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RESEARCH**

APPLICATION NUMBER:

21-802

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

**New Drug Application
Clinical Pharmacology and Biopharmaceutics Review**

NDA:	21-802
Types of Submissions:	NDA N-BB
Generic Name:	Dex-Methylphenidate Hydrochloride [REDACTED] Release Capsules
Formulation:	[REDACTED]
Strengths:	5 mg, 10 mg, 20 mg, [REDACTED]
Route:	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 (*E*_{max}), 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 [REDACTED] produce similar concentration profiles although beads with faster dissolutions (i.e. [REDACTED] 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 [REDACTED] and this tighter upper limit is clearly acceptable.
- Biowaivers for the 5 mg and [REDACTED] 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 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, (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, 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 °C
Speed of rotation:	100 rpm.
Sampling Times:	0.5, 4, 6, and 10 hours
Specifications % of Label Claim	30 minutes 240 minutes (4 hours) 360 minutes (6 hours) 600 minutes (10 hours) Not less than
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 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 dexamethylphenidate, the dextrorotary isomer of methylphenidate. Dexamethylphenidate 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. Dexamethylphenidate 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 dexamethylphenidate 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 three proposed strengths for marketing, 5 mg, 10 mg, 20 mg 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 Dexamethylphenidate 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

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,



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

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.



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

Formulation	API	Patient Age	Dosage and Administration			Switching from another Formulation
			Initial Dosage	Dose Increments / Dose Titration	Maximum Dosage	
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
		Children (≥ 6 yo)	5 mg bid before breakfast and lunch	5 – 10 mg weekly increments	60 mg	
		The following is the labeled D&A				
Ritalin IR	d,l-MPH	Adults	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	—	Racemic MPH – half of total daily dose
		Adults	10 mg / day	10 mg weekly	—	Focalin IR - same total daily dose

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 [REDACTED]. 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?

**** 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, _____ 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 _____ 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 T_{max2} 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?**

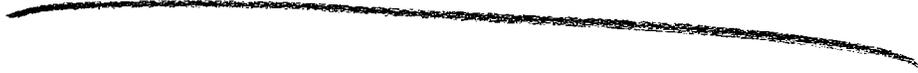
The sponsor's proposed two-stage *dissolution method* for the enteric-coated drug product *is acceptable* and identical to the method for Ritalin LA. However the *drug release specifications need to be modified*.

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:

<u>Time</u>	<u>Focalin XR</u>		<u>Ritalin LA</u>
	<u>Reviewer's</u>	<u>Sponsor's</u>	
0.5 hours			
4 hours			
6 hours			
10 hours			



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2.4 Signatures

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

Date

Senior Reviewer
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

Sally Yasuda, Pharm.D.

Date

Acting Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

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, RostoffB)
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.

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
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

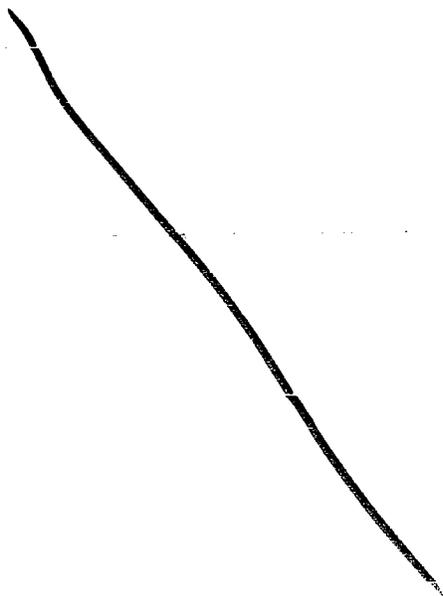
The TBM formulation is intended to mimic the release characteristics of two sequential doses of an immediate release tablet administered 4 – 5 hours apart.

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

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

Figure 1 Schematic of Focalin™ XR Beads



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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

1 Analytical and microbiological testing of excipients only

3.2.5 Primary Packaging Containers

Primary packaging will consist of 100 count bottles with an aluminum induction seal and a 38 mm 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	100
Tablet Strengths (mg)	Bottle Sizes by Tablet Count
5, 10, 20	

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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)
Dexamethylphenidate hydrochloride		
Polyethylene glycol		
Purified water ^a		
 		
 		
 		
Talc		
Triethyl citrate		
 		
Total Batch		

a Removed during processing

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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
Phase II Studies						
US08	Classroom PD Study in Peds	Focalin™ XR	20 mg	NR	RD020302	
		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						
<i>In Vitro</i> Applesauce Study		Ritalin LA	40 mg	NR	104H1035	NR
		Focalin™ XR	40 mg	NR		NR
<i>In Vitro</i> Dissolution Study		Focalin® LA	20 mg	NR	RD020303	Development Formulations
		Ritalin® LA	40 mg	NR	104H1035	
		Ritalin® LA	10 mg	NR	3B093	

a Focalin = dexamethylphenidate, (*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		2302
Study Descriptors	BE to Ritalin LA	Dose Proportionality		Phase III Pop PK
Sample Handling Procedures				

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.

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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.

