CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-303
SPONSOR: SHIRE
DRUG: ADDERALL XR
MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER
DATE SUBMITTED: 8-13-01, 8-14-01, 8-22-01

Review of individual submissions

August 13, 2001

This submission includes the worldwide regulatory update, some CMC information, Shire's agreement to conduct Phase IV bioavailability and juvenile animal studies, and the clinical safety update. (The approvable letter did not request a worldwide literature update).

Worldwide regulatory update: Adderall XR is not marketed in any country. [redacted]

Safety Update: The cutoff date for new safety data in this safety update was 4-30-01. The new safety data comes entirely from the ongoing open label study (302); the total number of subjects in study 302 for which safety data is available is now 516. There is also one ongoing open label study for which no data is yet available; this protocol was submitted to IND [redacted]

As of the cutoff date of 4-30-01, the total number of subjects exposed to either single or multiple doses was 685, an increase of 42 subjects since the previous safety update. Of these 685 subjects, 595 were children with ADHD participating in safety/efficacy trials, 70 were adult subjects in clinical pharmacology trials, and 20 were children with ADHD in a single dose pharmacokinetic trial.

Duration of exposure: The numbers of patients receiving Adderall XR by duration of treatment is shown below. (Information on duration of exposure by dosage was not available for a large number of these subjects who were in the open label study.) A total of 260 subjects received Adderall XR for over 12 months.

Duration of treatment	Number of subjects
≤2 mo	122
3-4 mo	52
5-6 mo	40
7-8 mo	24
9-10 mo	19
11-12 mo	78
13 mo	186
≥ 14 mo	74

Safety data

Serious adverse events: There have been no deaths in Adderall XR clinical trials. Since the previous safety update there has been one additional serious adverse event experienced by a patient receiving Adderall XR: Subject 41-10 in study 302, an 8-year old girl, was admitted to a psychiatric hospital for severe temper outbursts.

Adverse dropouts: The following were adverse dropouts from study 302 that had not been previously reported. There were a total of 12 such adverse dropouts, of which 5 involved weight loss or anorexia.

Study & Patient	Age & Gender	Adverse event leading to dropout
302/05-04	7 m	Acting drugged, not himself
302/07-03	9 m	Insomnia
302/11-25	8 f	Weight loss
302/11-30	7 m	Not gaining weight and decreased appetite
302/13-05	7 m	Weight loss and decreased appetite
302/22-04	? m	Depression
302/31-02	6 f	Weight loss
302/35-01	6 m	Facial tic (positive dechallenge)
302/35-16	9 m	Loss of appetite
302/38-02	10 f	Obsessive compulsive disorder
302/38-13	7 m	Isolated unusual play behavior
302/55-06	7 f	Depression

Common adverse events: There were no new data from placebo-controlled trials in this safety update. For the open label study 302, as of the cutoff date the following were the most frequent adverse events (incidence $\geq$ 10%) reported: decreased appetite, insomnia, headache, abdominal pain, infection, phayringitis.

Clinical Laboratory findings: The sponsor provided an analysis of laboratory findings in the interim study report for Study 302, submitted 8-22-01. For this analysis, the baseline values were those from the last visit of the double blind treatment in study 301. The difficulty with this is that three-fourths of the subjects in study 301 received Adderall XR during double blind treatment. For these subjects the final visit of double blind treatment occurred while they were already receiving Adderall XR, and thus should not be considered a true baseline.

The following mean laboratory values showed statistically significant changes post-baseline (after either 6 or 12 months of therapy): albumin (decreased), alkaline phosphatase (decreased), BUN (decreased), creatinine (increased), gamma-GT (decreased), glucose (decreased), SGPT (decreased), sodium (increased), total bilirubin (increased), total protein (decreased), uric acid (increased), platelet count (increased), hematocrit (increased), RBC count (increased). However, the magnitude of the mean changes was generally small (the largest proportional mean change was for alkaline phosphatase, a mean decrease of over 10%). With respect to outliers, the most notable finding was that 9.4% of the 318 subjects at month 12 had abnormally low uric acid. In addition, 5.0% of subjects had elevated glucose at month 12 and 3.7% had an elevated platelet count. There was no data reported for calcium, despite the fact that the protocol specified that serum calcium would be among the laboratories obtained. It will be recalled that in the double blind study 301, 9.6% of drug treated subjects and 2.9% of placebo treated subjects had end of study calcium values that were abnormally high.

On balance, these data are very difficult to interpret due to the absence of a comparator group and the sponsor's failure to employ a drug-free baseline for the analyses.

Vital signs: With respect to mean changes in vital sign parameters, there were modest increases from baseline in blood pressure and pulse at various timepoints during open label treatment.

However, as stated above, these data are difficult to interpret because the baseline values to which the on treatment values were compared were not always obtained prior to Adderall XR treatment.

Electrocardiogram data: ECGs were obtained at the end of double blind treatment and at month 12 (or upon discontinuation). With respect to mean changes in ECG parameters, there was a statistically significant increase in QRS duration of 6 msec at month 12. There were a large number of ECG abnormalities of various types reported (a total of 191 at either baseline or month 12), but no subjects discontinued treatment due to any of these abnormalities. As already stated, the sponsor failed to analyze these data relative to a drug-free baseline, making interpretation difficult.

August 22, 2001

This submission is the interim study report for Study 302. Please refer to the description of data from this trial above.

August 14, 2001

This submission contains a discussion of statistical issues pertaining to Study 201, additional analyses of blood pressure data in studies 201 and 301, additional CMC information and a labeling counter-proposal.

Study 201: The statistical issues involved were discussed at an internal meeting 9-14-01. The consensus of the clinical and statistical review teams was that the statistical methodology was not rigorous enough for inclusion of the results in the drug's label. Please refer to the statistical review for details.

Vital Sign data: In study 201, blood pressure was measured pre-dose, and at 1.5 hours, 4.5 hours and 7.5 hours post-dose. The sponsor provided an analysis in this submission showing the mean blood pressure values for each dose group and placebo, using the mean of all post-dose values. The mean change averaged across dose groups for systolic blood pressure was +2.9 mmHg compared to –2.7 mmHg for placebo. For diastolic blood pressure the mean change for all doses was –0.5 mm Hg compared to –1.9 mm Hg for placebo. Using the least squares mean the drug-placebo differences are smaller.

At our request, on 10-1-01 Shire submitted an analysis of mean changes in blood pressure and pulse for each timepoint in study 201, and mean maximum post-dose blood pressure and pulse. Again, there was little evidence for increased pulse or blood pressure with Adderall XR and in some instances the mean values for placebo were actually higher than for drug.

With respect to outliers for blood pressure and pulse, the sponsor provided the following data from study 301. For systolic blood pressure, the percentage of patients having a value > 118 mm Hg was 7.3% for Adderall XR and 8.2% for placebo. For diastolic blood pressure, the percentage of patients having a value > 80 mm Hg was 1.1% for drug and 0.5% for placebo. For pulse, the percentage of patients having a value > 107 bpm was 4.6% for drug and 4.8% for placebo. Thus there did not appear to be an association of outlier values with drug treatment.

Reviewer comment: Shire confirmed that all vital sign readings were obtained after recess, and this may be the explanation for the apparent lack of effect of amphetamine on these vital sign parameters. Physical activity would be expected to increase pulse and blood pressure, and thus

might obscure drug-placebo differences. I recommend omitting the vital sign data obtained in study 201 from the labeling, because of this methodological concern.

Conclusions and recommendations:

1. There are no safety findings in the response to the approvable letter that would preclude approval of this drug product.

2. The sponsor should provide an analysis of vital signs, ECG parameters, and clinical laboratory parameters for study 302 using baseline values obtained prior to double blind treatment in trial 301 as the baseline for analysis. This would provide a comparison of pre-drug to on-drug values for these safety parameters. The sponsor should also provide data on serum calcium values in study 302, or explain why these data are not available.

Andrew D. Mosholder, M.D.
Medical Officer, HFD-120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Mosholder
10/5/01 04:35:37 PM
MEDICAL OFFICER

Thomas Laughren
10/6/01 02:12:18 PM
MEDICAL OFFICER
I agree that this NDA can now be approved.--TPL

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COMPLETED AUG 2 1 2001

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 8/7/01, 8/9/01
8/13/01, 8/14/01

NDA:	21-303/017-020
Name of Drug:	Adderall XR (Mixed Amphetamine and Dextroaphetamine Salts) 10mg, 20mg and 30mg Capsules
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)
Type of Document:	Response to AE Letter
Sponsor:	Shire Laboratories Inc., Rockville, MD
Reviewer:	Hong Zhao, Ph.D.

Introduction

These four sets of submissions are the sponsor's full reply to the approvable letter from the Agency dated August 3, 2001 for NDA 21-303 (Adderall XR).

Shire's Response to CPB Related Issues

(1) Dissolution Method and Specifications

Shire accepted the Agency's recommended dissolution method and specifications (as shown below) for the 10 mg, 20 mg and 30 mg Adderall XR capsules.

Apparatus:
Media:

Proposed specifications

(2) Phase 4 Commitments

Shire is committed to performing the Phase 4 commitments that the Agency has requested. The CPB related commitments are as follows:

Provide information regarding the bioavailability of amphetamine from both Adderall IR and Adderall XR capsules relative to an optimally available dosage form, such as a solution, and the metabolic fate of amphetamine for labeling purposes. These data should be submitted within one year of the approval date of this application.

(3) Labeling (Pharmacokinetics)

The Pharmacokinetics section of labeling and sponsor's proposed changes are shown below:

In addition, to keep consistency, formulation should be specified whenever the drug name appears, i.e., ADDERALL XR™ capsule and ADDERALL® tablet.

Comment 2

Under the Special Populations section, the sponsor proposes to change the following sentence "...children showed 30% less systemic exposure compared to adults." to "...children showed 20% less systemic exposure compared to adults."

In this submission, the sponsor provided their new data analysis results. The approach used for both the adult and pediatric single dose studies was to combine the exposure information from the studies to obtain a weighted average exposure per subject per mg/kg body weight. In the submission, the sponsor only presents an example of dextroamphetamine exposure information per mg/kg for the single dose studies as shown below:

Adults (Single Dose)					Pediatrics (Single Dose)				
Study	State	Subjects(N)	Mean	Total	Study	State	Subjects(N)	Mean	Total
			(AUC_{0-inf})					(AUC_{0-inf})	
381.102	fed	20	2118.0	42360	381.201	fed	40	1738.6	69544
381.103	fasted	21	2015.0	42315	381.104	fasted	20	1564.3	31286
381.103	fed	21	1966.0	41286	381.104	fasted	18	1496.0	26928
381.103	sprinkled	20	1994.2	39884					
TOTAL		82		165845	TOTAL		78		127758
		weighted average	2022.5				weighted average	1637.9	

The weighted average exposure per subject per mg/kg shown in the table was ~20% lower for the pediatric than for the adult subjects. The sponsor claims that the levoamphetamine exposure information followed a similar trend. Also, the multiple dose study for the pediatric subjects (381.201) was directly compared with the adult multiple dose Study 381.105 and a similar reduction in exposure was found. But the sponsor did not provide the results in this submission.

In the original NDA submission, the quantitative exposure differences on a mg/kg basis (dose normalization) between children and adults were not analyzed. In the OCPB NDA review dated June 21, 2001, dose normalized exposure comparison between children and adults was based on 30 mg multiple dose data and resulted in 25% to 34% less exposure in children for AUC and Cmax of *d*- and *l*-amphetamine as shown in the following table:

Comparison of PK Parameters (Dose Normalized) between Adults and Children

Adderall XR		AUC_{0-inf}/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)
Multiple Dose	***Population***	***d-Amphetamine***	
30 mg	Adults (0.45mg/kg)	2064	148.7
	Pediatrics (0.88 mg/kg)	1550	101.1
Difference ((P-A)/A) x100%			
		l-Amphetamine	
30 mg	Adults (0.45 mg/kg)	729	48.2
	Pediatrics (0.88 mg/kg)	505	31.9
Difference ((P-A)/P) x100%			

Since multiple dose comparison is more clinically relevant than the single dose comparison and the results show approximately 30% less exposure in children than in adults, the 30% that the Agency evaluated, and not the 20% proposed by the sponsor, should be in the labeling.

Recommendation

OCPB is satisfied with sponsor's responses regarding CPB related issues. OCPB suggested labeling modifications are as follows:

- In the labeling to describe the exposure difference between children and adults, the original 30% should stay instead of the 20% proposed by the sponsor, because multiple dose comparison is more clinically relevant than the single dose comparison and the results show approximately 30% less exposure in children than in adults.
- Standard deviation values should be inserted in the Table 1 to describe the variability associated with the mean for each pharmacokinetic parameter (see Comment 1).
- For consistency, formulation should be specified whenever the drug name appears, i.e., ADDERALL XR™ capsule and ADDERALL® tablet.

Please convey the above OCPB Comments 1-2 and Recommendation to Medical Review Team.

Hong Zhao, Ph.D. /S/ 8/21/01

RD/FT Initialed by Raman Baweja, Ph.D. /S/ 8/21/01.

cc: NDA 21-303 (Adderall XR) HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Biopharm-CDR)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 10/3/00, 5/17/01

NDA:	21-303
Name of Drug:	Adderall XR (Mixed Amphetamine and Dextroamphetamine Salts) 10mg, 20mg and 30mg Capsules
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment of Narcolepsy
Type of Document:	New NDA (Modified-Release Dosage Form)
Sponsor:	Shire Laboratories Inc.
Reviewer:	Hong Zhao, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

TABLE OF CONTENTS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 10/3/00, 5/17/01

NDA:	21-303
Name of Drug:	Adderall XR (Mixed Amphetamine and Dextroamphetamine Salts) 10mg, 20mg and 30mg Capsules
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment of Narcolepsy
Type of Document:	New NDA (Modified-Release Dosage Form)
Sponsor:	Shire Laboratories Inc.
Reviewer:	Hong Zhao, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Overall Summary

Adderall XR (SLI 381) is a modified-release capsule formulation based on the existing immediate-release (IR) tablet of Adderall® (mixed salts of a single-entity amphetamine product). Both Adderall XR and Adderall IR contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1. The Adderall XR formulation consists of two types of pellets in the ratio of 1:1 in a gelatin capsule: an IR pellet and a delayed-release pellet with the pulsatile delivery scheme mimicking the effects of taking two doses of IR medication 4 hours apart. The mechanism of drug release from the delayed-release (enteric-coated) pellets is based on the higher pH values found in the small intestine compared with the stomach. The sponsor has conducted two clinical trials and several pharmacokinetic studies to support the use of Adderall XR formulation for treatment of attention-deficit/hyperactivity disorder (ADHD).

Major Findings:

1. Efficacy: The duration of action of Adderall XR with regard to both behavior and school performance appears to last up to 12 hours. The groups with 20 mg and 30 mg Adderall XR doses appear to have better efficacy scores than the groups with 10 mg of either IR or XR doses.

2. PK/PD: Plasma concentrations of Amphetamine are neither highly nor directly correlated with pharmacodynamic measures.

3. Safety: Amphetamine appears to be safe and well-tolerated in treatment of ADHD with doses of 10-30 mg/day.

4. PK (single dose, XR vs. IR): Adderall XR 10 mg capsule was bioequivalent to Adderall IR 10 mg tablet in terms of rate and extent of absorption, but the time to reach maximum plasma concentrations (T_{max}) was 3 hours longer for Adderall XR which is consistent with controlled release nature of the product.

