CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860)** **Tracking/Action Sheet for Formal/Informal Consults**

Maria Sunzel, Ph.D., Iftekar Mahmood, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **6/12/00**	IND No.: - Serial No.: -	NDA No. **21-121**	DATE OF DOCUMENT **6/1/00**	
NAME OF DRUG **Concerta®, methylphenidate HCl (Oros formulation)**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: **6/7/00**	JUN 12 2000

NAME OF THE SPONSOR: **Alza Corporation** COMPLETED JUN 13 2000

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUES

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☒ **LABELING REVISION**
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☒ **OTHER** *(SPECIFY BELOW)*:

Sponsor's response to approvable letter

REVIEW ACTION

- ☐ NAI (No action indicated)
- ☐ E-mail comments to:

☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)

- ☐ Oral communication with Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]
- ☐ Formal Review/Memo (attached)
- ☒ **See comments below**
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:

[ ]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor accepts the proposed *in vitro* dissolution specifications for the pharmaceutical formulations. The sponsor's minor labeling changes of the CLINICAL PHARMACOLOGY sections are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Please convey the comment to the sponsor.

SIGNATURE OF REVIEWER: /S/ Date 6/12/00

SIGNATURE OF REVIEWER: /S/ Date 6/12/00 JUN 12 2000

SIGNATURE OF TEAM LEADER /S/ Date 6/12/00

CC.: NDA 21-121; HFD-120; HFD-860 TL: R Baweja; DD: M. Mehta; Central Document Room (Biopharm files)

Project Manager:_____ **Date** _____

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

ADDENDUM to main review dated February 10, 2000:
In Vitro – In Vivo Correlation and Dissolution Specifications

Methylphenidate HCl (CONCERTA™), 18 mg and 36 mg extended release tablets (OROS®)

ALZA Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802

NDA 21-121
Submission Dates: Jul. 15, 1999, Jan. 13, Jan. 19, Feb. 7, Feb. 24, Mar. 31, Apr. 4, 2000
Reviewers: Maria Sunzel, Ph.D., Patrick Marroum, Ph.D.

Indication: Attention Deficit/Hyperactivity Disorder (ADHD)

Table of Contents:

1. Summary

This addendum to the CPB review dated February 10, 2000 concerns the validation of the *in vitro–in vivo* correlation for the pharmaceutical formulation and a review of the dissolution specifications set by the Sponsor for the methylphenidate HCl OROS® 18 and 36 mg dosage forms (CONCERTA™).

- A Type A *in vitro–in vivo* correlation has been established by the use of a convolution method
- The revised *in vitro* dissolution specifications proposed by the Sponsor are acceptable, and are as follows:

Time Point	Proposed specification of label claim (% range) Revised Specification
[redacted]	

2. *In Vitro-In Vivo* Correlation

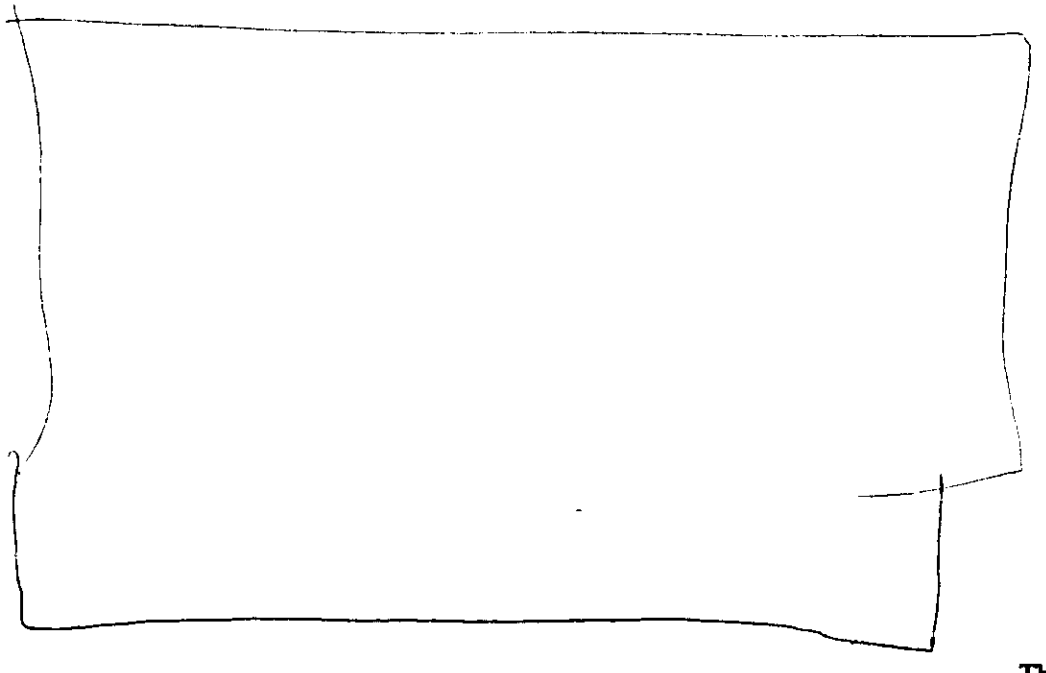
The Sponsor has developed an *in vitro–in vivo* correlation (IVIVC) for the methylphenidate (MPH) OROS® formulations. The OROS® formulations delivers MPH through a combined process of aqueous dissolution of the drug overcoat (immediate release layer) and osmotic delivery of the core drug over approximately 10 hours. Two different methods of calculation for the *in vitro–in vivo* correlation (IVIVC) were submitted.

Both methods for IVIVC were internally validated using data from three different batches used in pharmacokinetic studies, and externally validated by the use of two other batches also used in pharmacokinetic studies, see Table 2.1.

Table 2.1 Data used for the internal and external IVIVC's (OROS® formulations)

Validation	Lot# /Strength	Study*	No. Subjects
Internal	MV9800306/18 mg	C-99-001 (study # 6)	31
	MV9800299/18 mg	C-98-024 (study # 5)	36
	9901498/36 mg (profile B)	C-99-005 (study # 7)	35
External	MV9800064/18 mg	C-98-002 (study # 4)	24
	99000521/36 mg (profile A)	C-99-005 (study # 7)	34

* Study numbers in parentheses refer to main CPB review dated Feb. 10, 2000



The first derivative of the fitted model was used as the dissolution rates that were convolved by use of the pharmacokinetic disposition parameters given in Study #A-1 (2-compartment model) for the prediction of the plasma MPH concentration-time data.

The mean prediction errors for the internal validation for both C_{max} and AUC were less than 10%, as shown in Table 2.2. Table 2.3 depicts the mean prediction errors for the external validation for both C_{max} and AUC.

Table 2.2 Internal predictability of the IVIVC (Prediction Error = PE, numbers in bold indicate reviewers calculations)

Parameter	Lot# / Strength (Study)	Observed	Predicted	% PE†	% PE† (Sponsor; Study #A-1)	% PE† (Sponsor; Study #A-2)
C_{max}* (ng/mL)	MV9800306/18 mg (C-99-001)	3.30	3.75	**-13.6**	1.2	-12.6
	MV9800299/18 mg (C-98-024)	3.52	3.83	**-8.8**	10.5	-3.1
	9901498/36 mg Profile B (C-99-005)	6.96	7.34	**-5.5**	8.3	-4.6
mean				**9.3****	6.7	6.8**
$AUC_{0\text{-}inf}$ (ng.h/mL)	MV9800306/18 mg (C-99-001)	38.1	38.1	**0.0**	1.4	-7.1
	MV9800299/18 mg (C-98-024)	41.8	38.1	**8.9**	16.0	3.8
	9901498/36 mg Profile B (C-99-005)	75.8	76.0	**-0.3**	5.5	-4.4
mean				**3.1****	7.6	5.1**

* Observed C_{max} determined from the mean plasma concentration-time curves (not mean of individual C_{max})
† % Prediction error (PE) = [(observed value-predicted value)/ observed value] x 100
** based on absolute values of %PE

Table 2.3 External predictability of the IVIVC (Prediction Error = PE, numbers in bold indicate reviewers calculations)

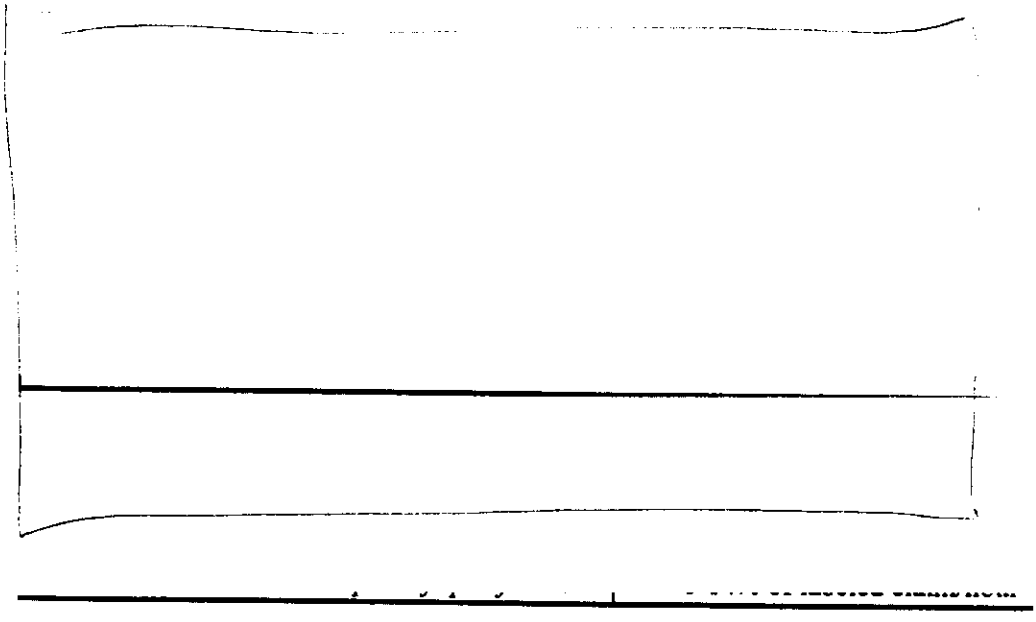
Parameter	Lot# / Strength (Study)	Observed	Predicted	% PE†	% PE† (Sponsor Study #A-1)	% PE† (Sponsor Study #A-2)
C_{max}* (ng/mL)	MV9800064/18 mg (C-98-002)	3.15	3.68	**-16.8**	6.4	-14.3
	9900521/36 mg Profile A (C-99-005)	8.16	9.20	**-12.7**	7.7	-1.3
mean				**14.8****	7.1	7.8**
$AUC_{0\text{-}inf}$ (ng.h/mL)	MV9800064/18 mg (C-98-002)	37.0	36.75	**0.7**	12.2	-8.4
	9900521/36 mg Profile A (C-99-005)	76.2	75.53	**0.9**	7.2	-5.2
mean				**0.8**	9.7	6.8**

* Observed C_{max} determined from the mean plasma concentration-time curves (not mean of individual C_{max})
† % Prediction error (PE) = [(observed value -predicted value)/ observed value] x 100
** based on absolute values of %PE

Our predictions of the t_{max} values were somewhat overestimated (predicted t_{max} occurred later than the observed), probably due to that our method did not account for the immediate release portion (drug overcoat) of the OROS® formulation. The t_{max} estimations gave a prediction error between 22-33%.

The internal validation is acceptable as a Type A correlation where both C_{max} and AUC estimations give a prediction error less that 10% (*Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997).* However, the C_{max} values for the external validations (FDA) are somewhat higher than 10% (mean prediction error 15%). The AUC predictions are well below 10%. The Sponsors predictions for both C_{max} and AUC gave a prediction error less that 10%. Since the prediction error of C_{max} (reviewer's estimations) is quite small, this is considered as acceptable ranges for a Type A correlation.

3. *In Vitro* Dissolution Specifications



According to the Sponsor, the original *in vitro* dissolution specifications yields the following upper and lower limits for AUC and C_{max} by using the proposed IVIVC (Study #A-1; deconvolution):

Parameter	OROS®	Lower	Upper	Middle	Lower/ Middle	Upper/ Middle
AUC (ng.h/mL)	18 mg	34.9	34.7	34.7	1.00	1.00
	36 mg	69.8	69.5	69.5	1.00	1.00
C_{max} (ng/mL)	18 mg	2.43	3.16	2.63	0.92	1.20
	36 mg	4.86	6.32	5.26	0.92	1.20

By the use of [redacted] upper/lower limits for AUC and C_{max} are predicted by the Sponsor for the 18 mg OROS® formulation:

Parameter	OROS®	Upper	Lower	Upper/Lower
		±10% range at 4 h		
AUC (ng.h/mL)	18 mg	40.7	36.1	1.13
C_{max} (ng/mL)	18 mg	2.86	2.83	1.01
		±12.5% range at 4 h		
AUC (ng.h/mL)	18 mg	40.6	36.1	1.12
C_{max} (ng/mL)	18 mg	3.03	2.91	1.04
		±15% range at 4 h		
AUC (ng.h/mL)	18 mg	40.6	36.6	1.12
C_{max} (ng/mL)	18 mg	3.20	2.98	1.07
		±20% range at 4 h		
AUC (ng.h/mL)	18 mg	40.6	36.2	1.12
C_{max} (ng/mL)	18 mg	3.54	3.14	1.13

The revised *in vitro* dissolution specifications would have release rates in the 3-6 h intervals of 7.5% - 14.2% as shown in Table 3.2. The Sponsor proposes a limit of 8% - 14% drug release (label claim) per hour for the dissolution specifications in the 3-6 h interval, where a linear release rate is obtained, as shown in Figure 3.1.

Table 3.2. Predicted limits of the proposed *in vitro* dissolution specifications by the Sponsor

	Cumulative percent released for systems at:		
	Lower limit	**Upper limit**	**Lower/Upper limit**
3 h	30.7	50.7	
6 h	55.0	73.3	
Release Rate 3-6 h (% label claim/h)	(55.0-30.7)/3 = 8.1	(73.3-50.7)/3 = 7.5	(73.3-30.7)/3 = 14.3*

*Lower limit at 3 h (30.7%) and upper limit at 6 h (73.3%)

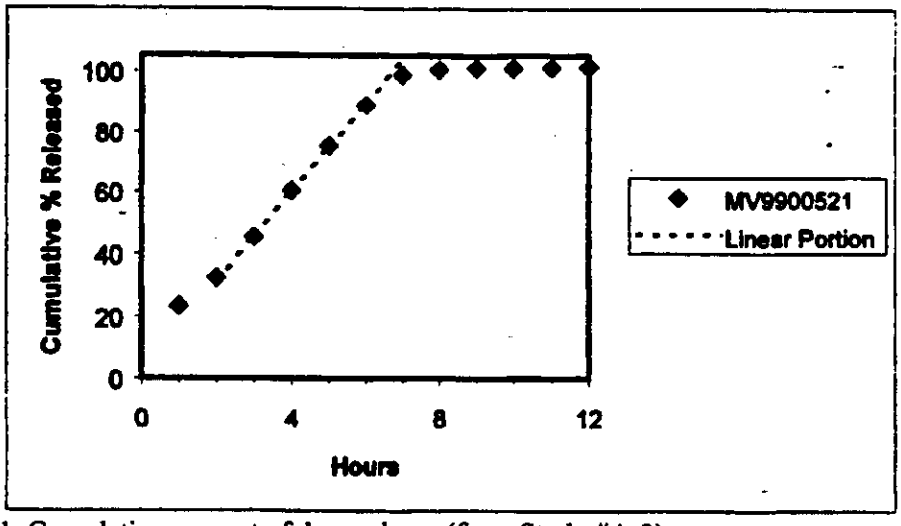


Figure 3.1. Cumulative amount of drug release (from Study #A-3).

The _____ yields estimates for AUC and C_{max} that are within acceptance limits. This indicates that the dissolution specifications are appropriate, and will ensure that different batches are comparable from a bioequivalence point of view. Therefore, the **revised** dissolution specifications are recommended, as described in Section 4, Comments.

4. Comments

1. An acceptable Type A *in vitro–in vivo* correlation has been established.

2. The **revised** *in vitro* dissolution specifications are proposed by the Sponsor are acceptable, with slight modifications as shown in the table below. The Sponsor is requested to adopt the following specification for the 18 mg and 36 mg OROS extended release tablets:

	Proposed specification of label claim (% range)
Time Point	**Revised Specification**
[redacted]	[redacted]

5. Recommendation

The Type A *in vitro–in vivo* correlation and the revised dissolution specifications, as outlined in the comments, are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The Type A *in vitro–in vivo* correlation may be used for waivers for *in vivo* bioequivalence studies of future manufacturing changes or new formulations according to *Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997.*

Please forward the comments and recommendation to the Sponsor.

Maria Sunzel, Ph.D., /S/ 4/17/2000

Patrick Marroum, Ph.D., /S/ 4/17/2000

RD/FT initialed by Ray Baweja, Ph.D., /S/ 4/17/2000

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

c.c.: NDA 21-121, HFD-120, HFD-860 (Mehta, Baweja, Marroum, Sunzel, Mahmood), HFD-340 (Viswanathan), CDR (Biopharm) and FOI files (HFD-19)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Methylphenidate HCl (CONCERTA™), 18 mg and 36 mg extended release tablets (OROS®)

ALZA Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802

NDA 21-121
Submission Dates: July 15, 1999; January 13, January 19, February 7, 2000
Reviewers: Iftekhar Mahmood, Ph.D., Maria Sunzel, Ph.D.

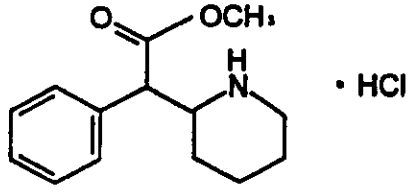
Indication: Attention Deficit/Hyperactivity Disorder (ADHD)

INTRODUCTION

The racemic d,l-threo-methylphenidate hydrochloride (d,l-MPH) has been marketed in the US since 1955 for various indications, and is currently marketed for treatment of attention deficit/ hyperactivity disorders (ADHD) and narcolepsy, in daily doses up to 60 mg as immediate and sustained release formulations. The sustained release formulation (Ritalin® SR) has been reported to have shorter duration of action than the immediate release formulations dosed twice or three times daily. This submission deals with MPH HCl OROS® (osmotic drug delivery system) by ALZA. The Sponsor is seeking approval of this dosage form based on one pivotal efficacy and safety study in children. Further, the Sponsor has provided supportive clinical pharmacology studies.

SYNOPSIS

What is the active moiety?



[$C_{14}H_{19}NO_2 \cdot HCl$; mw: 269.77; freely soluble in water and methanol, soluble in alcohol, slightly soluble in chloroform and acetone]

Methylphenidate (MPH), the methyl ester of a-phenyl-2-piperidineacetic acid, is a sympathomimetic agent classified as a mild CNS stimulant. MPH is a racemic mixture. The d-MPH is active moiety whereas l-MPH is pharmacologically inactive.

What is the clinical indication?

MPH is indicated for the treatment of Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD).

What is the mechanism of action?

While the mechanism of therapeutic efficacy in ADHD is uncertain, a number of neurotransmitter systems are altered by both acute and chronic MPH administration. In addition, MPH has been reported to affect endocrine, metabolic, and cardiovascular function in laboratory animals.

Although MPH undergoes extensive metabolism, the pharmacological action of MPH in humans is attributed to the parent compound.

What is the rationale for the current product?

Although sustained-release (SR) preparations of MPH have been developed, they are not considered as effective as multiple doses of immediate-release (IR) preparations and are not widely accepted for clinical use. The reasons for reduced efficacy with these once-a-day preparations are unknown. It is possible that the SR formulation yields a reduced or delayed bolus of drug as compared with the IR formulation. The result may be an insufficient increase in brain catecholamines to produce standard clinical effects. Alternatively, the continuous rate of drug delivery may produce acute tolerance (tachyphylaxis).

ALZA Corporation has developed a once-a-day, controlled release MPH formulation 'OROS', designed for patterned drug delivery. OROS is intended to provide comparable safety and efficacy profiles as of Ritalin IR t.i.d. The OROS system delivers 18 or 36 mg of MPH by a combined process of aqueous dissolution of the drug overcoat and osmotic delivery of the core drug. When the OROS system is ingested, the drug in the overcoat is quickly released and is available for absorption. After the dissolution of the drug overcoat, an osmotic gradient is established across the rate-controlling membrane, and water is imbibed into the system at a controlled rate, yielding controlled delivery of MPH for approximately 10 hours.

What are the basic pharmacokinetic characteristics of MPH (literature data)?

Absorption of methylphenidate (MPH) is rapid and almost complete. MPH is a racemic mixture. Following 40 mg oral administration of dl-threo-MPH, the peak plasma concentration of d-MPH is approximately 18 ng/mL which is almost 6 fold higher than l-MPH. The t_{max} of MPH following oral administration is between 1 to 3 hours. The absolute bioavailability of d- and l-MPH is 22 ± 8% and 5 ± 3%, respectively.

The volume of distribution at steady state for d- and l-MPH following 10 mg dl-threo-MPH IV dose in healthy volunteers is 2.65 ± 1.1 L/kg and 1.80 ± 0.91 L/kg, respectively. The plasma protein binding of MPH is 15%. The systemic clearance of d- and l-MPH is 0.4 ± 0.12 and 0.73 ± 0.28 L/hr/kg. The half-life of d- and l-MPH is 6 ± 1.7 and 3.6 ± 1.1 hours, respectively. The pharmacokinetics of MPH in children is comparable with those of adults. Gender has no effect on the pharmacokinetics of MPH. The effect of renal and hepatic impairment on the pharmacokinetics of MPH has not been established.

How variable is the pharmacokinetics of drug?

The inter- and intra-subject variability of OROS AUC was 36.7% and 9.6%, respectively.

What are the metabolic pathways?

The predominant metabolic pathway is de-esterification to form the corresponding carboxylic acid metabolite, alpha-phenyl-2-piperidineacetic acid (PPA), also called ritalinic acid. After oral administration of MPH, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Is the major metabolite active?

No. The metabolite of MPH has little clinical significance, since this metabolite does not cross the blood-brain-barrier and has no CNS activity.

What is the relative bioavailability of the OROS formulation compared to the immediate release tablets of MPH?

The relative bioavailability is 91 ± 10% (mean±SD).

Is there any accumulation following multiple dosing of MPH?

Following multiple dosing, there was about 14% increase in the AUC of methylphenidate as compared to the single dose. The half-life of methylphenidate was comparable following single and multiple dosing (3.9 hours). There was approximately 18% increase in the AUC of the metabolite PPA following multiple doses as compared to a single dose. There was no accumulation of MPH or PPA in plasma following multiple dosing.

Is the pharmacokinetics of MPH linear over the recommended therapeutic dose?

In a dose proportionality study, it was found that d-methylphenidate is linear over the dose range of 18 to 54 mg, whereas l-methylphenidate $AUC_{(0\text{-}inf)}$ increased disproportionally with respect to dose.

Did the Sponsor attempt any PK/PD modeling for MPH?

Yes. The Sponsor attempted to relate the clinical efficacy end points with the simulated plasma concentration of MPH in children. The clinical endpoints were the Conners, Loney, and Milich questionnaire (CLAM), and the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP). The Sponsor concluded that a tolerance pharmacodynamic model can be used to describe the PK/PD relationship. According to the Sponsor the model suggests the development of acute tolerance of MPH in children. However, the reviewers of this NDA do not agree with the Sponsor's statement that children develop acute tolerance following administration of MPH. The Sponsor has not provided strong evidence in support of the claim that acute tolerance is developed following the first dose of MPH in children. The Sponsor did not collect blood samples, rather simulated plasma drug concentrations were used to establish the concentration-effect relationships. The visual inspection of effect vs. time data also does not support this claim.

Are the formulations manufactured at the pilot plant and the commercial site bioequivalent? Are the 18 and 36 mg formulations bioequivalent?

Yes.

Does a high fat meal affect the rate and extent of MPH absorption?

Food increased the C_{max} of OROS by 11% and AUC by 17%, which may not be of any clinical significance.

What are the *in vitro* dissolution specifications? Are the specifications acceptable?

The Sponsor has set the cumulative drug release specifications for the 18 and 36 mg OROS® (MPH HCl) for the time intervals 0-1 h (· —— ·), 0-4 h —— ·) and 0-10 h ————%). The *in vitro* release profiles of 18 and 36 mg OROS® (MPH HCl) are independent of pH and agitation rates.

The dissolution specifications will be set after a further review of the pending data from the Sponsor.

TABLE OF CONTENTS

SUBMITTED, BUT NOT REVIEWED STUDIES:

Study C-94-022: The absorption study of methylphenidate administered colonically and orally to healthy subjects. *Methylphenidate pharmacokinetics was compared after administration in the colon (bolus and 6-h infusion), as an oral solution, and as an immediate release tablet (Ritalin®).*

Study C-95-026: Pilot study to determine the pharmacokinetics and bioavailability of methylphenidate administered as three different oral formulations. *The bioavailability of Ritalin® sustained (x1) and immediate release (x3) tablets were compared to an ascending dose profile of methylphenidate (MPH capsules, dose-intake every 30 min).*

1. ABSORPTION

1.1 Site of absorption

Is MPH well absorbed throughout the gastrointestinal (GI) tract?

A study was performed to evaluate the rate and extent of absorption of MPH from the proximal and distal colon relative to an oral solution (Study #1). Nine healthy male volunteers received 15 mg MPH as a 5-h infusion into the colon, and as a single dose of an oral solution. Due to the somewhat imprecise intubation technique, MPH was also administered into the transverse colon, as well as the proximal and distal parts. Plasma samples were analyzed for MPH and the major metabolite, ritalinic acid (PPA). As shown in Figure 1.1, MPH was relatively well absorbed after administration to the different parts of the colon.

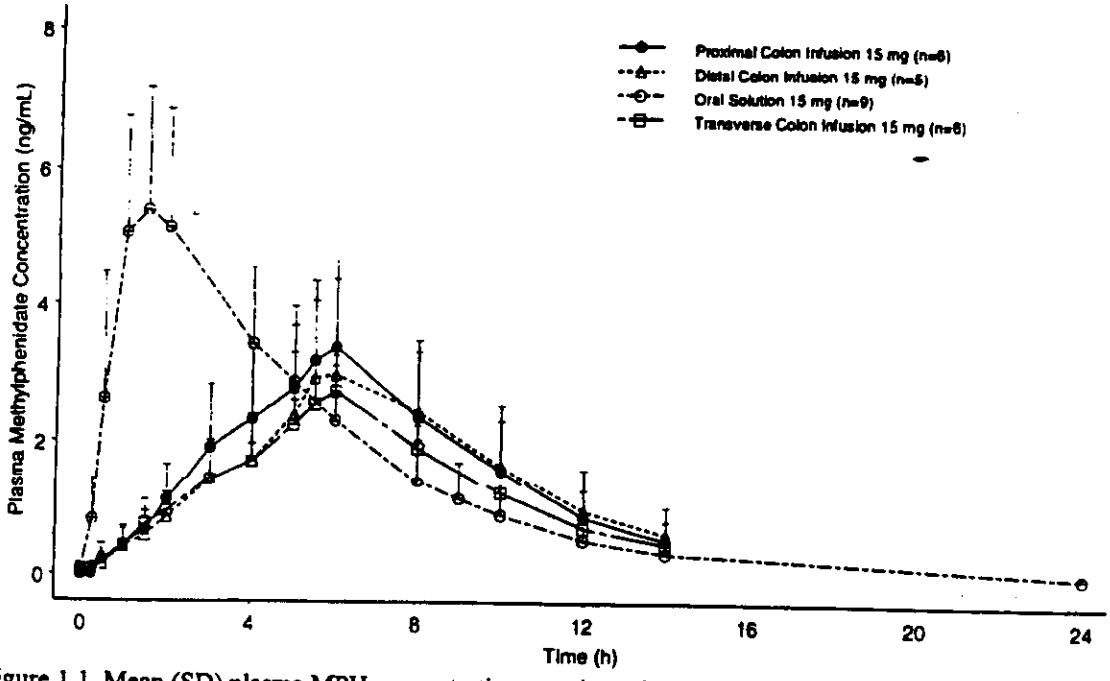


Figure 1.1. Mean (SD) plasma MPH concentrations vs. time after a 15 mg dose administered as an oral dose (solution) and as 5-h intracolonic infusions (proximal, transverse and distal parts).

The relative bioavailability of MPH after proximal, transverse and distal colon infusions were 74.5, 67.8, and 70.4%, compared to the oral dose. The corresponding values for ritalinic acid were 81.9, 78.8 and 72.5%, respectively. This suggests that the metabolism of MPH to ritalinic acid was similar throughout the GI tract.

In conclusion, the absorption of MPH is not limited to the upper parts of the GI tract, indicating that a controlled release formulation with a long duration of drug release would be functional.

1.2 Gastrointestinal (GI) transit times of the OROS® capsule

How long does it take before the OROS® formulation is excreted?

The GI transit times for the 18 mg OROS® formulation have been determined in three studies (Studies #2-4). Healthy male volunteers participated in the studies, and the influence of food was investigated in Study #4. The retrieved capsules were also analyzed for drug content. The transit times are shown in Table 1.2.

Table 1.2. Transit times for the 18 mg OROS® capsule after single doses to healthy, male volunteers.