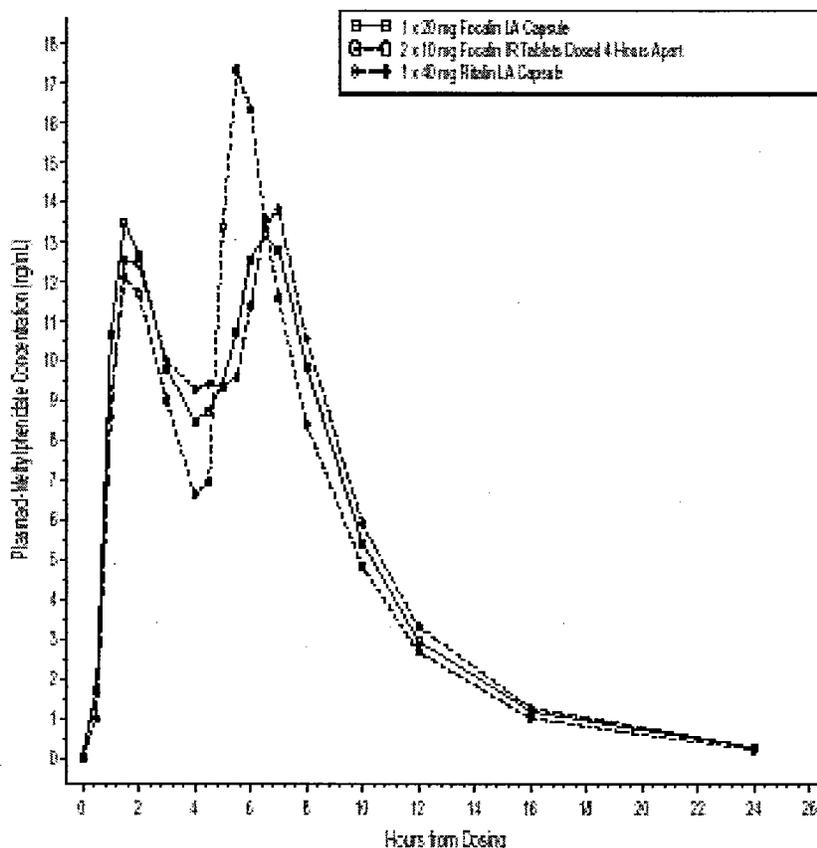
The data from this study indicates that Focalin XR and Ritalin LA exhibit similar bioavailability in terms of both rate and extent of absorption. Compared to Focalin IR, the extent of absorption was also similar. However, as expected the time metrics for Focalin IR were less variable resulting in a larger 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 C_{max} and T_{max} 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 (<i>d</i> -methylphenidate) 1 x 20 mg capsule	Focalin IR (<i>d</i> -methylphenidate) 1 x 10 mg tablet Dosed 4 hours apart (total 2 doses)	Ritalin LA (<i>d,l</i> -methylphenidate) 1 x 40 mg capsule
N	24	25	24
Tlag (hours)	0.5 ± 0.0 (0.0) [0.5]	0.5 ± 0.0 (0.0) [0.5]	0.5 ± 0.1 (19.6) [0.5]
Tmax1 (hours)	1.5 ± 0.6 (38.9) [1.5]	1.6 ± 0.3 (18.7) [1.5]	1.8 ± 0.6 (34.7) [1.75]
Cmax1 (ng/ml)	13.5 ± 4.2 (31.5) [12.5]	12.6 ± 3.9 (30.8) [11.6]	13.3 ± 3.0 (22.8) [13.1]
Tminip (hours)	4 ± 0.8 (20.5) [4]	4.3 ± 0.3 (5.8) [4.5]	4.4 ± 1.1 (25.8) [4.75]
Cminip (ng/ml)	7.6 ± 1.7 (22.5) [7.4]	6.3 ± 1.8 (29.4) [5.7]	7.4 ± 2.6 (34.6) [6.6]
Tmax2 (hours)	6.5 ± 0.7 (11.1) [6.5]	5.6 ± 0.3 (5.9) [5.5]	6.1 ± 1.1 (17.9) [6.5]
Cmax2 (ng/ml)	14.9 ± 4.0 (26.8) [14.35]	17.9 ± 5.3 (29.8) [16.9]	16.3 ± 4.5 (27.4) [15.85]
Tmax (hours)	4.6 ± 2.4 (51.6) [5.75]	5.6 ± 0.3 (5.9) [5.5]	5.9 ± 1.3 (22.3) [6.5]
Cmax (ng/ml)	15.5 ± 4.3 (27.7) [14.65]	17.9 ± 5.3 (29.8) [16.9]	16.1 ± 4.4 (27.5) [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	Treatment B	Treatment C
	Focalin XR Capsule 1 x 20 mg	2 Doses of Focalin IR Tablets 1 x 10 mg Dosed 4 Hours Apart	Ritalin LA Capsule 1 x 40 mg
N	24	25.0	24
Tmax(0-4) (hr)	1.57 ± 0.34 (21.71) [1.50]	1.64 ± 0.31 (18.58) [1.50]	1.96 ± 0.75 (38.26) [2.00]
	1.53 (23.42)	1.61 (19.87)	1.87 (29.57)
Cmax(0-4) (ng/ml)	13.7 ± 4.6 (34.0) [12.5]	12.6 ± 3.9 (30.8) [11.6]	13.2 ± 3.0 (22.8) [13.1]
	13.1 (29.6)	12.2 (26.3)	13.0 (21.7)
Tmax(4-10) (hr)	6.28 ± 0.72 (11.43) [6.50]	5.63 ± 0.33 (5.90) [5.51]	6.13 ± 1.09 (17.83) [6.50]
	6.24 (12.15)	5.62 (5.83)	6.03 (19.62)
Cmax(4-10) (ng/ml)	14.9 ± 4.0 (26.8) [14.4]	17.9 ± 5.3 (29.8) [16.9]	16.3 ± 4.5 (27.4) [15.9]
	14.4 (25.4)	17.3 (26.4)	15.8 (27.7)
Tmax (hr)	4.63 ± 2.39 (51.61) [5.76]	5.63 ± 0.33 (5.90) [5.51]	5.88 ± 1.31 (22.29) [6.50]
	3.79 (82.10)	5.62 (5.83)	5.69 (29.51)
Cmax (ng/ml)	15.5 ± 4.3 (27.7) [14.7]	17.9 ± 5.3 (29.8) [16.9]	16.4 ± 4.4 (27.0) [15.9]
	15.0 (26.0)	17.3 (26.4)	15.8 (26.7)
AUC(0-4) (ng/ml*hr⁻¹)	36.3 ± 10.6 (29.2) [34.2]	32.5 ± 10.2 (31.5) [30.5]	35.0 ± 8.7 (24.9) [32.6]
	35.1 (25.3)	31.3 (26.9)	34.1 (23.3)
AUC(4-10) (ng/ml*hr⁻¹)	59.1 ± 16.0 (27.0) [55.0]	61.6 ± 20.0 (32.5) [57.4]	60.9 ± 15.0 (24.6) [58.2]
	57.4 (23.9)	59.3 (27.4)	59.3 (23.8)
AUC(0-t) (ng/ml*hr⁻¹)	117.7 ± 39.3 (33.4) [107.5]	113.6 ± 39.1 (34.4) [102.9]	120.4 ± 34.9 (29.0) [112.4]
	113.3 (26.5)	109.0 (28.0)	116.6 (25.3)
AUC(0-inf) (ng/ml*hr⁻¹)	119.1 ± 40.7 (34.1) [108.4]	114.9 ± 40.0 (34.8) [103.2]	121.9 ± 36.3 (29.8) [113.6]
	114.5 (26.9)	110.1 (28.2)	117.9 (25.6)
%AUC(0-inf) extrapolated	1.1 ± 0.8 (71.4) [0.7]	1.0 ± 0.6 (61.4) [0.8]	1.1 ± 0.7 (64.9) [0.9]
	0.8 (81.0)	0.9 (69.6)	1.0 (64.9)
t1/2 (hr)	3.26 ± 0.51 (15.81) [3.14]	3.11 ± 0.52 (16.85) [3.05]	3.19 ± 0.51 (16.07) [3.09]
	3.22 (15.62)	3.07 (17.01)	3.15 (15.73)
Kel (1/hr)	0.218 ± 0.033 (15.261) [0.221]	0.229 ± 0.039 (17.131) [0.227]	0.223 ± 0.034 (15.286) [0.224]
	0.215 (15.624)	0.226 (17.008)	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
C_{max}(0-4) (ng/mL)	1.06 (1.00,1.13)	1.01 (0.96,1.06)
C_{max}(4-10) (ng/mL)	0.82 (0.77,0.88)	0.92 (0.87,0.96)
C_{max} (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.

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3.4.1.3 Dose Proportionality

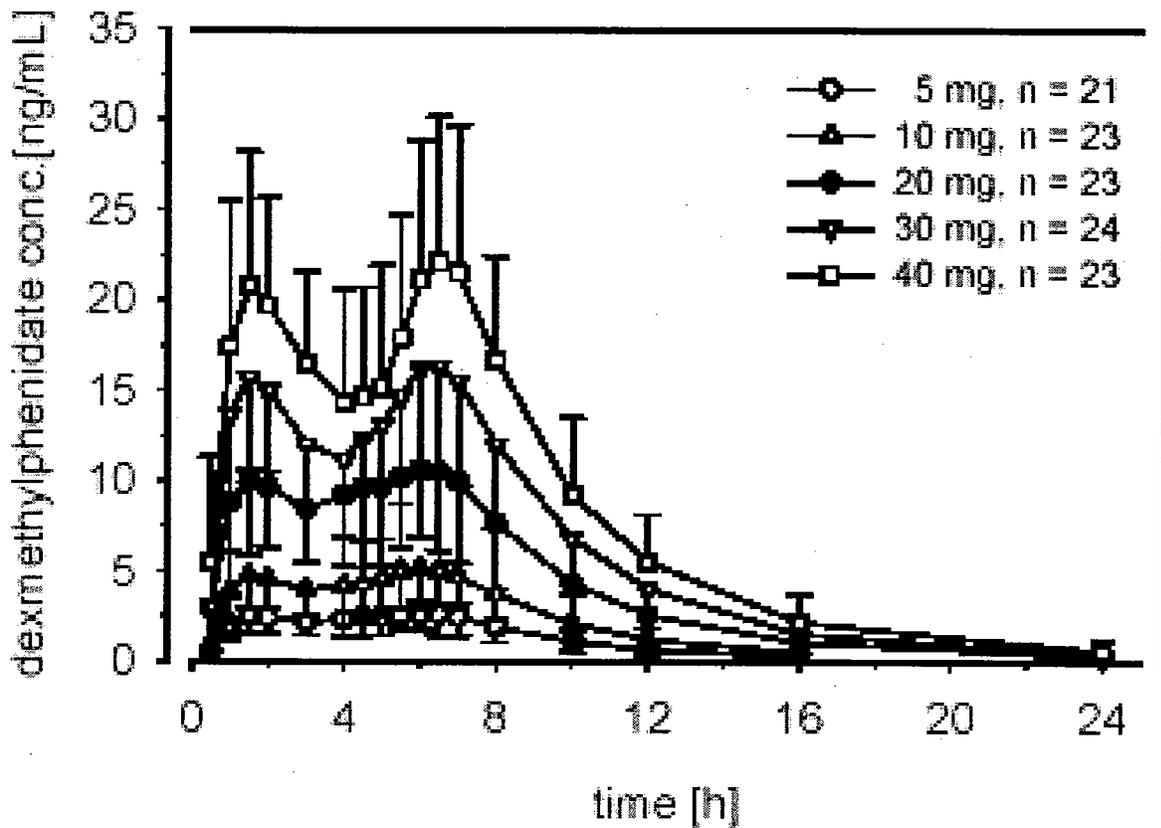
Study 2102 was a 5-way crossover in 25 healthy male and female adults subjects between 18 and 45 years of age to evaluate dose proportionality over the dose range of 5 mg to 40 mg. A dose proportionality study was performed as the proposed maximum dosage of 40 mg of *d*-MPH is greater than the currently 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 Dexamethylphenidate Pharmacokinetic Metrics

