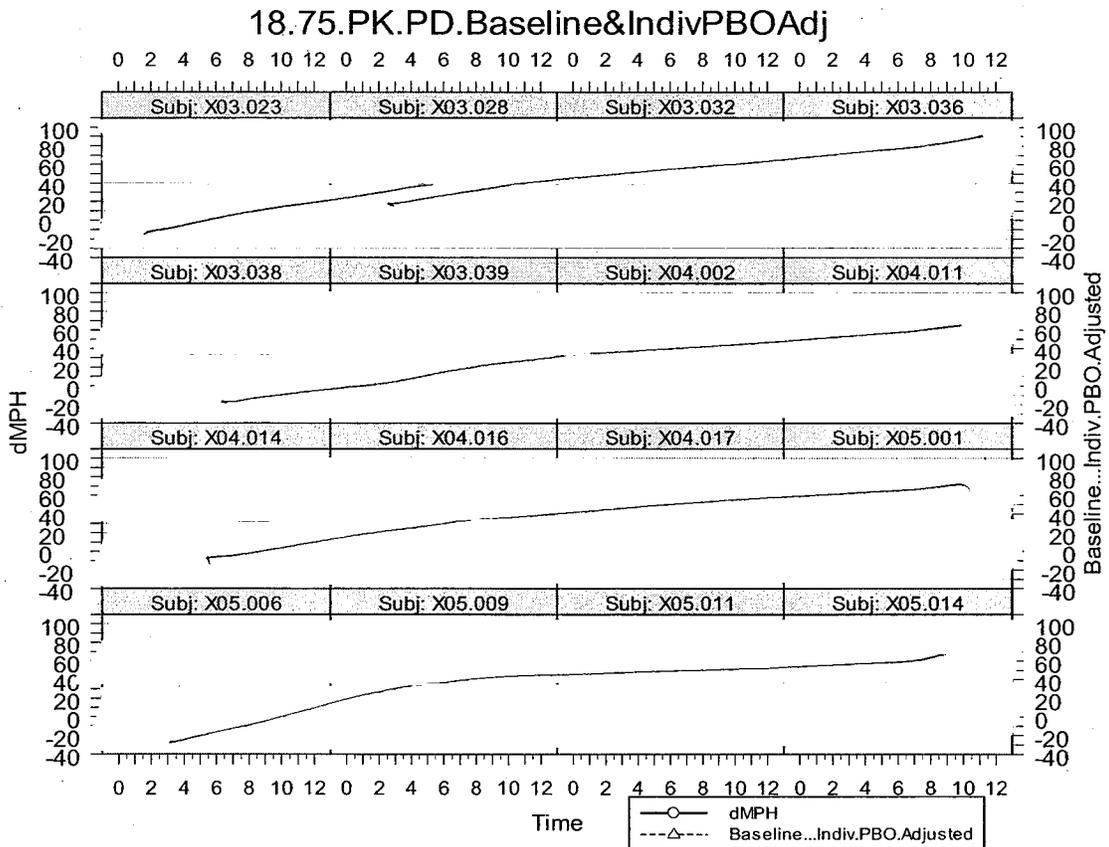
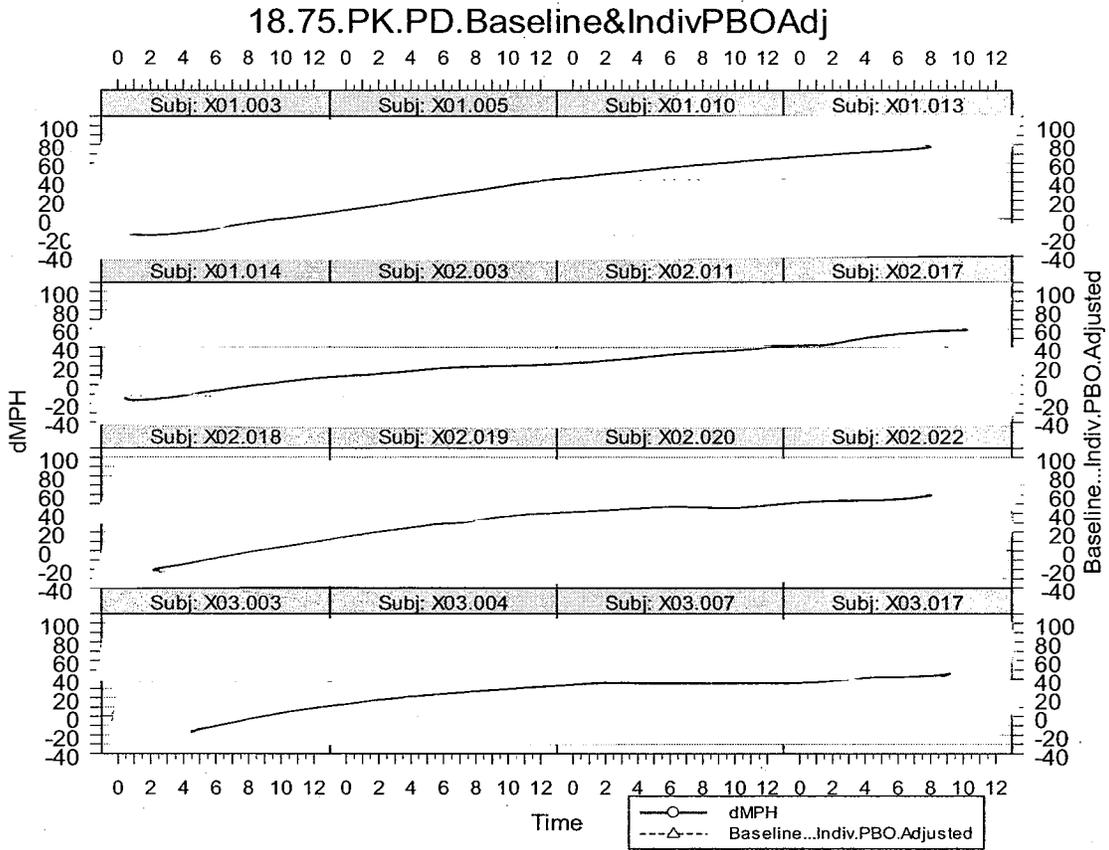
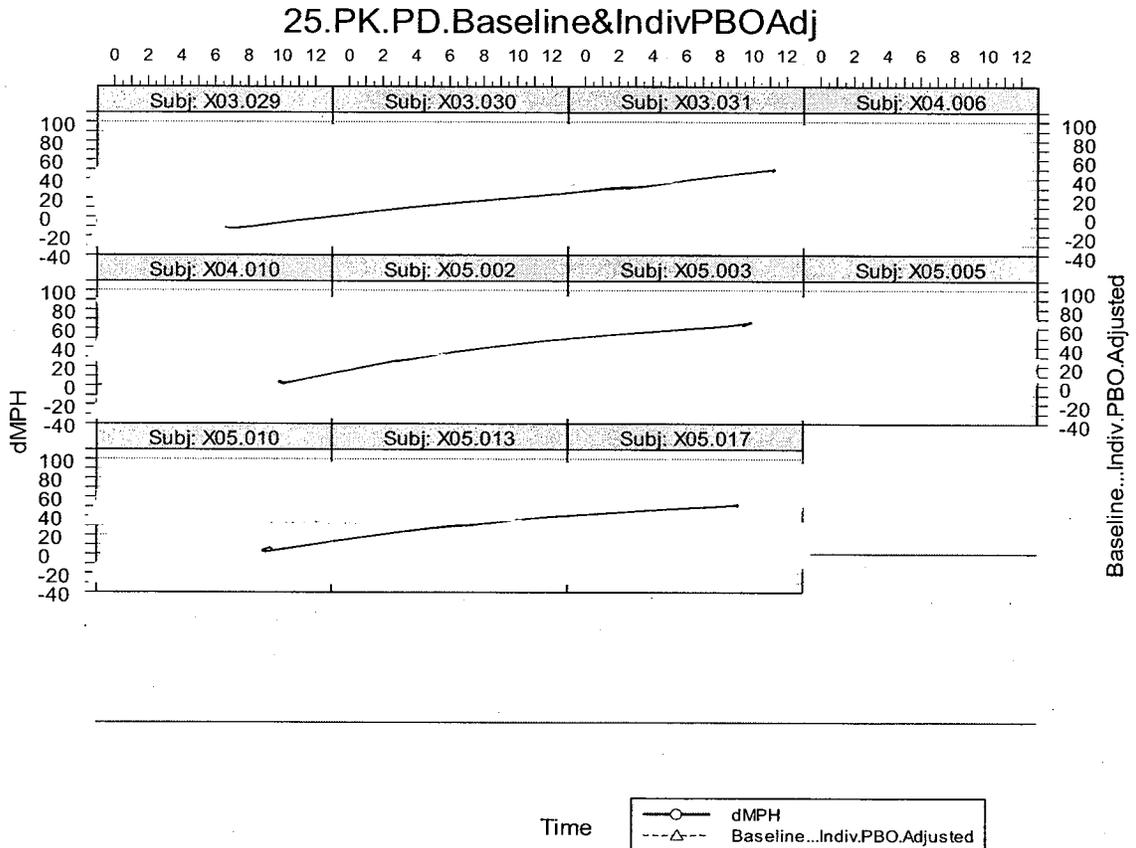
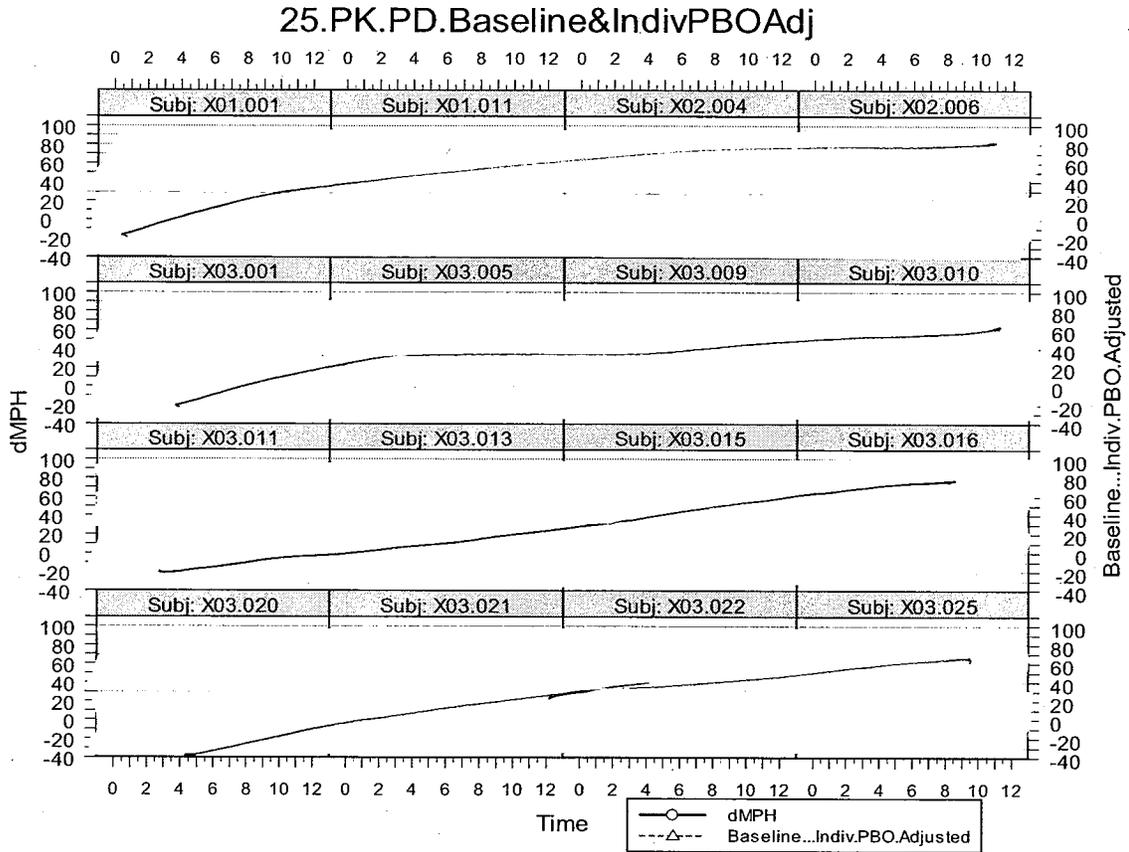
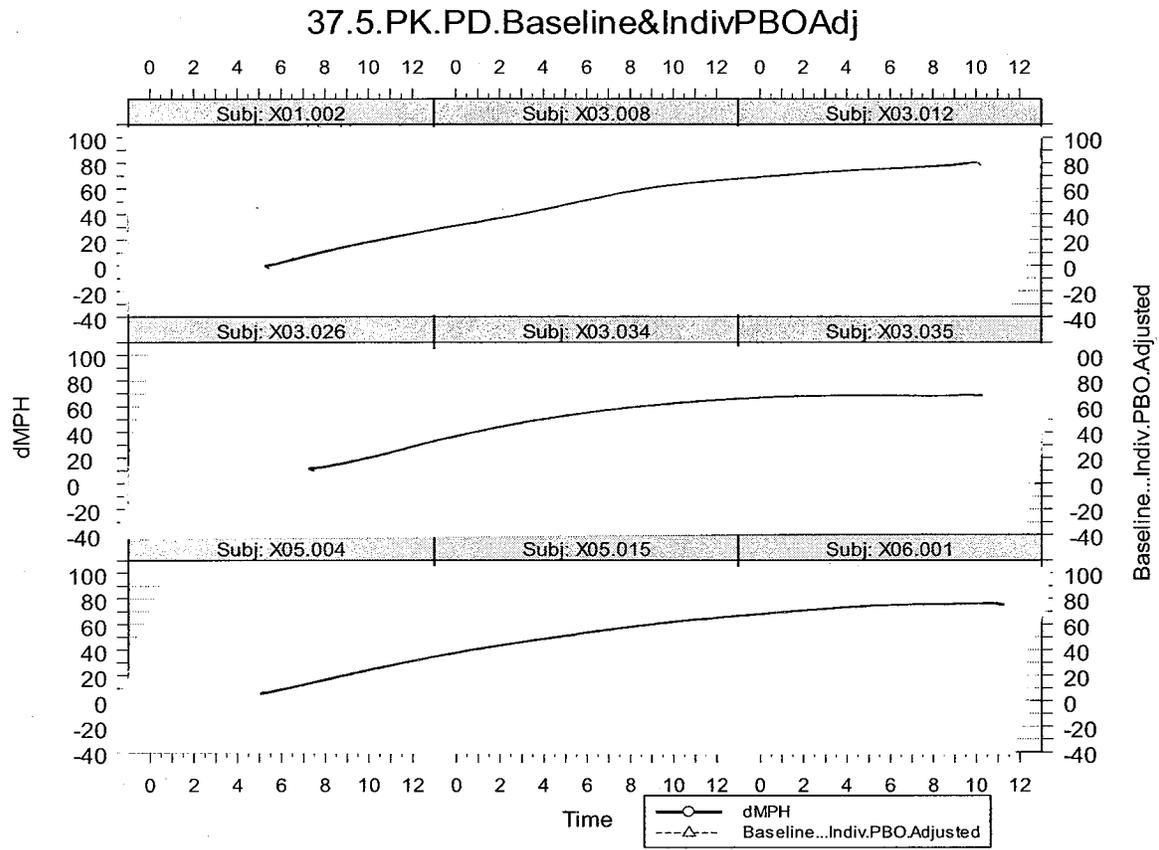