5. PK (daily dose, XR vs. IR): Adderall XR 20 mg capsule administered at 8 am was bioequivalent to Adderall IR 10 mg tablet b.i.d. administered at 8 am and 12 noon.

6. PK (steady state, XR vs. IR): After a 7-day daily administration of Adderall IR and Adderall XR 10 mg capsules to pediatric patients, the systemic exposure (AUC) is comparable between these two formulations; but Adderall XR had lower C_{max}, higher C_{min} (less fluctuation) and longer T_{max} compared to the Adderall IR formulation, which is consistent with the controlled-release nature of the product. The more relevant comparison should be Adderall IR b.i.d. vs. Adderall XR q.d. at steady state.

7. PK (single dose vs. multiple doses, XR formulation): There was no evidence of unexpected accumulation as evidenced by the mean ratio of 1.10 and 1.21 for d- and l-amphetamine for $AUC_{0\text{-}24h}$ at steady state to $AUC_{0\text{-}24h}$ after single dose in pediatric patients; the theoretical values (R) are 1.21 and 1.28 for d- and l-amphetamine, respectively.

8. PK (food effect): Food did not affect the rate and extent of absorption of Adderall XR capsule at the highest dosage strength of 30 mg, but prolonged T_{max} from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal.

9. PK (sprinkling): Opening the capsule and sprinkling the contents on applesauce resulted in comparable absorption to the intact capsule.

10. PK (dose strength equivalency): The 1x30-mg Adderall XR capsule (the highest to be marketed strength) is bioequivalent to the 3x10 mg Adderall XR capsules (the lowest to be marketed strength).

11. PK (dose proportionality): Linear relationship was observed for C_{max} and AUC over the dosage range of 10 to 30 mg of Adderall XR after multiple doses.

12. PK (stereo-selectivity): The metabolism and elimination of amphetamine isomers appeared not to be stereo-selective as evidenced by the ratio of systemic exposure to *d*- and *l*-isomer is the same as for the product composition (3:1).

13. PK (population- children vs. adults): Amphetamine systemic elimination is faster in children than in adults ($t_{1/2}$ is approximately 1 hours shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children). However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of Adderall XR, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. When the exposure parameters are normalized by dose (mg/kg), the result shows that children had 30% less in systemic exposure compared to that in adults.

14. PK (population-male vs. female): The systemic exposure to amphetamine was about 20-30% higher in women than in men. This difference is mainly attributed to body weight differences between women and men. When the exposure parameters are normalized by dose (mg/kg), the difference was diminished.

15. PK (population-race effect): Amphetamine PK appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

16. IVIVC: A "Level A" in vitro/in vivo correlation model has been established for Adderall XR capsules with acceptable internal and external predictability.

17. Dissolution: Dissolution method and specifications for Adderall XR capsules are proposed and the dissolution specifications are supported by the IVIVC model.

INTERNAL COMMENTS

Comment 1
Since no PK information is included in the Adderall IR Tablet labeling, this NDA review gives an opportunity to generate as much information as possible for general PK description in the labeling for both IR and XR products. Therefore, evaluation of dose-exposure relationship, comparison of PK between different populations (adults vs. children, men vs. women, Caucasians vs. Hispanics and Blacks) were conducted. However, information regarding the bioavailability of Adderall products and the metabolic fate of amphetamine is missing. The sponsor is requested to provide this information for labeling purposes.

Comment 2
The highest strength of Adderall XR was studied for steady state characterization (SLI 381.105), but the study did not include the reference product (Adderall IR). Therefore, the results from another study (SLI 381.201) in which pediatric patients received 10 mg Adderall XR or Adderall IR once daily for 7 days, was used to characterize steady state pharmacokinetics of Adderall XR compared to that of Adderall IR.

COMMENTS TO THE SPONSOR

Comment 1
The sponsor is requested to adopt the following dissolution method and specifications for all three strengths (10, 20 and 30 mg) of Adderall XR capsules:

Apparatus:
Media:
Specifications:

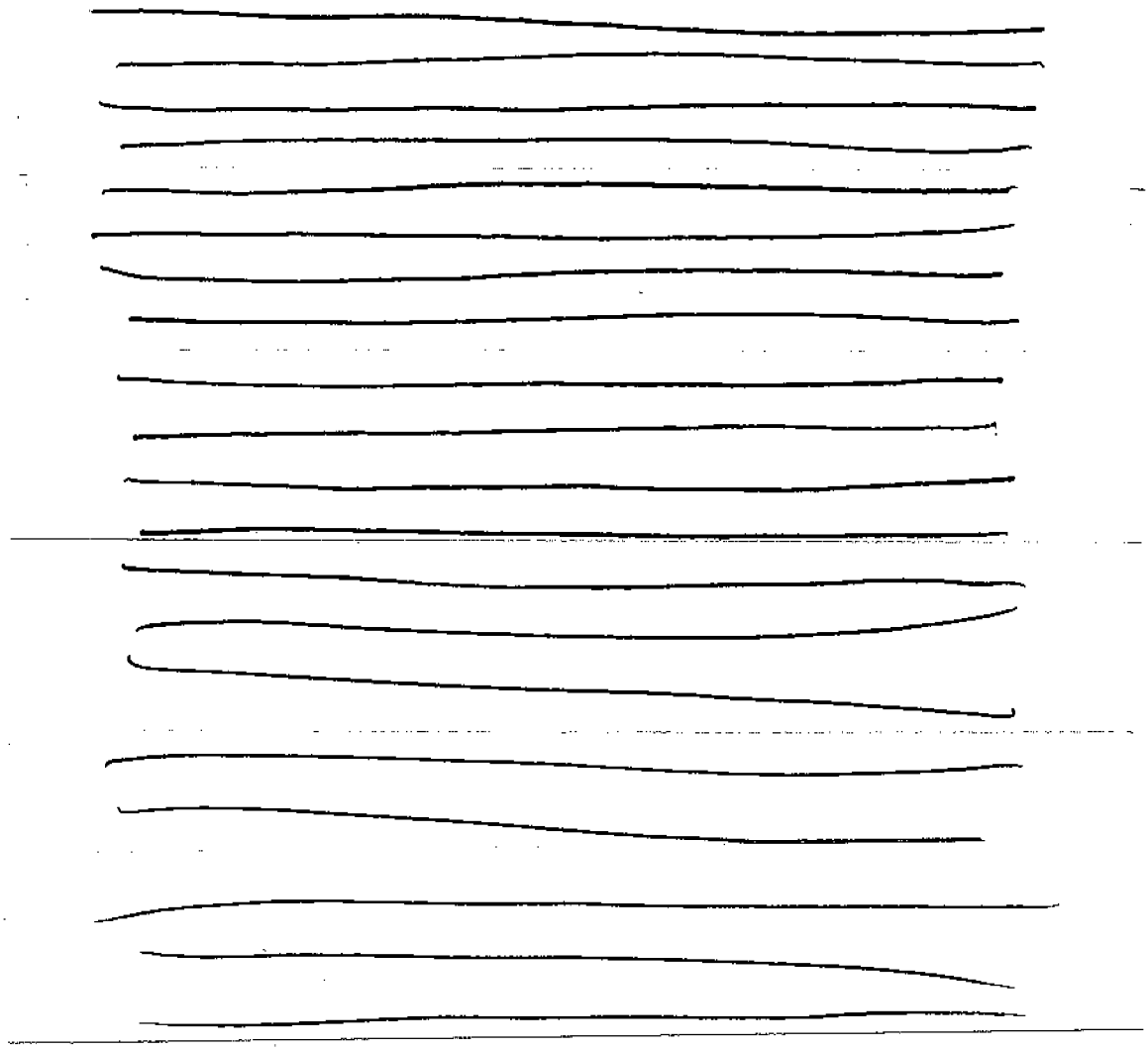
Comment 2
The sponsor is requested to adopt OCPB labeling as provided in Comment 3. In addition, the sponsor is requested to provide information regarding the bioavailability of

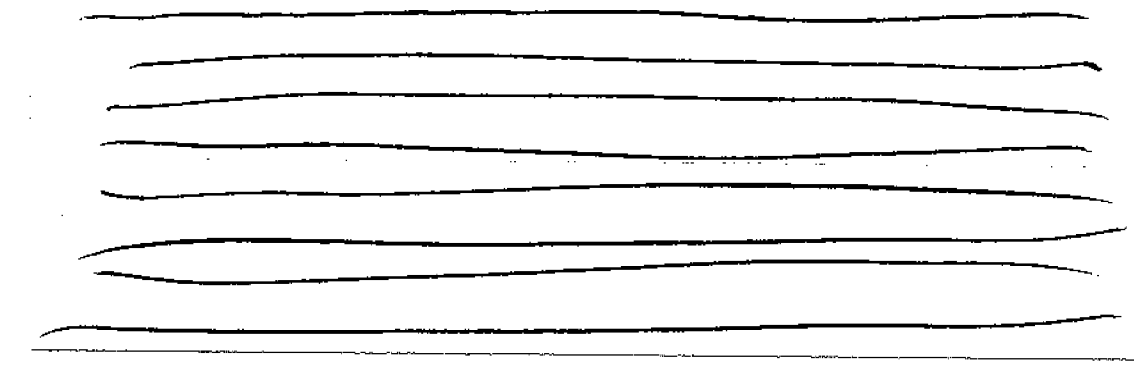
amphetamine from both Adderall IR tablets and Adderall XR capsules relative to an optimally available dosage form like solution, and the metabolic fate of amphetamine for labeling purposes.

Comment 3
Labeling for DOSAGE AND ADMINISTRATION:
The sponsor proposed "*the capsule may be opened and the entire contents sprinkled on soft food*". The term of soft food should be replaced by applesauce.

OCPB Suggested Statements for Pharmacokinetics Section of the Labeling:

CLINICAL PHARMACOLOGY
Pharmacokinetics





RECOMMENDATION

This submission (NDA 21-303) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements. The sponsor is requested

(1) to adopt the dissolution methodology and specifications for all three strengths of Adderall XR capsules, as outlined in Comment # 1 to the Sponsor.

(2) to adopt the OCPB labeling as provided in Comment #3 to the Sponsor.

(3) to provide information regarding the bioavailability of both Adderall IR and XR products, and the metabolic fate of amphetamine for labeling purposes.

Hong Zhao, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

cc: NDA 21-303 (Adderall XR) HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Biopharm-CDR)

Summary

Adderall XR (SLI 381) is a modified-release capsule formulation based on the existing immediate-release (IR) tablet of Adderall®, a single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate. Both Adderall XR and Adderall IR contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1. The Adderall XR formulation consists of two types of pellets in the ratio of 1:1 in a gelatin capsule: an IR pellet and a delayed-release pellet with the pulsatile delivery scheme mimicking the effects of taking two doses of IR medication 4 hours apart. The mechanism of drug release from the delayed-release (enteric-coated) pellets is based on the higher pH values found in the small intestine compared with the stomach.

Dosage regimen for Adderall IR product is as follows: For ADHD, start with 5 mg Adderall IR capsule once or twice daily in children 6 years and older; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. For narcolepsy, usual dose is 5 mg to 60 mg per day in divided doses, depending on the individual patient response. The proposed dosage recommendation for Adderall XR capsule is the same as for Adderall IR capsules except that the starting dose is 10 mg once daily and daily dose may be raised in increments of 10 mg at weekly intervals.

In support of the use of Adderall XR formulation for treatment of attention-deficit/hyperactivity disorder (ADHD), the sponsor has conducted the following clinical trials and pharmacokinetic studies:

Clinical Pivotal Trials - The sponsor has conducted two controlled clinical trials, one in a laboratory classroom setting (SLI 381.201), and the other in a natural home and school setting (SLI 381.301). For seven hundred children with ADHD enrolled in these two studies, 635 were randomized to receive treatment, and 425 of these received Adderall XR for one to three weeks at doses of 10, 20 and 30 mg once daily. In addition, 20 children with previous stimulant experience (SLI 381.104) and 70 healthy adult volunteers received at least one dose of Adderall XR. The sponsor is currently conducting a long-term safety study (SLI 381.302). At the time of the four-month safety update, the sponsor will provide an interim report on this study.

Pharmacokinetic Studies - Six pharmacokinetic studies have been conducted to characterize Adderall XR formulation. The first two studies (SPL 371.404 and SLI 381.102) were pilot experimental formulation selection single-dose studies. Study SLI 381.103 was to assess the bioequivalence of a single dose of the highest strength of 30 mg Adderall XR capsules following sprinkling on applesauce to the same dose administered as an intact capsule with and without a high-fat breakfast (N=19). Dose-equivalence of 1x30 mg to 3x10 mg of Adderall XR capsules was carried out in 6 to 12 years old pediatric volunteers (SLI 381.104, N=20). Twenty healthy adult volunteers received 30 mg Adderall XR once daily for 7 days and steady state pharmacokinetics was

characterized (SLI 381.105). In a phase 2 clinical trial (SLI 381.201), pharmacokinetic profiles of Adderall XR after a single dose and after multiple dosing to steady state were also examined in children with ADHD.

The following questions have been raised and answered through the review of this NDA:

Question 1.
Does the dose or amphetamine plasma concentrations correlate with the clinical efficacy end point?

According to the sponsor, Adderall XR was efficacious in treating the symptoms of ADHD in pediatric patients (SLI 381.201). All core symptoms of ADHD were significantly improved in patients receiving Adderall XR compared to the response observed in patients receiving placebo. The duration of action of Adderall XR with regard to both behavior and school performance appears to last up to 12 hours. The groups with 20 mg and 30 mg Adderall XR doses appear to have better efficacy scores than the groups with 10 mg of either IR or XR doses (see Table 1).

Table 1. Statistical Results Comparing Drug to Placebo Treatment (SLI 381.201)

Treatment	SKAMP		PERMP	
Adderall	Attention	Deportment	Number Attempted	Number Correct
		Efficacy Duration (h)		
IR 10 mg (n=9)	1.5-7.5 ($p<0.05$)	1.5-10.5 ($p<0.05$)	1.5-9.0 ($p<0.05$)	4.5-10.5 ($p<0.05$)
XR 10 mg (n=8)	4.5-7.5 ($p<0.05$)	4.5-9.0 ($p<0.05$)	1.5-12.0 ($p<0.05$)	4.5-10.5 ($p<0.05$)
XR 20 mg (n=9)	4.5-12.0 ($p<0.01$)	1.5-10.5 ($p<0.01$)	1.5-12.0 ($p<0.05$)	4.5-10.5 ($p<0.05$)
XR 30 mg (n=6)	1.5-12.0 ($p<0.01$)	1.5-12.0 ($p<0.01$)	1.5-12.0 ($p<0.01$)	1.5-12.0 ($p<0.01$)

An analysis of Pearson correlation between average plasma concentrations and the mean scores of efficacy measures at each time point was attempted and the results are shown in Table 2. Four out of the 16 coefficients for SKAMP scores and 12 out of the 16 coefficients for PERMP scores reached statistical significance at the 0.05 level (2-sided). These results indicate that plasma concentrations of amphetamine are neither highly nor directly correlated with pharmacodynamic measures.