	5mg		10 mg		20 mg		30 mg		40 mg
	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)	3.25 (29.0) [3.20]	6.27 ± 1.81 (28.8)	6.05 (27.1) [5.93]	13.2 ± 4.40 (33.2)	12.6 (31.9) [12.0]	19.4 ± 6.07 (31.3)	18.5 (31.7) [18.3]	26.2 ± 7.76 (29.6)
	0.68 ± 0.23 (33.5)	0.65 (29.0) [0.640]	0.63 ± 0.18 (28.8)	0.605 (27.1) [0.593]	0.66 ± 0.22 (33.2)	0.631 (31.9) [0.600]	0.65 ± 0.20 (31.3)	0.618 (31.7) [0.608]	0.66 ± 0.19 (29.6)
	5.36 ± 1.35 (25.1)	5.14 (34.8) [5.53]	4.74 ± 2.00 (42.2)	4.13 (67.2) [5.53]	4.94 ± 1.92 (38.9)	4.26 (77.4) [5.50]	4.21 ± 2.30 (54.6)	3.40 (85.0) [5.00]	5.28 ± 2.00 (37.8)
	2.84 ± 1.02 (35.9)	2.68 (37.1) [2.46]	5.30 ± 1.88 (35.6)	5.00 (35.7) [4.88]	11.7 ± 4.54 (38.9)	10.8 (41.9) [10.9]	16.8 ± 6.36 (37.9)	15.7 (38.4) [16.1]	22.0 ± 7.73 (35.2)
	0.57 ± 0.2 (35.9)	0.54 (37.1) [0.49]	0.53 ± 0.19 (35.6)	0.5 (35.7) [0.49]	0.59 ± 0.23 (38.9)	0.54 (41.9) [0.55]	0.56 ± 0.21 (37.9)	0.52 (38.4) [0.54]	0.55 ± 0.19 (35.2)
	2.62 ± 1.16 (44.2)	2.38 (47.1) [2.00]	2.18 ± 1.13 (51.6)	1.96 (48.3) [1.50]	2.62 ± 1.26 (48.1)	2.27 (64.2) [2.00]	1.61 ± 0.68 (42.5)	1.51 (36.0) [1.50]	1.85 ± 0.68 (36.8)
	3.31 ± 1.10 (33.1)	3.18 (27.5) [3.20]	6.07 ± 1.81 (29.8)	5.84 (27.7) [5.93]	13.1 ± 4.38 (33.5)	12.5 (31.7) [11.4]	18.5 ± 5.83 (31.5)	17.7 (31.6) [17.9]	24.6 ± 7.55 (30.7)
10	0.66 ± 0.22 (33.1)	0.64 (27.5) [0.64]	0.61 ± 0.18 (29.8)	0.58 (27.7) [0.59]	0.66 ± 0.22 (33.5)	0.63 (31.7) [0.57]	0.62 ± 0.19 (31.5)	0.59 (31.6) [0.6]	0.62 ± 0.19 (30.7)
	5.55 ± 0.99 (17.8)	5.47 (18.1) [5.53]	5.92 ± 0.94 (15.8)	5.84 (16.2) [6.00]	5.65 ± 0.98 (17.2)	5.57 (17.4) [5.50]	5.98 ± 0.77 (12.9)	5.93 (13.3) [6.00]	6.17 ± 0.90 (14.6)
	7.60 ± 2.45 (32.2)	7.24 (33.3) [7.12]	14.2 ± 4.93 (34.7)	13.4 (34.9) [12.8]	31.0 ± 12.1 (39.0)	28.7 (42.5) [28.7]	44.9 ± 14.8 (33.1)	42.5 (35.1) [43.4]	60.1 ± 20.2 (33.7)
	1.52 ± 0.49 (32.2)	1.45 (33.3) [1.42]	1.42 ± 0.49 (34.7)	1.34 (34.9) [1.28]	1.55 ± 0.61 (39)	1.44 (42.5) [1.44]	1.5 ± 0.49 (33.1)	1.42 (35.1) [1.45]	1.5 ± 0.51 (33.7)
	9.70 ± 2.89 (29.8)	9.36 (27.0) [9.39]	18.4 ± 6.09 (33.0)	17.7 (29.5) [16.7]	38.8 ± 12.8 (32.9)	36.8 (34.3) [36.8]	56.8 ± 18.4 (32.5)	54.1 (32.4) [53.5]	73.5 ± 21.9 (29.8)
	1.94 ± 0.58 (29.8)	1.87 (27) [1.88]	1.84 ± 0.61 (33)	1.77 (29.5) [1.67]	1.94 ± 0.64 (32.9)	1.84 (34.3) [1.84]	1.89 ± 0.61 (32.5)	1.8 (32.4) [1.78]	1.84 ± 0.55 (29.8)
	12.8 ± 4.04 (31.7)	12.3 (26.7) [12.1]	24.2 ± 7.79 (32.2)	23.3 (28) [23.4]	50.8 ± 17.8 (35.0)	48.2 (33.7) [49.4]	75.6 ± 24.6 (32.6)	72.2 (31.9) [73.0]	99.4 ± 30.3 (30.4)
	2.56 ± 0.81 (31.7)	2.46 (26.7) [2.42]	2.42 ± 0.78 (32.2)	2.33 (28) [2.34]	2.54 ± 0.89 (35)	2.41 (33.7) [2.47]	2.52 ± 0.82 (32.6)	2.41 (31.9) [2.43]	2.49 ± 0.76 (30.4)
	24.7 ± 9.55 (38.6)	23.5 (30.9) [22.2]	47.0 ± 16.6 (35.2)	44.9 (30.4) [45.9]	101 ± 40.4 (40.0)	95.1 (35.4) [93.0]	150 ± 52.3 (34.8)	143 (32.9) [147]	201 ± 65.4 (32.6)
ng]	4.95 ± 1.91 (38.6)	4.70 (30.9) [4.44]	4.70 ± 1.66 (35.2)	4.49 (30.4) [4.59]	5.05 ± 2.02 (40.0)	4.76 (35.4) [4.65]	5.00 ± 1.74 (34.8)	4.75 (32.9) [4.89]	5.02 ± 1.64 (32.6)
	25.5 ± 9.89 (38.7)	24.3 (30.7) [24.0]	48.1 ± 17.0 (35.4)	45.9 (30.2) [46.4]	102 ± 41.7 (40.6)	96.4 (35.5) [94.7]	152 ± 53.8 (35.5)	144 (33.3) [149]	204 ± 68.1 (33.4)
ng]	5.10 ± 1.98 (38.7)	4.86 (30.7) [4.81]	4.81 ± 1.70 (35.4)	4.59 (30.2) [4.64]	5.12 ± 2.08 (40.6)	4.82 (35.5) [4.74]	5.06 ± 1.79 (35.5)	4.80 (33.3) [4.96]	5.10 ± 1.70 (33.4)
ted	3.11 ± 1.59 (51.3)	2.84 (42.6) [2.70]	2.17 ± 1.08 (49.8)	1.91 (58.7) [1.86]	1.29 ± 0.97 (75.5)	0.993 (89.5) [1.08]	1.04 ± 0.61 (58.8)	0.897 (59.2) [0.834]	1.44 ± 1.69 (117)
	6.70 ± 1.09 (16.3)	6.62 (15.9) [6.83]	6.78 ± 1.13 (16.6)	6.70 (15.9) [6.30]	6.77 ± 1.18 (17.4)	6.68 (17.5) [6.41]	6.80 ± 0.83 (12.2)	6.75 (12.5) [6.83]	7.05 ± 1.03 (14.6)
	2.92 ± 0.67 (22.9)	2.86 (21.6) [2.63]	3.01 ± 0.73 (24.4)	2.93 (24.0) [2.83]	3.18 ± 0.71 (22.3)	3.11 (22.2) [3.19]	3.07 ± 0.50 (16.3)	3.03 (16.5) [3.00]	3.29 ± 0.90 (27.3)