Figure 37 Baseline and Individual Placebo Corrected SKAMP Scores vs. d-MPH Concentration by Subject for Subjects receiving the 25 cm<sup>2</sup> MTS – Study 201



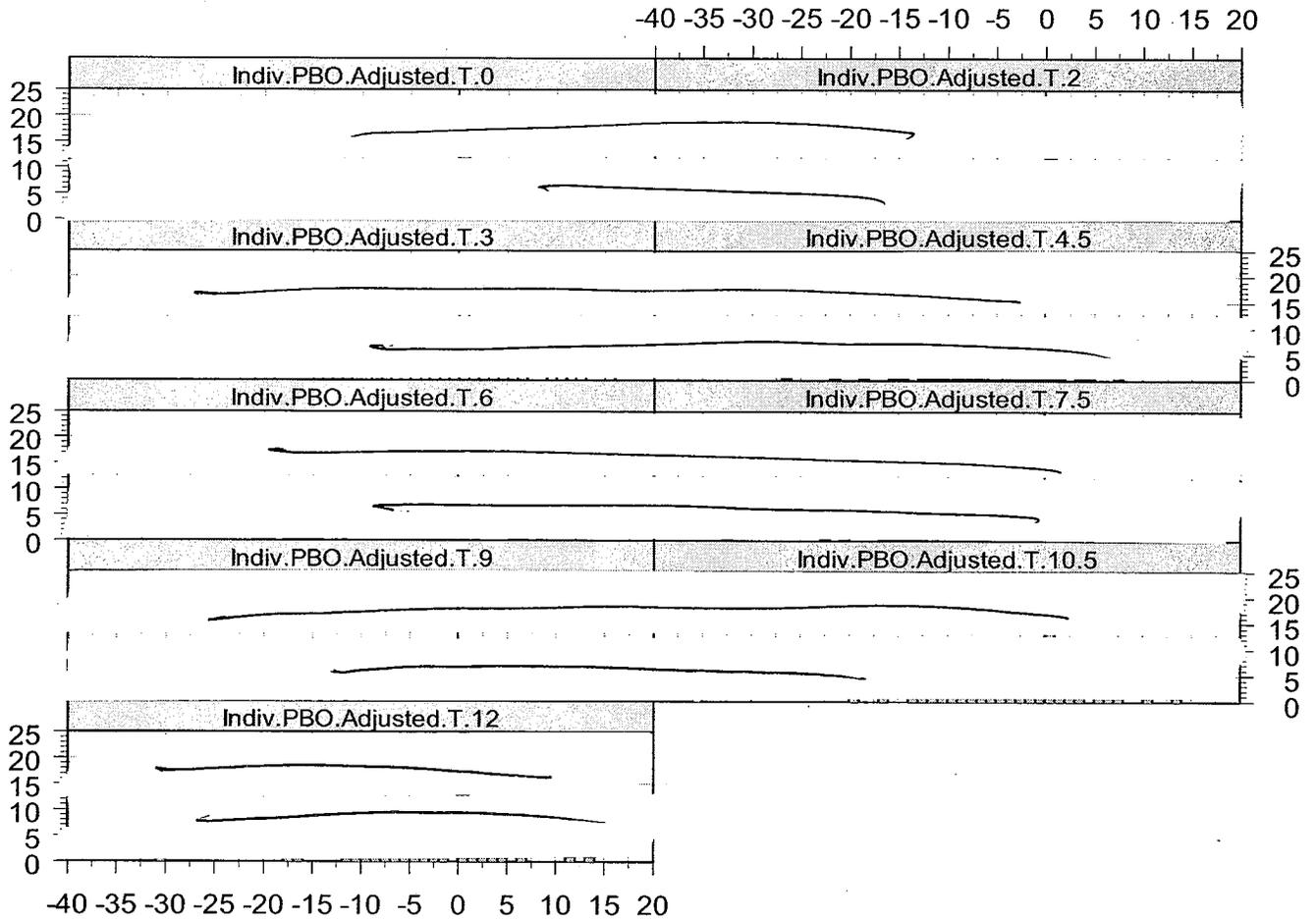
**Figure 38 Baseline and Individual Placebo Corrected SKAMP Scores vs. d-MPH Concentration by Subject for Subjects receiving the 37.5 cm<sup>2</sup> MTS – Study 201**



### 6.5.3 Time of Onset

Figure 39 shows that although there is a shift to the left in the SKAMP-D scores at 2 hours compared to prior to patch application and that this shift continues with throughout the 9 hour wear time. There's still significant overlap of the 2 and 3 hour SKAMP scores with the predose SKAMP scores such that only a minority of patients are actually having a clinical effect by 2 hours.

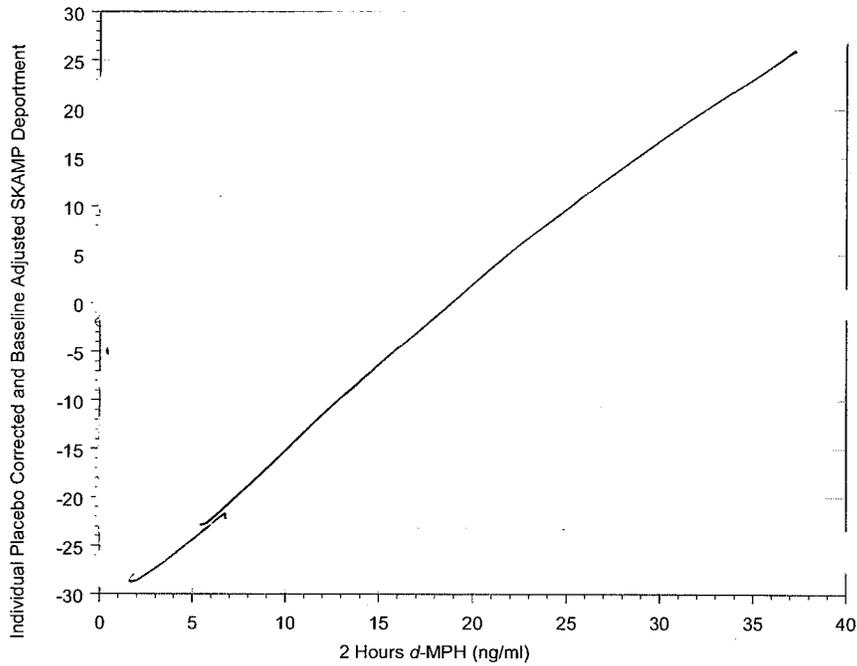
Figure 39 Histograms of Individual Placebo Adjusted SKAMP-D Scores by Time after Patch Application – Study 201



This is more evident in the next several figures.

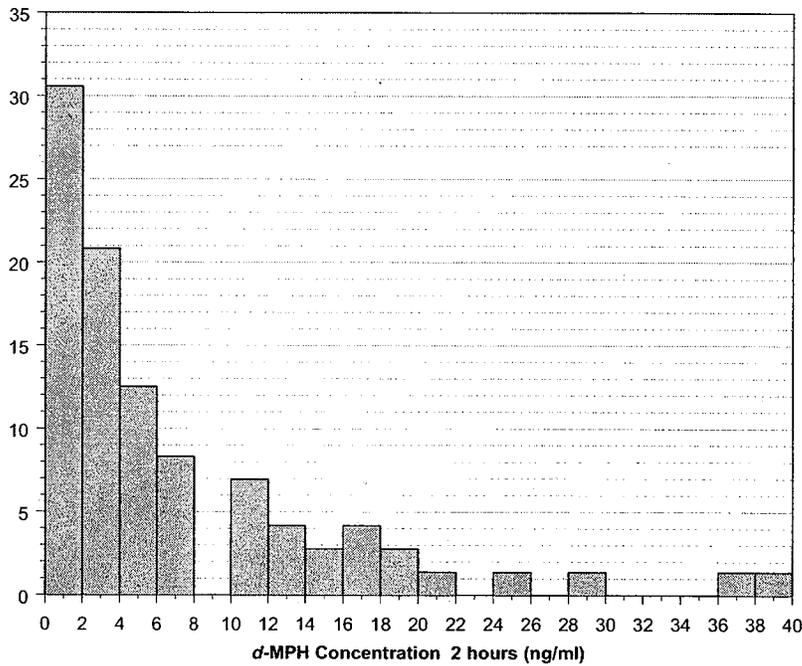
From Figure 40 we see that measurable changes in SKAMP score require a minimum d-MPH concentration of approximately 5 ng/ml, which is consistent with what has previously been observed in other NDAs.

**Figure 40 Individual Placebo Corrected and Baseline Corrected SKAMP-D Scores at 2 hours vs. d-MPH Concentration – Study 201**



Whereas from Figure 41 it's apparent that less than 50% of subjects had a 2 hour concentration of less than 4 ng/ml.

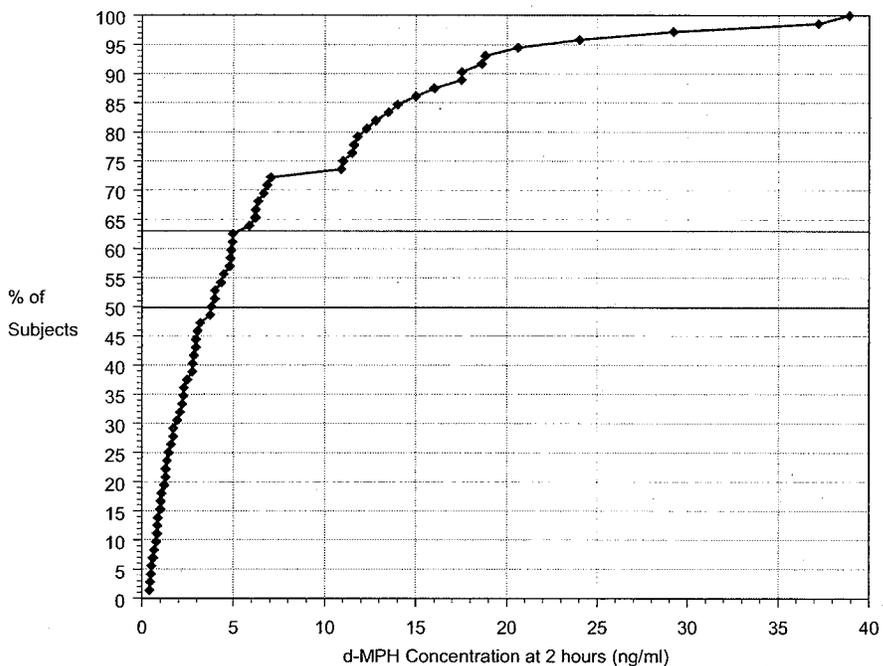
**Figure 41 Frequency Histogram of MTS 2 Hour d-MPH Concentrations - Study 201<sup>a</sup>**



a Y axis is % of subjects

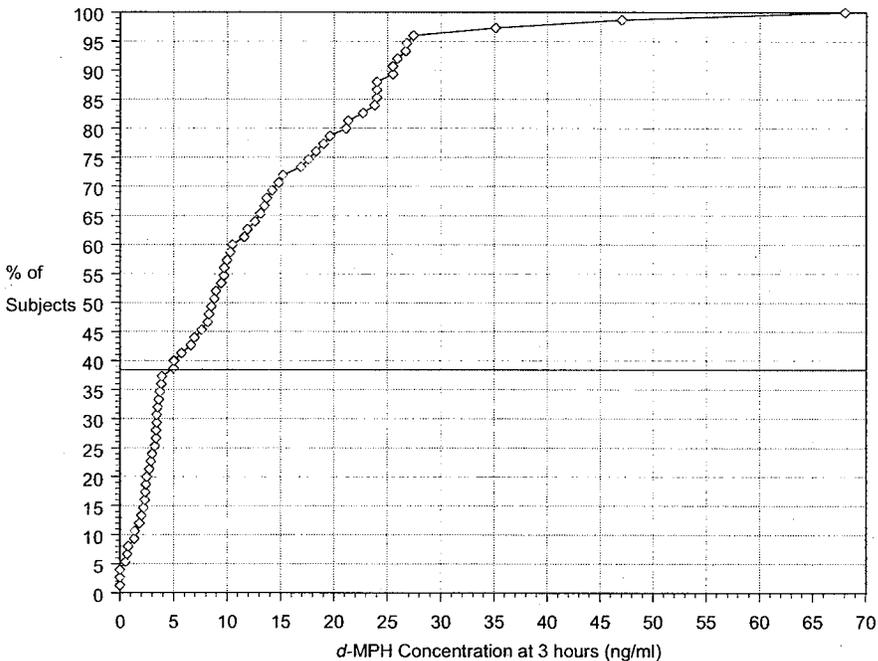
This is shown more clearly in Figure 42 from which we can see that approximately only about 1/3 of subjects had d-MPH concentrations of > 5ng/ml at 2 hours.

**Figure 42 Cumulative Frequency Distribution (%) vs. MTS 2 Hour d-MPH Concentrations - Study 201**



In addition at 3 hours 40% of subjects still had d-MPH concentrations less than 5 ng/ml.

**Figure 43 Cumulative Frequency Distribution (%) vs. MTS 3 Hour d-MPH Concentrations - Study 201**



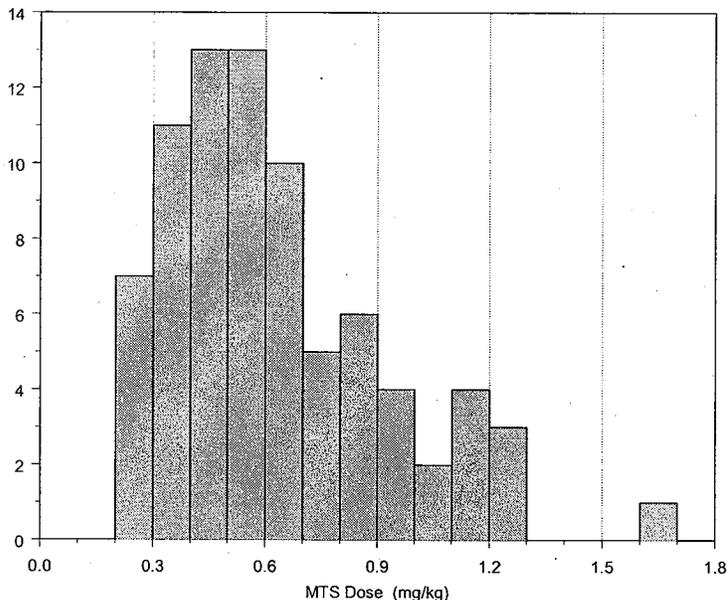
### 6.5.3.1 Prediction of Time of Onset

A variety of factors were examined to determine if the time of onset with or without high exposures (i.e.  $C_{max} > 30$  or  $40$  ng/ml) could be predicted.