Transit time (h)	Study # 2*	Study # 3**		Study # 4**	
	Fasting	Fasting	Fed	Fasting	Fed
No. subjects	18 (of 21)	12 (of 31)	10 (of 16)	3 (of 24)	4 (of 24)
Mean ± SD (h)	31 ± 17	39 ± 25	31 ± 16	25 ± 0.4	26 ± 1
Median (h)	26	26	25	25	26
Min (h)	11	25	11	24	25
Max (h)	74	99	54	25	27

* Bi-layer formulation (similar in weight and size to tri-layer formulation)
** Tri-layer formulation (total weight: 268 mg)

The mean transit times were similar between studies, although some individuals had 2-3 times longer transit times. According to the sponsor, this is the normal transit times for the OROS formulation. Food did not appear to influence the GI transit time. Small amounts (<1.2%) of drug residue were recovered from the discarded capsules.

2. RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE

2.1 Relative bioavailability

What is the relative bioavailability of the OROS® formulation compared to the currently marketed immediate and extended release formulations?

The relative bioavailability of the intended commercial formulation of OROS® 18 mg methylphenidate was compared to the two commercially available formulations of Ritalin® (immediate release, IR, 5 mg t.i.d., and sustained release, SR, 20 mg q.d.) [Study #5]. Single doses of the two extended release formulations, OROS® and SR, were tested against 15 mg Ritalin® (IR), the reference formulation, given as 5 mg at 8 a.m., 12 noon and 4 p.m. The resulting plasma concentration-time profiles are shown in Figure 2.1.

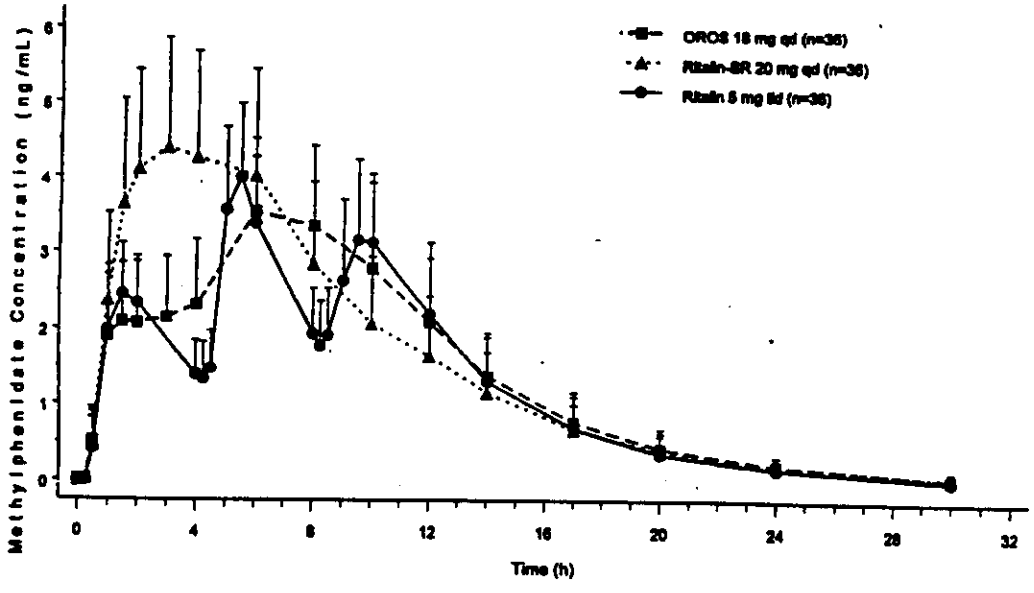


Figure 2.1. Mean (+ SD) methylphenidate plasma concentrations after administration of OROS (18 mg q.d.), Ritalin (5 mg t.i.d.), and Ritalin-SR (20 mg qd). Actual values are shown (not adjusted for different doses).

As shown in Table 2.1, the relative bioavailability (F_{rel}) of both extended release formulations were approximately 91% compared to the total AUC after 5 mg t.i.d, (every 4 h). The peak plasma concentrations of both extended release formulations were statistically significantly lower than the immediate release formulation, when the values were dose-normalized to a 15 mg dose.

Table 2.1. Pharmacokinetic parameters (mean ± SD) after administration of OROS (18 mg q.d.), Ritalin (5 mg t.i.d.), and Ritalin-SR (20 mg qd). The AUC, C_{max} and $C_{average}$ values are not adjusted for dose.

Parameter	OROS (18 mg q.d.) n=36	Ritalin (5 mg t.i.d.) n=35	Ritalin-SR (20 mg q.d.) n=36
C_{max} (ng/mL)	3.73 ± 1.01	4.17 ± 1.01	4.80 ± 1.59
t_{max} (h)	6.8 ± 1.8	6.5 ± 1.8	3.8 ± 1.6
AUC_{0-30h} (ng.h/mL)	41.2 ± 13.8	37.6 ± 11.0	45.7 ± 15.8
$AUC_{0-\infty}$ (ng.h/mL)	41.8 ± 13.9	38.0 ± 11.0	46.4 ± 15.9
$C_{average}$ (ng/mL)	1.37 ± 0.46	1.25 ± 0.36	1.52 ± 0.53
t½ (h)	3.5 ± 0.4	3.0 ± 0.5	3.9 ± 0.6
F_{rel} (%)	91.4 ± 9.8	Reference (100)	91.1 ± 10.6

The extent of formation (AUC) of the major inactive metabolite, ritalinic acid (PPA) was similar between treatments, the mean ratios of $AUC_{0-\infty}$ (MPH)/$AUC_{0-\infty}$ (PPA) for OROS, Ritalin IR and Ritalin-SR were 0.0190, 0.0203 and 0.0186, respectively. This indicates that the metabolite formation is independent of rate and site of absorption.

In conclusion, the relative bioavailability of MPH for the tested extended release formulations are about 10% lower than the immediate release formulation given three times daily. As expected, the C_{max} are significantly lower for the extended release formulations.

2.2 Bioequivalence

Are the formulations manufactured at the pilot plant and the commercial site bioequivalent?

Bioequivalence was tested between two different OROS® formulations manufactured at two different plants [Study #6]. The reference formulation was manufactured at the pilot plant .) and the test formulation was manufactured at the commercial manufacturing site . All formulations used in the clinical trials have been manufactured at the pilot plant, except for three studies [Studies #6-7, Study #10]. Bioequivalence was established in healthy adult volunteers between the reference and the intended commercial formulation of 18 mg OROS®, following a single dose. The resulting plasma concentration-time profiles are shown in Figure 2.2.

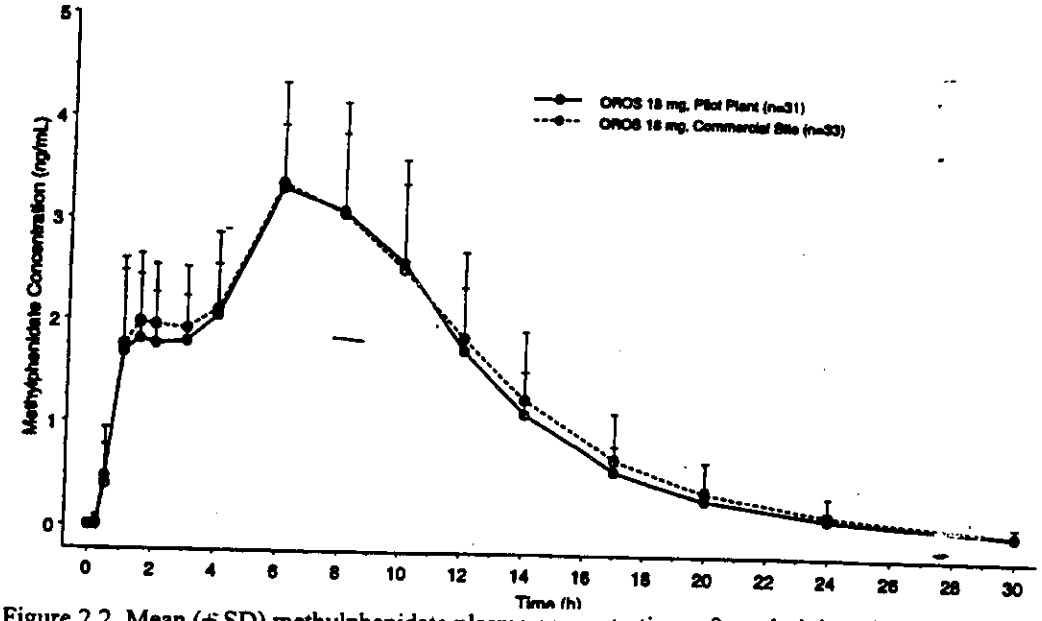


Figure 2.2. Mean (+ SD) methylphenidate plasma concentrations after administration of a single dose of 18 mg OROS® (filled circles = pilot plant, open circles = commercial site).

The mean $AUC_{0-\infty}$, C_{max} and t_{max} were 36.7 ng.h/mL, 3.46 ng/mL and 6.8 h for the reference formulation. The corresponding values for the test formulation were 38.6 ng.h/mL, 3.43 ng/mL and 7.0 h, respectively. As shown in Table 2.2, the formulations manufactured at the pilot plant and at the commercial manufacturing site were within the bioequivalence criteria of 80-125% for $AUC_{0-\infty}$ and C_{max}.

Table 2.2. Ratio of AUC and C_{max} [commercial site/pilot plant] and 90% CI's for 18 mg OROS®.

Parameter	Ratio (%)	90% Confidence Interval	
		Lower	Upper
C_{max}	94.2	88.9	99.8
$AUC_{0-\infty}$	99.7	95.5	104.2

In conclusion, bioequivalence was established between the 18 mg formulations manufactured at the pilot plant and at the commercial site.

Are the 18 mg and 36 mg OROS® dosage forms bioequivalent?

Bioequivalence was tested between the 18 mg and 36 mg OROS® formulations [Study #10, also see study description, Section 5. FOOD EFFECT]. Single doses of 1x36 mg (reference) and 2x18 mg (test) formulations were administered to 31 healthy adult volunteers.

The mean $AUC_{0-\infty}$, C_{max} and t_{max} were 67.6 ng.h/mL, 6.20 ng/mL and 6.5 h for the reference formulation. The corresponding values for the test formulation were 66.7 ng.h/mL, 6.34 ng/mL and 6.4 h, respectively. As shown in Table 2.3, the formulations manufactured were within the bioequivalence criteria of 80-125% for $AUC_{0-\infty}$ and C_{max}.

Table 2.3. Ratio for AUC and C_{max} [2x18 mg/36 mg] and 90% CI's after a single dose MPH.

Parameter	Ratio (%)	90% Confidence Interval	
		Lower	Upper
C_{max}	99.6	93.7	106.0
$AUC_{0-\infty}$	99.8	95.9	103.8

In conclusion, bioequivalence was established between the 18 mg and 36 mg MPH HCl (OROS®) formulations.

Does the drug release rate influence the bioavailability of the MPH OROS® formulation?

The bioequivalence of two 36 mg MPH OROS® formulations with different release rates was tested (Study #7; n=34). One of the capsules had the release rate of the intended commercial formulation, and the data was used for the model development of an *in vitro-in vivo* correlation (IVIVC), described in Section 9. The second capsule had an 11% faster release rate, and the data was used for the external validation of the IVIVC. Bioequivalence was established between the two OROS® formulations, as shown in Table 2.4. The t_{max} (mean ± SD) of the formulation with a faster release rate was 6.5 ± 0.9 h, and the intended commercial formulation had a t_{max} of 6.4 ± 1.0 h.

Table 2.4. Ratio for AUC and C_{max} [faster release profile / standard release profile] and 90% CI's for 36 mg OROS® (n=34).

Parameter	Ratio (%)	90% Confidence Interval	
		Lower	Upper
C_{max}	117.1	110.5	124.7
$AUC_{0-\infty}$	100.1	96.2	104.2

In conclusion, an 11% faster drug release rate does not influence the bioavailability of the MPH OROS® formulation.

3. MULTIPLE DOSE

Do the parent drug and metabolite(s) accumulate following multiple dosing of MPH?

A multiple dose study was conducted in 32 healthy subjects (20 males and 12 females; age = 18-45 years). The subjects received a single dose of 18 mg methylphenidate (MPH) on Day 1 and 48 hours later received 18 mg methylphenidate once a day for 4 days. Blood samples on days 1 and 6 were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30 and 36 hours post dose. Three blood samples were collected on days 3, 4 and 5 at pre-dose, 8 and 12 hours. Methylphenidate and its metabolite alpha-phenyl-2-piperidineacetic acid (PPA) concentrations were measured in plasma. The C_{max} of methylphenidate following single and multiple dosing was 2.81 ± 0.96 ng/mL and 3.00 ± 1.1 ng/mL, respectively. The $AUC_{(0-24)}$ of methylphenidate following single and multiple dosing was 30.4 ± 12 ng.h/mL and 35.2 ± 12 ng.h/mL, respectively. Following multiple dosing, there was about 14% increase in the AUC of methylphenidate as compared to the single dose. The half-life of methylphenidate was comparable following single and multiple dosing. For the metabolite PPA, the C_{max} following single and multiple dosing was 118± 23 ng/mL and 127 ± 19 ng/mL, respectively. The $AUC_{(0-24)}$ of PPA following single and multiple dosing was 1650 ± 212 ng.h/mL and 1941 ± 236 ng.h/mL, respectively. There was approximately 18% increase in the AUC of PPA following multiple dose as compared to single dose administration (Study #8). There was no accumulation of MPH or PPA in plasma following multiple dosing.

Table 3.1. Single and multiple dose pharmacokinetic parameters of MPH following 18 mg oral dose.

Parameters	single dose (n = 32)	Multiple dose (n = 32)
MPH:		
C_{max} (ng/mL)	2.81 ± 0.96	3.0 ± 1.1
t_{max} (hrs)	7.4 ± 2.0	6.6 ± 2.3
T1/2 (hrs)	3.9 ± 0.71	3.9 ± 0.76
$AUC_{(0-24)}$ (ng*hr/mL)	30.4 ± 12	35.2 ± 12
$AUC_{(0-inf)}$ (ng*hr/mL)	32.9 ± 12	-
PPA:		
C_{max} (ng/mL)	118 ± 23	127 ± 19
t_{max} (hrs)	8.1 ± 1.7	7.6 ± 1.9
T1/2 (hrs)	7.7 ± 1.1	8.2 ± 1.0
$AUC_{(0-24)}$ (ng*hr/mL)	1650 ± 212	1941 ± 236
$AUC_{(0-inf)}$ (ng*hr/mL)	1993 ± 218	-

4. DOSE PROPORTIONALITY

Is the pharmacokinetics of MPH linear over the recommended therapeutic dose?

Methylphenidate HCl dose linearity was investigated in 22 males and 13 females following a single dose of 18, 36, and 54 mg methylphenidate HCl. The age of the subjects ranged from 18 to 43 years and the subjects received methylphenidate after an overnight fast. Concentrations of d- and l-methylphenidate were measured in plasma. The peak plasma concentrations of l-methylphenidate were at least 30 to 40 times lower than the peak plasma concentrations of d-methylphenidate. The study indicated that d-methylphenidate is linear over the dose range of 18 to 54 mg, whereas l-methylphenidate AUC(0-inf) increased disproportionally with respect to dose (Study #9).

Table 4.1. Pharmacokinetic parameters of methylphenidate following three different oral doses

Parameters	1 x 18 mg	2 x 18 mg	3 x 18 mg
d-MPH:			
C_{max} (ng/mL)	3.8 ± 1.8	7.3 ± 2.8	10.5 ± 3.4
t_{max} (h)	7.9 ± 1.7	7.5 ± 1.3	7.2 ± 1.5
T1/2 (h)	3.7 ± 0.9	3.9 ± 0.7	3.9 ± 0.7
$AUC_{(0-inf)}$ (ng*h/mL)	41.1 ± 15.9	80.9 ± 30.8	118.9 ± 45.9
l-MPH:			
C_{max} (ng/mL)	0.09 ± 0.15	0.17 ± 0.21	0.35 ± 0.52
t_{max} (h)	7.1 ± 1.9	7.0 ± 1.7	6.3 ± 1.4
$AUC_{(0-inf)}$ (ng*h/mL)	0.40 ± 0.71	0.96 ± 1.39	1.80 ± 2.7

5. FOOD EFFECT

Does a high fat meal affect the rate and extent of MPH absorption?

(i) Effect of high fat meal on the pharmacokinetics of MPH was evaluated following 36 mg oral administration of OROS given to adult healthy subjects (19 males and 17 females). The C_{max} of OROS was 6.20 ± 2.2 ng/mL under fasting condition whereas under fed condition the C_{max} was 6.87 ± 2.3 ng/mL. The $AUC_{(0-inf)}$ was 67.6 ± 23.7 and 79.0 ± 26.8 under fasting and fed conditions, respectively. The T_{max} was prolonged approximately by an hour under fasting

condition. Overall, food increased the C_{max} of OROS by 11% and AUC by 17%, which may not be of any clinical significance. The confidence intervals for C_{max} and AUC were 105.4-119.3 and 115.1 to 124.6, respectively (Study #10).

(ii) Effect of high fat meal was also evaluated in children following 18, 36 and 54 mg qd oral administration of OROS. Thirty-two patients entered the study (age = 7 to 12 years). Sixteen patients (12 male and 4 female) were randomized to treatment in group I and another 16 patients (14 male and 2 female) were randomized to treatment in group II. One female patient in group I dropped out due to repeated systolic blood pressure >130 mm Hg. Also in group I, for two subjects blood samples could not be collected for the pharmacokinetic assessment. In group I, the OROS formulation was compared between fasting and fed conditions (high fat meal), whereas in group II, the OROS formulation was compared between a normal breakfast and a high fat breakfast (the data for group II have not been reviewed). Blood samples were collected at time 0, 1.5, 2.5, 4.0, 5.5, 6.5, 8.0, 9.5, and 11.5 hours. The C_{max} and the AUC(0-11.5 hours) of OROS increased with the increasing dose under both fed and fasting conditions. However, both C_{max} and AUC did not increase proportionally. This may be due to small sample size. Overall, food did not effect the pharmacokinetics of OROS in children (Study #11).

In this study, Laboratory school teacher observer ratings on the SKAMP, combined attention scales as well as deportment ratings on the SKAMP, activity monitor levels during academic seatwork periods, and Laboratory school teacher global assessment of efficacy were monitored as pharmacodynamic end points. These pharmacodynamic end points appear to be similar under both fed and fasting conditions.

Table 5.1. MPH pharmacokinetic parameters in children for the OROS under fed and fasting conditions.

Parameters	Fasting			Fed		
Dose (mg)	18	36	54	18	36	54
n	3	7	3	3	7	3
C_{max} (ng/mL)	6.0 ± 1.3	11.3 ± 2.6	15.0 ± 3.8	7.2 ± 0.5	12.5 ± 3.8	16.1 ± 4.9
t_{max} (h)	9.4 ± 0.02	8.1 ± 1.1	9.1 ± 2.5	9.6 ± 1.7	8.0 ± 2.8	10.3 ± 2.0
AUC (ng*h/mL)	50.4 ± 7.8	87.7 ± 18.2	121.5 ± 37.	57.1 ± 2.8	92.6 ± 30.4	118.9 ± 45.

6. PHARMACODYNAMICS: MPH SIMULATED PLASMA CONCENTRATIONS AND RESPONSE CORRELATION

Two clinical studies (Studies #12 and #13) were conducted in patients (children) with ADHD tc evaluate the influence of various MPH profiles on the duration of efficacy. In these two clinical studies, the OROS system as a dosage form was not used. All MPH or placebo doses were blinded; the dosage form was a capsule that was given orally. Behavioral measures, which were used to assess pharmacodynamic responses, were derived from the Conners, Loney, and Milich questionnaire (CLAM) and the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale.

The CLAM has 16 items, and each item is rated on a four-point scale (not at all, just a little, pretty much, and very much). Ratings of subsets of items are averaged to provide three scores: the Conners Hyperactivity Index (H), the Loney/Milich Inattention/Overactivity Index (I/O) and the Aggression/Defiance Index (ND). Morning and evening CLAM assessments were made by parents and used to identify unusual behaviors.

The SKAMP has 10 items describing classroom behavior, and each item is rated on a seven-point impairment scale (none, slight, mild, moderate, severe, very severe, or maximal).

Ratings of subsets of items are averaged to provide two scores: the Deportment Index and the Academic Index. Teachers used four behavioral rating measures derived from the SKAMP to assess schoolwork attention, non-schoolwork attention, combined attention, and behavior.

Study I

This study was a double-blind, randomized, four-way crossover design. Of the 38 children recruited for this trial, 31 children (aged 7 to 12 years) completed the study. In this study, the efficacy of an experimental delivery pattern designed to result in rising MPH concentrations (ASCEND-I) and a regimen providing a flat (FLAT) plasma profile were compared to the efficacy of standard Ritalin IR treatment (bid q4h) or placebo. All treatments were given in identical capsules given at 30-minute intervals throughout the day (starting at 7.30 in the morning and the last dose was given at 3 PM).

Plasma MPH concentrations were not measured, instead the effects were correlated with the simulated plasma concentration time profile (Figure 1). Efficacy was measured using the CLAM and SKAMP behavioral ratings to provide subjective but systematic ratings of several dimensions of behavior. The CLAM and SKAMP measurements were performed 4 times during the investigational period (AM peak, AM trough, PM peak, PM trough). Mean CLAM and SKAMP behavioral ratings during BID treatment were much better (lower scores) than during placebo treatment (Figure 2). For SKAMP combined attention, the FLAT treatment was significantly better than placebo ($p = 0.040$) at the second measurement point; however, the FLAT treatment was not significantly better than placebo in the afternoon. The ASCEND-I treatment approximated the placebo treatment at the first measurement point; thereafter the ASCEND-I treatment was better than placebo and approximated the BID treatment. At the afternoon peak (the most likely time when acute tolerance might occur), the ASCEND-I and BID regimens did not produce significantly different mean values for any of the measures. Analysis showed that the FLAT regimen was significantly less effective than either the BID or ASCEND-I regimens for six of the eight measures (4 measures of memory load; Figure 3).

These results indicate that an ASCEND-I MPH release profile is as effective as a BID regimen after the first measurement point. The decreased effectiveness of the FLAT MPH regimen following the afternoon peak (as compared with that of the BID dosing regimen) may be due to acute tolerance (according to the Sponsor) that develops from sustained levels of plasma MPH over the day.

Objectives:

Concentration-effect modeling was performed to relate the shape of the concentration-time profile to the shape of the effect-time profile. The specific objectives of the analysis were to:
(1) evaluate the concentration- effect relationship
(2) evaluate the effect of treatment on the concentration- effect relationship
(3) evaluate the influence of history/rate of delivery on the concentration-effect relationship.

Methods:

Plasma drug concentrations were NOT measured in this study. Therefore, the profiles for each treatment were simulated using published literature values at a nominal daily dose of 20 mg. It was assumed that there is no inter- and intra-subject variability in plasma concentrations for a given dose of methylphenidate. All analyses used a nonlinear mixed effect modeling technique (NONMEM) that fits all subjects' (n=31) data together to estimate the mean parameters, and that allows for individual differences in parameters.

Models:

A complete list of the mathematical models that were fitted to the data, and the estimated model parameters, is provided in Table 1. Models examined were linear, quadratic and E_{max} model with Hill Coefficient (γ). The values of γ were set from 3 to 6.

Results:

There was a counterclockwise hysteresis loop in the concentration-effect relationship, suggesting the development of tolerance (Figure 4). The area of the hysteresis loop was reduced after correcting for changes in baseline effect (Figure 5). Several mathematical models relating the simulated concentrations to the effect data were examined. A simple linear and a quadratic concentration-effect model were fit to the data. Although it provided a small reduction in the residual sums of squares, fitting a quadratic model to the simulated data did not produce a significant statistical improvement in model fit over that provided by a linear model. The relationship between effect (inattention/overactivity and schoolwork attention measures) and plasma concentration was best described by a sigmoidal E_{max} model (Figure 6). The estimated parameter values and the overall objective function for the various models are listed in Table 1. For each of the three active treatments, a linear model was fit to estimate the slope of the concentration-effect relationship. The concentration-effect relationship was similar for the ascending and BID treatments but statistically significantly different from the flat treatment. The slope values for the BID and ascending treatments did not differ and were about 25% higher than that for the FLAT treatment. This 25% decrease in slope represents a 25% decrease in the effect of the FLAT profile.

Conclusions:

Based on the modeling analysis and on the data available in the literature regarding Ritalin SR plasma concentrations, it is estimated that the onset of action for Ritalin-SR will commence 1 to 1.5 hours after ingestion and that it will remain effective for 5 to 7 hours.
For a TID dosing and its OROS equivalent:
1. If the total dose cannot be increased due to dose-related toxicity then 22% of the total dose should be administered as immediate release, and the remainder of the dose should be delivered so as to produce an ascending profile (e.g. a slope of 20 degrees, Figure 1).

2. If the total dose can be increased, then 22% of the total dose should be administered as immediate release, and the remainder of the dose should be delivered so as to produce an ascending profile (e.g. a slope of 35 degrees, Figure 1). To achieve the increased ascending profile, approximately 20% more total drug would be required (i.e. 36 mg to be equivalent to a 10 mg q4h regimen) (Figure 1).

