New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-802
Types of Submissions:	NDA N-BB
Generic Name:	Dex-Methylphenidate Hydrochloride Modified Release Capsules
Formulation: **Strengths:** **Route:**	50:50 immediate release and enteric-coated, delayed release beads 5 mg, 10 mg, 20 mg, 30 mg, (b) (4) PO
Brand Names	Focalin™ XR
Sponsor:	Novartis Pharmaceuticals Corporation East Hanover, NJ
Submission Dates:	July 28, 2004 November 30, 2004
Related IND	63,885 Focalin XR
Related NDA	21-284 Ritalin LA Methylphenidate Hydrochloride Modified Release Capsules)
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

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2 EXECUTIVE SUMMARY

2.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-802 submitted July 28, 2004 and November 30, 2004.

OCPB finds this application acceptable provided that currently outstanding issues are adequately resolved, (i.e. agreement on dissolution and labeling).

Comments should be communicated to the sponsor as appropriate (see Section 2.1.2 Comments to the Sponsor on page 7). Labeling comments should also be communicated to the sponsor as appropriate (see Section 4 Labeling Comments on page 78).

2.1.1 Comments to the Medical Division

2.1.1.1 Summary of Major Conclusions

- As expected Focalin XR results in a bimodal PK profile of *d*-MPH that mimics the profile obtained after administration of 2 IR tablets administered 4 hours apart. Focalin XR produces the same PK profile as produced by Ritalin LA.

- The duration of effect claim is not adequately supported, as the design of the classroom pharmacodynamic (SKAMP) study was flawed. The primary flaw being that all children received the same 20 mg dose. Thus younger children received an excessive dose that was up to 2 fold maintenance dosages. Less significant flaws included lack of hourly testing so effects at the interpeak trough was not measured, and a drug holiday on the day prior to dosing which could increase sensitivity to methylphenidate and thus result in a prolonged duration of effect compared to the duration under clinical conditions in those patients dosed appropriately. Plots of SKAMP scores over time by subject age suggests that the higher exposures achieved in younger children resulted in the achievement of maximum effects (Emax), and that the longer exposures to higher concentrations also resulted in maintaining concentrations above a minimum effective level for a longer time.

- Based on the similarity of the formulation to Ritalin LA and the comparable dissolution of Focalin XR to Ritalin LA in 3 different media, food effects with Focalin XR are likely similar to Ritalin LA and labeling regarding food effects for Focalin XR will be based on the labeling for Ritalin LA.

- *In vivo* PK studies comparing 3 formulations with different release rates for the delayed release beads indicate that a 6 hour dissolution specification of (b) (4) produce similar concentration profiles although beads with faster dissolutions (i.e (b) (4) dissolved at 6 hours) result in higher interpeak troughs with no major differences in peaks. This alleviates concerns of excessive peaks with faster dissolution. However, the sponsor has proposed as a 6 hours specification of (b) (4) and this tighter upper limit is clearly acceptable.

- Biowaivers for the 5 mg and 30 mg capsules for use in children are proposed based on formulations being compositionally proportional differing only in the number of beads, have similar dissolution profiles, and result in similar dose normalized bioavailability.

2.1.2 Comments to the Sponsor

2.1.2.1 Biowaivers

A biowaiver for the 5 mg and 30 mg capsules is granted.

2.1.2.2 Dissolution

The sponsor is requested to adopt the following regulatory dissolution method and specifications for Focalin XR 5mg, 10 mg, 20 mg, and 30 mg, (see Table 1).

Differences from the sponsor's proposed specifications are highlighted in bold text.

Table 1 Proposed Regulatory Dissolution Method and Specifications for Focalin XR 5 mg, 10 mg, 20 mg, and 30 mg Capsules

Parameter	Proposed Dissolution Method and Specifications
Apparatus type:	USP Apparatus I (basket)
Media:	Medium I: First 2 hours 0.01N HCl Medium II: Hours 2 – 10 Phosphate buffer pH 6.8
Volume:	500 ml for both medium I and medium II
Temperature:	37 ± 0.5 ^{o}C
Speed of rotation:	100 rpm.
Sampling Times:	0.5, 4, 6, and 10 hours
Specifications % of Label Claim	30 minutes (b) (4) 240 minutes (4 hours) (b) (4) 360 minutes (6 hours) (b) (4) 600 minutes (10 hours) Not less than (b) (4)
Acceptance Criteria:	As per USP XXVIII - NF 23 <724> Drug Release Acceptance Table 1

2.1.2.3 Labeling Comments

The sponsor is requested to adopt OCPB proposed labeling as outlined in §4 Labeling Comments on page 78.

2.2 Commitments to be Performed Prior to Approval

An *in vitro* interaction study with clinically relevant alcohol concentrations is requested to examine the effect of ethanol on dose dumping. Dissolution profiles for Focalin XR should be generated with the media, containing ethanol concentrations ranging from (b) (4) increments, (n.b. both acid and buffer phases should have the same ethanol concentration). Please note that the effect of ethanol on drug degradation should also be addressed when performing these experiments.

2.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

2.3.1 Introduction and Background

What is the active ingredient of Focalin XR?

The active pharmaceutical ingredient is dexmethylphenidate, the dextrorotary isomer of methylphenidate. Dexmethylphenidate is a CNS stimulant that acts by inhibiting the reuptake of dopamine into presynaptic neurons, thereby increasing the exposure to dopamine in the synaptic cleft. Dexmethylphenidate is the active component of all racemic methylphenidate compounds as the levorotary isomer is not active and does not exhibit any systemic bioavailability, or is just barely detectable, plus there are no interconversion or drug interactions between the two isomers at clinical doses. Thus dosage of dexmethylphenidate is exactly half of the dosage for racemic methylphenidate.

How is Focalin XR formulated?

Focalin™ XR capsules contain a 50:50 proportion of immediate release (IR) and enteric-coated, delayed-release beads (EC-DR) encased in a hard gelatin capsule. However, the product does not act as a typical enteric-coated product. Instead it behaves as a combination of an immediate release product and as a delayed release product.

There are (b) (4) proposed strengths for marketing, 5 mg, 10 mg, 20 mg, 30 mg, (b) (4) capsules. Each capsule releases half the dose immediately from the IR beads and half the dose several hours later from the EC-DR beads as shown in Table 2.

Table 2 Allocation of Dexmethylphenidate Release from Focalin XR Capsules by Total Dosage Strength

Capsule Strength (mg)	IR Bead Component (mg)	EC-DR Bead Component (mg)
5	2.5	2.5
10	5	5
20	10	10
30	15	15
(b) (4)		

The delayed release beads are produced by coating IR beads with a pH dependent slowly dissolving methacrylate copolymer.

The resulting bimodal release characteristics of this product is intended to mimic administration of two single doses administered 4 hours apart, but with only a single daily administration.

With minor differences, formulation of Focalin™ XR is almost exactly the same as Ritalin LA, the racemic version of this product. Specifically, since the amount of active ingredient in Focalin XR is exactly half of the amount in Ritalin LA, (b) (4)

(b) (4)

Consequently, these two formulations are expected to behave identically with virtually identical clinical properties for the same amount of dexmethylphenidate.

Consequently, the sponsor has appropriately relied on prior studies with Ritalin LA for labeling purposes when appropriate in order to minimize unnecessary human experimentation.

What is the proposed indication and how does it compare to indications of other methylphenidate products from the same sponsor?

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

This is the same indication as for Focalin IR tablets and Ritalin LA Capsules. Ritalin® IR and SR tablets, Ritalin® LA are also indicated for narcolepsy as well as for the treatment of ADHD.

How does the proposed *Dosage and Administration* for Focalin XR compare to the labeling for the sponsor's other methylphenidate products?

A comparative summary of dosage and administration proposed for Focalin XR and for the sponsor's other methylphenidate products is shown in Table 3.

Dosage and administration for children is generally consistent with other methylphenidate products when the amount of active drug is considered except that the smallest dosage increment achievable with IR formulations is not achievable with Focalin XR.

In addition, for adults the recommended weekly stepped dosage adjustment is twice as large as for any other formulation, (i.e. 10 mg vs. 2.5 - 5 mg *d*-MPH) and the maximum daily dosage is 1/3 higher, (i.e. 40 mg vs. 20 – 30 mg *d*-MPH)

Table 3 Comparative Summary of Dosage and Administration for Novartis Methylphenidate Products

Formulation	API	Patient Age	Dosage and Administration			
			Initial Dosage	Dose Increments / Dose Titration	Maximum Dosage	Switching from another Formulation
Focalin IR	*d*-MPH	Children 6 – 17 yo	5 mg / day (2.5 mg bid; 4 hours apart)	2.5 – 5 mg weekly increments	20 mg / day (10 mg bid)	Half of current racemic MPH dose
Ritalin IR	*d,l*-MPH	Children (≥ 6 yo)	5 mg bid before breakfast and lunch	5 – 10 mg weekly increments	60 mg	
		Adults	***The following is the labeled D&A***			
			10 – 60 mg daily in 2 – 3 divided doses administered 30 – 45 minutes before meals. Average is 20 – 30 mg			
			This corresponds to the following initial dosage, titration step, and maximum daily dosage.			
			10 mg bid – tid	Titrate up or down	60 mg	
Ritalin SR	*d,l*-MPH	Children (≥ 6 yo) & Adults	—	—	—	Same total daily dose as Ritalin IR but taken in a single daily dose
Ritalin LA	*d,l*-MPH	Children and Adults	20 mg qd If clinically indicated, 10 mg qd	10 mg weekly	60 mg (was initially 40mg)	Same total daily dosage as Ritalin IR or SR
Focalin XR	*d*-MPH	Children (6 - 17 yo)	5 mg /day	5 mg weekly	30 mg / day	Racemic MPH – half of total daily dose Focalin IR - same total daily dose
		Adults	10 mg / day	10 mg weekly	40 mg / day	

2.3.2 Pertinent Clinical Pharmacology and Biopharmaceutic Questions

[n.b. questions with double asterixes (**) are the major issues identified by OCPB]

Is the clinical trial formulation the same as the to-be-marketed formulation?

Yes.

Is the bioanalysis acceptable?

The assay was acceptable. The linear range of the method was doubled from when it was used for the Ritalin LA submission (b) (4). All measured concentrations were thus within the validated range. QC samples from a single analytical run were not acceptable, however the particular subject's data that was affected cannot be ascertained as adequate identifying information was not provided. However, as this was not in a pivotal BE study or in a study that would effect dosing this should not alter overall conclusions or pharmacokinetic metric summary statistics appreciably.

** **What are the bioavailability and pharmacokinetic characteristics of Focalin XR?**

Focalin XR demonstrates a ***bi-modal release*** pattern. There is an ***initial lag phase of ~0.5 hours*** followed by the ***first peak at about 1.5 hours***. This lag phase and first peak is attributable to the immediate release beads.

The second peak from the enteric coated delayed release beads occurs on average at 6.5 hours in adults with a range of 4.5 – 7 hours. On average the second peak concentration is similar to the first peak concentration, but is lower than after a second IR tablet during bid administration, and inter-peak minimum is on average about half as much.

** **How does the bioavailability of one Focalin XR capsule compare to one Ritalin LA capsule?**

The pharmacokinetic profile from equivalent doses of Focalin XR is comparable to Ritalin LA.

How does the bioavailability of one Focalin XR capsule compare to two Focalin IR tablets administered 4 hours apart?

The ***initial lag phase and the first peak*** from the Focalin XR capsules ***are comparable*** in both timing and concentration to what is seen with a similar dose from the first Focalin IR tablet.

The ***inter-peak minimum was 21% higher and occurred slightly earlier*** with the XR capsules compared to the IR formulation.

The second peak from the enteric coated delayed release beads occurs on average at 6.5 hours in adults with a range of 4.5 – 7 hours. On average ***the second peak concentration is similar to the first peak concentration, but is 17% lower than after a second IR tablet during bid administration***. This along with the higher inter-peak minimum suggests that typically ***absorption from the enteric coated delayed release beads begins well before a second dose of IR tablets would be dosed at 4 hours and continues for a longer duration.***

Due to the differences in the inter-peak minimums and second peak concentrations between the two dosage forms, ***the peak-trough fluctuation is lower with Focalin XR capsules compared to IR tablets***.

The total amount of d-MPH absorbed from Focalin XR capsules is similar to the amount absorbed from Focalin IR tablets and Ritalin LA capsules

**** Is there any 'dose dumping'?**

None of the pharmacokinetic studies showed any evidence of acute dose dumping.

However, coadministration of ethanol has been shown to effect the release profiles of other coated beaded formulations, therefore there is a concern of dose dumping with alcohol intake. Since, the cardiovascular effects are significant with Focalin XR an in vitro interaction study should be performed.

Is there dose linearity?

There is ***dose linearity up to 40 mg***, (b) (4)

**** Are biowaivers appropriate?**

Only capsules strengths up to 20 mg were studied in pivotal trials. However, as the capsules are all compositionally proportional differing only in the amount of beads, dissolution is similar regardless of strength biowaivers for the 5mg, 30 mg (b) (4) capsule strengths are appropriate. In addition, there is dose linearity over the entire dosage range using the various strength capsules. However as the Division of Neuropharmacologic Drug Products only has plans to approve the 20 mg strength in adults due to a lack of evidence for a differentiation in effect between the 20 mg and higher doses, **a biowaiver will only be granted for the 5 mg and 30 mg capsules for dosing in children at this time.**

**** Is there an age effect?**

Only studies in healthy young adults were performed therefore the effect of age could not be assessed. However, with Ritalin LA there is a slight age effect, with volume of distribution normalized to body weight being linearly related to age. These result in a slightly faster half-life in children compared to adults (2.64 ± 1.03 hours vs. ~3.4 hours) as clearance normalized to body weight is independent of age. However, the difference in volume of distribution is not so large that ***a particular mg/kg dose in children still produces relatively similar exposures as the same mg/kg dose in adults***.

**** Is there a gender effect?**

As with Ritalin LA, there appears to be a gender effect in adults. ***The first peak was on average 45% higher in women compared with men. The interpeak minimum and the second peak also tended to be slightly higher in women although the difference was not statistically significant***, and these patterns remained even after weight normalization.

Are there pharmacokinetic differences by ethnicity?

This cannot be determined from the data presented, due to inadequate numbers of subjects or lack of information on ethnicity. However, ***it seems unlikely*** based on the pharmacokinetic properties of the drug as it is primarily metabolized to ritalinic acid by plasma esterases.

**** Is there a food effect?**

No food effect was performed, however the sponsor has adequately justified that the food effect labeling with Ritalin LA should apply to Focalin XR due to similarity in formulation, kinetics, and dissolution in various media.

With Ritalin LA ***there was a clear food effect with a high fat breakfast resulting in a delay in absorption (Tlag) and time to peak concentrations (Tmax1 and Tmax2), with no evidence of dose dumping.***

The delay in both the lag time and the time to first peak is likely due to a delay in gastric emptying, and is thus likely related to the active ingredient and not the formulation. It was previously thought that the delay and lower concentrations observed for the second peak, with Tmax2 occurring as late as 11 hours, may indicate that there may also be some effect on the delay release properties due to changes in the intestinal milieu. Consequently, there might also be a food effect with a mid-day meal. However additional information provided on the composition and ingestion of the mid-day meal suggests that this may be due to other factors.

No food effect was observed when the capsule beads were sprinkled on applesauce. However, this does not mean there will be no food effect with other soft foods.

The data with Ritalin LA also suggest the possibility of a food effect with methylphenidate immediate release tablets. Upon examination it was found that the studies in the literature reporting no food effect or a slightly more rapid absorption have seriously flawed designs. The studies used low-calorie, low-fat meals with very few subjects and had inadequate blood sampling. The inadequate blood sampling probably gave rise to the erroneous conclusion of a possible more rapid absorption in the presence of food.

**** Are there any special instructions for Focalin XR?**

According to the sponsor Focalin XR capsules may be opened and the beads sprinkled over soft food (i.e. applesauce). Although the sponsor has shown that sprinkling on cold applesauce and waiting up to 30 minutes does not affect the dissolution of the EC-DR beads. The sponsor has proposed the following labeling: '***If sprinkled over applesauce, the applesauce should not be warm and the mixture should be consumed immediately in its entirety.'***

In addition, Focalin XR capsules and/or their contents ***should not be crushed, chewed, or divided***.

Both of these instructions are to minimize the possibility that the enteric delay release coating may be destroyed.

**** What is the time to onset and the duration of effect for Focalin XR?**

The sponsor examined the time to onset and duration of effect in a controlled classroom study utilizing SKAMP scoring in children. However the study design is inherently biased and no firm conclusions can be drawn. Specifically the study utilized the same dose for all children regardless of their 'optimum' clinical dose. Thus on average the children received a dose 1/3 higher than they would likely receive under clinical conditions with some children receiving twice their 'optimal' dose. Efficacy was also not examined at the interpeak trough, thus continuous efficacy cannot be assured. Plus, the sponsor employed a washout period on the day prior to testing and this may increase sensitivity to the drug and thus efficacy. A pilot analysis however does suggest that duration may be as long as 10 hours in children 9 – 12 years of age, although an appropriately designed study is needed to confirm this in the entire labeled treatment population at appropriate doses.

Although only a 20 mg dose will be approved in adults, the concentrations with a 20 mg dose are potentially lower in adults than in children due to larger body size and a larger weight normalized volume of distribution in spite of a longer half-life. Thus duration of effect with a 20 mg dose may be shorter than 10 hours in adults and the 30 mg and 40 mg doses may produce longer durations of effect in adults than the 20 mg dose. For a duration of effect claim in adults, additional studies at different dosages and possibly PK/PD bridging with psychometric testing (i.e. math tests) between adults and children may be needed.

**** Are the proposed drug product dissolution method and specifications acceptable?**

The sponsor's proposed two-stage ***dissolution method*** for the enteric-coated drug product ***is acceptable*** and identical to the method for Ritalin LA. However the ***drug release specifications need to be modified***.

The sponsor's proposed specifications at 0.5 and 4 hours have been widened compared to Ritalin LA's specifications. However, all data suggests that Focalin XR would readily achieve the tighter specifications and there is no reason that these specifications should be widened.

In contrast the sponsor has provided clinical data from 3 formulations with different dissolution characteristics at 6 hours that the specifications can be widened. However, the sponsor's proposed changes would only result in allowing slower dissolving capsules to pass and in fact tightens the current specifications so that previously acceptable faster dissolving capsules would no longer pass. Since concerns are primarily with faster dissolving capsules and as slightly slower dissolving capsules appear to result in minimal delays in absorption, the sponsor's proposed differences for the 6 hour sample for Focalin XR compared to the current specification for Ritalin LA are acceptable.

Current and proposed dissolution specifications follow:

	Focalin XR		**Ritalin LA**
Time	***Reviewer's***	***Sponsor's***	
0.5 hours			(b) (4)
4 hours			
6 hours			
10 hours			

2.4 Signatures

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

Senior Reviewer
Division of Pharmaceutical Evaluation I
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Sally Yasuda, Pharm.D. **Date**

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OCPB Briefing Meeting:

Date:	Wednesday, May 11, 2005
Time:	1:00 PM – 2:00 PM
Location:	WOC-2 3rd Floor Conference Room C
Level:	Required Inter-Divisional
Attendees:	KavanaghR, YasudaS, DoddapaneniS, RahmanA, MehtaM, GlassR, AndreasonP

CC: NDA 21-802 (orig., 1 copy)
HFD-120 (GlassR, AndreasonP, LaughrenT, KatzR, TaylorR, Chhagan Tele, RosloffB)
HFD-860 (KavanaghR, YasudaS, BawejaR, RahmanA, MehtaM)
Central Document Room (Barbara Murphy)

3 DETAILED REVIEW

3.1 Overview of Clinical Development Program

3.1.1 Description of Clinical Development Program

Focalin XR is a modified release formulation of the *d*-isomer of methylphenidate. The formulation is almost identical to the sponsor's modified release formulation of racemic methylphenidate, Ritalin LA, (b) (4) The clinical program consists of a BE study, a study for establishing ranges for dissolution conditions, a dose proportionality study that includes strengths on the *d*-isomer both higher and lower than previous equivalent strengths of the racemate, a classroom pharmacodynamic study, and pivotal efficacy and safety studies. Other studies examining factors such as food effect, and other extrinsic and intrinsic factors were not performed. For food effects labeling will rely on the approved labeling for the racemic formulation, Ritalin LA®.

3.1.2 List of Studies

Table 4 lists all human clinical studies with Focalin XR submitted in the NDA.

Table 4 Focalin XR Clinical Studies Included in NDA 21-802

Study #	Study Description	Study Title
	Phase I Studies	
2101	Relative Bioavailability vs. Ritalin LA	A randomized, open-label, 3-period, crossover study to compare the oral bioavailability between Focalin™ XR (d methylphenidate) 20 mg, Focalin™ IR two 10 mg capsules dosed 4 hours apart, and Ritalin® LA (*d,l*-methylphenidate) 40 mg in healthy volunteers
(b) (4)		
2102	Dose Proportionality in Adults	A randomized, open-label, single dose, five treatment, five period, crossover study to evaluate the dose proportionality of Focalin XR (5, 10, 20, 30, 40) capsule
	Phase II Pharmacodynamic Studies	
US08	Phase II Pharmacodynamic Testing in Children	A randomized, multi-center, double-blind, cross-over study comparing the efficacy, safety, and tolerability of Focalin™ XR 20 mg versus placebo in children (6-12 years) with Attention Deficit Hyperactivity Disorder (ADHD) in an analog classroom setting.
	Phase III Efficacy and Safety Studies	
2301	Phase III Pivotal Efficacy in Children & Adolescents	A multicenter, double-blind, randomized, placebo-controlled, parallel-group, study of the efficacy and safety of Focalin XR (dexmethylphenidate HCl extended release capsules) at 5-30 mg/day administered once daily in pediatric patients 6-17 years of age with Attention-Deficit/Hyperactivity Disorder
2302	Phase III Pivotal Efficacy in Adults	A 5-week, multicenter, double-blind, randomized, placebo-controlled, parallel group, fixed-dose study of the efficacy and safety of Focalin™ XR (dexmethylphenidate hydrochloride extended-release capsules) administered once daily in adults with Attention-Deficit/Hyperactivity Disorder
2302E1	Phase III Long Term Safety Extension to study 2302 in Adults	A 6-month, open-label extension to a 5- week, multicenter, double-blind, randomized, placebo-controlled, parallel group, fixed-dose study of the efficacy and safety of Focalin™ XR (dexmethylphenidate extended-release capsules) administered once daily in adults with Attention-Deficit/Hyperactivity Disorder

3.2 Chemistry

3.2.1 Formulation Description

The TBM formulation is intended to mimic the release characteristics of two sequential doses of an immediate release tablet administered 4 – 5 hours apart.

To accomplish this, the proposed to-be-marketed formulation is composed of a 50:50 combination of immediate release, (IR), beads and enteric coating delayed release, (EC-DR), beads encased in a hard gelatin capsule.

The immediate release beads are manufactured (b) (4)

The enteric coated, delayed release beads are then made by coating immediate release beads with a layer of an enteric coating (b) (4), (See Figure 1).

Figure 1 Schematic of Focalin™ XR Beads

(b) (4)

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3.2.4 Manufacturing, QC, Stability Testing and Packaging Sites

Manufacturing, quality control, stability testing and packaging sites for Focalin XR are shown in Table 8

Table 8 Manufacturing, Quality Control, Stability Testing and Packaging Sites for Focalin XR

Site	Manufacturing	Quality Control	Stability	Packaging
ELAN HOLDINGS, INC Gainesville, GA 30504	X	X	X	X
Novartis Pharmaceuticals Corporation (Suffern) Suffern, NY 10901		X	X	X

(b) (4)

3.2.5 Primary Packaging Containers

Primary packaging will consist of (b) (4) 100 count HDPE bottles with an aluminum induction seal and a 38 mm (b) (4) child resistant closure. Bottles sizes are shown in Table 9.

Table 9 Focalin XR HDPE Primary Packaging Containers by Tablet Strength and Quantity

Tablet Count	(b) (4)	100
Tablet Strengths (mg)	Bottle Sizes by Tablet Count	
5, 10, 20	(b) (4)	
30, 40		

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3.2.6.2 Capsule Batch Qualitative Quantitative Composition

Table 15 Qualitative Quantitative Composition for a Capsule Batch

Ingredients	Amount Used (kg)	Amount in Finished Beads (kg)
Dexmethylphenidate hydrochloride		(b) (4)
Polyethylene glycol (b) (4)		
Purified water[a]		
(b) (4)		
Talc		
Triethyl citrate		
(b) (4)		
Total Batch		

a Removed during processing

3.2.7 Formulation Batches Used in Clinical Studies and Selected In Vitro Experiments

Formulation batches used in clinical studies and selected *in vitro* experiments are shown in Table 16. Batches that were used in the pivotal clinical efficacy and safety studies are highlighted in **Bold**.