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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, parallel-group, fixed-dose study of the efficacy and safety of Focalin™ XR (dexamethylphenidate 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 dexamethylphenidate. 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 dexamethylphenidate after administration of Focalin XR across dose groups (20, 30, and 40 mg/day) to examine dose proportionality*
- *To compare dexamethylphenidate 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
<i>C(0.5-2.5)</i>	<i>Concentration around expected tmax (1.5 h) for IR (immediate release) dose</i>
<i>C(3-5)</i>	<i>Concentration around expected tmin (4h) between IR and DR (delayed release) doses</i>
<i>C(5.5-7.5)</i>	<i>Concentration around expected tmax (6.5 h) for DR dose</i>
<i>C(8-10)</i>	<i>Concentration at end of sampling time</i>
<i>C(0-4)*</i>	<i>Concentration from time zero to 4 hours (IR dose)</i>
<i>C(4-8)*</i>	<i>Concentration from time 4 to 8 hours (DR dose)</i>
<i>C(0-8)</i>	<i>Concentration from time zero to 8 hours, where 8 hours is the minimum desired duration of effect</i>
<i>C(0-10)</i>	<i>Concentration from time zero to 10 hours, where 10 hours is the maximum sampling time</i>

**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.

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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 [†]
	20 mg	30 mg	40 mg	20 mg	30 mg	40 mg	
C(0.5-2.5)	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)	0.11
C(3-5)	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)	0.29
C(5.5-7.5)	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)	0.49
C(8-10)	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)	0.85
C(0-4)	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)	0.09
C(4-8)	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)	0.03 [†]
C(0-8)	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)	0.26
C(0-10)	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)	0.58

^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

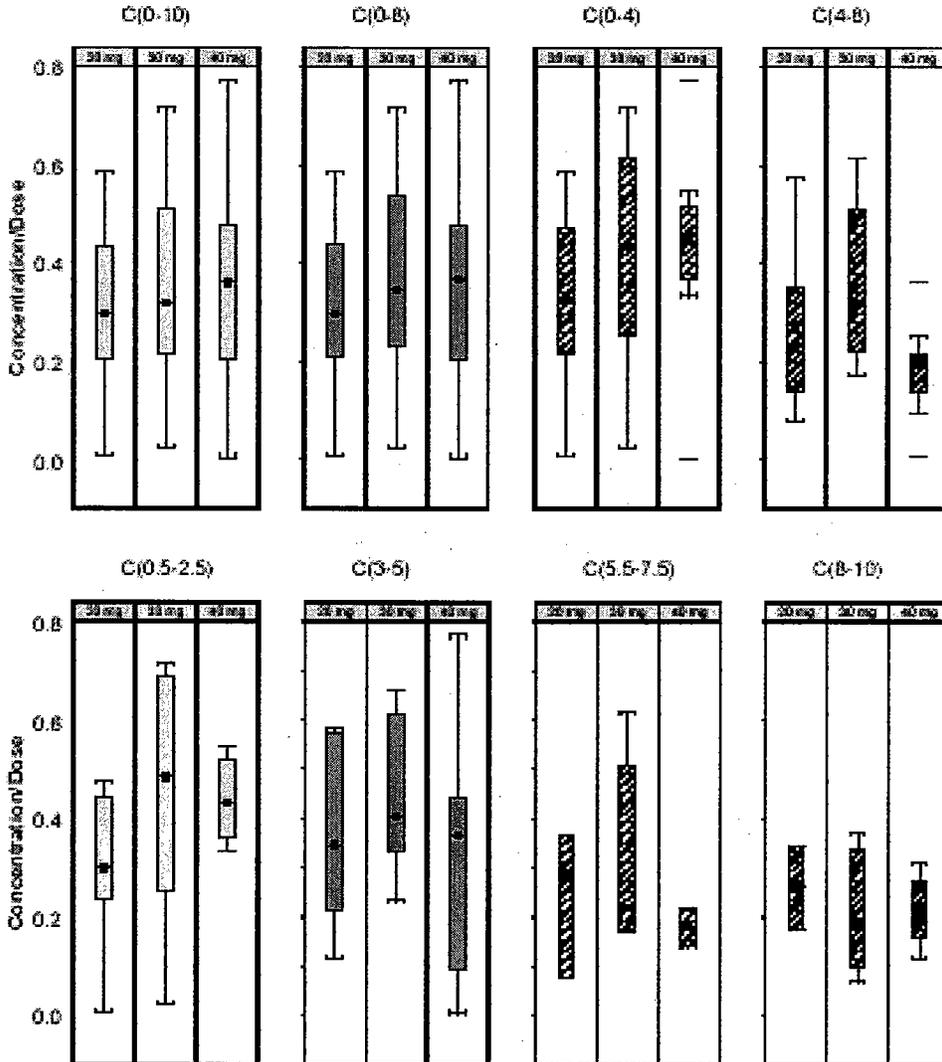
Comparison	Estimate of Difference	Standard Error	Lower Bound 95% CI	Upper Bound 95% CI
20 mg and 30 mg	-0.0881	0.06	-0.24	0.0638
20 mg and 40 mg	0.0891	0.0629	-0.0702	0.248
30 mg and 40 mg	0.177	0.0629	0.0179	0.336*

* 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

Figure 4-2 Boxplots of dose-normalized concentrations by time window

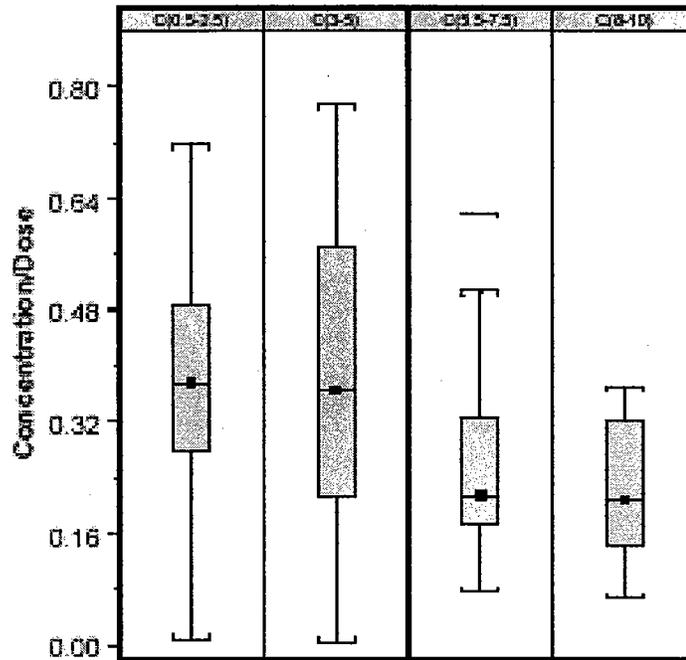


Peak-trough comparisons

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(5.5-7.5) and C(8-10) (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)	Tminip (Hours)	Cminip (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	
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	
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	
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	
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	

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.

**Appears This Way
On Original**

1	C	F	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	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]
20	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	155	61.7	2	12.8	4.5	8.8	6.5	14.9	0.0104	0.0071	0.0121
Other	F	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	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]	
5	C	M	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 - 0.001 [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]
	Other		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

	[60]	[110]	[1000]	[4]	[300]	[40]	[10000]	[100000]	[1000000]	[10000000]	[100000000]	
20	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	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]
40	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]
	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]
	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]
	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]
3	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]
	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 T_{max} 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.