Figura 1 (Study 1)

SIMULATION

FIGURE 23

Simulated Plasma Methylphenidate Concentrations
Ritalin TID Q4h Profile vs Four Ascending Profiles

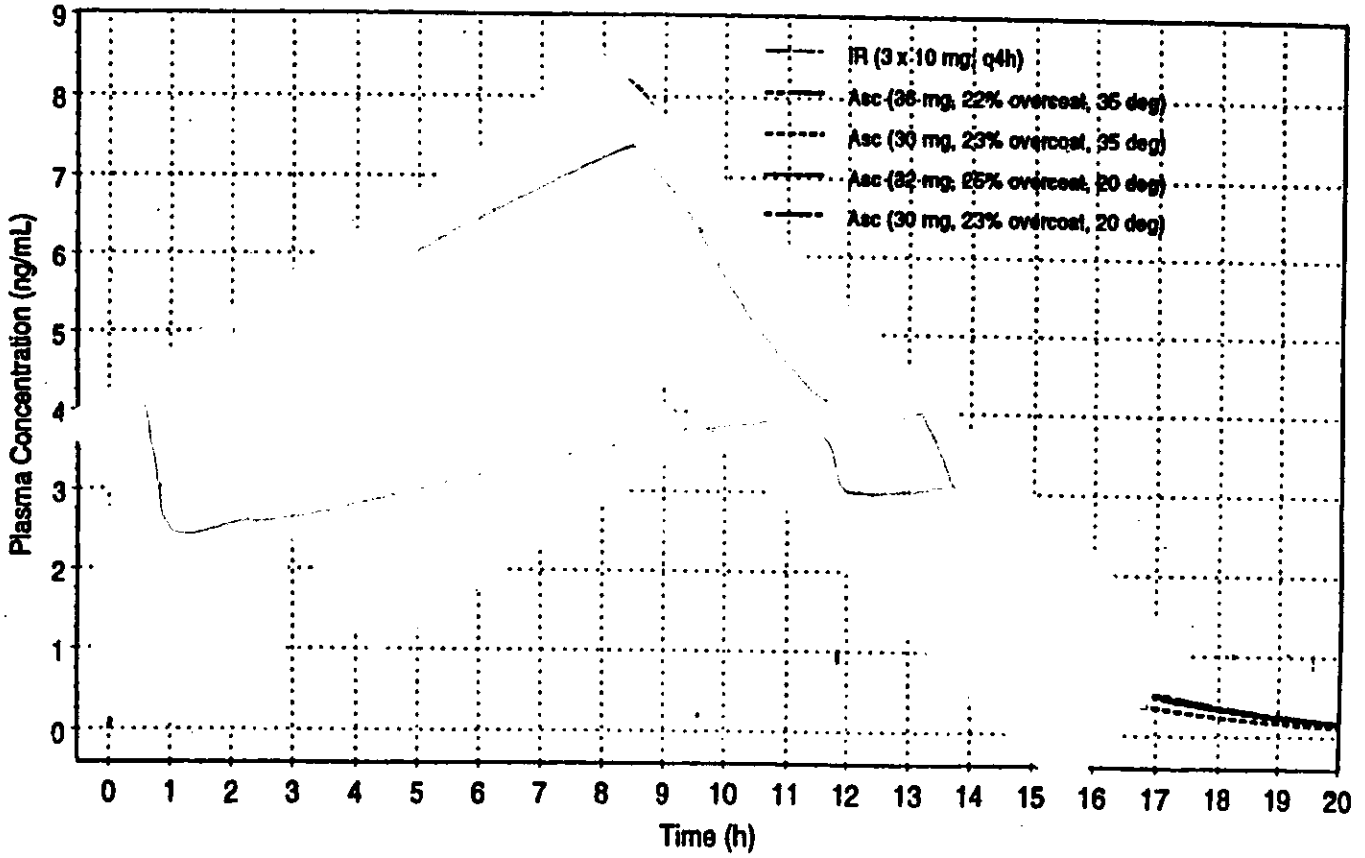


Figure 3 (Study 1)

FIGURE I: SKAMP BEHAVIORAL RATINGS

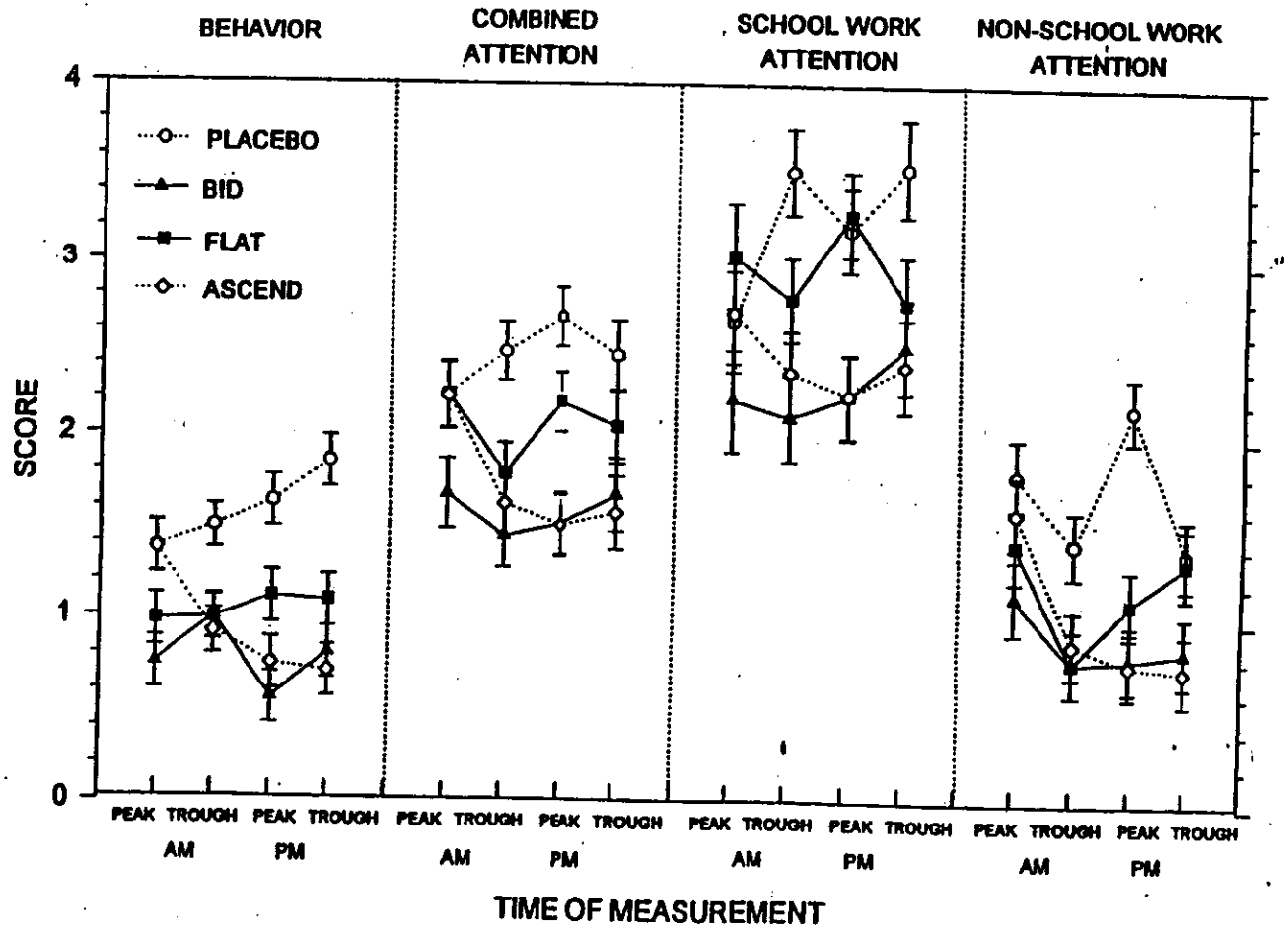
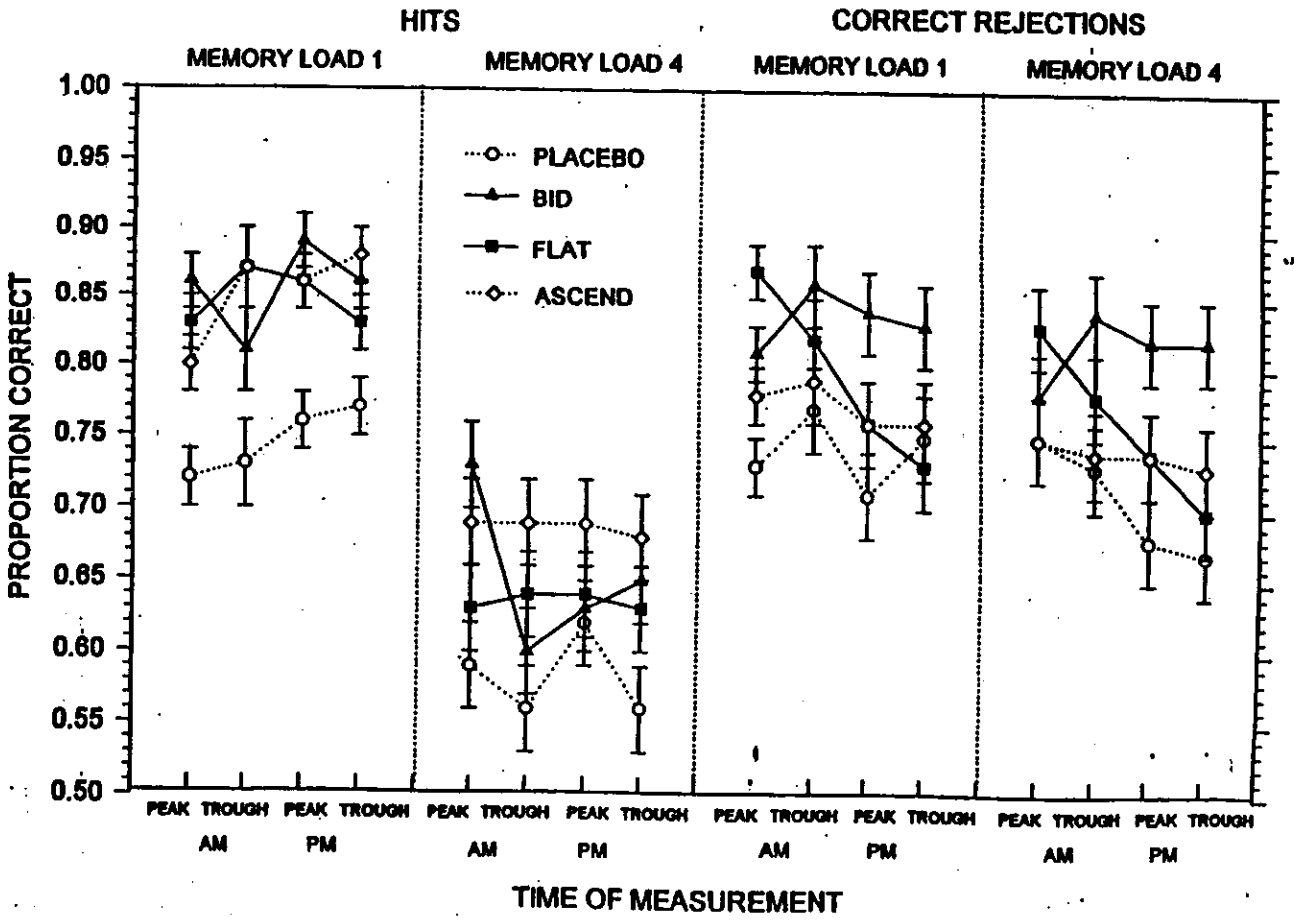


Figure 13 (Study 1)

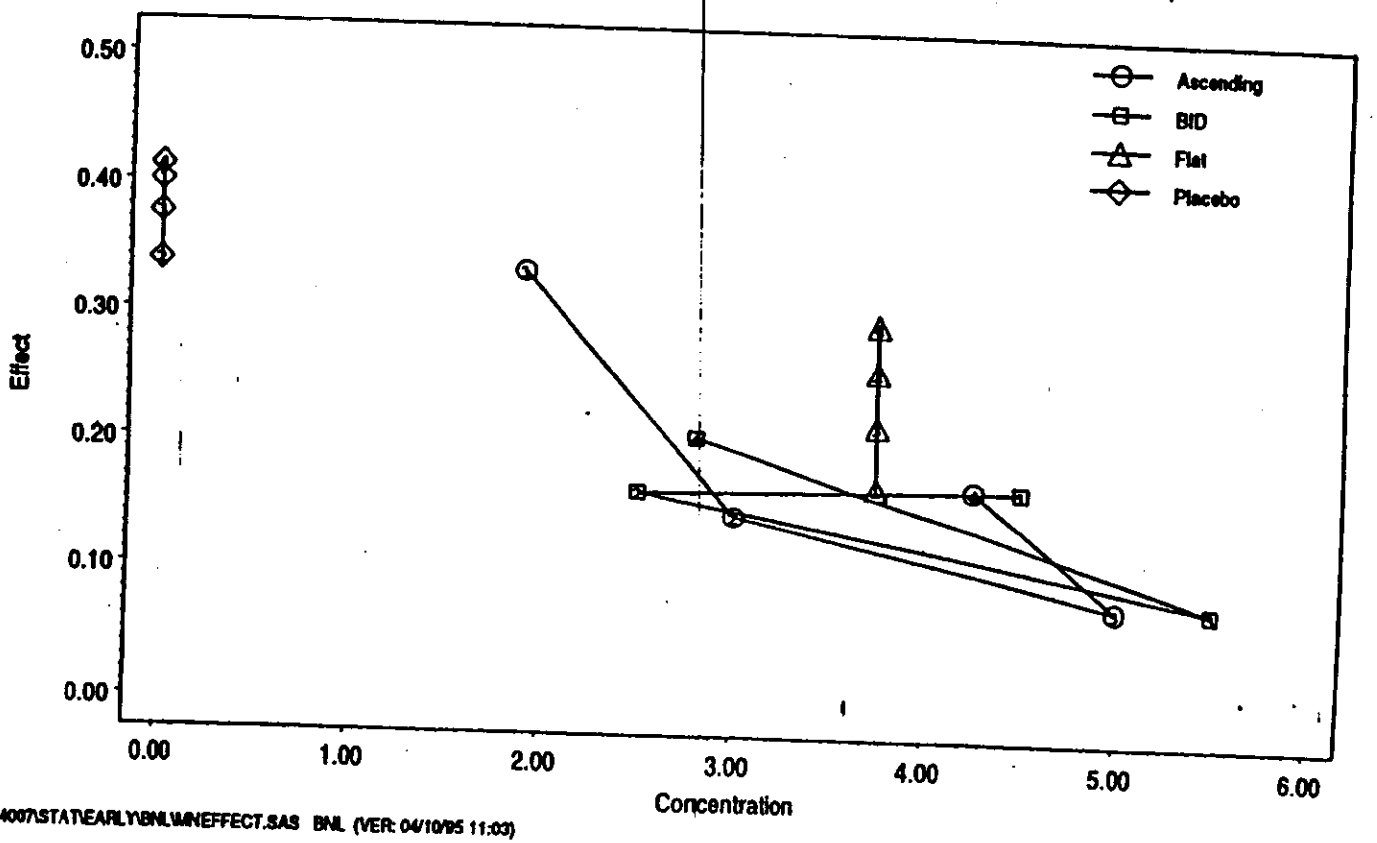
FIGURE II: MEMORY SCANNING



(Study 1)

FIGURE 26 #4

Mean Agressive/Defiant Behavior Effect vs Concentration
(n =34)



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(Study 1)

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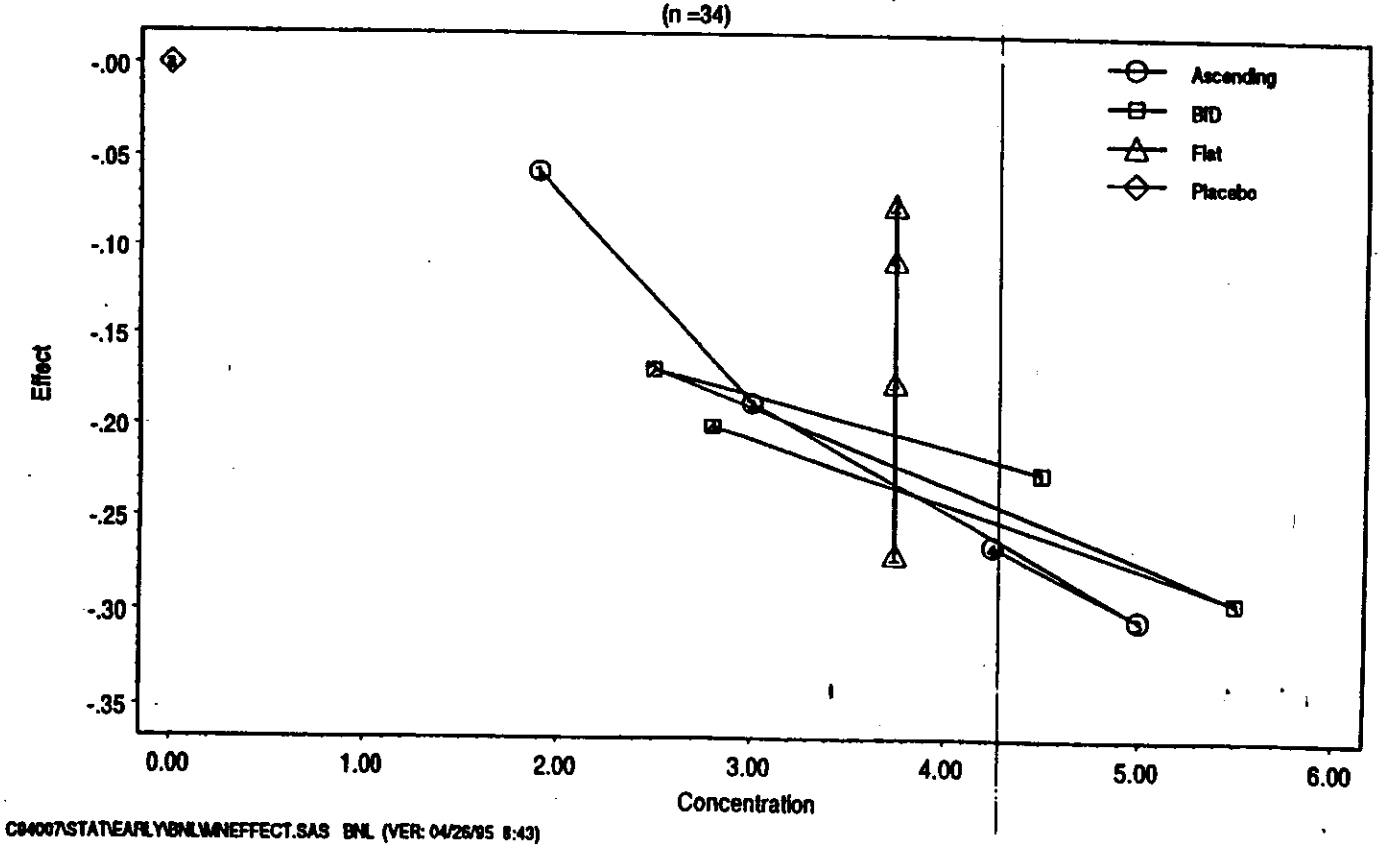
FIGURE 21

Relative Mean Agressive/Defiant Behavior Effect vs Concentration
(Effect = Treatment Effect - Placebo Effect)
(n =34)



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(Study 1)

FIGURE 22

Linear, Quadratic and Emax Prediction Models
for Relative Inattention/Overactivity Effect vs Concentration
(Effect = Treatment Effect - Placebo Effect)
(n =31)

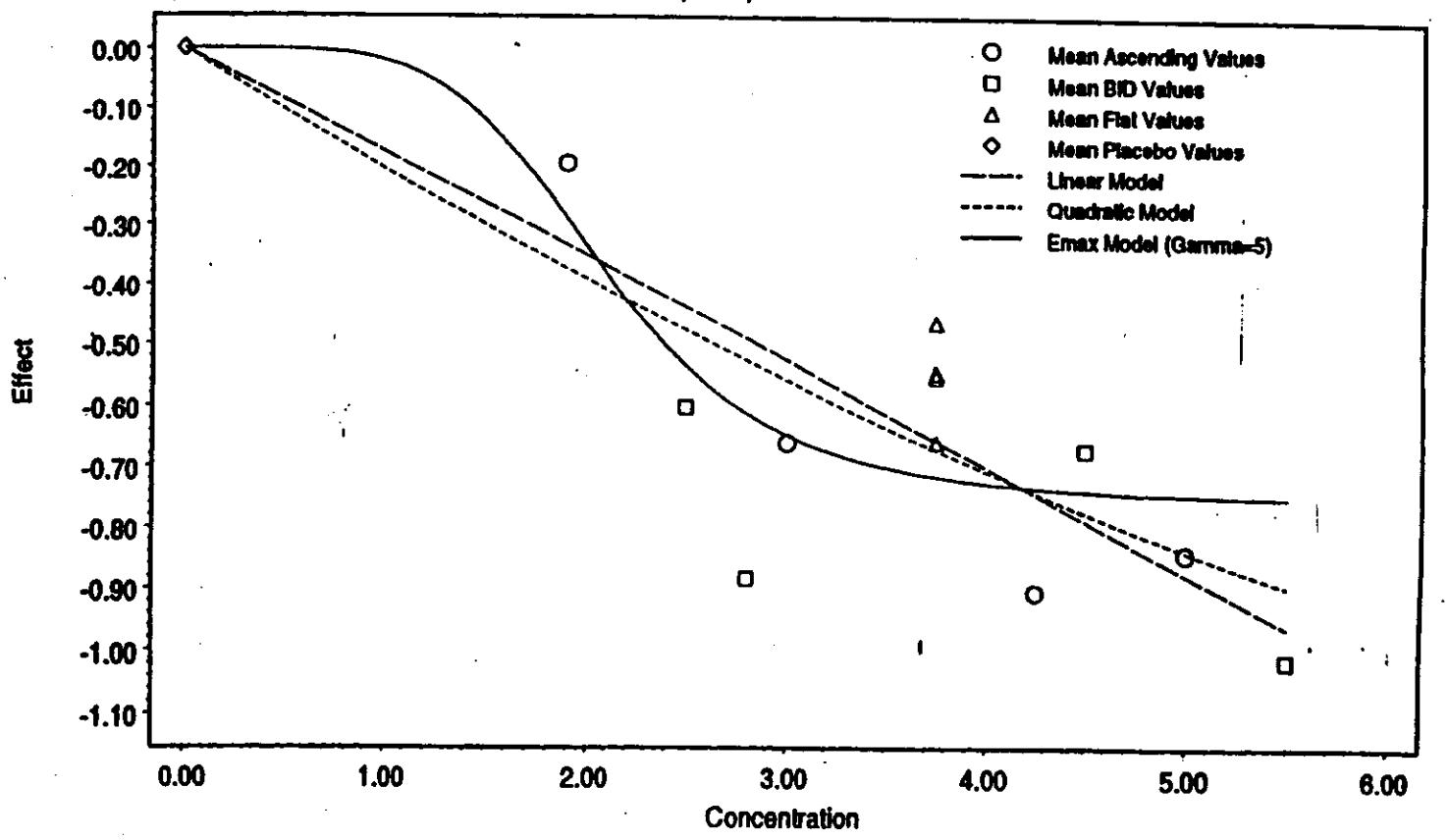

TABLE 1 (Study 1)

TABLE 1 (1 of 5)
Inattention/Overactivity Effect

Model	Objective Function	NONMEM Estimates	Within Subj. CV
Linear	140.3	Equation: $y = 1.44 - 0.154c + \epsilon$ CV: 10% 18% Betw. Subj. CV: 43% 71%	61%
Quadratic	136.2	Equation: $y = 1.48 - 0.247c + 0.195c^2 + \epsilon$ CV: 10% 29% 55% Betw. Subj. CV: 42% 45%	61%
Linear, Placebo ignored, Separate slope for Flat	76.2	Equation: $y = 1.41 - 0.161c\,[I_{con,s}(c)] - 0.120c\,[I_{cof}(c)] + \epsilon$ CV: 10% 15% 36% Betw. Subj. CV: 38% 26% 153%	47%
Linear, Placebo ignored, Separate slope and intercept for Flat	82.0	Equation: $y = (1.12 - 0.0923c)\,[I_{con,s}(c)]$ CV: 15% 31% Betw. Subj. CV: 41% - $+ (1.52 - 0.137c)\,[I_{cof}(c)] + \epsilon$ 10% 35% 48% 172%	53%
Linear, Placebo ignored, Separate slope for each treatment	70.8	Equation: $y = 1.39 - 0.148c\,[I_{con}(c)] - 0.164c\,[I_{cab}(c)]$ CV: 10% 15% 16% Betw. Subj. CV: 38% 30% 37% $- 0.114c\,[I_{cof}(c)] + \epsilon$ 35% 160%	40%
Linear, Placebo ignorcd Separate slope and intercept for each treatment	87.4	Equation: $y = (1.35 - 0.133c)\,[I_{con}(c)] + (0.88 - 0.047c)\,[I_{cab}(c)]$ CV: 17% 33% 23% 85% Betw. Subj. CV: 41% - 46% - $+ (1.50 - 0.133c)\,[I_{cof}(c)] + \epsilon$ 12% 40% 49% 177%	49%

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TABLE 26 (2 of 5)
School Work Attention Effect

Model	Objective Function	NONMEM Estimates	Within Subj. CV
Linear	850.3	Equation: $y = 3.14 - 0.159c + \epsilon$ CV: 4%, 30% Betw. Subj. CV: -, -	111%
Quadratic	850.2	Equation: $y = 3.15 - 0.172c + 0.00477c^2 + \epsilon$ CV: 6%, 108%, 706% Betw. Subj. CV: -, -	111%
Linear, Placebo ignored, Separate slope for Flat	823.5	Equation: $y = 3.12 - 0.201c\,[I_{coA,B}(c)] - 0.0321c\,[I_{cef}(c)] + \epsilon$ CV: 5%, 19%, 246%, 46% Betw. Subj. CV: -, 17%	119%
Linear, Placebo ignored, Separate slope and intercept for Flat	818.3	Equation: $y = (2.59 - 0.0730c)\,[I_{coA,B}(c)] + (3.23 - 0.0704c)\,[I_{cef}(c)] + \epsilon$ CV: 10%, 95%, 58%, 6%, 111%, 208% Betw. Subj. CV: -, -, -, -, -, -	110%
Linear, Placebo ignored, Separate slope for each treatment	821.2	Equation: $y = 3.13 - 0.197c\,[I_{coA}(c)] - 0.206c\,[I_{coB}(c)] - 0.0458c\,[I_{cef}(c)] + \epsilon$ CV: 4%, 22%, 21%, 136% Betw. Subj. CV: -, 45%, 49%, 324%	103%
Linear, Placebo ignored Separate slope and intercept for each treatment	813.8	Equation: $y = (2.80 - 0.115c)\,[I_{coA}(c)] + (2.35 - 0.0217c)\,[I_{coB}(c)] + (3.25 - 0.0796c)\,[I_{cef}(c)] + \epsilon$ CV: 12%, 74%, 17%, 506%, 5%, 90%, 189% Betw. Subj. CV: 14%, -, -, 469%	96%

TABLE 26 (3 of 5)
Relative Inattention/Overactivity Effect

Model	Objective Function	NONMEM Estimates		Within Subj. CV
Linear	229.3	Equation	$y = 0.00116 - 0.166c + e$	74%
		CV	24% 17%	
		Betw. Subj. CV	45390% 64%	
Quadratic	228.8	Equation	$y = 0.0188 - 0.218c + 0.0957c^2 + e$	74%
		CV	20% 39% 154%	
		Betw. Subj. CV	2759% 49%	
Linear, Intercept at 0	236.3	Equation	$y = -0.175c + e$	75%
		CV	18%	
		Betw. Subj. CV	97%	
Quadratic, Intercept at 0	235.6	Equation	$y = -0.213c + 0.00919c^2 + e$	75%
		CV	37% 153%	
		Betw. Subj. CV	79% -	
Linear, Intercept at 0, Separate slope for Flat	238.6	Equation	$y = -0.189c\ [I_{cel.s}(c)] - 0.148c\ [I_{cef}(c)] + e$	71%
		CV	13% 32%	
		Betw. Subj. CV	68% 173%	
Quadratic, Intercept at 0, Separate slope and quad. term coefficient for Flat	235.8	Equation	$y = (-0.271c + 0.0186c^2)\ [I_{cel.s}(c)]$	70%
		CV	25% 72%	
		Betw. Subj. CV	47% -	
			$+ (-0.148c + 0.0000817c^2)\ [I_{cef}(c)] + e$	
			19% 6659%	
			173% -	

TABLE 26 (4 of 5)

Relative Inattention/Overactivity Effect (Cont.)

Model	Objective Function	NONMEM Estimates	Within Subj. CV
Emax model, γ=3	220.2	Equation $y = -0.920 * C^3 / (3.40^3 + C^3) + e$ CV 22% 10% Betw. Subj. CV 53% 377%	72%
Emax model, γ=4	221.9	Equation $y = -0.775 * C^4 / (2.07^4 + C^4) + e$ CV 18% 6% Betw. Subj. CV 78% -	73%
Emax model, γ=5	220.7	Equation $y = -0.752 * C^5 / (2.09^5 + C^5) + e$ CV 18% 6% Betw. Subj. CV 75% -	75%
Emax model, γ=6	220.0	Equation $y = -0.738 * C^6 / (2.11^6 + C^6) + e$ CV 18% 5% Betw. Subj. CV 74% -	73%

TABLE 26 (5 of 5)

Relative School Work Attention Effect

Model	Objective Function	NONMEM Estimates	Within Subj. CV
Linear	891.7	Equation $y = -0.161c + e$ CV 35% Betw. Subj. CV 179%	183%
Quadratic	891.1	Equation $y = -0.250c + 0.0210c^2 + e$ CV 82% 196% Betw. Subj. CV 116% -	183%
Linear, Separate slope for Flat	902.7	Equation $y = -0.216c\,[I_{cel.s}(c)] - 0.0528c\,[I_{cel}(c)] + e$ CV 23% 73% Betw. Subj. CV 101% 750%	181%
Quadratic, Separate slope and quad. term coefficient for Flat	898.3	Equation $y = (-0.507c + 0.0690c^2)\,[I_{cel.s}(c)]$ CV 40% 68% Betw. Subj. CV 42% - $+ (-0.389c + 0.0893c^2)\,[I_{cel}(c)] + e$ 6% 25% 104% -	170%

Study II

After discovering that acute tolerance may develop to MPH response; PK/PD modeling was used to determine the input profile that would be needed to overcome it. The primary objective of this study was to compare the efficacy and safety of MPH given in two different dosing regimens. A continuous delivery pattern designed to result in rising MPH plasma concentrations for approximately 8 hours (ASCEND-II) and a TID pattern were compared to each other and against placebo. Another treatment (VAR) was also explored to provide additional information for PK/PD modeling and to confirm the development of tolerance. In this study, 32 children (28 boys and 4 girls) with ADHD aged 7 to 12 years old who had participated in Study #12 or met the entry criteria for Study #12 were recruited. Thirty children completed the study. The children's normal pre-study mean daily dose of MPH was 28.9 mg (15 to 50 mg). The children's mean daily assigned MPH TID dose was 30.7 mg (15 to 45 mg). The mean daily MPH ASCEND dose was 120% of the TID dose. The mean daily MPH VAR-AM and VAR-PM dose was equal to the TID dose for each child. The following treatments were administered during the study:

ASCEND-II: A continuous MPH delivery pattern designed to result in rising MPH plasma concentrations for approximately 8 hours, administered as an immediate release dose at 7.30 a.m. A dose of MPH (4, 6, 8, 10 or 12 mg) equal to 80% of the child's usual single AM dose given orally at 7.30 a.m., followed by placebo at 8.00 and 8.30 a.m., followed by small MPH doses given every 30 minutes starting at 9.00 and continuing until 15.30.
TID: Three doses of MPH, each equal to the child's usual study morning dose (5, 7.5, 10, 12.5 or 15 mg), administered q4h at 0730, 1130, and 1530. Placebo was given at every 30 minutes.
VAR: Two doses of MPH administered at 0730 and 1530 and an intermediate dose of MPH, which was given at 0930 (VAR-AM), or 1330 (VAR-PM).
PLACEBO: Lactose given every 30 minutes from 0730 to 1530.

Plasma MPH concentrations were not measured, instead the effects were correlated with the simulated plasma concentration time profile. The purpose of the pharmacokinetic/ pharmcodynamic (PK/PD) modeling was to determine if there was an influence of the rate of delivery on the concentration-effect relationship. Because patients were titrated to effect, the same MPH concentration was assumed for all subjects. This approach assumes that there is no inter- or intra-subject variability in the achieved plasma concentrations. All analyses used a nonlinear mixed effect modeling approach (NONMEM) which fitted subject data together to estimate the mean parameters while allowing for individual differences in parameters.