Table 2. Correlation Coefficients (r) between d- and l-Amphetamine Plasma Concentrations and Pharmacodynamic Measures

Treatment	SKAMP		PERMP	
Adderall	Attention	Deportment	Number Attempted	Number Correct
d-Amphetamine		**Correlation Coefficients (r)**		
IR 10 mg (n=9)	-0.150	-0.074	0.446*	0.469*
XR 10 mg (n=8)	-0.231	-0.156	0.453*	0.448*
XR 20 mg (n=9)	-0.320	-0.358*	0.463*	0.450*
XR 30 mg (n=6)	-0.388*	-0.305	0.456	0.466
l-Amphetamine				
IR 10 mg (n=9)	-0.130	-0.067	0.428*	0.451*
XR 10 mg (n=8)	-0.210	-0.145	0.457*	0.451*
XR 20 mg (n=9)	-0.347*	-0.369*	0.426*	0.410*
XR 30 mg (n=6)	-0.376	-0.315	0.462	0.473

* $p<0.05$ (2-sided).

Question 2.
What is the safety profile for Amphetamine in treatment of ADHD?

According to the sponsor, Amphetamine appears to be safe and well-tolerated. In 51 pediatric patients (clinical study, SLI 381.201), a total of 919 AEs were reported post randomization. Most of the AEs were mild or moderate in intensity. None of the AEs was considered definitely treatment-related. The incidence of subjects reporting AEs was similar across the 5 treatments (placebo, Adderall IR 10 mg, Adderall XR 10, 20, and 30 mg). No unusual or serious AEs were reported in this study. The most commonly reported AEs were nervousness, anorexia, abdominal pain, insomnia, and headache, all of which are typical side effects of amphetamine. Two subjects discontinued due to AEs, one while receiving placebo and the other while receiving Adderall 20 mg. Mean values for clinical laboratory tests, vital signs, physical examinations, and the Side Effect Rating Scale were similar across treatments. Abnormal chemistry, hematology, and urinalysis results were sporadic and infrequent.

Question 3.
Was the analytical method used for determination of amphetamine plasma concentrations validated and the results acceptable?

A LC-MS/MS method with a [redacted] system was used to determine plasma concentrations of d- and l-amphetamine. The deuterated analog of racemic amphetamine was used as an internal standard. The assay has a limit of quantitation (LOQ) of [redacted] The assay was used over two ranges [redacted] The lower range was used for all studies except the multiple dosing part of Study SLI 381.201. This analytical method has been validated with acceptable results for linearity, precision and accuracy, recovery, sensitivity and stability. Therefore, the plasma concentrations of d-amphetamine and l-amphetamine measured by this assay for all pharmacokinetic studies submitted in this NDA are acceptable.

Question 4.
What are the differences in pharmacokinetic profiles between Adderall IR and Adderall XR after a single dose administration?

As shown in Table 3, Adderall XR 10 mg capsule was bioequivalent to Adderall IR 10 mg capsule in terms of rate and extent of absorption, but the time to reach maximum plasma concentrations (T_{max}) was 3 hours longer for Adderall XR, which is consistent with controlled release nature of the product.

Table 3. Pharmacokinetic Parameters from Study 371.404 (Adult volunteers)

Single Dose (N=8)	AUC_{0-inf} (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
	d-Amphetamine			
Adderall IR 10 mg (Lot#B4655)	300±116	14.5±4.1	3.3±0.9	11.9±3.9
Adderall XR 10 mg (Lot#980073)	296±101	13.9±4.2	6.2±1.8	12.2±3.3
Point of Estimate (90%CI)	**1.01 (0.94-1.07)**	**0.96 (0.90-1.02)**		

Single Dose (N=8)	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
	l-Amphetamine			
Adderall IR 10 mg	124±71	4.7±1.4	3.5±1.2	15.2±7.8
Adderall XR 10 mg)	115±54	4.4±1.3	6.2±1.8	15.2±5.7
Point of Estimate (90%CI)	**0.97 (0.85-1.11)**	**0.96 (0.87-1.05)**		

Question 5.

Is the pharmacokinetic profile of Adderall XR 20 mg similar to that of Adderall IR 10 mg b. i. d. (4-hour apart)?

The pharmacokinetic data in Table 4 and the pharmacokinetic profiles in Figure 1 indicate that Adderall XR 20 mg administered at 8 am was bioequivalent to Adderall IR 10 mg b.i.d. administered at 8 am and 12 noon.

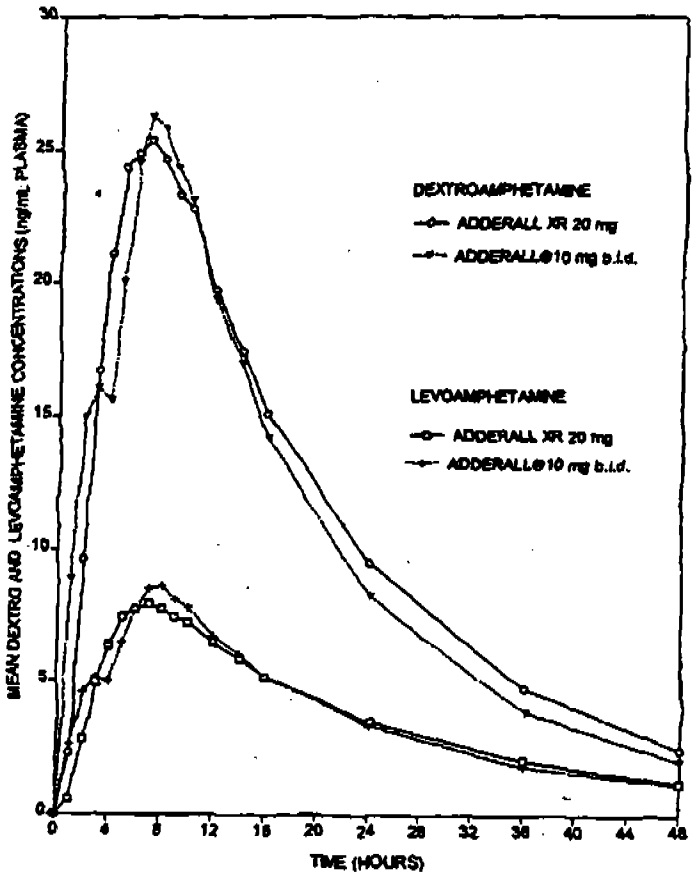


Figure.1 **Mean d-Amphetamine and l-Amphetamine Plasma Concentrations following 20 mg Administration (8 am) of Adderall XR (Lot # 980076A) under the Fed State and 10 mg Adderall IR b.i.d. (8 am and 12 noon).**

Table 4. Pharmacokinetic Parameters from Study 381.102 (Adult volunteers under fed conditions)

N=19	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
	d-Amphetamine			
Adderall IR 10 mg bid (Lot#B4655)	530±114	28.3±7.1	6.9±1.3	10.9±2.0
Adderall XR 20 mg (Lot#980076A)	567±114	28.1±8.8	7.0±2.4	11.8±2.7
Point of Estimate (90%CI)	**1.07 (1.02-1.13)**	**0.97 (0.92-1.04)**		
	l-Amphetamine			
Adderall IR 10 mg bid	203±49	9.3±2.4	7.1±1.4	13.2±2.7
Adderall XR 20 mg	203±47	8.7±2.8	8.2±4.4	13.7±2.8
Point of Estimate (90%CI)	**1.01 (0.95-1.07)**	**0.92 (0.86-0.98)**		

Question 6.

Is Adderall XR's steady state performance comparable to that of Adderall IR?

The mean steady state pharmacokinetic profiles and pharmacokinetic parameters following a 7-day daily administration of Adderall IR 10 mg and Adderall XR 10 mg capsules to pediatric patients are shown in Figure 2 and Table 5. The systemic exposure (AUC) is comparable between these two formulations, but Adderall XR had lower C_{max}, higher C_{min} (less fluctuation) and longer T_{max} compared to the Adderall IR formulation, which is consistent with the controlled-release nature of the product. The more relevant comparison should be Adderall IR b.i.d. vs. Adderall XR q.d. at steady state.

Table 5. Pharmacokinetic parameters from Study 381.201 (Pediatric Patients, 6-12 yrs)

	$AUC_{0\text{-}24\,h}$ (ng.hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	T_{max} (h)	Fluctuation
Multiple Dose d-Amphetamine					
Adderall IR 10 mg (N=9)	423±138	33.8±11.1	5.4±3.1	3.3±1.3	1.45
Adderall XR 10 mg (N=8)	432±123	28.8±6.2	7.4±3.0	6.4±3.5	1.18
l-Amphetamine					
Adderall IR 10 mg (N=9)	143±46	10.6±3.5	2.2±1.2	3.2±1.5	1.31
Adderall XR 10 mg (N=8)	138±40	8.8±1.9	2.8±1.0	6.4±3.5	1.03

Adderall IR 10 mg capsules-Lot# B4867, Adderall XR 10 mg capsules-Lot#9F2797.

Question 7.

Does food or sprinkling have an effect on PK profile of Adderall XR?

The PK parameters obtained from the food effect studies (SLI 381.103: 3-way crossover with the 30 mg highest dose strength and SLI 381.102: 2-way crossover with 20 mg dose strength in adult volunteers) are shown in Table 6 and Table 7. Plasma d- and l-amphetamine concentration-time profiles for the 30 mg Adderall XR capsules are shown in Figure 3. These data indicate the absence of a food effect on amphetamine systemic exposure. However, T_{max} was prolonged by 2.5 hours after a high-fat breakfast. The sprinkled on applesauce treatment under fasted state resulted in similar exposure to the capsule taken intact under both fed and fasted states. Therefore, opening the capsules and sprinkling the contents onto applesauce is an acceptable route of administration.

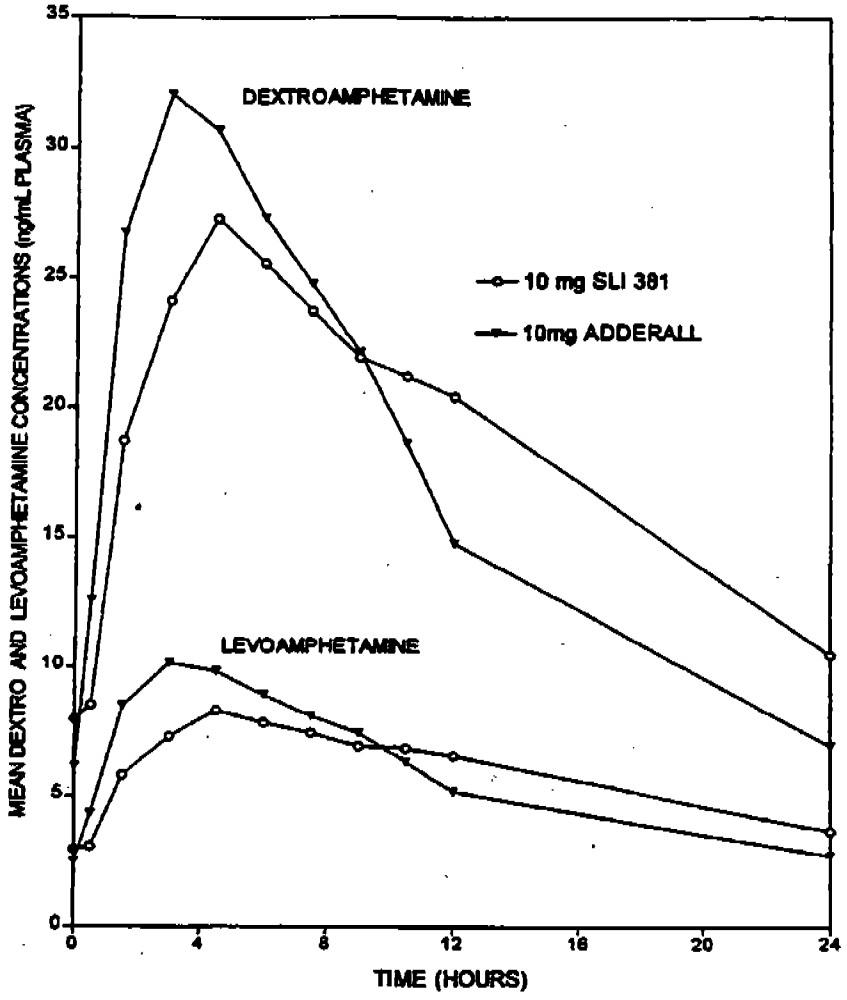


Figure 2 **The Steady State Mean d-Amphetamine and l-Amphetamine Plasma Concentrations following Multiple Dose Administration of 10 mg Adderall XR and 10 mg Adderall IR to Pediatric Patients**

Table 6. Pharmacokinetic Parameters from Study 381.103 (Adult Volunteers)-30 mg Dose

N=19 Adderall XR 30 mg (Lot#9F2703)	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
d-Amphetamine				
Fasted	851±214	44.3±11.1	5.2±2.0	10.4±2.3
Sprinkled	856±180	43.5±9.6	5.5±1.8	10.4±2.1
Fed (high-fat breakfast)	823±200	39.7±8.8	7.7±2.3	10.3±2.0
Point of Estimate (90%CI)				
Fed/fasted	**0.96 (0.91-1.02)**	**0.89 (0.85-0.95)**		
Sprinkled/fasted	**1.01 (0.96-1.07)**	**0.99 (0.93-1.04)**		
l-Amphetamine				
Fasted	289±79	13.3±3.7	5.6±2.1	12.7±3.3
Sprinkled	290±64	13.0±3.2	5.6±1.7	12.7±2.8
Fed (high-fat breakfast)	274±69	12.0±2.9	8.3±2.9	12.5±2.6
Point of Estimate (90%CI)				
Fed/fasted	**0.95 (0.88-1.01)**	**0.90 (0.85-0.95)**		
Sprinkled/fasted	**1.01 (0.95-1.09)**	**0.98 (0.93-1.04)**		

Table 7. Pharmacokinetic Parameters from Study 381.102 (Adult Volunteers)-20 mg Dose

N=7 Adderall XR 20 mg	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
d-Amphetamine				
Fasted	521±79	29.1±4.9	5.0±1.6	10.4±1.7
Fed (high-fat breakfast)	557±97	28.0±4.4	7.1±2.1	10.8±2.3
l-Amphetamine				
Fasted	197±35	9.4±1.6	5.0±1.5	12.6±2.5
Fed (high-fat breakfast)	205±39	8.7±1.4	7.4±2.2	13.4±2.7

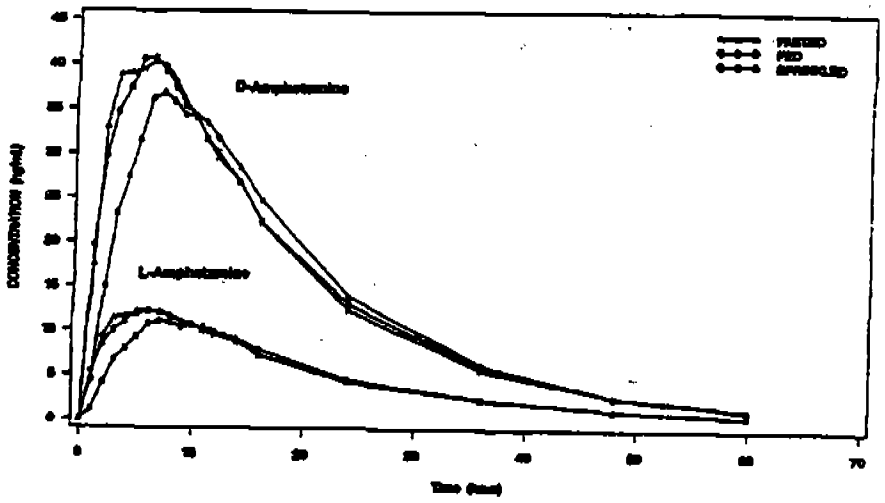


Figure 3. Plasma d-Amphetamine and l-Amphetamine Concentration-Time Plots after 30 mg Adderall XR under Fasted, Sprinkled, and Fed Conditions.