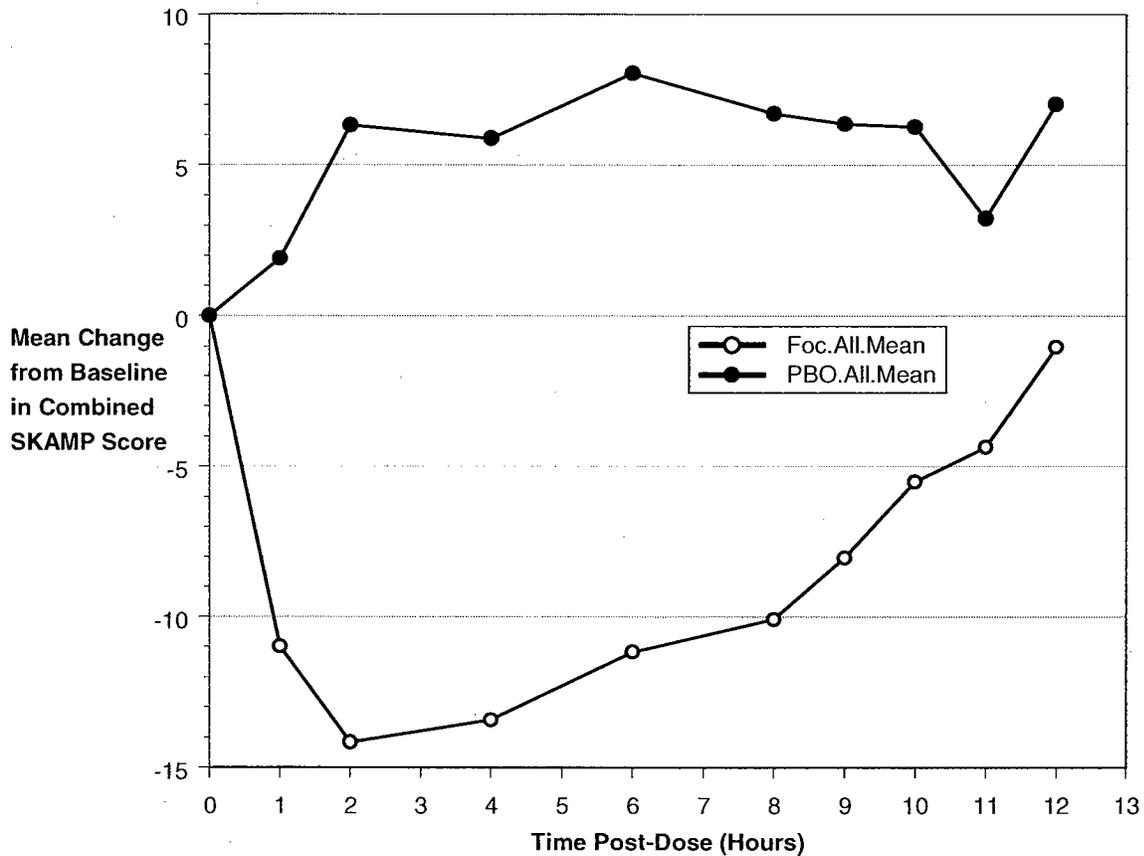
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3.5.3 Efficacy Results

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.

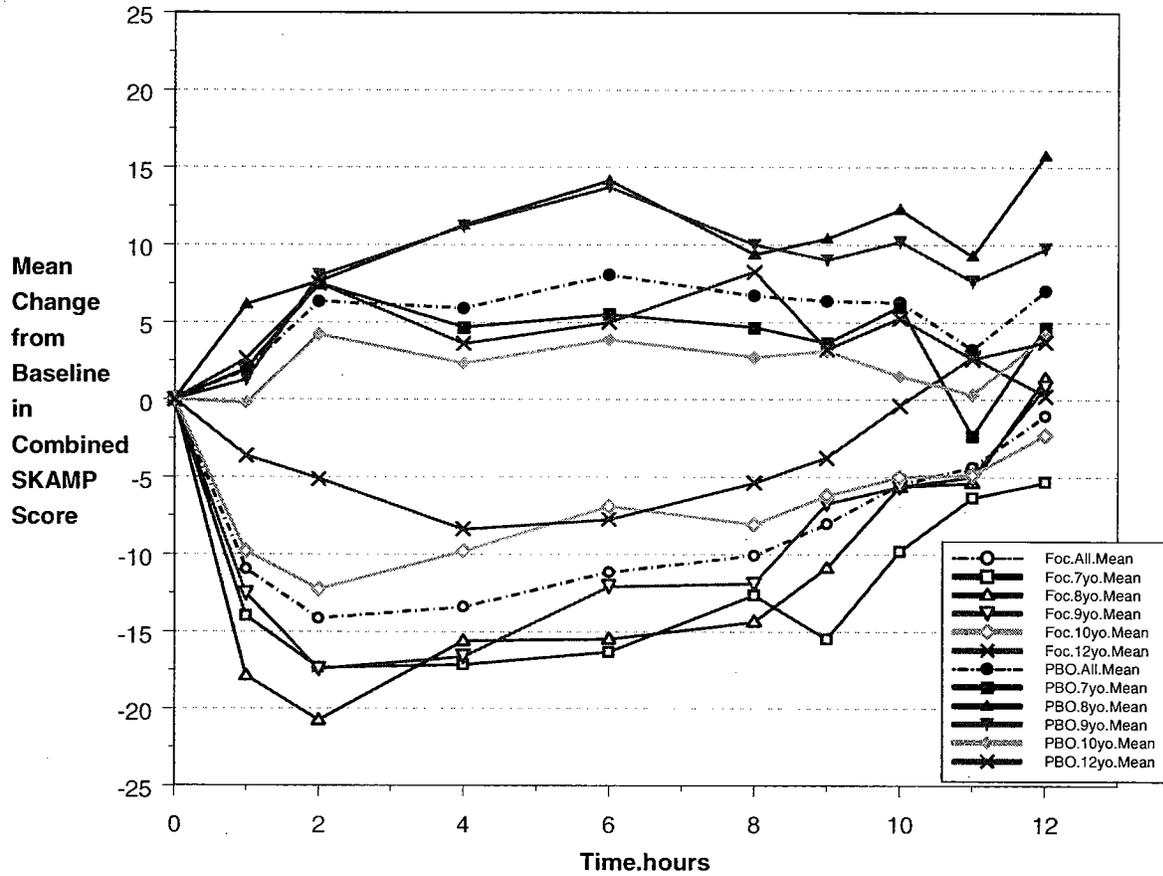
Figure 15 Mean Change from Baseline in Combined SKAMP Scores for Focalin XR (d-MPH) 20 mg Compared to Placebo in – Study US08



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

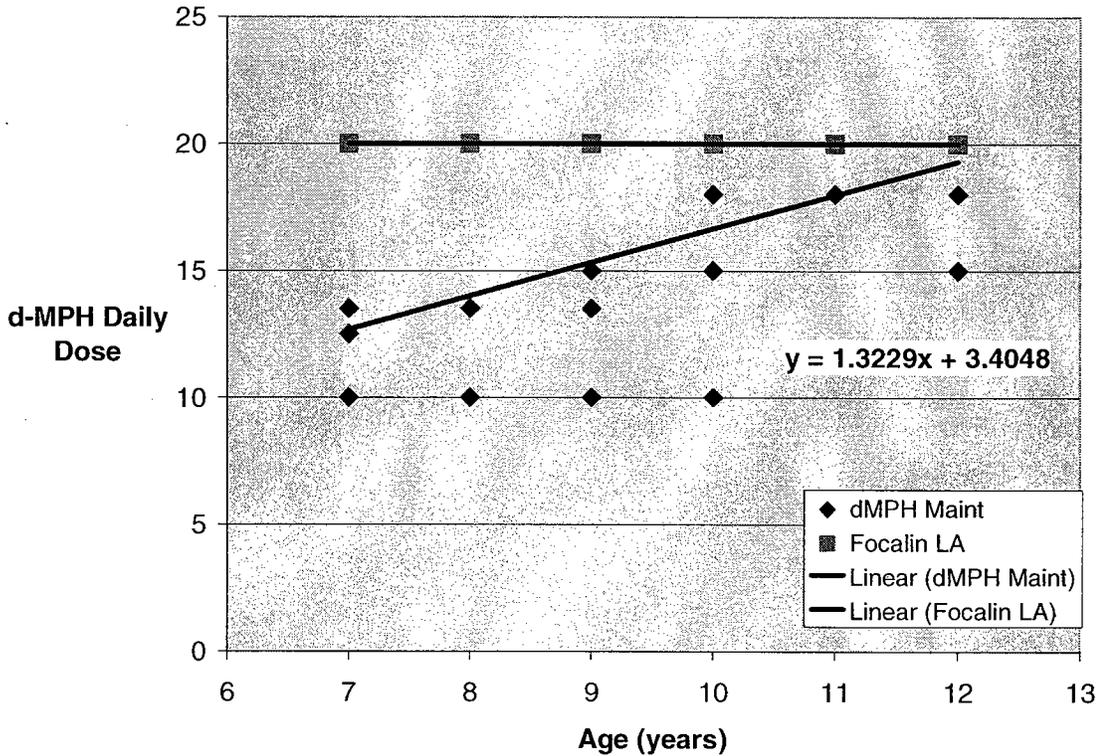


Table 30 Total Daily d-MPH Pre-Study Maintenance Dose by Age and Ratio of Focalin XR Dose to Pre-Study Dose by Age - Study US08