A PK/PD model of the MPH concentration-SKAMP assessment relationship was developed. An E_{max} model was fitted to the simulated MPH plasma concentrations and the SKAMP assessment scores.

$$E = E_{max} * C^{\gamma}/(EC_{50})^{\gamma} + C^{\gamma} \qquad \text{(Equation 1)}$$

Where E is the SKAMP assessment score, E_{max} is the maximum SKAMP assessment score, and EC_{50} is the concentration needed to reach the 50% SKAMP assessment score. C is the simulated plasma concentration and γ is the Hill coefficient.

A tolerance model (Figure A) similar to that reported by Porchet *et al* (J Pharmacol Exp Ther, vol 244: 231-236, 1988) was fitted to the SKAMP assessment scores. This model is a one-compartment pharmacokinetic model for first-order absorption and disposition of MPH. The pharmacokinetic model is linked to a pharmacodynamic model that relates the simulated plasma MPH concentration to the observed SKAMP assessment score. The link model

relates the simulated plasma concentration to the effect site concentration via a rate constant K_{eo}. It is hypothesized that a noncompetitive antagonist is produced by a first order rate constant (K_{tol}) that governs the rate of appearance and disappearance of the antagonist formed from C_e (concentration in the effect compartment) rather than plasma concentration C. The actual rate of tolerance development is the sum of K_{eo} and K_{tol}. This modification of Porchet *et al*'s model overcomes the possibility that tolerance can develop before emergence of a behavioral effect.

The simulated plasma concentrations vs time profile are shown in Figures 1-2. Figures 3-6 are plots of different efficacy measurements against time. The mean structured classroom activity level difference (placebo minus treatment) was plotted as a function of simulated MPH plasma concentration and the points were joined in ascending order of time. Activity level vs plasma concentration plots displayed counterclockwise hysteresis (Figures 7-10), indicating the development of tolerance.

The residual sums of squares for tolerance model was almost 50% less than the E_{max} model indicating that a tolerance model describes the data better than an E_{max} model. The summary of pharmacodynamic parameters obtained by E_{max} and tolerance model is presented in Tables 1 and 2, respectively.

The decrease in the effect of MPH in the presence of constant plasma concentrations (tolerance) was explained by assuming that a hypothetical antagonist forms at the effect site. The proposed model is similar to that developed by Porchet *et al* with an important difference. The Porchet model assumes that the formation of an antagonist is directly related to the plasma drug concentration time profile (i.e., drug concentration in the central compartment). Unlike the Porchet model, the proposed model assumes that tolerance cannot develop in the absence of an effect. The two models are similar when the tolerance half-life is longer than the distribution half-life and also when plasma concentrations are at steady state. When the tolerance-corrected effect was plotted as a function of the effect site concentration for the SKAMP combined attention and behavior measures, it showed that the hysteresis loop area was reduced in the tolerance model, suggesting that this model accounts for all the tolerance (Figures 11-18). The tolerance model half-life was about 18 + 36 = 54 minutes and the distribution half-life was about 36 minutes for SKAMP combined attention (Table 2). Similarly, the tolerance half-life was about 90 + 40 = 130 minutes and the distribution half-life was about 90 minutes for SKAMP behavior measurement (Table 2). There was a difference in the distribution half-life for the SKAMP combined attention and behavior measures. These differences suggest that after MPH administration, a change in the child's attention occurs sooner than does a change in the child's behavior; thus, it appears MPH affects attention earlier than behavior. A relatively high C_{ant50} (the antagonist concentration that reduces the agonist effect by 50%) value indicates less tolerance. In the present study, the C_{ant50} value for SKAMP combined attention is relatively high (5.50 ± 2.31) compared to SKAMP (2.73 ± 1.56) behavior.

Based on the PK/PD modeling, it was concluded by the Sponsor that measurable tolerance develops over a day.

Results from this study can be summarized as follows:

I. On SKAMP combined attention and behavior efficacy measures, an MPH dosing regimen designed to create an ascending plasma drug concentration (ASCEND-II) and three equal doses of MPH (TID) provided statistically and clinically significantly better treatment effect than did the PLACEBO treatment.

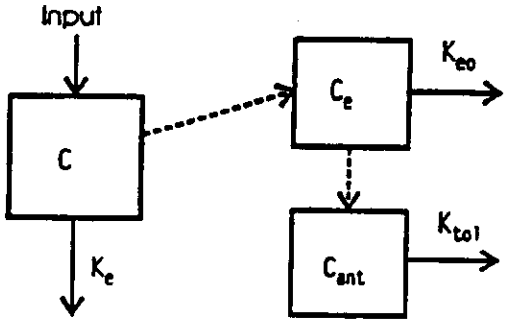
II. During structured-classroom periods, both the ASCEND-II and TID treatments reduced activity levels significantly as compared to PLACEBO. Although MPH treatment reduced activity during the early school day non-structured recess periods, the reduction in activity

was less than that found during structured-classroom periods. There were no significant activity level differences between ASCEND-II and TID during classroom time. Late in the afternoon (1500-1600 hours), ASCEND-II produced improvements in attention, behavior, and computer mathematics test performance, and a reduction in hyperactivity during structured-classroom time as compared to TID, however, these differences did not reach statistical significance.

ASCEND-II and TID treatments both improved global treatment effectiveness and safety significantly as compared to PLACEBO (as assessed by the teachers).

Figure A

Tolerance PK/PD Model



Tolerance Model

$$E_t = E_0 + \frac{S * C_{e_t}}{1 + \frac{C_{ant}}{C_{ant_{50}}}}$$

Equation 2

Where C_{ant} is the antagonist concentration at time t, $C_{ant\ 50}$ is the antagonist's concentration that reduces the agonist effect by 50%, and the slope (S) of the relationship is calculated as E_{max}/EC_{50}, because a true E_{max} cannot be estimated. The equations defining Ce_t and C_{ant} are respectively:

$$C_{ant} = f(K_{eo}, C_e)$$

TABLE 1

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Table D
E_{max} Model Estimated Parameters

Model Parameters	SKAMP Combined Attention	SKAMP Behavior
E_{max}		
Mean	-0.80	-0.76
CV	11%	12%
EC_{50}		
Mean	2.45	3.17
CV	13%	8%
Hill Coefficient		
Mean	5	5
Residual Sum of Squares	1352	1167

TABLE 2

Table E
Tolerance Model Estimated Parameters

Model Parameters	SKAMP Combined Attention	SKAMP Behavior
S Scaling: E_{max}/EC_{50}		
Mean	0.54	0.76
CV	37%	43%
Intercept (Baseline)		
Mean	0.23	0.28
CV	127%	62%
C_{emax50}(ng/mL)		
Mean	5.50	2.73
CV	42%	57%
$K_{eo}(h^{-1})$		
Mean	1.14	0.46
CV	23%	52%
K_{eo} $t_{1/2}$ (min)	36	90
$K_{tol}(h^{-1})$		
Mean	2.28	1.05
CV	38%	45%
K_{tol} $t_{1/2}$ (min)	18	40
Residual Sum of Squares	795	736

FIGURE 1

Simulated Plasma Methylphenidate Concentration Profiles:
Methylphenidate TID q4h and Ascending

(Study 2)

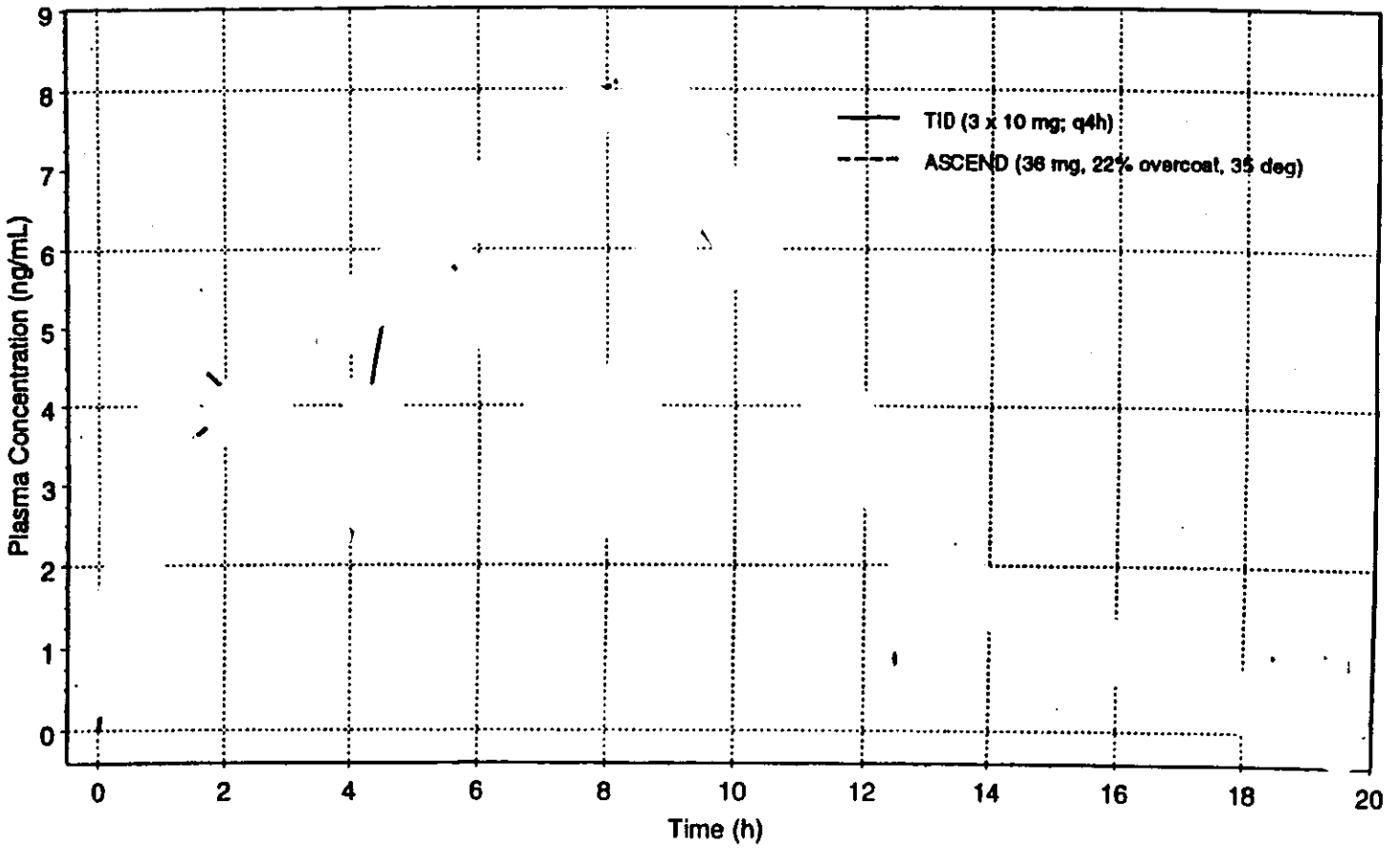
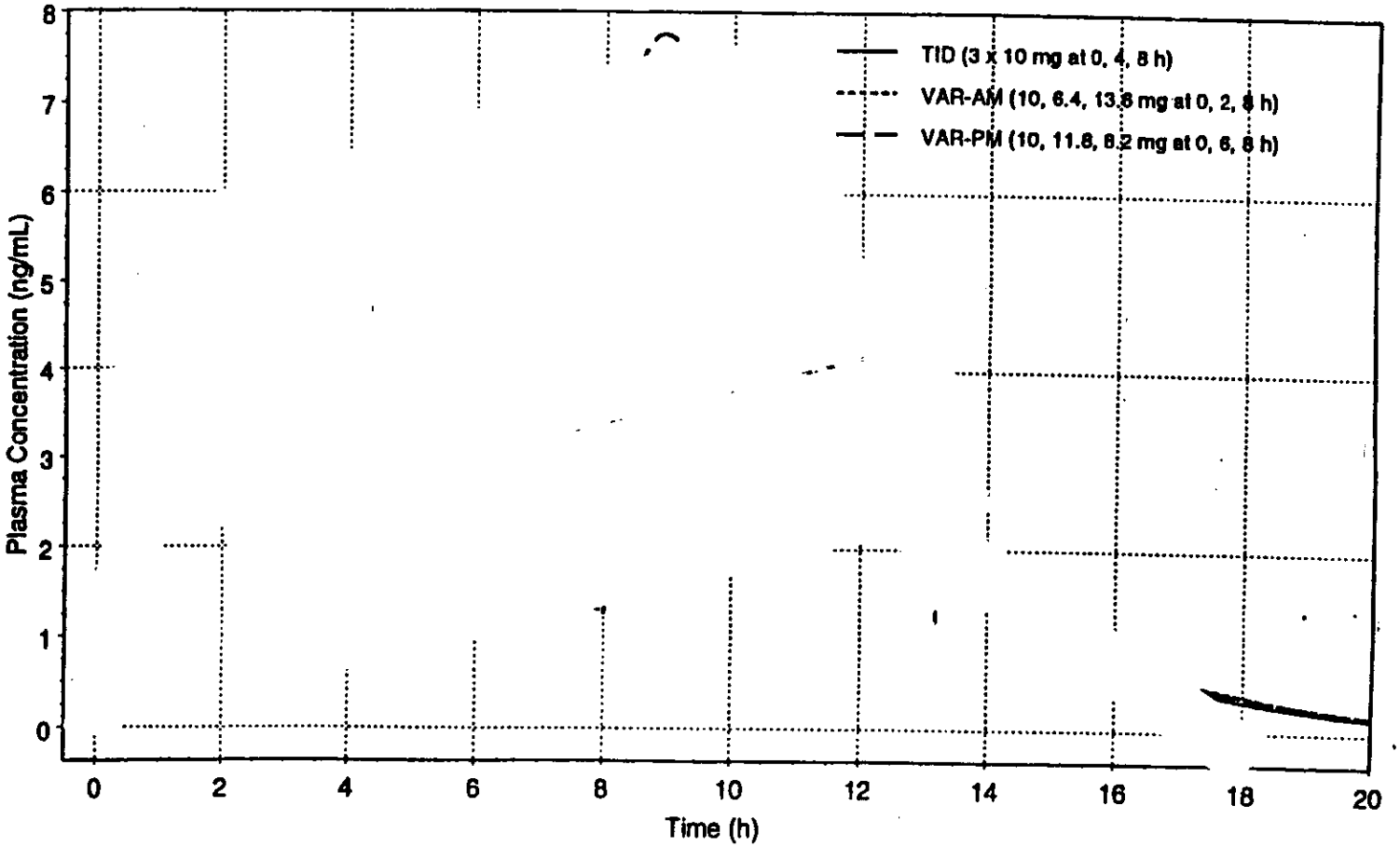


FIGURE 2

(Study 2)

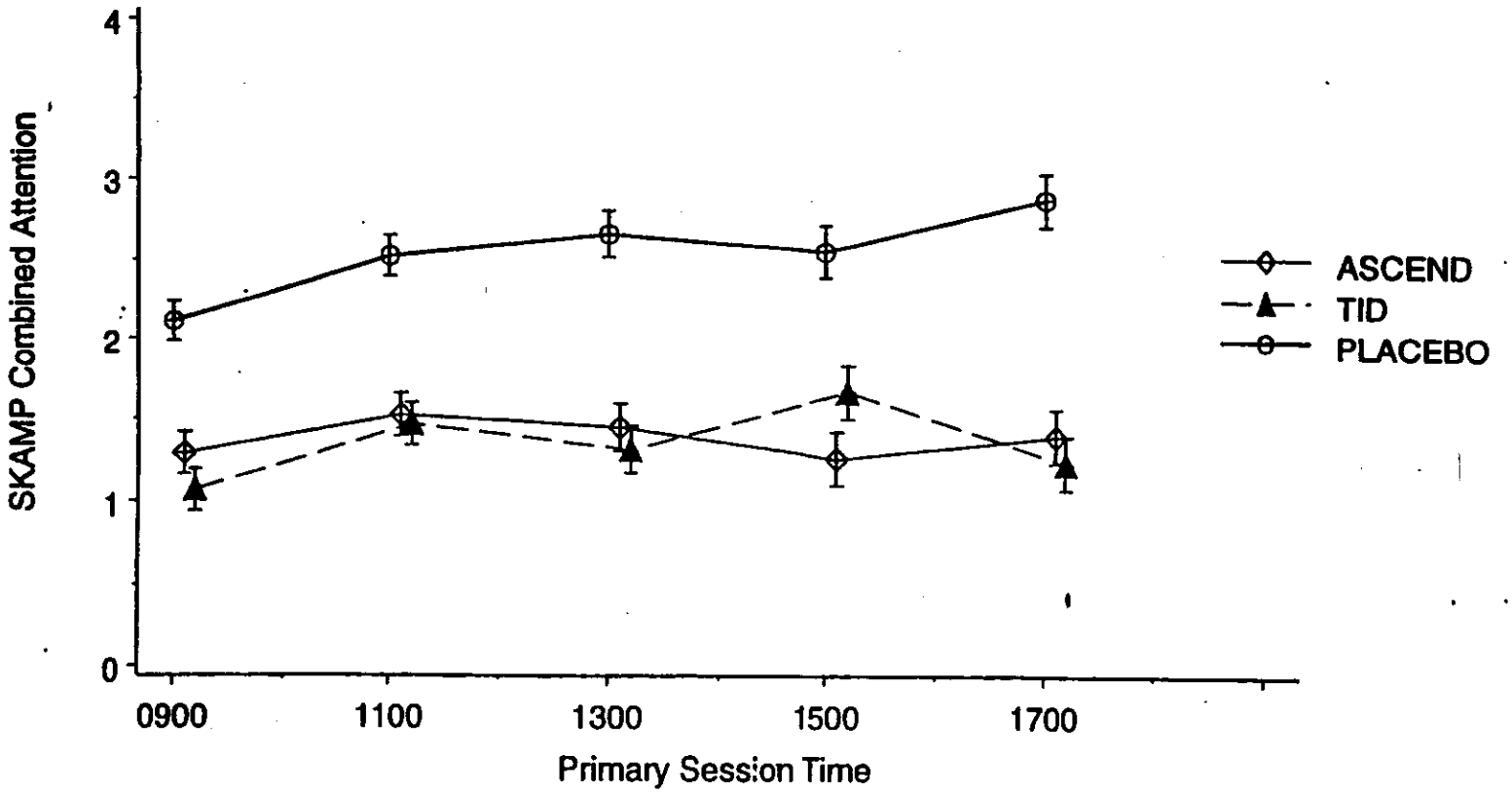
Simulated Plasma Methylphenidate Concentrations Profiles:
Effect of the Amount of the Second and Third Dose, and the First to Second Dose Interval



(Study 2)

FIGURE 3

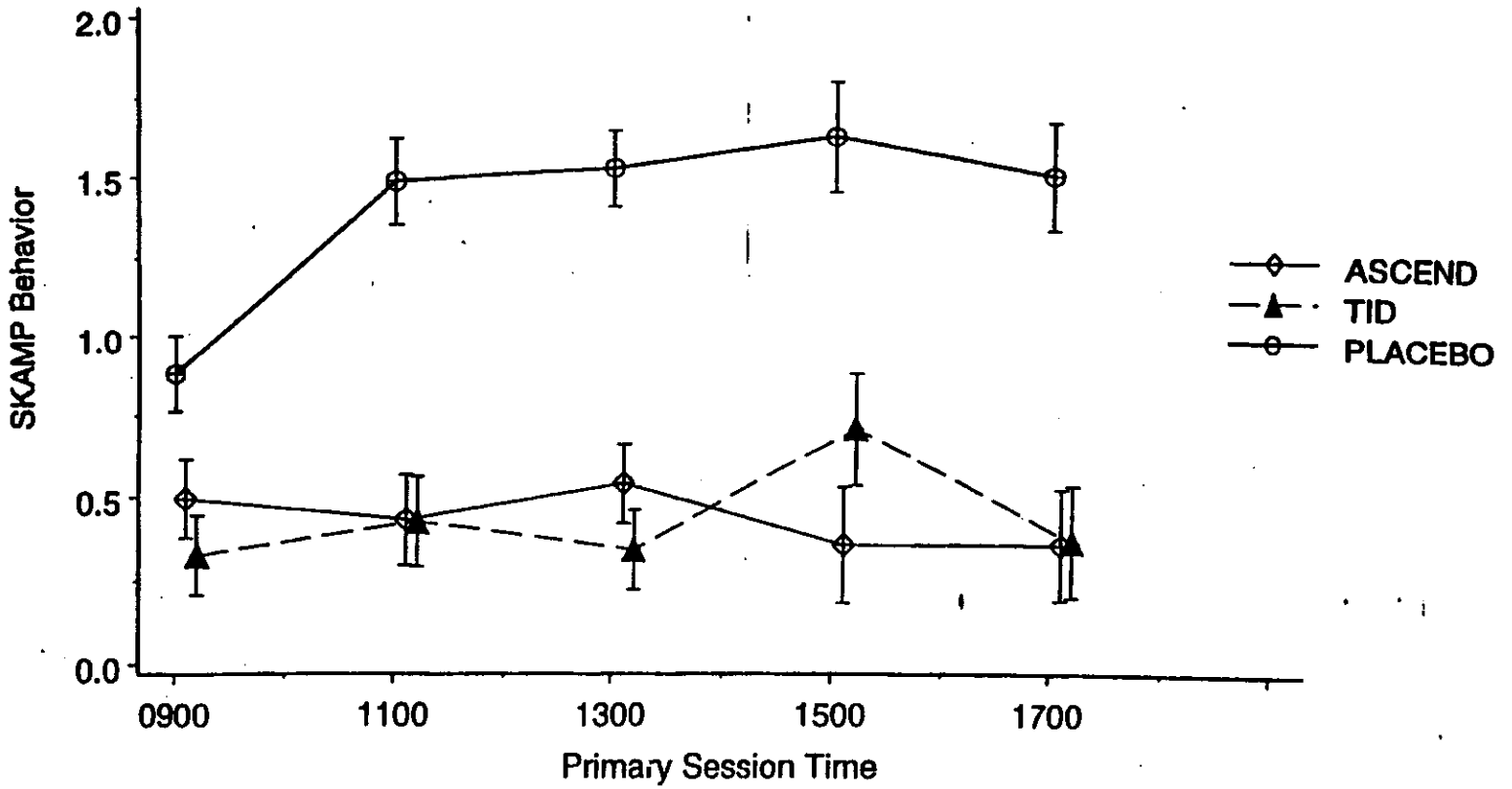
Mean (SEM) SKAMP Combined Attention Scores by Primary Session Time



(Study 2)

FIGURE 4

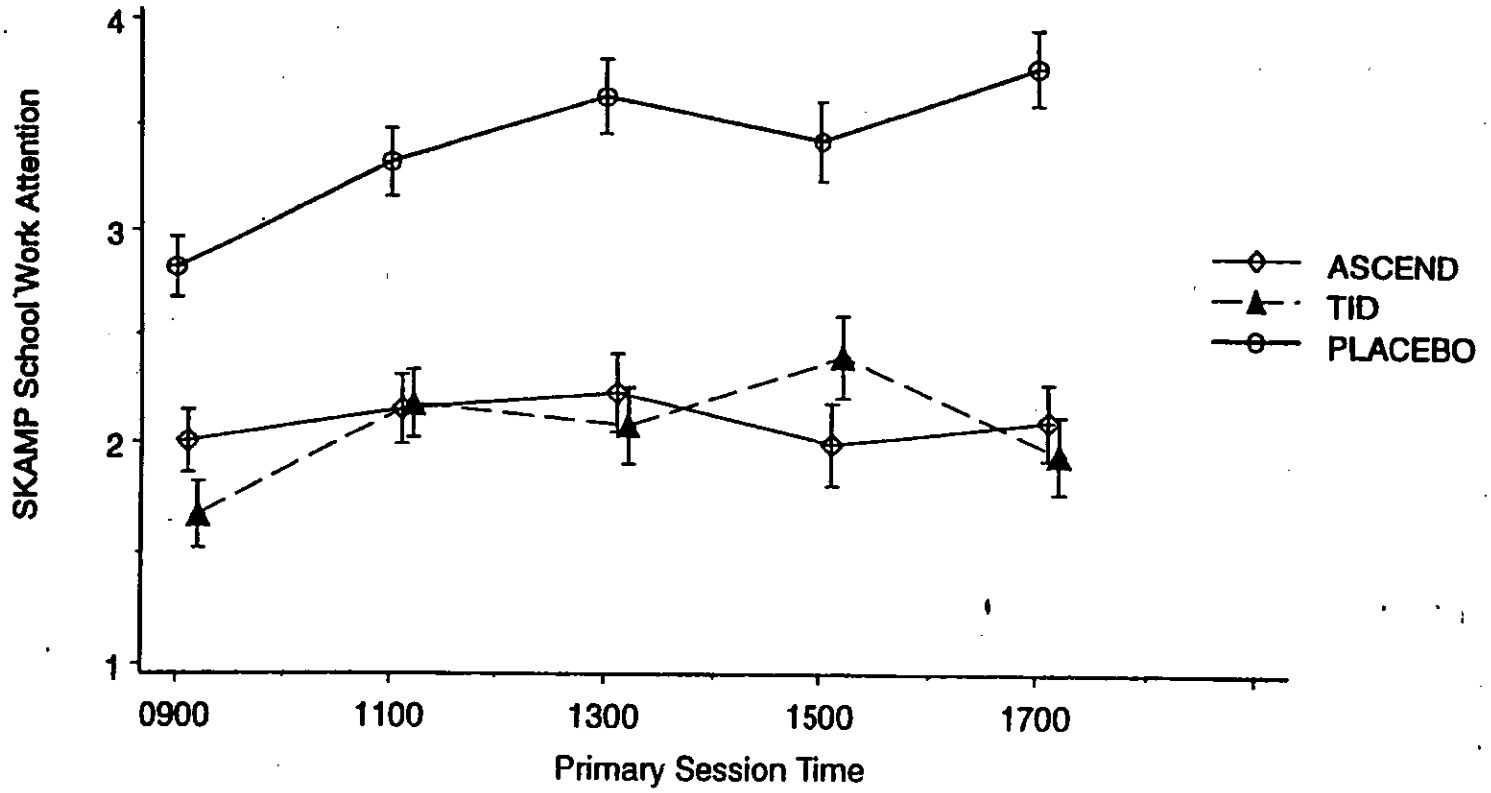
Mean (SEM) SKAMP Behavior Scores by Primary Session Time



(Study 2)

FIGURE 5

Mean (SEM) SKAMP School Work Attention Scores by Primary Session Time



(Study 2)

FIGURE 6

Mean (SEM) SKAMP Non-School Work Attention Scores by Primary Session Time

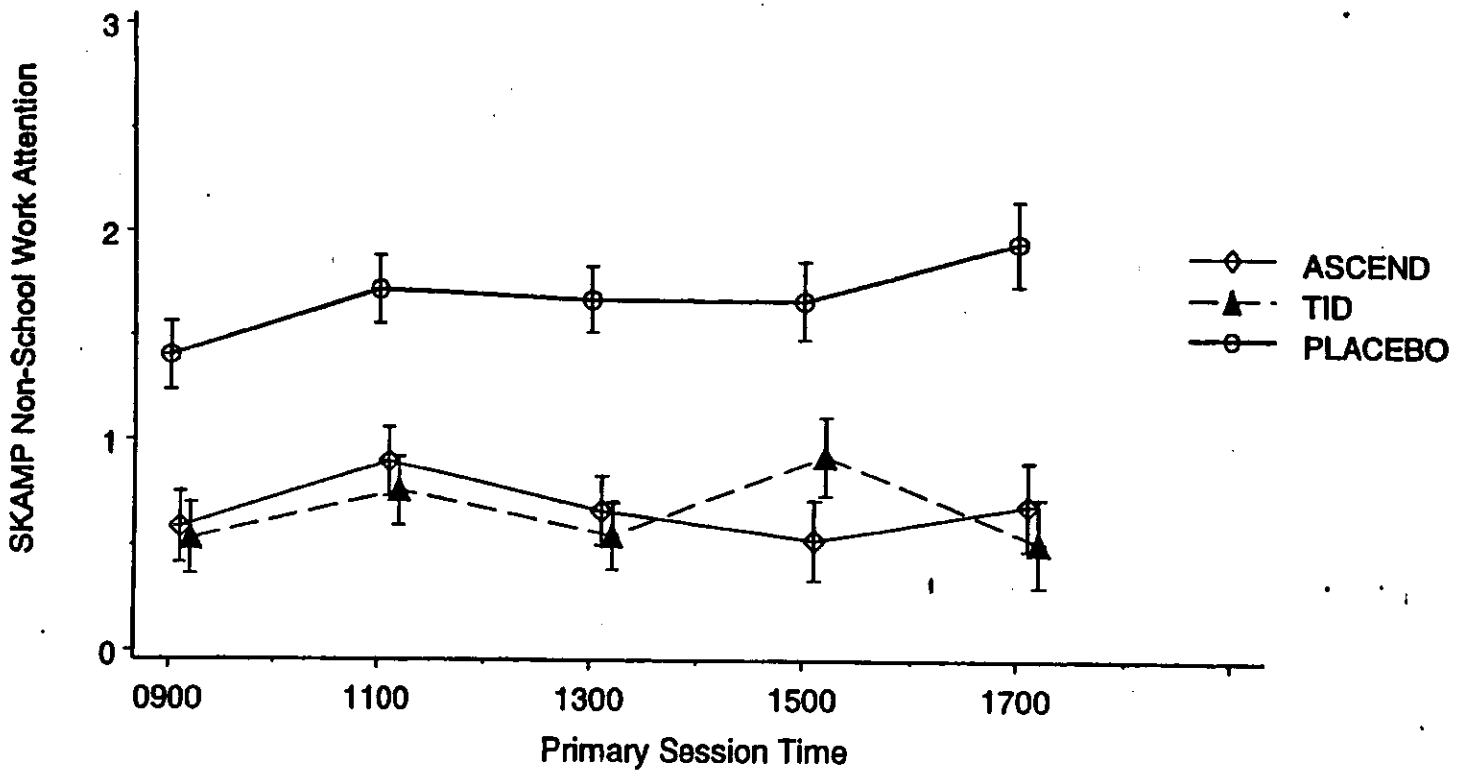


Figure 7

APPENDIX D3 (Page 1 of 4)

