CLINICAL REVIEW

Application Type	NDA 21-303
Submission Number	009
Submission Code	SE5
Letter Date	Sept. 17, 2004
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Reviewer Name	June Cai, M.D.
Review Completion Date	Feb. 8, 2004
Established Name	Mixed Amphetamine Salts
(Proposed) Trade Name	Adderall XR
Therapeutic Class	Sympathomimetic amine
Applicant	Shire Pharmaceutical Inc.
Priority Designation	P
Formulation	Capsules
Dosing Regimen	10-20mg once daily
Indication	Adolescent ADHD
Intended Population	Age 13-17 year-old

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approvable action. The sponsor needs to submitted required safety information to correct the deficiencies in the submission before final approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

Continue pursuing the long term safety tolerability study, Study SLI381-315, as stated in our pediatric exclusivity approve letter.

1.2.3 Other Phase 4 Requests

I would like to recommend including serum creatinine in the chemistry panel in future studies because this gives a more complete data on routine clinical assessment for renal function, esp. given four subjects had protenuria in Adderall XR group and none in placebo group in the submitted controlled study.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In response to the FDA Written Request for pediatric studies in adolescents with Attention Deficit Hyperactivity Disorder (ADHD), the sponsor submits this supplemental NDA which consists of one pharmacokinetic (PK) study (Study SL1381.110) and one controlled clinical trial in adolescents ages 13-17 year-old with ADHD (SL1381.314). This controlled clinical trial includes two parts: Part A and Part B. Part A is a phase III, randomized, multi-center, double-blind, parallel-group, placebo-controlled safety and efficacy study of ADDERALL XR in adolescents aged 13-17 with (ADHD), whereas Part B is a 6-month open label safety extension study of Part A.

The sponsor included a total of 327 subjects in the two cohorts of the controlled clinical trial: The 287 subjects with body weight of no more than 75kg /165lbs were included in the primary cohort and 40 subjects who weighted more than 75kg/165lbs were included in the secondary

cohort. Active treatment group completion rate for primary cohort was 89% (208/233) and that of secondary cohort was 88% (22/25).

1.3.2 Efficacy

Study SLI381-314 Part A is a four-week, fixed-dose, double-blind, placebo-controlled study. The fixed doses were 10, 20, 30, and 40 mg/day in the primary cohort and 50 and 60 mg/day in the secondary cohort. The primary efficacy variable was the mean change from baseline to endpoint in the ADHD-RS-IV total score. It demonstrates the efficacy of Adderall XR for treatment of adolescents (weighed ≤75kg/165lbs) with ADHD in the primary cohort. The most effective dose from this study is 20mg/day from the primary analysis. Increasing dose from 20 to 40mg/day did not show increased efficacy.

1.3.3 Safety

The primary safety database consisted of a four-week, placebo-controlled study and a six-month open-label safety study as well as a single dose crossover pharmacokinetic study. In addition, Four-Month Safety Update from a just started ongoing open-label safety study (Study SLI381-315) was also examined.

Though no significant previously unrecognized adverse events associated with Adderall XR treatment were discovered, it is noteworthy that major deficiencies in the assessment of safety exist, including lack of serum creatinine in the original safety database and missing narrative descriptions and case report forms of dropout cases in the Safety Update.

1.3.4 Dosing Regimen and Administration

10mg to 20mg daily.

1.3.5 Drug-Drug Interactions

No drug-drug interaction study was conducted for this submission.

1.3.6 Special Populations

No studies of subjects with liver, kidney, or any other organ failure were conducted. However, the subjects' age itself constitutes as a special population (13-17 year-old).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adderall XR is an extended-release formulation of Adderall®. It combines the following chemical entities: The neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l- amphetamine aspartate monohydrate.

Adderall XR capsule has a (b) (4) gelatin capsule (b) (4)

Adderall XR has been approved by FDA for treatment of ADHD in adults as well as in children ages 6-12 year-old. In this submission, the sponsor is proposing to use Adderall XR 10(b) (4) mg for treatment of ADHD in adolescents aged 13-17.

2.2 Currently Available Treatment for the Indication

Both pharmacologic and non-pharmacologic treatment modalities are available and needed for ADHD in adolescents. Among medication treatments, several antidepressants, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and bupropion (Wellbutrin) demonstrated some efficacy in children and adults with ADHD. However, psychostimulants remain to be the primary treatment of ADHD even though the non-stimulant atomoxetine (Strattera) is now available. Available psychostimulants for treatment of ADHD include methylphenidate (Ritalin), pemoline (Cylert), dextroamphetamine (Dexedrine), Adderall, and Adderall XR.

Psychosocial treatment (family and educational interventions that involve both parents and teacher) and behavioral therapies (biofeedback, meditation, perceptual stimulation and training) can provide effective and useful management and are adjunctive to medication treatment. Dietary management and herbal and homeopathic treatments have been proposed but with limited effect.

2.3 Availability of Proposed Active Ingredient in the United States

Active ingredients of Adderall XR include amphetamine, the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l- amphetamine aspartate monohydrate. Adderall XR has been widely available for both adults and children in the US for several years. Sudden death has been reported in

association with amphetamine treatment at usual doses in children with structural cardiac abnormalities, according to recent labeling. Thus, Adderall XR is generally not recommended to be used in anyone with structural cardiac abnormalities.

2.4 Important Issues With Pharmacologically Related Products

Amphetamine is racemic β-phenylisopropranolamine; Dextroamphetamine is the d-isomer of amphetamine that is three to four times more potent than its l-isomer as a central nervous stimulant. Amphetamine drug products are controlled substances (Schedule II). It is known that tolerance to the amphetamine-induced euphoria and its sympathomimetic effect develops rapidly but is rare to therapeutic effects in ADHD. Amphetamine can be abused orally and intravenously. Chronic abusers often take doses that would be otherwise very toxic or lethal for non-tolerant individuals. Chronic use of high dose amphetamine may also cause psychotic syndromes with prominent paranoid ideation, formication, emotional lability, irritability, and stereotype movements. Movement disorders, such as dyskinesia, tics, Gilles de la Tourette syndrome can be worsened or precipitated. When overdosed, toxic psychosis or delirium, marked sympathetic hyperactivity, and even grand mal seizures can occur. Death may result from uncontrolled seizures, hypertension, hyperthermia, and arrhythmias. With prolonged use of high doses, patients can develop hypersomnia, hyperphasia, severe depression and also experience anhedonia, dysphoria, and drug craving in the long-term. Currently, there is no proven pharmacologic treatment for its dependence or withdrawal. Patients should be observed for emergence of depressive syndrome and suicidality.

Data are insufficient to determine if chronic use of amphetamine in children is causally associated with suppression of growth. Thus, treatment should be only continued with continuing growth and weight gain in children.

2.5 Presubmission Regulatory Activity

The original FDA Written Request (WR) for this submission was issued on May 6, 2003. In the WR, Agency required the sponsor to conduct and submit a PK study, a pediatric efficacy and safety study, and a pediatric safety study in adolescents aged 13-17 year-old with DSM-IV diagnosis of ADHD.

According to the original WR, a minimum of 12 patients was required for a traditional PK study; or, population PK of safety trials or controlled efficacy trial, which should be effective, must be provided. PK parameters must be assessed on both dextro- and levo-amphetamine with full treatment dose range and compared with values from adults and children of 6-12 year-old.

For the pediatric efficacy and safety study, the WR specifies that it must be fixed dose study with sufficient number of subjects to provide a power of 85%. A detailed statistic plan to show this power at conventional levels of statistic significance (with α=0.05 and two-tailed analysis) was required. In addition, the sponsor was asked to justify an instrument being used as sensitive and specific and add CGI. Finally, the WR defined the primary outcome as changes from baseline to endpoint on ADHD scales.

To evaluate safety, the WR specifies that the trial can be controlled or open-label trial with a minimum of 100 patients for at least 6 months. Dosage must be at or above the dose or doses identified as effective. If lack of efficacy, long term safety data still must be collected at the doses at least as high as the typical treatment doses. Essential items to be monitored include: Vitals with weight and height, chemistry, hematology, urinalysis, ECG, and AEs. Tanner Stage on growth and development should also be monitored.

In addition, the WR requires the sponsor to commit to obtain follow-up data on a cohort of patients who have been treated chronically for at least two years. The data can be from both controlled trial and long term follow-up trial: The primary outcomes of interest are height and weight and they must be obtained at roughly 4-month intervals. Growth-curve data on height and weight may be used to assess open-label trials by using z-scores. Each subject's z-score should be determined at the beginning and at the end of observation. Detailed plan for this follow-up study with descriptive analysis of the safety data is required.

Afterwards, this original WR was amended three times:

1) Sept 17, 2003 –Though it indicated full text revision of the WR, this amendment focused on the following changes: i) Lowering the percentage of requirement for female subjects (20% instead of 25%) for the efficacy and safety study. ii) The requirement of total number of patients for the efficacy and safety study was also lowered (75 instead of 100). iii) Z-score for each subject's height and weight was required. The rest content remained the same as the original WR.