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

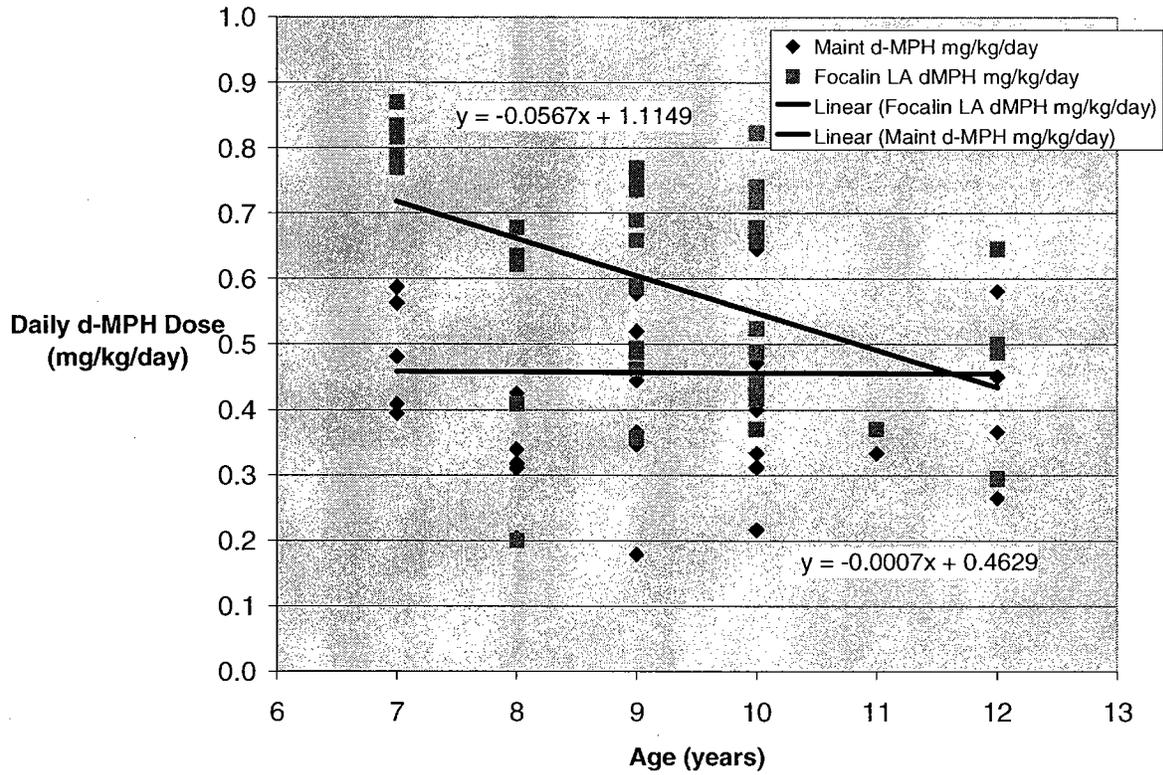
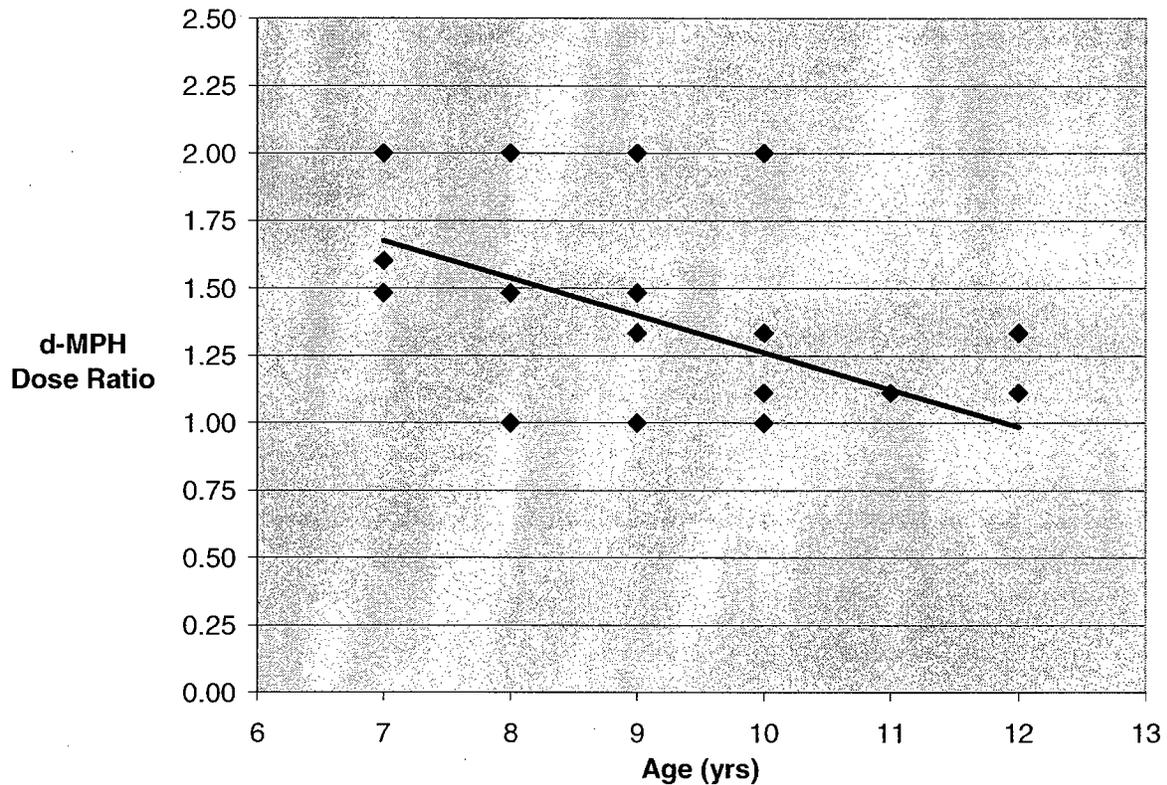


Figure 19 Ratio of Focalin XR Dose to Total Daily d-MPH Maintenance Dose by Age - Study US08



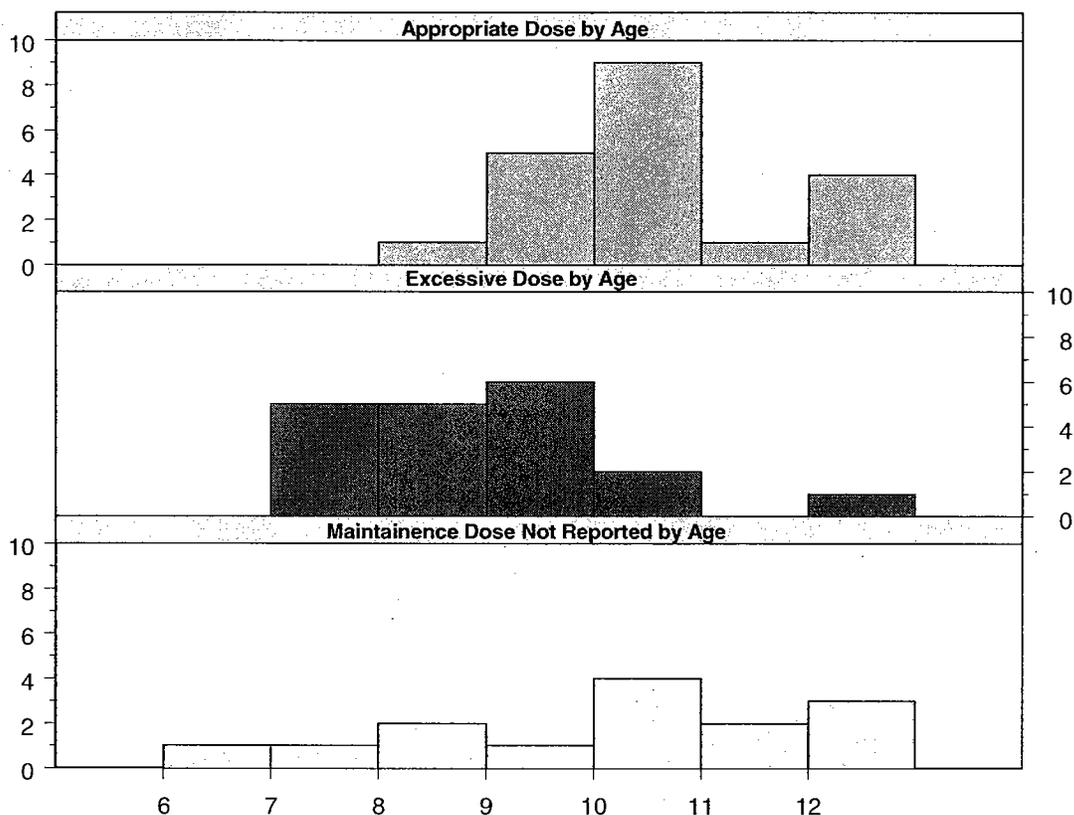
3.5.3.3 Efficacy for Subjects with Appropriate Dosing