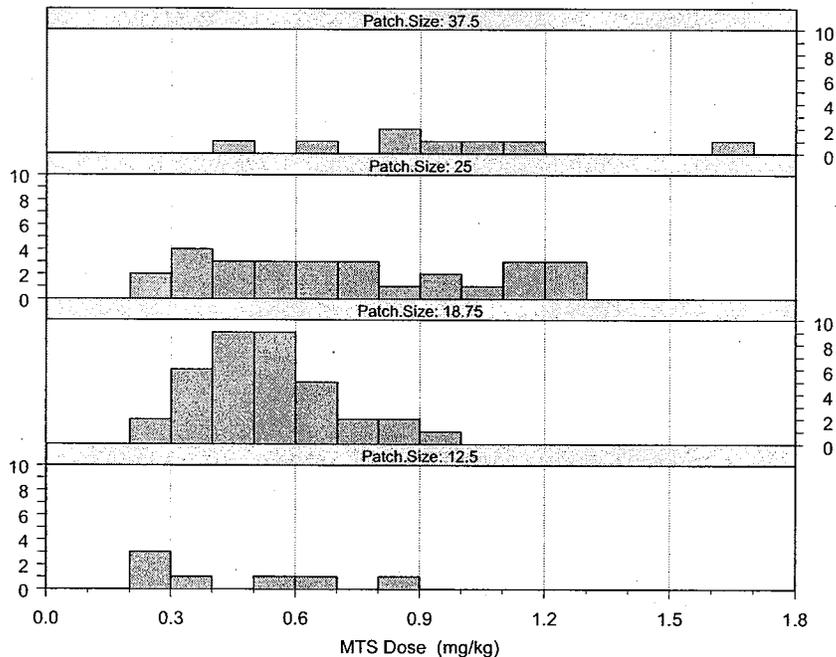
#### 6.5.3.1.1 Age and Time of Onset

Due to the limitation of available dose strengths as mentioned in section 6.4.2.2 due to the limitation of dosage strengths it's possible that a younger subjects could receive a higher weight normalized dosage compared to older children. This is potentially hinted at in Figure 44 and Figure 45.

**Figure 44 Histogram of Weight Normalized Dose in Study 201**

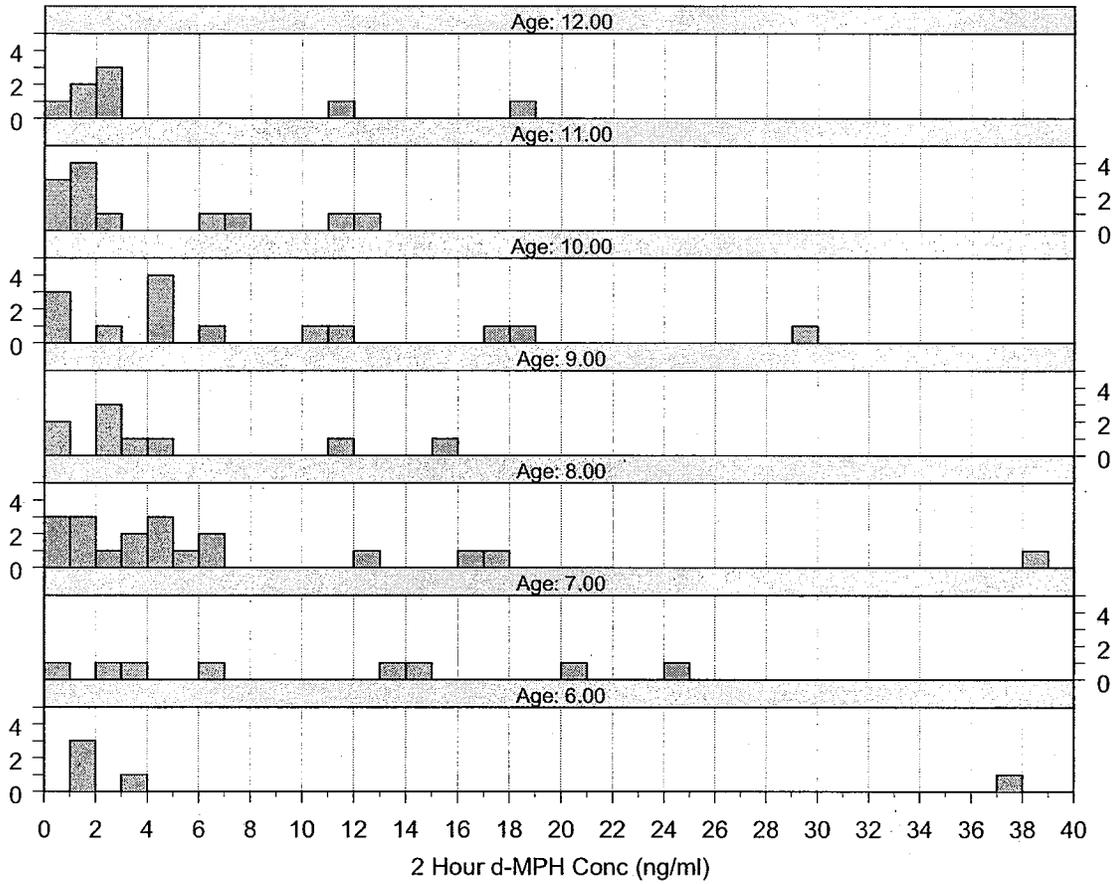


**Figure 45 Histograms of Weight Normalized Dose in Study 201 by Patch Size**



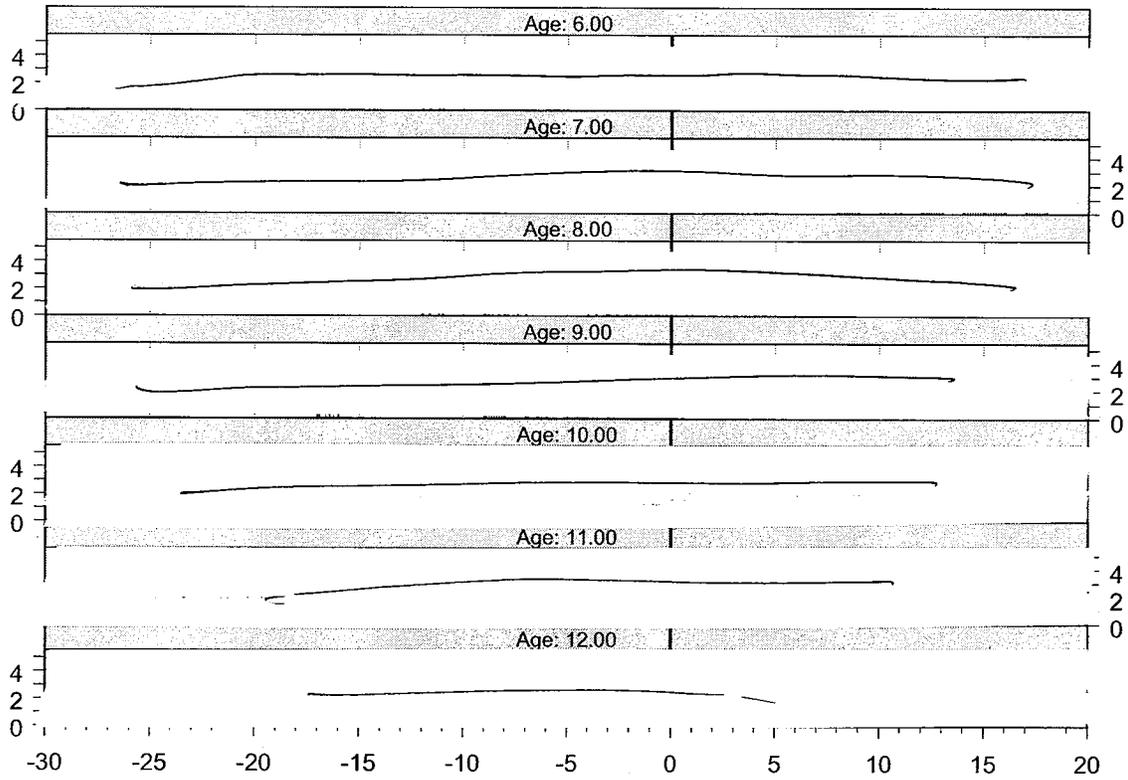
Ultimately patient age was shown to not be a good predictor as demonstrated by the distributions of d-MPH Concentrations and SKAMP-D scores by age in Figure 46 and Figure 47.

**Figure 46 Histogram of MTS 2 Hour d-MPH Concentrations by Subject Age- Study 201**



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**Figure 47 Comparative Histograms of Individual Placebo Adjusted SKAMP Scores at 0 and 2 hours by Age**



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6.5.3.1.2 Race and Time of Onset

Study 102 showed a possible relationship in exposures with race and gender, (see Figure 48 and Figure 49). Although there was no effect on Tlag except a slight inverse relationship with dose (see Figure 50). However these findings were not confirmed in study 101, (see Figure 51 and Figure 52).

Figure 48 Dose and Weight Normalized AUCt by Dose, Race, and Gender in Study 102

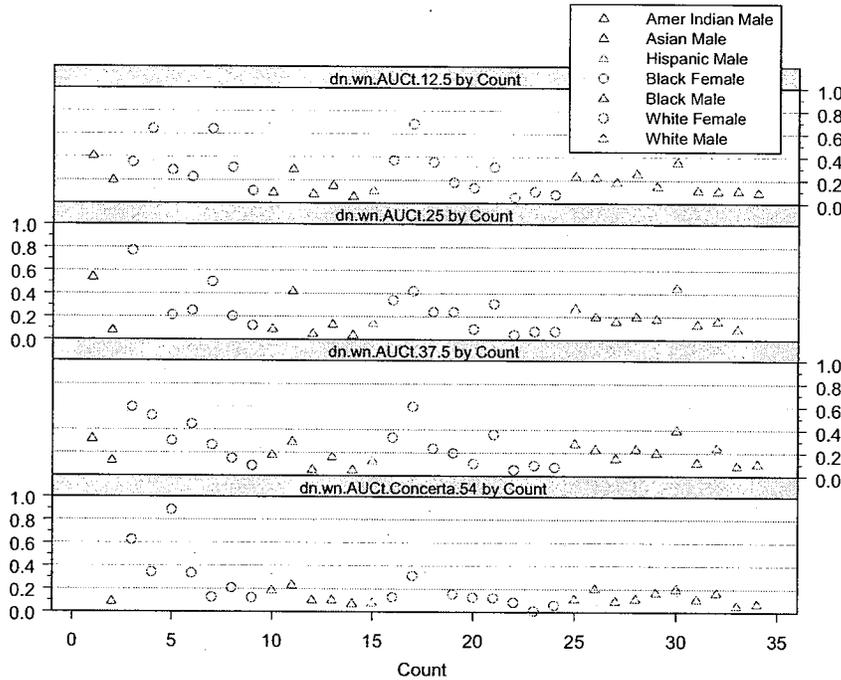
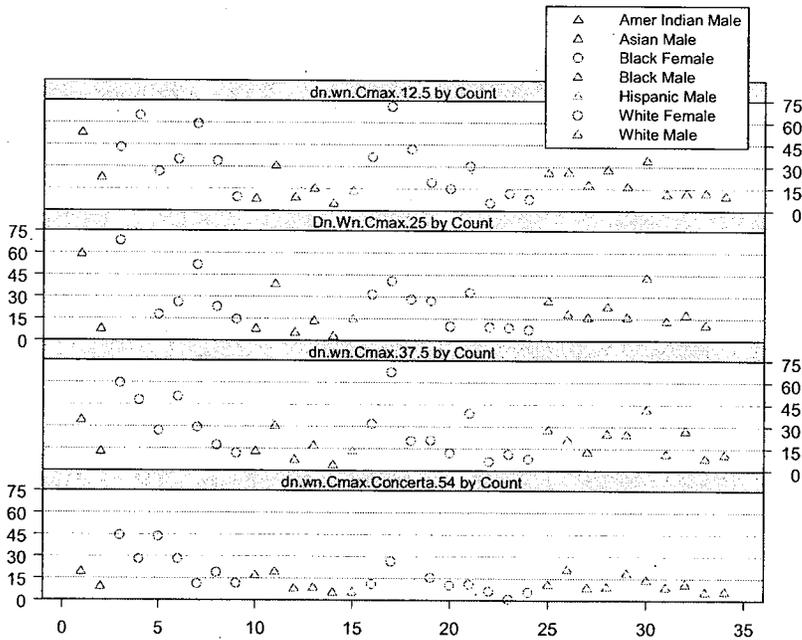
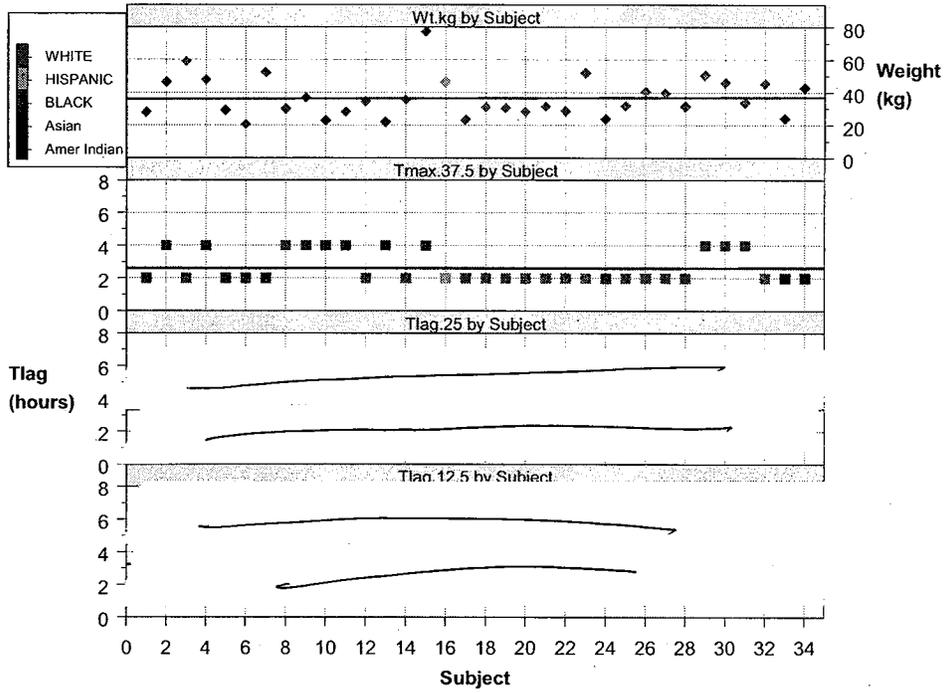