Table 16 Formulation Batches Used in Clinical and Selected *in Vitro* Studies

Study No	Description	Drug[a]	Strength	Manufacturer[b]	Batch No.[c]	Formulation[b,d]
Phase I Studies						
2101	BE Study	Focalin™ XR	20 mg	Novartis	RD020303	NR
		Focalin™ IR	10 mg	Novartis	H010475A	NR
		Ritalin® LA	40 mg	Novartis	013G8194	NR
2102	Dose Proportionality	**Focalin™ XR**	**5 mg**	**Elan Gainesville, GA**	**RD040301**	NR
		Focalin™ XR	**10 mg**	**Elan Gainesville, GA**	**RD020301**	NR
		Focalin™ XR	**20 mg**	**Elan Gainesville, GA**	**RD020302**	NR
		Focalin™ XR	30 mg	Elan Gainesville, GA	RD050301	NR
		Focalin™ XR	40 mg	Elan Gainesville, GA	RD050304	NR
						(b) (4)
Phase II Studies						
US08	Classroom PD Study in Peds	**Focalin™ XR**	**20 mg**	NR	**RD020302**	(b) (4)
		Placebo	—	NR	RD090201	
Phase III Studies						
2301	Pivotal Efficacy in Children and Adolescents	**Focalin™ XR**	**5 mg**	NR	**RD040301**	
		Focalin™ XR	**10 mg**	NR	**RD020301**	
		Focalin™ XR	**20 mg**	NR	**RD020302**	
		Placebo	—	NR	RD090201 RD090202	
2302	Pivotal Efficacy in Adults	**Focalin™ XR**	**10 mg**	NR	**RD020301**	
		Focalin™ XR	**20 mg**	NR	**RD020302**	
		Placebo	—	NR	RD090201	
2302E1	Long Term Safety in Adults	**Focalin™ XR**	**10 mg**	NR	**RD020301**	
		Focalin™ XR	**20 mg**	NR	**RD020302**	
***In Vitro* Experiments**						
In Vitro Applesauce Study		Ritalin LA	40 mg	NR	104H1035	NR
		Focalin™ XR	40 mg	NR	(b) (4)	NR
In Vitro Dissolution Study		Focalin® LA	20 mg	NR	RD020303	Development Formulations
		Ritalin® LA	40 mg	NR	104H1035	
		Ritalin® LA	10 mg	NR	3B093	

a Focalin = dexmethylphenidate, (*d*-MPH); Ritalin = methylphenidate, (*d,l*-MPH)
b NR – Not Reported
c Batch numbers in bold are used in pivotal phase III studies
d Formulation Numbers are 'KN' numbers (KN not explained)

3.3 Bioanalytic Methods

3.3.1 Methods Used and Assay Validations

The assay method was previously acceptable to OCPB per the Ritalin LA NDA 21-284. For the present NDA the assay method was transferred to a site in France, the concentration range was extended, and the length of the long term stability data was extended. However, there is still no interday variability information.

A more complete description of the partial assay validation can be found in Appendix 2.

3.3.2 Sample Handling and Storage

Methylphenidate is an ester and is hydrolyzed to ritalinic acid by plasma esterases. Consequently, samples should be collected in EDTA, placed on ice, and processed quickly.

Sample handling and storage per each protocol for each of the pharmacokinetic studies is shown in Table 17. However no mention was made of the anticoagulant used. In addition, for the population PK study, 2302, sample handling procedures were not detailed. Shipment procedures were unremarkable. Overall for the phase I PK studies procedures are acceptable.

Table 17 Sample Handling Procedures

Study Number	2101	2102	(b) (4)	2302
Study Descriptors	BE to Ritalin LA	Dose Proportionality		Phase III Pop PK
Sample Handling Procedures	(b) (4)			

3.3.3 In-Process Quality Controls

The in-process quality controls were acceptable for most of the analytical runs. However, for study 2101, a BE study used for formulation development purposes the analytical run performed on May 7, 2003 was unacceptable as it appears that there was a systematic change in the assay between the beginning and the end of the run, (i.e. decrease in QC samples). Unfortunately information was not included that would allow identification of the affected subject samples.

3.4 Pharmacokinetics

3.4.1 Single Dose Pharmacokinetics

3.4.1.1 Overview

Single dose pharmacokinetics of the TBM formulation under fasted conditions is available from 3 pharmacokinetic studies in adults. No pharmacokinetic data was obtained in children.

Methylphenidate IR tablets generally have a Tmax of between 1 and 3 hours. As IR tablets are usually dosed around breakfast and lunchtime, the sponsor dosed Focalin IR tablets 4 hours apart during comparative studies with Focalin XR. Consequently, the sponsor assessed the following pharmacokinetic metrics in adults for comparative purposes for Focalin XR capsules as well as Focalin IR tablets and Ritalin LA capsules:

Cmax 0-4
Tmax 0-4

Cmin 0-4
Tmin 0-4

Cmax 4-10
Tmax 4-10

Consequently, this reviewer redefined and recalculated the pharmacokinetic metrics. A comparison of the metrics used by the sponsor and those used by the reviewer are shown in Table 18.

Table 18 Comparison of Pharmacokinetic Metrics Calculated by the Sponsor and the Reviewer

Dosing Schedule (Time - hours)		PK Metrics Assessed Focalin IR Focalin XR Ritalin LA		Description of Sponsor's PK Metrics	Description of Reviewer's PK Metrics
Focalin IR	Focalin XR & Ritalin LA	by Sponsor	by Reviewer		
0	0	Cmax 0-4	Cmax 1	Peak concentration occurring between hours 0 - 4	First peak concentration
		Tmax 0-4	Tmax 1	Time of peak concentration occurring between hours 0 - 4	Time of first peak concentration
		Cmin 0-4	Cmin IP	Minimum concentration occurring after the first peak and between hours 0 - 4	Minimum concentration occurring between peaks 1 and 2
		Tmin 0-4	Tmin IP	Time of minimum concentration occurring after the first peak and between hours 0 - 4	Time of minimum concentration occurring between peaks 1 and 2
4		Cmax 4-10	Cmax 2	Peak concentration occurring between hours 4 - 8	Second peak concentration
		Tmax 4-10	Tmax 2	Time of peak concentration occurring between hours 4 - 8	Time of second peak concentration

3.4.1.2 Comparative Bioavailability of Focalin XR to Focalin IR and Ritalin LA

Study 2101 was a pilot study in healthy male and female adults that examined the comparative bioavailability of the to-be-marketed formulation of Focalin XR 20 mg capsules, (*d*-MPH), to a single dose of Ritalin LA 40 mg capsules, (*d,l*-MPH), and 2 doses of Focalin IR 10 mg tablets dosed 4 hours apart.

The data from this study indicates that Focalin XR and Ritalin LA exhibit similar bioavailability in terms of both rate and extent of absorption. Compared to Focalin IR, the extent of absorption was also similar. However, as expected the time metrics for Focalin IR were less variable resulting in a larger and less variable mid-day peak and a lower interpeak minimum..

Due to the complex absorption mechanism and the sponsor's use of inappropriate pharmacokinetic metrics, i.e. use of overall Cmax and Tmax as well as the sponsor's metrics from Table 18, the statistical evaluation of bioequivalence is not correct. However, the differences from appropriate metrics are minimal. Consequently, bioequivalence between Focalin XR and Ritalin LA is highly likely.

Figure 3 shows the mean *d*-MPH concentration vs. time plots after single doses of Focalin XR 20 mg capsules, (*d*-MPH), Ritalin LA 40 mg capsules, (*d,l*-MPH), and 2 doses of Focalin IR 10 mg tablets dosed 4 hours apart under fasting conditions in study 2101. As shown in Figure 3 Focalin XR gives the profiles as Ritalin LA, and they both result in lower second peaks and higher interpeak minimums.

Individual plots of *d*-MPH concentration vs. time after each treatment are shown in Figure 4, Figure 5, and Figure 6 on the following page. Frequency distributions of the time metrics for these treatments in Figure 7, Figure 8, and Figure 9 clearly show the greater variability for the 2nd peak for the modified release formulations, along with their similarity to each other.

Figure 3 Mean*d*-MPH Concentration vs. Time Plots after Equivalent Doses of Focalin XR, Focalin IR, and Ritalin LA – Study 2101

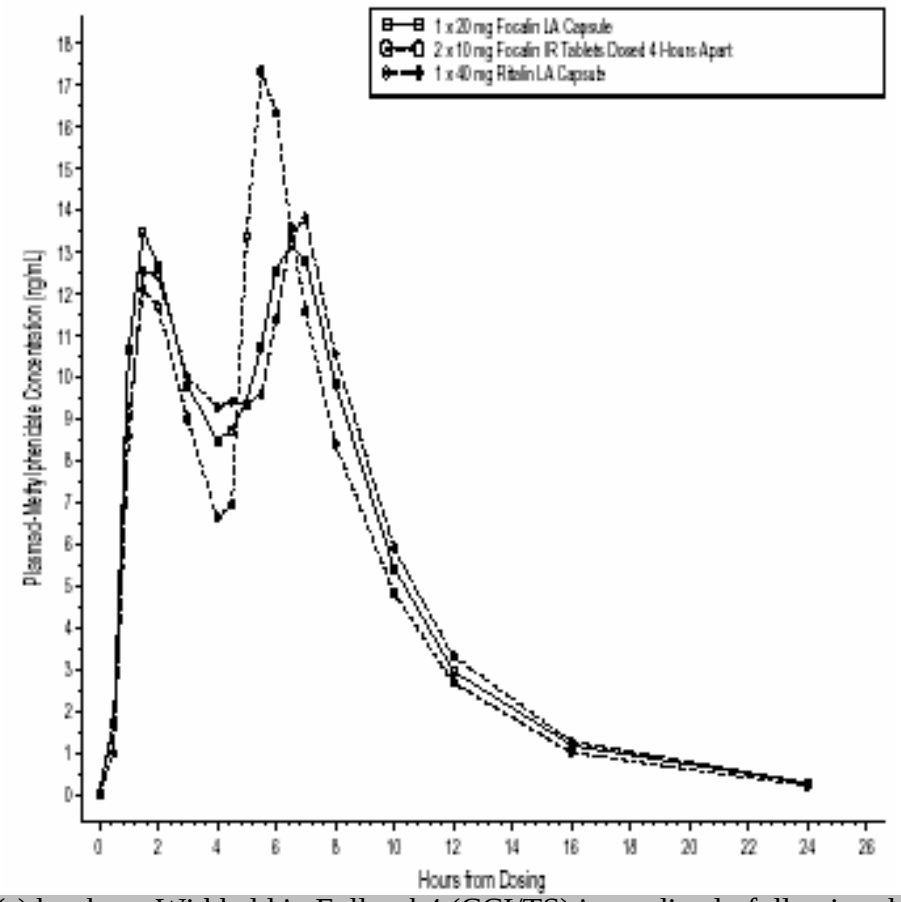

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Table 19 Comparison of Summary Statistics for OCPB Calculated Pharmacokinetic Metrics by Treatment in Focalin XR, Focalin IR and Ritalin LA Biocomparison Study - Study 2101

Metric[a]	Treatments		
	A	B	C
	Focalin XR (*d*-methylphenidate) 1 x 20 mg capsule	Focalin IR (*d*-methylphenidate) 1 x 10 mg tablet Dosed 4 hours apart (total 2 doses)	Ritalin LA (*d,l*-methylphenidate) 1 x 40 mg capsule
N	24	25	24
Tlag (hours)	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	0.5 ± 0.1 (19.6) 0.5 - 1 [0.5]
Tmax1 (hours)	1.5 ± 0.6 (38.9) 1 - 4 [1.5]	1.6 ± 0.3 (18.7) 1 - 2 [1.5]	1.8 ± 0.6 (34.7) 1 - 4.5 [1.75]
Cmax1 (ng/ml)	13.5 ± 4.2 (31.5) 8.3 - 28.5 [12.5]	12.6 ± 3.9 (30.8) 8.7 - 25.2 [11.6]	13.3 ± 3.0 (22.8) 8.9 - 22.6 [13.1]
$Tmin_{ip}$ (hours)	4 ± 0.8 (20.5) 2 - 5.5 [4]	4.3 ± 0.3 (5.8) 4 - 4.5 [4.5]	4.4 ± 1.1 (25.8) 2 - 5.5 [4.75]
$Cmin_{ip}$ (ng/ml)	7.6 ± 1.7 (22.5) 3.9 - 10.5 [7.4]	6.3 ± 1.8 (29.4) 4.3 - 12.7 [5.7]	7.4 ± 2.6 (34.6) 3.2 - 12 [6.6]
Tmax2 (hours)	6.5 ± 0.7 (11.1) 4.5 - 7 [6.5]	5.6 ± 0.3 (5.9) 5 - 6.5 [5.5]	6.1 ± 1.1 (17.9) 4 - 8 [6.5]
Cmax2 (ng/ml)	14.9 ± 4.0 (26.8) 8.8 - 27.8 [14.35]	17.9 ± 5.3 (29.8) 12.1 - 34.5 [16.9]	16.3 ± 4.5 (27.4) 8.1 - 29.6 [15.85]
Tmax (hours)	4.6 ± 2.4 (51.6) 1 - 7 [5.75]	5.6 ± 0.3 (5.9) 5 - 6.5 [5.5]	5.9 ± 1.3 (22.3) 2 - 7 [6.5]
Cmax (ng/ml)	15.5 ± 4.3 (27.7) 9.4 - 29.8 [14.65]	17.9 ± 5.3 (29.8) 12.1 - 34.5 [16.9]	16.1 ± 4.4 (27.5) 8.9 - 29.6 [15.65]

a Values are Mean ± SD, (CV%), Minimum – Maximum, (Median)

Table 20 Comparison of Sponsor's Summary Statistics for Pharmacokinetic Metrics by Treatment in Focalin XR, Focalin IR and Ritalin LA Biocomparison Study - Study 2101

Metric[a]	Treatment A Focalin XR Capsule 1 x 20 mg	Treatment B 2 Doses of Focalin IR Tablets 1 x 10 mg Dosed 4 Hours Apart	Treatment C Ritalin LA Capsule 1 x 40 mg
N	24	25.0	24
Tmax(0-4) (hr)	1.57 ± 0.34 (21.71) 1.00 - 2.01 [1.50] 1.53 (23.42)	1.64 ± 0.31 (18.58) 1.00 - 2.00 [1.50] 1.61 (19.87)	1.96 ± 0.75 (38.26) 1.50 - 4.50 [2.00] 1.87 (29.57)
Cmax(0-4) (ng/ml)	13.7 ± 4.6 (34.0) 8.3 - 29.8 [12.5] 13.1 (29.6)	12.6 ± 3.9 (30.8) 8.7 - 25.2 [11.6] 12.2 (26.3)	13.2 ± 3.0 (22.8) 8.9 - 22.6 [13.1] 13.0 (21.7)
Tmax(4-10) (hr)	6.28 ± 0.72 (11.43) 4.50 - 7.01 [6.50] 6.24 (12.15)	5.63 ± 0.33 (5.90) 5.00 - 6.50 [5.51] 5.62 (5.83)	6.13 ± 1.09 (17.83) 4.00 - 8.00 [6.50] 6.03 (19.62)
Cmax(4-10) (ng/ml)	14.9 ± 4.0 (26.8) 8.8 - 27.8 [14.4] 14.4 (25.4)	17.9 ± 5.3 (29.8) 12.1 - 34.5 [16.9] 17.3 (26.4)	16.3 ± 4.5 (27.4) 8.1 - 29.6 [15.9] 15.8 (27.7)
Tmax (hr)	4.63 ± 2.39 (51.61) 1.00 - 7.01 [5.76] 3.79 (82.10)	5.63 ± 0.33 (5.90) 5.00 - 6.50 [5.51] 5.62 (5.83)	5.88 ± 1.31 (22.29) 2.01 - 7.01 [6.50] 5.69 (29.51)
Cmax (ng/ml)	15.5 ± 4.3 (27.7) 9.4 - 29.8 [14.7] 15.0 (26.0)	17.9 ± 5.3 (29.8) 12.1 - 34.5 [16.9] 17.3 (26.4	16.4 ± 4.4 (27.0) 8.9 - 29.6 [15.9] 15.8 (26.7)
AUC(0-4) (ng/ml*hr^{-1})	36.3 ± 10.6 (29.2) 23.6 - 75.6 [34.2] 35.1 (25.3)	32.5 ± 10.2 (31.5) 21.8 - 62.7 [30.5] 31.3 (26.9)	35.0 ± 8.7 (24.9) 22.8 - 62.5 [32.6] 34.1 (23.3)
AUC(4-10) (ng/ml*hr^{-1})	59.1 ± 16.0 (27.0) 38.7 - 115.9 [55.0] 57.4 (23.9)	61.6 ± 20.0 (32.5) 40.5 - 135.3 [57.4] 59.3 (27.4)	60.9 ± 15.0 (24.6) 33.9 - 106.9 [58.2] 59.3 (23.8)
AUC(0-t) (ng/ml*hr^{-1})	117.7 ± 39.3 (33.4) 78.3 - 276.6 [107.5] 113.3 (26.5)	113.6 ± 39.1 (34.4) 74.0 - 263.6 [102.9] 109.0 (28.0)	120.4 ± 34.9 (29.0) 74.0 - 248.3 [112.4] 116.6 (25.3)
AUC(0-inf) (ng/ml*hr^{-1})	119.1 ± 40.7 (34.1) 78.9 - 284.2 [108.4] 114.5 (26.9)	114.9 ± 40.0 (34.8) 74.5 - 269.6 [103.2] 110.1 (28.2)	121.9 ± 36.3 (29.8) 74.6 - 257.0 [113.6] 117.9 (25.6)
%AUC(0-inf) extrapolated	1.1 ± 0.8 (71.4) 0.3 - 3.0 [0.7] 0.8 (81.0)	1.0 ± 0.6 (61.4) 0.3 - 2.7 [0.8] 0.9 (69.6)	1.1 ± 0.7 (64.9) 0.4 - 3.4 [0.9] 1.0 (64.9)
t1/2 (hr)	3.26 ± 0.51 (15.81) 2.41 - 4.45 [3.14] 3.22 (15.62)	3.11 ± 0.52 (16.85) 2.14 - 4.39 [3.05] 3.07 (17.01)	3.19 ± 0.51 (16.07) 2.37 - 4.32 [3.09] 3.15 (15.73)
Kel (1/hr)	0.218 ± 0.033 (15.261) 0.156 - 0.288 [0.221] 0.215 (15.624)	0.229 ± 0.039 (17.131) 0.158 - 0.324 [0.227] 0.226 (17.008)	0.223 ± 0.034 (15.286) 0.160 - 0.293 [0.224] 0.220 (15.728)

a Values are Mean ± SD, (CV%), Minimum – Maximum, (Median), Geometric Mean, (Geometric CV%)

Table 21 Geometric Mean Ratios and 90% Confidence Intervals for Sponsor's *d*-Methylphenidate Pharmacokinetic Metrics following Focalin™ LA 20 mg (test) Compared to 2 x Focalin™ IR 10 mg or Ritalin LA 40 mg – Study 2101

Pharmacokinetic Metrics	Ratio of Geometric Means (90% CI)	
	Focalin™ LA 20 mg : Focalin™ IR 2 x 10 mg	Focalin™ LA 20 mg : Ritalin LA 40 mg
Cmax(0-4) (ng/mL)	1.06 (1.00,1.13)	1.01 (0.96,1.06)
Cmax(4-10) (ng/mL)	0.82 (0.77,0.88)	0.92 (0.87,0.96)
Cmax (ng/mL)	0.86 (0.81,0.91)	0.95 (0.91,0.99)
AUC(0-inf) (ng*hr/mL)	1.02 (0.98,1.07)	0.97 (0.94,1.00)
AUC(0-t) (ng*hr/mL)	1.02 (0.98,1.07)	0.97 (0.94,1.00)
AUC(0-4) (ng*hr/mL)	1.11 (1.05,1.17)	1.03 (0.98,1.08)
AUC(4-10) (ng*hr/mL)	0.95 (0.91,1.00)	0.97 (0.94,1.00)

a Calculation of descriptive statistics, geometric mean ratio and 90% CI is based on 24 subjects.

3.4.1.3 Dose Proportionality

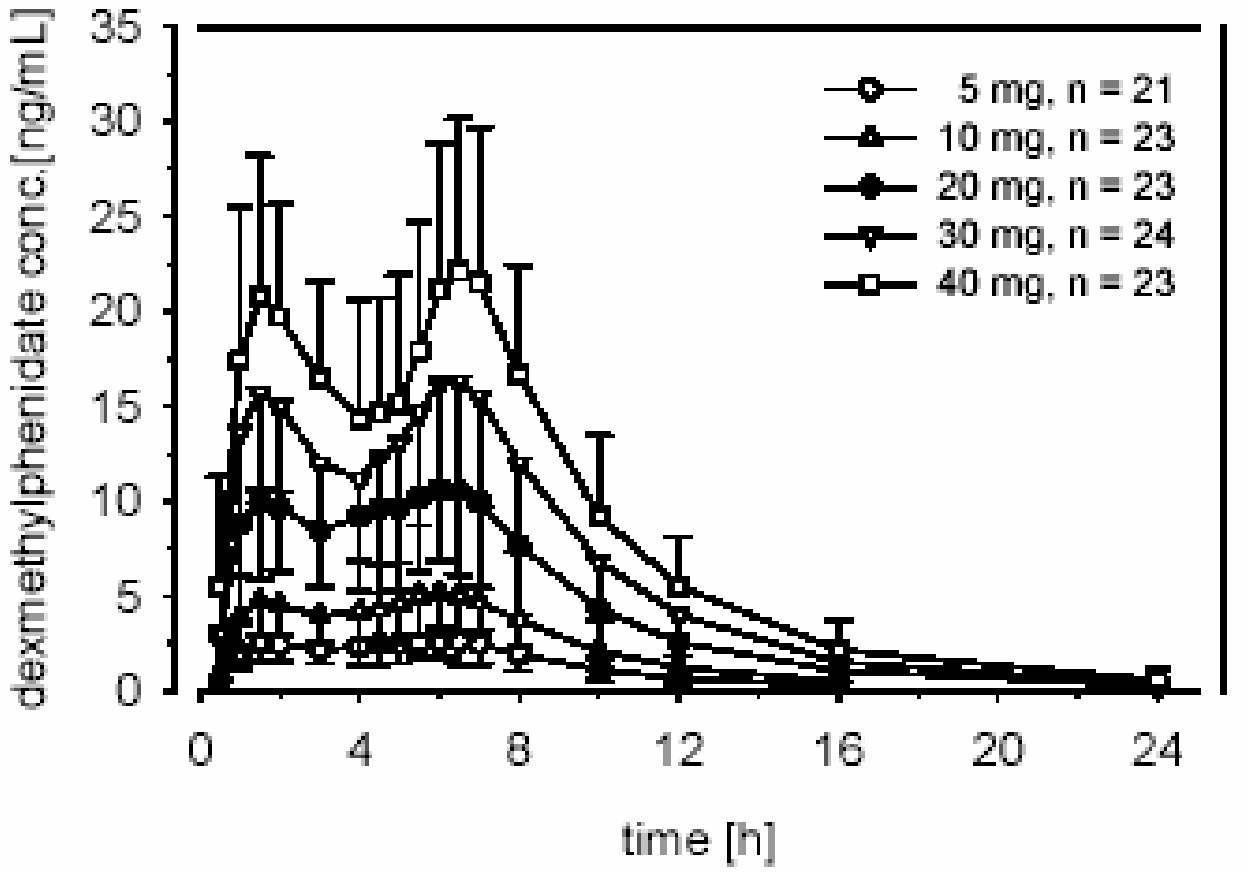
Study 2102 was a 5-way crossover in 25 healthy male and female adults subjects between 18 and 45 years of age to evaluate dose proportionality over the dose range of 5 mg to 40 mg. A dose proportionality study was performed as the proposed maximum dosage of 40 mg of *d*-MPH is greater than the currently labeled maximum daily dosage for methylphenidate products, and since the maximum dosage strength of Ritalin LA is 40 mg. A multiple dose study was not performed due to the short half-life and lack of accumulation. Five subjects were withdrawn from the study by the investigator. None of the withdrawals were due to the study drug.

As expected Focalin XR was dose proportional over the range of 5 mg to 40 mg of *d*-MPH.

Figure 10 of mean *d*-MPH concentration vs. time profiles show that average values are dose proportional.

Table 22 is a summary of pharmacokinetic metrics by dose including dose normalized metrics, and Figure 11 shows selected dose normalized metrics for individual subjects by dose.