2) May 7, 2004 –The second amendment focused on demographic categorization of patients according to §18 of Best Pharmaceutical Children Act (BPCA). It was required to categorize subjects to five race groups and ethnicities.

3) Sept 16, 2004 –The third amendment mainly changed "must" to "should" in using the above criteria for categorization of patients.

2.6 Other Relevant Background Information

"Pediatric Exclusivity" has been granted for Adderall XR at the Pediatric Exclusivity Board meeting on October 20, 2004 after this application was discussed. Based on the safety data in the current submission and the proposed 18-month trial, the board required the sponsor to commit a study lasting at least 24 months consecutively instead. The sponsor submitted changed protocol (SLI381-315) to comply with this issue on November 8, 2004.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Acceptable.--Please refer to CMC review by FDA Chemist, Chhagan G. Tele, PhD.

3.2 Animal Pharmacology/Toxicology

No new preclinical data were provided in this submission.

3.3 Biopharmaceutics

Please see review by FDA Biopharmaceutics Reviewer, Kofi Kumi, PhD.

3.4 Statistics

Please see review by FDA Statistician, Kun He, PhD.

3.5 Division of Scientific Investigations

Please see review by FDA Inspector, Robert Statsko, M.D.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The PK study (SLI381-110) was done at one site—the Clinical Study Centers of LLC. Samuel W. Boellner, MD recruited 23 subjects for this study.

The efficacy and safety study (SLI381-314) was done in 50 centers for Part A and 32 centers for Part B. Please see Table 1 in the Appendix for the centers and Principal Investigators involved in these two parts of the efficacy and safety study.

4.2 Tables of Clinical Studies

The following table shows the clinical studies in the overall clinical development program in this submission:

Table 1. Description of Overall Clinical Studies in This Submission

Study No.		Title of Studies	Dose Groups	Subjects		
SLI381.110		A Phase I Randomized, *Crossover* Study to Assess the Pharmacokinetics of *Single Doses* of ADDERALL XR in Adolescents Aged 13-17 with ADHD	-Adderall XR 10, 20, & 40mg	Primary Cohort 17		23
			-Adderall XR 20, 40 & 60mg	Second Cohort 6		
SLI381.314	Part A	A Phase III, Randomized, Multi-Center, *Double-Blind*, Parallel-Group, *Placebo-Controlled* Safety and Efficacy Study of ADDERALL XR in Adolescents Aged 13-17 with ADHD (*Fixed Doses*)	-Placebo	54	Primary Cohort 287	327
			-Adderall XR 10, 20, 30, & 40 mg/day	233		
			-Placebo	15	Second Cohort 40	
			-Adderall XR 50 & 60mg/day	25		
	Part B	A Phase III, Multi-Center, *Open-Label*, *Uncontrolled* Multi-dose Safety Study of ADDERALL XR in Adolescents Aged 13-17 with ADHD (*Flexible Doses)*	-Adderall XR 10 – 60mg /day	31* +107**		138[1]

[1]From the placebo* and Adderall XR** groups of Part A study, respectively.

4.3 Review Strategy

The above listed studies are reviewed separately as they have different designs. PK study is mostly reviewed by FDA biopharmaceutical science reviewer, Kofi Kumi, Ph.D. Nonetheless, its safety issues will be included in the Section of "Integrated Review of Safety" below.

4.4 Data Quality and Integrity

The study sites were audited and inspected by Robert Stasko, MD, Inspector of FDA Division of Scientific Investigations (DSI). Please see Dr. Stasko's review for details.

I have audited 5% of the Case Report Forms (CRF) and checked the appropriateness of the coding of verbatim terms to preferred terms (see below). Deficiencies of data are detailed in the Section 7.2.8 "Assessment of Completeness and Quality of Data."

4.5 Compliance with Good Clinical Practices

The sponsor declares that the studies were done under Good Clinical Practice standards. Please refer to the review by Dr. Robert Stasko of DSI for details.

Major protocol violations include being noncompliant with treatment (6, 1.8%), using incorrect study drug (2. 0.6%), using excluded medications (27, 8.3%), violations of inclusion/exclusion criteria (10, 3.1%), unblended to study drug (9, 2.8%), and others (5, 1.5%). Up to 54 subjects (16.5%) had at least one major protocol violation which excluded them. Using excluded medications was the most common protocol violation in all treatment groups.

4.6 Financial Disclosures

For Part A of Study SLI381-314, all (100%) investigators submitted certificates for financial disclosure; For Part B of the study, up to 93.8% (30/32) of the investigators submitted the certificate. (Exceptions are Mark Wolraich, MD and Lawrence Ginsberg, MD.) No investigator disclosed any financial interests as defined as 21 CFR 54.2.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Previously submitted PK studies of Adderall XR were conducted in healthy adults and in children of 6-12 years-old with or without ADHD. Mean $T_{1/2}$ is slightly shorter in children (9-11 hours) than that in adults (10-13 hours). However, children have higher systemic exposure to amphetamine (Cmax and AUC) than adults for a given dose unless it was a dose based on mg/kg. A previous study also showed linear pharmacokinetics over 20-60mg in adults and 5-30mg in children aged 6-12 years. Tmax is about 7 hours, which is 4 hours longer than Adderall. Food doesn't affect absorption of Adderall XR but prolongs its Tmax.

In this submission, Study SLI381-110 involves 23 adolescents aged 13-17 years with ADHD. The study is an open-label single-dose study with 3-treatment periods randomized crossover. There is a 7-day washout period in between these treatments. It included two cohorts of subjects:

Table 2. Subject Groups in Study SLI381-110

Cohorts			**Primary**	**Secondary**
Weight			≤75kg/165lbs	>75kg/165lbs
Dose Groups (mg)			10, 20, 40	20, 40, 60
Subject	**Age (year)**	**Mean**	14.8	15.7
		Range	13-17	15-17
	Numbers		17	6
	Gender (F:M)		29%:71%	33%:67%
	Ethnicity	**Black (%)**	5 (29%)	3 (50%)
		Caucasian (%)	12 (71%)	3 (50%)

Study design fulfills the requirements of FDA WR. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 10-40mg in pediatric patients with ADHD weighing ≤ 75kg/165lbs as well as over doses ranging from 20-60mg in the same population weighing ≥ 75kg/165lbs. Log-log plots of C_{max} and AUC∞ vs. dose were linear with slopes ≈ 1 in both groups. (See Dr. Kofi Kumi's review for detail.) According to FDA biopharmaceutics reviewer, Kofi Kumi, Ph.D., this PK study concludes that clearance and AUC of d- and l-amphetamine are related to weight across all age groups: Lower body weight is associated with lower clearance and thus, higher AUC∞ and Cmax. Age and gender have no effect on

pharmacokinetics of d- and l-amphetamine. Tmax is at about 6 hours. (For details, please see Dr. Kumi's review.)

5.2 Pharmacodynamics

Like Adderall and other psychostimulants, Adderall XR increases presynaptic norepinephrine, dopamine, and serotonin. At the same time, it inhibits reuptake of norepinephrine and dopamine and mild MAOI effects. Together, these two effects make it a potent stimulant for sympathetic nervous system and can increase blood pressure, both systolic and diastolic, as well as heart rate if dose is high enough. By stimulating monoamine release by the reticular activating system, it increases alertness. Its effect on hypothalamus probably is related to appetite suppression. Euphoria and locomotor stimulation are probably resulted from facilitating dopaminergic neurotransmitter in the striatum and limbic system. However, its exact mechanism for treatment of ADHD is still unclear. No psychodynamic studies performed for this submission.

5.3 Exposure-Response Relationships:

There is no PK data for the efficacy study SLI381-314 Part A. Efficacy increases with dose increase from 10mg to 20mg daily. However, beyond 20mg, there was no increased response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

ADHD is among one of the most commonly diagnosed psychiatric disorders in school-age children with a prevalence of 3-7%. It is found more often among first degree relatives of the patients and those families with mood and anxiety disorders, learning disorders, substance-related disorders, and antisocial personality disorders. Differential diagnosis include age appropriate behaviors in active children, under-stimulated academic environment, oppositional behavioral disorder, stereotyped movement disorder, pervasive developmental disorder, mental retardation, and other common psychiatric disorders.

As stated above, the sponsor performed one efficacy study in response to FDA WR for treatment of ADHD in adolescents aged 13-17.

6.1.1 Methods

This efficacy review is based on the one efficacy study that the sponsor conducted and submitted in response to FDA WR (see Presubmission Regulatory Activity section): Study SLI381-314 Part A--"A Phase III, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo-Controlled, Safety and Efficacy Study of ADDERALL XR in Adolescents Aged 13-17 with Attention Deficit Hyperactivity Disorder (ADHD)." Thus, the following general sections include specific study information from this individual study review.

6.1.2 General Discussion of Endpoints

The sponsor's primary study objective was to assess the safety and efficacy of Adderall XR (10–40 mg/day) compared to placebo in the treatment of adolescents, aged 13–17 year-old and weighed less than 75kg/165lbs, with ADHD using clinician administered ADHD-Rating Scale (ADHD-RS-IV).