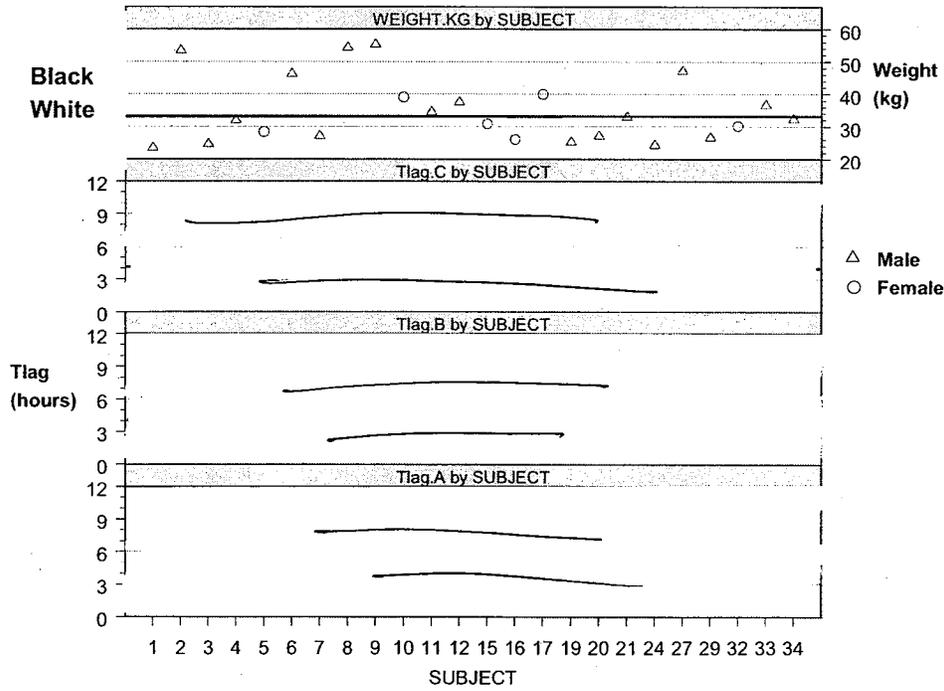
Figure 49 Dose and Weight Normalized Cmax by Dose, Race, and Gender in Study 102



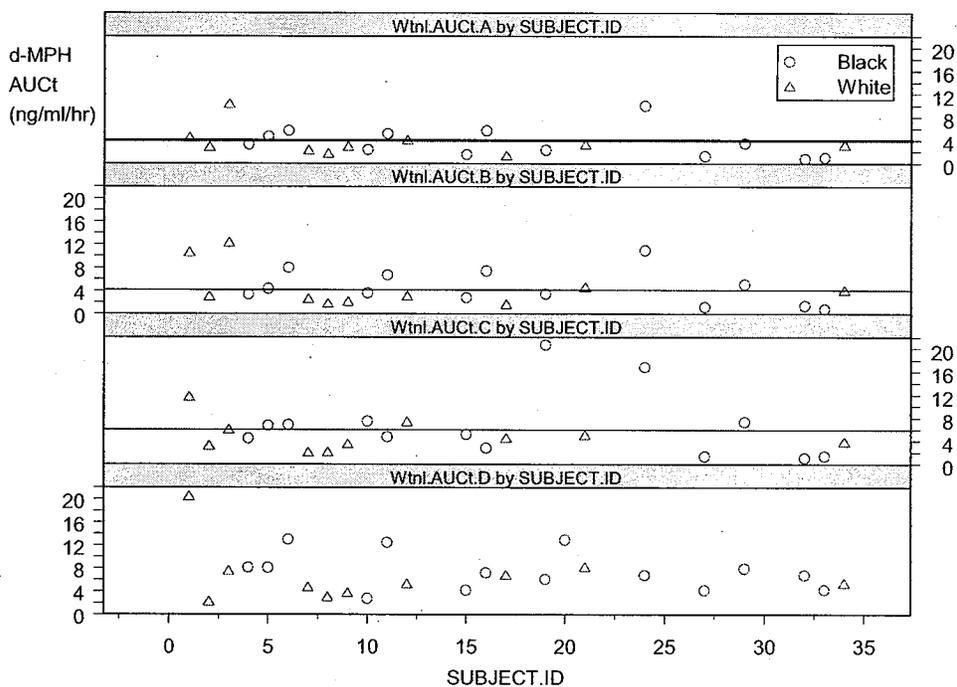
**Figure 50 Weight and Tlag by Dose vs. Race in Study 102**



**Figure 51 Lag Time by Treatment and Effect of Race and Gender in Study 101**



**Figure 52 Weight Normalized AUC by Treatment and Race in Study 101**

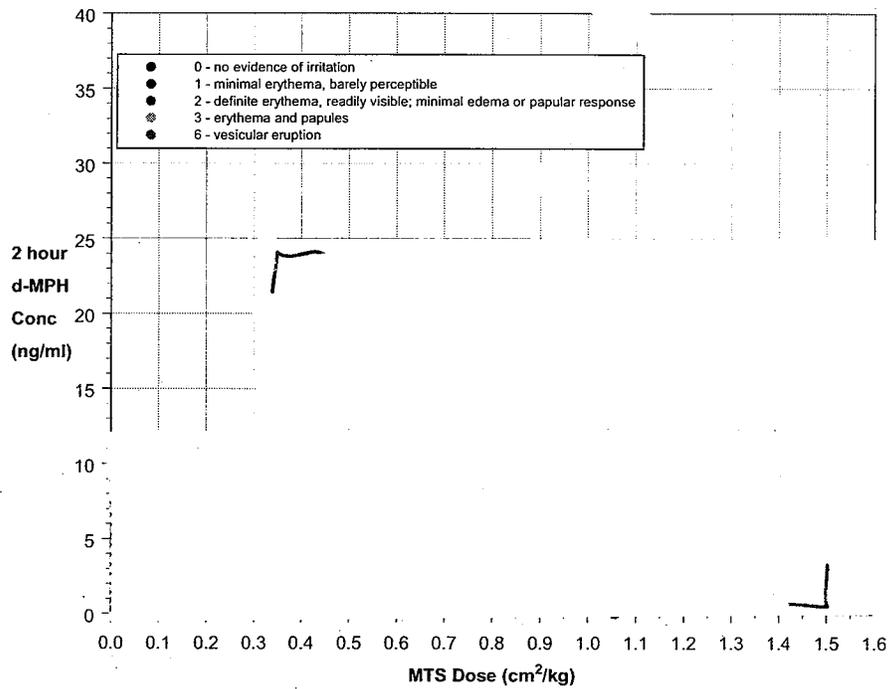


**6.5.3.1.3 Skin Irritation and Time of Onset**

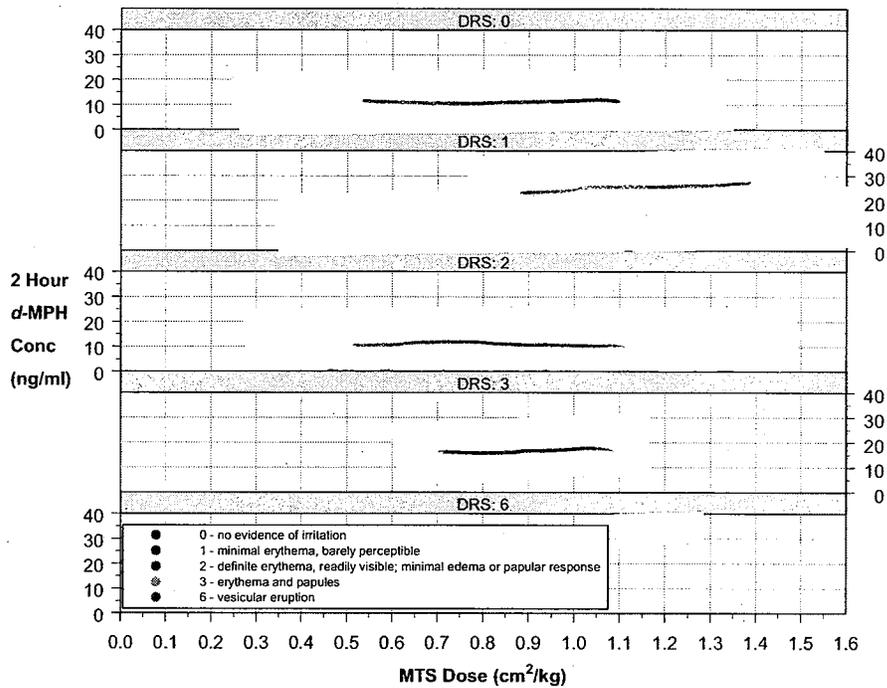
The effect of skin irritation scores after removal of the patch was examined as with respect to C<sub>max</sub> and 2 hour *d*-MPH concentration in study 201. There was an effect of erythema after patch removal on C<sub>2</sub> or C<sub>max</sub> although there appears to be increased absorption with vesicle formation as would be expected. The presence of edema is also expected to alter the skin barrier and increase absorption, however there were too few subjects to see a clear effect, (see Figure 53 to Figure 57).

**APPEARS THIS WAY  
ON ORIGINAL**

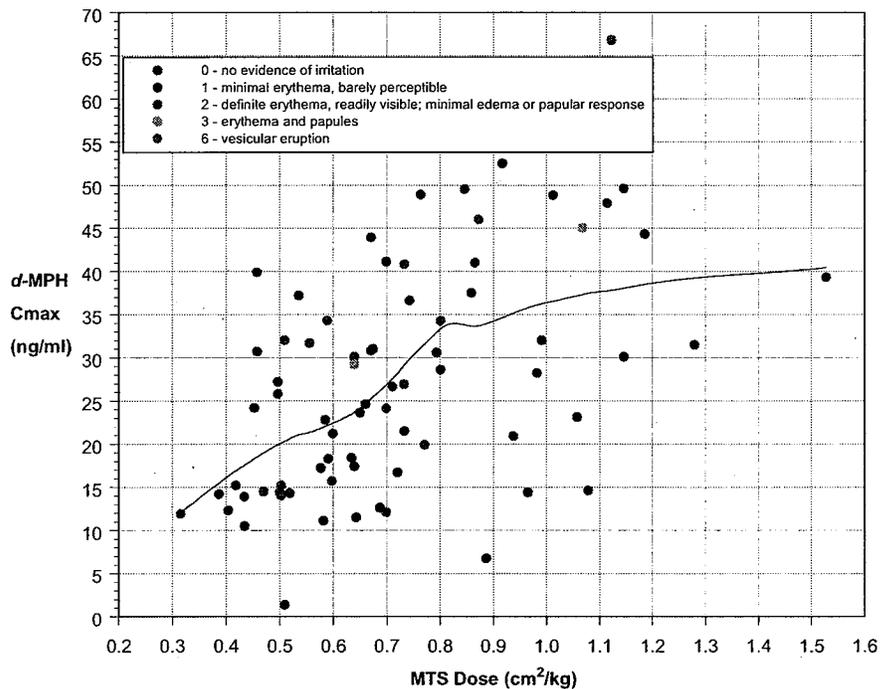
**Figure 53 Effect of MTS Dose and Degree of Skin Irritation on 2 hour d-MPH Concentrations – Study 201**



**Figure 54 Effect of MTS Dose on 2 hour d-MPH Concentrations by Degree of Skin Irritation – Study 201**



**Figure 55 Effect of MTS Dose and Degree of Skin Irritation on d-MPH Cmax Concentrations – Study 201**



**Figure 56 Effect of MTS Dose on d-MPH Cmax by Degree of Skin Irritation – Study 201**

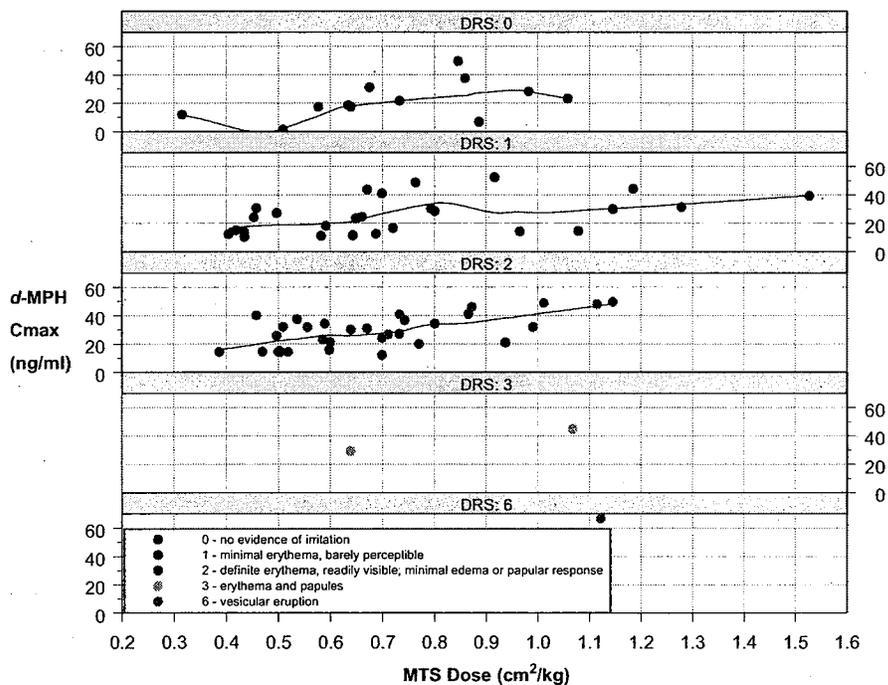
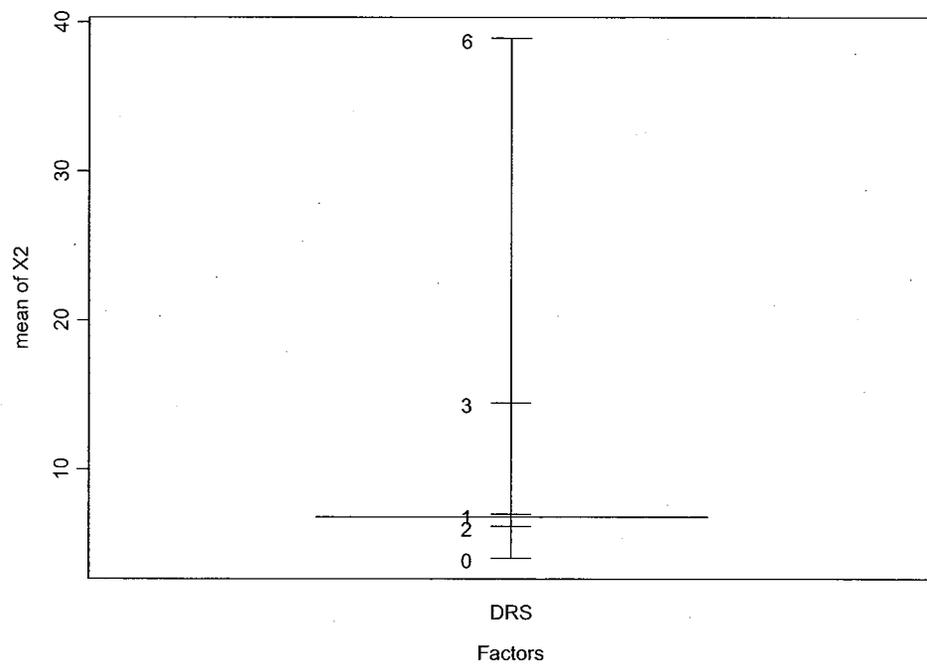


Figure 57 Factor Analysis Plot of the Influence of Degree of Skin Response on Cmax – Study 201