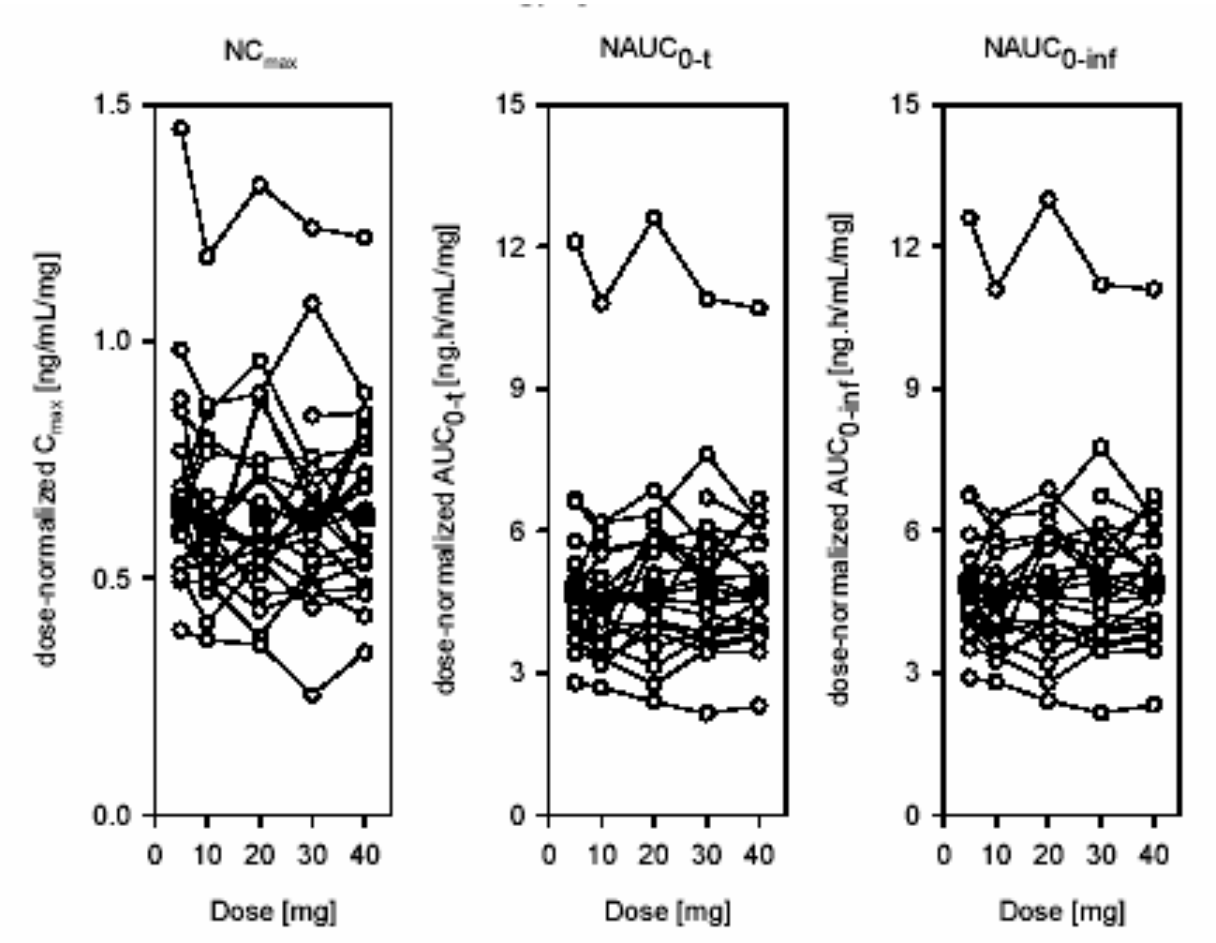
Figure 10 Mean*d*-MPH Concentration vs. Time Profiles after Single Rising Doses of Focalin IR – Study 2102



Summary Statistics of Single Dose Dexmethylphenidate Pharmacokinetic Metrics

	5mg		10 mg		20 mg		30 mg		40 m
	21	21	23	23	23	23	24	24	23
	Mean ± SD (CV) Range	GeoMean (CV) Median	Mean ± SD (CV) Range	GeoMean (CV) Median	Mean ± SD (CV) Range	GeoMean (CV) Median	Mean ± SD (CV) Range	GeoMean (CV) Median	Mean ± SD (CV) Range
	3.39 ± 1.14 (33.5) 1.95 - 7.27	3.25 (29.0) [3.20]	6.27 ± 1.81 (28.8) 3.69 - 11.8	6.05 (27.1) [5.93]	13.2 ± 4.40 (33.2) 7.19 - 26.6	12.6 (31.9) [12.0]	19.4 ± 6.07 (31.3) 7.60 - 37.3	18.5 (31.7) [18.3]	26.2 ± 7.76 (29.6) 13.7 - 48.9
	0.68 ± 0.23 (33.5) 0.39 - 1.45	0.65 (29.0) [0.640]	0.63 ± 0.18 (28.8) 0.37 - 1.18	0.605 (27.1) [0.593]	0.66 ± 0.22 (33.2) 0.36 - 1.33	0.631 (31.9) [0.600]	0.65 ± 0.20 (31.3) 0.25 - 1.24	0.618 (31.7) [0.608]	0.66 ± 0.19 (29.6) 0.34 - 1.22
	5.36 ± 1.35 (25.1) 1.50 - 7.05	5.14 (34.8) [5.53]	4.74 ± 2.00 (42.2) 1.05 - 7.00	4.13 (67.2) [5.53]	4.94 ± 1.92 (38.9) 0.52 - 7.00	4.26 (77.4) [5.50]	4.21 ± 2.30 (54.6) 1.00 - 7.00	3.40 (85.0) [5.00]	5.28 ± 2.00 (37.8) 1.00 - 7.00
	2.84 ± 1.02 (35.9) 1.28 - 4.85	2.68 (37.1) [2.46]	5.30 ± 1.88 (35.6) 2.76 - 9.24	5.00 (35.7) [4.88]	11.7 ± 4.54 (38.9) 3.76 - 23.7	10.8 (41.9) [10.9]	16.8 ± 6.36 (37.9) 6.42 - 37.3	15.7 (38.4) [16.1]	22.0 ± 7.73 (35.2) 7.44 - 35.6
4	0.57 ± 0.2 (35.9) 0.26 - 0.97	0.54 (37.1) [0.49]	0.53 ± 0.19 (35.6) 0.28 - 0.92	0.5 (35.7) [0.49]	0.59 ± 0.23 (38.9) 0.19 - 1.19	0.54 (41.9) [0.55]	0.56 ± 0.21 (37.9) 0.21 - 1.24	0.52 (38.4) [0.54]	0.55 ± 0.19 (35.2) 0.19 - 0.89
	2.62 ± 1.16 (44.2) 1.50 - 4.00	2.38 (47.1) [2.00]	2.18 ± 1.13 (51.6) 1.05 - 4.00	1.96 (48.3) [1.50]	2.62 ± 1.26 (48.1) 0.52 - 4.00	2.27 (64.2) [2.00]	1.61 ± 0.68 (42.5) 1.00 - 4.00	1.51 (36.0) [1.50]	1.85 ± 0.68 (36.8) 1.00 - 4.00
	3.31 ± 1.10 (33.1) 1.95 - 7.27	3.18 (27.5) [3.20]	6.07 ± 1.81 (29.8) 3.65 - 11.8	5.84 (27.7) [5.93]	13.1 ± 4.38 (33.5) 7.19 - 26.6	12.5 (31.7) [11.4]	18.5 ± 5.83 (31.5) 7.60 - 34.5	17.7 (31.6) [17.9]	24.6 ± 7.55 (30.7) 13.7 - 48.9
10	0.66 ± 0.22 (33.1) 0.39 - 1.45	0.64 (27.5) [0.64]	0.61 ± 0.18 (29.8) 0.37 - 1.18	0.58 (27.7) [0.59]	0.66 ± 0.22 (33.5) 0.36 - 1.33	0.63 (31.7) [0.57]	0.62 ± 0.19 (31.5) 0.25 - 1.15	0.59 (31.6) [0.6]	0.62 ± 0.19 (30.7) 0.34 - 1.22
	5.55 ± 0.99 (17.8) 4.07 - 7.05	5.47 (18.1) [5.53]	5.92 ± 0.94 (15.8) 4.48 - 8.00	5.84 (16.2) [6.00]	5.65 ± 0.98 (17.2) 4.48 - 7.00	5.57 (17.4) [5.50]	5.98 ± 0.77 (12.9) 4.50 - 7.00	5.93 (13.3) [6.00]	6.17 ± 0.90 (14.6) 4.50 - 8.00
	7.60 ± 2.45 (32.2) 3.65 - 13.7	7.24 (33.3) [7.12]	14.2 ± 4.93 (34.7) 7.18 - 26.6	13.4 (34.9) [12.8]	31.0 ± 12.1 (39.0) 9.96 - 63.5	28.7 (42.5) [28.7]	44.9 ± 14.8 (33.1) 19.2 - 83.6	42.5 (35.1) [43.4]	60.1 ± 20.2 (33.7) 20.6 - 101
	1.52 ± 0.49 (32.2) 0.73 - 2.74	1.45 (33.3) [1.42]	1.42 ± 0.49 (34.7) 0.72 - 2.66	1.34 (34.9) [1.28]	1.55 ± 0.61 (39) 0.5 - 3.18	1.44 (42.5) [1.44]	1.5 ± 0.49 (33.1) 0.64 - 2.79	1.42 (35.1) [1.45]	1.5 ± 0.51 (33.7) 0.52 - 2.53
	9.70 ± 2.89 (29.8) 5.91 - 18.9	9.36 (27.0) [9.39]	18.4 ± 6.09 (33.0) 10.4 - 39.3	17.7 (29.5) [16.7]	38.8 ± 12.8 (32.9) 17.2 - 70.9	36.8 (34.3) [36.8]	56.8 ± 18.4 (32.5) 25.7 - 104	54.1 (32.4) [53.5]	73.5 ± 21.9 (29.8) 35.3 - 141
	1.94 ± 0.58 (29.8) 1.18 - 3.78	1.87 (27) [1.88]	1.84 ± 0.61 (33) 1.04 - 3.93	1.77 (29.5) [1.67]	1.94 ± 0.64 (32.9) 0.86 - 3.55	1.84 (34.3) [1.84]	1.89 ± 0.61 (32.5) 0.86 - 3.47	1.8 (32.4) [1.78]	1.84 ± 0.55 (29.8) 0.88 - 3.53
	12.8 ± 4.04 (31.7) 7.98 - 27.3	12.3 (26.7) [12.1]	24.2 ± 7.79 (32.2) 14.7 - 52.5	23.3 (28.0) [23.4]	50.8 ± 17.8 (35.0) 26.0 - 108	48.2 (33.7) [49.4]	75.6 ± 24.6 (32.6) 33.4 - 150	72.2 (31.9) [73.0]	99.4 ± 30.3 (30.4) 50.5 - 200
)	2.56 ± 0.81 (31.7) 1.6 - 5.46	2.46 (26.7) [2.42]	2.42 ± 0.78 (32.2) 1.47 - 5.25	2.33 (28) [2.34]	2.54 ± 0.89 (35) 1.3 - 5.4	2.41 (33.7) [2.47]	2.52 ± 0.82 (32.6) 1.11 - 5	2.41 (31.9) [2.43]	2.49 ± 0.76 (30.4) 1.26 - 5
	24.7 ± 9.55 (38.6) 14.0 - 60.6	23.5 (30.9) [22.2]	47.0 ± 16.6 (35.2) 26.9 - 108	44.9 (30.4) [45.9]	101 ± 40.4 (40.0) 47.5 - 252	95.1 (35.4) [93.0]	150 ± 52.3 (34.8) 64.1 - 328	143 (32.9) [147]	201 ± 65.4 (32.6) 91.9 - 430
ng]	4.95 ± 1.91 (38.6) 2.79 - 12.1	4.70 (30.9) [4.44]	4.70 ± 1.66 (35.2) 2.69 - 10.8	4.49 (30.4) [4.59]	5.05 ± 2.02 (40.0) 2.38 - 12.6	4.76 (35.4) [4.65]	5.00 ± 1.74 (34.8) 2.14 - 10.9	4.75 (32.9) [4.89]	5.02 ± 1.64 (32.6) 2.30 - 10.7
	25.5 ± 9.89 (38.7) 14.5 - 63.1	24.3 (30.7) [24.0]	48.1 ± 17.0 (35.4) 28.1 - 111	45.9 (30.2) [46.4]	102 ± 41.7 (40.6) 48.1 - 260	96.4 (35.5) [94.7]	152 ± 53.8 (35.5) 64.6 - 337	144 (33.3) [149]	204 ± 68.1 (33.4) 92.7 - 445
ng]	5.10 ± 1.98 (38.7) 2.90 - 12.6	4.86 (30.7) [4.81]	4.81 ± 1.70 (35.4) 2.81 - 11.1	4.59 (30.2) [4.64]	5.12 ± 2.08 (40.6) 2.41 - 13.0	4.82 (35.5) [4.74]	5.06 ± 1.79 (35.5) 2.15 - 11.2	4.80 (33.3) [4.96]	5.10 ± 1.70 (33.4) 2.32 - 11.1
ted	3.11 ± 1.59 (51.3) 1.62 - 9.03	2.84 (42.6) [2.70]	2.17 ± 1.08 (49.8) 0.67 - 4.53	1.91 (58.7) [1.86]	1.29 ± 0.97 (75.5) 0.20 - 4.29	0.993 (89.5) [1.08]	1.04 ± 0.61 (58.8) 0.37 - 2.72	0.897 (59.2) [0.834]	1.44 ± 1.69 (117) 0.20 - 8.34
	6.70 ± 1.09 (16.3) 5.04 - 9.14	6.62 (15.9) [6.83]	6.78 ± 1.13 (16.6) 5.23 - 9.97	6.70 (15.9) [6.30]	6.77 ± 1.18 (17.4) 4.78 - 9.15	6.68 (17.5) [6.41]	6.80 ± 0.83 (12.2) 5.17 - 8.33	6.75 (12.5) [6.83]	7.05 ± 1.03 (14.6) 4.90 - 9.41
	2.92 ± 0.67 (22.9) 2.04 - 4.49	2.86 (21.6) [2.63]	3.01 ± 0.73 (24.4) 2.00 - 4.54	2.93 (24.0) [2.83]	3.18 ± 0.71 (22.3) 2.16 - 5.03	3.11 (22.2) [3.19]	3.07 ± 0.50 (16.3) 2.07 - 4.13	3.03 (16.5) [3.00]	3.29 ± 0.90 (27.3) 2.22 - 6.59

Figure 11 Selected Dose Normalized Pharmacokinetic Metrics for Individual Subjects by Dosage – Study 2102.



3.4.2 Multiple Dose Pharmacokinetics

3.4.2.1 Population Pharmacokinetics

Population pharmacokinetic sampling was performed as part of Study CRIT124E2302: a 5- week, multicenter, double-blind, randomized, placebo-controlled, paralle*l*-group, fixed-dose study of the efficacy and safety of Focalin™ XR (dexmethylphenidate hydrochloride extended-release capsules) administered once daily in adults with Attention- Deficit/Hyperactivity Disorder. Due to the complex absorption characteristics of Focalin XR and the collection of only a single sample from each subject reliable population metrics can not be obtained. In spite of this the results tend to reflect what is known about Focalin XR from other studies. Thus the highlights of the sponsor's conclusions mostly in the sponsor's own words with some commentary by the reviewer and with minor editing of table and figures follow. *(Sponsor's wording is italicized.)*

"A single pharmacokinetic sample was collected (at visit 7) from each subject after daily dosing with Focalin XR for several weeks, and analyzed for the concentration of dexmethylphenidate. Because repeated samples are necessary for each subject in order to separate the variability in pharmacokinetic parameters between subjects from within-subject sources of variability, traditional population pharmacokinetic modeling could not be done with this single-sample design. Thus the objectives of population pharmacokinetics in this study were limited and restricted to confirm dose proportionality and to determine if the average concentration around the anticipated time of maximal concentration (peak) is greater than the average concentration around the anticipated time of minimal concentration (trough). This was accomplished by the creation of several concentration summaries that capture important features of the concentration-time profile, which were compared across and within dose groups.

The specific objectives of the population pharmacokinetic analysis were:

- *To compare dose-normalized concentrations of dexmethylphenidate after administration of Focalin XR across dose groups (20, 30, and 40 mg/day) to examine dose proportionality*

- *To compare dexmethylphenidate concentrations after administration of Focalin XR across time windows within a dose group to determine if the peak (i.e., the average concentration around the anticipated time of maximal concentration) is greater than the trough (i.e., the average concentration around the anticipated time of minimal concentration)*

Table 23 Time windows for subsetting concentration data – Study 2302

Time Window	***Description***
C(0.5-2.5)	*Concentration around expected tmax (1.5 h) for IR (immediate release) dose*
C(3-5)	*Concentration around expected tmin (4h) between IR and DR (delayed release) doses*
C(5.5-7.5)	*Concentration around expected tmax (6.5 h) for DR dose*
C(8-10)	*Concentration at end of sampling time*
*C(0-4)**	*Concentration from time zero to 4 hours (IR dose)*
*C(4-8)**	*Concentration from time 4 to 8 hours (DR dose)*
C(0-8)	*Concentration from time zero to 8 hours, where 8 hours is the minimum desired duration of effect*
C(0-10)	*Concentration from time zero to 10 hours, where 10 hours is the maximum sampling time*

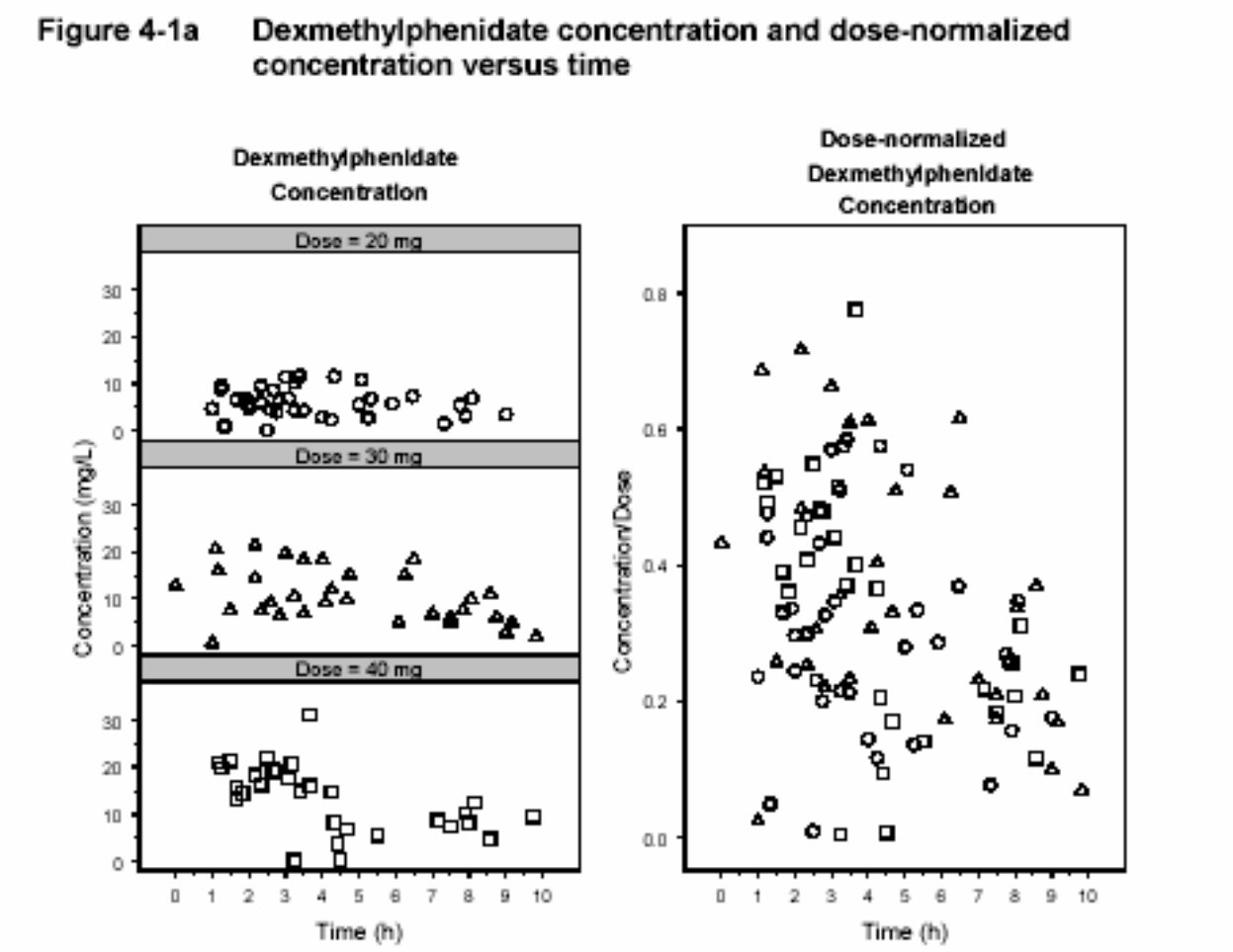
**C(0-4) and C(4-8) both include samples measured at exactly 4 hours, so there may be overlap between these two time windows*

Summarization of Data

From the 169 patients on active treatment (20 mg: n = 58, 30 mg: n = 55, 40 mg: n = 56), 99 (59%) provided samples that were available for evaluation. The missing and excluded data are summarized in Table 4-1 in the study report.

From Figure 12 of *d*-MPH concentrations plotted vs. time post-dose by daily dose, and after dose normalization we can roughly make out the expected double peak and concentrations also appear to increase roughly proportionally to dose.

Figure 12 Population*d*-MPH Concentrations vs. Time by Dose, and for All Samples after Dose Normalization – Study 2302



Assessment of Dose Proportionality

In Table 24, the only comparison that showed a significant difference in the mean dose-normalized concentration across dose groups was the time window C(4-8).

Table 24 Summary Statistics for Dexmethylphenidate Concentration and Dose-Normalized Concentration[a] – Study 2302

Metric	*Concentration (ng/ml)*			*Dose Normalized Concentration (ng/ml x mg^{-1})*			*p†*
Dose	*20 mg*	*30 mg*	*40 mg*	*20 mg*	*30 mg*	*40 mg*	
$C_{(0.5-2.5)}$	(b) (4)						*0.11*
	4.02 (131) (0.16, 9.52)	*8.86 (123.8) (0.702, 21.5)*	*17.18 (61.8) (13.3, 21.9)*	*0.2 (131) (0.008, 0.476)*	*0.3 (123.8) (0.023, 0.717)*	*0.43 (61.8) (0.333, 0.548)*	
$C_{(3-5)}$	(b) (4)						*0.29*
	6.48 (72.7) (2.31, 11.7)	*12.69 (64.8) (6.99, 19.9)*	*5.85 (311.6) (0.129, 31)*	*0.32 (72.7) (0.116, 0.585)*	*0.42 (64.8) (0.233, 0.663)*	*0.15 (311.6) (0.003, 0.775)*	
$C_{(5.5-7.5)}$	(b) (4)						*0.49*
	4.01 (86.6) (1.53, 7.37)	*8.31 (70.9) (5.16, 18.5)*	*7.09 (62.2) (5.59, 8.68)*	*0.2 (86.6) (0.077, 0.369)*	*0.28 (70.9) (0.172, 0.617)*	*0.18 (62.2) (0.14, 0.217)*	
$C_{(8-10)}$	(b) (4)						*0.85*
	4.93 (68.2) (3.5, 6.94)	*5.29 (75.7) (2.07, 11.1)*	*8.21 (66.2) (4.63, 12.4)*	*0.25 (68.2) (0.175, 0.347)*	*0.18 (75.7) (0.069, 0.37)*	*0.21 (66.2) (0.116, 0.31)*	
$C_{(0-4)}$	(b) (4)						*0.09*
	5.17 (94.3) (0.16, 11.7)	*10.35 (87.5) (0.702, 21.5)*	*13.69 (122) (0.129, 31)*	*0.26 (94.3) (0.008, 0.585)*	*0.35 (87.5) (0.023, 0.717)*	*0.34 (122) (0.003, 0.775)*	
$C_{(4-8)}$	(b) (4)						*0.03†*
	4.6 (74) (1.53, 11.5)	*9.81 (67.7) (5.16, 18.5)*	*5.47 (113.8) (0.266, 14.6)*	*0.23 (74) (0.077, 0.575)*	*0.33 (67.7) (0.172, 0.617)*	*0.14 (113.8) (0.007, 0.365)*	
$C_{(0-8)}$	(b) (4)						*0.26*
	5.05 (86.7) (0.16, 11.7)	*9.88 (77.6) (0.702, 21.5)*	*9.86 (128.4) (0.129, 31)*	*0.25 (86.7) (0.008, 0.585)*	*0.33 (77.6) (0.023, 0.717)*	*0.25 (128.4) (0.003, 0.775)*	
$C_{(0-10)}$	(b) (4)						*0.58*
	5.04 (85.2) (0.16, 11.7)	*8.79 (79.1) (0.702, 21.5)*	*9.69 (120.3) (0.129, 31)*	*0.25 (85.2) (0.008, 0.585)*	*0.29 (79.1) (0.023, 0.717)*	*0.24 (120.3) (0.003, 0.775)*	

a Values include number of observations geometric mean (gCV%) (minimum, maximum)
†p>0.05 indicates that null hypothesis (20 = 30 = 40) is not rejected; i.e. the data are consistent with dose proportionality

Thus, the multiple comparison test described in Section 3.2 was completed. The results are shown in Table 25, indicating that the difference is between the 30 and 40 mg dose groups. This difference can be observed in the boxplots of dose-normalized concentrations for the C(4-8) time window, (see Figure 13).