Hence, the sponsor used the following efficacy measures:

1) Primary Variable: Change of ADHD-Rating Scale total score in Primary Cohort from baseline to endpoint of the study.

ADHD-RS-IV is a semi-structured interview with the subjects' parents or primary caregiver and the subject. It consists 18 items that reflect current symptomatology of ADHD based on DSM-IV criteria with a total possible score of 54. Each item is scored from a range of 0 (no symptoms) to 3 (severe symptoms). These items can be grouped into two subscales: Even numbered items contribute to hyperactivity/impulsivity subscale; Odd numbered items contribute to inattentiveness (inattentive subscale). It has been commonly used in the trials for ADHD. This scale was rated at baseline, and at every visit. (See Appendix Table 2)

2) Secondary Variables:

- CGI-I change of Primary Cohort.
- Change from baseline of ADHD-RS-IV total score in Secondary Cohort.

CGI-I is Clinical Global Impressions Rating Scale-Improvement which is rated by the clinician investigators on a 7-point scale, ranging from 0 (not assessed) to 7 (most extremely ill) with 4 indicating no change.

There were no key secondary efficacy variables.

Subjects were assessed for six visits. CGI-Severity was performed at screening (Visit A-1) and baseline (Visit A0); ADHD-RS-IV and CGI-I were performed at baseline (Visit A0) and then on weekly basis (Visits A1, A2, A3, and A4).

6.1.3 Study Design

The sponsor randomized 327 subjects into two cohorts based on their weight in this study (randomization stratified by subject cohort) and each cohort received different dosages (see Table 3). Subjects were then randomly assigned into each dose groups within each cohort roughly at 1:1:1:1 or 1:1:1 ratio. The main part of the trial with primary cohort was 4 weeks long. A total of 233 subjects in primary cohort received the active drug treatment, Adderall XR and almost 90% of subjects completed the trial. Thus, it fulfills the requirement set by the FDA WR. The completion rate for the secondary cohort is comparable, up to 88%.

Table 3. Study Design and Dose Schedule of SLI381-314 Part A

	Primary Cohort	**Secondary Cohort**
Sample/Subjects	Weighed ≤75kg/165lbs	Weighed >75kg/165lbs
Length of Study	4 weeks*	4weeks**
Dose Range	10-40mg/day	50-60mg/day
Dose Groups (*forced dose titration*)	Placebo Adderall XR 10mg 20mg 30mg 40mg	Placebo Adderall XR 50mg Adderall XR 60mg
Numbers of Subjects Randomized	287	40
Radomization Ratio	1:1:1:1:1	1:1:1
Completers in Active Treatment Group	89% (208/233)	88% (22/25)

*Not all dose groups were on a specific dose for 4 weeks. –See next paragraph.
**Starting doses were 20mg/day. Doses were increased gradually and reached the maximum target by Week 4.

Dose Schedule:
All Adderall XR treatment groups were started at 10mg/d for Primary Cohort. Dose was then increased to 20mg/d on Week 2 for groups 20mg, 30mg, and 40mg; Dose was further increased to 30mg/d on Week 3 for groups 30mg and 40mg, and eventually increased to 40mg/d on Week 4 for group 40mg. Thus, the placebo group and 10mg-group received their target dose for four weeks, while 20mg-group was on that dose for three weeks, 30mg-group was for two weeks, and 40mg-group was for one week only.

For Secondary Cohort, doses in the two Adderall XR dose groups were increased gradually as follows:

1) From 20mg/day (Week 1)→30mg/day (Week 2)→ 40mg/day (Week 3)→50mg/day (Week 4);
2) From 20mg/day (Week 1)→40mg/day (Week 2)→ 50mg/day (Week 3)→60mg/day (Week 4).

Protocol Amendments:
The protocol of SLI381-314 was amended several times. However, important amendments have been incorporated into the overview and description of the study in this review.

Criteria for Subjects Selection:
In addition to subjects' legal representatives' willingness and ability to comply with the requirements and signing the consents, the subjects must meet the following criteria:

1) Age between 13–17 year-old (inclusive) with a minimum 80 IQ;
2) Meeting diagnostic criteria of ADHD, either hyperactive or predominantly inattentive subtype, or combined;
3) BP (blood pressure) must be within 95 percentile for age, gender, and height;
4) No clinically significant ECG or other comorbid illness (including, other psychiatric disorders such as conduct disorder, substance abuse at the screening or within 6 months of screening, seizure during the last 2 years, hypertension, uncontrolled thyroid

abnormality, or allergic to Adderall XR, etc) that would affect efficacy, safety, or tolerability, or in any way interfere with the subject's participation in the study.

Moreover, subjects must not:

1) Be known non-responder to stimulants;
2) Be underweight (BMI-for-age<5th percentile) or overweight (BMI-for-age≥95th percentile)
3) Have a history of tic disorder and/or current diagnosis or a family history of Tourette's disorder.
4) Take a medication that would affect HR or BP;
5) Take an investigational drug within 28 days prior to baseline.
6) Be pregnant or lactating as female subjects.
7) Take any drugs that would affect CNS performance, such as antihistamines, decongestants, etc.

Subjects were screened for a period of 1-7 days. Eligible ones then enter "baseline" period which was also up to 7 days. Previous treatments were washed out if necessary during this period.

Demographics: The following tables illustrate subject demographic distribution of each study group in ITT population of primary cohort. "Other" denotes biracial. No subject was considered Asian or Pacific Islander. There were 34.5% female subjects, which meets the requirement of FDA WR. The treatment groups were reasonably balanced in terms of demography.

Table 4. Subject Demographics of Primary Cohort in Part A of Study SLI381-314 (ITT)

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR				
			10mg	20mg	30mg	40mg	Total
Subjects in ITT		**N=52**	**N=54**	**N=53**	**N=58**	**N=61**	**N=278**
AGE (Years)	**Mean**	14.5	14.4	14.2	14.2	14.0	14.2
	SD	1.3	1.2	1.2	1.2	1.2	1.2
	Range	13-17	13-17	13-17	13-17	13-17	13-17
Sex	**F (%)**	17(32.7)	21(38.9)	16 (30.2)	20 (34.5)	22 (36.1)	96 (34.5)
	M (%)	35(67.3)	33 (61.1)	37 (69.8)	38 (13.2)	39 (63.9)	182 (65.5)
RACE (%)	**White**	38(73.1)	38 (70.4)	39 (73.6)	43 (74.1)	47 (77.0)	205 (73.7)
	Black	11(20.4)	10 (17.9)	9 (16.1)	8 (13.8)	6 (9.5)	44 (15.3)
	Hispanic	3 (5.8)	2 (3.7)	3 (5.7)	5 (8.6)	6 (9.8)	19 (6.8)
	Native American	0	2 (3.7)	0	0	2 (3.3)	4 (1.4)
	Other	0	2 (3.7)	2 (3.8)	2 (3.4)	0	6 (2.2)

Analysis:

The efficacy review will be drawn from the Part A of Study SLI381-314, which is double-blind, placebo controlled, fixed dose study. The primary outcome is the change of total score of ADHD-RS-IV from baseline to endpoint in the Primary Cohort. The ITT population is defined

as all subjects who were randomized to a treatment and had one baseline and at least one post baseline ADHD-RS-IV measurement recorded in the Case Report Forms (CRF), regardless of protocol compliance or study completion. The primary efficacy endpoint score was the last valid score (LOCF). The primary analysis, a two-way analysis of covariance, ANCOVA, was used to analyze the data from the ITT population. The sponsor used this analysis for active treatment (all doses combined) vs. placebo with site as a main effect and the corresponding baseline score as covariate. For the ANCOVA, the type one error rate for rejecting a null hypothesis was set at an alpha level of 0.05. Each active dose was then further compared with placebo using the same ANCOVA model and alpha level (pairwise comparisons). The significant treatment effect of each active dose vs. placebo was based on a closed-testing procedure starting from the highest dose (i.e. the 40mg/day) to control the type one error rate at 0.05. If the assumptions for ANCOVA model didn't meet, non-parametric methods would be used where appropriate.

One of the secondary efficacy variables, CGI-I, was suggested in FDA WR. The result of CGI-I was summarized and analyzed through dichotomized method: Improvement verses no improvement. The "improvement" category includes those very much improved and much improved while "no improvement" category includes the rest of the changes.

6.1.4 Efficacy Findings

Baseline Characteristics:

Most subjects were diagnosed with ADHD, inattentive type or with both inattentive and hyperactive features (combined type). Very few were hyperactive type only. (When analyzing the efficacy on subtypes of ADHD, the sponsor pooled the hyperactive type with the combined type together to compare with the inattentive type.) CGI-S at baseline showed that up to 48% subjects in placebo group were markedly ill and 44% were moderately ill. The rest were distributed equally among the mildly and severely ill. In Adderall XR treatment groups, average over 50% (50-62%) were moderately ill and 31-43% were markedly ill; the higher dosage groups (30-40mg/day) included some more severely ill subjects (4.9-8.6%).