Question 8.
Is the 1x30-mg Adderall XR capsule bioequivalent to 3x10-mg Adderall XR capsules?

The results listed in Table 8 show that bioequivalence for *d*-amphetamine and *l*-amphetamine between the highest dosage strength to be marketed (1x30-mg capsule) and the lowest dosage strength (3x10-mg capsules) for marketing was established.

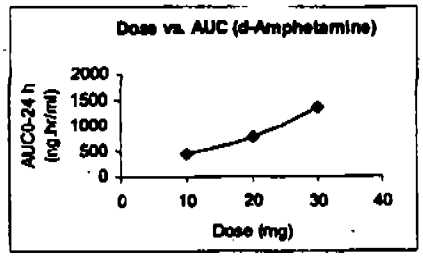
Table 8. Pharmacokinetic Parameters from Study 381.104 (Pediatric Volunteers, 6-12 yrs)

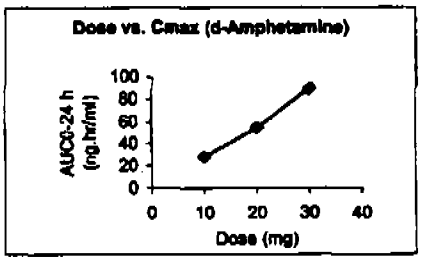
N=20	AUC_{0-t} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
d-Amphetamine					
Adderall XR 3x10 mg	1240±239	1255±231	73.9±21.4	5.5±2.7	8.0±1.7
Adderall XR 1x30 mg	1301±265	1338±281	75.9±20.6	5.5±3.6	8.6±1.9
GLSM Ratio (1x30/3x10)	**1.05**	**1.04**	**1.04**		
90% CI	**1.00-1.10**	**1.00-1.09**	**0.94-1.15**		
l-Amphetamine					
Adderall XR 3x10 mg	403±100	425±95	22.7±6.3	5.6±2.7	9.0±1.6
Adderall XR 1x30 mg	425±110	454±123	22.7±5.9	5.6±3.5	10.2±2.8
GLSM Ratio (1x30/3x10)	**1.05**	**1.02**	**1.01**		
90% CI	**1.00-1.10**	**0.97-1.06**	**0.92-1.10**		

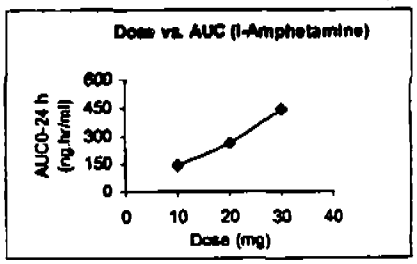
GLSM-Geometric Least Squares Means. Adderall XR 10 mg -Lot#9F2797, Adderall XR 30 mg -Lot#9F2703.

Question 9.
What is the relationship between dose and systemic exposure?

The mean steady state AUC and C_{max} following a 7-day daily administration of Adderall XR 10 mg, 20 mg and 30 mg capsules to pediatric patients are shown in Table 9 and in the following figures. Pharmacokinetics of Adderall XR is linear over the dose range of 10-30 mg.







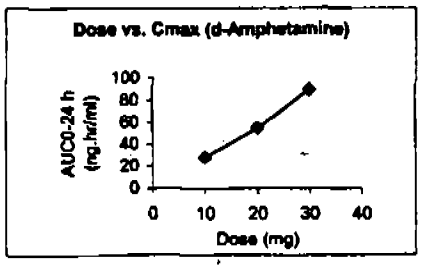


Table 9. Pharmacokinetic Parameters from Study 381.201 (Pediatric patients, 6-12 yrs)

Adderall XR Dose	N	$AUC_{0\text{-}24h}$ (ng.hr/ml)	C_{max} (ng/ml)	$AUC_{0\text{-}24h}$ (ng.hr/ml)	C_{max} (ng/ml)
		d-Amphetamine		*l-Amphetamine*	
10 mg	8	432±123	28.8±6.2	138±40	8.8±1.9
20 mg	9	777±304	54.6±18.8	262±120	17.2±6.8
30 mg	6	1364±364	89.0±15.6	444±134	28.1±6.5
Correlation Coefficient (R^2)		**0.9780**	**0.9966**	**0.9882**	**0.9918**

Question 10.

Is there any unusual accumulation after multiple doses compared to the single dose?

There was no evidence of unexpected accumulation in pediatric patients as evidenced by the mean ratio of 1.10 and 1.21 for d- and l-amphetamine for $AUC_{0\text{-}24h}$ at steady state to $AUC_{0\text{-}24h}$ after single dose (see Table 10); the theoretical values (R) are 1.21 and 1.28 for d- and l-amphetamine, respectively.

Table 10. Comparison of PK between Single Dose and Multiple Dose in Children

Adderall XR 20 mg	$C_{min\ at\ 24\ h}$ (ng/ml)	C_{max} (ng/ml)	$AUC_{0\text{-}24}$ (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
			d-Amphetamine		
Single Dose (N=48)	16.5±8.3	48.8±13.5	704±190	6.8±3.2	9.5±2.4
Multiple Dose (N=9)	15.4±9.3	54.6±18.8	777±304	5.8±1.8	ND
R (M/S)	**0.93**	**1.12**	**1.10**		
			l-Amphetamine		
Single Dose (N=48)	5.6±2.8	14.8±4.3	216±60	6.9±3.3	10.9±3.1
Multiple Dose (N=9)	5.8±3.7	17.2±6.8	262±120	5.7±2.2	ND
R (M/S)	**1.04**	**1.16**	**1.21**		

For adults, cross study comparison is conducted to compare steady state PK with the single dose PK as shown in Table 11. The mean accumulation factor (the ratio of $AUC_{0\text{-}24h}$ at steady state to $AUC_{0\text{-}24h}$ after single dose) is 1.44 for d- amphetamine and 1.64 for l-amphetamine; the theoretical values (R) are 1.25 and 1.37 for d- and l-amphetamine, respectively.

Table 11. Comparison of PK between Single Dose and Multiple Dose in Adults (SLI 381.105-multiple dose vs. SLI 381. 103-single dose)

Adderall XR 30 mg		$AUC_{0\text{-}24}$ (ng.hr/ml)	C_{min} (ng /ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
				d-Amphetamine		
Single (N=19)		645±175	12.3±4.1	44.3±11.1	5.2±2.0	10.4±2.3
Multiple (N=20)		929±180	18.2±5.3	66.9±13.8	4.2±1.2	11.3±1.1
R=M/S		**1.44**	**1.48**	**1.51**		
				l-Amphetamine		
30 mg	Single (N=19)	200±72	4.3±1.3	13.3±3.7	5.6±2.1	12.7±3.3
	Multiple (N=20)	328±63	7.4±2.2	21.7±4.6	4.3±1.1	13.8±3.4
R=M/S		**1.64**	**1.72**	**1.63**		

Question 11.

Are metabolism and elimination of amphetamine isomers stereo-selective?

The metabolism and elimination of amphetamine isomers appeared not to be stereo-selective as evidenced by the ratio of systemic exposure to *d*- and *l*-isomer is the same as for the product composition (3:1).

Table 12. The Ratio between *d*-Amphetamine and *l*-Amphetamine

30 mg Dose	C_{max} (ng/ml) Multiple-dose in Children	$AUC_{0\text{-}24\,h}$ (ng.h/ml)	C_{max} (ng/ml) Single-dose in Children	$AUC_{0\text{-}inf}$ (ng.h/ml)
d-isomer	89.0±15.6	1364±364	75.9±20.6	1338±281
l-isomer	28.1±6.5	444±134	22.7±5.9	454±123
R=d-/l-isomer	**3.17**	**3.07**	**3.34**	**2.95**

Question 12.

Are there any differences in rate and extent of Adderall XR's systemic exposure between adults and children?

As shown in Table 13, the exposure to *d*- and *l*-amphetamine in pediatric population is 52-74% higher after a single dose of Adderall XR compared to that in Adult population; this difference is reduced to 29-47% at steady state. The difference in exposure was attributed to the higher dose employed with children on a mg/kg body weight basis compared with adults. Dose normalized AUC and C_{max} provided about 30% less exposure values (Table 14) for the pediatric population than the adult population.

Table 13. Comparison of Pharmacokinetic Parameters between Adults and Children

Adderall XR		$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Single Dose	***Population (N)***		***d-Amphetamine***		
20 mg	Adults (N=19, fed)	567±114	28.1±8.8	7.0±2.4	11.8±2.7
	Pediatrics (N=48, fed)	937±319	48.8±13.5	6.8±3.2	9.5±2.4
Difference ((P-A)/A) x100%					
30 mg	Adults (N=19)	851±214	44.3±11.1	5.2±2.0	10.4±2.3
	Pediatrics (N=20)	1338±281	75.9±20.6	5.5±3.6	8.6±1.9
Difference ((P-A)/A) x100%					
Multiple Dose		*0-24 h*			
30 mg	Adults (N=20)	929±180	66.9±13.8	4.2±1.2	11.3±1.1
	Pediatrics (N=6)	1364±364	89.0±15.6	5.5±2.1	ND
Difference ((P-A)/A) x100%					

Adderall XR		$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Single Dose	***Population (N)***		***l-Amphetamine***		
20 mg	Adults (N=19, fed)	203±46	8.7±2.8	8.2±4.4	13.7±2.8
	Pediatrics (N=48)	309±115	14.8±4.3	6.9±3.3	10.9±3.1
Difference ((P-A)/A) x100%					
30 mg	Adults (N=19)	272±72	13.3±3.7	5.6±2.1	12.7±3.3
	Pediatrics (N=20)	454±123	22.7±5.9	5.6±3.5	10.2±2.8
Difference ((P-A)/A) x100%					
Multiple Dose		*0-24 h*			
30 mg	Adults (N=20)	328±63	21.7±4.6	4.3±1.1	13.8±3.4
	Pediatrics (N=6)	444±134	28.1±6.5	5.5±2.1	ND
Difference ((P-A)/A) x100%					

Table 14. Comparison of PK Parameters (Dose Normalized) between Adults and Children

Adderall XR		$AUC_{0\text{-}inf}$/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)
Multiple Dose	***Population (N)***	***d-Amphetamine***	
30 mg	Adults (0.45mg/kg)	2064	148.7
	Pediatrics (0.88 mg/kg)	1550	101.1
Difference ((P-A)/A) x100%			
		l-Amphetamine	
30 mg	Adults (0.45 mg/kg)	729	48.2
	Pediatrics (0.88 mg/kg)	505	31.9
Difference ((P-A)/P) x100%			

Question 13.

Was there any gender difference or race difference in Amphetamine disposition?

Gender:

Gender difference in amphetamine was evaluated by this reviewer using PK data obtained from Study 381.103 (single 30 mg dose) and Study 381.105 (steady state, 30-mg daily dose for 7 days) in adult healthy subjects. The results are shown in Table 15. The systemic exposure to amphetamine was higher in women than in men. This difference is mainly attributed to body weight differences between women and men, therefore, women had higher dose per kg body weight. When the exposure parameters were normalized by dose (mg/kg), the difference was diminished (see Table 16).

Table 15. Comparison of Pharmacokinetic Parameters by Gender (Studies 381.103, 381.105)

Adderall XR		$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Single Dose	***Population (N)***		***d-Amphetamine***		
30 mg	Males (N=10)	791±215	37.7±6.1	5.9±2.1	10.9±2.3
	Females (10)	881±157	51.0±11.2	4.8±1.5	9.9±2.3
Difference ((F-M)/M) x100%					
Multiple Dose		*0-24 h*			
30 mg	Males (N=10)	840±141	57.7±12.1	4.1±1.4	11.1±1.2
	Females (N=10)	1018±175	76.0±8.3	4.3±1.0	11.4±1.1
Difference ((F-M)/M) x100%					

Adderall XR		$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Single Dose	***Population (N)***		***l-Amphetamine***		
30 mg	Males (N=10)	265±82	11.0±1.8	6.7±2.1	13.5±3.5
	Females (N=10)	312±73	15.7±3.6	5.0±1.8	11.9±3.0
Difference ((F-M)/M) x100%					
Multiple Dose		*0-24 h*			
30 mg	Males (N=10)	292±48	18.6±3.8	4.3±1.3	12.6±3.6
	Females (N=10)	364±57	24.8±3.0	4.4±0.9	14.8±2.9
Difference ((F-M)/M) x100%					

Table 16. Comparison of PK Parameters (Dose Normalized) by Gender

Adderall XR		$AUC_{0\text{-}inf}$/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)	$AUC_{0\text{-}inf}$/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)
Single Dose					
	Population (Dose/kg)	***d-Amphetamine***		***l-Amphetamine***	
30 mg	Males (0.354 mg/kg)	2237	106.6	750	31.2
	Females (0.486 mg/kg)	1811	104.8	641	32.2
Difference ((F-M)/M) x100%					
Multiple Dose					
30 mg	Males (0.398 mg/kg)	2109	145.0	733	46.7
	Females (0.493 mg/kg)	2063	154.2	738	50.3
Difference ((F-M)/M) x100%					

Race:

In addition, race difference in amphetamine PK was evaluated using PK data obtained from Study 381.105 (adults) and Study 381.201 (Pediatrics). The results shown in Table 17, Table 18 and Table 19 indicate that the amphetamine PK is comparable among Caucasians, Blacks and Hispanics.

Table 17. Comparison of Pharmacokinetic Parameters by Race (Study 381.105 in Adults)

Adderall XR		$AUC_{0\text{-}24h}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Multiple Dose	***Population (N)***		***d-Amphetamine***		
30 mg	**Caucasians** (N=14)	918±177	64.2±13.3	4.2±1.2	11.2±1.1
	B & H (N=6)	954±200	73.1±14.0	4.1±1.2	11.5±1.1
Difference ((B&H-C)/C) x100%					
			l-Amphetamine		
30 mg	**Caucasians** (N=14)	321±66	20.9±4.4	4.4±1.2	13.8±3.8
	B & H (N=6)	345±57	23.7±4.8	4.0±0.8	13.6±1.7
Difference ((B&H-C)/C) x100%					

Table 18. Comparison of PK Parameters (Dose Normalized) by Race

Adderall XR		$AUC_{0\text{-}24h}$/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)	$AUC_{0\text{-}24h}$/dose (ng.hr/ml)/(mg/kg)	C_{max}/dose (ng/ml)/(mg/kg)
Multiple Dose	***Population (Dose/kg)***	***d-Amphetamine***		***l-Amphetamine***	
30 mg	C (0.434 mg/kg)	2117	148.1	739	48.1
	B & H (0.458 mg/kg)	2083	159.7	754	51.8
Difference ((B&H-C)/C) x100%					

Table 19. Comparison of Pharmacokinetic Parameters by Race (Study 381.201 in Pediatrics)

Adderall XR		AUC_{0-t} (ng.hr/ml)	C_{max} (ng/ml)
Single Dose	***Population (N)***		***d-Amphetamine***
20 mg	**Caucasians** (N=19)	721±170	48.5±14.3
	Blacks (N=5)	801±376	54.1±16.4
	Hispanics (N=7)	721±150	50.9±11.5
Difference	((B-C)/C) x100%	**11%**	**12%**
	((H-C)/C)x100%	**0%**	**5%**
			l-Amphetamine
	Caucasians (N=19)	222±55	14.7±4.2
	Blacks (N=6)	243±112	16.4±4.7
	Hispanics (N=7)	217±44	14.9±3.7
Difference	((B-C)/C) x100%	**9%**	**12%**
	((H-C)/C)x100%	**-2%**	**1%%**

Question 14.