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.

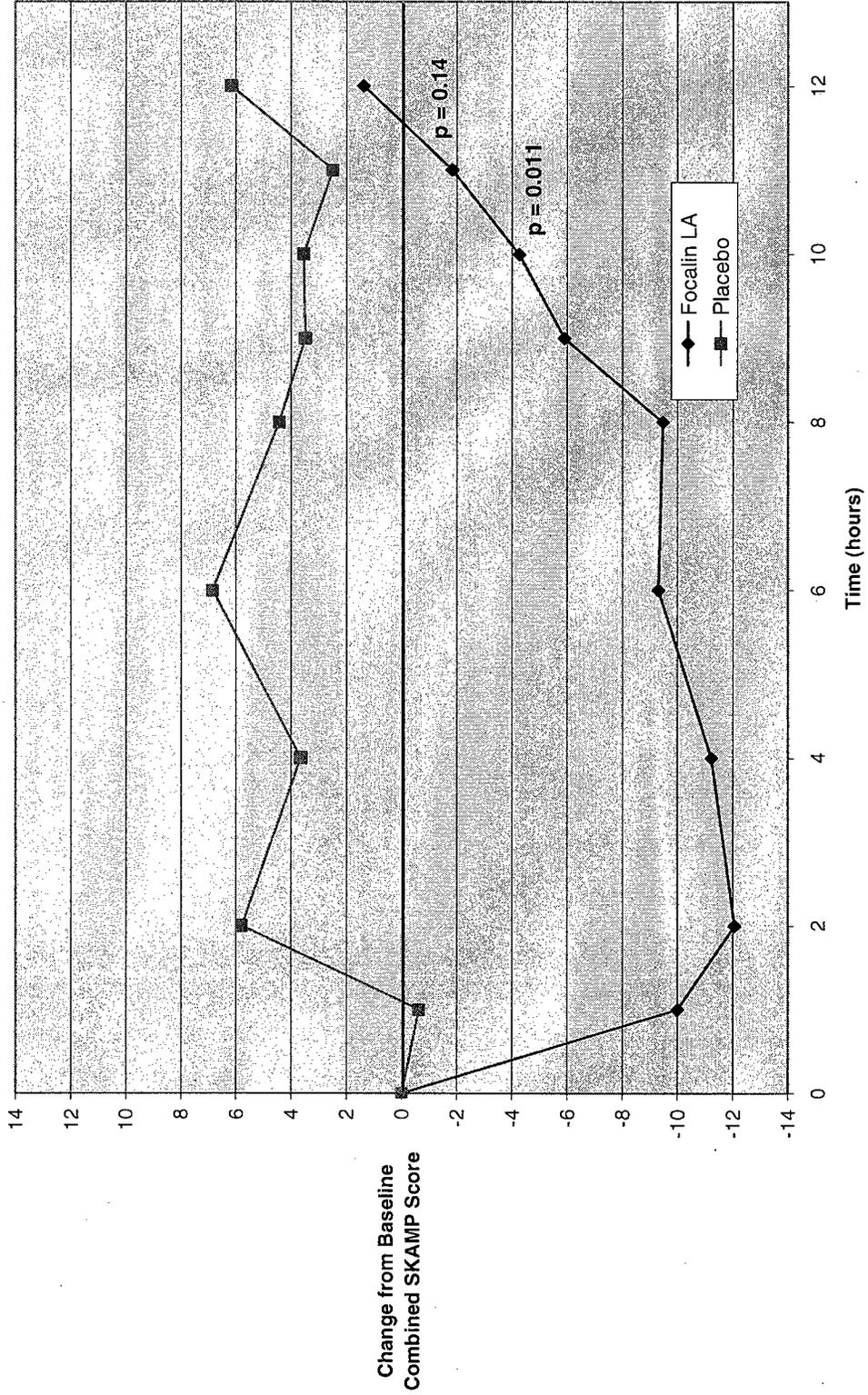
Table 32 Summary Statistics for SKAMP Scores by Time Post-Dose for Subjects Appropriately Dosed – Study US08

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												

^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

Duration of Effect with Appropriate Dosing



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, whereas 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

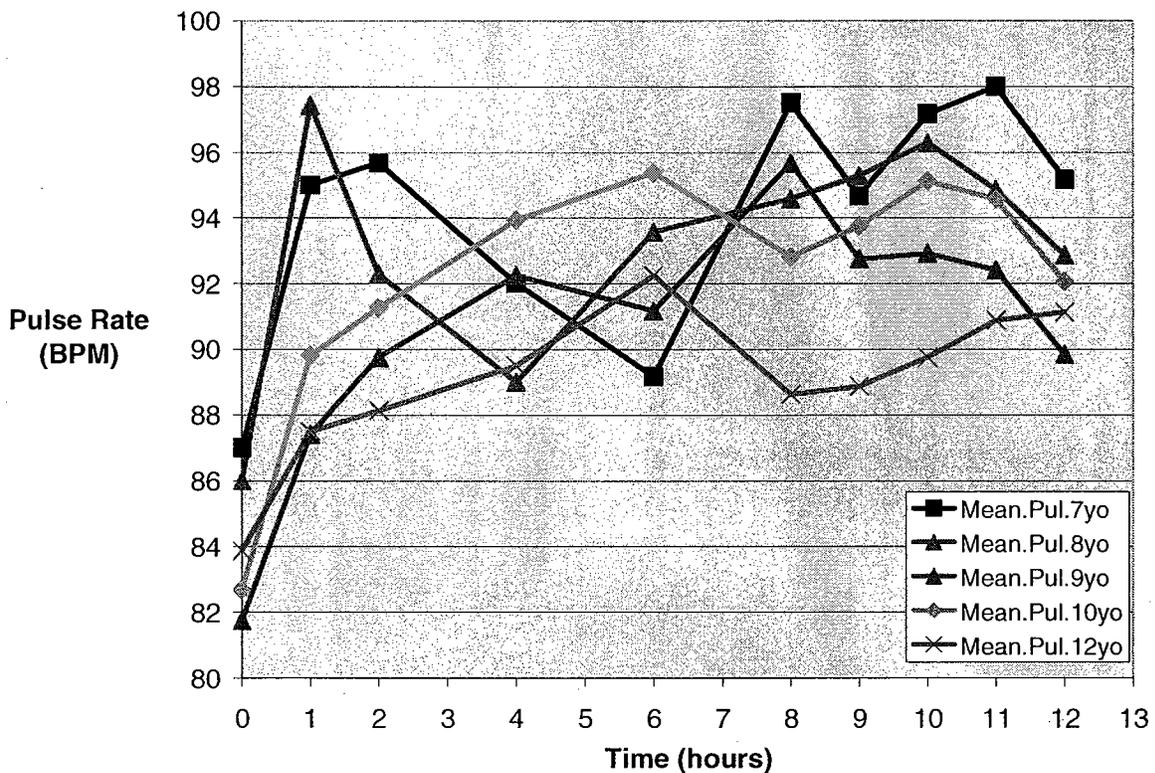


Figure 23 Mean Change in Systolic BP vs. Time post-Dose of Focalin XR 20 mg by Age – Study US08