The table below (Table 5) exhibits baseline characteristics of the subjects' mental and physical condition. Note that height was only measured at screening (A-1 visit), which could be up to 7 days for the procedures, per protocol. Following this, another period of up to 7 days for wash-out of prior treatment may be needed before a subject entering baseline (Visit 0). Thus, the period between screening and baseline could be up to 14 days. The baseline BMI listed was apparently calculated from weight at baseline and height at screening. There were no large imbalances among the treatment groups in terms of these factors.

Table 5. Baseline Characteristics of Primary Cohort of Part A of Study SLI381-314

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR			
			10mg	20mg	30mg	40mg
ITT Population		**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Type of ADHD	**Inattentive (%)**	23 (44.2)	20 (37.0)	25 (47.2)	20 (34.5)	26 (42.6)
	Hyperactive* (%)	0	3 (5.6)	1 (1.9)	1 (1.7)	2 (3.3)
	Combined (%)	29 (55.8)	31 (57.4)	27 (50.9)	37 (63.8)	33 (54.1)
ADHD-RS-IV Total Score	**Mean**	35.1	34.9	33.9	35.1	32.6
	-(SD)	(9.7)	(10.4)	(9.1)	(10.8)	(10.8)
ADHD-RS-IV Subscale Mean Scores	**Inattentiveness**	21.4	19.9	21.0	20.0	19.6
	-(SD)	(4.6)	(4.8)	(4.9)	(5.2)	(5.0)
	Hyperactivity	13.8	15.0	13.0	15.1	13.0
	-(SD)	(7.2)	(7.0)	(6.8)	(6.9)	(7.5)
Weight (lbs) at Baseline	**Mean**	131.6	125.7	124.6	128.6	125.3
	-SD	18.2	22.7	20.7	18.9	22.9
	Range	78-165	83-162	83-161	80-164	70-165
Height (Inches) at *Screening*	**Mean**	65.4	64.1	64.4	64.1	64.3
	-SD	3.6	3.6	3.6	3.1	3.6
	Range	58-72	57-71	57-73	56-72	55-72
BMI at Baseline	**Mean**	21.7	21.4	21.1	22.0	21.2
	-SD	2.8	2.6	2.9	2.9	2.6
	Range	16-29	16-27	15-27	16-28	15-26

*Hyperactive type is also referred as hyperactive/impulsive type. Hyperactivity subscale is also referred as hyperactivity/impulsivity subscale.

Disposition:

The disposition of the 287 primary cohort patients who were randomized is summarized in Table 6 below. Nearly 97% of the Primary Cohort subjects (278/287) turned into the Intent-To-Treat (ITT) population and almost 90% completed the trial (see table below). Overall, the most common reason for drop-out was withdrawal of consent (10/287=3.5%, 5 of them from 40mg group), followed by lost to follow-up (2.1%, 6/287), adverse events, and protocol violation, each of which was 1.7% (5/287). Three subjects dropped out for "other" reasons, one from placebo group and two from Adderall XR groups.

Table 6. Primary Cohort Subject Disposition in Part A of Study SLI381-314

Treatment Groups & Disposition	Placebo Group	Adderall XR				Total
		10mg	20mg	30mg	40mg	
Subjects Randomized	54	56	56	58	63	287
Subjects in ITT (Baseline) (%)	52 (96.3)	54 (96.4)	53 (94.6)	58 (100.0)	61 (96.8)	278 (96.9)
Subjects Completed (%)	50 (92.6)	49 (87.5)	51 (91.1)	55 (94.8)	53 (84.1)	258 (89.9)

The next table shows enumeration of ITT patients in-study over time:

Table 7. Part A: Enumeration of Patients In-Study over Time

Time Interval & Disposition	Total Subjects	Placebo Group	Adderall XR			
			10mg	20mg	30mg	40mg
	N	N	N	N	N	N
Baseline	278	52	54	53	58	61
Week 1	277	52	54	53	58	60
Week 2	269	51	52	53	55	58
Week 3	259	50	49	50	55	55
Week 4	257	50	49	50	55	53

Dose information:

As stated above in the Study Design Section, this study is fixed dose study with forced-dose titration design. However, not all subjects reached the targeted dose for the same length of the time. Since doses needed to be titrated up on a weekly basis, the higher dose groups were only exposed to the higher doses for shorter period of time. (Please see Table 7 above.)

Prior and Concomitant Medications:
Overall, up to 20% (66/327) of all the subjects (both primary cohort and secondary cohort) had previous treatment for ADHD. Most common treatments received were methylphenidate hydrochloride (27/66, 40.9%) and Obetrol (26/66, 39.4%).

A total of 56% (183/327) of all the subjects (both primary and secondary cohorts) used a concomitant medication during the study. The most common ones are ibuprofen (66/183, 36.1%), paracetamol (39/183, 21.3%), and salbutamol (17/183, 9.3). Among medications that might affect CNS, one subject in secondary cohort received Trazodone and another received methylphenidate. Two subjects received pseudoephedrine (one in placebo, one in secondary cohort)

6.1.5 Efficacy Results and Conclusions:

Results of the primary efficacy analysis in Primary Cohort showed statistically significant difference among all the treatment groups ($p<0.0001$) . Pairwise comparisons were examined next: The table displayed below illustrates these differences in ITT population (LOCF). The results are similar in observed cases. The mean change was smallest largest at a dose of 10mg; the largest mean change was observed at 20mg. As dose increased from 20 to 40mg, the magnitude of mean change was actually lessened. The difference was also increased as weeks passed by during the study with the final week being most significant across all dose groups. Similar trends are also seen in the analysis of the two subscales of ADHD-RS-IV, inattentiveness and hyperactivity/impulsivity subscales.

Table. 8 Change of ADHD-RS-IV Total Score from Baseline to Endpoint in Primary Cohort (ITT Population) (LOCF)

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR				*P**-value
			10mg	20mg	30mg	40mg	
ITT Population		N=52	N=54	N=53	N=58	N=61	
Endpoint ADHD-RS-IV Total Score	Mean Score	25.7	20.0	13.3	16.1	16.0	< 0.0001
	(SD)	(13.4)	(11.8)	(10.3)	(11.0)	(11.2)	
	Mean Change	-9.4	-14.9	-20.7	-19.0	-16.5	
	(SD)	(10.6)	(12.1)	(11.2)	(11.1)	(11.6)	
	p-value**	--	0.043	<0.0001	<0.0001	<0.0001	

*P-value here is based on type III sum of squares from an ANCOVA model for the change from baseline in ADHD score, including treatment and pooled center as fixed effects, and baseline balue as a covariate.
**A closed testing procedure is used to test for a difference between each active treatment group and the placebo beginning with 40mg vs. placebo and stopping when significance (p-value<0.05) is not reached.

Dichotomized analysis of CGI-I shows that the differences in percentage with improvement in Adderall XR group versus placebo increase with the length of treatment. Pairwise comparison shows such difference is statistically most significant in the 30mg Adderall XR group (44.9%, p<0.0001, versus 44.0%, 41.9% and p=0.0001 in both 20mg and 40mg groups). (See Vol. 4-13 Page 8A-1449—Table 2.4.3.)

Demographic Factors on Efficacy:

Gender: Table 9 shows the sponsor's analysis of change of ADHD-RS-IV total score from baseline to endpoint by gender. Statistical significance seems to favor Adderall XR is apparent in male subjects, with 20mg group being most significant. However, according to our FDA statistician, Kun He, PhD, the study is not powered for subgroup analysis. (Please see Dr. He's review.)

Table 9. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Gender

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR				*p*-Value
		10mg	20mg	30mg	40mg	
ITT Population	N=52	N=54	N=53	N=58	N=61	
Female	17	21	16	20	22	
Mean Change (SD)	-12.4 (10.6)	-10.4(8.8)	-21.4(10.5)	-17.5(10.7)	-15.1(13.1)	0.0692
***p*-value**		--	--	--	0.1738	
Male	35	33	37	38	39	
Mean Change (SD)	-7.9 (10.4)	-17.8(13.1)	-20.4(11.6)	-19.8(11.4)	-17.3(10.7)	<0.0001
***p*-value**		0.0002	<0.0001	<0.0001	<0.0001	

Race: Race effect on efficacy was analyzed by grouping subjects into Caucasian group and non-Caucasian group. The two groups are not balanced. Thus, no conclusion can be drawn here.

Age: Though the sponsor provides the analysis of the age effect, the two age groups are not balanced and not powered enough. (See Dr. Kun He's statistic review.)

Table 10 and Table 11 show the magnitude of changes of ADHD-RS-IV total score from baseline to endpoint by race and age, respectively.

Table 10. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Race

Treatment Groups Of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Caucasian	38	38	39	43	47
Mean Change (SD)	-11.3 (9.5)	-16.1(13.3)	-20.6(11.3)	-19.0 (10.2)	-16.2 (11.5)
Non-Caucasian	14	16	14	15	14
Mean Change (SD)	-4.0 (11.8)	-12.8(8.1)	-20.9(11.3)	-19.2(13.9)	-17.6(12.2)

Table 11. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Age

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
13-14 year-old	31	30	37	37	44
Mean Change (SD)	-8.0(10.9)	-17.2(13.3)	-21.4(11.7)	-20.1 (11.2)	-16.0 (11.1)
15-17 year-old	21	24	16	21	17
Mean Change (SD)	-11.3(10.0)	-12.1(9.9)	-19.1(10.1)	-17.2(11.1)	-17.9(12.8)

Subtypes of ADHD: The following table shows mean changes of ADHD-RS-IV total score by analysis of subtype of ADHD in this population. (Also see Table 2.1.10 on page 8A-1380 of Vol. 4.13.) Again, Dr. Kun He, the Statistician of FDA, considers the groups are not powered enough to calculate p-Values here.