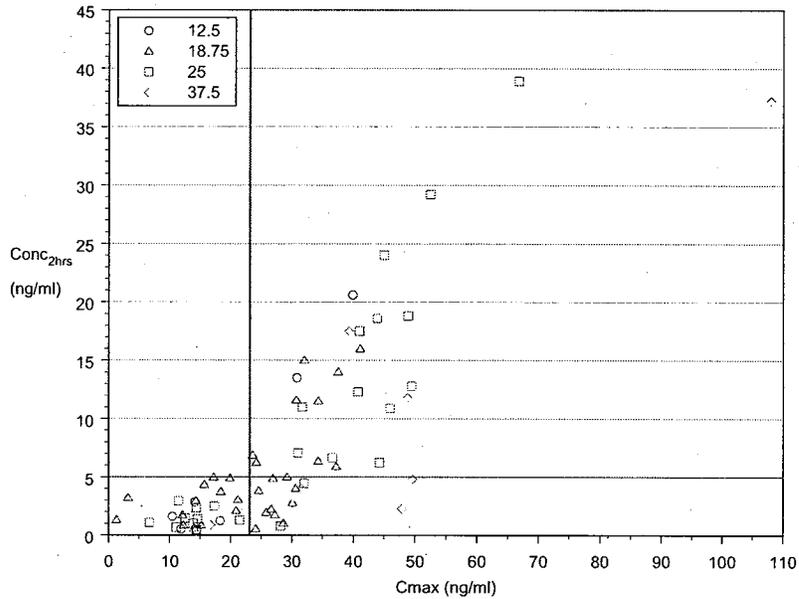


APPEARS THIS WAY  
ON ORIGINAL

**6.5.3.1.4 Dose and Time of Onset**

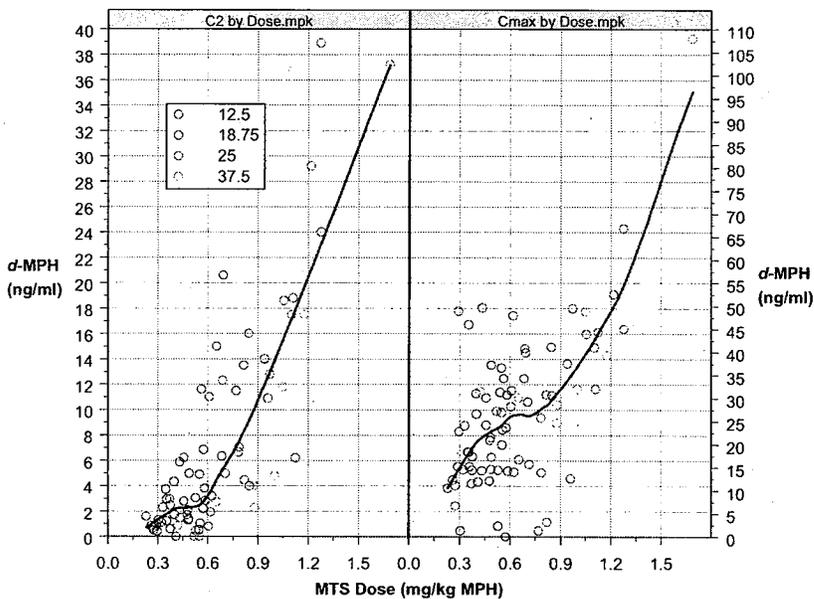
Plotting 2 hour concentrations vs. C<sub>max</sub> reveal a relationship when 2 hour concentrations are greater than 5 ng/ml which is the target 2 hour concentration, C<sub>max</sub>s achieved with 2 hour concentrations of 5 - 10 ng/ml, are in generally the range of 23 - 45 ng/ml, (see Figure 58).

**Figure 58 2 Hour d-MPH Concentration vs. d-MPH C<sub>max</sub> by MTS Strength – Study 201**



This also relates to a delivered dose of about 0.8 mg/kg.

**Figure 59 2 Hour d-MPH Concentration vs. d-MPH C<sub>max</sub> by MTS Strength – Study 201**



## 6.5.4 Transdermal Drug Delivery Rate

Summary statistics for drug delivery rates normalized in various ways are shown in Table 15.

The sponsor's proposed nominal drug delivery rates are shown in Table 13.

The sponsor's nominal drug delivery rates appear to be based upon all available data for 9 hour wear times. This however results in the amount of drug dose delivered and the dosage rate to not be strictly proportional to patch size or drug content. Even though greater than proportional delivery sometimes occurs with extremely large patches this does not appear to be case in the present situation.

In order to make it easier for practitioners I have proposed new nominal delivery rates that are strictly proportional. These new rates are shown in Table 14. The differences from the true mean rates sample are less than 10% which is very good for a transdermal system.

**Table 13 Sponsor's Proposed Nominal Delivery Rates**

Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch (mg)	Dose Delivered Over 9 Hours (mg)	Dosage Rate (mg/hr)
12.5	27.5	10	1.1
18.75	—	—	—
25	55.0	20	2.2
37.5	82.5	—	—

**Table 14 Reviewer's Proposed Nominal Delivery Rates**

Patch Size (cm <sup>2</sup> )	Methylphenidate Content per Patch (mg)	Dose Delivered Over 9 Hours (mg)	Dosage Rate (mg/hr)
12.5	27.5	10	1.1
18.75	—	15	—
25	55.0	20	2.2
37.5	82.5	30	3.3

Table 15 Statistical Summaries of Drug Delivery by Study

Study	Patch Size (cm <sup>2</sup> )	Nominal Drug Content (mg)	Application Duration (hr)	N	Batch No.	Actual Drug Content		% Depletion	Residual	Dose	Normalized Dosages			Delivery Rates																	
						N	mg				%C	mg / unit	mg / unit	mg / cm <sup>2</sup>	mg / kg	mcg / cm <sup>2</sup> / kg	mg / hr	mcg / cm <sup>2</sup> / hr	mcg / cm <sup>2</sup> / kg / hr												
101	25	55	6	23	Noven 8463102	16	56.3 ± 0.44 (0.8) 55.5 - 57.2 [56.3]	102.4 100.9 - 104.0 [102.4]	21.23 ± 7.42 (36.0) 11.01 - 41.21 [19.89]	44.35 ± 4.18 (9.42) 33.10 - 50.10 [45.1]	11.95 ± 4.18 (35.0) 6.20 - 23.20 [11.2]	0.48 ± 0.17 (36.0) 0.25 - 0.93 [0.45]	0.36 ± 0.12 (33.0) 0.19 - 0.62 [0.37]	14.4 ± 4.8 (33.0) 7.6 - 24.8 [14.6]	1.99 ± 0.70 (35.0) 1.03 - 3.87 [1.87]	79.7 ± 27.9 (35.0) 41.3 - 154.7 [74.7]	2.4 ± 0.79 (33.0) 1.26 - 4.13 [2.44]														
																		8	23	56.3 ± 0.44 (0.8) 55.5 - 57.2 [56.3]	102.4 100.9 - 104.0 [102.4]	23.75 ± 7.57 (31.87) 12.08 - 41.39 [23.09]	42.93 ± 4.26 (9.92) 33.00 - 49.50 [43.3]	13.37 ± 4.26 (31.87) 6.80 - 23.30 [13]	0.53 ± 0.17 (31.87) 0.27 - 0.93 [0.52]	0.41 ± 0.15 (37.3) 0.20 - 0.74 [0.40]	16.4 ± 6.1 (37.3) 8.1 - 29.8 [16.0]	1.67 ± 0.53 (31.9) 0.85 - 2.91 [1.63]	66.8 ± 21.3 (31.9) 34.0 - 116.5 [65.0]	2.05 ± 0.76 (37.3) 1.01 - 3.72 [2.00]	
																															10
			12.5	27.5		34	8463104	4 Site 80	27.5 ± 0.44 (1.6) 27 - 27.9 [27.5]	100.0 98.2 - 101.5 [100.0]	33.6 ± 9.7 (28.9) 16.9 - 59.0 [32.0]	18.5 ± 2.6 (13.9) 11.6 - 22.3 [19.3]	9.4 ± 2.8 (29.7) 5.2 - 16.7 [9.1]	0.8 ± 0.2 (29.7) 0.4 - 1.3 [0.7]	0.283 ± 0.1 (41.8) 0.1 - 0.6 [0.3]	22.6 ± 9.4 (41.8) 7.0 - 44.2 [20.8]	1.0 ± 0.3 (29.7) 0.6 - 1.9 [1.0]	83.7 ± 24.8 (29.7) 46.2 - 148.4 [80.4]	2.51 ± 1.05 (41.80) 0.78 - 4.91 [2.31]												
																				4 Site 81	28.3 ± 0.2 (0.7) 28.1 - 28.5 [28.2]	102.7 102.2 - 103.6 [102.5]									
4 Site 81	56.6 ± 0.93 (1.6) 55.6 - 57.6 [56.6]	102.9 101.1 - 104.7 [102.9]																													
													4 Site 80	80.9 ± 1.22 (1.5) 79.3 - 82 [81.15]	98.1 96.1 - 99.4 [98.4]	31.2 ± 8.7 (27.9) 15.7 - 53.5 [30.8]	56.4 ± 6.8 (12.0) 38.7 - 66.2 [57.4]	25.7 ± 7.4 (28.6) 12.7 - 44.5 [25.6]	0.7 ± 0.2 (28.6) 0.3 - 1.2 [0.7]	0.8 ± 0.3 (38.7) 0.2 - 1.4 [0.7]	20.4 ± 7.9 (38.7) 5.9 - 38.2 [19.3]	2.9 ± 0.8 (28.6) 1.4 - 4.9 [2.8]	76.1 ± 21.8 (28.6) 37.6 - 131.9 [75.9]	2.27 ± 0.88 (38.66) 0.66 - 4.24 [2.14]							
4 Site 81	83.2 ± 1.52 (1.8) 81.8 - 85.2 [83.0]	100.9 99.2 - 103.3 [100.6]																													
													34	8463101																	
25	55	9	34	8463102																											
													37.5	82.5																	

Study	Patch Size (cm <sup>2</sup> )	Nominal Drug Content (mg)	Application Duration (Hr)	N	Batch No.	Actual Drug Content		% Depletion	Residual mg / unit	Dose mg / unit	Normalized Dosages			Delivery Rates														
						N	mg				%C	mg / cm <sup>2</sup>	mg / kg	mcg / cm <sup>2</sup>	mg / hr	mcg / cm <sup>2</sup> / hr	mcg / cm <sup>2</sup> / kg / hr											
102	Ratios	55 : 27.5	9	34								1.0 ± 0.2	2.0 ± 0.4	1.0 ± 0.2	2.0 ± 0.4	1.0 ± 0.2												
												(21.3)	(21.3)	(21.3)	(21.3)	(21.3)	(21.3)											
												0.6 - 1.7	1.2 - 3.3	0.6 - 1.7	1.2 - 3.3	0.6 - 1.7	1.2 - 3.3											
												[0.9]	[1.9]	[0.9]	[1.9]	[0.9]	[1.9]											
												0.9 ± (21.4)	2.8 ± (21.4)	0.9 ± (21.4)	2.8 ± (21.4)	0.9 ± (21.4)	2.8 ± (21.4)											
												0.6 - 1.5	1.8 - 4.4	0.6 - 1.5	1.8 - 4.4	0.6 - 1.5	1.8 - 4.4											
	37.5 : 12.5	82.5 : 27.5	9	33									1.0 ± 0.2	1.5 ± 0.3	1.0 ± 0.2	1.5 ± 0.3	1.0 ± 0.2											
													(21.3)	(21.3)	(21.3)	(21.3)	(21.3)	(21.3)										
													0.5 - 1.5	0.9 - 2.2	0.5 - 1.5	0.9 - 2.2	0.5 - 1.5	0.9 - 2.2										
													[1.0]	[1.5]	[1.0]	[1.5]	[1.0]	[1.5]										
													1.0 ± 0.2	1.5 ± 0.3	1.0 ± 0.2	1.5 ± 0.3	1.0 ± 0.2	1.5 ± 0.3										
													0.6 - 1.5	0.9 - 2.2	0.6 - 1.5	0.9 - 2.2	0.6 - 1.5	0.9 - 2.2										
37.5 : 25	82.5 : 55		34									1.0 ± 0.2	0.5 ± 0.2	37.2 ± 18.5	1.4 ± 0.6	109.1 ± 47.6												
												(43.7)	(49.8)	(49.8)	(43.7)	(43.7)	(43.7)											
												0.5 - 1.5	0.2 - 0.8	18.4 - 65.2	0.7 - 2.1	58.7 - 168.0	0.7 - 2.1											
												[0.9]	[0.4]	[28.4]	[1.2]	[96.9]	[1.2]											
												1.0 ± 0.2	0.5 ± 0.2	37.2 ± 18.5	1.4 ± 0.6	109.1 ± 47.6	1.4 ± 0.6											
												0.6 - 1.5	0.2 - 0.8	18.4 - 65.2	0.7 - 2.1	58.7 - 168.0	0.7 - 2.1											
201	12.5	27.5	7	8463104	48	27.3 ± 1.1 (4.0)	99.2 ± 4.0 (4.0)	45.9 ± 20.9 (45.4)	14.6 ± 5.8 (39.7)	12.3 ± 5.4 (43.7)	1.0 ± 0.4 (43.7)	0.5 ± 0.2 (49.8)	37.2 ± 18.5 (49.8)	1.4 ± 0.6 (43.7)	109.1 ± 47.6 (43.7)	4.1 ± 2.1 (49.8)												
																	22.7 - 29.8 [27.5]	82.5 - 108.5 [100]	24.6 - 71.9 [39.2]	7.4 - 20.2 [16.9]	6.6 - 18.9 [10.9]	0.5 - 1.5 [0.9]	0.2 - 0.8 [0.4]	18.4 - 65.2 [28.4]	0.7 - 2.1 [1.2]	58.7 - 168.0 [96.9]	2.0 - 7.2 [3.2]	
																	41.0 ± 1.3 (3.1)	99.4 ± 3.1 (3.1)	39.2 ± 9.5 (24.4)	24.8 ± 3.9 (15.6)	16.0 ± 3.9 (24.6)	0.9 ± 0.2 (24.6)	0.5 ± 0.2 (30.3)	28.3 ± 8.6 (30.3)	1.8 ± 0.4 (24.6)	94.9 ± 23.3 (24.6)	3.1 ± 1.0 (30.3)	
																	37.4 - 44.0 [41.0]	90.7 - 106.7 [99.4]	24.1 - 59.9 [36.9]	16.4 - 30.2 [25.8]	9.6 - 24.5 [15.1]	0.5 - 1.3 [0.8]	0.3 - 0.9 [0.5]	13.9 - 50.1 [28.5]	1.1 - 2.7 [1.7]	56.9 - 145.2 [89.5]	1.5 - 5.6 [3.2]	
																	40.5 ± 15.0 (37.1)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)	
																	16.6 - 72.1 [40.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]	
	18.75	41.25	9	36	8463103	64	41.0 ± 1.3 (3.1)	99.4 ± 3.1 (3.1)	39.2 ± 9.5 (24.4)	24.8 ± 3.9 (15.6)	16.0 ± 3.9 (24.6)	0.9 ± 0.2 (24.6)	0.5 ± 0.2 (30.3)	28.3 ± 8.6 (30.3)	1.8 ± 0.4 (24.6)	94.9 ± 23.3 (24.6)	3.1 ± 1.0 (30.3)											
																		37.4 - 44.0 [41.0]	90.7 - 106.7 [99.4]	24.1 - 59.9 [36.9]	16.4 - 30.2 [25.8]	9.6 - 24.5 [15.1]	0.5 - 1.3 [0.8]	0.3 - 0.9 [0.5]	13.9 - 50.1 [28.5]	1.1 - 2.7 [1.7]	56.9 - 145.2 [89.5]	1.5 - 5.6 [3.2]
																		40.5 ± 15.0 (37.1)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)
																		16.6 - 72.1 [40.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]
																		40.5 ± 15.0 (37.1)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)
																		16.6 - 72.1 [40.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]
25	55	28	8463102	55	54.5 ± 1.6 (3.0)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)													
																49.2 - 58.4 [54.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]		
																40.5 ± 15.0 (37.1)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)		
																16.6 - 72.1 [40.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]		
																40.5 ± 15.0 (37.1)	99.1 ± 3.0 (3.0)	40.5 ± 15.0 (37.1)	32.5 ± 8.2 (25.2)	22.1 ± 8.2 (37.1)	0.9 ± 0.3 (37.1)	0.7 ± 0.3 (45.1)	28.7 ± 12.9 (45.1)	2.5 ± 0.9 (37.1)	98.4 ± 36.5 (37.1)	3.2 ± 1.4 (45.1)		
																16.6 - 72.1 [40.6]	89.5 - 106.5 [99.3]	16.6 - 72.1 [40.6]	15.2 - 45.8 [32.7]	9.1 - 39.3 [22.3]	0.4 - 1.6 [0.9]	0.3 - 1.3 [0.6]	11.0 - 51.1 [26.0]	1.0 - 4.4 [2.5]	40.4 - 174.7 [99.1]	1.2 - 5.7 [2.9]		
37.5	82.5	8	8463101	56	80.8 ± 2.8 (3.5)	97.7 ± 3.4 (3.5)	38.3 ± 12.4 (32.3)	50.6 ± 10.4 (20.5)	31.3 ± 9.8 (31.4)	0.8 ± 0.3 (31.4)	1.0 ± 0.4 (38.7)	25.8 ± 10.0 (38.7)	3.5 ± 1.1 (31.4)	92.7 ± 29.1 (31.4)	2.9 ± 1.1 (38.7)													
																72.1 - 86.5 [80.9]	87.4 - 104.8 [98.0]	26.0 - 63.6 [35.8]	29.2 - 60.6 [52.5]	21.3 - 51.0 [29.3]	0.6 - 1.4 [0.8]	0.4 - 1.7 [0.9]	11.3 - 45.0 [25.1]	2.4 - 5.7 [3.3]	63.1 - 151.1 [86.8]	1.3 - 5.0 [2.8]		
																80.8 ± 2.8 (3.5)	97.7 ± 3.4 (3.5)	38.3 ± 12.4 (32.3)	50.6 ± 10.4 (20.5)	31.3 ± 9.8 (31.4)	0.8 ± 0.3 (31.4)	1.0 ± 0.4 (38.7)	25.8 ± 10.0 (38.7)	3.5 ± 1.1 (31.4)	92.7 ± 29.1 (31.4)	2.9 ± 1.1 (38.7)		
																72.1 - 86.5 [80.9]	87.4 - 104.8 [98.0]	26.0 - 63.6 [35.8]	29.2 - 60.6 [52.5]	21.3 - 51.0 [29.3]	0.6 - 1.4 [0.8]	0.4 - 1.7 [0.9]	11.3 - 45.0 [25.1]	2.4 - 5.7 [3.3]	63.1 - 151.1 [86.8]	1.3 - 5.0 [2.8]		
																80.8 ± 2.8 (3.5)	97.7 ± 3.4 (3.5)	38.3 ± 12.4 (32.3)	50.6 ± 10.4 (20.5)	31.3 ± 9.8 (31.4)	0.8 ± 0.3 (31.4)	1.0 ± 0.4 (38.7)	25.8 ± 10.0 (38.7)	3.5 ± 1.1 (31.4)	92.7 ± 29.1 (31.4)	2.9 ± 1.1 (38.7)		
																72.1 - 86.5 [80.9]	87.4 - 104.8 [98.0]	26.0 - 63.6 [35.8]	29.2 - 60.6 [52.5]	21.3 - 51.0 [29.3]	0.6 - 1.4 [0.8]	0.4 - 1.7 [0.9]	11.3 - 45.0 [25.1]	2.4 - 5.7 [3.3]	63.1 - 151.1 [86.8]	1.3 - 5.0 [2.8]		