Mean Structured Classroom Activity Level Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Simulated Plasma Methylphenidate Concentration (Study 2)
Treatment = ASCEND
(n = 28)

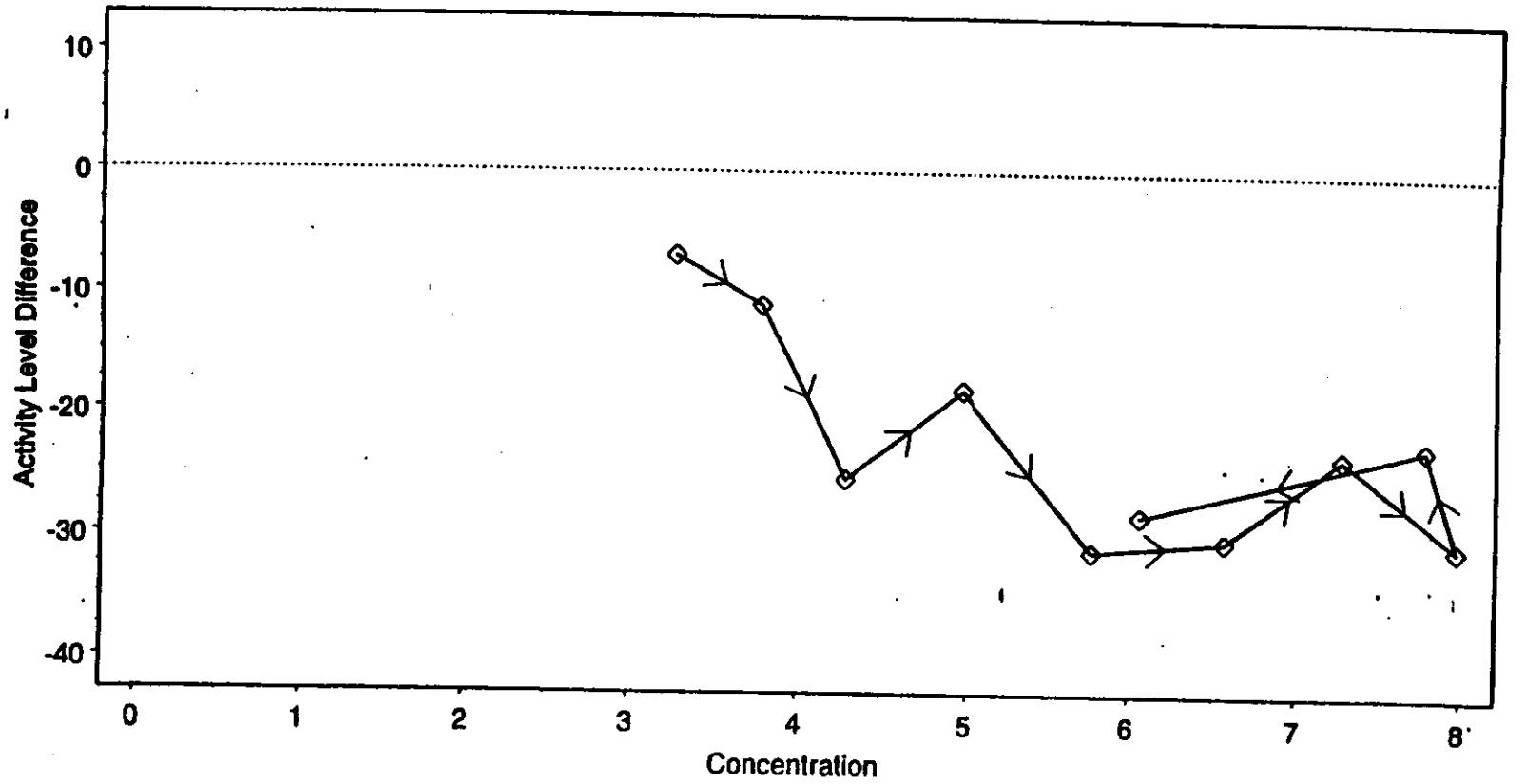


Figure 8

APPENDIX D3 (Page 2 of 4)

Mean Structured Classroom Activity Level Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Simulated Plasma Methylphenidate Concentration
Treatment = TID
(n = 29)

(Study 2)

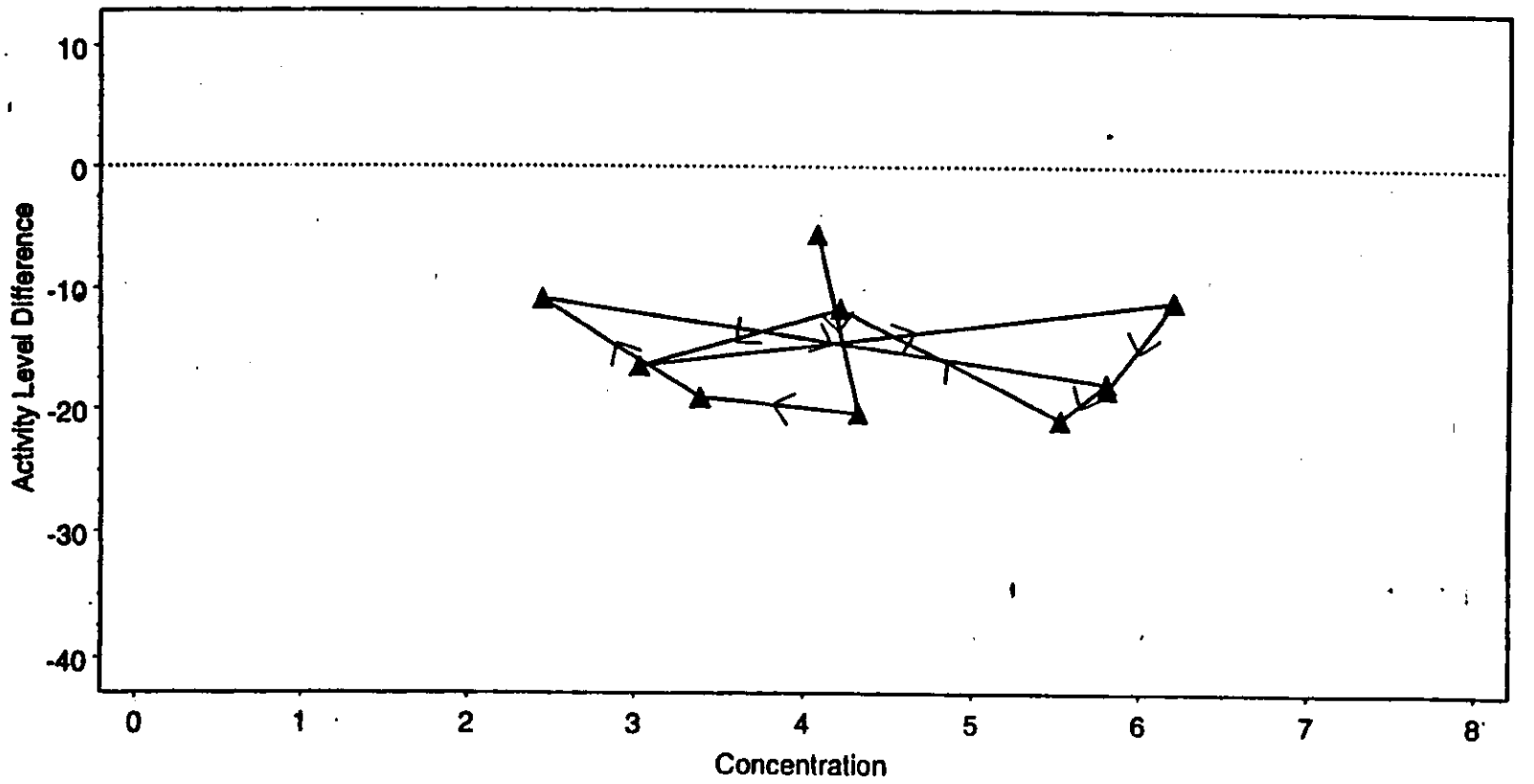
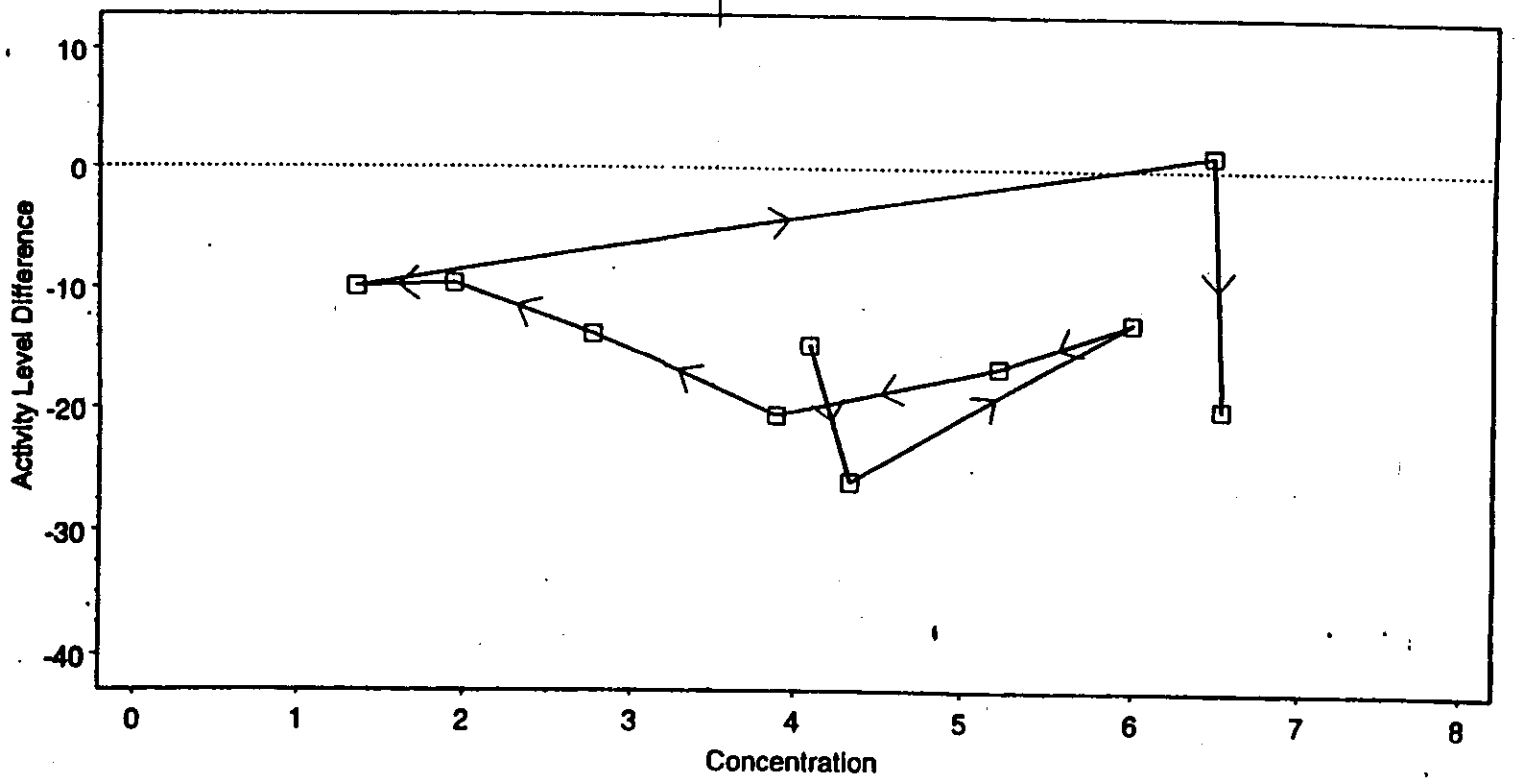


Figure 9

APPENDIX D3 (Page 3 of 4)

(Study 2)

Mean Structured Classroom Activity Level Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Simulated Plasma Methylphenidate Concentration
Treatment = VAR-AM
(n = 13)



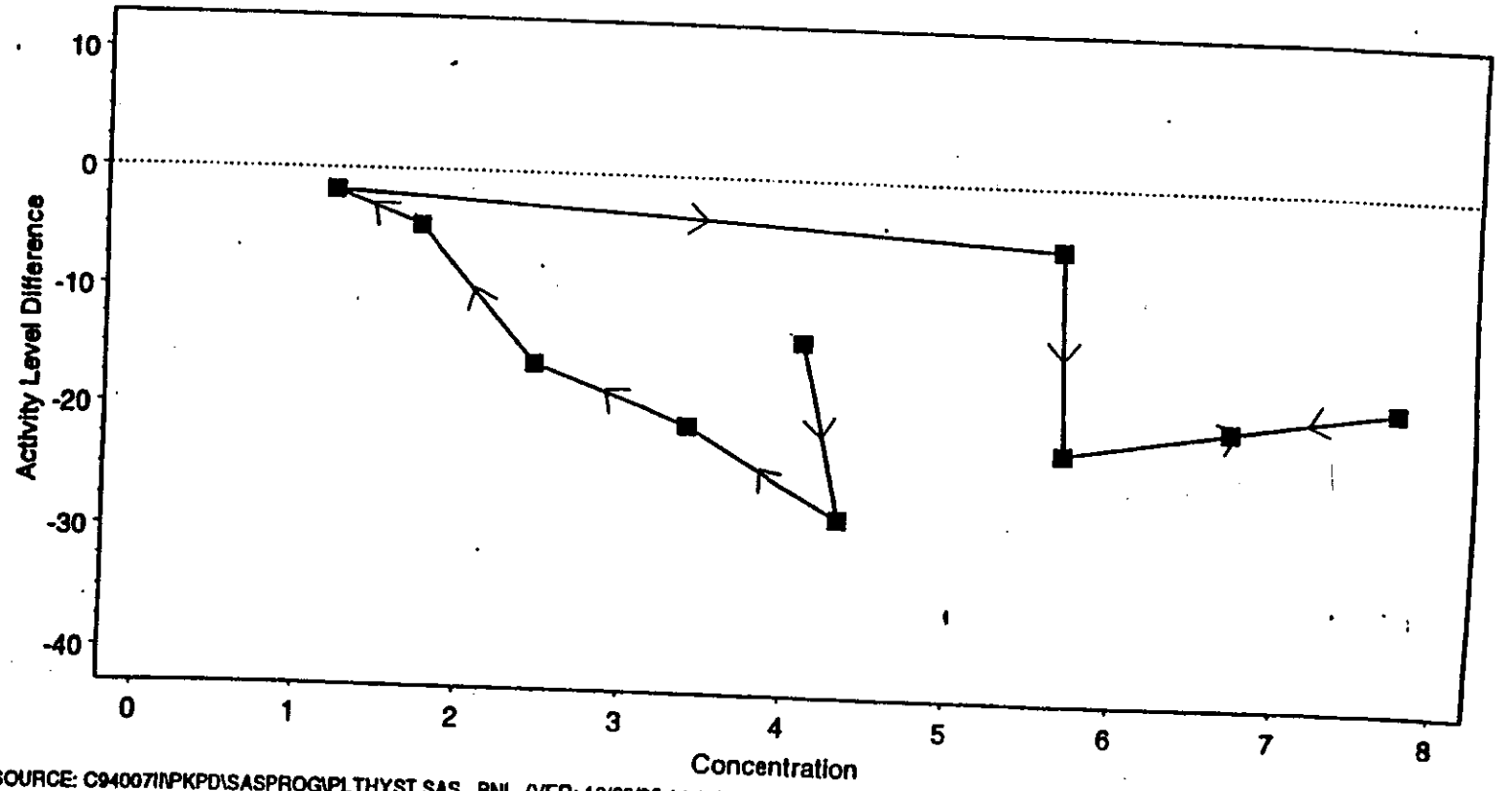
SOURCE: C94007II\PKPD\SASPROG\PLTHYST.SAS BNL (VER: 10/2095 14:10)

Figure 10

APPENDIX D3 (Page 4 of 4)

(Study 2)

Mean Structured Classroom Activity Level Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Simulated Plasma Methylphenidate Concentration
Treatment = VAR-PM
(n = 14)



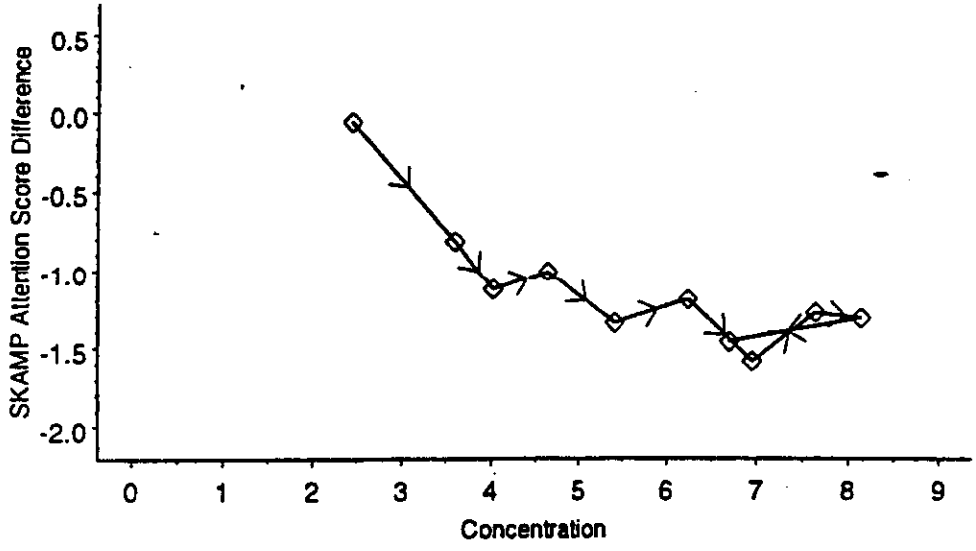
SOURCE: C94007I\NPKPD\SASPROG\PLTHYST.SAS BNL (VER: 10/20/95 14:11)

Figure 11

(Study 2)

APPENDIX D4 (Page 1 of 4)

Mean Observed and Tolerance Modeled SKAMP Attention Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = ASCEND
(n =31)



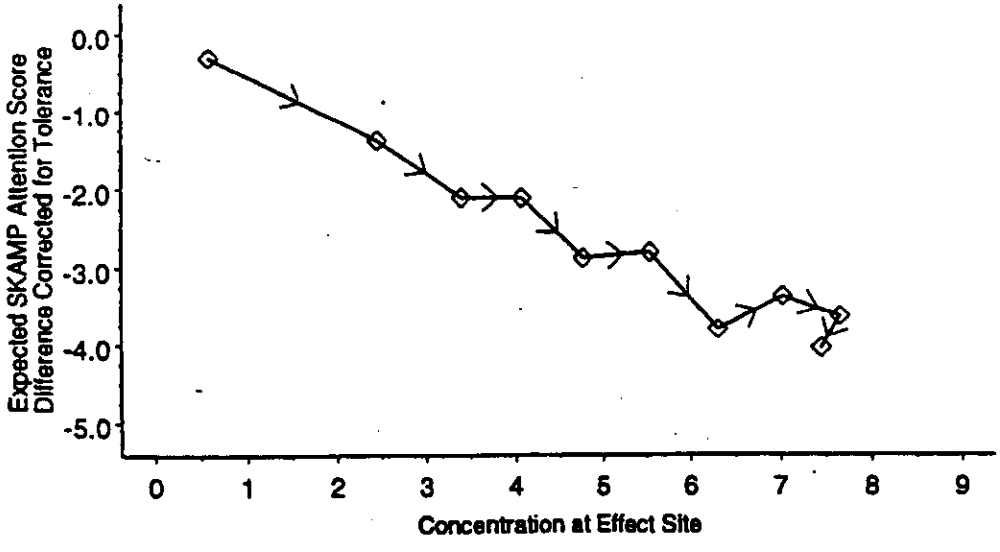
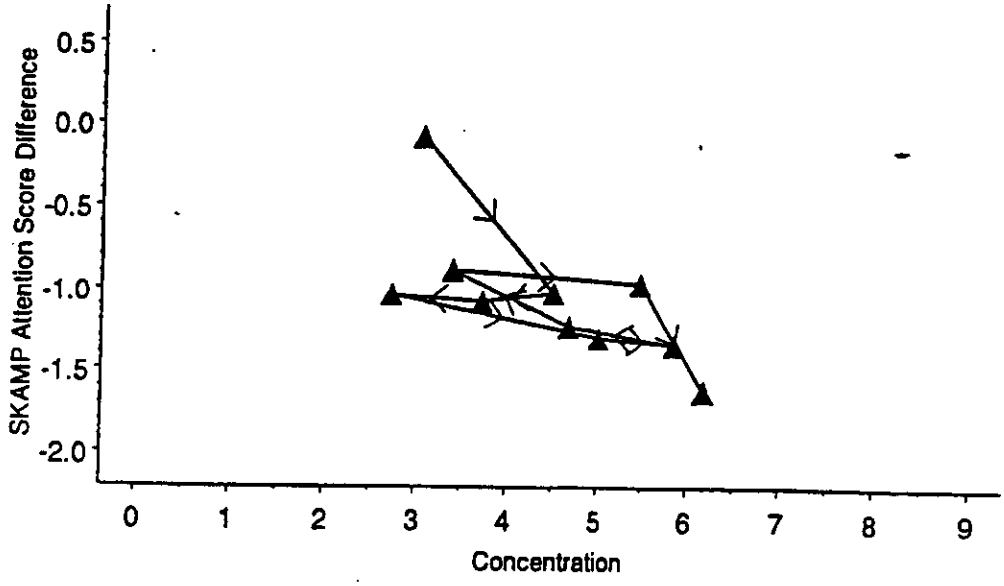


Figure 12

(Study 2)

APPENDIX D4 (Page 2 of 4)

Mean Observed and Tolerance Modeled SKAMP Attention Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = TID
(n =31)



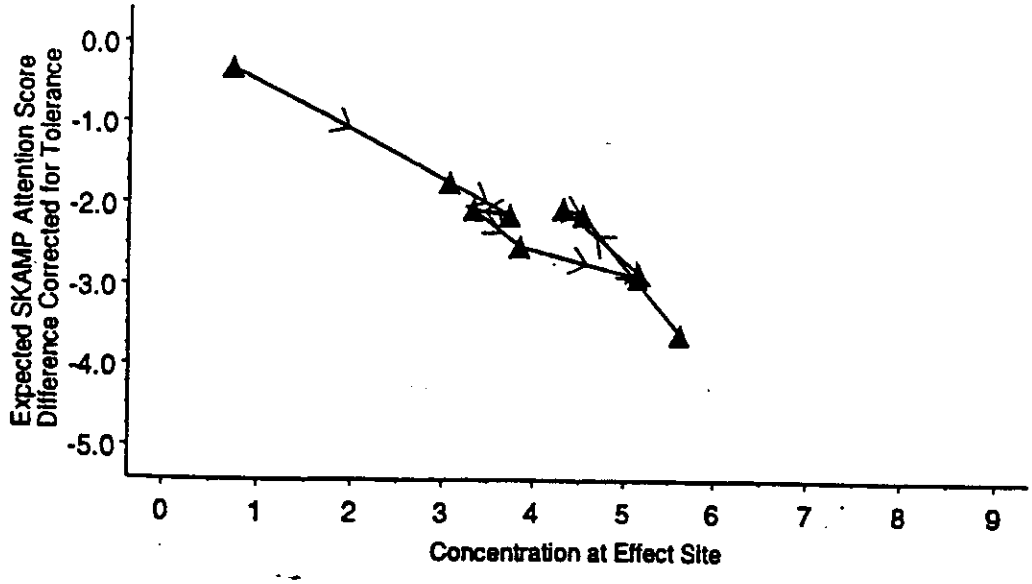


Figure 13

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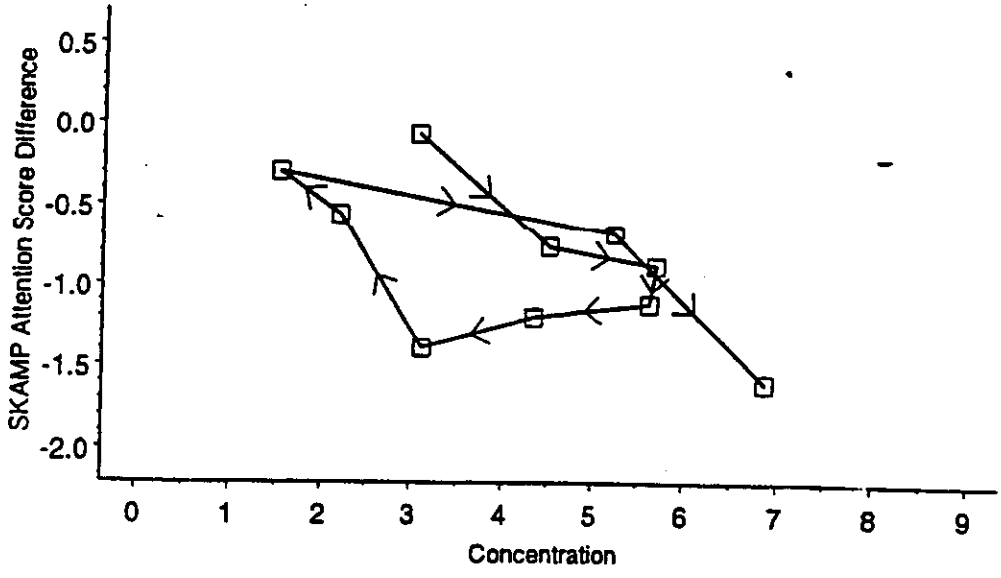
(Study 2)

APPENDIX D4 (Page 3 of 4)

Mean Observed and Tolerance Modeled SKAMP Attention Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = VAR-AM
(n =14)



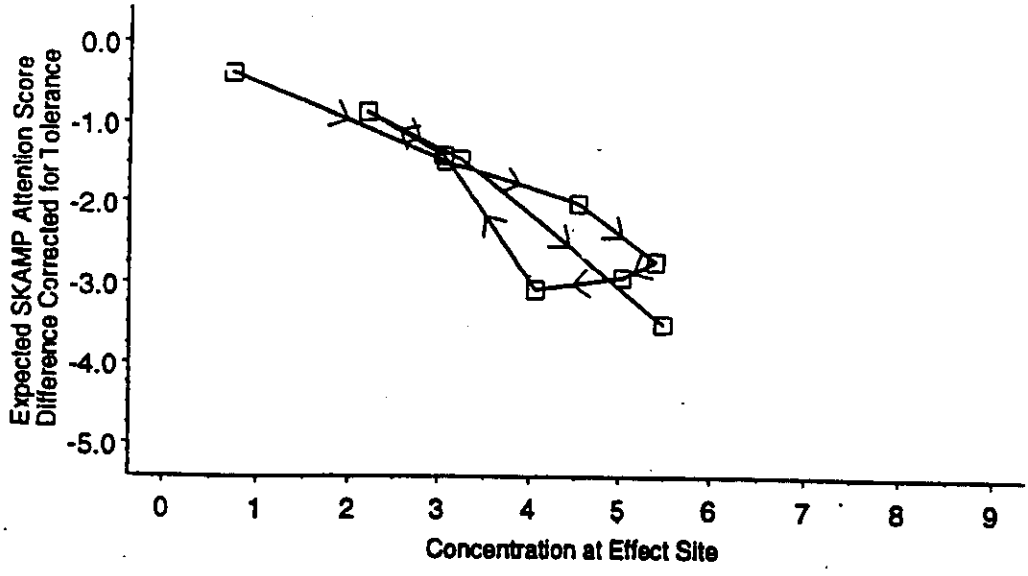
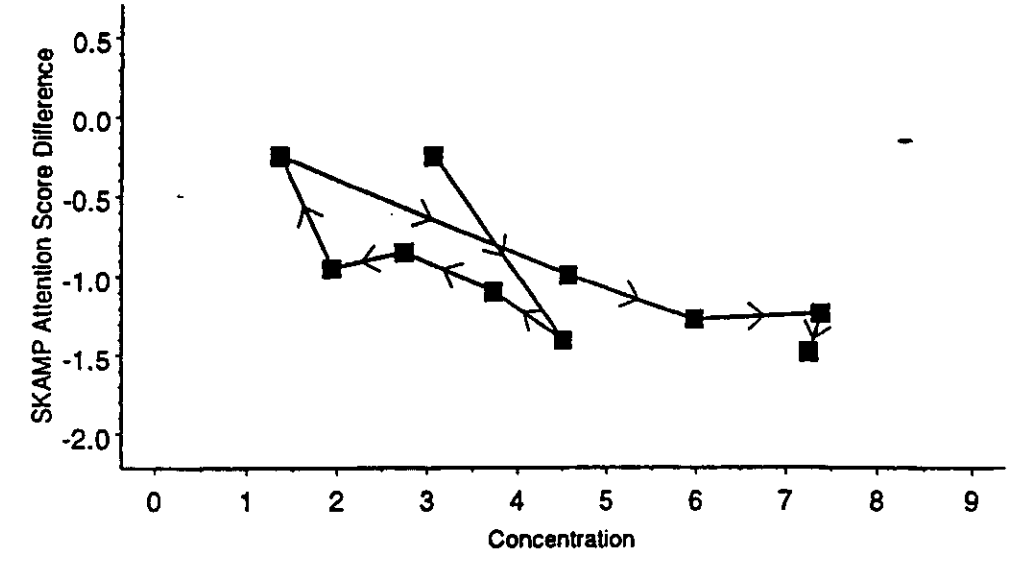