Table 12. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Subtypes of ADHD

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Inattentive Subtype	23	20	25	20	26
Mean Change (SD)	-11.3 (9.3)	-14.4 (12.9)	-18.4(8.3)	-15.3 (10.7)	-13.7 (8.8)
Combined Subtype*	29	34	28	38	35
Mean Change (SD)	-7.8 (11.4)	-15.2 (11.7)	-22.7 (13.0)	-21.0 (11.0)	-18.6 (13.0)

*It includes subjects of hyperactive/impulsive subtype as well

CGI-I: CGI-I was requested in FDA WR. The following table shows the percentage of CGI-I improvement at the endpoint. Dichotomized analysis of CGI-I over time also shows the efficacy increases with duration of treatment (see page 8A-1449-50 of Vol 4.13).

Table 13. Summary and Analysis of Dichotomized CGI-I in Primary Cohort

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Dichotomized CGI-I Improvement	26.9%	51.9%	66.0%	70.7%	63.9%
Difference in % with Improvement in Active Group vs Placebo		24.9%	39.1%	43.8%	37.0%
***P*-Value**		0.0098	0.0002	<0.0001	0.0001

Conclusion:
The results of this short term, fixed dose, double-blind, placebo-controlled study, Study SLI381-314 Part A, demonstrate the efficacy of Adderall XR for treatment of adolescents (weighed ≤75kg/165lbs) with ADHD. The most effective dose from this study is 20mg/day from the primary analysis. Increasing dose from 20 to 40mg/day doesn't show increased efficacy. Along with the ADHD-RS-IV total scores, there are improvements in both subscales.

Similar efficacy trend can be seen in the secondary cohort, however, due to limited subjects, secondary cohort is statistically not powered enough.

The demographic analysis of gender, race, and age effect on efficacy are inconclusive, so is the subtype analysis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Since both the PK study (Study SLI138-110) and Part B of Study SLI381-314 are open-label studies, only deaths, serious adverse events, and drop-outs are reviewed from those datasets. For the efficacy and safety study part, Part A, which is double-blind and placebo-controlled, detailed safety review, including common adverse events and special searches, are reviewed.

7.1.1 Deaths

No death occurred in these studies.

7.1.2 Other Serious Adverse Events

No serious adverse event (SAE) was reported in the PK study (Study SLI381-110). A total of

three subjects in Study SLI381-114 (one in Part A, two in Part B of the study) reported three serious adverse events. The table below describes these three events.

Table 14. Descriptive Summary of Subjects with Serious Adverse Events in SLI381-314 (Part A & Part B)

Subject Number	Study Group	Dosage Given	Treatment Duration	Serious Adverse Events
49-008	Part A: Second Cohort (50mg group)	40mg/day	15 days	17 year-old Native American male received Adderall XR (b) (6) He developed chest pain with spontaneous pneumothorax (COSTAR term: lung disorder) on (b) (6) Adderall XR was continued. The subject recovered in 6 days and completed the study. He also experienced severe mid-clavicle chest pain secondary to incision. I agree that this incidence is probably not drug-related.
34-006	Part B	30mg/day	At least 27 weeks	14 year-old female of "other" ethnicity received her first dose of Adderall XR in Part B on Sept 2, 2003. She developed symptoms of depression in Feb. 2004 and (b) (6) she was hospitalized for suicidal ideation (COSTAR term: thinking abnormal). Two days later, the subject was prescribed with sertraline hydrochloride and was discharged from the hospital. Due to her concomitant use of sertraline, she was determined becoming ineligible for the study and Adderall XR was discontinued on Mar 7, 2004. "Depression" has been one of the AEs that caused dropouts in pediatric patients in current Adderall XR labeling. I disagree that this event is totally unrelated to the study drug.
37-004	Part B	30mg/day	At least 9 weeks	14 year-old white male was prescribed first dose of study drug on July 2, 2003. (b) (6) later, he had a right ankle fracture (COSTAR term: accidental injury). On (b) (6) he went through surgical repair of the fracture. He recovered shortly afterwards. Adderall XR was withheld on the same day of his surgery (b) (6) In the meantime, he was given oxycodone and acetaminophen for treatment. Though it is unclear how the accident happened, I agree that this is probably unrelated.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Three subjects (13%, 3/23) dropped out from the PK study prematurely, one of them was due to adverse event (see next section 7.1.3.2). A total of 20.2% (66/327) subjects dropped out from Study SLI381-314: Among them, 33 (11.5%, 33/287) from Part A and 33 (23.9%, 33/138) from Part B. In Part A, 28 (10.9%, 28/258) subjects were from those who received Adderall XR and 5 (7.2%, 5/69) from the placebo group. In both Part A of the study (10/258, 3.9%) and overall (18/289, 6.2%), withdrawal of consent was the most common reason for dropout among those who received Adderall XR.

7.1.3.2 Adverse events associated with dropouts

During the PK study (Study SLI381-110), a 13 year-old boy (weighed 84lbs and height 60" tall) in primary cohort dropped out two days after receiving Adderall XR 20mg due to "emotional distress". It was determined as a "drug-unrelated event". (This subject also had a BP changed from 106/64mmHg to 138/70mmHg at 2 hours after dosing, accompanied by anxiety, nausea, and syncope).

Although the sponsor states that in Study SLI381-314 a total of 14 subjects discontinued the study due to adverse events (8 in Part A and 6 in Part B), these numbers didn't include the one subject (#34-006) who had SAE and dropped out (see above section). Thus, the total number for dropouts is 15 (8 in Part A and 7 in Part B).

Among those dropped from Part A study, five of them were from the Primary Cohort (5/287 =1.7%) and three from the Secondary Cohort (3/40 = 7.5%). No subject dropped from the placebo group. (In the 40mg, and 50mg dose groups of Part A study, there were two dropouts; in each of the other dose groups, there was one dropout.) Reasons lead to drop-out include: Insomnia (3), depression (1), anxiety (1), dizziness (1), headache (1), and twitching/motor tics (1).

Among the seven subjects dropped from Part B of the study, four (57.1%) were in the 30mg dose group, including subject #34-006 (see above section). In the open-label, Part B of the study, the most common reason for discontinuation was anorexia, weight loss, abdominal pain, nervousness/anxiety, and depression (2 for each of these symptoms). One of these depressed patients also had suicidal ideation.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

No other search strategies conducted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In addition to review of system and laboratory tests at certain study points, the subjects were asked a non-leading question, such as "how are you feeling," or questions regarding any changes in their health or concomitant medication usage since their last visit in the PK study; For both the short term placebo-controlled study and the long term safety study, AEs were elicited through spontaneous reports during each visit. The principal investigator reviewed each AE and made the determination of relationship to study drug, such as unrelated, possibly related, and probably related. If SAE occurs, it was reported to the (b) (4) Medical Monitor, by phone or fax, within 24 hours. The investigators followed SAEs until resolution (either the subject's health returned to his/her baseline status or all parameters returned to normal), the event stabilized, an outcome is reached, or the event could be explained otherwise.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Verbatim coding was mostly appropriate based on my audit of the coding for all verbatim (or investigator) terms. Some of them include broad information, such as "accidental injury" that varies from abrasions, laceration, to burns; from tooth cap break to injuries in legs and wrists. Still, "ecchymosis" includes "bruises" and "contusion" which may be part of injury as well. Any appetite decreases, from "mild appetite loss" to "no appetite" were coded under "anorexia". Both "depression" and "dysphoric" were coded as "depression." yet, "increased moodiness, crying, moody, labile mood, mood swings" were all coded as "emotional lability," and "irritability, jitteriness, increased irritability, and restlessness" were all included in "nervousness." Though not common, it is noted that "feeling hyper" was coded as "hyperkinesia."

7.1.5.3 Incidence of common adverse events

Only Part A of Study SLI381.314 is fixed dose, placebo-controlled study. It includes two cohorts: Primary cohort (weighted less than 75kg/165lbs and on one of four fixed Adderall XR doses: 10, 20, 30, or 40mg/day) and secondary cohort (those weighted at least 75kg/165lbs and were given Adderall XR up to 50-60mg/day.) The sponsor states that 71.3% of subjects (233/278) in this part of the study reported 624 treatment-emergent events. Overall, compared to the placebo group, the subjects taking Adderall XR have a higher incidence of adverse events (74.0% vs 60.9%), particularly anorexia, insomnia, abdominal pain, and weight loss.

7.1.5.4 Common adverse event tables

Common adverse events that are ≥ 2% in any Adderall XR dose groups in primary and secondary cohorts of Study SLI381.314 Part A are listed separately in the Appendix (see Appendix Tables 2 and 3.)