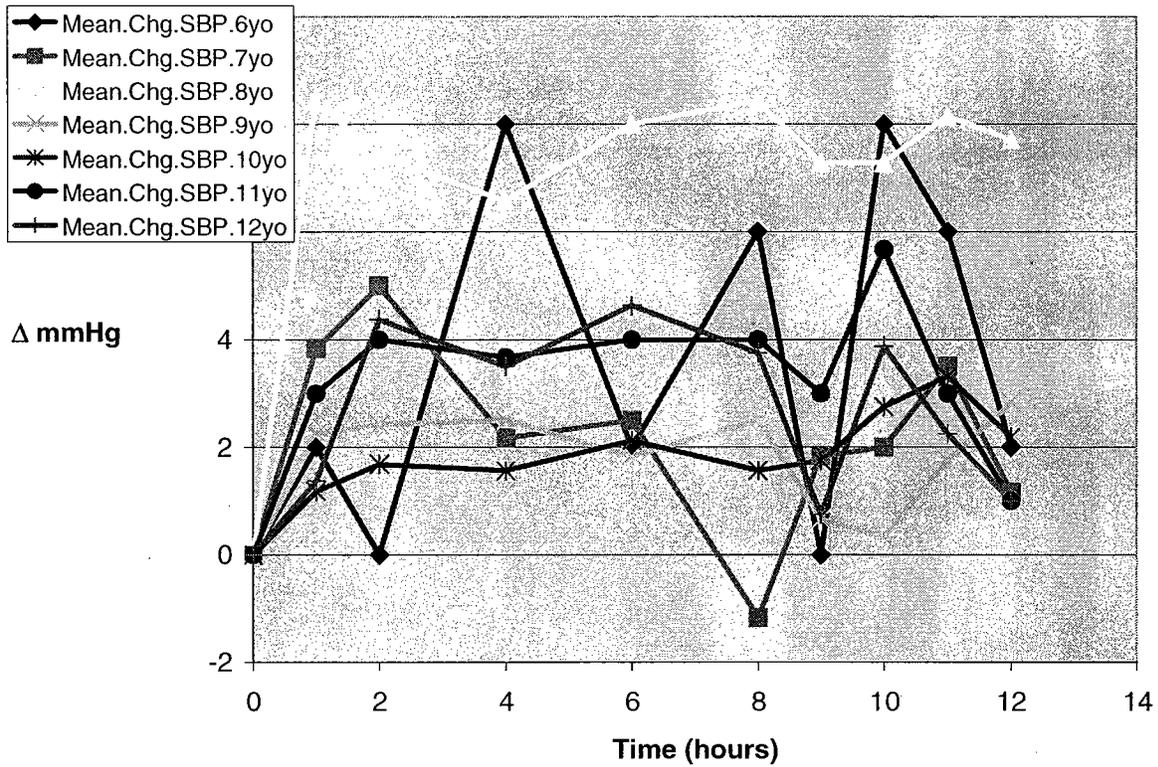


Figure 24 Mean Change in Diastolic BP vs. Time post-Dose of Focalin XR 20 mg by Age – Study US08

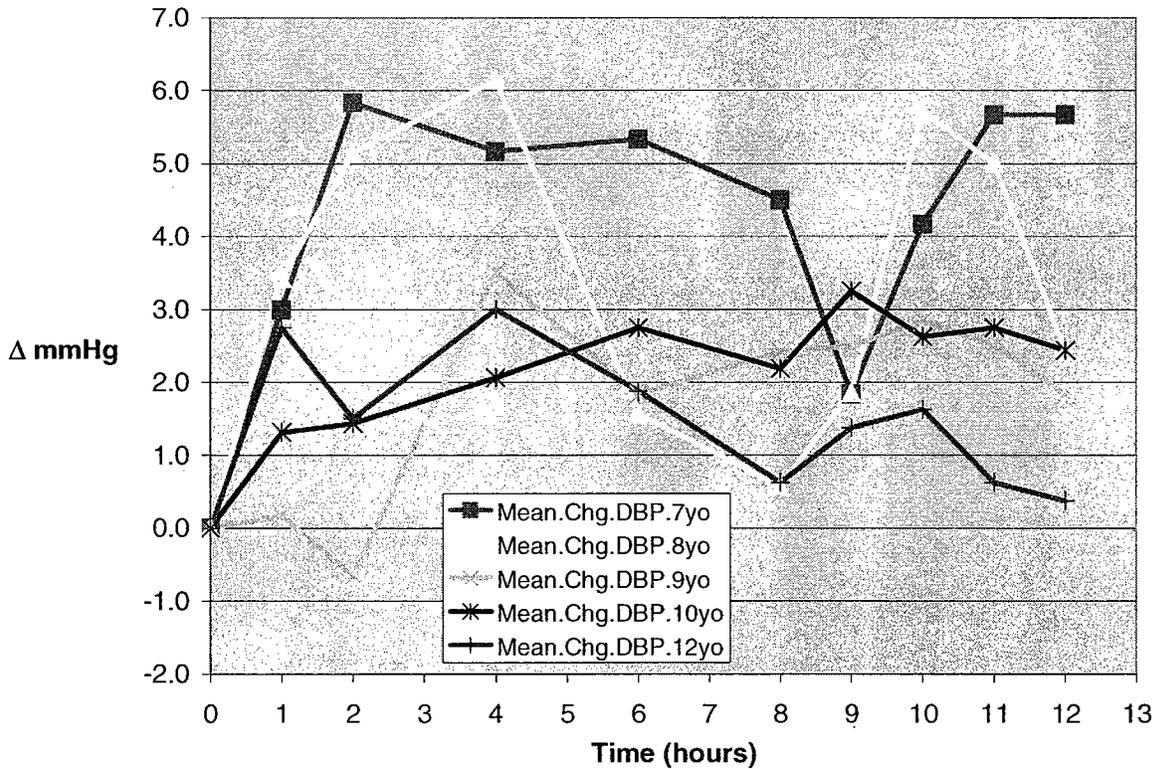


Table 33 Number (%) of patients with AEs by primary system organ class, preferred term, and treatment (Safety population) – Study US08

Primary system organ class / Preferred term¹	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.

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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 °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) Not less than

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 °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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Sally Yasuda
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BIOPHARMACEUTICS

*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. [REDACTED]
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	<p>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 <i>a priori</i> 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.</p> <p>See Appendix 1 for comparison of OCPB submissions for the <i>d</i>-isomer (Focalin XR) and the racemate (Ritalin LA) for comparison and appropriateness of cross-referencing.</p>	
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

Appendix 1 Comparison of Bioavailability / Pharmacokinetic Studies Submitted for Focalin XR (NDA 21-802) and Ritalin LA (21-284)

Study No.	Study Type	Title	Study No.	Study Type	Title
In Vivo					
Protocol 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 Focalin™ LA (d methylphenidate) 20 mg, Focalin™ IR two 10 mg capsules dosed 4 hours apart, and Ritalin® LA (dl-methylphenidate) 40 mg in healthy volunteers
Protocol 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.	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
Protocol 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
Protocol 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 nonmeat meals for Focalin LA and Ritalin LA studies
<hr/>					
			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 (dexamethylphenidate 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 Focalin™ LA 20 mg versus placebo in children (6-12 years) with Attention Deficit Hyperactivity Disorder (ADHD) in an analog classroom setting.
In Vitro					
	In Vitro Applesauce Study	Phase IV	04010B	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	BAPK(EU) R0200226	Bioanalytical Methods	Quantitative determination of d- and l-methylphenidate (Ritalin®) in human plasma by an antiselective liquid chromatography tandem mass spectrometry method. Transfer of a validated method and additional stability data
	Dissolution	Yes	04012	Dissolution	Drug release testing comparison using three different test media

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Ron Kavanagh
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Sally Yasuda
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2 SIGNATURES

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCP/DCP-1

Date

Raman Baweja, Ph.D., Team Leader, OCP/DCP-1

Date

CC:

DFS

NDA 21-802 4S June 22, 2005

NDA 21-802 4P August 1, 2005

ONDQA

OliverT

DPP

KhinN, HardemannS, DavidP

DCP-1

KavanaghR, BawejaR, UppoorR, MehtaM

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Ron Kavanagh
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