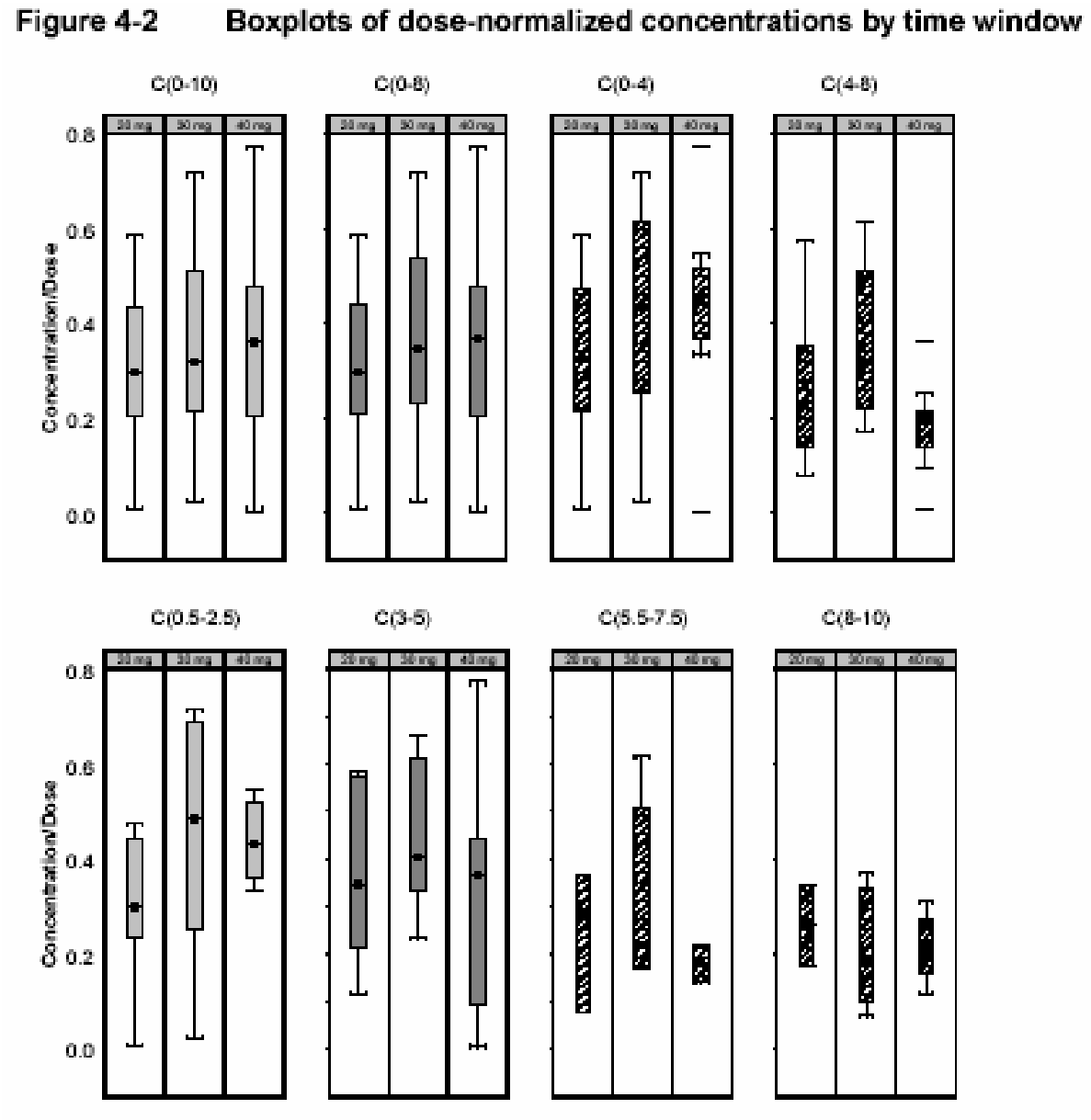
Table 25 *Multiple Comparison Test for Concentration/Dose Comparison: C(4-8)* – Study 2302

Comparison	*Estimate of Difference*	*Standard Error*	*Lower Bound 95% CI*	*Upper Bound 95% CI*
20 mg and 30 mg	*-0.0881*	*0.06*	*-0.24*	*0.0638*
20 mg and 40 mg	*0.0891*	*0.0629*	*-0.0702*	*0.248*
30 mg and 40 mg	*0.177*	*0.0629*	*0.0179*	*0.336**

** 95% CI includes 0, indicating a significant difference*

In addition, Figure 13 showing boxplots of dose normalized concentrations by dose from various sampling windows are also consistent with dose linearity.

Figure 13 Boxplots of Dose Normalized Concentrations by Focalin XR Dose from Various Sampling Windows – Study 2302

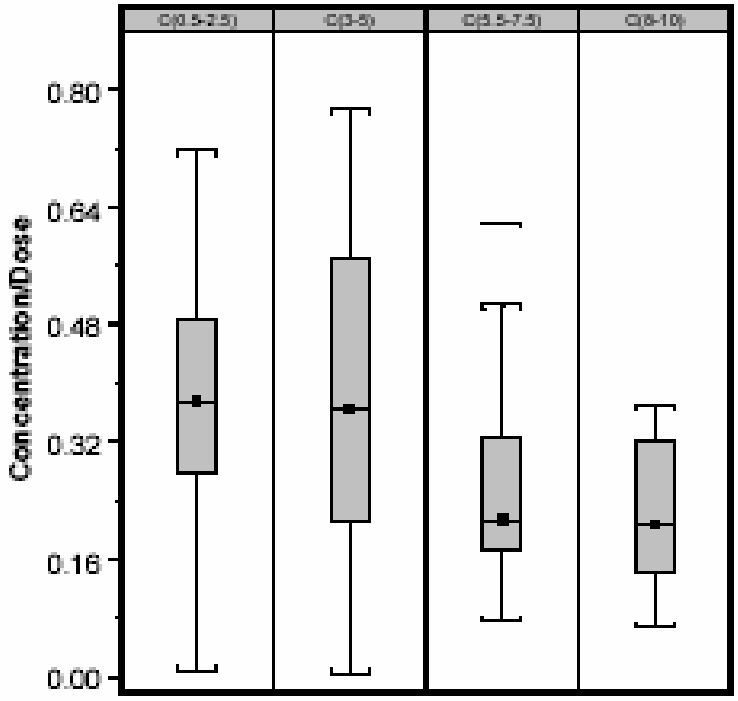


Peak-trough comparisons

The concentration in the time windows (0.5-2.5) and (3-5) were compared to determine if the expected peak concentration was greater than the expected trough concentration resulting from the IR component. Similarly, $C_{(5.5\text{-}7.5)}$ and $C_{(8\text{-}10)}$ (DR) were evaluated. Since the evidence against dose proportionality was not strong, the assumption of proportionality was retained, so the dose-normalized concentrations for the three doses were pooled for the analysis. The p-values for the comparisons were 0.93 for the IR peak-trough comparison and 0.42 for the DR peak-trough comparison, indicating no significant difference between the peak and trough dose-normalized concentrations." (See Figure 14)

Figure 14 Boxplots of Dose Normalized Concentrations by Focalin XR Dose from Various Sampling Windows – Study 2302

Figure 4-3 Boxplots comparing peak and trough dose-normalized concentrations



In general, the population analyses of the sparse sampling data indicate dose proportionality although these aren't rigorous tests. The differences seen with dose normalized data are highly variable and are not internally consistent. Thus the observed differences may be spurious.

3.4.3 Intrinsic Factors

3.4.3.1 Gender

Examination of pharmacokinetic metric summary statistics by gender from studies 2101 and 2102 show slightly higher concentrations for women than men. In addition when dose and weight normalized these differences are even greater. The differences are statistically significant for Cmax1 but not for Cminip or Cmax2. For Focalin IR and Ritalin LA in study 2101 there was no difference by gender for Cmax1. The reasons for the difference in Cmax1 are unclear, and overall they are not great enough to result in any labeled changes to dosing, especially as Cmax2 is typically slightly higher than Cmax1, (see Table 26 and Table 27.)

Table 26 *d*-MPH Pharmacokinetic Metrics by Treatment and Gender- Study 2101

Treatment	Gender	N	Tlag (Hours)	Tmax1 (Hours)	Cmax1 (ng/ml)	$T_{min_{ip}}$ (Hours)	$C_{min_{ip}}$ (ng/ml)	Tmax2 (Hours)	Cmax2 (ng/ml)	Tmax (Hours)	Cmax (ng/ml)
A **Focalin XR 20 mg Capsule**	**F**	12	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	1.5 ± 0.8 (53.4) 1 - 4 [1.5]	14.45 ± 4.6 (32.1) 12.2 - 28.5 [14.45]	4.25 ± 0.7 (16.7) 3 - 5.5 [4.25]	7.85 ± 1.6 (20.4) 5.5 - 10.5 [7.85]	6 ± 0.7 (12.3) 4.5 - 7 [6]	14.65 ± 4.3 (29.6) 12.2 - 27.8 [14.65]	1.5 ± 2.2 (146.6) 1 - 6.5 [1.5]	15.3 ± 4.7 (30.8) 12.5 - 29.8 [15.3]
	M	12	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	1.5 ± 0.3 (17.2) 1.5 - 2 [1.5]	10.7 ± 2.2 (20.7) 8.3 - 16.4 [10.7]	4 ± 0.9 (23.3) 2 - 5.5 [4]	7 ± 1.8 (26.0) 3.9 - 10 [7]	6.75 ± 0.6 (9.2) 5 - 7 [6.75]	13.5 ± 3.6 (26.8) 8.8 - 19.9 [13.5]	6.5 ± 1.6 (24.1) 1.5 - 7 [6.5]	13.5 ± 3.5 (26.1) 9.4 - 19.9 [13.5]
	p-value		—	—	0.008	—	0.34	—	0.33	—	—
B **Focalin IR 20 mg Tablet 4 hours Apart**	**F**	13	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	1.5 ± 0.3 (19.2) 1 - 2 [1.5]	12.7 ± 4.8 (37.7) 8.7 - 25.2 [12.7]	4.5 ± 0.3 (5.6) 4 - 4.5 [4.5]	5.5 ± 2.3 (42.2) 4.3 - 12.7 [5.5]	5.5 ± 0.4 (6.9) 5 - 6.5 [5.5]	18.2 ± 6.5 (35.5) 12.1 - 34.5 [18.2]	5.5 ± 0.4 (6.9) 5 - 6.5 [5.5]	18.2 ± 6.5 (35.5) 12.1 - 34.5 [18.2]
	M	12	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	2 ± 0.3 (12.9) 1.5 - 2 [2]	10.75 ± 2.0 (18.2) 8.8 - 15.8 [10.75]	4.5 ± 0.3 (5.7) 4 - 4.5 [4.5]	6.05 ± 1.2 (20.5) 4.3 - 8.2 [6.05]	5.5 ± 0.3 (4.7) 5.5 - 6 [5.5]	15.35 ± 3.3 (21.8) 12.1 - 22.4 [15.35]	5.5 ± 0.3 (4.7) 5.5 - 6 [5.5]	15.35 ± 3.3 (21.8) 12.1 - 22.4 [15.35]
	p-value		—	—	0.083	—	0.89	—	0.15	—	—
C **Ritalin LA 40 mg Capsule**	**F**	12	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.5]	1.5 ± 0.2 (16.4) 1.5 - 2 [1.5]	13.7 ± 3.1 (22.3) 10.7 - 22.6 [13.7]	4.25 ± 1.1 (26.8) 2 - 5.5 [4.25]	7.15 ± 2.6 (35.9) 4 - 12 [7.15]	6.5 ± 1.1 (16.9) 4 - 7 [6.5]	17.5 ± 4.8 (27.6) 12.3 - 29.6 [17.5]	6.5 ± 1.1 (16.9) 4 - 7 [6.5]	16.25 ± 5.0 (30.7) 12.3 - 29.6 [16.25]
	M	12	0.5 ± 0.1 (28.9) 0.5 - 1 [0.5]	2 ± 0.9 (42.6) 1 - 4.5 [2]	11.4 ± 2.7 (24.0) 8.9 - 18.5 [11.4]	5.25 ± 1.2 (22.3) 2 - 5.5 [5.25]	6.45 ± 2.7 (41.5) 3.2 - 11.2 [6.45]	6.5 ± 1.1 (17.2) 4 - 8 [6.5]	14.35 ± 3.7 (25.9) 8.1 - 20.9 [14.35]	6.25 ± 1.5 (24.7) 2 - 7 [6.25]	14.35 ± 3.6 (25.0) 8.9 - 20.9 [14.35]
	p-value		—	—	0.10	—	0.88	—	0.11	—	—

Table 27 Summary Statistics of Selected *d*-Methylphenidate Pharmacokinetic Metrics by Gender and Dose - Study 2102

Dose (mg)	Sex	N	Tmax1 (hrs)	Cmax1 (ng/ml)	Tminip (hrs)	Cminip (ng/ml)	Tmax2 (hrs)	Cmax2 (ng/ml)	Tmax (hrs)	Cmax (hrs)	DN Cmax1	DN Cmax2	DN Cminip
5	F	9	1.6 ± 0.2 (13.7) 1.5 - 2.0 [1.5]	3.3 ± 0.8 (25.4) 2.3 - 4.9 [3.4]	3.7 ± 1.1 (31.2) 2.0 - 5.5 [3.0]	2.1 ± 0.6 (27.8) 1.2 - 2.8 [2.4]	4.8 ± 1.7 (34.8) 1.5 - 7.0 [5.0]	3.8 ± 1.5 (37.7) 2.5 - 7.3 [3.5]	4.8 ± 1.7 (34.8) 1.5 - 7.0 [5.0]	3.9 ± 1.4 (37.3) 2.5 - 7.3 [3.5]	0.0102 ± 0.0027 (26.3) 0.0061 - 0.0131 [0.0106]	0.0118 ± 0.0039 (33.4) 0.0066 - 0.0194 [0.0124]	0.0066 ± 0.0017 (26.2) 0.0035 - 0.0086 0.0073]
	M	11	1.6 ± 0.4 (23.4) 1.0 - 2.0 [1.5]	2.0 ± 0.4 (20.2) 1.3 - 2.6 [2.2]	3.8 ± 1.3 (33.3) 2.0 - 6.0 [3.0]	1.5 ± 0.5 (31.8) 0.9 - 2.0 [1.5]	5.7 ± 1.1 (18.9) 4.0 - 7.0 [6.0]	2.8 ± 0.4 (15.7) 2.0 - 3.5 [2.9]	5.6 ± 1.1 (19.4) 4.0 - 7.0 [6.0]	3.0 ± 0.7 (23.8) 2.0 - 4.9 [3.0]	0.0055 ± 0.0014 (26.3) 0.003 - 0.008 [0.005]	0.0075 ± 0.0015 (19.4) 0.005 - 0.011 [0.007]	0.0041 ± 0.0015 (36.7) 0.002 - 0.006 0.004]
	p-value		—	0.002	—	0.02	—	0.075	—	—	0.0005	0.012	0.003
10	F	10	1.4 ± 0.2 (15.1) 1.0 - 1.5 [1.5]	6.1 ± 1.7 (27.8) 4.2 - 9.2 [5.5]	3.8 ± 0.7 (18.1) 3.0 - 4.5 [4.0]	3.6 ± 1.6 (44.8) 1.7 - 7.6 [3.4]	6.0 ± 1.1 (17.9) 4.5 - 8.0 [6.0]	6.5 ± 2.3 (35.1) 4.3 - 11.8 [5.8]	3.9 ± 2.2 (55.3) 1.5 - 6.5 [4.5]	6.8 ± 2.2 (32.3) 4.9 - 11.8 [6.0]	0.0095 ± 0.0026 (26.8) 0.0062 - 0.0140 [0.0089]	0.0102 ± 0.0032 (31.3) 0.0058 - 0.0158 [0.0096]	0.0055 ± 0.0020 (36.8) 0.0032 - 0.0101 0.0052]
	M	13	1.9 ± 1.0 (50.7) 1 - 4 [1.5]	4.5 ± 1.7 (36.7) 2.8 - 8.7 [4.22]	3.9 ± 1.0 (26.4) 2 - 5.5 [4]	3.1 ± 0.9 (29.4) 1.16 - 4.5 [2.91]	5.5 ± 1.6 (30.0) 1 - 7 [6]	5.9 ± 1.4 (23.9) 3.6 - 8.6 [6.07]	5.4 ± 1.7 (31.3) 1 - 7 [6]	5.8 ± 1.4 (23.4) 3.7 - 8.7 [5.93]	0.0060 ± 0.0025 (41.3) 0.0033 - 0.0112 [0.0055]	0.0078 ± 0.0023 (29.7) 0.0045 - 0.0126 [0.0078]	0.0041 ± 0.0013 (31.9) 0.0014 - 0.0062 0.0040]
	p-value		—	0.04	—	0.39	—	0.44	—	—	0.004	0.067	0.076
20	F	10	1.4 ± 0.3 (22.6) 1 - 2 [1.5]	13.3 ± 4.8 (36.0) 7.5 - 23.7 [12]	4.0 ± 0.8 (19.3) 3 - 5 [4]	7.5 ± 2.5 (32.7) 4.2 - 10.7 [7.22]	5.7 ± 1.2 (20.4) 4 - 7 [5.75]	14.2 ± 5.6 (39.5) 7.5 - 26.6 [11.95]	5.1 ± 1.8 (35.3) 1 - 7 [5.375]	14.3 ± 5.6 (38.9) 7.5 - 26.6 [12.3]	0.0103 ± 0.0036 (35.3) 0.0050 - 0.0172 [0.0095]	0.0110 ± 0.0041 (37.0) 0.0051 - 0.0178 [0.0098]	0.0058 ± 0.0019 (32.7) 0.0029 - 0.0088 0.0059]
	M	13	2.1 ± 1.3 (63.6) 0.5 - 6 [2]	9.1 ± 2.8 (30.6) 3.8 - 15 [8.86]	3.8 ± 1.6 (42.5) 1.5 - 6.5 [3]	7.2 ± 2.4 (33.1) 2.1 - 10.6 [7.4]	5.6 ± 1.2 (21.7) 4 - 7 [5.5]	12.3 ± 3.2 (26.3) 7.2 - 17.8 [11.4]	5.2 ± 1.8 (34.5) 0.5 - 7 [5.5]	12.4 ± 3.3 (26.3) 7.2 - 17.8 [11.4]	0.0061 ± 0.0023 (38.1) 0.0023 - 0.0123 [0.0062]	0.0081 ± 0.0024 (29.9) 0.0044 - 0.0124 [0.0073]	0.0047 ± 0.0016 (32.9) 0.0013 - 0.0072 0.0049]
	p-value		—	0.03	—	0.77	—	0.35	—	—	0.01	0.09	0.11
30	F	11	1.3 ± 0.4 (26.7) 0.75 - 2 [1.5]	19.7 ± 6.8 (34.6) 14 - 37.3 [17.8]	4.4 ± 0.7 (16.3) 3 - 5.5 [4]	9.7 ± 2.8 (28.5) 5.84 - 15 [9.34]	6.1 ± 0.9 (14.1) 4.5 - 7 [6.5]	18.5 ± 6.0 (32.3) 13.6 - 34.5 [16.4]	2.6 ± 2.1 (80.6) 1 - 6.5 [1.5]	20.4 ± 6.4 (31.4) 14.6 - 37.3 [18.3]	0.010 ± 0.003 (32.6) 0.0065 - 0.0166 [0.0091]	0.010 ± 0.003 (28.5) 0.0070 - 0.0154 [0.0089]	0.005 ± 0.001 (28.4) 0.0031 - 0.0078 0.0054]
	M	13	1.7 ± 0.5 (30.8) 1 - 3 [1.5]	14.1 ± 4.5 (31.9) 6.4 - 21.6 [14.7]	4.1 ± 0.8 (19.9) 3 - 5.5 [4]	10.2 ± 3.5 (34.6) 5.3 - 16.4 [10.2]	5.9 ± 0.7 (11.9) 5 - 7 [6]	18.5 ± 6.0 (32.2) 7.6 - 32.3 [18.2]	5.6 ± 1.3 (23.0) 2 - 7 [6]	18.5 ± 5.9 (31.8) 7.6 - 32.3 [18.2]	0.0063 ± 0.0023 (36.0) 0.003 - 0.010 [0.007]	0.0082 ± 0.0028 (34.7) 0.003 - 0.014 [0.008]	0.0045 ± 0.0016 (35.2) 0.002 - 0.007 0.005]
	p-value		—	0.03	—	0.72	—	1.00	—	—	0.003	0.19	0.30
40	F	11	1.5 ± 0.2 (14.9) 1 - 2 [1.5]	25.9 ± 5.9 (22.9) 18.8 - 34.7 [25.3]	4.4 ± 0.8 (17.8) 3 - 6 [4]	13.3 ± 4.7 (35.0) 7.1 - 21.3 [12.4]	6.2 ± 0.9 (15.0) 5 - 8 [6.5]	26.1 ± 9.0 (34.6) 15.1 - 48.9 [23.3]	4.4 ± 2.5 (56.0) 1 - 7 [5.5]	28.9 ± 8.2 (28.2) 21.2 - 48.9 [28.6]	0.0103 ± 0.0022 (21.1) 0.0070 - 0.0130 [0.0112]	0.0103 ± 0.0033 (31.9) 0.0058 - 0.0163 [0.0099]	0.0052 ± 0.0017 (32.1) 0.0032 - 0.0084 0.0049]
	M	12	2.0 ± 0.6 (29.7) 1 - 3 [2]	17.4 ± 5.7 (32.7) 7.44 - 25.5 [17.1]	4.2 ± 0.9 (21.8) 2 - 5.25 [4.5]	12.2 ± 4.6 (38.1) 4 - 20.8 [11.4]	6.2 ± 1.0 (16.6) 4 - 7 [6.625]	23.7 ± 6.7 (28.4) 13.7 - 35.6 [22.2]	6.2 ± 1.0 (16.6) 4 - 7 [6.625]	23.7 ± 6.7 (28.4) 13.7 - 35.6 [22.2]	0.0058 ± 0.0023 (39.6) 0.0023 - 0.0105 [0.0058]	0.0079 ± 0.0027 (34.0) 0.0041 - 0.0127 [0.0070]	0.0040 ± 0.0014 (36.1) 0.0012 - 0.0066 0.0039]
	p-value		—	0.002	—	0.56	—	0.48	—	—	0.0001	0.07	0.07

3.4.3.2 Race Ethnicity

Race and ethnicity was not formally examined, however Table 28 shows pharmacokinetic metrics presented by race, gender, treatment, and study.

In study 2101, subjects identified as 'Other' had higher concentrations than Caucasians when data from females is compared, and mixed results when data from males is examined.

In study 2102 there were too few non-Caucasians for comparison, and in study 2103 Blacks tended to have higher concentrations than Caucasians.

However, variability is so large that no conclusions can be reached.