7.1.5.5 Identifying common and drug-related adverse events

In primary cohort, Adderall XR 40mg group had the highest incidences of insomnia, abdominal pain, and also somnolence; Adderall XR 30mg group had the highest incidences of anorexia, diarrhea, weight loss, and emotional lability. Nausea and Vomiting happened even at 10-20mg doses. Incidences of nervousness and dizziness among subjects taking Adderall XR were not significantly more than those taking placebo in primary cohort; however, they were more common in secondary cohort. Note, since only 40 subjects were in secondary cohort (25 taking Adderall XR, 15 taking placebo), even 1 subject can change the percentage of the listing significantly (6.7%). Tables 5 and 6 in the appendix list the drug-related adverse events in the short-term placebo-controlled fixed dose study.

7.1.5.6 Additional analyses and explorations

The sponsor provides the tables for demographic effects on adverse event reporting rates for those AEs that were reported at >5% and with greater incidence than placebo in both Part A and Part B of Study SLI381-314. The sponsor essentially compares the placebo group with all subjects taking Adderall XR. The sponsor neither separates the dose groups for these demographic analyses nor provides analysis for drug:placebo odds ratios of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds ratios between the subgroups. Thus, effects of age, gender, and ethnicity/race can't be readily determined. Of note, emotional lability is not in the table presented for ethnicity analysis.

7.1.6 Less Common Adverse Events

Less common adverse events are listed in the table provided by the sponsor. Please see Tables 6 and 7 in the Appendix.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests include clinical chemistry (including thyroid function), hematology, and urinalysis. They were drawn at screening and at the end of PK study as well as in the controlled trial where the endpoint was the fourth week or when the subject discontinued from the study. Mean changes from baseline to endpoint are compared across treatment groups using ANCOVA.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Since PK study is a single dose study, the analysis below will focus on the data from the controlled pivotal study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Mean changes of clinical chemistry:
Analyses of clinical chemistry of primary cohort in each dose group (Vol.14, page 8A-1754–1768) show no significant changes from baseline to endpoint in regard to sodium, potassium, chloride, bicarbonate, BUN, glucose, bicarbonate calcium and total calcium, AST, ALT, GGT, total protein, and TSH; there were significant changes in total bilirubin (p=0.0381), albumin (p=0.0049), and free T4 (p=0.0002).—Further analyses comparing with the placebo group show significant changes of albumin in the Adderall XR 10mg group (p=0.0135) as well as free T4 in the Adderall XR 30mg (mean change of +0.15 with p<0.0001) and 40mg groups (mean change of +0.15 with p=0.0004). However, these changes don't seem to be clinically significant.

In the secondary cohort (Vol.14, page 8A-1769–1783), there was significant change in total calcium (p=0.0345), albumin (p=0.0020), and free T4 (p=0.0299). As in the primary cohort, there was significant change of albumin and free T4 in the Adderall XR 50mg (p=0.0459 and mean change of free T4 +0.17 with p=0.0275, respectively) and 60mg (p=0.0005 and mean change of free T4 +0.21 with p=0.0129, respectively) dose groups comparing with the placebo group; Only Adderall XR 60mg group has significant change of total calcium (p=0.0105).

There was no mention of serum creatinine as part of clinical chemistry in the protocol or study report.

Mean changes of hematological tests:
Analyses of hematological tests of primary cohort in each dose group (Vol.14, page 8A-1713–1725) show no significant changes from baseline to endpoint in platelet count or white blood cell count and its differentials. There was statistically significant change of red blood cell count (p=0.0185), hematocrit (p=0.0137), and hemoglobin (p=0.0165). Further analysis show statistically significant changes of red blood cell in dose groups 20mg (p=0.0426), 30mg (p=0.0070), and 40mg (0.0042); Similarly, statistically significant change in both hematocrit and hemoglobin in dose groups 30mg (mean change of -0.20 with p=0.0029, -0.07 with p= 0.0082, respectively) and 40mg (mean change of -0.16 with p0.0070, +0.04 with p=0.0020, respectively). Again, these changes don't seem to be clinically significant.

In secondary cohort, none of the hematological tests show statistical significant difference from baseline to endpoint in each dose group (Vol.14, page 8A-1726–1738)

7.1.7.3.2 Analyses focused on outliers:

In the response to our filing letter, the sponsor provides subject listing for outliers without enumeration table for outliers.

Review of Urinalysis:

The sponsor reports that four subjects in Part A of Study SLI381-314 had proteinuria, three of them in Adderall XR 40mg group and one in Adderall XR 60mg group at endpoint of the study (see page 8A-1873 of Vol 4.14, Table 3.6.8), and none in placebo group. In addition, only a shift table for PH changes in urinalysis of those taking Adderall XR 10-40mg group and 50-60mg group comparing with placebo is provided. No more detailed information on parameters of urinalysis is provided.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See above section. The sponsor needs to provide the table for enumeration of outliers. No dropout was reported due to laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

No additional analyses conducted.

7.1.7.5 Special assessments

No special assessments conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs in both protocols of PK study and efficacy-safety study (SLI381-314) included blood pressure, respiratory rate, pulse, and temperature. (However, no data on temperature assessment presented from either of the above.) During PK study, they were obtained at screening, check-in (Day-1), and at 0, 2, 4, 24, and 60 hours of treatment periods 1-3 (Day 1-3). For study SLI381-314, vital sign changes from baseline at endpoint will be reviewed.

The sponsor provides the following items for vital sign assessments: Pulse, respiratory rate, systolic and diastolic blood pressure. All measurements were obtained at sitting position. Weight is also included as part of the vital signs. (See Section "Effect on Weight" below.)

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Since the design of PK study, Part A and Part B of Study SLI381-314 are all different, all data from these studies will be analyzed separately. As Part B is an open label, flexible dose study that inherits patients from both placebo group and Adderall XR group of Part A, its data on vital signs will not be included here. Thus, the following review includes data on vital signs from PK study and the double-blind, placebo-controlled, Part A study.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The sponsor defines "hypertension" ("increased blood pressure") as the blood pressure measured ≥95th percentile for age and gender.

The following tables list the changes of blood pressure (Table 15), pulse (Table 16), and respiratory rate (Table 16) seen in PK study. P-values reflect the difference form baseline, with significant p-values in bold type. Measures at 4-hour is the closest to Tmax which is about 6-hour.

Table 15. Mean Changes of Blood Pressure from Baseline during PK Study

Subjects & Cohorts		**Adderall XR Groups**					
		Primary Cohort			**Secondary Cohort**		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	15*	15	6	6	6
Systolic Blood Pressure Changes (mmHg)	**Baseline**	107.1	109.6	108.9	111.5	109.3	107.7
	@ 2-hour (p-Value)	4.7 (0.0557)	12.4 (**0.0031**)	17.7 (**0.0004**)	8.0 (0.0574)	25.7 (**0.0006**)	18.7 (**0.0227**)
	@ 4-hour (p-Value)	6.3 (**0.0415**)	7.7 (**0.0407**)	20.9 (**0.0002**)	12.7 (0.0522)	25.0 (**0.0084**)	20.3 (**0.0327**)
	@ 24-hour (p-Value)	3.1 (0.2522)	2.3 (0.4406)	7.1 (**0.0315**)	6.0 (0.1970)	7.8 (0.2367)	13.2 (**0.0353**)
	@ 60-hour (p-Value)	7.7 (**0.0011**)	8.5 (**0.0040**)	8.9 (**0.0008**)	8.0 (**0.0192**)	11.8 (**0.0133**)	17.5 (**0.0162**)
Diastolic Blood Pressure Changes (mmHg)	**Baseline**	60.6	60.4	63.8	58.7	59.2	60.7
	@ 2-hour (p-Value)	0.1 (0.9543)	7.0 (**0.0121**)	8.5 (**0.0011**)	5.7 (0.0671)	11.3 (**0.0170**)	10.0 (0.0774)
	@ 4-hour (p-Value)	2.6 (0.3743)	8.5 (**0.0035**)	7.7 (**0.0061**)	2.8 (0.2329)	8.8 (0.0907)	9.7 (0.1491)
	@ 24-hour (p-Value)	3.1 (0.3091)	3.1 (0.1978)	2.9 (0.2202)	0.3 (0.8840)	5.5 (0.1369)	4.3 (0.3241)
	@ 60-hour (p-Value)	3.5 (0.2155)	6.8 (**0.0142**)	3.5 (0.0697)	4.7 (0.3782)	5.5 (0.1454)	8.8 (0.0554)

*Though initially there was 16 subjects, from second hour and on, subject number became 15 in this dose group as well. –This is the same in the next table on changes of pulse and respiratory rate. (This may explain the case of "early termination" mentioned earlier. However, no explanation is found in the submission.)

In primary cohort, there were significant changes of systolic BP at 4-hour in all dose groups (10, 20, and 40mg), but changes of diastolic BP at 4-hour only in 20mg and 40mg groups. These changes can appear as early as at 2-hour. In secondary cohort, significant changes of systolic BP at 4-hour in both 40mg and 60mg groups, but such change of diastolic BP is only seen in 40mg group.