What are the dissolution method and specifications proposed by the sponsor?

The sponsor proposed the following dissolution method and specifications and provided dissolution data for Adderall XR capsules (Table 20). All dissolution data from biobatches met the proposed specifications. The specification at lower side is the same for 1- hour and 2-hour time points (i.e., 40%), and 5% higher at the higher side for the 2-hour point than that for 1-hour point (65% vs. 60%). One specification at 2-hour time point (40-65%) should be adequate for testing dissolution of IR portion of the Adderall XR product (see Comment 1 at Page 3).

Apparatus:
Media:

Specifications:

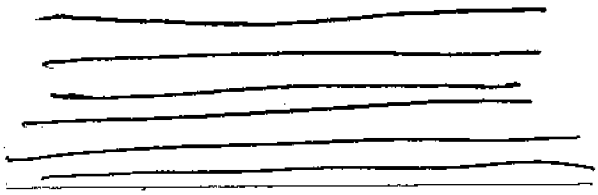


Table 20. Dissolution Data for Adderall XR Capsules (Biobatches)

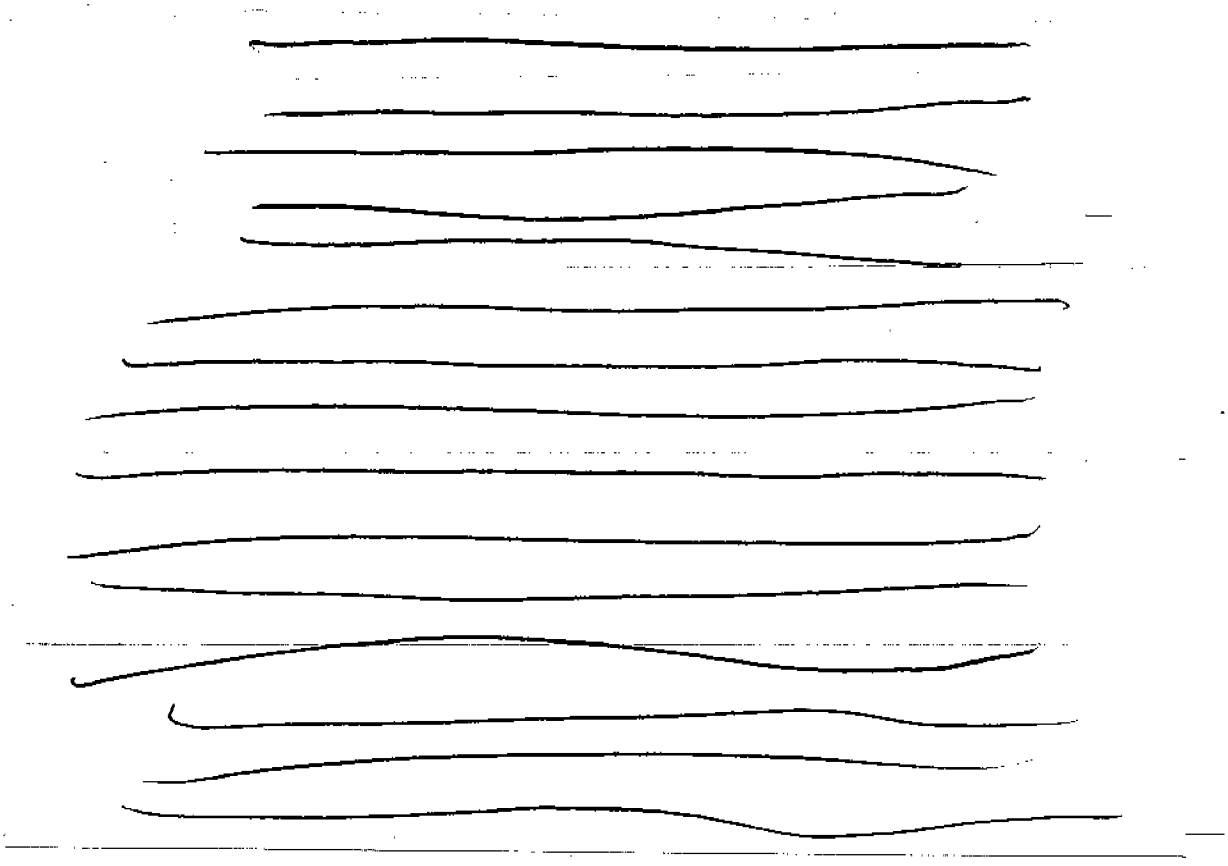
	Mean % Amphetamine Released		
Time (h)	10-mg (Lot#9F2797)	20-mg (Lot#9F2702)	30-mg (Lot#9F2703)
N	6	6	12
pH 1.1 Dilute HCL			
0.5	54±1.0 (53-56)	53±1.7 (50-55)	51±2.0 (47-55)
1	55±0.8 (54-56)	55±1.5 (52-56)	53±1.0 (51-55)
2	55±0.8 (55-57)	56±0.9 (55-57)	55±1.0 (54-56)
pH 6.0 Phosphate Buffer			
2.5	96±3.3 (93-101)	86±2.7 (82-89)	86±2.0 (83-90)
3	106±0.8 (105-107)	103±3.6 (100-110)	98±2.0 (95-101)

Question 15.

Was the IVIVC model established and properly validated?

The sponsor has developed IVIVC model using four formulations: three 20-mg formulations with different dissolution profiles ( ) and one 30-mg formulation . Mean dissolution data for these four formulations in three dissolution media were obtained. In vivo 20-mg d-amphetamine plasma profiles were from clinical study (SLI 381-102) in which subjects received single doses of the experimental formulations (A, B, and C) in the fasted state. In vivo 30 mg d-amphetamine plasma profiles were from clinical study (SLI 381.103) which was a single dose 3-way crossover food effect study. A convolution-based, Level A approach was undertaken to develop an IVIVC (see Figure 4 and Tables 21 and 22) with acceptable internal and external predictability.

The d-amphetamine plasma concentrations were correlated with the total amphetamine concentrations from the dissolution results. In the IVIVC evaluation, each formulation's best fit dissolution model is convoluted, using the single PK model, to predict its plasma profile. The final IVIVC Model is shown below:



3 page(s) of revised draft labeling has been redacted from this portion of the review.

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 10/3/00, 5/17/01

NDA:	21-303
Name of Drug:	Adderall XR (Mixed Amphetamine and Dextroamphetamine Salts 10mg, 20mg and 30mg Capsules
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment of Narcolepsy
Type of Document:	New NDA
Sponsor:	Shire Laboratories Inc.
Reviewer:	Hong Zhao, Ph.D.

Individual Study Review

Study 371.404 (Pilot Study) – Formulation Selection

Study Design

This study was a randomized, open-label, single-dose, 3-way crossover study with a 7-day washout between each formulation administered. Eight healthy volunteers completed the study, each received one 10 mg dose of two test formulations (SLI 381 A, Lot#980073, SLI 381 B, Lot#980074) and one 10 mg dose of reference drug (Adderall 10 mg IR tablet, Lot#B4655) under fasting conditions with a 7-day washout period between doses. Blood samples were collected 5 minutes before dosing, and at the following hours after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, and 48 hours for determination of d-amphetamine and l-amphetamine (by LC-MS/MS).

Results

N=8	C_{max} (ng/ml)	AUC_{0-inf} (ng.h/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{0-inf} (ng.h/ml)	T_{max} (h)
Formulation	*d-amphetamine*			*l-amphetamine*		
Adderall IR 10 mg	14.5±4.1	300±116	3.3±0.9	4.7±1.4	124±71	3.5±1.2
SLI 381 A 10 mg	13.9±4.2	296±101	6.2±1.8	4.4±1.3	115±54	6.2±1.8
SLI 381 B 10 mg	11.7±3.3	273±103	7.7±1.1	3.7±1.1	101±49	8.5±1.6
Point of Estimate (90%CI)						
(SLI 381 A/IR)	0.96 (0.90-1.02)	1.01 (0.94-1.07)		0.96 (0.87-1.05)	0.97 (0.85-1.11)	
(SLI B/IR)	0.83 (0.78-0.88)	0.95 (0.89-1.02)		0.79 (0.72-0.86)	0.85 (0.75-0.97)	

Summary

Both of the experimental SLI 381 Delayed Release (DR) Formulation A and Formulation B had delayed-release characteristics compared with Adderall IR product. Of the two formulations, SLI 381 DR Formulation A was bioequivalent to Adderall IR in terms of rate and extent of absorption with 3 hours delayed in reaching maximum plasma concentrations.

Study 381.102 (Formulation Selection)

Study Design

Twenty healthy volunteers were enrolled in the study and 19 subjects completed the study. On Day 1 of each of the 4 periods, all subjects received one of the four treatments: SLI 381 Formulations A, B and C (20 mg capsules, Lot# 980076A, 980077, and 990006, respectively), and Adderall 10 mg tablet b.i.d. (Lot# B4655). All subjects were fed a high fat breakfast approximately 20 minutes prior to drug administration and completed the meal within 5 minutes of dosing. On Day 1 of the 5th period, subjects received one of the SLI 381 Formulations A, B and C under fasting condition (following a 10-hour overnight fast with continued fasting until 3.5 hours post dose). Blood samples were collected 5 minutes before dosing, and at the following hours after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, and 48 hours on the dosing day of each period for determination of d-amphetamine and l-amphetamine (by LC-MS/MS at ————).

Results

Pharmacokinetic parameters for SLI 381 Formulation A (20 mg) and Adderall IR (10 mg b.i.d.) taken under fed condition are shown below:

	d-amphetamine		*l-amphetamine*	
N=19	Adderall 10mg b.i.d.	SLI 381 A 20mg	Adderall 10mg b.i.d.	SLI 381 A 20mg
C_{max} (ng/ml)	28.3±7.1 (25%)	28.1±8.8 (31%)	9.3±2.4 (26%)	8.7±2.8 (32%)
AUC_{0-t} (ng.hr/ml)	495±103 (21%)	522± 101(19%)	181±42 (23%)	178±40 (22%)
$AUC_{0-\infty}$ (ng.hr/ml)	530±114 (22%)	567± 114 (20%)	203±49 (24%)	203±46 (23%)
T_{max} (hr)	6.9±1.3	7.0±2.4	7.1±1.4	8.2±4.4
$t_{1/2}$ (h)	10.9±2.0	11.8±2.7	13.2±2.7	13.7±2.8

Geometric Least Squares Mean Ratio (90% CI)
(SLI 381 A/Adderall 10mg b.i.d.)

	d-amphetamine	*l-amphetamine*
C_{max} (ng/ml)	0.97 (0.92-1.04)	0.92 (0.86-0.98)
AUC_{0-t} (ng.hr/ml)	1.06 (1.01-1.11)	0.99 (0.94-1.04)
$AUC_{0-\infty}$ (ng.hr/ml)	1.07 (1.02-1.13)	1.01 (0.95-1.07)

See Figure 1 on Page 9 of this review package:

Figure 1. Mean d-Amphetamine and l-Amphetamine Plasma Concentrations following 20 mg Administration (8 am) of SLI 381 (Lot # 980076A) under the Fed State and 10 mg Adderall IR b.i.d. (8 am and 12 noon).

Pharmacokinetic parameters for SLI 381 Formulation A (20 mg) taken under fasted condition and under fed condition are listed below:

	d-amphetamine		*l-amphetamine*	
N=7	Fasted	Fed	Fasted	Fed
C_{max} (ng/ml)	29.1±4.9	28.0±4.4	9.4±1.6	8.7±1.4
AUC_{0-t} (ng.hr/ml)	494±75	520±88	180±31	180±39
$AUC_{0-\infty}$ (ng.hr/ml)	521±79	557±97	197±35	205±39
T_{max} (hr)	5.0±1.6	7.1±2.1	5.0±1.5	7.4±2.2
$t_{1/2}$ (h)	10.4±1.7	10.8±2.3	12.6±2.5	13.4±2.7

Summary

The PK data indicated that of the three experimental formulations administered 20 mg SLI 381 A q.d. was bioequivalent to Adderall 10 mg b.i.d. for both d-amphetamine and l-amphetamine. For SLI 381 A, comparison of the fed and fasted states indicated comparable pharmacokinetic parameters for all the measures, with one exception where T_{max} was shorter by 2 hours under fasted condition than under fed condition. Formulation SLI 381 A was selected for future development work.

Appendix

Table 1. Pharmacokinetic Parameters of d-Amphetamine (Fed State)-Study 381.102

		d-amphetamine		
N=19	Adderall 10mg b.i.d.	SLI 381 A	SLI 381 B	SLI 381 C
C_{max} (ng/ml)	28.3±7.1	28.1±8.8	18.5±4.8	22.9±5.8
AUC_{0-t} (ng.hr/ml)	495±103	522± 101	426±95	497±102
$AUC_{0-\infty}$ (ng.hr/ml)	530±114	567± 114	474±114	547±126
T_{max} (hr)	6.9±1.3	7.0±2.4	5.6±2.6	9.4±3.0
$t_{1/2}$ (h)	10.9±2.0	11.8±2.7	13.9±3.3	12.2±3.0
	Geometric Least Squares Mean Ratio (90% CI) (SLI 381 /Adderall 10mg b.i.d.)			
	SLI 381 A	SLI 381 B	SLI 381 C	
C_{max} (ng/ml)	0.97 (0.92-1.04)	**0.65 (0.61-0.70)**	0.82 (**0.77-0.88**)	
AUC_{0-t} (ng.hr/ml)	1.06 (1.01-1.11)	0.86 (0.82-0.90)	1.01 (0.97-1.06)	
$AUC_{0-\infty}$ (ng.hr/ml)	1.07 (1.02-1.13)	0.90 (0.86-0.95)	1.06 (1.01-1.11)	

Table 2. Pharmacokinetic Parameters of l-Amphetamine (Fed State)-Study 381.102

		l-amphetamine		
N=19	Adderall 10mg b.i.d.	SLI 381 A	SLI 381 B	SLI 381 C
C_{max} (ng/ml)	9.3±2.4	8.7±2.8	5.8±1.6	7.2±2.0
AUC_{0-t} (ng.hr/ml)	181±42	178±40	145±36	169±40
$AUC_{0-\infty}$ (ng.hr/ml)	203±49	203±46	169±47	197±50
T_{max} (hr)	7.1±1.4	8.2±4.4	5.7±2.6	9.7±3.2
$t_{1/2}$ (h)	13.2±2.7	13.7±2.8	15.8±3.6	14.7±3.6
	Geometric Least Squares Mean Ratio (90% CI) (SLI 381 /Adderall 10mg b.i.d.)			
	SLI 381 A	SLI 381 B	SLI 381 C	
C_{max} (ng/ml)	0.92 (0.86-0.98)	**0.62 (0.58-0.66)**	**0.79 (0.74-0.84)**	
AUC_{0-t} (ng.hr/ml)	0.99 (0.94-1.04)	0.80 (**0.76-0.84**)	0.95 (0.90-1.00)	
$AUC_{0-\infty}$ (ng.hr/ml)	1.01 (0.95-1.07)	0.84 (**0.79-0.89**)	1.00 (0.94-1.06)	

Table 3. Mean SLI 381 B PK Parameters (Fasted vs. Fed)-Study 381.102

	d-amphetamine		*l-amphetamine*	
N=6	Fasted	Fed	Fasted	Fed
C_{max} (ng/ml)	22.7±4.8	15.2±2.5	7.3±1.6	4.7±0.8
AUC_{0-t} (ng.hr/ml)	489±60	407±71	168±23	136±29
$AUC_{0-\infty}$ (ng.hr/ml)	545±75	447±50	193±30	156±31
T_{max} (hr)	6.2±1.6	6.3±3.0	7.0±1.5	6.5±3.2
$t_{1/2}$ (h)	13.6±2.4	15.7±1.6	15.2±2.3	17.3±2.3

Table 4. Mean SLI 381 C PK Parameters (Fasted vs. Fed)-Study 381.102

	d-amphetamine		*l-amphetamine*	
N=6	Fasted	Fed	Fasted	Fed
C_{max} (ng/ml)	29.6±8.0	23.4±8.2	9.6±2.6	7.2±2.7
AUC_{0-t} (ng.hr/ml)	551±162	496±147	196±59	169±54
$AUC_{0-\infty}$ (ng.hr/ml)	583±182	531±191	216±69	192±73
T_{max} (hr)	6.7±1.5	7.5±3.1	6.7±1.0	8.0±3.3
$t_{1/2}$ (h)	10.4±2.4	10.9±2.5	12.3±2.2	13.5±3.6

Study 381.103 (Food Effect)

Study Design

This study was a randomized, open-label, 3-way crossover, single dose study with a 7-day washout between each treatment. It was carried out in 21 adult healthy volunteers (11 males and 10 females) to compare the bioequivalence of a single 30 mg dose of SLI 381 capsules Lot# 9F2703) following sprinkling on applesauce to the same dose administered as an intact capsule with and without a high-fat breakfast; and to compare the bioavailability of a single 30 mg dose of SLI 381 extended-release capsule administered in fasted state to the same dose administered with a high-fat breakfast.