Figure 14

(Study 2)

APPENDIX D4 (Page 4 of 4)

Mean Observed and Tolerance Modeled SKAMP Attention Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = VAR-PM
(n =16)



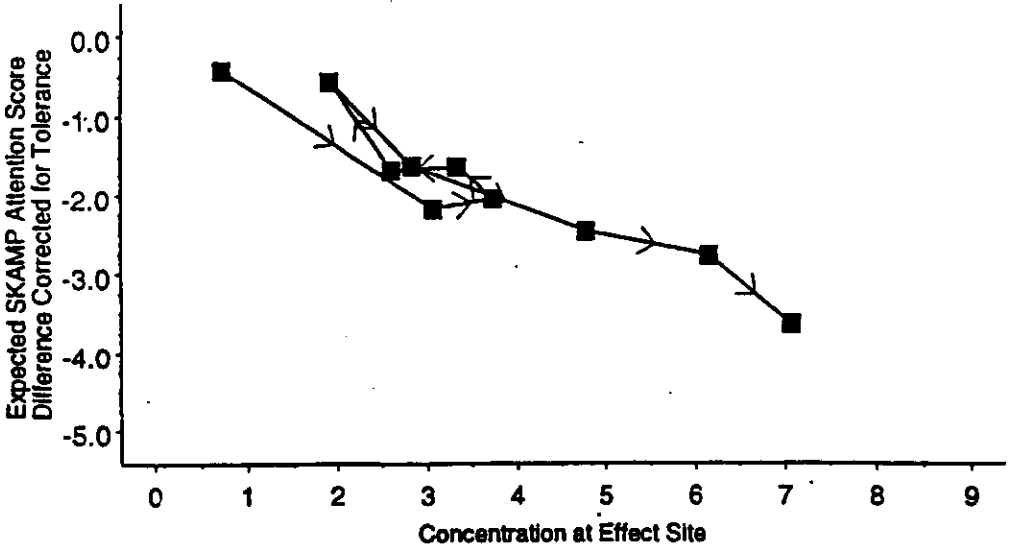
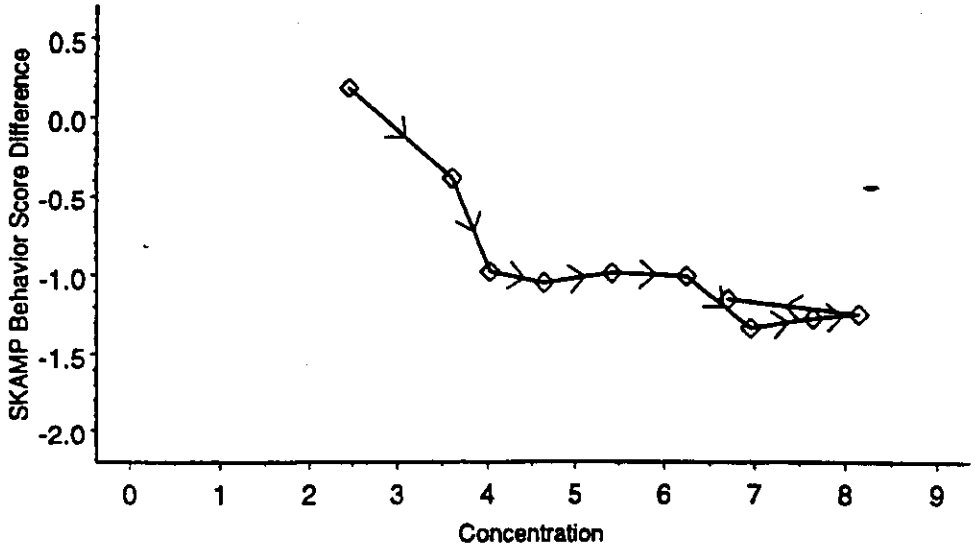


Figure 15

(Study 2)

APPENDIX D5 (Page 1 of 4)

Mean Observed and Tolerance Modeled SKAMP Behavior Score Difference (Treatment - Placebo) Joined In Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = ASCEND
(n =31)



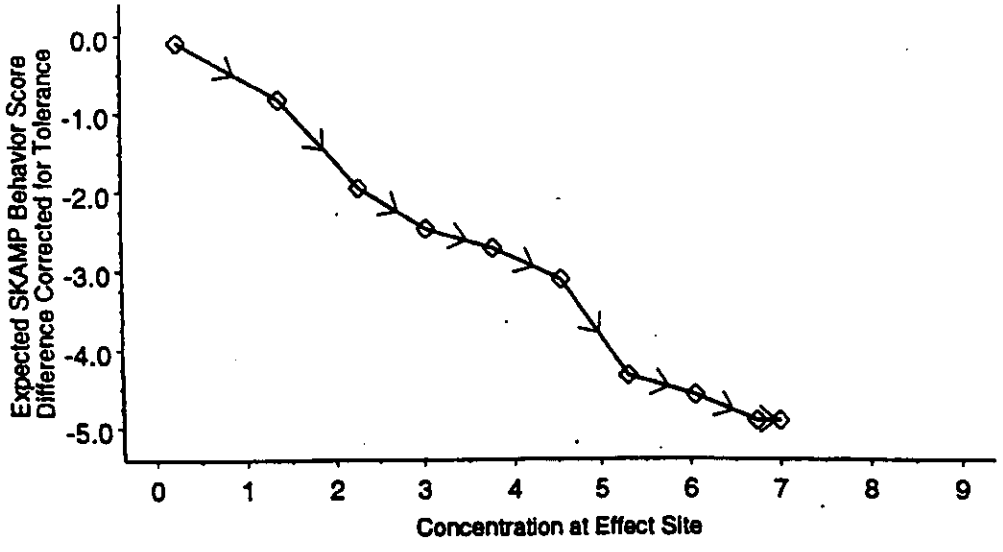
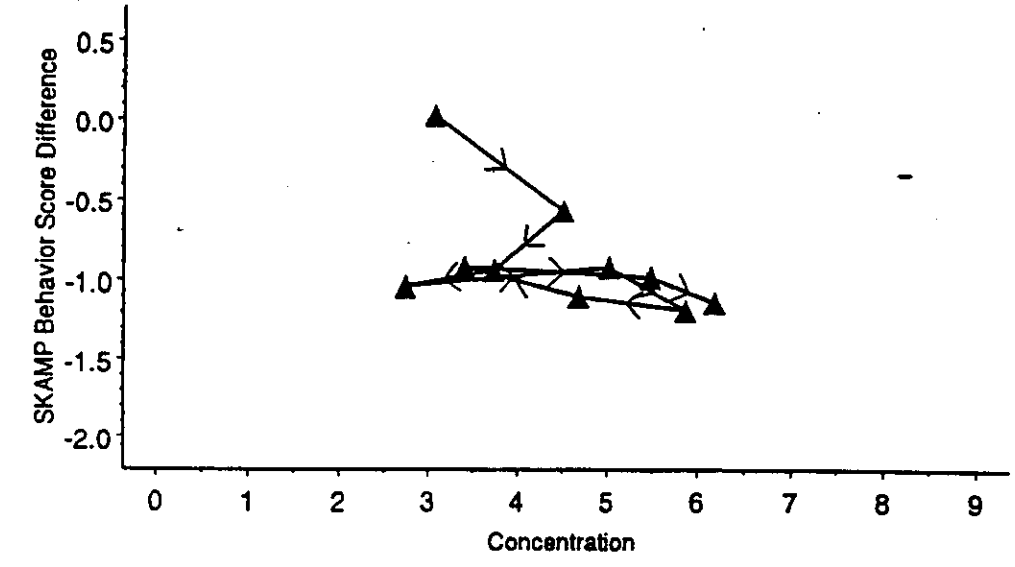


Figure 16 (Study 2)

APPENDIX D5 (Page 2 of 4)

Mean Observed and Tolerance Modeled SKAMP Behavior Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = TID
(n =31)



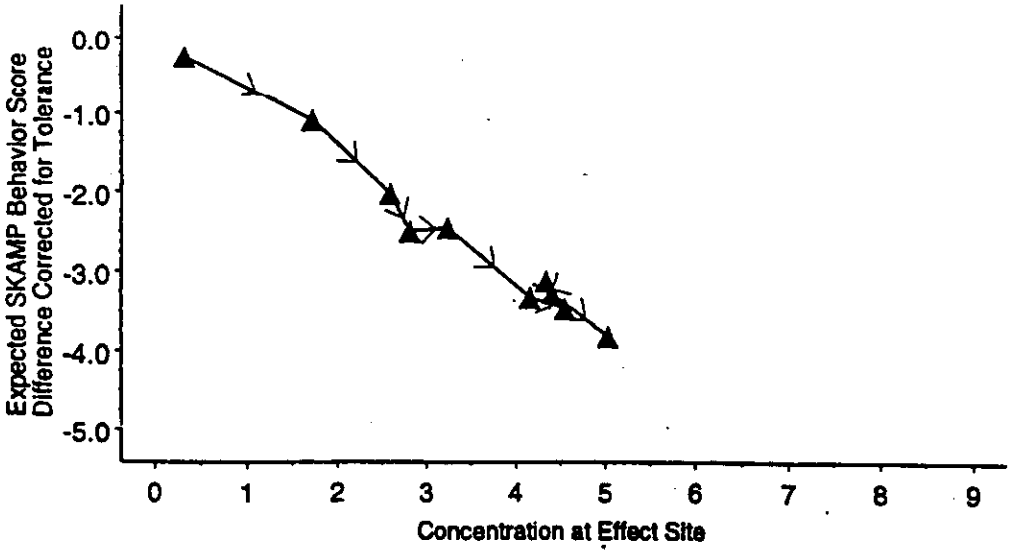
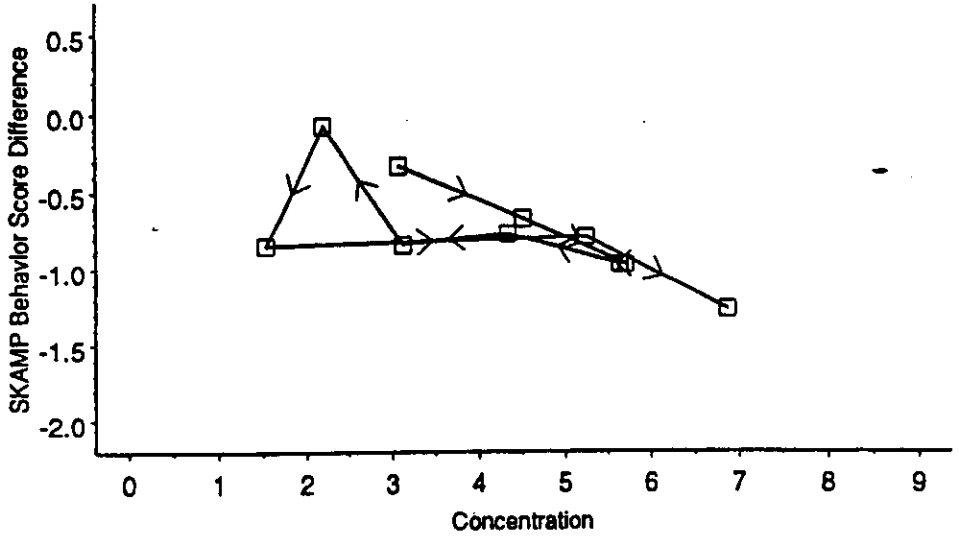


Figure 17

(Study 2)

APPENDIX D5 (Page 3 of 4)

Mean Observed and Tolerance Modeled SKAMP Behavior Score Difference (Treatment - Placebo) Joined in Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = VAR-AM
(n =14)



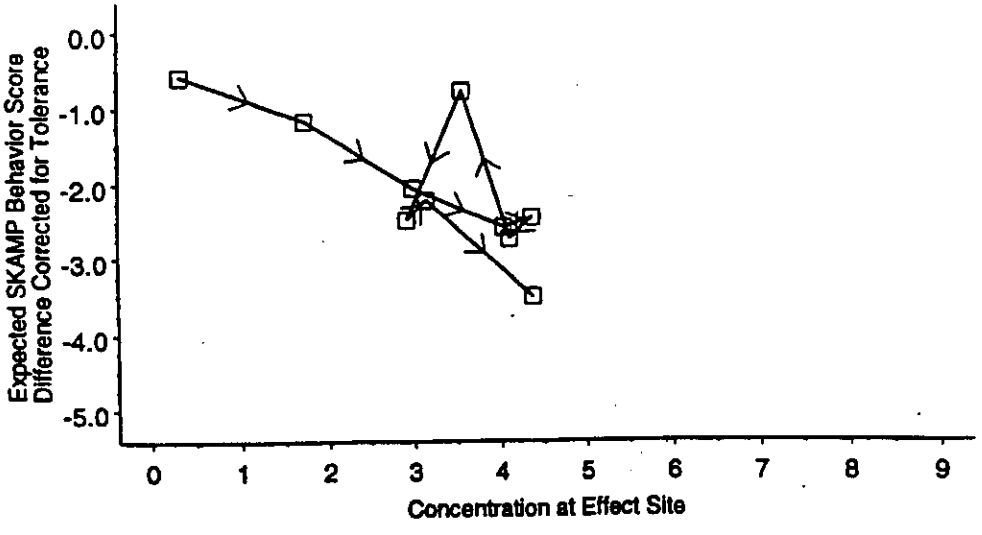
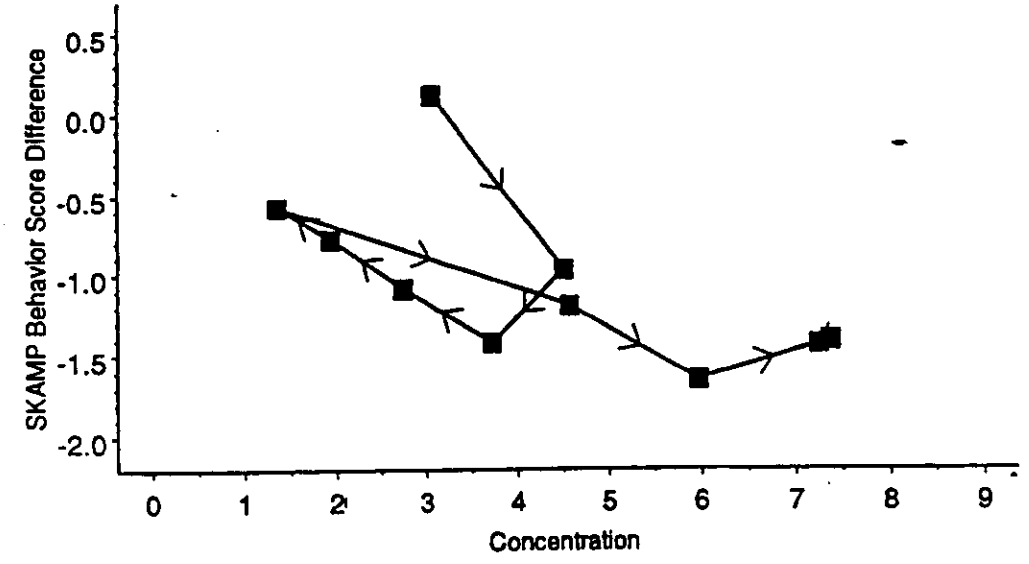


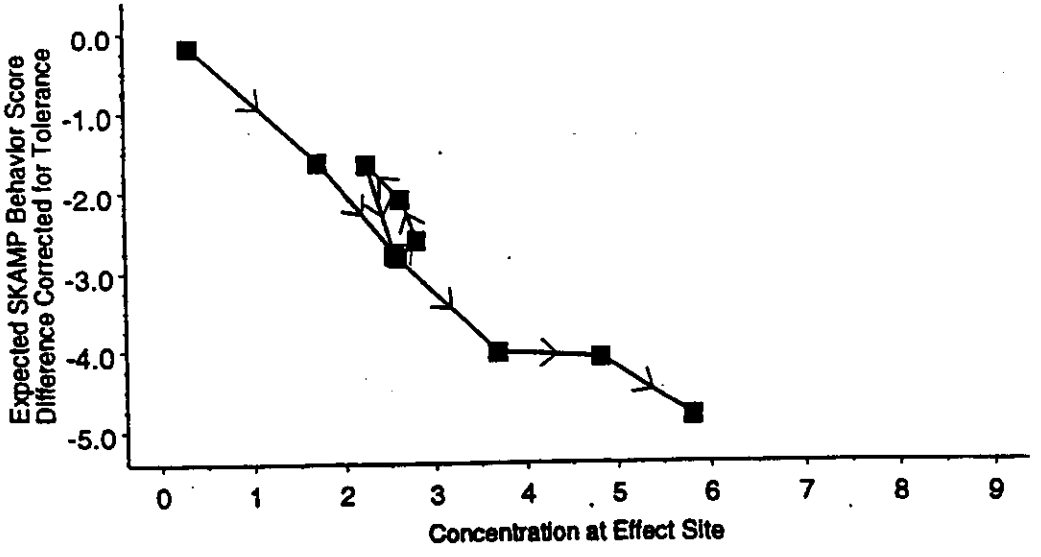
Figure 18

(Study 2)

APPENDIX D5 (Page 4 of 4)

Mean Observed and Tolerance Modeled SKAMP Behavior Score Difference (Treatment - Placebo) Joined In Ascending Order of Time as a Function of Concentration and Concentration at Effect Site
Treatment = VAR-PM
(n =16)





Comment

The Sponsor claims that following the first dose of MPH, acute tolerance is developed in children. There are several conceptual and scientific issues with this claim.

The Sponsor did not collect blood samples for the analysis of plasma concentrations of MPH rather simulated plasma concentrations based on the previous knowledge of PK parameters and these simulated plasma concentrations of MPH were used to establish concentration-effect relationship. No inter- or intra-subject variability was incorporated in the simulation despite the fact that the inter- and intra-subject variability of OROS AUC was 36.7% and 9.6%. This assumption to generate plasma concentration vs time profiles may not be accurate and may have a significant impact on PK-PD relationship. In addition, neither the presence of a counterclockwise hysteresis nor describing the data by a tolerance model provide sufficient evidence of acute tolerance (a clockwise hysteresis has been reported in the literature, Kimko et al., Clin Pharmacokinet, Vol 37: 457, 1999). There is no clinical evidence of development of tolerance and also the visual inspection of effect data (see next page, Figure 3, reference Swanson et al., Clin. Pharmacol, Vol 66: 295, 1999) does not indicate the development of tolerance. Furthermore, in the absence of the validation of the model it is difficult to conclude that the chosen model is indeed a correct model.

An appropriate approach to address this issue is that the Sponsor should collect blood samples and relate the actual plasma concentrations of MPH with the observed effect. Several tolerance models should be tested and validated in a separate group of subjects. In other words the model should be capable of predicting effect in a different group of subjects based on observed plasma concentration.

Overall, the sponsor has not provided strong evidence in support of the claim that acute tolerance is developed following the first dose of MPH in children. The visual inspection of effect vs. time data also does not support this claim.

(Study 2)

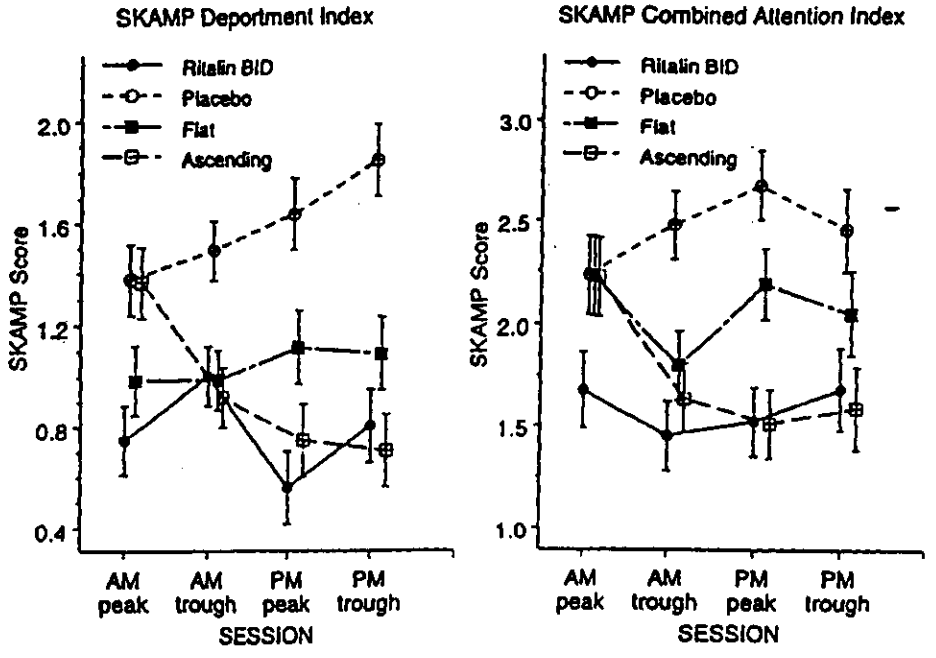
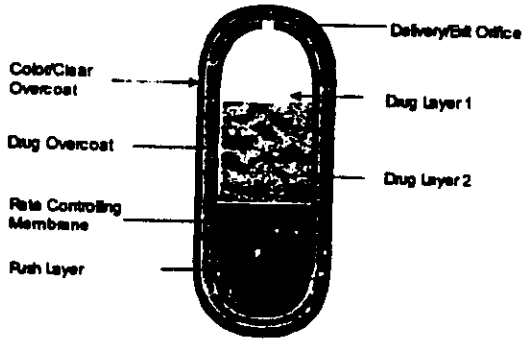


Fig 3. Study 1: Peak and trough responses for an example efficacy measure (attention subscale of the SKAMP rating scale) for the bid, flat, ascending, and placebo treatments.

7. DRUG FORMULATION



	OROS (MPH)	
	18 mg	36 mg
Weight	268 mg	515 mg
Diameter	5.3 mm	6.8 mm
Length	12 mm	15 mm

The OROS® system delivers 18 or 36 mg of methylphenidate HCl by a combined process of aqueous dissolution of the drug overcoat and osmotic delivery of the core drug. Seven lots of 18 mg OROS® systems and two lots of 36 mg OROS® systems were used in clinical studies. All nine lots of OROS® dosage forms were based on OROS® push-pull osmotic pump technology. Initially, the OROS® 18 mg system was an elongated bi-layer core design but later the proposed commercial formulation was optimized to a tri-layer design. The details of drug formulation can be found in Study #14.

8. DISSOLUTION

What are the *in vitro* dissolution specifications? Are the specifications acceptable?

The Sponsor has set the following cumulative drug release specifications for the 18 and 36 mg OROS® (MPH HCl):

Time Intervals	Specification (% of label)
[redacted]	

The first interval, 0-1 h, captures the immediate release portion of the drug release and evaluates potential dose dumping, and the second interval, 0-4 h, monitors the release just short of the mid point of the delivery profile. The last interval, 0-10 h, evaluates the release of the labeled quantity (≥85% at 10 h) of MPH HCl (Study #15).

[redacted]

The dissolution specifications will be set after a further review of data from the Sponsor (data received 2/7/00). This review will be added as an addendum to this document.

9. IN VITRO-IN VIVO CORRELATION (FORMULATION)

Is the proposed *in vitro-in vivo* correlation (IVIVC) acceptable?

An *in vitro-in vivo* correlation (IVIVC) was performed for the OROS® (MPH HCl), by use of a [redacted]y #16). *In vivo* data from three studies (Studies # 5-7, the standard *in vitro* profile was used from Study #7) using 18 or 36 mg were [redacted] concentration time data from an IR formulation as the impulse response to estimate the *in vivo* release profile. A linear relationship was established between the *in vivo* cumulative release and the *in vitro* release profile, see Figure 9.1. The internal validation showed a mean prediction error of <10% for both AUC and C_{max}.

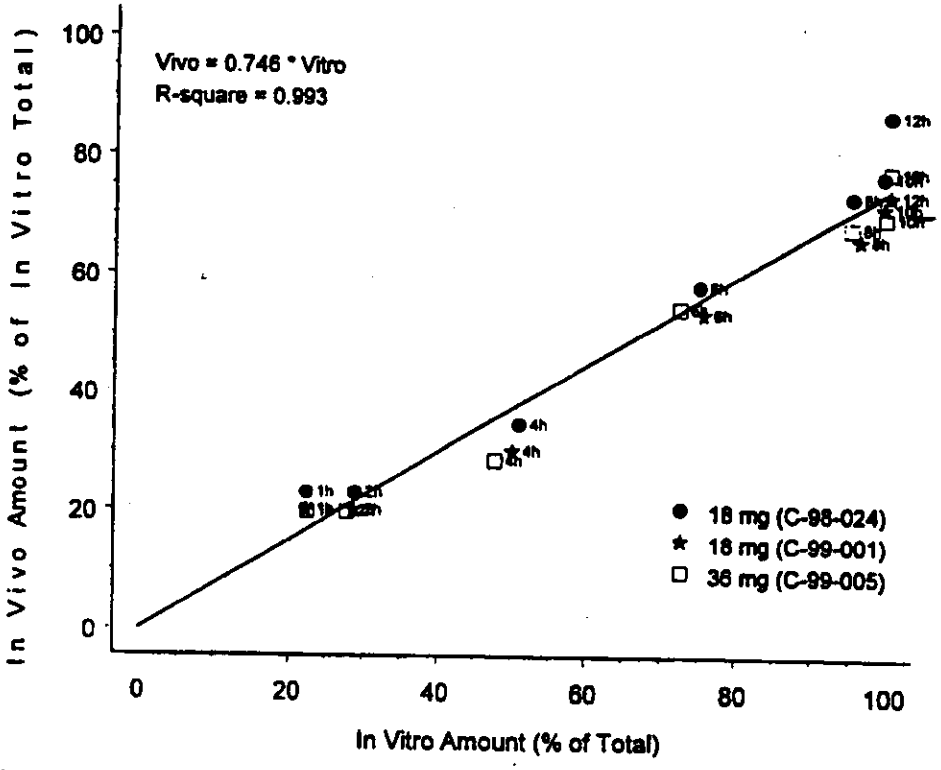
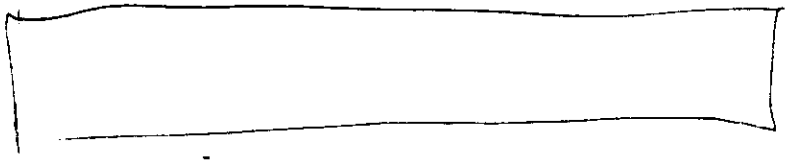


Figure 9.1. The relationship between estimated *in vivo* cumulative release and the *in vitro* release profiles for methylphenidate HCl (OROS®).

The external predictability was tested by use of data from two lots that was not used in the development of the IVIVC (Studies #4 and # 7, the 11% faster than standard release profile was used from the latter study). The AUC and C_{max} from these lots were predicted using the IVIVC, and were compared to the observed AUC and C_{max} values. Good agreement between the *in vitro* and estimated *in vivo* release profiles and the low prediction error for both internal and external validation indicates a Level A correlation according to the Sponsor.

Additional data was requested from the Sponsor (data received 2/7/00). The review of the IVIVC will be added as an addendum to this document.

10. ANALYTICAL METHODS



APPEARS THIS WAY
ON ORIGINAL

11. COMMENTS

1. The Sponsor claims that following the first dose of MPH, acute tolerance is developed in children. There are several conceptual and scientific issues with this claim..

   The Sponsor did not collect blood samples for the analysis of plasma concentrations of MPH rather simulated plasma concentrations based on the previous knowledge of PK parameters and these simulated plasma concentrations of MPH were used to establish concentration-effect relationship. No inter- or intra-subject variability was incorporated in the simulation despite the fact that the inter- and intra-subject variability of OROS AUC was 36.7% and 9.6%. This assumption to generate plasma concentration vs time profiles may not be accurate and may have a significant impact on PK-PD relationship. In addition, neither the presence of a counterclockwise hysteresis nor describing the data by a tolerance model provide sufficient evidence of acute tolerance (a clockwise hysteresis has been reported in the literature, Kimko et al., Clin Pharmacokinet, vol 37: 457, 1999). There is no clinical evidence of development of tolerance and also the visual inspection of effect data (Figure 3, reference Swanson et al., Clin. Pharmacol, vol 66: 295, 1999) does not indicate the development of tolerance. Furthermore, in the absence of the validation of the model it is difficult to conclude that the chosen model is indeed a correct model.