Table 16. Mean Changes of Pulse and Respiratory Rate from Baseline during PK Study

Subjects & Cohorts		Adderall XR Groups					
		Primary Cohort			Secondary Cohort		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	16*	15	6	6	6
Pulse Change (bpm)	**Baseline**	68.5	68.3	73.3	72.3	63.7	64.0
	@ 2-hour (p-Value)	10.2 (**0.0016**)	9.8 (**0.0050**)	1.5 (0.6537)	-0.8 (0.8358)	13.0 (**0.0042**)	11.8 (0.1052)
	@ 4-hour (p-Value)	8.2 (**0.0248**)	8.2 (**0.0238**)	4.1 (0.2828)	0.2 (0.9646)	16.0 (**0.0112**)	21.3 (**0.0026**)
	@ 24-hour (p-Value)	6.1 (**0.0106**)	4.7 (0.1405)	8.7 (0.0577)	-1.0 (0.8785)	17.7 (**0.0048**)	21.8 (**0.0009**)
	@ 60-hour (p-Value)	4.1 (0.2140)	8.9 (**0.0310**)	8.3 (0.0605)	3.8 (0.3277)	9.8 (0.1143)	9.3 (**0.0113**)
Respiratory Rate Change (bpm)	**Baseline**	17.7	17.8	17.1	15.3	16.0	16.3
	@ 2-hour (p-Value)	-0.1 (0.6702)	-0.3 (0.4320)	0.8 (0.0824)	-0.8 (0.8358)	1.3 (0.1019)	0.0 (1.0000)
	@ 4-hour (p-Value)	-0.3 (0.4985)	-0.1 (0.7744)	1.1 (**0.0406**)	0.2 (0.9646)	1.0 (0.2031)	-0.3 (**0.0026**)
	@ 24-hour (p-Value)	0.3 (0.4985)	-0.1 (0.7513)	1.3 (**0.0031**)	-1.0 (0.8785)	1.3 (0.1019)	0.7 (0.3632)
	@ 60-hour (p-Value)	0.8 (0.1109)	0.0 (1.0000)	1.7 (**0.0005**)	3.8 (0.3277)	2.3 (**0.0127**)	2.3 (0.1099)

In primary cohort, pulse seems to be more affected in the lower dose groups (10 and 20mg), while respiratory rate is more affected in the higher dose group (40mg). In secondary cohort, change of pulse are more affected in the higher dose groups (40 and 60mg)

Tables 17 and 18 on the next two pages list changes of blood pressure, pulse, and respiratory rate during Part A of Study SLI381-314. Again, p-values reflect the difference form baseline, with significant p-values in bold type.

It is noted that the p-value (ANCOVA) for change from baseline is based one ANCOVA model including treatment as a fixed effect and baseline value as covariate. The sponsor indicates that p-value is < 0.05, T-test of the LS means from the ANCOVA model are used to test for a difference between treatment groups and the placebo group. Otherwise, no further statistic analysis performed. This applies to the p-values in the next table as well.

Table 17. Endpoint Mean Changes of Vital Signs from Baseline among Primary Cohort in Part A of Study SLI381-314 (LOCF)

Vital Signs	Time Points	Analysis	Adderall XR				Placebo
			10mg	20mg	30mg	40mg	
			N=52	N=54	N=58	N=61	N=54
Systolic Blood Pressure	Baseline	Mean (SD)	106.3 (7.6)	109.3 (9.4)	107.9 (9.8)	107.8 (9.3)	108.1 (9.2)
	Endpoint	Mean (SD)	104.4 (8.8)	108.6 (9.9)	109.6 (9.5)	107.0 (8.8)	108.4 (8.2)
		Change (SD)	-1.9 (8.0)	-0.6 (10.4)	1.7 (9.8)	-1.1 (9.3)	0.3 (10.3)
		p-Value	0.0513				
Diastolic Blood Pressure	Baseline	Mean (SD)	67.1 (7.6)	67.4 (8.2)	67.1 (7.0)	66.2 (6.6)	67.0 (8.2)
	Endpoint	Mean (SD)	67.4 (7.8)	69.0 (7.8)	68.5 (6.1)	68.5 (7.4)	66.8 (7.0)
		Change (SD)	0.4 (7.8)	1.7 (9.0)	1.4 (6.6)	2.3 (7.5)	-0.2 (8.8)
		p-Value	0.3635				
Pulse	Baseline	Mean (SD)	75.6 (8.2)	73.9 (8.1)	74.1 (9.8)	75.8 (9.2)	73.7 (8.9)
	Endpoint	Mean (SD)	76.0 (9.3)	78.6 (11.0)	73.1 (9.8)	78.5 (13.3)	74.5 (9.4)
		Change (SD)	0.2 (7.8)	4.9 (11.5)	-1.0 (11.1)	2.8 (10.7)	0.5 (9.5)
		p-Value	**0.0111**				
			0.7889	**0.0226**	0.4297	0.0940	
Respiratory Rate	Baseline	Mean (SD)	16.6 (3.0)	17.0 (2.6)	17.2 (3.4)	17.6 (2.9)	17.0 (3.0)
	Endpoint	Mean (SD)	16.9 (3.0)	17.4 (3.0)	17.1 (2.9)	17.5 (3.0)	17.0 (2.6)
		Change (SD)	0.2 (2.0)	0.4 (2.8)	-0.1 (2.9)	-0.1 (3.1)	-0.1 (2.8)
		p-Value	0.8023				

In primary cohort, the only statistically significant change is pulse, which is especially noteworthy in Adderall XR 20mg group. However, from this data the magnitude of change doesn't seem to have clinical significance.

In secondary cohort, the only statistically significant change is also pulse, and it is more noteworthy in Adderall XR 50mg group. Again, its magnitude doesn't seem to be clinically significant.

Table 18. Endpoint Mean Changes of Vital Signs from Baseline among Secondary Cohort in Part A of Study SLI381-314

Vital Signs	Time Points	Analysis	Adderall XR		Placebo
			50mg	60mg	
			15	10	15
Systolic Blood Pressure	Baseline	Mean (SD)	115.9 (9.7)	115.3 (8.1)	115.5 (11.8)
	Endpoint	Mean (SD)	115.7 (9.5)	117.5 (11.4)	116.0 (9.0)
		Change (SD)	-0.2 (9.1)	2.2 (11.3)	0.5 (8.3)
		p-Value	0.8132		
Diastolic Blood Pressure	Baseline	Mean (SD)	71.1 (8.2)	72.3 (7.0)	69.7 (8.8)
	Endpoint	Mean (SD)	70.2 (5.8)	73.9 (8.2)	71.5 (7.4)
		Change (SD)	-0.9 (6.1)	1.6 (11.9)	1.8 (9.8)
		p-Value	0.4825		
Pulse	Baseline	Mean (SD)	76.5 (9.1)	77.3 (14.8)	78.7 (13.4)
	Endpoint	Mean (SD)	85.0 (9.5)	81.4 (13.6)	74.3 (11.7)
		Change (SD)	8.5 (12.1)	4.1 (17.3)	-4.5 (9.0)
		p-Value	**0.0145**		
			0.0043	0.0782	
Respiratory Rate	Baseline	Mean (SD)	17.4 (4.1)	15.5 (2.9)	16.9 (3.4)
	Endpoint	Mean (SD)	18.3 (3.5)	18.3 (2.7)	16.9 (2.4)
		Change (SD)	0.9 (3.6)	2.8 (4.3)	0.0 (3.0)
		p-Value	0.2302		

7.1.8.3.2 Analyses focused on outliers of vital sign measures:

In the PK study, the sponsor reports that in the primary cohort (dosing 10, 20, and 40mg) up to 76% (13/17) subjects had clinically significant elevation in blood pressure. Overall, the sponsor reports that most frequent AE was hypertension, which seems to have increased occurrence with at 20 and 40mg. In the secondary cohort (dosing 20, 40, and 60mg), again, hypertension is the most commonly reported AE (83%).

Table 19. Occurrence of Hypertension with Different Dosage in Pharmacokinetic Study (SLI381-110)

Cohorts	Dosing	Subjects who had Hypertension[1]
Primary	10mg	3/15 = 20%
	20mg	7/16 = 43.7%
	40mg	7/15 = 46.6%
Secondary	20mg	2/6 = 33.3%
	40mg	5/6 = 83.3%
	60mg	4/6 = 66.7%

[1] The Sponsor defines "Hypertension" as measures that are above 95th percentile. In ISS, the sponsor only reported the number of subjects who reported hypertension which was 1 in 10mg group and 3 in 60mg group.

The following tables show number of outliers from blood pressure and pulse analyses among primary cohort (Table 20) and secondary cohort (Table 21) of Part A of Study SLI381-314. Criteria of change are also listed in the tables below.