1	20	C	F	5	29.4 ± 10.0 (33.9) 18 - 43 [25]	166.4 ± 3.2 (1.9) 163 - 171 [166]	65.1 ± 2.8 (4.3) 61.3 - 68.6 [65.8]	1.8 ± 1.3 (69.7) 1 - 4 [1.5]	13.2 ± 1.3 (9.7) 12.2 - 15.3 [12.8]	4.3 ± 1.0 (22.7) 3 - 5.5 [4]	7.9 ± 1.9 (24.0) 5.5 - 10 [8.3]	5.6 ± 0.7 (13.2) 4.5 - 6.5 [5.5]	13.4 ± 1.6 (12.0) 12.2 - 15.7 [12.5]	0.0102 ± 0.0012 (11.3) 0.0089 - 0.0120 [0.0100]	0.0061 ± 0.0015 (24.1) 0.0045 - 0.0079 [0.0063]	0.0103 ± 0.00 (13.4) 0.0089 - 0.01 [0.0102]
			M	2	24.5 ± 2.1 (8.7) 23 - 26 [24.5]	181.5 ± 2.1 (1.2) 180 - 183 [181.5]	69.0 ± 1.3 (1.8) 68.1 - 69.9 [69]	1.8 ± 0.4 (20.2) 1.5 - 2 [1.75]	9.8 ± 0.5 (5.1) 9.4 - 10.1 [9.75]	4.3 ± 0.4 (8.3) 4 - 4.5 [4.25]	7.3 ± 1.3 (17.4) 6.4 - 8.2 [7.3]	6.3 ± 0.4 (5.7) 6 - 6.5 [6.25]	15.5 ± 3.3 (21.5) 13.1 - 17.8 [15.45]	0.0071 ± 0.0005 (6.9) 0.0067 - 0.0074 [0.0071]	0.0053 ± 0.0008 (15.6) 0.0047 - 0.0059 [0.0053]	0.0112 ± 0.00 (23.3) 0.0094 - 0.01 [0.0112]
		B	M		27	174	74.5	1.5	11.6	4	8.7	7	11.7	0.0078	0.00588	0.0078
		A	F	1	33	155	61.7	2	12.8	4.5	8.8	6.5	14.9	0.0104	0.0071	0.0121
		Other	F	6	32.7 ± 5.9 (18.0) 23 - 41 [33]	156.0 ± 3.9 (2.5) 151 - 161 [156.5]	62.9 ± 3.3 (5.3) 59 - 68.1 [61.7]	1.4 ± 0.2 (14.4) 1 - 1.5 [1.5]	18.3 ± 5.5 (30.1) 12.6 - 28.5 [16.45]	4.4 ± 0.6 (13.2) 4 - 5.5 [4.25]	7.9 ± 1.6 (20.6) 6.5 - 10.5 [7.2]	6.3 ± 0.7 (11.0) 5.5 - 7 [6.25]	17.8 ± 5.4 (30.3) 13.6 - 27.8 [15.4]	0.0146 ± 0.0045 (30.9) 0.0102 - 0.0231 [0.0135]	0.0063 ± 0.0013 (21.3) 0.0048 - 0.0085 [0.0060]	0.0141 ± 0.00 (31.3) 0.0100 - 0.02 [0.0127]
			M	9	28.4 ± 5.1 (17.9) 23 - 36 [27]	165.0 ± 6.5 (3.9) 156 - 175 [166]	68.5 ± 5.1 (7.5) 57.2 - 74.5 [69]	1.7 ± 0.3 (15.3) 1.5 - 2 [1.5]	11.5 ± 2.5 (21.5) 8.3 - 16.4 [10.9]	4.1 ± 1.1 (26.4) 2 - 5.5 [4]	7.1 ± 2.0 (28.4) 3.9 - 10 [6.6]	6.6 ± 0.7 (10.4) 5 - 7 [7]	14.1 ± 3.9 (28.0) 8.8 - 19.9 [13.9]	0.0084 ± 0.0020 (23.7) 0.0060 - 0.0124 [0.0080]	0.0051 ± 0.0013 (24.8) 0.0034 - 0.0071 [0.0049]	0.0104 ± 0.00 (30.8) 0.0059 - 0.01 [0.0098]
2	5	C	M	9	31.2 ± 8.50 (27.2) 23 - 45 [30]	179.8 ± 4.79 (2.7) 173 - 188 [178]	76.0 ± 8.83 (11.6) 60.8 - 88.5 [74.5]	1.6 ± 0.42 (25.4) 1 - 2 [1.75]	2.1 ± 0.41 (19.5) 1.28 - 2.56 [2.21]	3.4 ± 1.04 (30.3) 2 - 5.5 [3]	1.7 ± 0.42 (25.3) 0.885 - 2.04 [1.9]	5.6 ± 1.10 (19.8) 4 - 7 [6]	2.9 ± 0.48 (16.5) 1.95 - 3.47 [2.95]	0.0057 ± 0.0015 (26.1) 0.0031 - 0.0082 [0.0053]	0.0077 ± 0.0016 (20.4) 0.0047 - 0.0106 [0.0074]	0.0045 ± 0.00 (30.8) 0.0021 - 0.00 [0.0043]
		Other		2	22.5 ± 2.12 (9.4) 21 - 24 [22.5]	183.0 ± 7.07 (3.9) 178 - 188 [183]	76.8 ± 1.91 (2.5) 75.4 - 78.1 [76.75]	1.5 ± 0.00 (0.0) 1.5 - 1.5 [1.5]	1.7 ± 0.23 (13.2) 1.55 - 1.87 [1.71]	5.5 ± 0.71 (12.9) 5 - 6 [5.5]	0.9 ± 0.01 (0.6) 0.897 - 0.905 [0.901]	6.5 ± 0.71 (10.9) 6 - 7 [6.5]	2.6 ± 0.09 (3.6) 2.52 - 2.65 [2.585]	0.0045 ± 0.0007 (15.7) 0.0040 - 0.0050 [0.0045]	0.0067 ± 0.0001 (1.1) 0.0067 - 0.0068 [0.0067]	0.0023 ± 0.00 (1.9) 0.0023 - 0.00 [0.0023]
	10	C		10	30.7 ± 8.18 (26.6) 23 - 45 [28]	180.1 ± 4.63 (2.6) 173 - 188 [179]	76.1 ± 8.34 (11.0) 60.8 - 88.5 [75.85]	1.9 ± 0.82 (44.2) 1 - 4 [1.5]	4.2 ± 1.27 (30.5) 2.76 - 6.82 [3.84]	4.0 ± 0.96 (24.2) 3 - 5.5 [4]	3.0 ± 0.93 (30.8) 1.16 - 4.49 [2.87]	5.9 ± 1.03 (17.6) 4 - 7 [6]	5.8 ± 1.09 (18.9) 3.69 - 7.65 [5.965]	0.0057 ± 0.0023 (40.7) 0.0033 - 0.0112 [0.0053]	0.0078 ± 0.0023 (29.0) 0.0045 - 0.0126 [0.0078]	0.0040 ± 0.00 (34.5) 0.0014 - 0.00 [0.0040]
					21.3 ± 2.52	179.7 ± 7.64	77.3 ± 1.69	2.2 ± 1.61	5.7 ± 2.58	3.7 ± 1.44	3.4 ± 0.98	4.2 ± 2.84	6.3 ± 2.51	0.0073 ± 0.0032	0.0081 ± 0.0031	0.0044 ± 0.00

	20			[28]	[179]	[75.85]	[2]	[9.38]	[4.5]	[0.905]	[0.25]	[12.25]	[0.0062]	[0.0077]	[0.0046]
		Other		3	21.3 ± 2.52 (11.8) 19 - 24 [21]	179.7 ± 7.64 (4.3) 173 - 188 [178]	77.3 ± 1.69 (2.2) 75.4 - 78.5 [78.1]	1.2 ± 0.29 (24.7) 1 - 1.5 [1]	9.0 ± 2.13 (23.7) 7.1 - 11.3 [8.55]	1.8 ± 0.29 (15.7) 1.5 - 2 [2]	8.3 ± 1.98 (23.8) 6.97 - 10.6 [7.4]	4.5 ± 0.87 (19.2) 4 - 5.5 [4]	13.3 ± 3.91 (29.4) 10.7 - 17.8 [11.4]	0.0058 ± 0.0013 (22.9) 0.0045 - 0.0072 [0.0057]	0.0086 ± 0.0024 (27.9) 0.0071 - 0.0113 [0.0073]	0.0054 ± 0.00 (22.6) 0.0045 - 0.00 [0.0049]
	30	C		10	30.7 ± 8.18 (26.6) 23 - 45 [28]	180.1 ± 4.63 (2.6) 173 - 188 [179]	76.1 ± 8.34 (11.0) 60.8 - 88.5 [75.85]	1.8 ± 0.54 (29.9) 1 - 3 [1.75]	13.5 ± 4.13 (30.5) 6.42 - 19 [14.5]	4.2 ± 0.82 (19.7) 3 - 5.5 [4]	9.5 ± 2.82 (29.6) 5.27 - 13.3 [9.935]	6.0 ± 0.65 (10.8) 5 - 7 [6]	17.2 ± 4.39 (25.5) 7.6 - 22.7 [18.15]	0.0061 ± 0.0023 (37.6) 0.0026 - 0.0099 [0.0062]	0.0077 ± 0.0025 (32.3) 0.0031 - 0.0124 [0.0076]	0.0042 ± 0.00 (32.6) 0.0021 - 0.00 [0.0043]
		Other		3	21.3 ± 2.52 (11.8) 19 - 24 [21]	179.7 ± 7.64 (4.3) 173 - 188 [178]	77.3 ± 1.69 (2.2) 75.4 - 78.5 [78.1]	1.3 ± 0.29 (21.7) 1 - 1.5 [1.5]	16.1 ± 6.09 (37.9) 9.55 - 21.6 [17.1]	4.0 ± 1.00 (25.0) 3 - 5 [4]	12.4 ± 5.40 (43.6) 6.24 - 16.4 [14.5]	5.5 ± 0.87 (15.7) 5 - 6.5 [5]	22.7 ± 9.60 (42.4) 13.1 - 32.3 [22.6]	0.0069 ± 0.0025 (36.2) 0.0042 - 0.0092 [0.0073]	0.0097 ± 0.0040 (40.8) 0.0058 - 0.0137 [0.0096]	0.0053 ± 0.00 (42.2) 0.0028 - 0.00 [0.0062]
	40	C		9	31.2 ± 8.50 (27.2) 23 - 45 [30]	179.8 ± 4.79 (2.7) 173 - 188 [178]	76.0 ± 8.83 (11.6) 60.8 - 88.5 [74.5]	1.9 ± 0.53 (27.1) 1 - 3 [2]	17.3 ± 5.84 (33.7) 7.44 - 25.5 [16.3]	4.3 ± 0.66 (15.3) 3 - 5.25 [4.5]	11.8 ± 4.15 (35.3) 4 - 19 [10.9]	6.3 ± 0.85 (13.6) 4.5 - 7 [6.5]	22.9 ± 6.36 (27.7) 13.7 - 31.7 [21.4]	0.0059 ± 0.0025 (42.6) 0.0023 - 0.0105 [0.0056]	0.0078 ± 0.0028 (36.4) 0.0041 - 0.0127 [0.0067]	0.0039 ± 0.00 (33.4) 0.0012 - 0.00 [0.0038]
		Other		3	21.3 ± 2.52 (11.8) 19 - 24 [21]	179.7 ± 7.64 (4.3) 173 - 188 [178]	77.3 ± 1.69 (2.2) 75.4 - 78.5 [78.1]	2.0 ± 0.87 (43.3) 1.5 - 3 [1.5]	17.5 ± 6.46 (36.9) 10.6 - 23.4 [18.5]	3.8 ± 1.61 (41.9) 2 - 5 [4.5]	13.5 ± 6.79 (50.3) 7.35 - 20.8 [12.4]	5.9 ± 1.66 (28.1) 4 - 7 [6.75]	25.8 ± 8.78 (34.1) 18.7 - 35.6 [23]	0.0056 ± 0.0020 (35.3) 0.0035 - 0.0075 [0.0059]	0.0083 ± 0.0027 (32.5) 0.0062 - 0.0113 [0.0074]	0.0043 ± 0.00 (48.8) 0.0024 - 0.00 [0.0040]
3	40	C	F	2	26.5 ± 9.2 (34.7) 20 - 33 [26.5]	166.5 ± 9.2 (5.5) 160 - 173 [166.5]	71.1 ± 3.5 (5.0) 68.6 - 73.6 [71.1]	1.25 ± 0.4 (28.3) 1 - 1.5 [1.25]	24.1 ± 5.4 (22.3) 20.3 - 27.9 [24.1]	4.25 ± 1.8 (41.6) 3 - 5.5 [4.25]	13.15 ± 0.6 (4.8) 12.7 - 13.6 [13.15]	5.5 ± 1.4 (25.7) 4.5 - 6.5 [5.5]	24.4 ± 10.3 (42.3) 17.1 - 31.7 [24.4]	0.0085 ± 0.0023 (27.1) 0.0069 - 0.0102 [0.0085]	0.0046 ± 0.0005 (9.8) 0.0043 - 0.0050 [0.0046]	0.0087 ± 0.00 (46.8) 0.0058 - 0.01 [0.0087]
		C	M	15	33.0 ± 9.1 (27.5) 18.0 - 42.0 [38.0]	173.3 ± 9.4 (5.4) 152.0 - 188.0 [173.0]	76.7 ± 9.4 (12.2) 63.6 - 93.6 [76.4]	1.4 ± 0.4 (27.7) 1.0 - 2.0 [1.5]	18.8 ± 5.0 (26.8) 8.2 - 26.8 [19.1]	4.1 ± 0.7 (18.4) 3.0 - 5.0 [4.0]	11.0 ± 3.2 (29.1) 5.1 - 16.1 [10.4]	5.7 ± 0.7 (12.4) 4.0 - 6.5 [6.0]	23.1 ± 6.0 (25.8) 13.5 - 33.5 [23.6]	0.0063 ± 0.0021 (33.1) 0.0023 - 0.0092 [0.0063]	0.0037 ± 0.0013 (35.6) 0.0015 - 0.0063 [0.0033]	0.0077 ± 0.00 (30.2) 0.0039 - 0.01 [0.0072]
		B	M	6	29.3 ± 8.7 (29.8) 22.0 - 43.0	176.8 ± 2.9 (1.7) 173.0 - 180.0	74.2 ± 6.2 (8.4) 65.0 - 81.8	1.6 ± 0.4 (23.8) 1.0 - 2.0	21.7 ± 10.0 (46.1) 13.9 - 41.3	3.8 ± 0.7 (17.8) 3.0 - 4.5	15.8 ± 10.7 (68.0) 7.1 - 36.5	5.7 ± 0.8 (13.3) 4.5 - 6.5	27.5 ± 14.5 (52.7) 12.6 - 49.2	0.0075 ± 0.0042 (55.7) 0.0046 - 0.0159	0.0055 ± 0.0043 (78.3) 0.0026 - 0.0140	0.0095 ± 0.00 (58.6) 0.0042 - 0.01

3.4.3.3 Age

Pharmacokinetic studies were only performed in adults, however the pharmacokinetics of methylphenidate have been shown to be relatively consistent at ages of 6 years of age and above when normalized for dose and weight, (see OCPB review for Ritalin LA NDA 21-282). However, there was some question with Ritalin LA whether the Tmax for the second peak was more variable in children. Focalin XR is expected to behave similarly to Ritalin LA in children.

3.4.4 Extrinsic Factors

3.4.4.1 Food Effect

Food effect studies have not been performed with Focalin XR, however, as requested the sponsor has shown that both Focalin XR's pharmacokinetics and dissolution in a variety of media are similar to Ritalin LA, (see§3.7.1.2 Sponsor's Selection of Dissolution Method on page 64), and they have provided sufficient justification based on the similarity of the formulations that food effect labeling for Ritalin LA should also hold for Focalin XR. Thus a delay in the rate of absorption is expected without a decrease in extent.

3.4.4.2 Alcohol Use

No studies were performed on interactions with alcohol use and no subjects were listed as alcohol users. However, alcohol might affect the EC-DR coating and cause dose-dumping, because of the cardiovascular effects this is potentially of clinical concern, albeit less so than it might be as Focalin XR is primarily taken in the morning by children, and both of these factors are likely to mitigate the probability of this risk. However, it still exists.

An *in vitro* interaction study with clinically relevant alcohol concentrations is therefore in order examining the effect on the dissolution profiles. Assuming 1 – 4 30 cc shots ranging from 80 to 150 proof and a base stomach volume of 250 ml and no absorption relevant stomach alcohol concentrations might range from 4% to 24%, with typical concentrations in the 7.5% – 15% range, (see Table 29).

Table 29 Rough Estimates of *In Vivo* Ethanol Concentrations

Shots	Volume (ml)	Proof	Ethanol (ml)	Base Stomach Volume (ml)	Total Volume (ml)	% EtOH
1	30	80	12	250	280	4.3%
1	30	100	15	250	280	5.4%
1	30	150	22.5	250	280	8.0%
2	30	80	24	250	310	7.7%
2	30	100	30	250	310	9.7%
2	30	150	45	250	310	14.5%
3	30	80	36	250	340	10.6%
3	30	100	45	250	340	13.2%
3	30	150	67.5	250	340	19.9%
4	30	80	48	250	370	13.0%
4	30	100	60	250	370	16.2%
4	30	150	90	250	370	24.3%

3.4.4.3 Tobacco Use

No studies were performed on interactions with tobacco use and no subjects were listed as tobacco users. However, no interactions are expected.

3.4.4.4 Concomitant Medications

No studies were performed on interactions with concomitant medications. No pharmacokinetic interactions are expected although a variety of pharmacodynamic interactions with amphetamines and other drugs are expected. Such as drugs that increase central dopamine concentrations (such as antidepressants and amphetamines) or antagonizes the action of dopamine like e.g. the dopamine antagonist haloperidol, as well as pharmacodynamic interactions by other mechanisms.

3.5 Pharmacodynamics

3.5.1 Overview

The degree and duration of effect of Focalin XR after a single dose in children with ADHD was evaluated by SKAMP score in a laboratory classroom setting in study US08. The sponsor claims that this study demonstrates Focalin XR's duration of effect for at least 12 hours. However, the design of the study is inherently biased as all children received too large of a dose therefore no conclusions regarding duration of effect under clinical dosing can be made and any labeling regarding duration of effect based on this study would be misleading.

3.5.2 Study Design

Study US08 was a randomized, multi-center, double-blind, placebo controlled two period cross-over study in 54 male and female children with ADHD aged 6 to 12 years who were on a stable dose of racemic methylphenidate 20 to 40 mg for at least 1 month prior to the screening.

Treatments consisted of Focalin™ XR 20 mg and placebo. For each treatment period patients received study drug Sunday to Thursday and again on Saturday. Pharmacodynamic evaluations were performed on Saturday by laboratory classroom assessments using SKAMP scores, .i.e. for a total of 6 days of treatment with a one day washout on the Friday prior to the Saturday classroom evaluation.

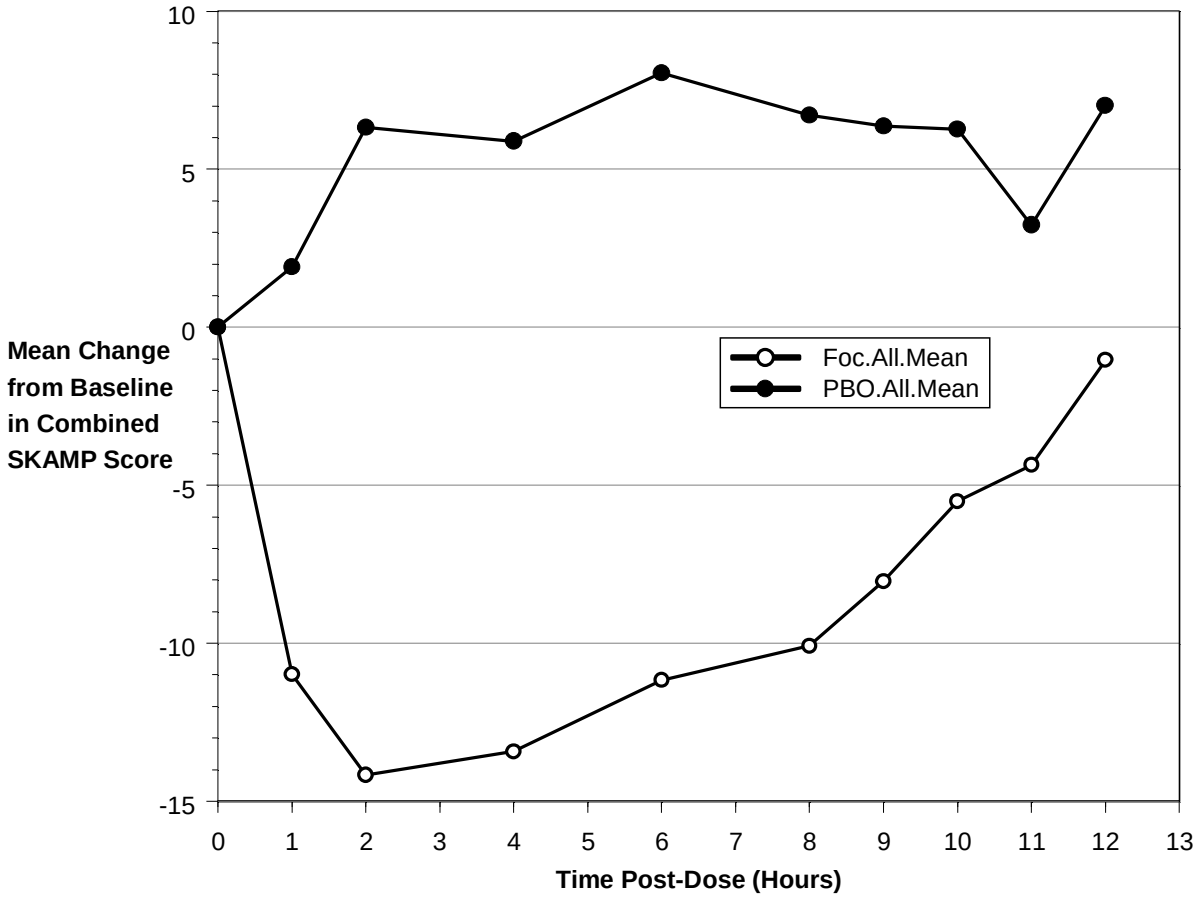
Pharmacodynamic endpoints of efficacy were the effect of Focalin™ XR 20 mg versus placebo as measured by the change from pre-dose on the SKAMP Attention, Deportment, Math test scores and combined scores at 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours post-dose.

3.5.3 Efficacy Results

3.5.3.1 Combined Efficacy Results for All Subjects

Figure 15 shows the mean change from baseline in the primary objective, the combined SKAMP score, for Focalin XR as compared to placebo in all 53 children. This appears to show differentiation from placebo as soon as 1 hour after dosing and extending through at least 12 hours.

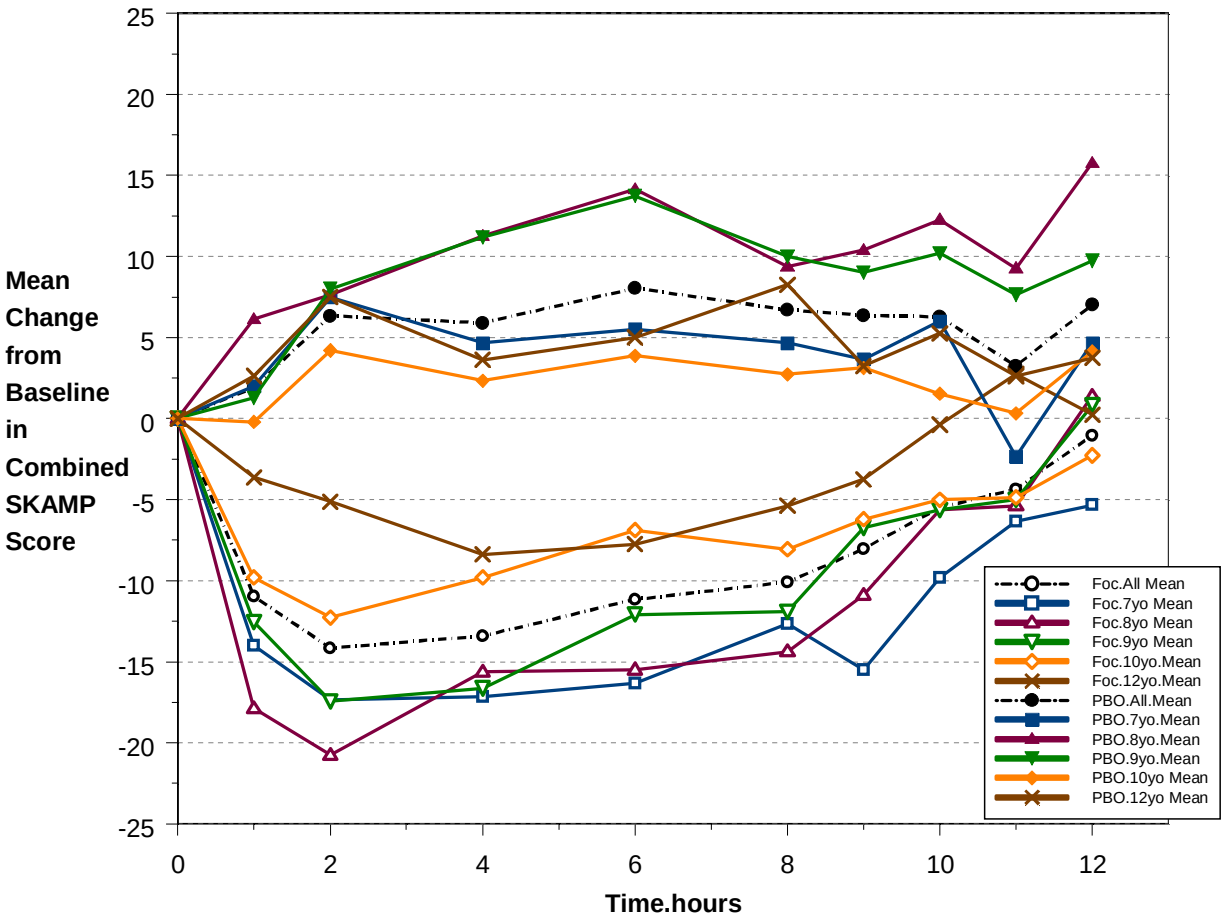
Figure 15 Mean Change from Baseline in Combined SKAMP Scores for Focalin XR (*d*-MPH) 20 mg Compared to Placebo in – Study US08



3.5.3.2 Efficacy Results by Age

However, when the data is examined by subject age, excluding those ages with 3 or fewer subjects, i.e. ages 6 and 11, a pattern emerges as shown in Figure 16.

Figure 16 Mean Change from Baseline in Combined SKAMP Scores for Focalin XR (*d*-MPH) 20 mg and Placebo by Age



Although the mean change from baseline for placebo when examined by age varies randomly around the mean, when the effect of Focalin XR is examined, there is an inverse relationship of SKAMP score with age. Specifically 10 year olds have a greater effect than 12 year olds, and although the degree of effect in younger children is greater a maximum effect appears to have been reached. In spite of this the duration of effect increases with decreasing age.

This inverse relationship of age to effect was not unexpected as the sponsor was twice advised in IND reviews of the protocol under IND 63,885 submission numbers 020 and 028 that the dose was too high and that a dose equivalent to each individual's maintenance dose should be used. In addition, the holiday from treatment on the day prior to testing may bias the study and allow a greater effect as it would insure complete recovery of synaptic dopamine stores.

Figure 17, Table 30, Figure 18, and Figure 19 illustrate this point.