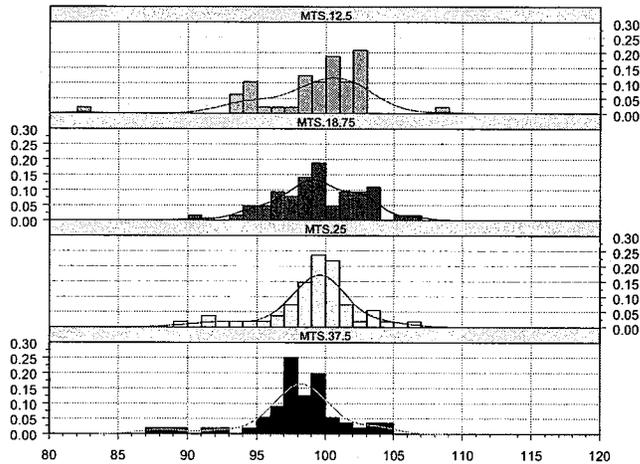
### 6.5.5 Drug Content

Drug content was reported in study 201 for a large number of patches. This data is presented since this is useful information that is typically not available for such a large number of samples and since distribution of drug in an adhesive matrix is difficult, (see Table 16 and Figure 61). It was noted that the drug content was highly variable, (see Table 16 and Figure 61).

**Table 16 Summary Statistics of Patch Drug Content (% LC) by Strength from the Batches Used in Study 201**

Patch Size	12.5	1.875	25	37.5
Batch Number	8463104	8463103	8463102	8463101
N	48	64	55	56
Mean SD	99.2 ± 4.0	99.4 ± 3.1	99.1 ± 3.0	97.9 ± 3.5
Range	82.5 - 108.4	90.7 - 106.7	89.5 - 106.2	87.4 - 104.8
[Median]	[100.0]	[99.4]	[99.3]	[98.0]

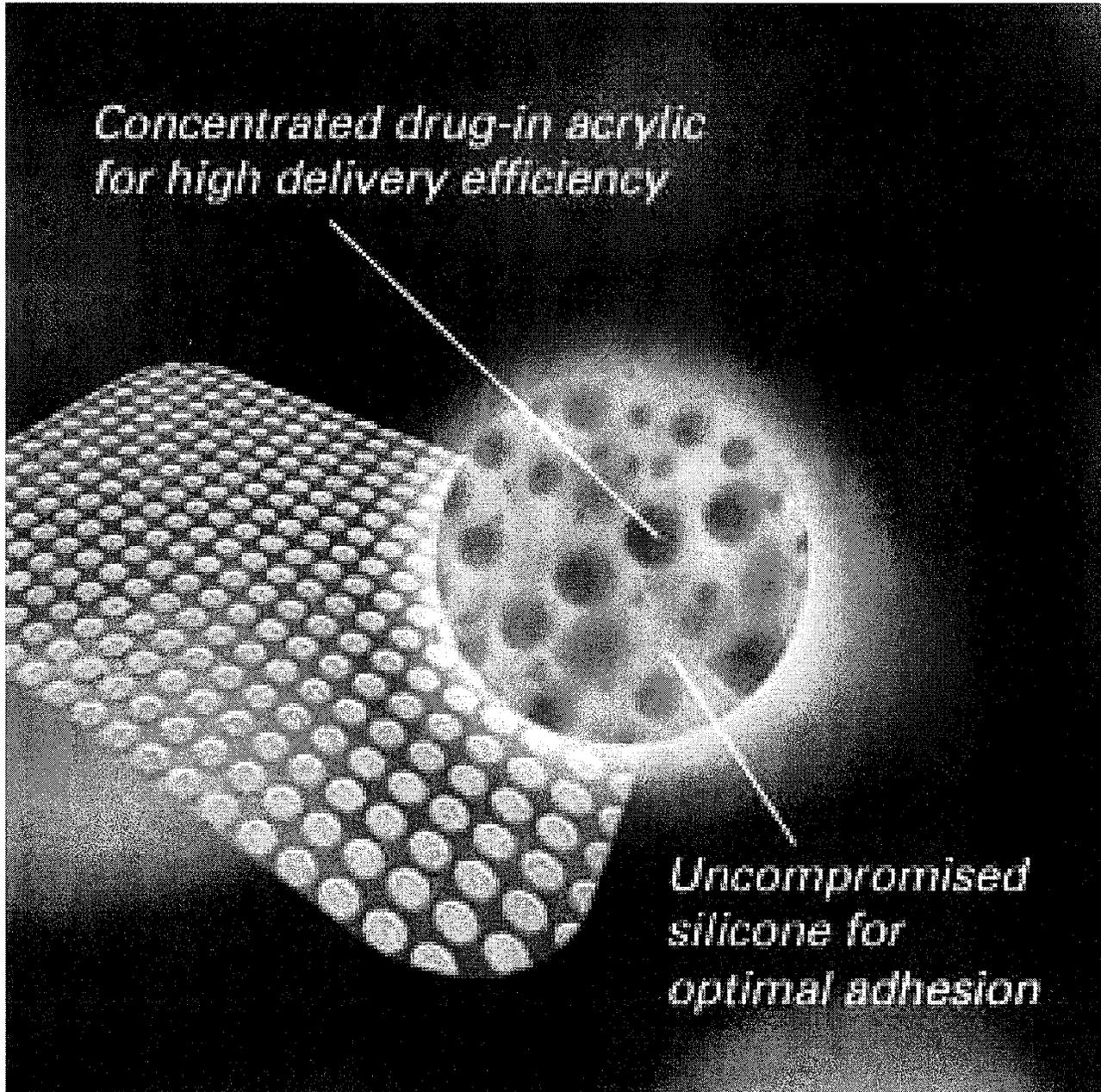
**Figure 61 Frequency Histograms of Patch Drug Content (%LC) by Strength from the Batches Used in Study 201**



## 7 APPENDICES

### 7.1 APPENDIX 1 –DOT Matrix Formulation Used for MTS

Figure 62 Noven's DOT Matrix® Formulation



*The circular image is a digital photograph of the adhesive layer of a DOT Matrix® patch taken with a scanning electron microscope*

## 7.2 APPENDIX 1 Subject Demographics by Study

Table 17 Subject Demographics for Study 101

Study / Rx	GENDER	RACE	N	AGE (years)	WEIGHT (kg)	HEIGHT (m)
101	All Subjects		24	8.8 ± 2.0 (22.9) 6 - 12 [9]	34.9 ± 9.9 (28.5) 23.59 - 55.34 [32.2]	1.34 ± 0.09 (6.9) 1.17 - 1.54 [1.3]
	Male	—	18	8.8 ± 1.9 (21.7) 23.6 - 12 [9]	35.7 ± 11.0 (30.8) 1.17 - 55.34 [32.77]	1.3 ± 0.1 (7.0) 14.73 - 1.54 [1.37]
	Female	—	6	8.5 ± 2.4 (28.6) 6 - 11 [8.5]	32.4 ± 5.7 (17.7) 26.08 - 39.92 [30.5]	1.3 ± 0.1 (7.2) 1.22 - 1.49 [1.3]
	Male & Female	White	10	9.4 ± 1.9 (20.2) 6 - 12 [10]	36.1 ± 13.5 (37.3) 23.59 - 55.34 [29.825]	1.3 ± 0.1 (8.5) 1.17 - 1.54 [1.34]
		Black	14	8.3 ± 2.0 (24.3) 6 - 11 [9]	34.0 ± 6.9 (20.2) 25.4 - 47.17 [32.5]	1.3 ± 0.1 (5.9) 1.22 - 1.49 [1.34]
	Male	White	8	9.1 ± 2.0 (22.3) 6 - 12 [9.5]	37.0 ± 14.7 (39.8) 23.59 - 55.34 [29.8]	1.3 ± 0.1 (9.5) 1.17 - 1.54 [1.34]
		Black	10	8.6 ± 1.9 (22.1) 6 - 11 [9]	34.7 ± 7.6 (21.9) 25.4 - 47.17 [33.9]	1.4 ± 0.1 (4.6) 1.22 - 1.45 [1.37]
	Female	White	2	10.5 ± 0.7 (6.7) 10 - 11 [10.5]	32.5 ± 9.1 (28.1) 26.08 - 39.01 [32.5]	1.3 ± 0.1 (4.2) 1.3 - 1.38 [1.34]
		Black	4	7.5 ± 2.4 (31.7) 6 - 11 [6.5]	32.3 ± 5.2 (16.0) 28.35 - 39.92 [30.5]	1.3 ± 0.1 (8.9) 1.22 - 1.49 [1.285]

Table 18 Subject Demographics for Study 102

Study / Rx	GENDER	RACE	N	AGE (years)	WEIGHT (kg)	HEIGHT (m)
102	All Subjects		34	9.6 ± 1.9 (20.2) 6.0 - 12.0 [9.5]	36.8 ± 12.4 (33.8) 20.5 - 77.3 [32.7]	1.4 ± 0.1 (8.60) 1.2 - 77.3 [1.4]
	Male	—	18	10.2 ± 1.9 (18.2) 7.0 - 12.0 [10.0]	39.7 ± 12.5 (31.6) 24.1 - 77.3 [36.1]	1.4 ± 0.1 (6.4) 1.2 - 1.6 [1.4]
	Female	—	16	8.9 ± 1.9 (21.0) 6.0 - 12.0 [9.0]	33.4 ± 11.8 (35.3) 20.5 - 59.1 [29.3]	1.369 ± 0.143 (10.5) 1.168 - 1.638 [1.353]
	Male & Female	White	19	9.8 ± 1.6 (16.7) 7.0 - 12.0 [10.0]	37.0 ± 9.5 (25.8) 23.2 - 59.1 [33.6]	1.4 ± 0.1 (7.7) 1.2 - 1.6 [1.4]
		Black	12	9.0 ± 2.2 (24.2) 6.0 - 12.0 [9.0]	36.2 ± 17.0 (46.9) 20.5 - 77.3 [28.6]	1.4 ± 0.1 (9.2) 1.2 - 1.5 [1.3]
	MALE	WHITE	10	9.9 ± 1.7 (16.8) 8.0 - 12.0 [10.0]	35.8 ± 7.2 (20.0) 28.2 - 50.5 [32.7]	1.4 ± 0.1 (4.4) 1.3 - 1.5 [1.4]
		BLACK	5	10.6 ± 1.9 (18.4) 8.0 - 12.0 [12.0]	48.6 ± 18.4 (37.9) 29.1 - 77.3 [47.7]	1.4 ± 0.1 (7.1) 1.3 - 1.5 [1.5]
		Asian	1	12	42.72727	1.5748
		HISPANIC	1	12	46.36364	1.4986
		Amer Indian	1	7	24.09091	1.2446
	FEMALE	WHITE	9	9.8 ± 1.7 (17.5) 7.0 - 12.0 [10.0]	38.2 ± 12.0 (31.3) 23.2 - 59.1 [34.5]	1.4 ± 0.2 (10.5) 1.2 - 1.6 [1.4]
BLACK		7	7.9 ± 1.6 (20.0) 6.0 - 10.0 [8.0]	27.3 ± 8.9 (32.6) 20.5 - 46.4 [23.6]	1.3 ± 0.1 (8.20) 1.2 - 1.5 [1.2]	