Blood samples were collected 5 minutes before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48 and 60 hours post-dosing. Plasma d-amphetamine and l-amphetamine levels were determined by LC-MS/MS method at ——————.

Results

30 mg SLI 381	*d-amphetamine*			*l-amphetamine*		
N=19	Fasted	.Sprinkled	Fed	Fasted	Sprinkled	Fed
C_{max} (ng/ml)	44.3±11.1	43.5±9.6	39.7±8.8	13.3±3.7	13.0±3.2	12.0±2.9
AUC_{0-t} (ng.hr/ml)	828±202	834±175	799±191	272±72	275±61	258±64
$AUC_{0-\infty}$ (ng.hr/ml)	851±214	856±180	823±200	289±79	290±64	274±69
T_{max} (hr)	5.2±2.0	5.5±1.8	7.7±2.3	5.6±2.1	5.6±1.7	8.3±2.9
$t_{1/2}$ (h)	10.4±2.3	10.4±2.1	10.3±2.0	12.7±3.3	12.7±2.8	12.5±2.6

Geometric Least Squares Mean Ratio (90% CI)

	d-Amphetamine		*l-Amphetamine*	
	Fed/Fasted	Sprinkle/fasted	Fed/Fasted	Sprinkle/fasted
C_{max}	0.89 (0.85-0.95)	1.01 (0.96-1.08)	0.90 (0.85-0.95)	1.02 (0.96-1.08)
AUC_{0-t}	0.96 (0.91-1.01)	0.99 (0.93-1.04)	0.95 (0.89-1.01)	0.98 (0.93-1.04)
$AUC_{0-\infty}$	0.96 (0.91-1.02)	0.99 (0.93-1.04)	0.95 (0.88-1.01)	0.99 (0.92-1.05)

See Figure 3 on Page 12 of this review package:

Figure 3. Plasma d-amphetamine and l-amphetamine concentration-time plots after 30 mg SLI 381 under fasted, sprinkled, and fed conditions.

Summary

There were less than 10% differences between fasted and fed states in C_{max} and AUC indicating the absence of a food effect. The sprinkled on applesauce treatment under fasted state resulted in similar exposure to the capsule taken intact under both the fed and fasted states; therefore opening the capsules and sprinkling the contents onto applesauce is an acceptable route of administration. T_{max} were comparable between fasted and sprinkle treatments (5 hours); food delayed T_{max} by 2 hours, similar to that seen for 20 mg capsule in the previous study.

Study 381.104 (Dose Equivalence)

Study Design

This study was an open-label, randomized, single-dose, two-treatment and two-period crossover study. This study was carried out in 20 pediatric volunteers under the fasted state to determine dose-equivalence of 1x30 mg of SLI 381 capsule to 3x10 mg of SLI 381 capsules following a single dose administration to pediatric subjects. The two dosing days were separated by a 7-day washout period. Blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 48 hours post-dose and analyzed for d- and l-amphetamine.

Results

	d-amphetamine	**SLI 381**	***l-amphetamine***	
N=20 (6-12 yrs)	1x30 mg	3x10 mg	1x30 mg.	3x10 mg
C_{max} (ng/ml)	75.9±20.6	73.9±21.4	22.7±5.9	22.7±6.3
AUC_{0-t} (ng.hr/ml)	1301±265	1240±239	425±110	403±100
$AUC_{0-\infty}$ (ng.hr/ml)	1338±281	1255±231	454±123	425±95
T_{max} (hr)	5.5±3.6	5.5±2.7	5.6±3.5	5.6±2.7
$t_{1/2}$ (h)	8.6±1.9	8.0±1.7	10.2±2.8	9.0±1.6

Geometric Least Squares Mean Ratio (90% CI)
(SLI 381 1x30 mg/3x10 mg.)

	d-amphetamine	***l-amphetamine***
C_{max} (ng/ml)	1.04 (0.94-1.15)	1.01 (0.92-1.10)
AUC_{0-t} (ng.hr/ml)	1.05 (1.00-1.10)	1.05 (1.00-1.10)
$AUC_{0-\infty}$ (ng.hr/ml)	1.04 (1.00-1.09)	1.02 (0.97-1.06)

Summary

The results show that the 1x30 mg capsule was bioequivalent for d- and l-amphetamine to the 3x10 mg capsules. The bioequivalence of 1x30 mg capsule, the highest dosage strength to be marketed and the 3x10 mg, the lowest dosage strength to be marketed, was established.

Study 381.105

Study Design

This study was an open-label, single period, multiple-dose study. It was carried out in 20 adult healthy volunteers (50% males and 50% females). Each subject received a single 30 mg SLI 381 capsule (Lot 9F2703) in the morning for seven consecutive days. The final dose (the seventh dose) was administered under fasting condition. Blood samples were collected 5 minutes pre-dosing on Days 1, 5, 6, 7, and on Day 7 at 1, 1.5, 2, 2.5, 3, 3.5, 4,

5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours post dosing. Plasma d- and l-amphetamine levels were determined by LC-MS/MS method at [redacted]. Pharmacokinetic parameters were also calculated by [redacted].

Results

	C_{max}	C_{avg} (ng/ml)	C_{min}	AUC_{0-24} (ng.hr/ml)	$AUC_{0-\infty}$	T_{max} (h)	$t_{1/2}$	Fluctuation
d-Amphet	66.9±13.8	38.7±7.5	18.2±5.3	929±180	1294±290	4.2±1.2	11.3±1.1	1.26
l-Amphet	21.7±4.6	13.7±2.6	7.4±2.2	328±63	506±125	4.3±1.1	13.8±3.4	1.04

Summary

The pharmacokinetics of the SLI 381 formulation at steady state was characterized at highest dose strength (30 mg). However, this study did not include Adderall IR capsules as reference product. Cross study comparison is conducted to compare steady state PK with the single dose PK as shown below. The mean accumulation factor (the ratio of AUC_{0-24h} at steady state to AUC_{0-24h} after single dose) is 1.44 for d- amphetamine and 1.64 for l-amphetamine; the theoretical value (R) are 1.25 and 1.37 for d- and l-amphetamine, respectively.

Comparison of PK parameters at Steady state (SLI 381.105 vs. Single dose (SLI 381. 103)

Adderall XR 30 mg		AUC_{0-24} (ng.hr/ml)	C_{min} (ng /ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
				d-Amphetamine		
Single (N=19)		645	12.3±4.1	44.3±11.1	5.2±2.0	10.4±2.3
Multiple (N=20)		929±180	18.2±5.3	66.9±13.8	4.2±1.2	11.3±1.1
R=M/S		**1.44**	**1.48**	**1.51**		
				l-Amphetamine		
30 mg	Single (N=19)	200	4.3±1.3	13.3±3.7	5.6±2.1	12.7±3.3
	Multiple (N=20)	328±63	7.4±2.2	21.7±4.6	4.3±1.1	13.8±3.4
R=M/S		**1.64**	**1.72**	**1.63**		

Study 381.201

Study Design

This study evaluated both the single dose and steady state pharmacokinetics of SLI 381 in children with ADHD. The single dose PK was characterized following a single dose of 20 mg SLI 381. The multiple dose PK of SLI 381 in ADHD children was investigated with a parallel group design by dosing q.d. with SLI 381 10 mg (Lot 9F2797), 20 mg (Lot 9F2702), 30 mg (Lot 9F2703) and Adderall IR 10 mg (Lot B4861) each for one week. Blood samples were collected pre-dose (0 hour), and at 0.5, 1.5, 3,0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0 and 24 hours after the single or multiple dosing.

Results

The PK Parameters following a Single 20 mg Dose SLI 381 (N=48)

	C_{max} (ng/ml)	AUC_{0-24} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
d-Amphetamine	48.8±13.5	704±190	937±319	6.8±3.2	9.5±2.4
l-Amphetamine	14.8 ±4.3	216±60	309±115	6.9±3.3	10.9±3.1

The total AUC value (0-inf) should be viewed with caution since the last blood sample was collected at 24 hours post dosing and more than 30% of the AUC portion was extrapolated.

The Steady State PK Parameters following a 7-Day Daily Administration of SLI 381

	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{0-24} (ng.hr/ml)	T_{max} (h)
		d-Amphetamine		
SLI 381 30 mg (N=6)	89.0±15.6	23.7±10.6	1364±364	5.5±2.1
20 mg (N=9)	54.6±18.8	12.3±10.9	777±304	5.8±1.8
10 mg (N=8)	28.8±6.2	7.4±3.0	432±123	6.4±3.5
Adderall 10 mg (N=9)	33.8±11.1	5.4±3.1	423±138	3.3±1.3
		l-Amphetamine		
SLI 381 30 mg (N=6)	28.1±6.5	8.5±3.9	444±134	5.5±2.1
20 mg (N=9)	17.2±6.8	4.9±4.3	262±120	5.7±2.2
10 mg (N=8)	8.8±1.9	2.8±1.0	138±40	6.4±3.5
Adderall10 mg (N=9)	10.6±3.5	2.2±1.2	143±46	3.2±1.5

C_{min} values are mean values of measures of three consecutive days.

See Figure 2 on Page 11 of this review package:
Figure 2. The Steady State Mean d-Amphetamine and l-Amphetamine Plasma Concentrations following Multiple Dose Administration of 10 mg SLI 381 and 10 mg Adderall IR to Pediatric Patients

Correlation between Dose and Exposure for d-Amphetamine and l-Amphetamine

Adderall XR Dose	N	AUC_{0-24h} (ng.hr/ml)	C_{max} (ng/ml)	AUC_{0-24h} (ng.hr/ml)	C_{max} (ng/ml)
		d-Amphetamine		***l-Amphetamine***	
10 mg	8	432±123	28.8±6.2	138±40	8.8±1.9
20 mg	9	777±304	54.6±18.8	262±120	17.2±6.8
30 mg	6	1364±364	89.0±15.6	444±134	28.1±6.5
Correlation Coefficient (R^2)		**0.978**	**0.9966**	**0.9882**	**0.9918**

Comparison of PK Parameters between Single and Multiple Doses of 20 mg SLI 381

d-Amphetamine	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{24} (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
20 mg Single Dose (N=48)	16.5±8.3	48.8±13.5	704±190	6.8±3.2	9.5±2.4
20 mg Multiple Dose (N=9)	15.4±9.3	54.6±18.8	777±304	5.8±1.8	ND
R=M/S	**0.93**	**1.12**	**1.10**		
l-Amphetamine					
20 mg Single Dose (N=48)	5.6±2.8	14.8 ±4.3	216±60	6.9±3.3	10.9±3.1
20 mg Multiple Dose (N=9)	5.8±3.7	17.2 ±6.8	262±120	5.7±2.2	ND
R=M/S	**1.04**	**1.16**	**1.21**		

Summary

The results from both single and multiple dose treatments indicated that the SLI 381 formulation exhibited extended-release characteristics in children with ADHD. The mean

T_{max} at steady state occurred approximately 3 hours later than the Adderall IR treatment. Dose proportionality was demonstrated over the range of 10 mg to 30 mg SLI 381. There was no evidence of unexpected accumulation as evidenced by the mean ratio of 1.10 and 1.21 for d- and l-amphetamine for $AUC_{0\text{-}24h}$ at steady state to $AUC_{0\text{-}24h}$ after single dose; the theoretical values (R) are 1.21 and 1.28 for d- and l-amphetamine, respectively.

Dissolution Program

Dissolution Method

Apparatus:
Media:

Development of IVIVC

Four formulations were studied including three 20-mg formulations with different dissolution profiles and a 30-mg formulation as shown below:

Mean dissolution data for these four batches in three dissolution media at different time periods are summarized in the following table:

Time (h)	0.5	1	2	2.5	3	3.5	4	5	6	8	12
			(Percent Release from a Formulation)								
A	52	53	55	84	97		101	102			
B	51	53	54		59			78		90	96
C	50	53	55		54	70	101	106	107		
D	51	53	55	86	98		104	105			

In vivo 20 mg d-amphetamine plasma profiles were from clinical study (SLI 381.102) in which subjects were received single doses of the experimental formulation (A, B and C, 20 mg) in the fasted state. A convolution-based, Level A approach was undertaken to develop an IVIVC with both internal and external predictability.

IVIVC development consisted of two stages:

(b4)

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hong Zhao
6/21/01 09:23:33 AM
BIOPHARMACEUTICS

Raman Baweja
6/21/01 10:33:46 AM
BIOPHARMACEUTICS

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION
NDA: 21-303
Sponsor: Shire Laboratories Inc.
Drug: Adderall XR (amphetamine product)
Material submitted: Original NDA
Date submitted: October 3, 2000
User fee due date: August 3, 2001
Medical officer: Andrew D. Mosholder, M.D.
Completion Date:

Contents

1.0 Material Reviewed

October 3, 2000, original NDA (data cutoff date August 15, 2000)
December 27, 2000, submission of investigator information
February 13, 2001, 4 month safety update (data cutoff date December 15, 2000)

2.0 Background

Related INDs and NDAs:

NDA 11-522(Shire) for Adderall

Administrative history: Adderall is a single entity amphetamine drug product, and its current labeling is based on that approved for all amphetamine products by the DESI committee in the early 1970's. The sponsor submitted the original IND application for this modified release formulation on 3/25/99 ← Representatives of Shire and of FDA met 7/20/99 to discuss the clinical development program for this product. A

pre-NDA meeting took place 8/16/00, and this application was submitted approximately seven weeks later.
Adderall XR has been referred to as SLI 381 during its development, and I will continue to use this designation for this review.

Proposed directions for use: This product is intended for once-a-day morning administration. For patients already receiving marketed Adderall, Shire's proposed labeling suggests conversion of the total daily dosage of immediate release Adderall to the same mg amount of SLI 381. For patients 6 years old or older who are not receiving current Adderall treatment, the suggested starting dose is 10 mg, with titration at weekly intervals. The proposed labeling also indicates that the contents of the capsule may be sprinkled on food. In addition, the proposed labeling preserves the Narcolepsy indication from the Adderall labeling.