Figure 17 Comparison of Study Dose (Focalin XR) to Total Daily*d*-MPH Maintenance Dose by Age - Study US08

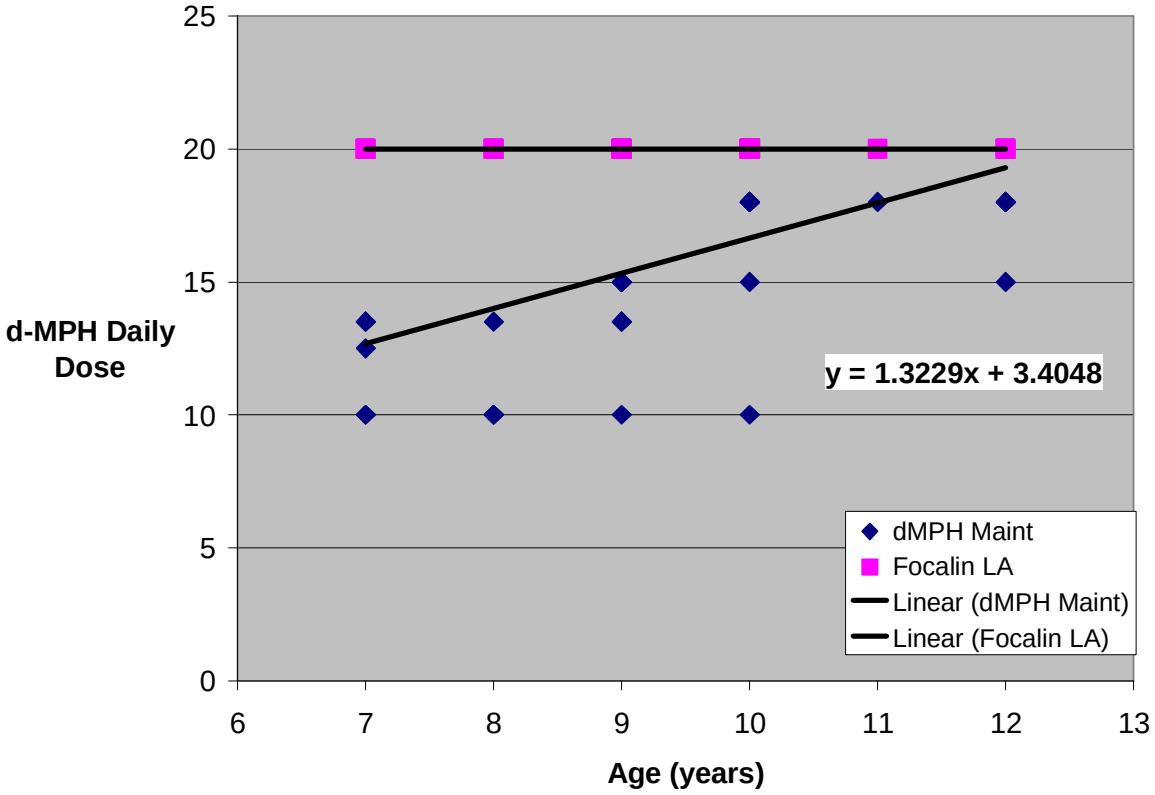


Table 30 Total Daily *d*MPH Pre-Study Maintenance Dose by Age and Ratio of Focalin XR Dose to Pre-Study Dose by Age - Study US08

Age (years)	6	7	8	9	10	11	12	All
N		5	6	11	11	1	5	48
Ratio of Study *d*-MPH Dose to pre-Study Maintenance Dose		1.71 ± 0.27 (15.6) 1.48 - 2.00	1.75 ± 0.42 (24.1) 1.00 - 2.00	1.27 ± 0.32 (24.9) 1.00 - 2.00	1.18 ± 0.29 (24.3) 1.00 - 2.00	—	1.16 ± 0.10 (8.6) 1.11 - 1.33	1.36 ± 0.37 (27.1) 1.00 - 2.00
pre-Study *d*-MPH Maintenance Dose (mg)		11.9 ± 1.8 (15.0) 10.0 - 13.5 [12.5]	12.3 ± 4.0 (33.0) 10.0 - 20.0 [10.0]	16.5 ± 3.6 (21.6) 10.0 - 20.0 [15.0]	17.5 ± 2.9 (16.4) 10.0 - 20.0 [18.0]	18.0	17.4 ± 1.3 (7.7) 15.0 - 18.0 [18.0]	15.7 ± 3.7 (23.3) 10.0 - 20.0 [18.0]
pre-Study *d*-MPH Maintenance Dose (mg/kg/day)		0.49 ± 0.09 (18.0) 0.39 - 0.59 [0.48]	0.30 ± 0.09 (28.6) 0.20 - 0.42 [0.31]	0.52 ± 0.18 (34.1) 0.18 - 0.75 [0.52]	0.51 ± 0.19 (37.3) 0.22 - 0.82 [0.47]	0.33	0.39 ± 0.13 (34.8) 0.26 - 0.58 [0.37]	0.46 ± 0.17 (36.5) 0.18 - 0.82 [0.44]
N	1	6	8	12	15	3	8	53
Focalin XR Dose (mg/kg/day)	0.87	0.82 ± 0.05 (6.4) 0.77 - 0.91 [0.82]	0.57 ± 0.21 (37.1) 0.20 - 0.8 [0.63]	0.62 ± 0.14 (22.4) 0.36 - 0.77 [0.67]	0.55 ± 0.14 (25.0) 0.37 - 0.82 [0.52]	0.47 ± 0.13 (28.5) 0.37 - 0.63 [0.57]	0.46 ± 0.14 (31.0) 0.29 - 0.65 [0.49]	0.59 ± 0.17 (29.1) 0.20 - 0.91 [0.62]

Figure 18 Comparison of *d*-MPH Daily Dose by Age Normalized to Weight - Study US08

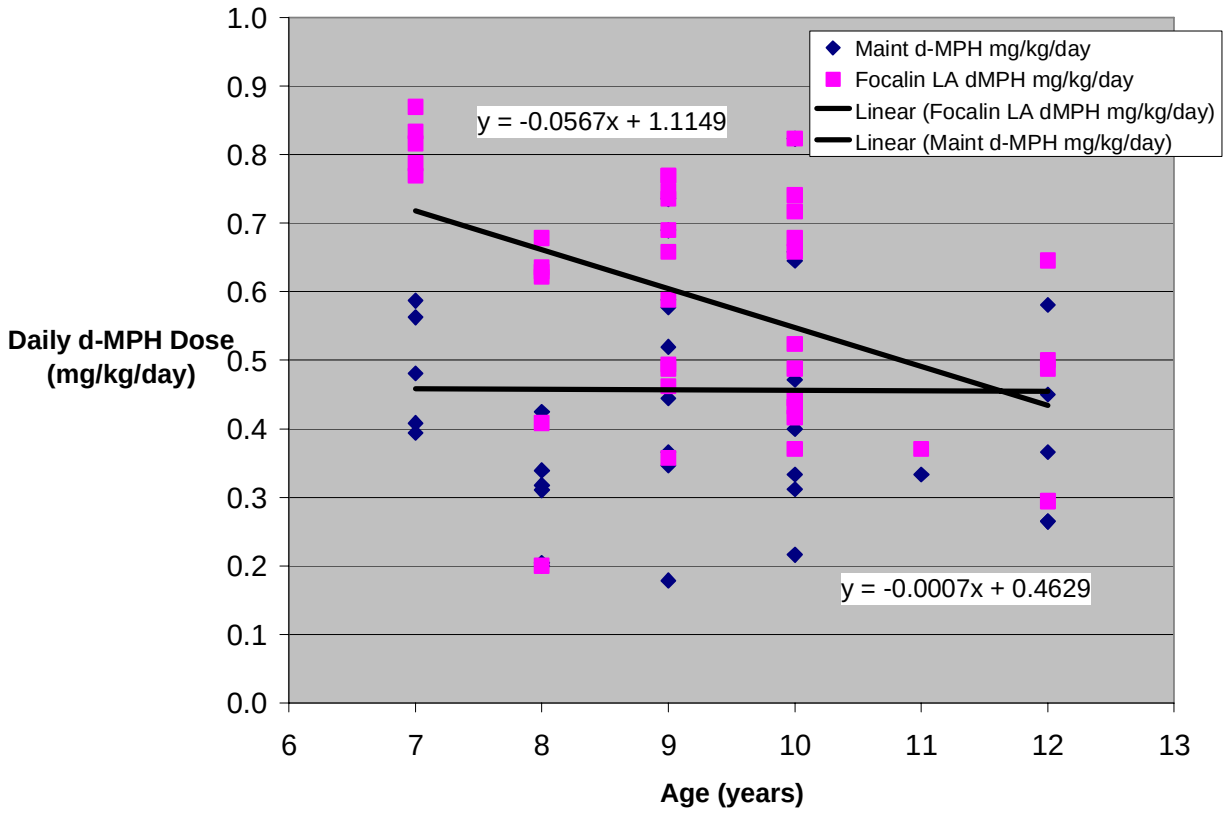
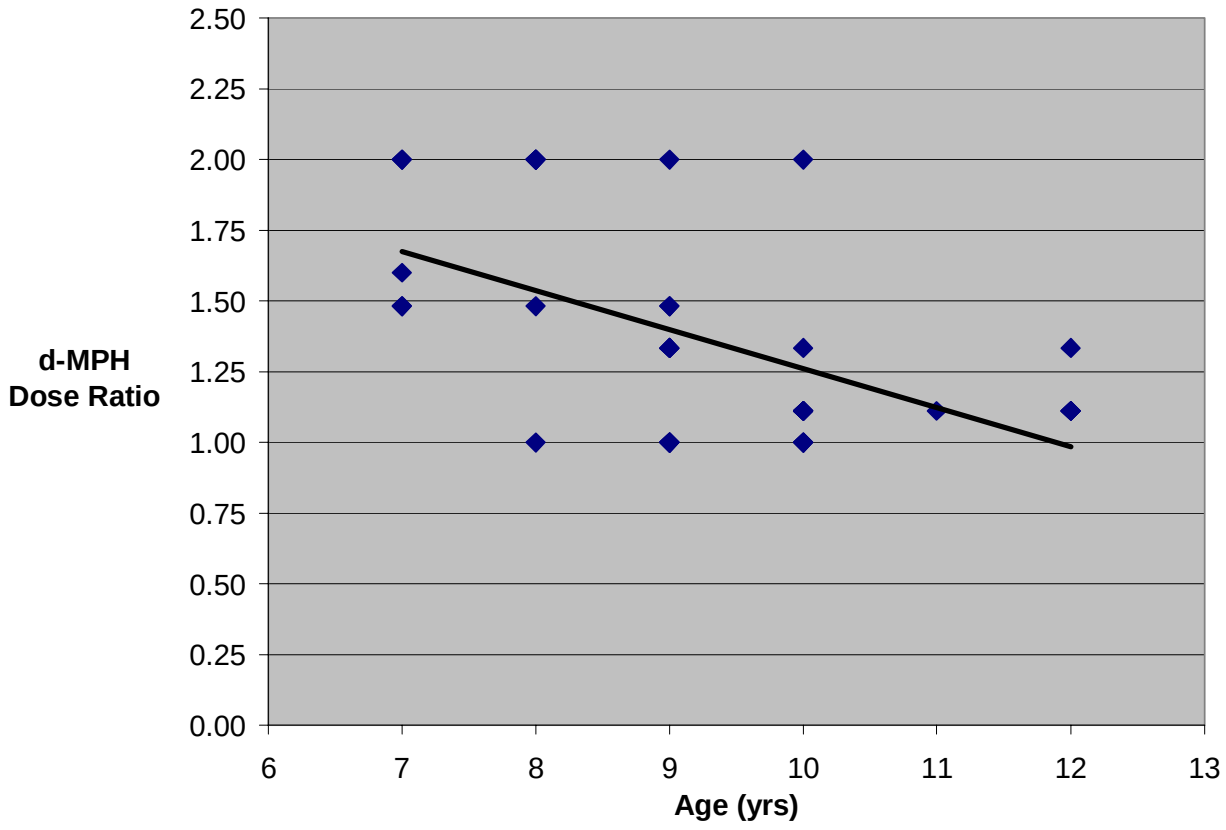


Figure 19 Ratio of Focalin XR Dose to Total Daily *d*-MPH Maintenance Dose by Age - Study US08



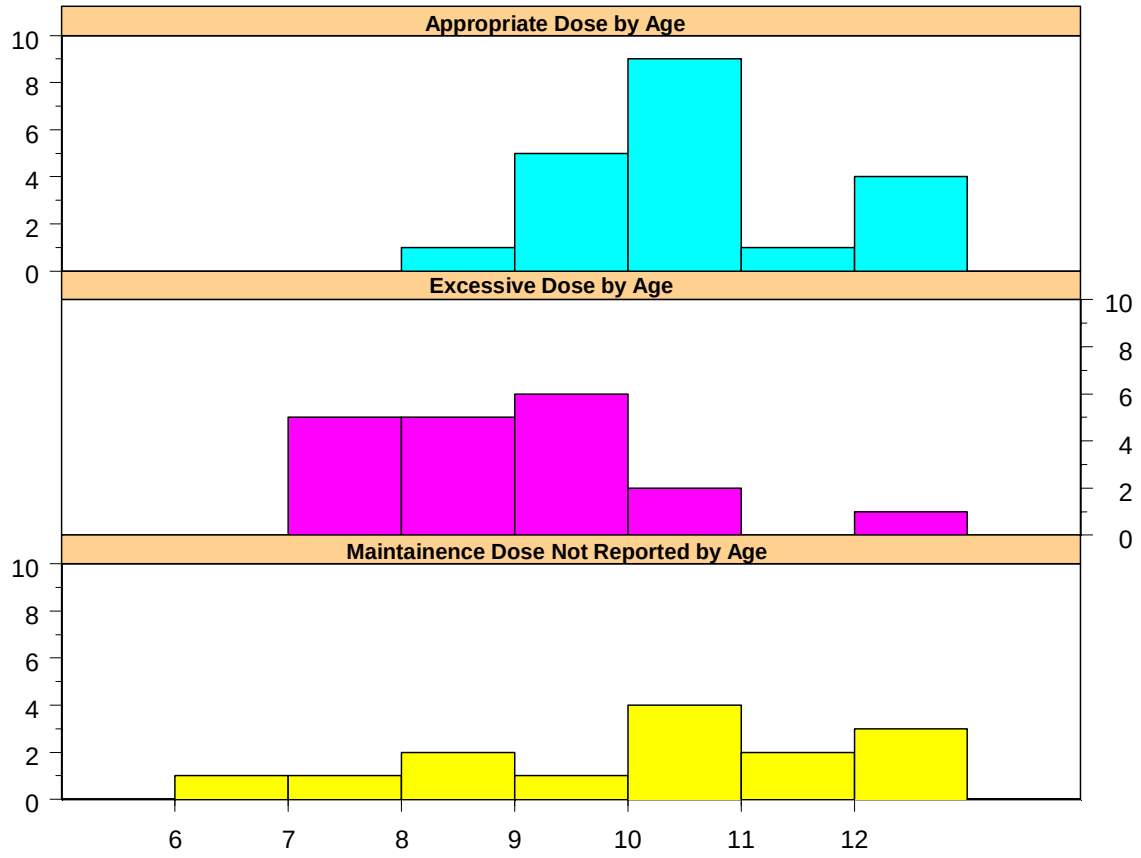
3.5.3.3 Efficacy for Subjects with Appropriate Dosing

For this review an exploratory analysis was also performed for those subjects for whom a 20 mg Focalin XR dose was considered appropriate, i.e. subjects whose maintenance dose had been Concerta 36 mg qd, Ritalin LA 40 mg qd, or the equivalent. Table 31 and Figure 20 show that only 20 subjects were known to be dosed appropriately. Of these only 19 subjects provided usable data.

Table 31 Appropriateness of Dosing in Study US08 by Age

Age	6	7	8	9	10	11	12	Subtotal	Total
Appropriate Dose	—	—	1	5	9	1	4	20	53
Excessive Dose	—	5	5	6	2	—	1	19	
Maintenance Dose Unknown	1	1	2	1	4	2	3	14	

Figure 20 Frequency Histograms of Appropriateness of Dosing in Study US08 by Age



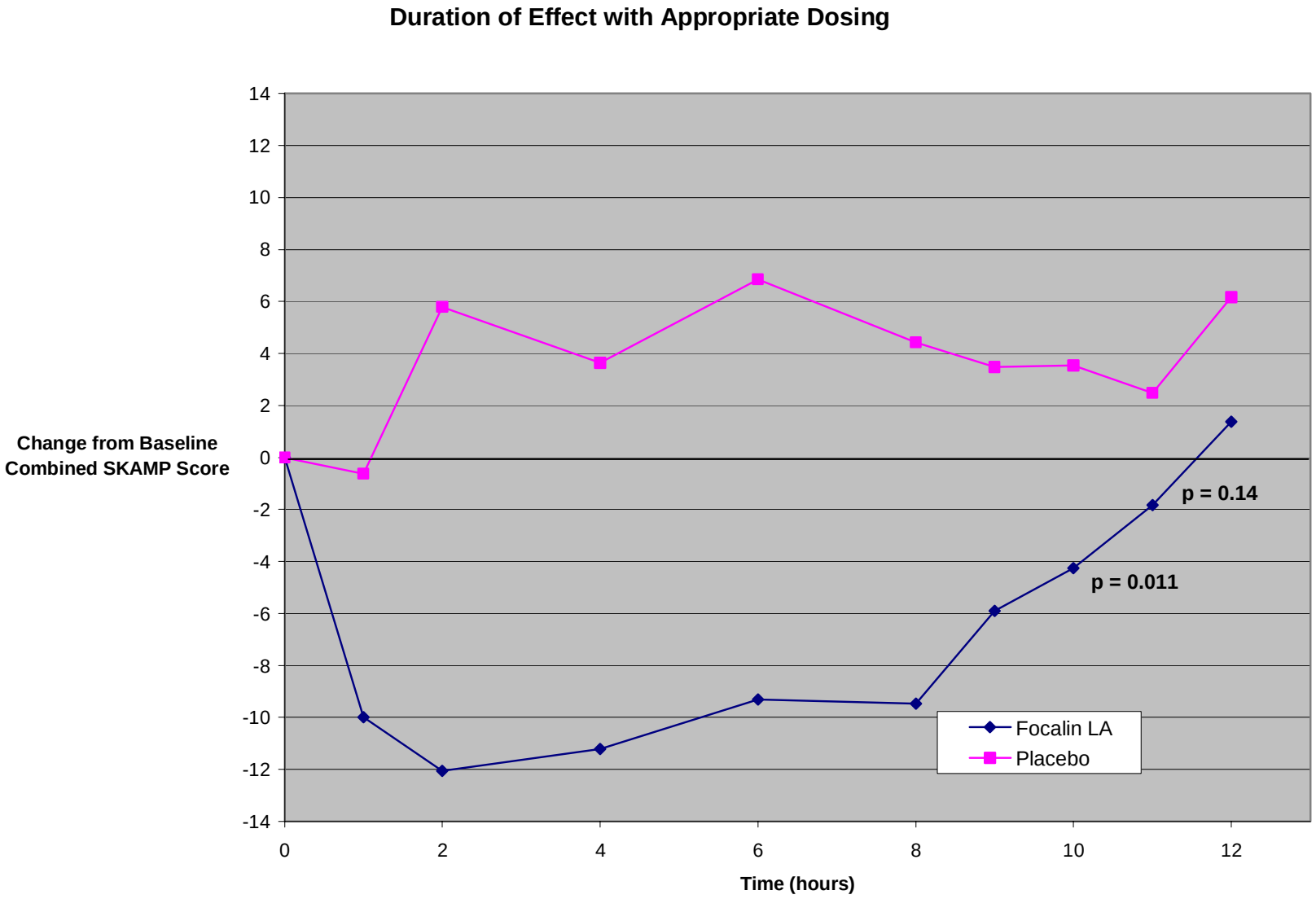
When combined SKAMP scores for these subjects are examined, the duration of effect was only up to 10 hours post dose, see Table 32 and Figure 21. It should be noted however that power analysis has not been performed, there are insufficient subjects under 9 years of age and there is still the problem of the inappropriate drug holiday.

Table 32 Summary Statistics for SKAMP Scores by Time Post-Dose for Subjects Appropriately Dosed – Study US08

Treatment	Time Post Dose (hours)									
	0	1	2	4	6	8	9	10	11	12
	Combined SKAMP Score									
Placebo	19.1 ± 12.3 (64.3) 4 - 43 [17]	18.4 ± 10.7 (57.9) 4 - 46 [17]	24.8 ± 12.9 (51.8) 4 - 50 [22]	22.7 ± 14.2 (62.6) 2 - 53 [22]	25.9 ± 12.1 (46.6) 6 - 54 [26]	23.5 ± 12.1 (51.7) 5 - 52 [23]	22.5 ± 12.2 (54.1) 1 - 42 [22]	22.6 ± 12.3 (54.4) 4 - 45 [21]	21.5 ± 13.1 (60.6) 4 - 46 [17]	25.2 ± 14.8 (58.7) 5 - 49 [22]
Focalin LA	20.8 ± 10.9 (52.4) 6 - 43 [20]	10.8 ± 8.8 (81.9) 2 - 33 [9]	8.7 ± 6.3 (71.8) 1 - 19 [7]	9.6 ± 5.8 (60.4) 3 - 23 [8]	11.5 ± 9.7 (85.0) 2 - 36 [9]	11.3 ± 8.5 (74.9) 2 - 37 [9]	14.9 ± 12.0 (80.4) 2 - 52 [11]	16.5 ± 10.1 (61.3) 2 - 40 [17]	18.9 ± 9.7 (50.9) 4 - 37 [16]	22.2 ± 14.5 (65.2) 4 - 46 [18]
	Change from Baseline in Combined SKAMP Score									
Placebo	0.0	-0.6 ± 10.0 (1589.7) -26 - 11 [2]	5.8 ± 7.9 (136.7) -6 - 20 [6]	3.6 ± 7.1 (196.0) -9 - 14 [3]	6.8 ± 9.5 (139.5) -8 - 28 [5]	4.4 ± 9.5 (215.5) -14 - 21 [6]	3.5 ± 8.0 (230.2) -12 - 26 [4]	3.5 ± 9.4 (265.6) -10 - 28 [3]	2.5 ± 10.4 (419.1) -9 - 37 [2]	6.2 ± 11.7 (190.3) -12 - 42 [4]
Focalin LA	0.0	-10.0 ± 11.0 (109.9) -41 - 3 [-7]	-12.1 ± 10.8 (89.2) -41 - 1 [-9]	-11.2 ± 9.6 (85.7) -33 - 1 [-8]	-9.3 ± 9.8 (105.0) -41 - 3 [-8]	-9.5 ± 9.0 (95.4) -29 - 2 [-6]	-5.9 ± 7.0 (118.9) -25 - 9 [-4]	-4.3 ± 11.3 (265.5) -29 - 12 [-1]	-1.8 ± 9.7 (527.6) -25 - 14 [-1]	1.4 ± 10.8 (791.3) -27 - 22 [3]
p-Value[a]	0.17	**0.00035**	**0.00001**	**0.00011**	**0.00008**	**0.00052**	**0.00273**	**0.0108**	0.1375	0.1373
0.05 / N	(b) (4)									

a p-values are for a one-side paired t-test at each time point analyzed sequentially.

Figure 21 Change from Baseline in Combined SKAMP Scores over Time for Subjects Appropriately Dosed – Study US08



However the results are encouraging, a duration of effect of 10 hours as compared to the 12 hour duration shown with Concerta is not surprising as the analysis by age shows that duration of effect is likely affected by prolonged higher MPH concentrations, and Concerta produces a higher second peak similar to the peak from a second IR dose, where as Focalin LA produces a lower second peak. In addition, Concerta's second peak is due to a typical sustained release of a higher total dose whereas Focalin's second peak is due to more modified sustained release characteristics and also a lower dose for the sustained release component. Thus concentrations with Focalin LA likely fall to a subtherapeutic level sooner than with Concerta.

3.5.4 Safety Data

Safety data from study US08 is presented here since the dose used in this study was higher than typically used

From Figure 22 we see that the effect on mean pulse rate is probably already maximized at a dose of 20 mg in children 10 and younger. Whereas from Figure 23 and Figure 24 it appears that increases in systolic and diastolic blood pressure may be slightly higher in subjects 8 and younger.