Table 19 Subject Demographics for PK-PD Study - Study 201

Study / Rx	GENDER	RACE	N	AGE (years)	WEIGHT (kg)	HEIGHT (m)
201	All Subjects		80	9.1 ± 1.7 (19.1) 6.0 - 12.0 [9.0]	32.3 ± 8.3 (25.9) 18.6 - 59.6 [31.1]	1.363 ± 0.113 (8.3) 1.105 - 1.651 [1.372]
	Male	—	58	9.2 ± 1.7 (18.6) 6.0 - 12.0 [9.0]	32.5 ± 8.6 (26.5) 18.6 - 59.6 [31.3]	1.4 ± 0.1 (8.6) 1.1 - 1.7 [1.4]
	Female	—	22	9.0 ± 1.8 (20.5) 6.0 - 12.0 [8.5]	31.6 ± 7.7 (24.4) 20.0 - 46.4 [29.9]	1.4 ± 0.1 (7.8) 1.2 - 1.6 [1.4]
	Male & Female	White	56	9.2 ± 1.7 (18.2) 6.0 - 12.0 [9.0]	32.6 ± 8.9 (27.2) 21.1 - 59.6 [31.3]	1.4 ± 0.1 (8.3) 1.2 - 1.7 [1.4]
		Black	8	9.0 ± 1.5 (16.8) 7.0 - 11.0 [8.5]	30.6 ± 3.3 (10.9) 26.8 - 36.8 [29.2]	1.4 ± 0.0 (3.1) 1.3 - 1.4 [1.4]
		Hispanic	11	9.0 ± 2.3 (25.3) 6.0 - 12.0 [9.0]	33.8 ± 8.4 (25.0) 18.6 - 44.8 [36.4]	1.3 ± 0.1 (10.8) 1.1 - 1.5 [1.4]
	Male	White	42	9.3 ± 1.7 (18.0) 6.0 - 12.0 [10.0]	33.1 ± 9.3 (28.2) 21.1 - 59.6 [31.6]	1.4 ± 0.1 (8.6) 1.2 - 1.7 [1.4]
		Black	7	8.9 ± 1.6 (17.8) 7.0 - 11.0 [8.0]	30.9 ± 3.5 (11.3) 26.8 - 36.8 [29.5]	1.4 ± 0.0 (3.2) 1.3 - 1.4 [1.4]
		Hispanic	7	9.0 ± 2.4 (26.4) 6.0 - 12.0 [9.0]	31.9 ± 9.2 (28.7) 18.6 - 43.0 [36.4]	1.3 ± 0.2 (12.20) 1.1 - 1.5 [1.3]
		Asian	2	8.5 ± 0.7 (8.3) 8.0 - 9.0 [8.5]	27.8 ± 2.1 (7.5) 26.4 - 29.3 [27.8]	1.3 ± 0.0 (1.4) 1.3 - 1.3 [1.3]
	Female	White	14	8.9 ± 1.7 (19.2) 6.0 - 12.0 [8.0]	30.9 ± 7.3 (23.5) 21.8 - 46.4 [29.4]	1.4 ± 0.1 (7.7) 1.2 - 1.6 [1.4]
		Black	1	10	28.6	1.3843
		Hispanic	4	9.0 ± 2.4 (27.2) 6.0 - 12.0 [9.0]	37.2 ± 6.8 (18.4) 30.2 - 44.8 [36.8]	1.4 ± 0.1 (8.6) 1.3 - 1.5 [1.4]
		Other: ASIAN/ WHITE	1	7	20.0	1.168
		Other: WEST INDIAN	1	8	24.0	1.278
PUERTO-RICAN		1	12	41.4	1.410	

Table 20 Subject Demographics for Phase III Pivotal Efficacy Study - Study 302

Study / Rx	GENDER	RACE	N	AGE (years)	WEIGHT (kg)	HEIGHT (m)		
Concerta	All Subjects		93	8.8 ± 1.9 (21.9) 6.0 - 12.0 [9.0]	32.8 ± 8.9 (27.2) 18.6 - 59.3 [31.6]	1.4 ± 0.1 (9.3) 1.1 - 1.7 [1.3]		
	All Subjects			99	8.9 ± 1.9 (21.8) 6.0 - 12.0 [9.0]	32.8 ± 10.5 (32.1) 16.8 - 67.4 [30.9]	1.4 ± 0.1 (9.3) 1.1 - 1.7 [1.3]	
Concerta	M	—	61		8.8 ± 2.0 (23.0) 6.0 - 12.0 [9.0]	33.5 ± 9.7 (29.0) 18.6 - 59.3 [32.3]	1.4 ± 0.1 (9.8) 1.1 - 1.7 [1.3]	
	F	—		32	8.8 ± 1.7 (19.9) 6.0 - 12.0 [9.0]	31.6 ± 7.2 (22.7) 19.8 - 43.8 [29.6]	1.3 ± 0.1 (8.3) 1.2 - 1.6 [1.3]	
MTS	M	—	60		8.6 ± 1.8 (20.8) 6.0 - 12.0 [8.0]	31.6 ± 9.5 (30.1) 18.9 - 58.2 [29.6]	1.3 ± 0.1 (9.0) 1.1 - 1.7 [1.3]	
	F	—		39	9.3 ± 2.1 (22.4) 6.0 - 12.0 [9.0]	34.7 ± 11.8 (34.1) 16.8 - 67.4 [32.7]	1.4 ± 0.1 (10.6) 1.1 - 1.7 [1.4]	
Concerta	Male	White	50		8.7 ± 2.1 (23.7) 6.0 - 12.0 [9.0]	33.2 ± 9.6 (29.1) 18.6 - 59.3 [31.9]	1.3 ± 0.1 (9.6) 1.1 - 1.7 [1.3]	
		Black		7	8.6 ± 2.1 (25.1) 6.0 - 12.0 [9.0]	32.5 ± 10.1 (31.0) 20.9 - 47.3 [30.1]	1.3 ± 0.2 (13.1) 1.1 - 1.6 [1.3]	
		Hispanic			3	9.0 ± 1.0 (11.1) 8.0 - 10.0 [9.0]	33.6 ± 1.2 (3.5) 32.3 - 34.5 [33.9]	1.4 ± 0.0 (2.7) 1.3 - 1.4 [1.4]
		Other				1	11.0	55.1
	Female	White	24				9.4 ± 1.5 (16.0) 6.0 - 12.0 [9.0]	32.6 ± 7.4 (22.6) 21.8 - 43.8 [30.8]
		Black		6			6.7 ± 0.8 (12.2) 6.0 - 8.0 [6.5]	28.8 ± 6.2 (21.6) 19.8 - 38.2 [27.5]
		Hispanic			2		8.5 ± 2.1 (25.0) 7.0 - 10.0 [8.5]	27.9 ± 6.8 (24.4) 23.1 - 32.7 [27.9]
MTS	Male	White	50			8.5 ± 1.8 (21.4) 6.0 - 12.0 [8.0]	30.9 ± 9.5 (30.6) 18.9 - 58.2 [27.9]	1.3 ± 0.1 (9.2) 1.1 - 1.7 [1.3]
		Black		7		9.1 ± 1.5 (16.0) 8.0 - 12.0 [9.0]	35.4 ± 9.6 (27.2) 28.0 - 56.0 [33.2]	1.4 ± 0.1 (7.9) 1.2 - 1.6 [1.4]
		Hispanic			2	8.0 ± 2.8 (35.4) 6.0 - 10.0 [8.0]	29.8 ± 10.7 (35.8) 22.3 - 37.4 [29.8]	1.3 ± 0.1 (10.9) 1.2 - 1.4 [1.3]
		Asian				1	10.0	43.2
	Female	White	28				9.2 ± 2.0 (21.6) 6.0 - 12.0 [9.0]	32.7 ± 10.6 (32.4) 18.4 - 58.1 [31.1]
		Black		4			9.5 ± 3.0 (31.6) 6.0 - 12.0 [10.0]	39.5 ± 22.1 (56.0) 16.8 - 67.4 [36.9]
		Hispanic			6		9.5 ± 2.3 (23.8) 6.0 - 12.0 [10.0]	39.2 ± 9.2 (23.6) 28.6 - 54.5 [37.8]
Asian	1	12	42.6			1.6		

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/s/

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Ron Kavanagh  
12/12/2005 11:08:35 AM  
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Raman Baweja  
12/12/2005 12:41:29 PM  
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
NEW DRUG APPLICATION – MINOR AMENDMENT**

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<b>NDA:</b>	21-514	
<b>Submission Date(s):</b>	May 14, 2003	
<b>Brand Name</b>	MethyPatch	
<b>Generic Name</b>	Methylphenidate Transdermal System	
<b>Reviewer</b>	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.	
<b>Team Leader</b>	Raman Baweja, Ph.D.	
<b>OCPB Division</b>	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860	
<b>ORM division</b>	Division of Neuropharmacological Drug Products (DNDP) HFD-120	
<b>Relevant IND(s)</b>	54,732	
<b>Sponsor</b>	Noven Pharmaceuticals Inc. Miami, Florida	
<b>Submission Type; Code</b>	N(BB) – New Drug Application – Minor Amendment – Biopharmaceutics	
<b>Formulation(s); Strength(s)</b>	Adhesive Transdermal System (Patch); 27.5 mg / 12.5 cm <sup>2</sup> 10 mg delivered over 12 hours         mg / hr) <del>37.5 mg / 18.75 cm<sup>2</sup></del> 15 mg delivered over 12 hours         mg / hr) 55.0 mg / 25 cm <sup>2</sup> 20 mg delivered over 12 hours         mg / hr) 82.5 mg / 37.5 cm <sup>2</sup> 30 mg delivered over 12 hours         mg / hr) <del>100 mg / 50 cm<sup>2</sup></del> 40 mg delivered over 12 hours         mg / hr)	
<b>Route(s) of Administration</b>	Transdermal	
<b>Indication(s)</b>	Attention Deficit Hyperactivity Disorder	

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## 1 BACKGROUND

The sponsor has requested clarification to issues identified in the not approvable action letter as shown below:

- 12. Please indicate which batches were used in the bioequivalence study. Your response should include the dosage, batch number, batch size, manufacturer, drug substance batch number, clinical trial number and certificates of analysis.**

Question: Which study number is the Agency interested in? The MethyPatch program did not include a bioequivalence study but did include a study to compare the relative bioavailability of MethyPatch and Ritalin in adults (N17-006).

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

**Table 1 Dissolution Method and Acceptance Criteria**

<b>Apparatus:</b>	USP Drug Release Apparatus 6 (modified cylinder)		
<b>Medium:</b>	0.1N HCl		
<b>Temperature:</b>	32 ± 0.5°C		
<b>Volume:</b>	900 mL		
<b>Rotation Speed:</b>	50 rpm		
<b>Sampling Times:</b>	0.5 hour 1.5 hour 3.0 hour		
<b>Acceptance Criteria:</b>	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		

## 2 OCPB RESPONSE

### Question 12:

The bioequivalence study of interest is study 17-005, bioequivalence between hip and scapular administration sites.

### Dissolution Method and Specifications:

The sponsor is correct that their submitted dissolution media is 0.01 N HCl. The request to adopt a dissolution method and specification was communicated to the sponsor in error. Adoption of a dissolution method and specification will be requested in the future if the product is determined to be approvable.

**APPEARS THIS WAY  
ON ORIGINAL**

### 3 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

#### 3.1 CC LIST:

NDA 21-514 N(BB) 5-14-03	(orig., 1 copy)
HFD-120	(Hommonay, MannheimG, AndreasonP, KatzR, FisherE)
HFD-860	(KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR	(Barbara Murphy)

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/s/

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Ron Kavanagh  
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Raman Baweja  
6/19/03 01:53:04 PM  
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
NEW DRUG APPLICATION - REVIEW**

<b>NDA:</b>	21-514	
<b>Submission Date(s):</b>	June 27, 2002 February 25, 2003	
<b>Brand Name</b>	MethyPatch	
<b>Generic Name</b>	Methylphenidate Transdermal System	
<b>Reviewer</b>	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.	
<b>Team Leader</b>	Raman Baweja, Ph.D.	
<b>OCPB Division</b>	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860	
<b>ORM division</b>	Division of Neuropharmacological Drug Products (DNDP) HFD-120	
<b>Relevant IND(s)</b>	54,732	
<b>Sponsor</b>	Noven Pharmaceuticals Inc. Miami, Florida	
<b>Submission Type; Code</b>	N – New Drug Application	
<b>Formulation(s); Strength(s)</b>	Adhesive Transdermal System (Patch); 27.5 mg / 12.5 cm <sup>2</sup> 10 mg delivered over 12 hours 37.5 mg / 18.75 cm <sup>2</sup> 15 mg delivered over 12 hours 55.0 mg / 25 cm <sup>2</sup> 20 mg delivered over 12 hours 82.5 mg / 37.5 cm <sup>2</sup> 30 mg delivered over 12 hours 110 mg / 50 cm <sup>2</sup> 40 mg delivered over 12 hours	(    mg / hr) (    5 mg / hr) (    mg / hr) (    mg / hr) (    mg / hr)
<b>Route(s) of Administration</b>	Transdermal	
<b>Indication(s)</b>	Attention Deficit Hyperactivity Disorder	

**1 EXECUTIVE SUMMARY**

**1.1 BACKGROUND**

MethyPatch® (methylphenidate transdermal system) is an adhesive-based matrix transdermal patch that provides continuous systemic delivery of methylphenidate, a central nervous system stimulant, during application to intact skin.

The proposed indication for MethyPatch® is 'In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication'.

The intent of this formulation is to provide a once daily administration schedule to minimize the problems associated with having to take oral methylphenidate during the school day.

The proposed dosage regimen for children starting treatment for the first time and those switching from another medication is to start with the lowest strength 12.5 cm<sup>2</sup> patch applied once daily upon awakening to the hip. It is recommended the patch be worn initially for 8 to 12 hours. Daily dosage may be raised at weekly intervals by not more than 12.5 cm<sup>2</sup> to the maximum patch size of 37.5 cm<sup>2</sup>. The MethyPatch® system may be removed earlier than 12 hours based on the needs of the patient. Individualization of wear time may help manage some of the side effects caused by methylphenidate.

As methylphenidate is approved for use in ADHD in both immediate release and modified release formulations, the sponsor intends that the present application be a 505b(2) application for toxicology information. In addition, only a single positive pivotal efficacy study is being submitted and there is

limited safety information included in the NDA as methylphenidate has been marketed in the USA for years.

## **1.2 RECOMMENDATIONS**

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-514 submitted June 27, 2002.

OCPB finds this application acceptable. However, the clinical pharmacology of methylphenidate in conjunction with the biopharmaceutic properties of MethyPatch® raises concerns whether a transdermal formulation is clinically appropriate for this drug. The clinical appropriateness of this particular methylphenidate transdermal formulation should be medically assessed

Comments should be communicated to the sponsor as appropriate:  
(See Section 3.1.2 on page 10).