   An appropriate approach to address this issue is that the Sponsor should collect blood samples and relate the actual plasma concentrations of MPH with the observed effect. Several tolerance models should be tested and validated in a separate group of subjects. In other words the model should be capable of predicting effect in a different group of subjects based on observed plasma concentration.

   Overall, the sponsor has not provided strong evidence in support of the claim that acute tolerance is developed following the first dose of MPH in children. The visual inspection of effect vs. time data also does not support this claim.

2. Dissolution – comments will be incorporated after review of Sponsor's additional data
3. IVIVC – comments will be incorporated after review of Sponsor's additional data

APPEARS THIS WAY
ON ORIGINAL

13. RECOMMENDATION

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The Sponsor is requested to incorporate all labeling changes.

Please forward comment 1 and the labeling changes to the Sponsor.

Iftekhar Mahmood, Ph.D., /S/

Maria Sunzel, Ph.D., /S/

FT initialed by Vijay Tammara, Ph.D., /S/ 2/11/00

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

Draft review (RD) signed on February 8, 2000

OCPB Briefing Date: February 10, 2000

Attendees: Drs. Mehul Mehta, Chandra Sahajwalla, Tom Laughren, Andy Mosholder, Jurgen Venitz, Shiew-Mei Huang, Ray Baweja, Paul Hepp, Elena Mishina, Hong Zaho, Sayed El-Habet, Gabriel Robbie, Vijay Tammara, Iftekhar Mahmood, Maria Sunzel, Anna-Marie Homonnay, R.Ph. and Julie Canal, Clinical Pharmacology fellow

c.c.: NDA 21-121, HFD-120, HFD-860 (Mehta,, Tammara, Baweja, Sunzel, Mahmood), HFD-340 (Viswanathan), CDR (Biopharm) and FOI files (HFD-19)

APPEARS THIS WAY
ON ORIGINAL

Attention: Mike Klein

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Div Anesthesia & Critical Care / HFD-170	Div Neuropharm / HFD-120

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/24/99		21-121	Orig NDA	7/15/99

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Concerta® (methylphenidate hydrochloride) Extended-Release Tablets		Standard	Jan 2000

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Abuse Liability Assessment

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
/S/	SIGNATURE OF DELIVERER

REVIEW AND EVALUATION OF DRUG ABUSE DATA
CONSULTATIVE REVIEW
Division of Anesthetic, Critical Care & Addiction Drug Products (HFD-170)

REQUESTING DIVISION: Division of Neuropharmacology (HFD-120)

NDA #: 21-121

SPONSOR: ALZA Corporation

DRUG: CONCERTA® OROS®
(Methylphenidate hydrochloride)
18 mg and 36 mg Extended-Release Tablets

DATE OF DOCUMENT: July 15, 1999

DATE OF REQUEST: September 24, 1999

REVIEWER: Michael Klein, Ph.D. /S/

DATE OF REVIEW: January 6, 2000

BACKGROUND:

Methylphenidate, a Schedule II substance, is indicated for treatment of Attention Deficit/Hyperactivity Disorder (ADHD)/Attention Deficit Disorder (ADD). Sponsor is proposing to develop an extended release formulation of methylphenidate which would decrease the number of drug administrations that would have to be given to children at school. Sponsor recommends that the new product continue as a CSA Schedule II; data is presented to support C-II for the product. The OROS formulation of methylphenidate hydrochloride is planned for two dosage strengths, 18 mg and 36 mg. Taken once daily, each tablet is designed to provide efficacy for approximately 12 hours. Ritalin is typically dosed 2 to 3 times a day (bid to tid), in strengths of 5mg, 10mg and 20mg tablets. Ritalin-SR is marketed as a one-strength 20mg tablet. Ritalin-SR's duration of action is reported to be approximately 8 hours. However, the sponsor cites a 1995 CHADD survey that reported that Ritalin-SR is often taken bid or tid and/or in combination with IR methylphenidate.

Description of OROS extended release formulation: OROS is similar in appearance to a conventional tablet, and consists of an osmotically active drug core surrounded by a semipermeable membrane. Drug core and semipermeable membrane are encapsulated by an immediate release drug overcoat, a color overcoat, and a clear overcoat. The drug core is divided into 3 layers: 2 "active" layers containing drug and a "push" layer containing pharmacologically inert but osmotically active polymer excipients. The system has a laser-drilled orifice in the semipermeable membrane. In the GI system, drug

overcoat dissolves within approximately one hour, thus providing immediate release of methylphenidate. As the drug coat dissolves, water passes through the semipermeable membrane into the tablet core. As the osmotically-active polymer excipients expand, methylphenidate is released through the orifice at a rate intended to provide efficacy for 12 hours. Inert tablet components remain intact in the GI system and are eliminated in feces as an insoluble shell.

The sponsor's package addresses methylphenidate use in treatment, potential for abuse and misuse, and chronic use, overdose, and off-label use.

Data sources searched were:

1. Literature in the public domain (1964-1999)
2. DAWN (SAMHSA, 1975-1999)
3. MedWatch (1969-1997)
4. ***Substance Abuse: A comprehensive Textbook***, 2nd Edition, 1992.
5. ***PDR 1999*** for information on Ritalin, Ritalin-SR, Adderall, Cylert, and Dexedrine.

Relative Abuse Potential of Methylphenidate: There is evidence that methylphenidate is abused. Chait (1994) investigated the reinforcing and subjective effects of oral methylphenidate in 35 adults with no history of drug dependence, and concluded that methylphenidate was less reinforcing than d-amphetamine. Its estimated potency ratio of 1.9 mg compared to 1 mg for d-amphetamine. Volkow *et al.* (1995) reported that in the human brain the pharmacokinetics of methylphenidate differed markedly from cocaine. Methylphenidate caused rapid onset of blockade of dopamine receptors and was slowly cleared from the brain. Reports of being "high" also decreased over time, despite sustained concentrations in the brain. Also, uptake of oral methylphenidate in the brain (peaking at 60 minutes) may be too slow to produce a "high" (Volkow *et al.* 1998). Wang *et al.* (1997) reported that tolerance to the "high" develops faster than tolerance to other effects, and speculated that with repeated administrations, this tolerance may decrease the reinforcing properties of methylphenidate because of unwanted side effects.

Actual Abuse of Methylphenidate: Ritalin abuse over the past 20 years has been described as sporadic but persistent (NIDA, CEWG, 1995). Abuse has been for the same reason as most stimulants, for production of a "high". Methylphenidate abuse is reported in individuals for whom the medication was either prescribed inappropriately or obtained through illegal means (from diversion of the legitimately prescribed medication). Of 161 children diagnosed with ADHD/ADD, 16% reported that they had been approached to sell, give, or trade their methylphenidate; 4% reported their drug being stolen (Musser *et al.*, 1998). Of 192 consecutive admissions from a central intake unit to 17 substance abuse treatment clinics (which included methadone maintenance, drug-free outpatient and residential treatment programs), 113 (59%) admitted to having abused methylphenidate (Haglund & Howerton, 1982). 89% reported no current abuse while 3% reported current daily use. Methylphenidate in combination with other drugs, usually opioids, was used by 79%. Numerous cases of patients with extensive drug abuse histories self-

administered methylphenidate intravenously; they included parents of children with ADHD who were taking methylphenidate (Fulton & Yates 1988; Parran & Jasinski 1991; McCann & Roy-Byrne, 1998). Concern has been raised about the possibility of diversion in schools where the drug is held for students and may be considered a burden. Most abuse is by injection (Hahn *et al.* 1969; Lewman 1972; Elenbaas *et al.* 1976; Mizutani *et al.* 1980; Chillar *et al.* 1981; Mehta *et al.* 1984; Levine *et al.* 1986; Lundquest *et al.* 1987; Debooy *et al.* 1993) and also by intranasally (snorting) (Struzzi 1995; Massello *et al.* 1999). Procedures for crushing and extraction of active ingredient in the tablets with water for these alternative routes of administration are chemically simple. Many of the complications from abuse of methylphenidate have been described as related to injection of excipients and other substances found in the oral formulations. Vascular emboli of talc and cornstarch have been found in liver, spleen, skin, kidney, bone marrow, lymph nodes and lungs (Gunby 1979) and eyes (Brucker 1979; Schatz & Drake 1979; Lederer & Sabates 1982). Injection of extracted methylphenidate from the OROS system would be expected to produce similar adverse events.

Overdose: Of almost 500 children who took the drug in clinical trials, there were 6 occasions when a patient took a double dose. These instances were all tolerated and without sequelae. This is an inherent risk any time a patient is switched from dosage several times a day to a once-daily SR medication. Oral LD_{50} is in the range of 300-900 mg/kg in rodents and rabbits (Meier *et al.* 1954). As this dose is approximately 100-300 times greater than the maximum dose in children, a fatal overdose is unlikely. OROS tablets are tough and resistant to disruption from chewing. If the tablet is sucked on by an infant or small child, the IR drug overcoat would dissolve and stimulant side effects would be expected. Taste of the drug overcoat is very bitter and once the clear overcoat dissolves, the taste of the drug will most likely cause a child to discontinue sucking the tablet. If swallowed, CNS stimulant effects would be expected.

ALZA concluded that the OROS product will have lower abuse potential primarily because of the once-a-day dosing regimen. Because ALZA did not demonstrate that the technical features of OROS does not reduce the abuse potential of methylphenidate, ALZA did not request that the product be rescheduled, and further indicated that as a C-II drug, its abuse will likely be reduced.

CONCLUSION & RECOMMENDATION:

The sponsor anticipates marketing Concerta® OROS® (methylphenidate hydrochloride) 18 mg and 36 mg extended-release tablets as a Schedule II drug. Rescheduling to a lower level of control has not been requested and data in support of a lower potential for abuse the product has not been provided.

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cc: HFD-120/Div. files
HFD-170/SCalderon
HFD-170/MKlein
HFD-170/CMcCormick
HFD-170/BRapaport
HFD-170/CShumaker
HFD-120/AHomonnay-Weikel
HFD-120/RKatz
HFD-009/CMoody

MEMORANDUM OF TELECON

DRUG: CONCERTA™ Tablets

SPONSOR: Alza Corp

NDA: 21-121

DATE: 7/18/00

TELEPHONE NUMBER: (650) 564-2543

CONVERSATION BETWEEN:

FDA:
Don Klein, PhD Reviewing Chemist
Anna M. Homonnay-Weikel Project Manager

Alza Corp:
Jennifer Ecklund Regulatory Affairs
Tracy Lin Regulatory Affairs

****

2) [redacted] It was then agreed that it was acceptable to list this term.

/S/
Anna Marie Homonnay-Weikel, RPh
Regulatory Project Manager

Fax

DATE: July 6, 2000

TO:	Anna Marie Homonnay-Weikel, RPh	**FROM:**	Jennifer Ekelund
FAX:	301-594-2859	**FAX:**	650-564-2581
PHONE:	301-594-5535	**PHONE:**	650-564-2543
		PAGES:	1

CONFIDENTIAL

Subject: NDA 21-121 for CONCERTA™ (methylphenidate HCl) Extended-release Tablets
July 7, 2000 Teleconference to Further Discuss Duration of Effect-Related Label Comments

Dear Anna Marie:

I'm sending this fax to confirm our teleconference scheduled for July 7, 2000 at 1:30pm EST. Thank you for setting the meeting up so quickly. We hope to clarify our positions and understanding regarding the newly proposed duration of effect language as well as obtain brief updates on the other issues remaining prior to final approval of the NDA. We will phone you at 301-594-6649. In case of any problems, we may be reached at 650-564-7231. The following people will participate from ALZA:

Jennifer Ekelund	Regulatory Affairs – Facilitator
Steve Ketchum	Regulatory Affairs
Ching-Lin Lai	Statistics and Data Management
Martin O'Connell	Statistics and Data Management
Sue Rinne	Regulatory Affairs
Ed Schnipper, MD	Clinical Operations

Several other ALZAns will be present to observe and hear any updates:

Paula Elster, MD	Medical Safety
Mary Prevo	Safety / R&D Quality
Steve Sherman	Regulatory Affairs
Amy Stephenson	Project Management
Barbara Stewart	Nonclinical R & D
Dan Swisher	Product Management
Tracy Woody	Pediatric/Psychiatric Product Management
Peter Working	Nonclinical / R&D Technical Services

Please feel free to contact me with any questions or comments. If you cannot reach me, please contact Steve Ketchum at 650-564-2510.

Sincerely,

Jennifer Ekelund

ALZA CORPORATION
1900 CHARLESTON ROAD P.O. BOX 7210
MOUNTAIN VIEW CA 94039-7210
PHONE 650.564.5000
http://www.alza.com

HOMONNAYA
APPOINTMENT DETAILED
7-Jul-2000 to 7-Jul-2000

Date: Friday, 7-Jul-2000 Time: 01:30pm Length: 00:30 Hrs:Min

Subject: Telecon w/ Alza Loc: #WOC2_4FL_E

Attendees

HOMONNAYA, LAUGHREN, MOSHOLDERA, YANS, SHENY,

Agenda

NDA 21-121
Topic: Discussion of duration of action labeling claims

Key to Attendee Status

Bold = Confirmed Underline = Rejected All Others = Pending

Calendar Manager 5-Jul-2000

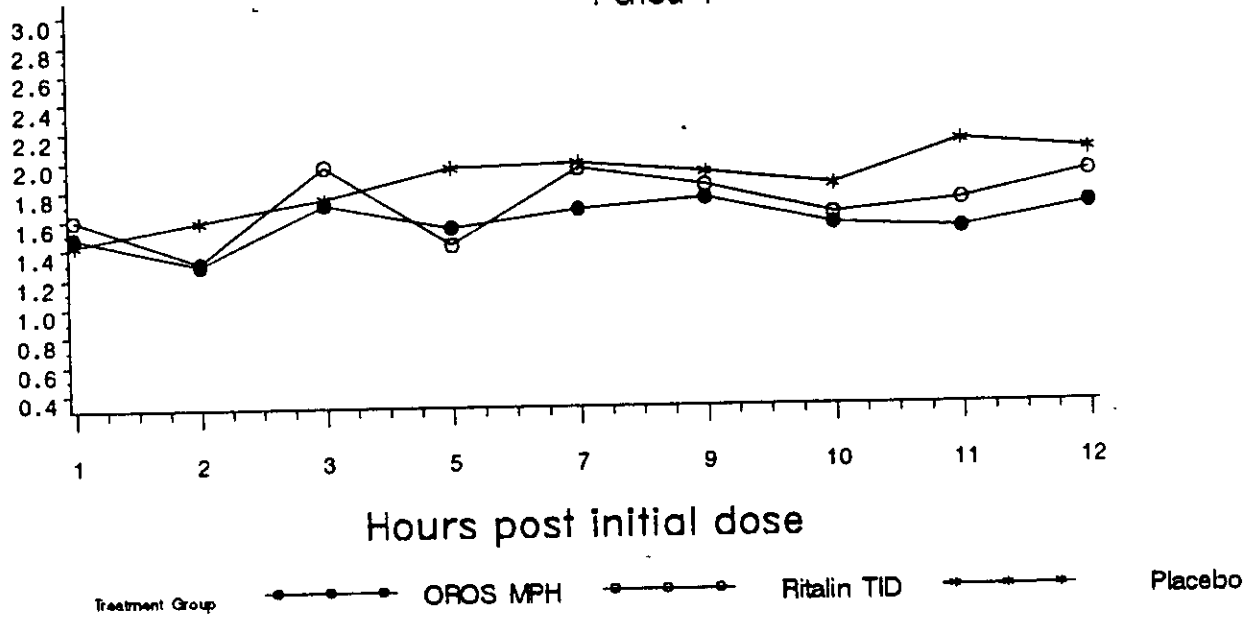
To simplify the analysis by avoiding using any statistical models, this reviewer plotted the mean SKAMP combined attention score by treatment, period and time points (see Figures A.II.2a, A.II.2b and A.II.2c) to descriptively demonstrate the treatment effect across time in three periods. The three figures showed that the time courses of the treatment effect were not consistent across periods: no apparent treatment difference was observed in period 1 but more favorable results of OROS and Ritalin were observed in periods 2 and 3 at and after 2 hours, as compared with controls. The sponsor's claimed onset and loss of treatment efficacy time was obtained by **averaging over all three periods**, but the evidence was not consistent across periods.

Study 003

Figure A.II.2a

Mean of LS teacher SKAMP Combined Attention Rating

Period 1



Study 003

Figure A.II.2b

Mean of LS teacher SKAMP Combined Attention Rating

Period 2

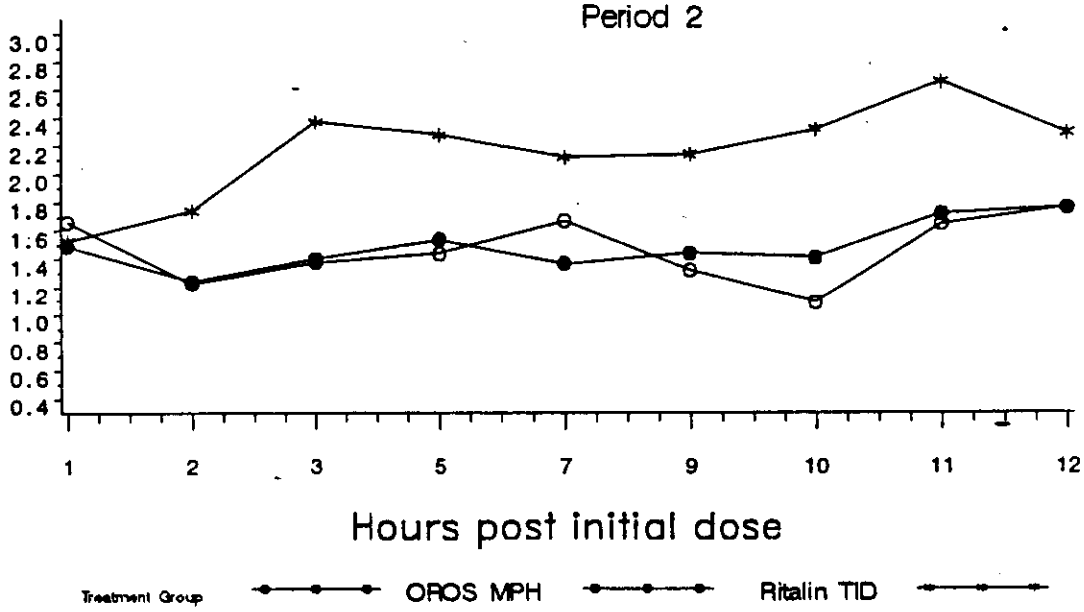
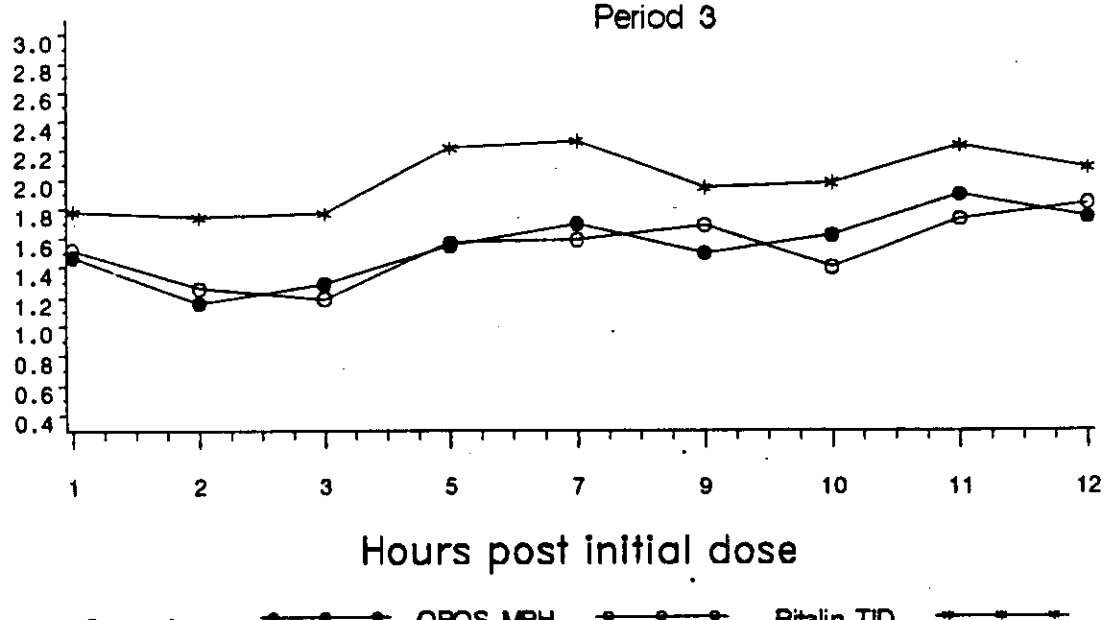


Figure A.II.2c

Mean of LS teacher SKAMP Combined Attention Rating

Period 3



Study 025

Figure B.II.2a

Mean of LS teacher SKAMP Combined Attention Rating

Period 1

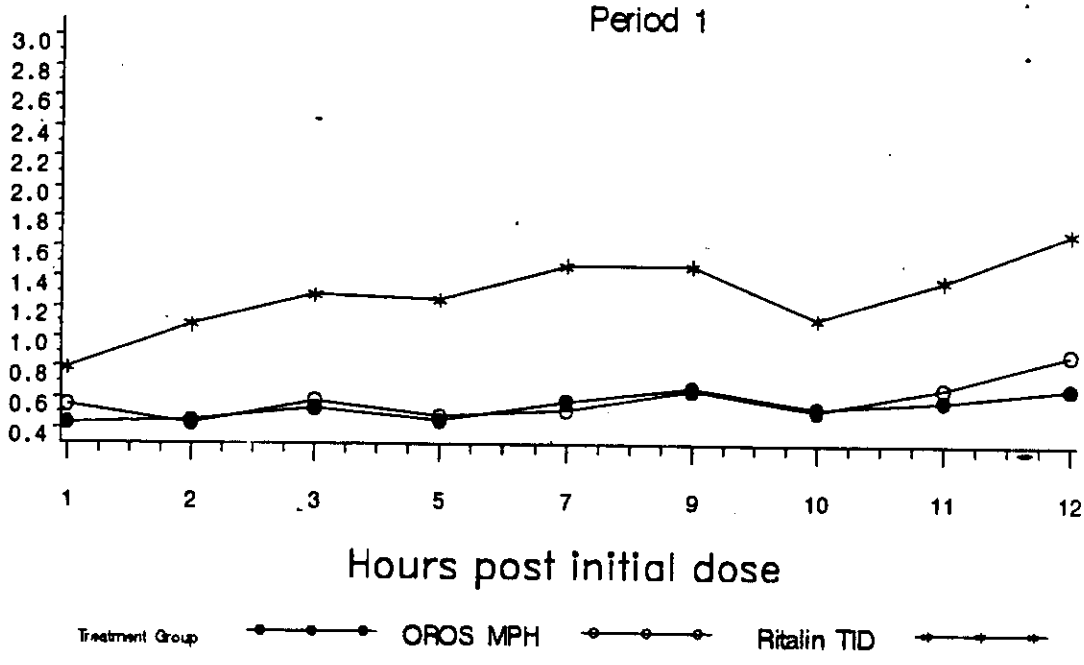
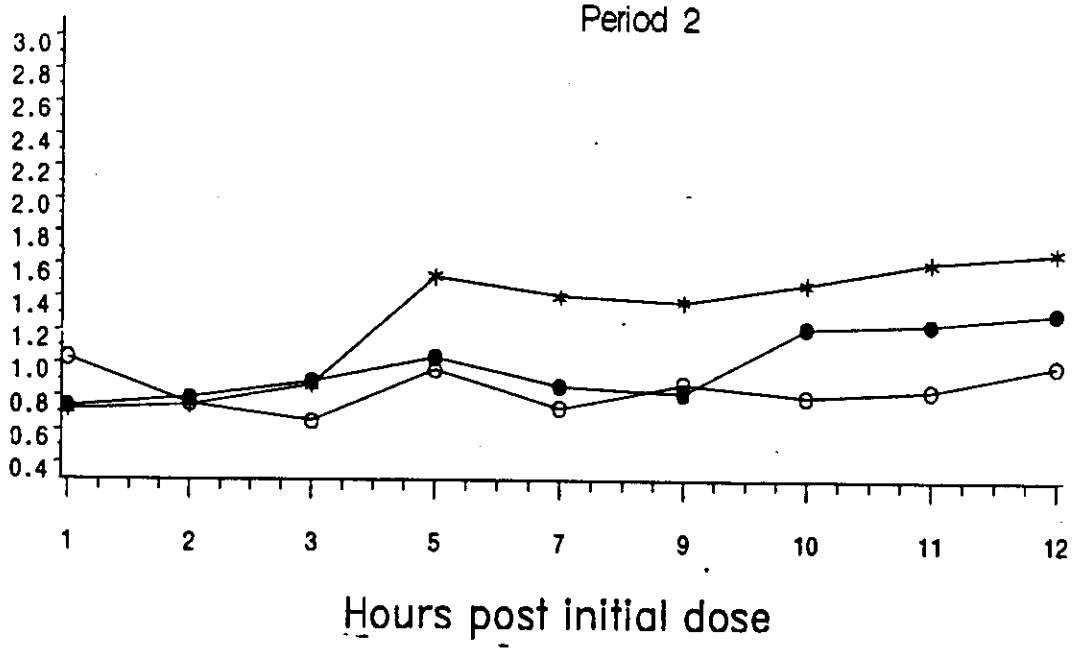


Figure B.II.2b

Mean of LS teacher SKAMP Combined Attention Rating

Period 2

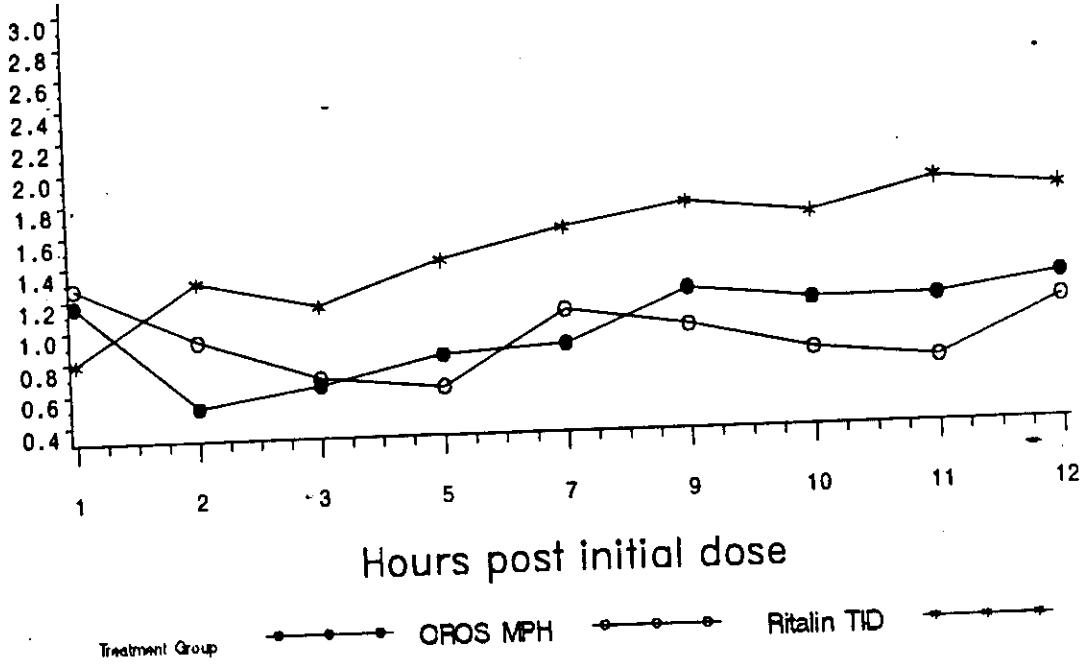


Study 025

Figure B.II.2c

Mean of LS teacher SKAMP Combined Attention Rating

Period 3



APPEARS THIS WAY
ON ORIGINAL

July 7, 2000 Telecon w/ Alza re: Duration of Action Claims for CONCERTA™ Extended-release Tablets

During the review FDA found different period effects for the two studies involving variability in onset time and duration and are therefore concerned about the analysis that was done by Alza.

Alza felt that since the studies were designed as crossover studies to account for baseline differences, the alternate analysis that was conducted by FDA was based on a parallel design resulting in a small sample size with no adjustment for baseline differences. Further maintained that a period effect is not unusual for crossover designs.

FDA was still not convinced and requested an alternate approach for looking a period effects since Alza's approach does not account for baseline differences either.

Alza agreed to pursue this issue post-approval and in the interest of time decided to go back to the original language proposed in our approvable letter.

1. Clinical Pharmacology/Clinical Trials

Presentation of the comparative data between Concerta and Ritalin:
FDA reiterated the current policy that only pre-specified primary outcomes can be summarized in labeling; and that, in Study 5, the comparison should be between Concerta versus placebo since the comparison with methylphenidate was not identified as primary. The sponsor was also reminded of a previous letter from the division dealing with this subject.