Financial disclosure: Tami Martin, R.N., has signed the Form 3454 on behalf of Shire certifying that no financial incentives were offered to any of the clinical investigators in exchange for specific results. Also, no investigator indicated any financial interests in Adderall XR.

3.0 Chemistry: The drug product is available in 10, 20 and 30 mg strengths. The capsules contain equal portions of immediate release pellets and delayed release pellets, to deliver two boluses of drug substance after ingestion. The immediate release pellets dissolve at low pH (corresponding to gastric pH) and the delayed release pellets dissolve at higher pH (corresponding to the pH of the small intestine). The pellets consist of the drug substance, hydroxypropyl methylcellulose, a [redacted] enteric coating polymer, and a sugar core. The capsules may be opened and the contents added to food.

The salts and isomers of the drug substance are in the same proportion as marketed Adderall, i.e., equal amounts of the following 4 components:
Dextroamphetamine Saccharate
Amphetamine Aspartate
Dextroamphetamine Sulfate
Amphetamine Sulfate.
Because amphetamine is a racemic mixture, this results in a 3:1 ratio of dextro-amphetamine to levo-amphetamine.

At the time of this writing, there are unresolved Good Manufacturing Process issues for the production of the drug product. Please refer to the Chemistry review for details.

4.0 Preclinical: As a relatively older drug, amphetamine has not undergone the extensive preclinical evaluation that is now routine for human drugs. The sponsor has submitted reports on their genetic and reproductive toxicity studies. In addition, Shire provided a literature survey of preclinical data with amphetamine. Among the

publications reviewed were a number of studies showing behavioral tetatogenicity of amphetamine, and these findings may be appropriate for labeling. Please refer to the Pharmacology review for details.

5.0 Clinical Data Sources

The following is a listing of the studies submitted.

Study	Description
Clinical Pharmacology studies	
371.404	Single dose crossover pharmacokinetic study of two test formulations and Adderall, n= 9 adult volunteers
102	Single dose crossover pharmacokinetic study of three test formulations and Adderall, n=20 adult volunteers
103	Single dose crossover pharmacokinetic study, SLI 381 30 mg fed, fasted, and sprinkled, n=21 adult volunteers
104	Single dose 2 way crossover pharmacokinetic study, 1-30 mg SLI 381 versus 3-10 mg SLI 381, n=20 children with ADHD
105	Multiple dose pharmacokinetic study, 30 mg SLI 381 X 7 days, n=20 adult volunteers
Clinical Trials	
201	Multicenter, randomized, double blind, placebo controlled 5-way crossover trial; 1 week of once-a-day Adderall 10 mg; SLI 381 10, 20, 30 mg; and placebo; n=51 children with ADHD
301	Multicenter, randomized, double blind, placebo controlled, parallel group, 4-arm trial; SLI 381 10 mg/day, 20 mg/day and 30 mg/day, and placebo; n=584 children with ADHD
302	Open label treatment with SLI 381 10, 20, or 30 mg/day for up to 2 years; n=566 (ongoing)

Number of subjects:The following table is adapted from the sponsor's Table 8.1.1 in the safety update.

Number of subjects according to type of study and treatment

Type of study	SLI 381	Marketed Adderall	Placebo
Single dose PK- adults	50	28	0
Single dose PK-children	20	0	0
Multiple dose PK-adults	20	0	0
Safety and efficacy trials-children	553	48	259
Total	643	76	259

It should be noted that 128 children received placebo in study 301 and subsequently received open label SLI 381 in study 302; thus, these subjects are listed twice here, under both placebo and SLI 381.

Demographics

In the pharmacokinetic studies, the 70 adult volunteers were between 18 and 55 years of age and were predominantly Caucasian males. The 20 children who participated in the pediatric pharmacokinetic study were also predominantly Caucasian males, and were between 6 and 12 years of age.

For the phase 2-3 studies, (i.e., studies 201, 301, and 302), the demographic characteristics are shown below.

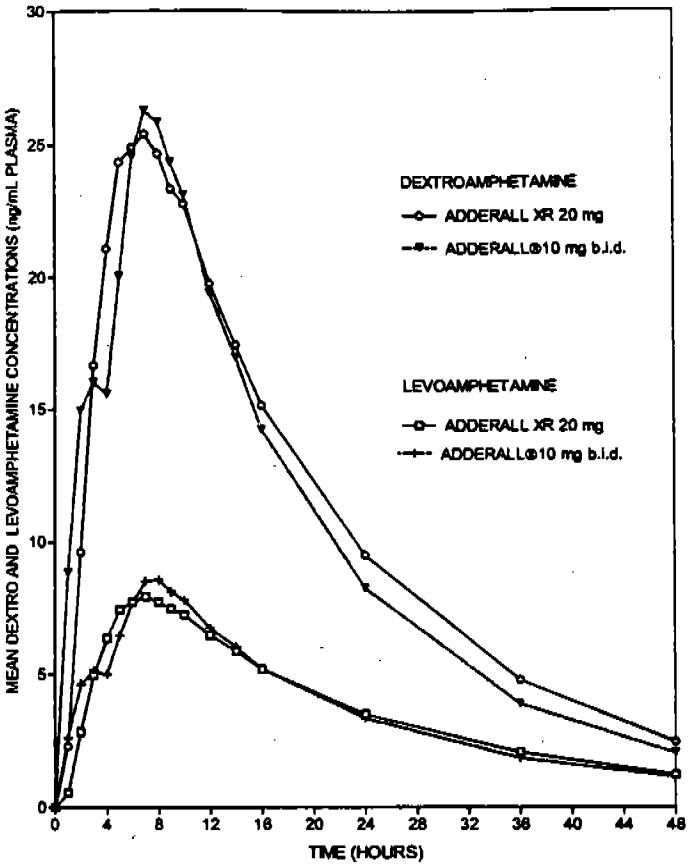
Characteristic	SLI 381 (n=553)	Adderall (n=48)	Placebo (n=259)
Age (yrs)			
Mean	8.6	9.5	8.7
Range	6-12	6-12	6-12
Sex (number male:female)	432:121	42:6	196:63
Ethnic origin (n)			
Caucasian	406	22	183
African-American	68	8	37
Hispanic	55	12	27
Other	24	6	12
ADHD type (n)			
Combined	517	47	245
Hyperactive	27	1	9
Inattentive	9	0	5
Patients with a psychiatric comorbidity (n)	161	10	75
No prior psychotropic drug use (n)	172	0	81

The subjects were predominantly males (as expected based on the epidemiology of ADHD) and were predominantly Caucasian. Approximately one-third were naïve to drug treatment of ADHD.

Extent of exposure: Of the 553 children exposed in clinical trials by the time of the safety update, 195 received SLI 381 for more than 6 months, and 336 for more than 3 months. A total of 196 children were exposed to the highest dose (30 mg/day), but 109 of these 196 subjects received 30 mg/day for only a week or less.

6.0 Pharmacokinetics

The figure below (from Shire's draft labeling) shows the plasma concentration-time curves for a single 20 mg dose of SLI 381 compared to marketed Adderall 10 mg, administered in two doses four hours apart. The data are from protocol 102, and the subjects were 20 adult volunteers.



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The table below summarizes the pharmacokinetic results obtained in study 201.

Pharmacokinetic results obtained from study 201 following multiple dosing (n= 51 children with ADHD). Adapted from Shire's draft labeling.

Treatment	Dextroamphetamine			Levoamphetamine		
	AUC_{0-24} (ng·hr/mL)	T_{max} (hours)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	T_{max} (hours)	C_{max} (ng/mL)
SLI 381 (10 mg)	432	6.4	28.8	138	6.4	8.8
SLI 381 (20 mg)	777	5.8	54.6	262	5.7	17.2
SLI 381 (30 mg)	1364	5.5	89.0	444	5.5	28.1
ADDERALL® (10 mg)	423	3.3	33.8	143	~3.2	10.6

In study 103, a high fat meal delayed the mean tmax following a 30 mg dose by 2.5 hours.

7.0 Efficacy

7.1 Study 201

7.1.1 Investigators/sites:

Site	Investigator	Location
1	J. Biederman, M.D.	Massachusetts General Hospital, Boston MA
2	L. L. Greenhill, M.D.	New York State Psychiatric Institute, New York NY
3	J. T. McCracken, M.D.	UCLA Neuropsychiatric Institute, Los Angeles CA
4	J. M. Swanson, Ph.D.	University of California-Irvine, Irvine CA

7.1.2 Objective: The purpose of this study was to assess the safety and efficacy of three doses of SLI 381, compared to placebo and marketed Adderall, with all study treatments administered once daily.

7.1.3 Population: The intended sample size was 60 subjects. To be eligible, subjects were to be 6 -12 years old, with a primary diagnosis of ADHD, combined or hyperactive-impulsive subtype. Subjects were to be receiving stimulant medication for ADHD prior to the study. Seizures, tic disorders, aggressive behavior, substance abuse, hyperthyroidism, glaucoma, significant medical illness, and comorbid psychiatric disorders were among the exclusion criteria.

7.1.4 Design: This was a randomized, double blind, 5 treatment crossover study. Each subject received each of the 5 treatments for one week, in random order. Assessments of treatment response were to be obtained in laboratory classroom settings. Following screening procedures all subjects were to participate in a practice session, involving a single dose of SLI 381 20 mg and laboratory classroom assessments. Subjects who tolerated this test dose were to be randomized to double blind treatment, with laboratory classroom assessments (including vital signs, pharmacokinetic sampling and efficacy ratings) occurring each Saturday. The one-week treatment conditions were placebo, marketed Adderall 10 mg, and SLI 381 10, 20 and 30 mg; each study medication was to be administered once daily in the morning. Concomitant psychotropic medications were prohibited. A sixth crossover period was included in the design to allow a makeup week for subjects who missed one of the previous weeks; subjects who did not need to makeup a treatment arm received a randomly selected second week of a previous treatment.

7.1.5 Analysis plan: The SKAMP was the primary efficacy measure. Repeated measures analysis of variance with session and medication as the independent variables was the specified analytic method.

7.1.6 Results

Demographics: Fifty one subjects were randomized, and 49 of these were assessed

post-randomization and were thereby included in the Intent-to-treat sample. The following is a summary of the demographic characteristics of the 51 randomized patients.

Age (yrs) Mean Range	 9.5 6-12
Ethnic origin (n) Caucasian Asian African-American Hispanic Other	 25 3 8 12 3
Male (n) Female (n)	44 7
ADHD subtype (n) Hyperactive Combined	 1 50

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Note that the majority of subjects were male, with ADHD combined subtype.

Patient disposition

The table below summarizes the disposition of the 51 subjects.

Reason for discontinuation	Number of subjects
Completed study	44
Adverse event	2
Lack of efficacy	0
Withdrew consent	1
Lost to follow up	2
Other	2

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Although the protocol allowed subjects to make up a treatment week that they had missed, this was provision was not used, and subjects instead received an extra week of a treatment they had previously received.

Concomitant medications: The sponsor provided a line listing of concomitant medications administered, but no summary was provided.

Efficacy measures: The following table shows the time points at which there was a statistically significant difference between the drug and placebo on mean SKAMP rating scores (not corrected for multiple comparisons). At time=0, the mean scores for placebo on both attention and deportment were numerically lower (better) than for any drug group, but if this caused any bias it would have been against finding a drug effect.

SKAMP-Attention

Timepoint	Adderall 10 mg	SLI 381 10 mg	SLI 381 20 mg	SLI 381 30 mg
1.5 hr	+			
4.5 hr	+	+	+	+
6 hr	+	+	+	+
7.5 hr	+	+	+	+
9 hr			+	+
10.5 hr		+	+	+
12 hr			+	+

SKAMP-Deportment

Timepoint	Adderall 10 mg	SLI 381 10 mg	SLI 381 20 mg	SLI 381 30 mg
1.5 hr	+		+	+
4.5 hr	+	+	+	+
6 hr	+	+	+	+
7.5 hr	+	+	+	+
9 hr	+	+	+	+
10.5 hr	+		+	+
12 hr				+

Note that the immediate release Adderall showed an effect at the earliest timepoint, and that it separated from placebo for 7.5 hours on the attention scale. The higher doses of SLI 381 appeared to show a longer duration of effect (up to 12 hours).

The pharmacokinetic results of this trial are summarized above in section 6.0.

7.1.7 Conclusions: This trial provides clear evidence of an effect of SLI 381 in the treatment of ADHD. It is somewhat problematic, however, to specify the time of onset and offset of the effect from these data, although the sponsor contends that this trial shows the duration of action to be 12 hours. For comparison, immediate release Adderall 10 mg was statistically separated from placebo for up to 7.5 hours, but in my opinion few clinicians would feel that a single 10 mg dose would be effective for that duration of time in a typical child with ADHD. This suggests that interpreting the data in this manner may not provide optimum external validity.

7.2 Study 301

7.2.1 Investigators/sites:

H. Abikoff, Ph.D., NYU Child Study Center, New York NY, site #50
P. Ahmann, M.D., Marshfield Clinic, Marshfield WI, site #59
P. J. Ambrosini, M.D., Eastern Pennsylvania Psychiatric Institute, Phila. PA, site #55
L.E. Arnold, M.D., and M. Aman, Ph.D., Ohio State University, Columbus OH, site #52
J. Biederman, M.D., Massachusetts General Hospital, Boston MA, site #05
M. Blum, D.O., Heart of America Research Institute, Mission KS, site #49
J. L. Blumer, M.D., Ph.D., University Hospitals of Cleveland, Cleveland OH
S. W. Boellner, M.D., Clinical Study Centers, Little Rock AK, site #07
L. Brown, M.D., and J. Elia, M.D., Children's Hospital of Philadelphia, Phila. PA, site #8
R. T. Brown, Ph.D., Medical University of South Carolina, Charleston SC, site#9
O. G. Bukstein, M.D., University of Pittsburgh Medical Center, Pittsburgh PA, site #52
C. D. Casat, M.D., Behavioral Health Center, Charlotte NC, site #10
M. C. Chandler, M.D., North Carolina Neuropsychiatry, Chapel Hill NC, site #12
E. Cherlin, M.D., Behavioral and Medical Research, El Centro CA, site #13
C. K. Conners, Ph.D., Duke University Medical Center, Durham NC, site #14
D. F. Connor, M.D., University of Massachusetts, Worcester MA, site #47
D. Coury, M.D., Pediatric Clinical Trials International, Columbus OH, site #15
A. J. Cutler, M.D., Coordinated Research of Florida, Winter Park FL, site #16
W. B. Daviss, M.D., and C. L. Donnelly, M.D., Dartmouth-Hitchcock Medical Center, Lebanon NH, site #17
C. Figueroa, M.D., Advanced Psychiatric Group, Rosemead CA, site #18
L. M. Frank, M.D., Monarch Research Associates, Virginia Beach VA, site #19
S. Grcevich, M.D., Family Medical Center by the Falls, Chargin Falls OH, site #66
L. Greenhill, M.D., NYSPI, New York NY, site #2 and #20
S. Helfing, M.D., Oregon Center for Clinical Investigations, Lake Oswego OR, site #21
S. L. Hirsch, M.D., Children's Memorial Hospital, Chicago IL, site #22
J. P. Horrigan, M.D., University of North Carolina, Chapel Hill NC, site #23
J Hudziak, M.D., Univ. of Vermont, Burlington VT, site #24
M Kremenitzer, M.D., Danbury CT, site #56
D. Lee, M.D., Emory University, Atlanta GA, site #57
M. Levin, M.D., San Ramon CA, site #63
K. S. Lewis, M.D., Barrow Neurological Group, Phoenix AZ, site #25
R. S. Lipetz, D.O., Encompass Clinical Research, Spring Valley CA, site #26
T. M. Lock, M.D., Children's Hospital of Buffalo, Buffalo NY, site #34
P. D. Londborg, M.D., Seattle Clinical Research Center, Seattle WA, site #27
F. A. Lopez, M.D., Children's Developmental Center, Maitland FL, site #28
K. McBurnett, Ph.D., University of Chicago, Chicago IL, site # 29
J T. McCracken, M.D., UCLA Neuropsychiatric Institute, Los Angeles CA, site #3 & #30
Denis Mee-Lee, M.D., Hawaii Clinical Research Center, Honolulu HI, site #61
J. Newcorn, M.D., Mt. Sinai Medical Center, New York NY, site #31
D. Palumbo, Ph.D., University of Rochester Medical Center, Rochester NY, site #32
A. Patel, M.D., Damluji Research Center, Vista CA, site #33
S. R. Pliszka,M.D., UTHSCSA, San Antonio TX, site #35
G. Realmuto, M.D., University of Minnesota Medical School, Minneapolis MN, site #53
M. Rosenthal, D.O., Behavioral and Medical Research, San Diego CA, site #48
R. L. Rubin, M.D., Miami Research Associates, Miami FL, site #38
K. Saylor, Ph.D., Neuro Science, Bethesda MD, site #51
L. Scahill, M.S.N., Ph.D., Yale Child Study Center, New Haven CT, site #39
T. M. Shiovitz, M.D., and P. D. Tigel, M.D., California Clinical Trials, Beverly Hills CA, site #40
W. T. Smith, M.D., Pacific Northwest Clinical Research, Portland OR, site #41
V. Spratlin, Mercer University, Atlanta GA, site #58
M. Sternberg, M.D., Woodbridge VA, site #54
J. J. Storlazzi, M.D., ADHD Behavioral Learning Disabilities Center, Wilmington DE, site #64
H. Tilker, Ph.D., and J.T. Cecil, M.D., Four Rivers Clinical Research, Paducah KY, site#43
S. Wigal, Ph.D., University of California-Irvine, Irvine CA, site #4 and #42