Labeling comments should also be communicated to the sponsor as appropriate:  
(See Section 3.3 Labeling Comments on page 10).

**APPEARS THIS WAY  
ON ORIGINAL**

## 2 CPB FINDINGS

### What was the formulation used in the pharmacokinetic and clinical pharmacology studies?

With the exception of the initial pharmacokinetic study (17-002), all other clinical studies used the to-be-marketed formulation with patches that varied only in the area of the patch. Of the sizes studied the smallest (6.24 cm<sup>2</sup>) is not proposed for approval and the largest (50 cm<sup>2</sup>) is not proposed for marketing at the present time.

### Is the pharmacokinetics of MethyPatch® linear with dose?

Linearity was demonstrated with doses up to 330 mg / 150 cm<sup>2</sup> (6 x 55 mg / 25 cm<sup>2</sup>) applied to the back.

### \* What is the pharmacokinetics of MethyPatch® upon multiple dosing?

When 55 mg / 25 cm<sup>2</sup> patches were applied to the hip daily for 16 hours in adults, steady-state was achieved by day 4.

As can be seen in Figure 1 there's an initial lag in absorption, (mean 3 hours range 1 – 5 hours), followed by a slow steady increase in concentration until C<sub>max</sub> is achieved at around 10 – 12 hours and then a plateau until the patch is removed at 16 hours. This plateau is due to the depletion of methylphenidate from the patch resulting in a slowing of the delivery rate so that the rate of elimination from the body becomes approximately the same as the rate of delivery. Once the patch is removed at 16 hours the decline in concentrations is similar to the oral dosing situation with a half-life of around 3 hours. In addition when spaghetti plots of individual concentration time profiles are examined, we see that some individuals have low concentrations throughout most of the day, and some individuals with long half-lives have high C<sub>mins</sub> at 0 and 24 hours.

If patches are applied for shorter periods than 16 hours, the decline in concentrations occurs whenever the patch is removed. In addition, when higher doses are used the plateau is also reached earlier as the rate of elimination becomes equal to the rate of delivery earlier.

### Figure 1 Comparative Concentration Time Profiles of MethyPatch and Oral Methylphenidate

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

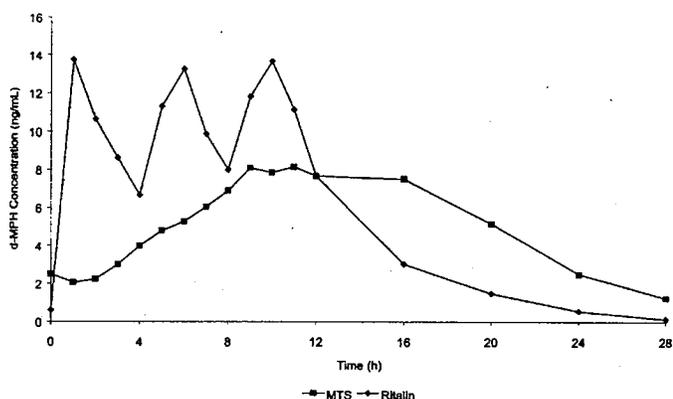
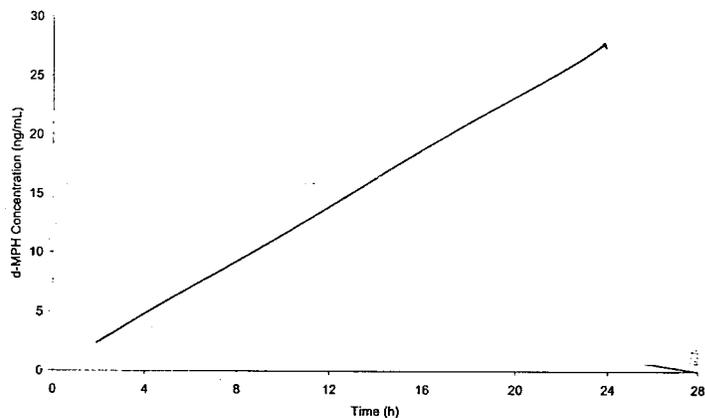


FIGURE 6. INDIVIDUAL PLASMA PROFILES (SPAGHETTI PLOTS) OF D-THREO-METHYLPHENIDATE (D-MPH) FROM DAY 6 AFTER DOSING WITH 25 CM<sup>2</sup> MTS UNITS ONCE DAILY FOR 16 H (N=29).



**How does MethyPatch's pharmacokinetics compare to oral methylphenidate pharmacokinetics in children?**

Pharmacokinetic studies in children indicate that the actual patch strengths used in the pivotal clinical study produced higher concentrations than indicated by Figure 1.

Specifically, the mean age of subjects in the multiple dose pharmacokinetic study (17-016) was 11.5 years of age. Table 1 shows the age distribution of subjects in the pivotal clinical efficacy study, (17-018) (see Table 1). It can also be seen from Table 1 that the distribution of patch sizes containing active methylphenidate follows the age distribution of the subjects.

**Table 1 Age and MethyPatch Distributions in Pivotal Clinical Efficacy Study 17-018**

Age Groups	% of Subjects Enrolled	Patch Sizes (cm <sup>2</sup> )	% of Subjects Wearing at End of Study
6 to 8	54	18.75 & 25	45
9 to 10	25	37.5	27
10 to 11	21	50	21

Since, the mean age in the pharmacokinetic study was 11.5 years we can assume that children need exposures similar to that achieved by the 50 cm<sup>2</sup> patch, in the pediatric PK study. Table 2 shows the peak concentrations at 8 and 12 hours achieved with this patch size in children in the multiple-dose pharmacokinetic study (study 17-016). Thus, if this product is approved the sponsor may wish reconsider their marketing plans regarding the 50 cm<sup>2</sup> patch.

**Table 2 Mean Methylphenidate Cmax in Children with 50 cm<sup>2</sup> at Steady-State (Study 17-016)**

Analyte	Cmax (ng/ml)	
	Patch Wear Duration (hours)	
	8 hr	12
d-MPH	34.5	31.4
l-MPH	21	18.1

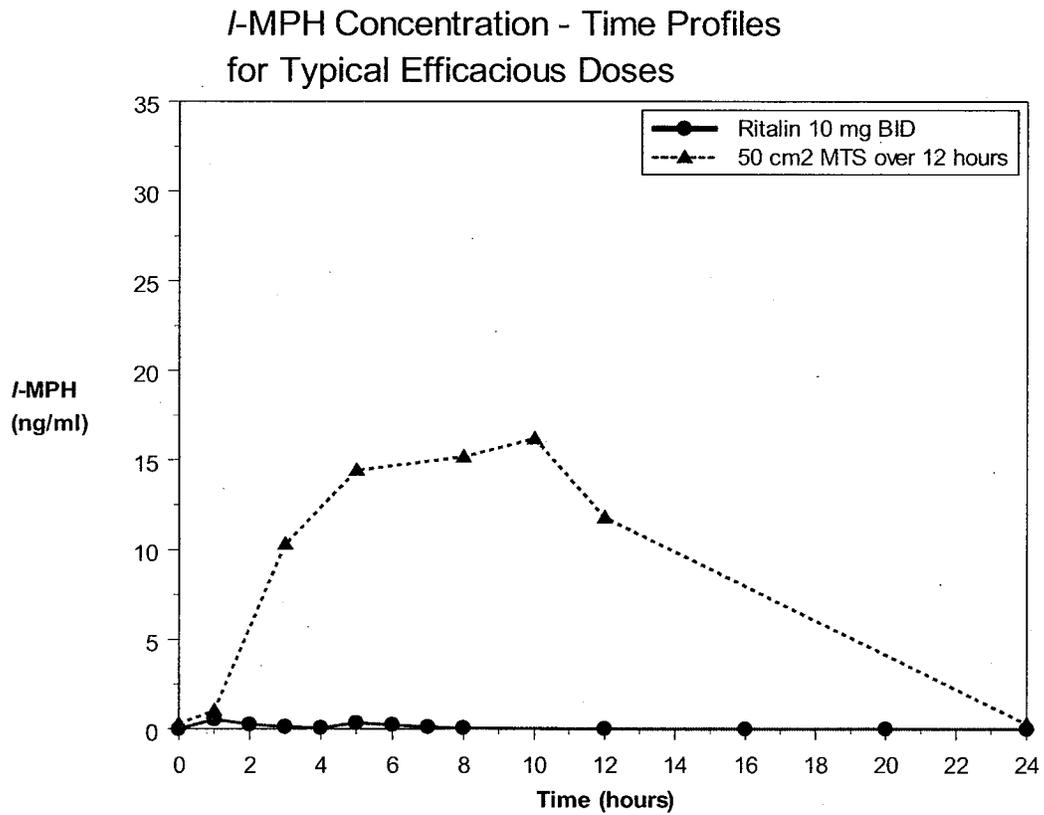
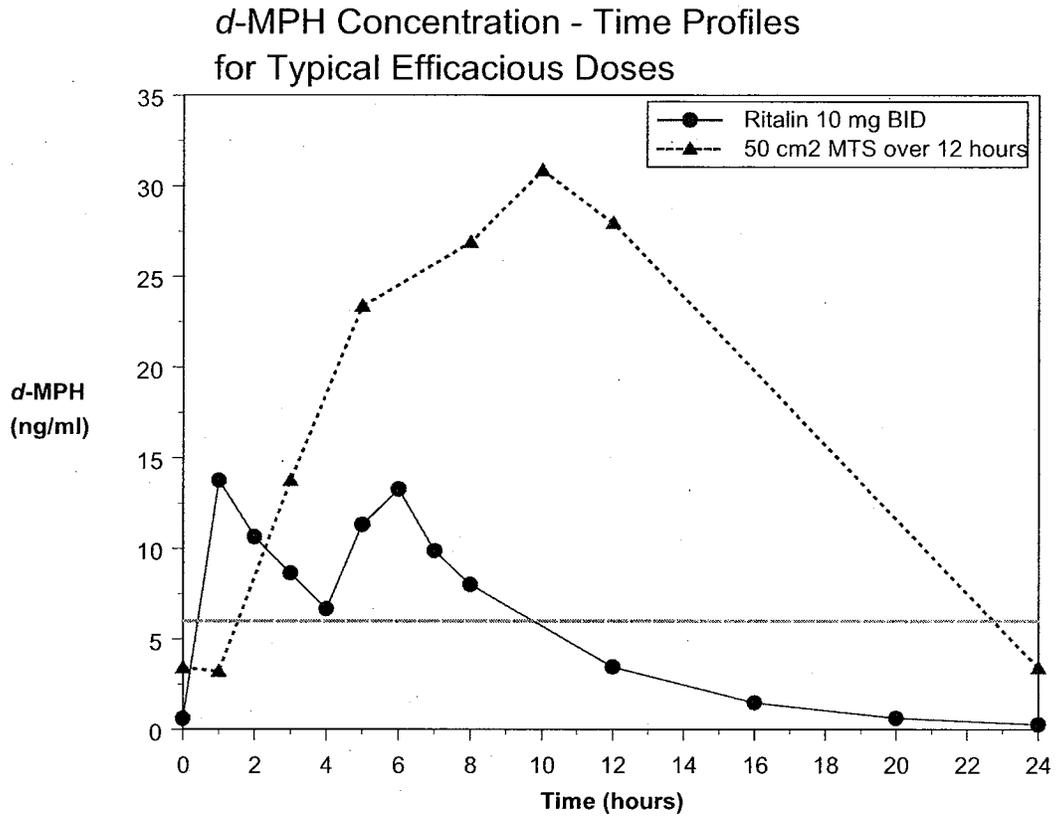
Mean patch wear duration in the pivotal efficacy study was about 11 hours with a range of 8 to 12 hours. The relatively flat concentrations from 8 to 12 hours indicates that somewhere after 8 hours of wear the rate of drug delivery begins to equal the elimination rate and then begins to be less than the elimination rate. Thus these peak concentrations are likely applicable even with wear duration's of 8 hours.

Figure 2 shows a comparison of mean plasma concentration time profiles produced by expected efficacious doses of MethyPatch in children relative to the profile for 2 doses of orally administered Ritalin 10 mg at 4 hour intervals in adults. Based upon what is known about oral methylphenidate these for Ritalin concentration profiles are close to what is expected with efficacious doses in children.

Ritalin is usually dosed BID in the morning and around lunchtime 4 – 5 hours later, thus concentrations that are expected to have minimal effect are achieved by about 12 hours after the first dose. In contrast, concentrations for MethyPatch are still significantly elevated.

In fact mean concentrations are above 6 ng/ml for most of the dosing interval. 6 ng/ml is the approximate minimum effective concentration, and is based upon preliminary research data analysis from regulatory research.

**Figure 2 Comparison of Mean *d*-MPH and *l*-MPH Concentration Profiles for Expected Efficacious Doses of MethyPatch in Children with Typical Profiles for Oral Ritalin.**



Although not exact, these concentration profile lines illustrate several important pharmacokinetic issues.

- a) Likely therapeutic concentrations are achieved in a short time with oral administration, whereas with transdermal administration they are likely to take several hours with the initial low doses until titration occurs, and even after titration in some individuals.
- b) By late afternoon plasma concentrations from MethyPatch are still rising whereas the concentrations after oral administration are probably subtherapeutic.
- c) With the recommended wear time of 8 hours and a half life of 3 hours, mean *d*-methylphenidate concentrations from MethyPatch are expected to still be 7 ng/ml 6 hours after patch removal (18 hours post application), and 3.9 ng/ml 3 hours before applying the next patch. Thus *d*-MPH concentrations are likely to be high enough to have a pharmacologic effect until the early morning hours.

Lastly, study 17-014 that examined the pharmacokinetics of MethyPatch on two occasions suggests that there may be a larger inter-occasion variability in absorption lag and T<sub>max</sub>.

\*

#### **What are the potential clinical implications of MethyPatch's concentration time profile?**

By extension there's several implications of MethyPatch's pharmacokinetics.

- a) There is likely going to be a lack of efficacy in the morning with MethyPatch®, unless a sufficiently high dose is used. Thus, clinical studies or studies comparing the time course of MethyPatch's pharmacokinetics/pharmacodynamic in ADHD (e.g. hourly classroom testing) to oral methylphenidate may be needed.
- b) There's likely to be side effects in the late afternoon, evening, and possibly at night. Adverse effects that might be expected at these times might include appetite suppression at dinner, and insomnia.
- c) It's been proposed that tolerance to methylphenidate following oral dosing occurs over the course of the day and the relative drug free period overnight allows a return to baseline. However, the high methylphenidate concentrations that occur at night with MethyPatch, with measurable concentrations in the morning, may not allow a return to baseline. This might result in less efficacy and/or the need for higher doses.
- d) To overcome the early morning lack of efficacy and side effects late in the day clinicians are likely to find that using large doses (i.e. large patches) and removing them after fewer hours may be advantageous. However, this results in used patches containing large amounts of methylphenidate that could be extracted for abuse.
- e) The high and prolonged plasma concentrations might predispose patients on MethyPatch to depression upon drug withdrawal.

#### **What is the bioavailability of MethyPatch®?**

The mean bioavailability of *d,l*-methylphenidate for MethyPatch applied to the back relative to subcutaneously administered methylphenidate is 90% with a range of 67% to 134%. However, the recommended application site of MethyPatch is the hip.