Presentation of time course of effect of Concerta:
Alza maintained that the laboratory studies had pre-specified a conditional analysis using SKAMP as the measure of duration of action over the course of the day. FDA brought up the possibility of mutiple endpoints and different period effects. Finally, it was agreed that the protocols will be reexamined by FDA regarding this issue.

Additionally, FDA also pointed out that figure 2 should only include week 4 data to reflect what was studied.

2. Contraindications:

Tic issue:
Alza felt that tic-related language should be within PRECAUTIONS since their data shows that use of methylphendiate in patients with tic disorders is safe, and that methylphenidate is commonly used in these patients. [redacted]

[redacted] FDA also felt that the labeling for Concerta should be consistent with that for Ritalin in this respect.

GI Obstruction Issue:
Alza indicated that other Oros products, such as, Volmax and Tegretol XR, had warnings about GI obstruction in PRECAUTIONS only. It was agreed that Alza would submit a rationale for this in their response to the AE letter.

3. Precautions:

Pregnancy labeling:
FDA indicated that they intend to harmonize the reproductive warnings listed in the Concerta labeling with the Ritalin labeling which may involve modifications to the current Ritalin labeling.
review for Ritalin.

4. Adverse Reactions:

Naïve patients:
It was agreed that Alza would propose alternate language in the response to the AE letter.

Action Items:

1. A future in-house meeting will be convened to further discuss the issues of using the SKAMP measure for duration of action statements in the labeling.

2. [redacted]

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

Date: September 7, 1999
NDA: 21-121
Location: Woodmont II, Conference Room E
Sponsor: Alza Corp
Drug: Concerta (methlphenidate HCl) Extended-release Tablets
Indication: Attention Deficit Disorder
Meeting Type: 45 Day Filing Meeting
Participants:

Russell Katz, M.D.
Tom Laughren, M.D.
Andrew Mosholder, M.D.
Glenna Fitzgerald, Ph.D.
Barry Rosloff, Ph.D.
Bob Seevers, Ph.D.
Don Klein, Ph.D.
Kun Jin, Ph.D.
Yuan-li Shen, Ph.D.
Hong Zhao, Ph.D.
Anna M. Homonnay-Weikel, R.Ph. (Project Manager)
Matthew Thomas, M.D. (DSI)

BACKGROUND:
Alza corporation has submitted a once-daily extended-release tablet (18 mg and 36 mg strengths) for methylphenidate hydrochloride for the treatment of attention deficit disorder. The original product, Ritalin® and Ritalin® SR, manufactured by Novartis, was approved in the 1950's and 1980's, respectively, and has had considerable clinical usage. The sponsor has conducted nine clinical studies and 15 clinical pharmacology studies in support of this application. In addition, some preclinical studies were conducted to supplement and update the current body of knowledge in the literature about this drug, including Segment II and neurobehavioural studies. The original IND [redacted] was submitted to the Division on November 14, 1997. There was a face-to-face End-of-Phase II meeting on August 20, 1998.

DISCUSSION:

CHEMISTRY
The chemistry information seems acceptable for filing. [redacted]. Safety will need review by the pharmacologist. (An internal consult will be requested.) A microbiology consult has also been requested from the CDER microbiology staff. As previously agreed to, additional stability data will be submitted at the 7 month time point.

PRECLINICAL

The application is fileable. The study report for the NTP mouse reproductive study should be requested from the sponsor. Alza's proposals to update the NDA at 7 months with the final study report for the Segment II study in rats and updated summary of the on-going neurobehavioral study rats is acceptable.

CLINICAL

- The application appears to be fileable.

ONCLUSION:

The application appears on its face to be acceptable for filing.

Minutes prepared by. /S/

Anna M. Homonnay-Weikel, R.Ph.
Project Manager

cc: Orig NDA & Div File

C:\WP

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

Date: August 20, 1998

Location: Woodmont II, Conference Room E
Firm: Alza Corporation
Drug: OROS (methylphenidate HCl)
Indication: ADHD
Meeting Type: EOP2
Attendees:

Division of Neuropharmacological Drug Products
T Laughren, MD, Medical Teamleader
A Mosholder, MD, Medical Reviewer
J Choudhury PhD, Statistician
B Rosloff, PhD, Pharmacologist
E Fisher, PhD Pharmacologist
G Fitzgerald, PhD, Pharmacologist
VTammara, PhD, Clinical Pharmacologist
AM Homonnay, Project Manager

Alza Corporation
S Saks MD, Senior Vice President, Medical Affairs
S Gupta, PhD, Senior Director, Clincal Pharmacology
S Rinne, Vice President Regulatory Affairs
N Livesey, Associate Director Regulatory Affairs
D Kardatzke, PhD, Statistician
M Prevo, Vice President, Environmental and Product Safety
B Stewart, PhD, Nonclinical Development Manager
I Shoulson, MD CNS Consultant to ALZA Corporation, Professor of Neurology Pharmacology and Medicine, University of Rochester Medical Center, New York

BACKGROUND:

This meeting was requested by Alza to obtain guidance on the phase III clinical development program for OROS (methylphenidate HCl) once-daily caplets.

DISCUSSION:

- The Division was interested in the extent of experience with already marketed OROS dosage forms in children and a specific question was raised about appendicitis and GI obstruction. The albuterol product, Volmax, and the OTC pseudoephedrine product, Sudafed-24, have been used in children, although they are not approved specifically for this population. ALZA stated it will reference in the NDA its OROS safety database. Additionally, the NDA will

include an extensive safety database in children with OROS (methylphenidate HCl) and the proposed labeling will contain warnings concerning chewing pre-existing GI narrowing, and appearance of depleted shells in feces. The OROS dosage form was designed to be small enough for children to swallow.

- The possibility of withdrawal/rebound effects or other adverse effects following discontinuation of a product with a different input profile was raised. Dr. Gupta replied that in effect there was a washout period every evening and no unusual phenomena had been seen to date. Safety will be monitored longer term in the planned clinical studies, including sleep quality and actigraphy data.

- The recruitment of patients with co-morbidities was discussed to ensure a representative sample of the ADHD population. The current inclusion/exclusion criteria were deemed adequate.

- The Division expects that OROS (methylphenidate HCl) would be prescribed to adolescents and adults, despite the proposed 6-12 age range. ALZA agreed to consider a Phase IV study in an older population, although it was recognized that diagnostic criteria/outcome measures are not fully established for adults.

- Patient/caregiver information (patient package insert) will be required. ALZA agreed to develop this in time for the NDA submission.

- The Division advised that if comparative claims against Ritalin (IR or SR) were planned in the labeling, then the current clinical plan may not be adequate. No comparative claims are currently proposed.

- The possibility of period effects and confounding factors which could result from the crossover designs was discussed. ALZA's planned statistical treatments were considered adequate. The possibility of stratifying patients in the multicenter efficacy study (C-98-005) according to previous treatments was raised. It was agreed that this was not appropriate owing to the number of patients at each site and stratification of patients by dose level. In addition to the primary analysis for the above study which is a simple ANOVA with only treatment in the model ALZA agreed to conduct a baseline covariate analysis.

- The issue of differential effects at the beginning versus the end of the assessment week for the primary efficacy variable, and whether this could be investigated was raised. It was agreed that the current designs would be acceptable, assuming adequate randomization, with both single day laboratory school teacher assessments at the end of the treatment week, and weekly community teacher and parental assessments during the week. It was mentioned that the community school daily report card was collected for study C-97-025 and will be analyzed by day so an investigation of effects on different days of the week is possible.

- A detailed statistical analysis plan for study C-98-005 will be sent to the Division prior to unblinding

- The proposed statistical analysis plan for the integrated database may be submitted for the Division's review.

- It is not necessary to repeat the 30 day dog GI study for the new formulation in view of the minor excipient changes.

- The Division was prepared to accept that the Segment I, II and III reproductive requirements for one species could be considered to have been met by the existing NTP mouse study which was summarized in the package. Dr. Rosloff agreed to accept the mouse study as fulfilling these requirements, provided the sponsor can demonstrate that this study was adequately conducted and showed no reproductive toxicity. A segment II study in a second species will still be required; such a study should examine neurobehavioral development in addition to the standard morphological exams. After discussion, it was agreed that, owing to timing constraints, a summary report could be submitted for filing followed by the final report during the NDA review process prior to approval.

- The Division expressed an interest in behavioral and developmental assessments in young animals. ALZA agreed to conduct a review of the clinical and nonclinical literature and to produce a white paper for inclusion in the NDA. If additional studies in this area are deemed appropriate, it was agreed they could be conducted as Phase IV work.

- ALZA agreed to include toxicokinetic exposure assessment in the segment II study that will be conducted. Dr. Rosloff indicated that although additional pharmacokinetic data in rats and mice would be helpful in the interpretation of the NTP carcinogenicity studies it was not considered essential for approval of OROS (methyphenidate HCl).

- ALZA's mouse micronucleus study synopsis, with a standard acute design using gavage administration, was acceptable to the Division.

Signature, minutes prepare.. /S/
Anna M. Homonnay-Weikel
Project Manager

Concurrence Chair: /S/ 9-16-98
Tom Laughren, M.D.
Teamleader, PDP

APPEARS THIS WAY
ON ORIGINAL

cc:

Orig IND
Div File
HFD-120/Leber
HFD-120/Laughren/9.15.98/Mosholder/9.15.98
HFD-120/Fitzgerald/9.14.98/Rosloff/9.14.98

C:\

MEETING MINUTES

MINUTES OF TELECONFERENCE

Date: August 6, 1998

Location: Woodmont II, Conference Room E
Firm: Alza Corp
Drug: OROS Methylphenidate HCl
Indication: ADHD in children
Meeting Type: CMC Issues

FDA Participants:

Bob Seevers, Ph.D.	Chemistry, Teamleader
Anna M. Homonnay-Weikel, RPh	Project Manager

ALZA Participants:

Doris Boesch Stability Manager
Donald Chaisson, Vice President, Quality Sciences
Karen Chang, PhD, Manager Analytical Sciences
Ivan Chin, Director, Microbiology
Elizabeth Clark, Associate Director, Regulatory Affairs
Jennifer Ekelund, Senior Regulatory Affairs Associate
Suneel Gupta, PhD, Sr. Director Clinical Pharmacology
Andrew Lam, Product Development Manager
Nigel Livesey, Associate Director, Regulatory Affairs
Barbara Stewart, PhD, Non-clinical Development Manager
Ylan Tran Associate Director, Development Material Sciences

BACKGROUND:

ALZA requested a teleconference with FDA to gain concurrence on the key issues for the Chemistry, Manufacturing, and Controls program for an NDA submission.

DISCUSSION:

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dy

[redacted]

posal

ACTION ITEMS:

- Primary stability package is acceptable with 12, 9, and 9 months on the 3 registration lots. This will potentially yield an 18 month expiry date which could possibly be extended to 24 months if additional data to support a longer dating is provided during the NDA review.
- One site qualification lot in Vacaville with 3 months of stability data may be acceptable. A written justification should be submitted to the IND for review by Dr. Seevers.
- [redacted]
- [redacted]

Minutes Prepared by: /S/
Anna M. Homonnay-Weikel, R.Ph.
Project Manager

Concurrence Chair: /S/
Bob Seevers, Ph.D.
Chemistry Team Leader

Oric
Div File
HFD-120/BSeevers 5/25/98
HFD-120/AHomonnay

C:\

TELECONFERENCE MINUTES

APPEARS THIS WAY
ON ORIGINAL

********** -COMM. JOURNAL- ********** DATE JUL-31-2000 ***** TIME 12:36 *** P.01

MODE = MEMORY TRANSMISSION START=JUL-31 12:35 END=JUL-31 12:36

FILE NO.= 143

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-FDA/DNDP

********** - - ***** - 3015942959- *********

facsimile
TRANSMITTAL

[redacted]

To: Jennifer Ecklund
Sponsor: Alza Corp
Fax #: (650) 564-2581
Re: NDA 21-121
Date: 7/31/00
Pages: (including cover sheet) 2

From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

WARNINGS

Potential for gastrointestinal obstruction

Because the CONCERTA™ tablet does not appreciably change in shape or consistency in the GI tract, CONCERTA™ should ordinarily not be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cyctic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). With other drugs, there have been rare reports of GI obstruction, in patients with known strictures, following ingestion of this type of controlled release formulation. Due to the design of the controlled-release tablet tablet, CONCERTA™ should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

alza

Fax

DATE: July 12, 2000

TO:	Anna Marie Homonnay-Weikel, RPh Project Manager, DNDP	**FROM:**	Jennifer Ekelund Manager, Regulatory Affairs
FAX:	301-594-2859	**FAX:**	650-564-2581
PHONE:	301-594-5535	**PHONE:**	650-564-2543
		PAGES:	2 (including this cover page)

CONFIDENTIAL

Subject: NDA 21-121 for CONCERTA™ (methylphenidate HCl) Extended-release Tablets
Revised Page for Physician Insert

Dear Anna Marie:

As we discussed, I am faxing a revised page for the physician insert. Within the Clinical Studies section, we have deleted the three p values from Figure 2 and added the word "statistically" to the beginning of the sentence describing the reduction in the Inattention/Overactivity subscale. The new sentence now reads: "Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA™ qd."

I would value confirmation of the Division's acceptance of these changes at your earliest possible convenience. Based on that confirmation, we plan to destroy the version of the PI which has been printed and print the new version at risk. We would also greatly value your confirmation of the expiration dating for the product as soon as possible prior to final approval as this is the other element of our packaging process which is very time sensitive.

Please feel free to contact me with any questions or comments. If you are unable to reach me, please contact Steve Ketchum at 650-564-2510. We share the same facsimile number.

Sincerely,

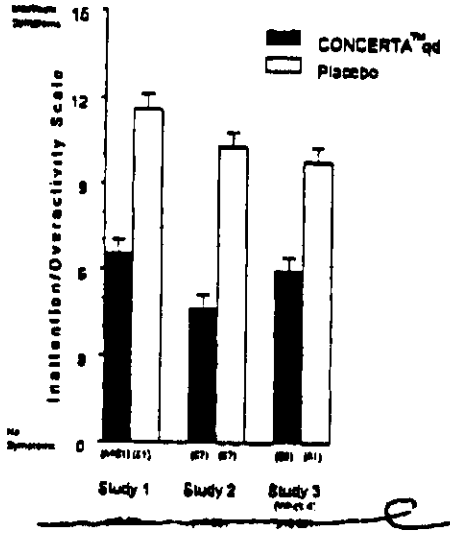
Jennifer Ekelund
Manager, Regulatory Affairs

ALZA CORPORATION
1900 CHARLESTON ROAD P.O. BOX 7210
MOUNTAIN VIEW CA 94039-7210
PHONE 650.564.5000
http://www.alza.com

for diagnosis in all three studies.

Symptoms of ADHD were evaluated by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA™ qd. The scores for CONCERTA™ and placebo for the three studies are presented in Figure 2.

FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners Inattention/Overactivity Scores



delete p values from figure

Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA™ qd (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

CONCERTA™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of CONCERTA™ in the treatment of ADHD was established in three controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment,

Fax

DATE: July 9, 2000

TO:	Anna Marie Homonnay-Weikel, RPh	**FROM:**	Jennifer Ekelund
	Project Manager, DNDP		Manager, Regulatory Affairs
FAX:	301-594-2859	**FAX:**	650-564-2581
PHONE:	301-594-5535	**PHONE:**	650-564-2543
		PAGES:	36 (including this cover page)

CONFIDENTIAL

Subject: NDA 21-121 for CONCERTA™ (methylphenidate HCl) Extended-release Tablets
Copy of Amendment 16.1 Containing Final Proposed Labeling

Dear Anna Marie:

I am faxing a copy of the amendment that contains ALZA's final version of the proposed labeling and the formal submission of the July 6, 2000 fax sent to the Review Chemist. This amendment was sent via Federal Express on July 8, 2000 and should reach the Agency on Monday, July 10, 2000.

Please feel free to contact me with any questions or comments. If you are unable to reach me, please contact Steve Ketchum at 650-564-2510. We share the same facsimile number.

Sincerely,

Jennifer Ekelund
Manager, Regulatory Affairs

ALZA CORPORATION
1900 CHARLESTON ROAD P.O. BOX 7210
MOUNTAIN VIEW CA 94039-7210
PHONE 650.564.5000
http://www.alza.com

July 7, 2000
NDA 21-121; Volume 16.1

Food and Drug Administration; CDER/ODE I
Division of Neuropharmacological Drug Products (DNDP/HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

Attention: Russell Katz, MD, Director, DNDP

Subject: **NDA 21-121 for Concerta™ (methylphenidate HCl) Extended-release Tablets: Labeling Amendment (Final Version of Proposed Label) and Formal Submission of 7/6/00 Chemistry Facsimile**

Dear Dr. Katz:

Reference is made to ALZA Corporation's (ALZA) pending NDA 21-121 for Concerta™ (methylphenidate HCl) Extended-release Tablets submitted on July 15, 1999.

Pursuant to 21 CFR 314.60(a), ALZA is submitting a one-volume amendment to pending NDA 21-121 to provide the Agency with the final version of the proposed label, which was the subject of a teleconference earlier today. Additionally, we are enclosing a copy of the fax sent to the Review Chemist on July 6, 2000.

In accordance with 21 CFR § 314.50 (l)(3), ALZA hereby certifies that the field copy of this submission is a true copy of the technical section contained in the archival and review copies.

Please feel free to contact me with any questions or comments at 650-564-4282 or via facsimile at 650-564-2581. In the event that you are unable to reach me, please contact either Jennifer Ekelund, Manager of Regulatory Affairs, at 650-564-2543 or Dr. Steve Ketchum, Senior Director of Regulatory Affairs, at 650-564-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President, Operations

Enclosed: Archival Copy (1)
Review Copies (6): Pharmacology, Pharmacokinetics, Clinical, Statistics, Chemistry, and Field Chemistry
Desk Copies (2): Ms. Homonnay-Weikel, RPh, Project Manager, DNDP, HFD-120

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

THE MATERIAL CONTAINED IN THIS DOCUMENT IS CONSIDERED TO BE OF A TRADE SECRET AND CONFIDENTIAL COMMERCIAL NATURE AND, THEREFORE, SPECIFICALLY EXEMPT FROM DISCLOSURE PURSUANT TO THE EXPRESS TERMS OF THE PUBLIC INFORMATION SECTION OF THE ADMINISTRATIVE PROCEDURES ACT, KNOWN COMMONLY AS THE FREEDOM OF INFORMATION ACT, AND THE PERTINENT AMENDMENTS THERETO.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALZA Corporation	July 7, 2000
TELEPHONE NO. *(Include Area Code)* (650) 564-4282	FACSIMILE (FAX) Number *(Include Area Code)* (650) 564-2581
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* ALZA Corporation 1900 Charleston Road P.O. Box 7210 Mountain View, CA 94039-7210	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-121

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Methylphenidate HCl	CONCERTA™ a proposed tradename

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
a-Phenyl-2-piperidineacetic acid methyl ester hydrochloride

CODE NAME *(If any)*
ORDS® (methylphenidate HCl)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Oral Osmotic Tablet	18 mg and 36 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Not applicable	Not Applicable

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☑ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: Not Applicable

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Labeling Amendment and Copy of 7/6/00 Chemistry Facsimile

PROPOSED MARKETING STATUS *(check one)* ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 (one) THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). (Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Not applicable to this submission

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, SMFs, and DMFs referenced in the current application)

Not applicable to this submission

This application contains the following items: *(Check all that apply)*	
✔	1. Index
✔	2. Labeling *(check one)* ☑ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
✔	4. Chemistry section
✔	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
✔	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 680, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature] JW	Janne Wissel, Senior Vice President, Operations	July 7, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1900 Charleston Road, Mountain View, CA 94039-7210	(650) 564-4282

Concerta™ (methylphenidate HCl) Extended-release Tablets

Amendment To Pending NDA 21-121

Volume 16.1

Labeling Amendment and Formal Submission of 7/6/00 Chemistry Facsimile

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

FINAL PROPOSED LABELING

The Division's July 5, 2000 version of the Physician and Patient Inserts were used as a basis for the attached final proposed version of the labeling for Concerta™. Based on agreements reached between the Division and ALZA during our July 7, 2000 teleconference, the following changes have been made:

Physician Insert

- The paragraph describing the SKAMP results has been deleted from the **Clinical Studies** section.
- The words "up to" and "-3" have been deleted from the sentence within **PRECAUTIONS, Pregnancy: Teratogenic Effects** (second paragraph). The sentence now reads, "The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA™ based on the AUC."
- The language describing onset and duration of effect has been deleted from the first sentence under **DOSAGE AND ADMINISTRATION.**

Patient Insert

- The language describing onset and duration of effect has been deleted from the **How should I take CONCERTA™?** section.

Additional Minor Modifications

As discussed with the Division's Project Management staff, a number of minor modifications and corrections have been made to facilitate the formatting, printing, and distribution of the inserts; these are described in detail on the following pages.

Additional Minor Modifications
As discussed with the Division's Project Management staff, the following minor modifications and corrections have been made to facilitate the formatting, printing, and distribution of the inserts:

Globally (both inserts)

- Unnecessary spaces (following bolded headings and subheadings) have been eliminated.

Physician Insert

- The CONCERTA™ title at the beginning of the Physician Insert has been bolded.
- All cross-references to other label sections have been put into the appropriate case to match the respective heading or subheading, for example "(see WARNINGS)."
- The alpha symbol (α) has been reinserted in the chemical name for methylphenidate in the **DESCRIPTION** section.
- In the **CLINICAL PHARMACOLOGY**, **Pharmacodynamics** section, the spellings of "monoamine" and "extraneuronal" have been corrected.
- The legends/descriptions for Figures 1 and 2 have been bolded; in addition, the orientation of the y-axis title for Figure 1 has been corrected.
- In the Metabolism and Excretion section, the word "alpha" has been replaced with the alpha symbol (α).
- In the **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, Special Populations, Race section, a hyphen has been inserted between "dose" and "adjusted" ("dose-adjusted") to be consistent with the previous use of the term.
- In the **PRECAUTIONS** section, "**Potential for gastrointestinal obstruction**" has been modified to use title case capitalization ("**Potential for Gastrointestinal Obstruction**"). Additionally, the spelling of "cystic" in "cystic fibrosis" has been corrected.
- In the **ADVERSE REACTIONS**, **Adverse Findings in Clinical Trials with CONCERTA™**, Adverse Events Occurring at an Incidence of 1% or more Among CONCERTA™-Treated Patients section, a dash has been inserted between "treatment" and "emergent" ("treatment-emergent") to be consistent with previous similar use of the term. In this same section, under the subheading Tics, a dash has been inserted between "long" and "term" ("long-term") for consistency.
- In Table 2, the listings under Preferred Terms and the percentage incidences have been de-bolded.
- The title and headings in Table 3 have been bolded and the table lines have been restored.
- The last sentence in the "**HOW SUPPLIED**" section of the Division's 7/5/00 version of the label has been corrected to reflect that both dosage strengths are only supplied in bottles containing 100 tablets (not 30 or 100 tablets).

Physician Insert (continued)

- The heading "Storage" has been bolded.
- The words "Rx Only." have been bolded.
- The contact phone number for more information has been corrected to read "1-888-440-7903" rather than "1-800-440-7973".
- The identification number has been inserted, along with the edition date.
- As agreed with the Division, the Patient Insert will be supplied as part of the Physician Insert as well as separately. The document containing both inserts will be perforated to enable separation of the Patient Insert from the Physician Insert (e.g., by the pharmacist). The words "Tear Here" will be inserted next to the perforation line.
- Two bar codes, accompanying identification numbers, an eye spot (for machine reading), and the words "CONCERTA™" and "SEE INSIDE FOR PATIENT INFORMATION" will be added to the top of the insert.

Patient Insert

- The trademark symbol (™) has been added to CONCERTA in the title.
- All headings have been bolded.
- Under the **Who should NOT take CONCERTA™?** section, a period has been added at the end of the last bullet point.
- "For more information call 1-888-440-7903 or visit www.concerta.net" has been added.
- The ALZA/McNeil addresses, the ALZA logo, identification number, and edition date have been added.
- A bar code will be added to the final printed Patient Insert.

Facsimile Cover Sheet

Today's Date:	July 6, 2000
Number of pages: *(including this page)*	5
To:	Dr. Donald Klein
Company:	Division of Neuropharmacological Drug Products FDA
Phone Number:	(301) 594-5537
Fax Number:	(301) 594-2859
From:	Tracy Lin
Company:	ALZA Corporation 1950 Charleston Road Mountain View, CA 94043
Phone Number:	(650) 564-4135
Fax Number:	(650) 564-2581

M E S S A G E

Dear Dr. Klein:

[redacted]

Please call me if you have any questions.

Sincerely,

Tracy Lin

Hommany

NDA 21-121

MAY 18 2000

Alza Corporation
Attention: Jane-Wissel
Senior Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your new drug application dated July 15, 1999, received July 19, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CONCERTA™ (methylphenidate HCl) Extended-release Tablets.

We acknowledge receipt of your submissions dated August 20; September 21; October 1; December 20, 1999; and January 31; February 15 (revised draft labeling); March 29 and 31; and April 3, 4, and 20, 2000.

The User Fee goal date for this application is May 19, 2000.

We have completed the review of this application, as submitted with draft labeling, and it is approvable. Before this application may be approved however; it will be necessary for you to respond to the following issues:

Labeling Issues

Accompanying this letter as an attachment, is our proposal for the labeling for Concerta™. We would be amenable to further discussion of the proposed changes through a teleconference.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update to your NDA.

NDA 21-121

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Concerta™, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to the approval of Concerta™, we will require an updated report on the world archival literature pertaining to the safety of this product.

Biopharmaceutics Issues

The following in vitro dissolution specifications should be adopted for the 18 mg and 36 mg strengths:

Time Point	Proposed specification of label claim(%range) Revised Specification
[redacted]	

Pharmacology/Toxicology Issues

Please provide a written commitment, including a targeted submission date, to conduct a phase IV study to examine the effects of methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters.

proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or teleconference with this Division to discuss what further steps need to be taken before the application may be approved.

This drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please contact Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301)594-5535.

Sincerely yours,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment

NDA 21-121

cc:
Archival NDA 21-121
HFD-120/Div. Files
HFD-120/Katz
HFD-120/Laughren/5.5.00
HFD-120/Mosholder/5.5.00
HFD-120/Fitzgerald/Rosloff/5.2.00
HFD-120/Seevers/5.11.00/Klein/5.10.00
HFD-710/Shen
HFD-860/Sunzel/5.1.00/Mahmood/5.1.00/Baweja/5.1.00
HFD-120/Homonnay
HFD-002/ORM
HFD-101/ADRA
HFD-40/DDMAC (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: ahw/4.27.00
revised by: ahw/5.2.00
revised by: ahw/5.12.00
final by: ahw/5.12.00

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-121

INFORMATION REQUEST LETTER

JUN 28 2000

Hand carry

ALZA Corporation
Attention: Ms. Janne Wissel
Senior Vice President
Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your June 1, 2000 submission for your new drug application for CONCERTA™ (methylphenidate HCl) Oral Osmotic Tablets, 18mg and 36mg.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Refer to the response to the first CMC deficiency on page 12.2/1 and to Attachment 1. As in the original NDA submission, please provide a copy of the ALZA COA for the drug [redacted].

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301) 594-5537.

Sincerely,

/S/ 6/28/00

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-121
HFD-120/Div. Files
HFD-120/A.Homonnay-Weikel
HFD-120/D.Klein
HFD-120/R.Seevers
DISTRICT OFFICE

Drafted by: dnk/June 27, 2000
Initialed by:
final: DMC 6/29/00
filename:

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 8 2000

NDA 21-121

INFORMATION REQUEST LETTER

ALZA Corporation
Attention: Ms. Janne Wissel
Senior Vice President
Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Hand delivered

Dear Ms. Wissel:

Please refer to your June 1, 2000 submission for your new drug application for CONCERTA™ (methylphenidate HCl) Oral Osmotic Tablets, 18mg and 36mg.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

[redacted]

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301) 594-5537.

Sincerely,

/S/ 6/8/00

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-121
HFD-120/Div. Files
HFD-120/A.Homonnay-Weikel
HFD-120/D.Klein
HFD-120/R.Seevers
DISTRICT OFFICE

Drafted by: dnk/June 8, 2000
Initialed by:
final:
filename: ~~~~~~~~~~~~~~~~~~~~

INFORMATION REQUEST (IR)

Homonnay

NDA 21-121

JUN 8 2000

Alza Corporation
Attention: Jane Wissel
Senior Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

We acknowledge receipt on June 5, 2000, of your June 1, 2000, resubmission to your new drug application (NDA) for CONCERTA™ (methylphenidate HCl) Extended-release Tablets.

This resubmission contains additional information submitted in response to our May 18, 2000, approvable letter, including revised draft labeling.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date will be August 5, 2000.

If you should have any questions, please contact Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

/S/

John S. Purvis (for)
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 21-121
HFD-120/Div. Files
HFD-120/Homonnay
DISTRICT OFFICE

Drafted by: ahw/June 8, 2000

CLASS 1 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)