M. Wolraich, M.D., and S. Couch, M.D., Child Development Center, Nashville TN, site #45
D. R. Wynn, M.D., Consultants in Neurology, Northbrook IL, site #46

7.2.2 Objective: The purpose of this trial was to assess the safety and efficacy of SLI 381 versus placebo in the treatment of children with ADHD.

7.2.3 Population: The subjects were to be 450 children aged 6-12 years with ADHD, hyperactive-impulsive or combined subtype. The protocol required subjects to have the same schoolteacher in both morning and afternoon classes. Exclusion criteria included the following: significant psychiatric comorbidity, history of poor response to stimulants, seizures, tic disorder, substance abuse, hyperthyroidism, glaucoma, and allergy to Adderall.

7.2.4 Design: This was a multicenter, randomized, parallel group, 4-arm, placebo controlled trial. Prior to randomization subjects, were to receive a one-week single blind placebo washout. Following this, subjects were to be randomized to one of the following four treatments: SLI 381 10 mg/day, 20 mg/day, 30 mg/day, or placebo. The ratio for randomization was 2:2:2:3, to yield 100 subjects in each of the active treatment arms and 150 in the placebo arm. The duration of treatment was to be 3 weeks. If appropriate, subjects could be offered open label treatment with SLI 381 following this trial. The screening assessments included history and physical exam, clinical laboratories, ECG, psychiatric evaluation including the DISC, and pregnancy testing if indicated. Safety monitoring included vital signs at each visit, and end of treatment clinical laboratories and ECG. Concomitant medications were generally not allowed, except for bronchodilators.

The designated primary efficacy measure was the 10 item Conners Global Index Scale by the teacher (CGIS-T). Teachers were to phone in ratings of the subject in the morning and afternoon on Monday, Wednesday, and Friday of each week. With respect to the time period for reporting. the instructions to the teacher on the case report form were, "Rate each item according to how much of a problem it has been during this session." In other words, the case report form did not indicate a specific time period (e.g., Wednesday afternoon). As a secondary measure, parents were to complete the parental version of the Conners scale three times per day (at 10:00 am, 1:00 pm and 4:00 pm) on a Saturday or Sunday of each week. Additionally, parents completed a Global Assessment and the investigator completed a CGI rating.

7.2.5 Analysis: The intent to treat population was defined as subjects who had at least one post-randomization CGIS-T score. The primary efficacy measure was the average of the last week's CGIS-T scores (up to 6 individual scores, morning and afternoon on Monday, Wednesday and Friday). Morning and afternoon scores were also to be averaged separately. Analysis of covariance was to be employed, with treatment and site as independent variables and baseline score as a covariate.

7.2.6 Results

Patient disposition: A larger number of subjects were randomized than was specified in the protocol (564 randomized, versus 450 planned). The following table summarizes the reasons that patients discontinued prematurely from the study, by randomized treatment group.

Reason	30 mg (n=124)	20 mg (n=121)	10 mg (n=129)	Placebo (n=210)
Adverse event	5	4	0	6
Lack of efficacy	0	1	2	10
Consent withdrawn	4	7	4	11
Protocol violation	2	1	2	1
Lost to follow-up	0	2	0	6
Other	1	1	2	3
Total dropouts	12	16	10	37

The intent-to-treat population included 120 30 mg/day patients, 112 20 mg/day patients, 128 10 mg/day patients, and 203 placebo patients. The sponsor did not provide information on patient disposition by week.

Demographics and baseline characteristics:
The following table summarizes the baseline characteristics for the intent-to-treat sample.

Characteristic	30 mg (n=120)	20 mg (n=112)	10 mg (n=128)	Placebo (n=203)
Male:female (n)	96:24	90:22	100:28	148:55
Race (n)				
Caucasian	84	92	98	156
African American	20	9	11	27
Hispanic	11	10	12	14
Asian/PI	1	0	1	2
Native American	0	0	1	0
Other	4	1	5	4
Mean Age (yr)	8.8	8.4	8.5	8.6
Diagnostic type (n)				
Combined type	112	104	117	190
Hyperactive	6	6	8	8
Inattentive	2	2	3	5
No prior treatment (n)	37	34	48	76
No comorbidity (n)	83	81	87	142

Concomitant medications: The most commonly used concomitant medication during the trial was Tylenol, used by at least 10% of subjects in each group.

Efficacy results:
The mean change from baseline to endpoint on the CGIS-T (the primary outcome measure) by treatment group was as follows:

Treatment	Overall	Morning	Afternoon
Placebo	-0.9	-0.7	-1.2
10 mg	-5.3	-5.0	-5.4
20 mg	-6.0	-5.4	-6.8
30 mg	-6.4	-5.8	-7.2

All comparisons to placebo were highly statistically significant (p-value $\leq$0.0001). Furthermore, superiority over placebo for all three doses was statistically significant at weeks 1, 2, and 3 as well as at endpoint, for the weekly average CCGIS-T.

The results on the parent's CGIS were also highly statistically significant for superiority of all active treatments over placebo, at morning, afternoon and evening timepoints.

Boys on average had higher baseline CGIS-T scores and slightly greater mean improvement with active treatments than did girls. All doses were shown to be effective on the CGIS-T for both the subgroup of patients naïve to treatment and the subgroup of those previously treated.

Analysis of the subgroup of the first 450 subjects (i.e., the protocol specified number to be randomized) also showed superiority of all three doses over placebo, on the CGIST.

An agency inspection of Dr. Frank Lopez's site revealed some problems with documentation of the primary efficacy data; please refer to the letter from Dr. El-Hage of the Division of Scientific Investigations to Dr. Lopez (July 3, 2001). Generally speaking, the lapses in documentation reflected the fact that the subjects' teachers, and not staff involved in the trial, generated the efficacy ratings in this study.

7.2.7 Conclusions: This study provides evidence for the efficacy of all three doses studied in the treatment of ADHD.

8.0 Safety

8.1 Safety methods: This safety review is based primarily on the sponsor's Integrated Summary of Safety and Four Month Safety Update. At the time of the safety update, one clinical trial (study 302) was still ongoing; the cutoff date for including safety data from study 302 was 12/15/00. For ascertainment of common adverse events and drug related changes in monitored safety parameters, study 301, the parallel group study, is more informative by virtue of its design than is the crossover trial 201. Accordingly I will concentrate on the safety findings from study 301 in the following sections. In evaluating the findings described below with respect to vital signs, laboratories, and ECGs in study 301, it is important to recall that the baseline values for these parameters were obtained after a one-week placebo washout.

8.2 Deaths: There were no deaths in these studies.

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

The following table shows the pattern of premature discontinuations for the controlled efficacy trials, 201 and 301.

Reason for discontinuation	Percentage of patients discontinuing	
	SLI 318 (n=425)	Placebo (n=259)
Adverse events	2.4	2.7
Withdrawn consent	3.5	4.6
Protocol violation	1.2	0.4
Lost to follow up	0.7	2.3
Lack of efficacy	0.7	3.9
Other	1.4	1.2
Total	9.9	15.1

In the long term open label study (302), there was a higher proportion of dropouts (26.7%), with 10.1% of dropouts related to adverse events.

8.3.2 Adverse Events Associated with Dropout

The most frequent adverse events associated with dropout are shown below, with the incidence of dropout among the 553 pediatric patients treated with SLI 381 (source: safety update).

Adverse event	% of patients dropping out (n=553)
Anorexia	3.3
Insomnia	1.8
Weight loss	1.3
Emotional lability	1.1
Depression	0.7

Among the remaining adverse events associated with dropout, a few deserve particular mention. Subject 28-46 in study 302, an 11 year old boy, discontinued after loosing 20 lbs. Subject 11-10 in study 302, a 6 year old boy, developed new onset seizures. Two subjects in study 302 (28-24 and 16-03) discontinued because of tics.

8.4 Serious adverse events: There were four serious adverse events among patients who received SLI 381:

Subject 301/10-08--10 year old girl hospitalized for abdominal pain (final diagnosis constipation)
Subject 301/52-15--9 year old boy hospitalized for dehydration and gastroenteritis

Subject 302/11-18--10 year old boy hospitalized for antibiotic treatment of lymphadenitis
Subject 302/29-10--11 year old boy diagnosed with acute myelogenous leukemia

8.5 Other safety findings

8.5.1 Adverse event incidence

As the interpretation of adverse events in a crossover study is not straightforward, I will concentrate here on the findings from the parallel group study. The following is the sponsor's table of adverse events in study 301, pooling all doses of SLI 381 versus placebo. Adverse events shown had an incidence with drug of at least 1% and were also more frequent with drug than placebo.

Body System	Preferred Term	SLI 381 (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

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From this table, the following adverse events would meet the usual criteria for being common and drug related (i.e., relative risk of at least 2 and incidence with drug of at least 5%): fever, loss of appetite, emotional lability, insomnia, nervousness.

Dose related adverse events: In trial 301, the following adverse events were reported at an incidence of at least 5% in the high dose group, and also appeared to show a dose related pattern of incidence:

Adverse event	Incidence (%)			
	Placebo	10 mg	20 mg	30 mg
Anorexia	11.4	16.3	23.1	26.6
Weight loss	0	1.6	2.5	8.9
Insomnia	1.9	11.6	19.0	19.4

8.5.2 Laboratory findings: No patients discontinued because of laboratory

abnormalities. In the placebo controlled parallel group study 301, the following treatment emergent laboratory value abnormalities occurred at the end of treatment in at least 1% of SLI 381 treated patients, with a relative risk of at least 2 compared to placebo:

Laboratory abnormalitiy	SLI 381 incidence (%)	Placebo incidence (%)
High albumin	2.9	1.0
Low BUN	1.6	0.5
High protein	3.7	1.0

In addition, 36 drug treated subjects and 6 placebo treated subjects had end of study calcium values that were abnormally high; however, a large number of subjects had abnormally high calcium values at baseline, and it was not clear from the study report or the Integrated Summary of Safety if the abnormal values were treatment-emergent or not.

Shire also provided an analysis of mean change from baseline in laboratory values. The following changes from baseline among drug treated groups were statistically significant compared to placebo:
Increased: albumin, creatinine, bilirubin, total protein, RBC count, hematocrit, and hemoglobin.
Decreased: SGOT, SGPT
Shire concluded that all of these mean changes were of modest degree and not likely to be clinically relevant.

Shire also presented data on long term changes in laboratory parameters in the open label study 302; however, the baseline values for these analyses were the values obtained at the end of study 301, so they were not unexposed values (except for the placebo patients). Most of the mean changes observed were of a small magnitude; however, the mean alkaline phosphatase decreased over 6 months from a baseline of 256 IU/L to 226 IU/L.

8.5.3 Vital signs, height and weight

In the parallel group study (301), there were no statistically significant changes in pulse or blood pressure from baseline, for any dose of active drug versus placebo. The sponsor did not provide an analysis of height or weight data from study 301.

In the laboratory classroom study (201), sitting blood pressure and pulse were measured at 0, 1.5, 4.5 and 7.5 hours. The mean pulse rate increased by 14-18 bpm for all treatment groups including placebo. For blood pressure, the greatest difference between drug and placebo was for the 30 mg SLI 318 group in sitting systolic blood pressure at 1.5 hours (change of +7 mmHg for drug versus –1 mmHg for placebo).

In the pharmacokinetic studies with adults mean increases in blood pressure of a few

mmHg were frequently observed post dosing. Mean pulse also tended to increase, although in study 103 the greatest increase in mean pulse was seen at 24 hours post dosing.

In study 104, a single dose bioequivalence trial comparing bioavailability of 3X10 mg SLI 381 to 1X30 mg SLI 381 in children with ADHD, mean systolic blood pressure in the post dosing observation period increased by a much as 16 mmHg, with smaller increases in mean diastolic blood pressure, and increases in mean pulse of up to 12 bpm.

8.5.4 Electrocardiograms

No ECG tracings were obtained in study 201. In study 301, subjects had ECGs recorded at baseline and at the end of the study. The following table lists mean changes from baseline for ECG parameters in study 301.

ECG parameter	Placebo mean change	SLI 381 mean change
PR interval (msec)	2.5	-0.3*
QRS interval (msec)	0.2	1.1
Heart rate (bpm)	-1.0	0.3
QTc interval (msec)	2.5	2.1

*p-value = 0.01

There were treatment emergent ECG abnormalities of various types reported in 37 SLI 381 treated patients; however, the sponsor states that all ECG abnormalities were considered clinically insignificant although some were referred to a cardiologist for a second reading. Two subjects (13-01 and 12-25) had premature atrial systoles on drug; a cardiologist deemed the finding in the first subject harmless, and a repeat ECG on the second subject was normal, although it was not clear if that was performed in follow up after the study. A variety of ECG abnormalities were reported in the interim report for the ongoing open label study 302, including Wolff-Parkinson-White syndrome in one subject and junctional rhythm in two subjects. However, no patients discontinued SLI 381 because of an ECG abnormality.

8.5.5 Other safety topics

There have been no reported overdosages with SLI 381. Shire correctly points out in their proposed labeling that in the event of an overdose the treating physician should be mindful of the drug's extended release profile.

Literature review: The sponsor's clinical literature review (provided in the original submission, volumes 41 and 42) did not appear to disclose any new information specifically relevant to SLI 381.

Demographic subgroups: In studies 201 and 301 combined, among subjects receiving