Figure 22 Mean Pulse vs. Time post-dose Focalin XR 20 mg by Age

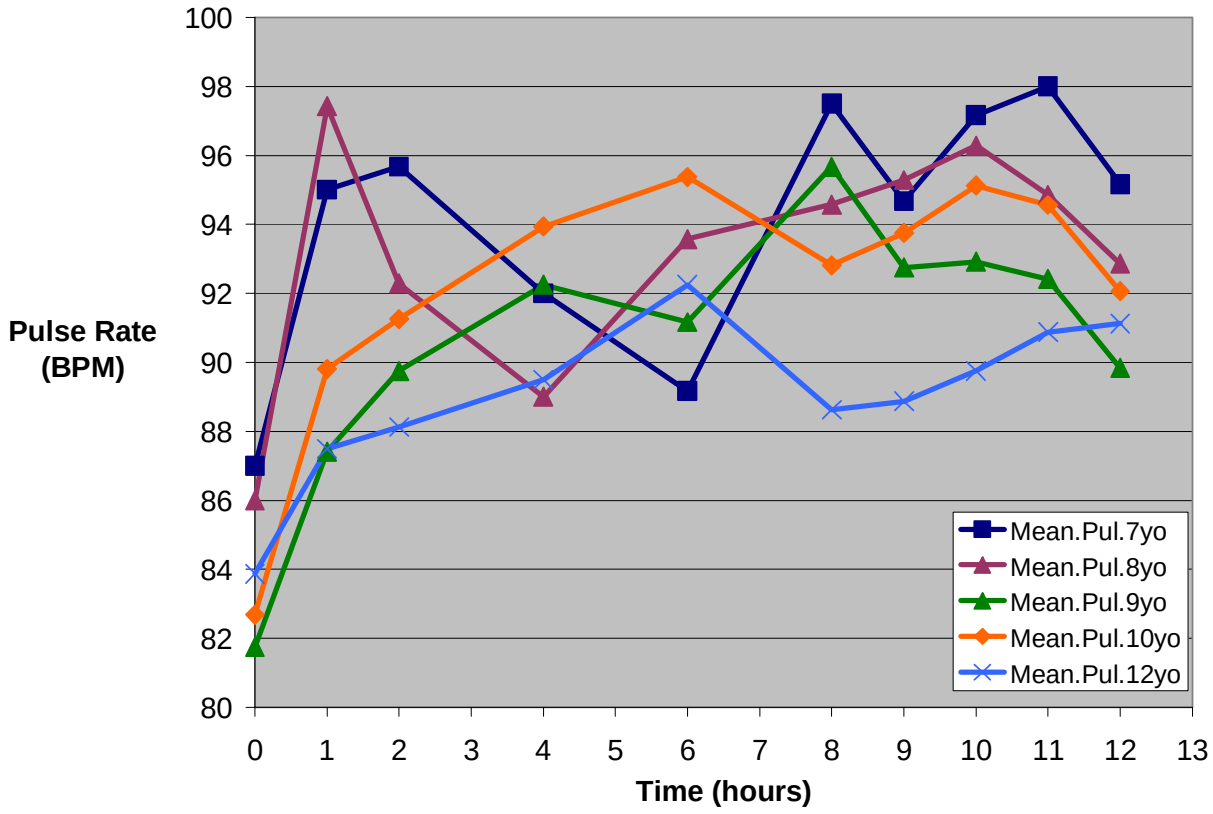


Figure 23 Mean Change in Systolic BP vs. Time post-Dose of Focalin XR 20 mg by Age – Study US08

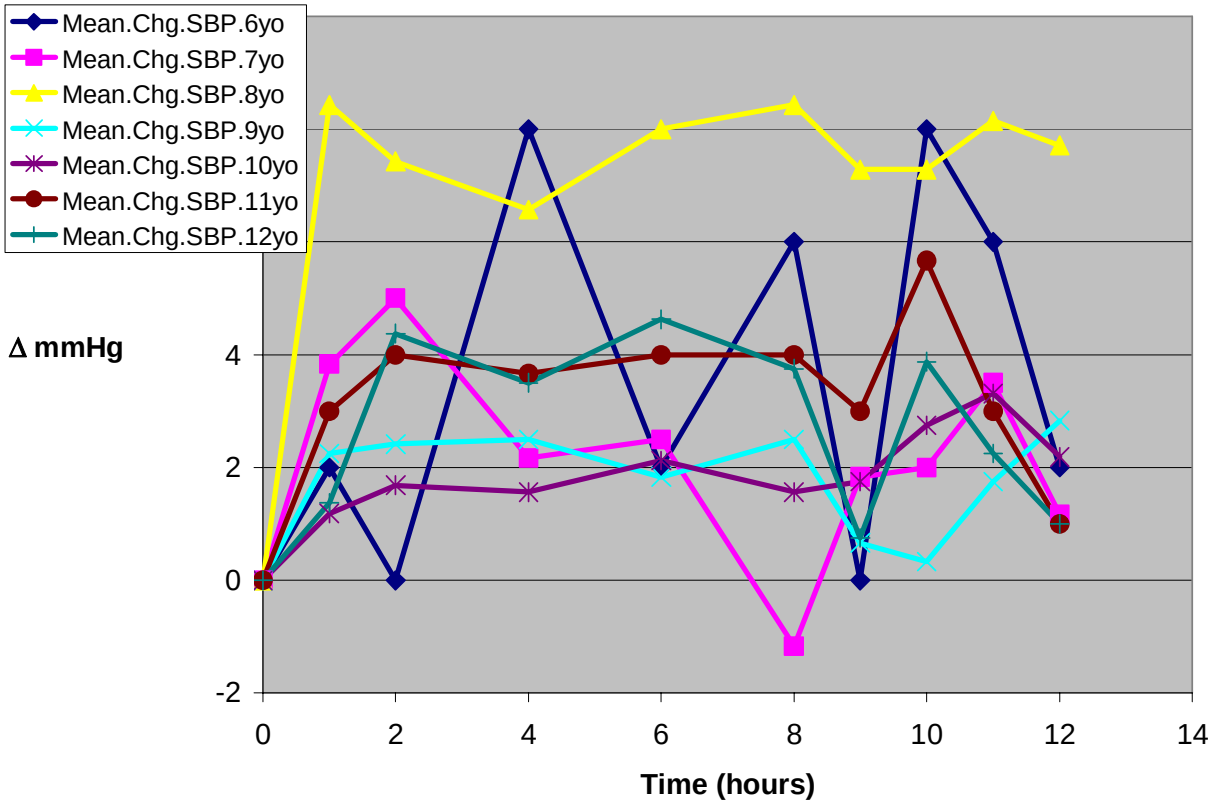


Figure 24 Mean Change in Diastolic BP vs. Time post-Dose of Focalin XR 20 mg by Age – Study US08

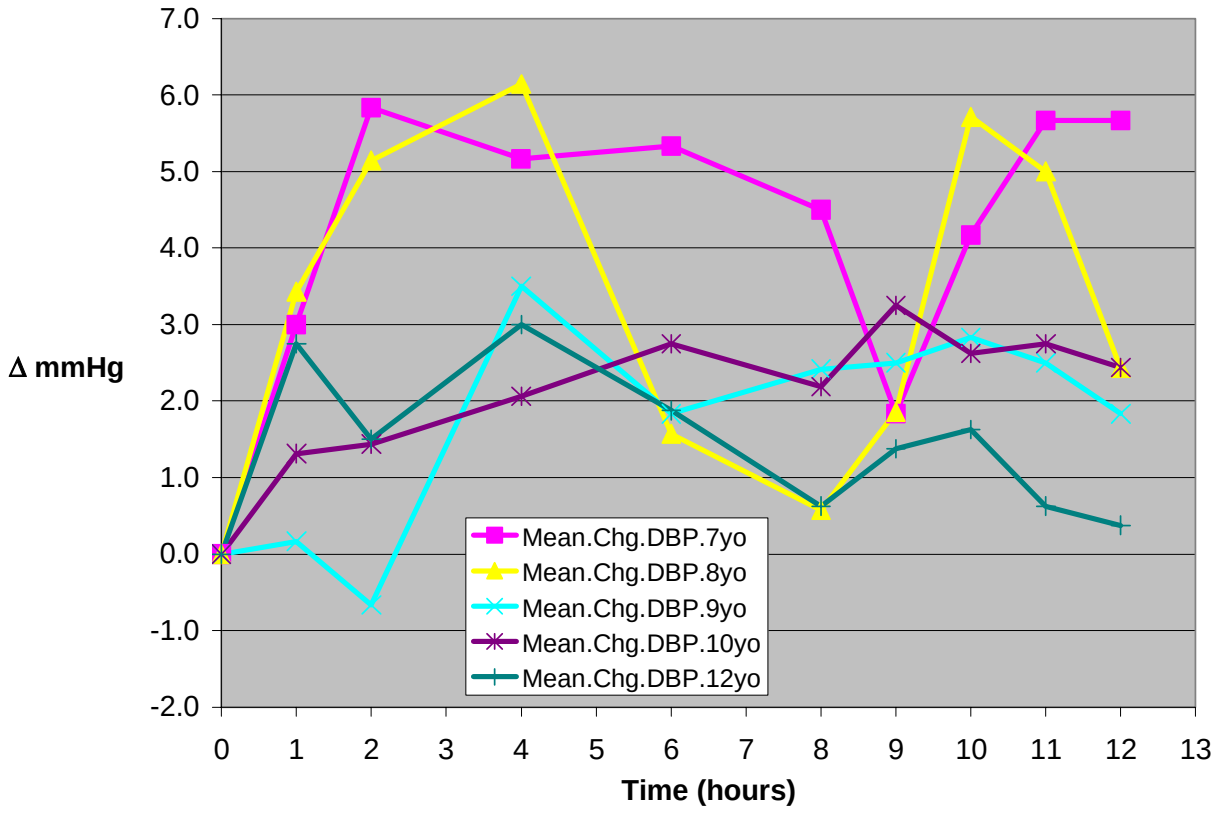


Table 33 Number (%) of patients with AEs by primary system organ class, preferred term, and treatment (Safety population) – Study US08

Primary system organ class / Preferred term[1]	Placebo N=54 n (%)	Focalin XR N=53 n (%)
Any primary system organ class	12 (22.2)	15 (28.3)
Metabolism and nutrition disorders	**0**	**9 (17.0)**
Appetite decreased NOS	0	5 (9.4)
Anorexia	0	4 (7.5)
Gastrointestinal disorders	**1 (1.9)**	**4 (7.5)**
Abdominal pain upper	0	3 (5.7)
Diarrhea NOS	0	1 (1.9)
Vomiting NOS	0	1 (1.9)
Nausea	1 (1.9)	0
Psychiatric disorders	**4 (7.4)**	**2 (3.8)**
Insomnia	0	2 (3.8)
Irritability	3 (5.6)	0
Affect lability	1 (1.9)	0
General disorders and administration site conditions	**0**	**2 (3.8)**
Fatigue	0	2 (3.8)
Nervous system disorders	**3 (5.6)**	**1 (1.9)**
Headache	3 (5.6)	1 (1.9)
Injury, poisoning, and procedural complications	**0**	**1 (1.9)**
Skin laceration	0	1 (1.9)
Infections and infestations	**2 (3.7)**	**0**
Gastroenteritis viral NOS	1 (1.9)	0
Upper respiratory tract infection NOS	1 (1.9)	0
Renal and urinary disorders	**1 (1.9)**	**0**
Urinary frequency	1 (1.9)	0
Skin and subcutaneous tissue disorders	**1 (1.9)**	**0**
Contusion	1 (1.9)	0

NOS = not otherwise specified.
Note: A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment. A patient with multiple AEs within a primary system organ class was counted only once in the total row.
[1] Primary system organ classes are sorted in descending frequency as reported in the Focalin XR column, and preferred terms are sorted within primary system organ class in descending frequency as reported in the Focalin XR column.

3.6 Dosing Experience

3.6.1 Dosing Experience in Children

The sponsor is proposing dosages in children 6 - 12 years of age of up to 30 mg per day which is greater than the 20 mg per day of *d*-MPH with Ritalin IR, Ritalin SR, or Ritalin LA. Since there was no PK data provided for children or adolescents and since dosing in the classroom pharmacodynamic study, (study US08), was excessive, the dosing experience with Focalin XR will be reviewed here.

Study 2301 was a pivotal efficacy study in children and adolescents with dosing beginning at 5 mg daily and increased at weekly intervals until a dose of 30 mg or a maximally tolerated dose was reached. Once a dose of 30 mg was reached, subjects were dosed for a one week trial for tolerance and back titration if necessary, followed by 2 weeks of maintenance therapy prior to evaluation.

A total of 53 subjects received active drug and the breakdown of patient ages along with the final tolerated doses that were evaluated for efficacy are shown in Table 34. As can be seen only 12 subjects below 10 years of age received a dose of 30 mg, only 16 subjects 10 -12 years of age received a dose of 30 mg, and only 2 adolescents received such a dose.

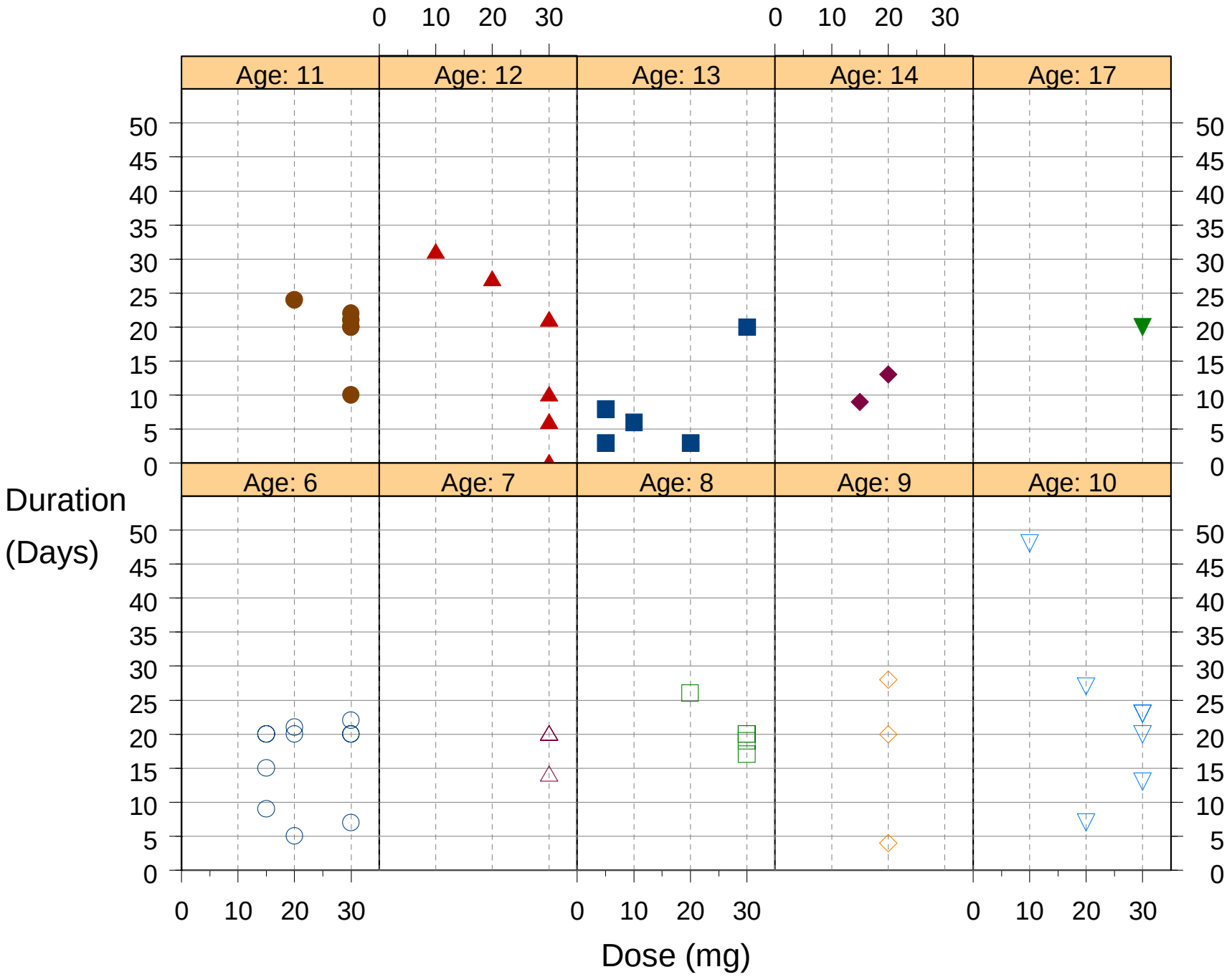
Figure 25 shows the duration of exposure to the highest dosages achieved by subjects in this study. It's apparent that down titration results in a duration of exposure to the 30 mg dose that may not be even as long as the maximum allowed 21 days.

Therefore based on the data in this submission there does not appear to be adequate exposures in either numbers of subjects or duration to a dose of 30 mg to adequately evaluate safety, although 30 mg is equivalent to dosages of *d*-MPH and racemic MPH that are currently approved for children.

Table 34 Final Focalin XR Dosages by Patient Age in Pivotal Efficacy Study 2301

Age (years)	Dose (mg)					Total Subjects by Age	Number of Subjects receiving 30 mg by Age Group
	5	10	15	20	30		
6	—	—	4	3	**4**	***11***	12
7	—	—	—	—	**4**	***4***	
8	—	—	—	1	**4**	***5***	
9	—	—	—	3	—	***3***	
10	—	1	—	2	4	***7***	16
11	—	—	—	1	7	***8***	
12	—	1	—	1	5	***7***	
13	2	1	—	1	1	***5***	2
14	—	—	1	1	—	***2***	
17	—	—	—	—	1	***1***	
Total Subjects by Dose	***2***	***3***	***5***	***13***	***30***	**53**	

Figure 25 Duration of Exposure to Various Dosages of Focalin XR by Age – Phase III Study 2301



3.6.2 Dosing Experience in Adults

Since the 40 mg dose is 1/3 higher than currently used an analysis of drug exposure duration for this dose in adults was performed. Only 99 subjects received a 40 mg dose, and overall 15% of subjects could not tolerate 40 mg for 1 week and another 10% completed a second week were evaluated and then did not continue into the open label extension. Thereafter dose decreases tended to occur at a fairly constant rate until about 4 ½ months of treatment. Thereafter the rate of dosage decreases slowed however the maximum duration of dosing for any subject at 40 mg was 5.3 months. Thus not a single subject was able to take the full 6.5 months of treatment, with an average duration of treatment of 2.5 months, (see Table 35, Figure 26, and Figure 27).

Table 35 Duration of Treatment with Focalin XR 40 mg in Adults

Days of Therapy	# of Dropouts since last Count	Total Dropouts	% Dropouts
14	24	24	24.2
30	10	34	34.3
60	12	46	46.5
90	11	57	57.6
120	9	66	66.7
150	25	91	91.9
160	8	99	

Figure 26 Frequency Histogram of Dosing Duration of Focalin XR 40 mg in Adults in Phase III

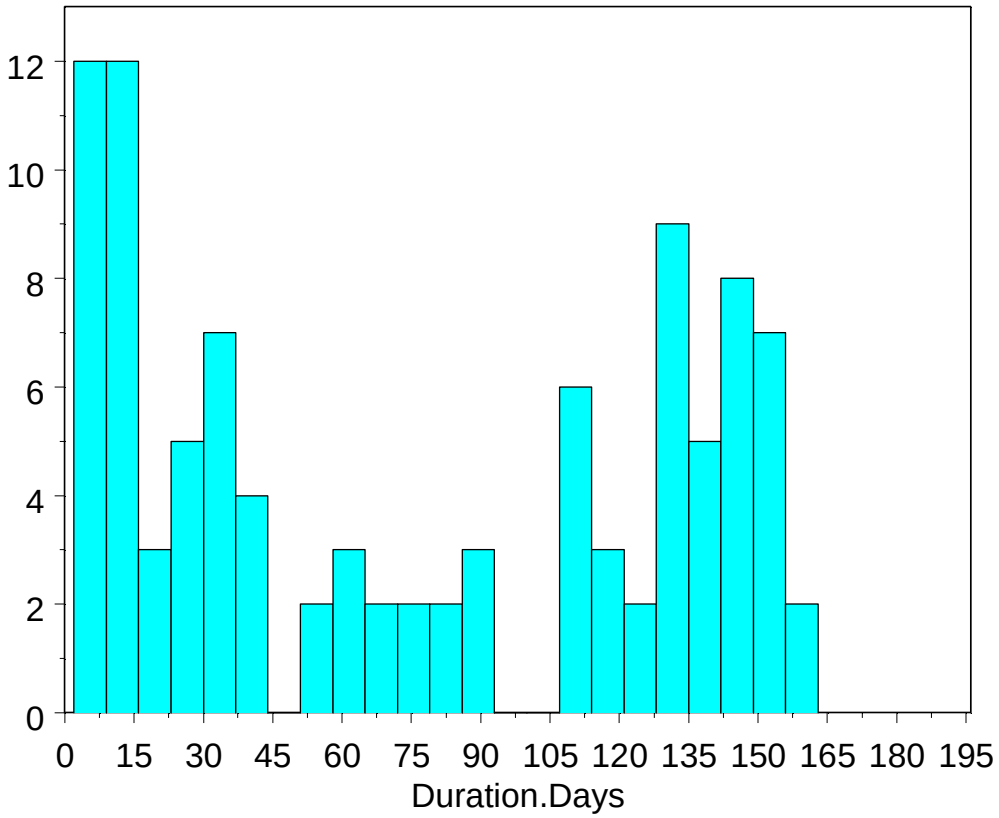
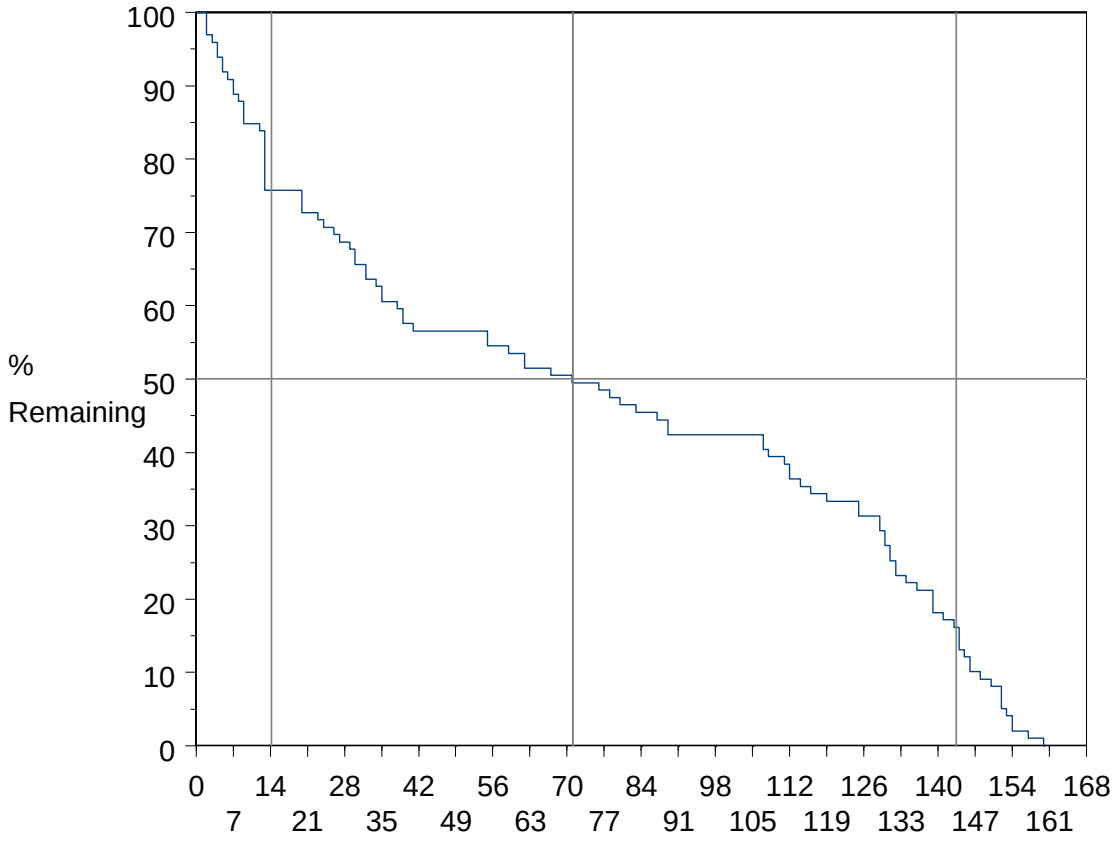


Figure 27 Step Plot of Dosing Duration (Days) of Focalin XR 40 mg in Adults in Phase III



This raises the question of whether such a dose is tolerated by adults. If it isn't tolerated by adults then the next question is what are the implications for dosing in children as there is a lack of long term data.

Specifically, since children are smaller doses of even 20 mg would produce concentrations that are similar to the higher 30 mg and 40 mg doses in adults. Therefore if adults can't tolerate such concentrations is it because adults can't tolerate cardiovascular effects as well as children, or is it because adults are better able to recognize the mild adverse CNS effects, whereas children may not be as adept at recognizing and communicating such AEs, whereas their dosages are based upon observations by adults?

3.7 General Biopharmaceutics

3.7.1 Dissolution

3.7.1.1 Sponsor's Proposed Focalin XR Dissolution Method

Table 36 Sponsor's Proposed Focalin XR Dissolution Method and Specifications

Parameter	Proposed Dissolution Method and Specifications
Apparatus type:	USP Apparatus I (basket)
Media:	Medium I: First 2 hours 0.01N HCl Medium II: Hours 2 – 10 Phosphate buffer pH 6.8
Volume:	500 ml for both medium I and medium II
Temperature:	37 ± 0.5 ^{o}C
Speed of rotation:	100 rpm.
Sampling Times:	0.5, 4, 6, and 10 hours
Acceptance Criteria:	Drug release by HPLC: percent of the declared content according to acceptance table 1 of USP 30 minutes 240 minutes (4 hours) 360 minutes (6 hours) 600 minutes (10 hours) (b) (4)

3.7.1.2 Sponsor's Selection of Dissolution Method

The sponsor began the development of a dissolution method based on the regulatory dissolution method for Ritalin LA. Next as requested the sponsor tested dissolution of Focalin XR in 3 dissolution media of different pH. Table 37 shows the current regulatory dissolution method for Ritalin LA with the exploratory conditions for Focalin XR.

Table 37 Current Regulatory Dissolution Method and Specifications

Parameter	Ritalin LA Dissolution Method As of Dec 2003	Exploratory Dissolution Media for Focalin XR
Apparatus type:	USP Apparatus I (basket)	USP Apparatus I (basket)
Media:	Medium I: First 2 hours 0.01N HCl Medium II: Hours 2 – 10 Phosphate buffer pH 6.8	**0.01 N HCl** **Phosphate Buffer pH 4.5** **Phosphate Buffer pH 6.8**
Volume (ml):	500 ml for both medium I and medium II	500 ml
Temperature:	37 ± 0.5 ^{o}C	37 ± 0.5°C.
Speed of rotation:	100 rpm.	100 rpm
Sampling Times:	0.5, 4, 6, and 10 hours	Sample was removed at: 2, 4, 6, 8 and 10 hours.

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3.7.3 Biowaiver

Only Focalin XR 5, 10, and 20 mg strengths were used in the pivotal clinical studies, (see Table 16). However all strengths including the 30 mg (b) (4) capsules are compositionally proportional and have demonstrated similar dissolution profiles and dose normalized pharmacokinetics, (see Table 40 in §3.7.1.3.1 Dissolution of Pivotal Clinical Batches and §3.4.1.3 Dose Proportionality). Consequently, biowaivers for the 30 mg (b) (4) capsule strengths are appropriate, however as the Division of Neuropharmacologic Drug Products only has plans to approve the 30 mg strength due to a lack of evidence for a differentiation in effect and a lack of safety information at this dose, a biowaiver will only be granted for the 5 mg and 30 mg capsules at this time.

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5 APPENDICES

5.1 Appendix 1 STUDY SYNOPSES

5.1.1 Study Number: 2101

Title: A randomized, open-label, 3-period, crossover study to compare the oral bioavailability between Focalin™ LA (*d*-methylphenidate) 20 mg, Focalin™ IR two 10 mg capsules dosed 4 hours apart, and Ritalin® LA (*d,l*-methylphenidate) 40 mg in healthy volunteers.

Objectives:

Primary: To compare the bioavailability of Focalin™ LA 20 mg (dexmethylphenidate) with Focalin™ IR 2 X 10 mg, and Ritalin® LA 40 mg in healthy volunteers

Secondary: To monitor the safety and tolerability of oral dose administrations of Focalin™ LA 20 mg, Focalin™ IR 2 X 10 mg and Ritalin® LA 40 mg.

Study Design:

This was an open-label, single-dose, three-treatment, three-period, randomized crossover in 25 healthy non-smoking male (n = 12) and female (n = 12) subjects between 18 and 45 years of age.

Screening Phase:

Subjects were screened for 21-day period. Subjects were randomized into 6 dosing sequence groups with four subjects per sequence group.

Treatment Phase:

Subjects were admitted to the study center at least 12 hours prior to initial dosing in each period for baseline evaluations, and were confined to the clinic for at least 24 hours after the morning dose of the study drug in each period. Following an inter-dose interval of at least 7 days, each subject returned to the study site and crossed-over to receive the alternate treatment.

All subjects received each of the following treatments once during the study according to a randomization schedule:

Treatment A: Focalin™ LA (*d*-methylphenidate) 20 mg capsule, single dose
Treatment B: Focalin™ IR two 10 mg (*d*-methylphenidate) tablets, dosed 4 hours apart
Treatment C: Ritalin® LA (*d,l*-methylphenidate) 40 mg capsule, single dose

For all treatment periods, subjects fasted for a minimum of 10 hours prior to dosing. The morning dose was administered between 0700 and 0800 a.m., and, when applicable, the second dose of Focalin™ IR was administered 4 hours after the first dose. No breakfast was provided. Lunch was provided 5 hours after the first dose.

End of Study Phase:

An end of study evaluation was performed prior to discharge from the study site. Subjects were considered to have completed the study when all safety and pharmacokinetic evaluations were completed.

Pharmacokinetic Sampling

Predose (0 hr) 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24 hours post dose.

Evaluations:

Plasma samples for determination of *d*-methylphenidate (*d*-MPH) and *l*-methylphenidate (*l*-MPH) were obtained during a 24-hour period after the morning dose in each treatment segment.

Safety and Tolerability:

Physical and ophthalmologic examinations
Vital signs
Electrocardiogram (ECG)
Laboratory evaluations (hematology, serum chemistry, urinalysis)
Adverse events (AE) recording
Concomitant medication recording

Pharmacokinetic evaluations:

Metrics in all subjects for *d*-MPH (and *l*-MPH, if possible):

- $AUC_{(0-t)}$
- $AUC_{(0-inf)}$
- $\%AUC_{(0-inf)ext}$
- C_{max}
- t_{max}
- K_{el}
- terminal $t_{½}$

In addition, AUC, C_{max}, and t_{max} values for the first peak (from 0 to 4 hours) and the second peak (from 4-10 hours), were calculated.

The mean and individual plasma *d*-MPH and *l*-MPH concentration versus time curves were presented graphically for the three formulations.

All subjects with valuable data were included in the pharmacokinetic data analysis, i.e. data from the subject who dropped out were included when available.

Statistical methods:

Demographic data were summarized using descriptive statistics for continuous data (age, height, weight, and elbow breadth) and using frequency counts for categorical data (gender, race, and frame size).

Descriptive statistics (mean, standard deviation [SD], number of observations [N], minimum [min], and maximum [max]) were calculated for laboratory tests, vital signs measurements, and ECG intervals. In addition to these safety summaries presented by treatment group, all safety data were presented by individual subject.

Descriptive statistics (mean, SD, CV, N, min, max, median, geometric mean, and coefficient of variation of geometric mean) were calculated for the concentration data by nominal time and for each pharmacokinetic parameter, and were presented by treatment. In addition, *d*-MPH pharmacokinetic parameters were summarized by gender.

Statistical evaluations were performed on overall and partial *d*-MPH AUC and C_{max} values, with p-value, geometric means, ratio of geometric means, and 90% confidence interval (CI) for ratio of population means determined from an analysis of variance (ANOVA) model for the log-transformed values with sequence, subject (sequence), period, and treatment as factors, where subject (sequence) was treated as a random variable.

Statistical evaluations were also performed on overall and partial *d*-MPH t_{max} values, with p-value determined by Wilcoxon Signed Rank Test. Relative bioavailability of *d*-MPH was evaluated based on the ratio of AUC values corresponding to the test formulation, Focalin™ LA, and the two reference formulations, Focalin™ IR and Ritalin® LA.

5.1.2 Study Number: 2102

Title: A randomized, open-label, single dose, five treatment, five period, crossover study to evaluate the dose proportionality of Focalin LA (5, 10, 20, 30, 40 mg) capsule in healthy subjects

Objectives:

Primary: To evaluate the dose proportionality of Focalin™ LA, 5, 10, 20, 30, 40 mg in healthy subjects

Secondary: To monitor the safety and tolerability of oral dose administrations of Focalin™ LA, 5, 10, 20, 30, 40 mg.

Study Design:

This was an open-label, single-dose, five period, five treatment, randomized crossover design with at least 7 days of washout between periods. A total of 25 healthy non-smoking male and female subjects enrolled between 18 and 45 years of age enrolled in the study. Five subjects were withdrawn by the investigator from the study. A total of 20 subjects completed all five treatment periods of the study. Subjects were screened during a 21 Day period, and those eligible proceeded to a baseline visit prior to each treatment period, and one end-of-study evaluation prior to discharge from the study site on the day following the last treatment. Subjects were randomized into five dosing sequence groups with five subjects per group. The subjects were admitted to the study center at least 12 hours prior to the initial dosing for baseline evaluations, and confined to the clinic for at least 24 hours post dose in each period. Following an inter-dose interval of seven days, each subject returned to the study site and received the next assigned treatment. Subjects received each of the following treatments once during the study according to a randomization schedule:

- Treatment A: Focalin™ LA (dexmethylphenidate, *d*-MPH) 5 mg capsules, single dose
- Treatment B: Focalin™ LA (dexmethylphenidate, *d*-MPH) 10 mg capsules, single dose
- Treatment C: Focalin™ LA (dexmethylphenidate, *d*-MPH) 20 mg capsules, single dose
- Treatment D: Focalin™ LA (dexmethylphenidate, *d*-MPH) 30 mg capsules, single dose
- Treatment E: Focalin™ LA (dexmethylphenidate, *d*-MPH) 40 mg capsules, single dose

For all treatment periods, subjects fasted for a minimum of 10 h predose to 4 h post dose.

Plasma samples for determination of dexmethylphenidate (*d*-MPH) were obtained for 24 hours post dose after each treatment.

Criteria for evaluation:

Pharmacokinetic evaluations:

Pharmacokinetic parameters were calculated for dexmethylphenidate (*d*-MPH) concentrations in serially collected plasma samples after administration of 5 to 40 mg dexmethylphenidate. Parameters comprised Cmax, tmax, Cmax0-4, tmax0-4, Cmax4-10, tmax4-10, AUC0-t, AUC0-∞, AUC0-4, AUC4-8, AUC4-10, MRTtot, Kel as well as t½. While not all subjects completed each treatment, all completed treatment data were included in the pharmacokinetic evaluation. Individual and mean *d*-MPH plasma concentration time curves were presented for all five doses. The enantioselective assay was able to detect *d*-MPH as well as *l*-MPH.

Safety and tolerability evaluations: Safety and tolerability were assessed via physical examinations, vital signs, electrocardiogram (ECG), safety laboratory evaluations (hematology, clinical blood chemistry, urinalysis), adverse events (AE) recording, and concomitant medications recording.

Statistical methods:

Descriptive statistics were generated for demographic data (age, body weight, height) *d*-MPH plasma concentrations and pharmacokinetic parameters including arithmetic mean, SD, %CV, min, median, max, geometric mean and g%CV. Statistical evaluations were performed with overall and partial *d*- MPH AUC and Cmax values to explore the dose proportionality of these parameters by the power model. Parameters were also normalized to a dose of 20 mg, tabulated and plotted vs. dose in comparison to the non-normalized parameters.

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5.1.4 Study Number: US08

Title: A randomized, multi-center, double-blind, cross-over study comparing the efficacy and duration of effect of FocalinTM LA 20 mg versus placebo in children (6-12 years) with Attention- Deficit/Hyperactivity Disorder (ADHD) in a laboratory classroom setting

Objectives:

Primary Objective:

- To evaluate the efficacy of Focalin™ LA 20 mg versus placebo as measured by the change from pre-dose on the SKAMP Combined score to the 1 hour post-dose score during the 12 hour laboratory classroom day.

Secondary Objectives:

- To evaluate the duration of effect of Focalin™ LA 20 mg versus placebo as measured by the change from pre-dose on the SKAMP Combined score at 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours post-dose during the 12-hour laboratory classroom day.

- To evaluate the effect of Focalin™ LA 20 mg versus placebo as measured by the change from pre-dose on the SKAMP Attention, Deportment and Math test scores at 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours post-dose during the 12-hour laboratory classroom day.

- To examine safety and tolerability of Focalin™ LA 20 mg versus placebo throughout the study.

Study Design:

This was a randomized, multi-center, double-blind, placebo controlled two period cross-over in 54 male and non-pregnant female children aged 6 to 12 years with ADHD per DSM-IV and were on a stable dose of methylphenidate 20 to 40 mg for at least 1 month prior to the screening.

Patients were excluded from the study if they had comorbid disorders (e.g., a tic disorder, seizures, psychiatric illness, or substance use disorder), were taking prohibited concomitant medications or medications other than methylphenidate for symptoms of ADHD, or were home-schooled.

For each treatment patients were on study drug Sunday to Thursday and again on Saturday, i.e. for a total of 6 days of treatment with one day washout on the Friday prior to the laboratory classroom assessments.

Evaluations:

Pharmacodynamics:

The primary efficacy variable was the change from pre-dose in the SKAMP-Combined score to the 1-hour post-dose score during the 12-hour laboratory classroom day.

Pharmacokinetics: Drug levels were not measured.

The secondary efficacy variables were the duration of effect of Focalin LA 20 mg versus placebo as measured by the change from pre-dose on the SKAMP-Combined score at 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours post-dose during the 12-hour laboratory classroom day, and the effect of Focalin LA 20 mg versus placebo as measured by the change from pre-dose on the SKAMP-Attention and Deportment and Math

Test-Attempted and Correct scores at 1, 2, 4, 6, 8, 9, 10, 11, and 12 hours post-dose during the 12-hour laboratory classroom day.

Safety:

- adverse events (AEs) (including serious AEs [SAEs])
- vital signs
- body weight
- Laboratory parameters (including hematology, blood chemistry, and urinalysis)
- physical examinations

Statistical Analysis:

The data from all centers participating in this protocol were combined for analysis, and were summarized by treatment group (and by visit when applicable) with respect to demographic and baseline characteristics, and efficacy and safety observations. All hypotheses were tested at the 2-sided alpha level of 0.05.

The primary efficacy variable was the change from pre-dose in SKAMP-Combined score at 1 hour post-dose.

The secondary efficacy variables were:

- duration of effect of Focalin LA 20 mg, estimated using change from pre-dose data in SKAMP Combined score at 1 to 12 hours post-dose;
- change from pre-dose in the SKAMP-Attention subscale score at 1 to 12 hours post-dose;
- change from pre-dose in the SKAMP-Deportment subscale score at 1 to 12 hours post-dose;
- change from pre-dose in Math Test-Attempted 1 to 12 hours post-dose; and change from pre-dose in Math Test-Correct at 1 to 12 hours post-dose.

The efficacy variables at each post-dose time point were compared between treatments using an analysis of covariance (ANCOVA) model that included the fixed effects of center, sequence, treatment, period, and baseline (Hour 0 pre-dose value), and the random effects of patients within sequences and within-patient errors.

To control for Type I error for multiple comparisons over time, the null hypotheses of equal treatment effect was tested at the 0.05 level at each time point starting at 1 hour. Testing would proceed to the next time point only if the treatment difference at the previous time point was significant.

Test for unequal carryover effects was performed using the pre-treatment evaluations. Paired differences were formed by subtracting the Period 1 pre-dose values from the Period 2 pre-dose values. These paired differences were analyzed with an analysis of variance (ANOVA) model including sequence effect to test unequal carryover effects, i.e., whether the paired differences in pre-dose values were different between treatment sequences. If the test for unequal carryover effects was statistically significant, a supportive post-hoc analysis would be performed based on Period 1 data only.

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data were summarized as appropriate.

Safety and tolerability evaluations: Safety and tolerability were assessed via physical examinations, vital signs, electrocardiogram (ECG), safety laboratory evaluations (hematology, clinical blood chemistry, urinalysis), adverse events (AE) recording, and concomitant medications recording.

5.1.5 Study Number: 2302

Title of study: A 5-week, multicenter, double-blind, randomized, placebo-controlled, paralle*l*-group, fixed-dose study of the efficacy and safety of Focalin™ LA (dexmethylphenidate hydrochloride extended-release capsules) administered once daily in adults with Attention-Deficit/Hyperactivity Disorder

Objectives:

Primary: Evaluate the efficacy and safety of Focalin LA (dexmethylphenidate hydrochloride extended-release capsules) administered once daily as compared with placebo in adults who met DSM-IV criteria for ADHD.

Secondary: Explore the population pharmacokinetics of Focalin LA in adults with ADHD.

Methodology:

This was a 5-week, multicenter, double-blind, randomized, placebo-controlled, paralle*l*- group, fixed-dose study in 220 adult male or female outpatients from 18 through 60 years of age who met DSM-IV criteria for ADHD (either combined or single type) and had a history of childhood onset of ADHD. Patients were to have a DSM- IV ADHD Rating Scale total score greater than or equal to 24 at Screening and Baseline, and functional impairment, defined as a Global Assessment of Functioning (GAF) score less than or equal to 60, at Screening and Baseline. Patients with a history of alcohol or substance abuse or dependence within the last 6 months were excluded. Subjects were randomized to either Focalin LA: 20 mg, 30 mg, 40 mg or placebo, (55 patients in each of the four treatment groups).

Daily dose options included 10, 20, 30, or 40 mg, achieved by taking 2 capsules once daily (i.e., one 10-mg capsule plus one placebo capsule, two 10-mg capsules, one 20-mg capsule plus one 10-mg capsule, or two 20-mg capsules), with the duration of treatment being 5 weeks.

Criteria for evaluation:

Efficacy:

Primary efficacy variable: Change from Baseline to final visit in the total score of the DSM-IV ADHD RS.

Secondary efficacy variables:

- the proportion of patients with at least 30% improvement in the total score of the DSM-IV ADHD RS at the final visit as compared with Baseline;
- change from Baseline to final visit in the Inattention subscore and Hyperactivity/Impulsivity subscore of the DSM-IV ADHD RS;
- the proportion of patients with improvement on the CGI-I scale (defined as patients with a final visit score of 1 “very much improved” or 2 “much improved” on the CGI-I scale);
- the proportion of patients at each level of improvement on the 7-point CGI-I scale at the final visit;
- the proportion of patients with improvement on the CGI-S scale (defined as patients with a decrease on the CGI-S score at final visit as compared with Baseline);
- change from Baseline to final visit in the total score and subscale scores of the CAARS (Observer and Self-Report separately);
- change from Baseline to final visit in the GAF score;
- change from Baseline to final visit in the Q-LES-Q total score.

Other variables of exploratory nature to be assessed included the subjective assessment of study drug onset and duration of action.

Safety: monitoring and recording all adverse events (including serious adverse events)
vital signs
body weight.
Laboratory parameters (including hematology, blood chemistry, and urine)
ECGs
physical examinations

Pharmacokinetics: Blood samples were to be collected at the final scheduled study visit, Visit 7. One blood sample was to be taken from all patients after all efficacy measurements had been performed. The objective was to explore the population pharmacokinetics of Focalin LA in adults with ADHD.

Pharmacogenetic assessments: No pharmacogenetic analyses are available at the time of completion of the Clinical Study Report.

Statistical methods: Data were summarized by treatment group with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements.

Evaluation of the primary efficacy variable was performed using an analysis of covariance (ANCOVA) model with treatment group, center and the baseline DSM-IV ADHD RS total score as explanatory variables. The primary comparison was between each of the two highest dose Focalin LA groups (30 and 40 mg) and placebo using Hochberg's procedure to adjust for multiplicity.

Secondary efficacy variables were analyzed as follows:

- Proportion of patients with at least 30% improvement in the DSM-IV ADHD RS total score was analyzed using a logistic regression model with treatment, center, and baseline DSM-IV ADHD RS total score as explanatory variables;

- Changes from Baseline to final visit in the DSM-IV ADHD RS subscale scores were analyzed by ANCOVA models similar to the analysis of the primary efficacy variable;

- Proportions of patients with improvement on the CGI-I and on the CGI-S scales were analyzed using logistic regression models with treatment and center as explanatory variables;

- Rating of the CGI-I at the final visit was analyzed by an extended Cochran-Mante*l*-Haenszel (CMH) test stratified by center.

Changes from Baseline to final visit in the CAARS total scores and subscale scores, the GAF score, and the Q-LES-Q total score were analyzed by ANCOVA models similar to the analysis of the primary efficacy variable.

No adjustment for multiplicity was performed for analyses of the secondary variables. Last observation carried forward (LOCF) was used to impute missing values for all final visit analyses.

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-specified ranges. Other safety data (e.g., vital signs, electrocardiogram) were considered as appropriate.

5.2 Appendix 2 BIOANALYTIC ASSAY VALIDATION

Table 48 Methylphenidate Assay Validation Report 1

(b) (4)

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5.3 Appendix 3 CONSULTS

None.

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

5.5 Appendix 5 FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
NDA Number	21-802	Brand Name	Focalin XR
Related IND(s)	63,885	Generic Name	dexmethylphenidate Modified Release Capsules
Related NDA(s)	21-282 Ritalin LA Capsules 21-278 Focalin IR Tablets	Pharmacologic Class	CNS Stimulant
OCPB Division (I, II, III)	I HFD-860	Chemical Class	
Medical Division	Neuropharmacology HFD-120	Indication(s)	ADHD
OCPB Reviewer	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	Dosage Form	Modified Release Capsule
Acting OCPB Team Leader	Sally Yasuda, B.S. Pharm.D.	Strengths	5 mg, 10 mg, 20 mg, 30 mg (b) (4)
Dosing Regimen	po qd		
Date of Submission	July 28, 2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	April 9, 2005	Sponsor	Novartis
Division Due Date	April 26, 2005	Priority Classification	1S
PDUFA Due Date	May 27, 2005		

Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1		Classroom – verification of duration of action. Will be reviewed by MO.
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		Single sample as expected due to multiple absorption phases (2 peaks) data is likely uninterpretable
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		IR tablets and Racemate MR
Route:	Oral			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		In Vitro study with Applesauce Otherwise references FE studies with racemic MR formulation
Dissolution:	X	1		
(IVIVC):	X	1		
Bio-wavier request based on BCS	No			
BCS class				MR – Not Applicable
Product Performance				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7		

File-ability and QBR comments		
	"X" if yes	**Comments**
Application file-able?	X	No pediatric PK for drug primarily used in a pediatric indication. However, racemic version of formulation is characterized in children and no differences are expected with *d*-isomer.

Comments to be sent to firm:	None.
QBR questions (key issues to be considered)	Effect of Noontime meal. – Sponsor has included additional information on composition of noon time meals from food studies with the racemate and from studies in this application. This was agreed to at pre-NDA meeting.
Other comments or information not included above	Population PK in phase III study is claimed by sponsor as being uninterpretable. This was expected by both the sponsor and FDA as the formulation has multiple absorption phases (2 peaks) yet only a single sample was drawn per patient. This raises the question of the ethics of subjecting subjects to invasive medical procedures when it's known a priori that no useful information is likely to be obtained, nor is there any benefit for blinding, etc.. Either no samples should be drawn or sufficient samples should be drawn such that they are likely to provide useful information. See Appendix 1 for comparison of OCPB submissions for the *d*-isomer (Focalin XR) and the racemate (Ritalin LA) for comparison and appropriateness of cross-referencing.
Primary reviewer Signature and Date	September 22, 2004
Team Leader Signature and Date	

CC: NDA 21-802
HFD-850 (P. Lee, Lesko)
HFD-860 (Kavanagh, Yasuda, Baweja, MehtaM, Rahman)
HFD-120 (TaylorR)
HFD-120 (AndreasonP, KatzR, GlassR)
CDR

tudy No.	Study Type	Title	Study No.	Study Type	Title
n Vivo					
rotocol 01	Relative Bioavailability	A single dose study in healthy volunteers to compare the bioavailability of two Elan methylphenidate hydrochloride 20 mg capsule formulations relative to Ritalin® 10 mg tablet (dosed twice at a four hourly interval) (Novartis).	2101	Relative Bioavailability	A randomized, open-label, 3-period, crossover study to compare the oral bioavailability between FocalinTM LA (d methylphenidate) 20 mg, FocalinTM IR two 10 mg capsules dosed 4 hours apart, and Ritalin® LA (*d,l*-methylphenidate) 40 mg in healthy volunteers
			2102	Dose Proportionality	A randomized, open-label, single dose, five treatment, five period, crossover study to evaluate the dose proportionality of Focalin LA (5, 10, 20, 30, 40) capsule in healthy subjects
rotocol 09	Formulation Development	A single dose study in healthy volunteers to assess the effect of food on the bioavailability of each of two Elan 20 mg methylphenidate hydrochloride modified release capsule formulations.			
rotocol 02	PK/PD in Kids	A double-blind, randomized, five treatment crossover study of the pharmacodynamic and pharmacokinetic profiles of four formulation/dose variances of Ritalin-QD and placebo in ADHD children treated with Ritalin®.	*N/A*	*Pediatric PK*	*Refs Ritalin LA*
rotocol 04	Food Effect inc. Applesauce	A three-period crossover study to evaluate the effect of a high fat meal on the pharmacokinetics of a 40-mg modified release Ritalin-QD capsule in healthy adult subjects.	*N/A*	*Food Effect*	*Refs Ritalin LA* *Includes caloric breakdown of noontime meals for Focalin LA and Ritalin LA studies*
			[redacted] (b) (4)		
			2302	Pop PK - Adults	A 5-week, multicenter, double-blind, randomized, placebo-controlled, parallel group, fixed-dose study of the efficacy and safety of Focalin™ LA (dexmethylphenidate hydrochloride extended-release capsules) administered once daily in adults with Attention-Deficit/Hyperactivity Disorder
			US08	PD	A randomized, multi-center, double-blind, cross-over study comparing the efficacy, safety, and tolerability of FocalinTM LA 20 mg versus placebo in children (6-12 years) with Attention Deficit Hyperactivity Disorder (ADHD) in ar analog classroom setting.
n Vitro					
	In Vitro Applesauce Study	Phase IV	[redacted] (b) (4)	*In Vitro* Applesauce Study	Analytical study of the effect of mixing the contents of Ritalin LA and Focalin LA 40 mg capsules with applesauce
	Bioanalytical Methods	Yes		Bioanalytical Methods	[redacted] (b) (4)
	Dissolution	Yes		Dissolution	Drug release testing comparison using three different test media

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/s/

Ron Kavanagh
5/16/05 10:41:48 AM
BIOPHARMACEUTICS

Sally Yasuda
5/16/05 12:35:44 PM
BIOPHARMACEUTICS