Table 20. Outliers from Blood Pressure and Pulse Analysis among Primary Cohort of Part A of Study SLI381-314

Vital Signs	Indicators Of Change	Adderall XR				Placebo
		10mg	20mg	30mg	40mg	
		N=54	N=54	N=58	N=61	N=52
Systolic BP	<20mmHg	54 (100%)	50 (92.6%)	56 (96.6%)	61 (100%)	51 (98.1%)
	≥20mmHg	0 (0%)	4 (7.4%)	2 (3.4%)	0 (0%)	1 (1.9%)
Diastolic BP	<10mmHg	48 (88.9%)	42 (77.8%)	51 (87.9%)	50 (82.0%)	43 (82.7%)
	≥10mmHg	6 (11.1%)	12 (22.2%)	7 (12.1%)	11 (18.0%)	9 (17.3)
Pulse	<25bpm	54 (100%)	51 (94.4%)	58 (100%)	59 (96.7%)	51 (98.1%)
	≥25bpm	0 (0%)	3 (5.6%)	0 (0%)	2 (3.3%)	1 (1.9%)

Table 21. Outliers from Blood Pressure and Pulse Analysis among Secondary Cohort of Part A of Study SLI381-314

Vital Signs	Indicators Of Change	Adderall XR		Placebo
		50mg	60mg	
		N=15	N=10	N=15
Systolic BP	<20mmHg	15 (100%)	10 (100%)	15 (100%)
	≥20mmHg	0 (0%)	0 (0%)	0 (0%)
Diastolic BP	<10mmHg	14 (93.3%)	8 (80.0%)	12 (80.0%)
	≥10mmHg	1 (6.7%)	2 (20.0%)	3 (20.0%)
Pulse	<25bpm	13 (86.7%)	9 (90%)	15 (100%)
	≥25bpm	2 (13.3%)	1 (10%)	0 (0%)

In primary cohort, compared with other dose groups, Adderall XR 20mg group had the highest rate of increase of systolic and diastolic BP as well as pulse. There doesn't seem to have significant increase of BP in secondary cohort, while pulse increase is obvious in the both Adderall XR groups.

The sponsor's also presents tables to show that in all dose groups of Adderall XR, whether among primary cohort or secondary cohort, all subjects had pulse less than 110bpm and blood pressure less than 150/100mmHg.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Among primary cohort, Adderall XR 20mg group had the most outliers in terms of blood pressure (systolic and diastolic) and pulse change. In Adderall XR treated groups, maximum change of pulse was 44bpm, of systolic blood pressure, 26mmHg, and of diastolic blood pressure 30mmHg; In placebo group the maximum changes were 32 bpm, 20mmHg, and 24, respectively.

Nonetheless, the analysis in this study is confounded by duration of treatment with the target dose. For example, 40mg patients received 40mg for only one week, which may not be long enough to fully assess effects of higher dose on blood pressure or pulse.

7.1.8.4 Additional analyses and explorations

Statistics on weekly changes of above vital signs from baseline are mostly insignificant, except pulse changes during week 3 and 4 among both primary (p=0.0079 and 0.0209) and secondary cohorts (p=0.0137 and 0.0088).

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No preclinical ECG study for this submission. ECG was only obtained at screening and at the end (Day 3) of PK study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

As mentioned above, only Part A of Study SLI381-314 is a placebo-controlled study. Thus, the ECG analysis is focused on this part. It includes two cohorts with different weight and given different dosages. Therefore, the analysis presented in two separate tables.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

ECG was obtained at Visit -1 (Screening) and Visit 4 (or early termination).

Tables 22 and 23 on the next two pages show changes of ECG parameters from screening to the endpoint in the two cohorts of Part A of Study SLI381-314.

No change was statistically significant except for heart rate (HR) among the secondary cohort (those who weighed at least 165lbs/75kg and received 50 and 60mg of Adderall XR). (Please see Table 23.)

Table 22. Change of ECG Parameters from Screening of Primary Cohort in Part A of Study SLI381-314

ECG Parameters	Time Points	Analysis	Adderall XR				Placebo
			10mg	20mg	30mg	40mg	
			N=53	N=53	N=56	N=59*	N=51
PR (msec)	Screening	Mean (SD)	148.0 (20.5)	142.1 (17.2)	147.3 (18.7)	144.3 (18.1)	144.6 (17.7)
	Endpoint	Mean (SD)	149.0 (21.6)	137.0 (14.9)	145.6 (17.5)	142.5 (19.3)	144.2 (18.3)
		Change (SD)	-0.1 (14.8)	-4.9 (16.3)	-2.2 (12.3)	-1.7 (14.3)	-0.1 (11.8)
		p-Value	0.0942				
QRS (msec)	Screening	Mean (SD)	83.2 (8.3)	82.2 (9.3)	81.8 (7.6)	84.2 (9.2)	84.1 (9.3)
	Endpoint	Mean (SD)	84.3 (9.4)	83.4 (10.1)	84.3 (9.4)	85.7 (8.8)	84.1 (10.3)
		Change (SD)	1.2 (8.5)	1.4 (7.8)	2.5 (10.3)	1.6 (8.4)	0.1 (8.2)
		p-Value	0.8333				
QTcF (msec)	Screening	Mean (SD)	392.3 (19.8)	393.0 (17.3)	389.0 (18.8)	393.3 (15.3)	393.0 (20.1)
	Endpoint	Mean (SD)	391.5 (17.6)	390.2 (18.2)	387.7 (16.1)	393.1 (17.9)	395.2 (22.1)
		Change (SD)	0.1 (16.9)	-2.2 (15.2)	-0.8 (15.9)	-0.3 (16.7)	2.5 (19.3)
		p-Value	0.4154				
HR (bpm)	Screening	Mean (SD)	67.1 (10.1)	71.0 (10.7)	69.0 (9.7)	70.0 (11.8)	67.1 (8.9)
	Endpoint	Mean (SD)	70.2 (9.2)	75.9 (13.3)	72.2 (10.0)	75.3 (14.5)	71.4 (10.2)
		Change (SD)	3.5 (10.9)	4.7 (12.0)	3.6 (10.7)	5.1 (10.2)	4.5 (9.8)
		p-Value	0.4032				

*For PR interval the subject number was 58.

Table 23. Change of ECG Parameters from Screening of Secondary Cohort in Part A of Study SLI381-314

ECG Parameters	Time Points	Analysis	Adderall XR		Placebo
			50mg	60mg	
			N=15	N=10	N=14
PR (msec)	Screening	Mean (SD)	157.0 (17.4)	152.4 (15.8)	151.6 (19.1)
	Endpoint	Mean (SD)	147.9 (15.6)	143.5 (17.4)	153.4 (18.6)
		Change (SD)	-9.1 (11.2)	-8.9 (20.6)	1.3 (14.5)
		p-Value	0.1445		
QRS (msec)	Screening	Mean (SD)	87.7 (9.9)	84.3 (9.6)	87.6 (9.3)
	Endpoint	Mean (SD)	90.0 (10.0)	86.0 (10.0)	84.2 (8.9)
		Change (SD)	2.3 (9.2)	1.7 (7.8)	-2.0 (5.9)
		p-Value	0.2326		
QTcF (msec)	Screening	Mean (SD)	390.3 (14.2)	391.6 (19.7)	390.1 (13.6)
	Endpoint	Mean (SD)	387.5 (21.5)	385.7 (18.1)	387.0 (15.7)
		Change (SD)	-2.9 (20.3)	-5.9 (16.0)	-2.9 (13.1)
		p-Value	0.9162		
HR (bpm)	Screening	Mean (SD)	71.4 (9.8)	68.5 (13.4)	67.9 (14.7)
	Endpoint	Mean (SD)	77.3 (10.5)	81.0 (7.8)	66.9 (13.5)
		Change (SD)	5.9 (14.9)	12.5 (15.3)	0.4 (8.1)
		p-Value	**0.0103**		
			0.0327	**0.0036**	

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor analyzed the QTc, QTcB, and QTcF. The following tables show number of subjects who had significant changes of Q-T intervals in primary and secondary cohorts of SLI381-314 Part A. Though 12 subjects of those who received Adderall XR and 4 of those who received placebo didn't have follow up ECG, the sponsor reports no subject had QT ≥500msec in either groups.

Table 24. Subjects with Change of QTcF from Screening to Endpoint among Primary Cohort of Part A of Study SLI381-314

ECG Parameters	Indicators of Change at Endpoint	Adderall XR				Placebo
		10mg	20mg	30mg	40mg	
		N=53	N=53	N=56	N=59	N=51
QTcF (msec)	<30 msec	51 (96.2%)	52(98.1%)	53(94.6%)	58 (98.3%)	48(94.1%)
	30-59 msec	2 (3.8%)	1 (1.9%)	3 (5.4%)	1 (1.7%)	3 (5.9%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QT (msec)	<30 msec	51 (96.2%)	51(96.2%)	53(94.6%)	53 (89.8%)	49(96.1%)
	30-59 msec	2 (3.8%)	2 (3.8%)	3 (5.4%)	6 (10.2%)	1 (2.0%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 25. Subjects with Change of QTcF from Screening to Endpoint among Secondary Cohort of Part A of Study SLI381-314

ECG Parameters	Indicators of Change at Endpoint	Adderall XR		Placebo
		50mg	60mg	
		N=15	N=10	N=14
QTcF (msec)	<30 msec	14 (93.3%)	10 (100%)	13 (92.9%)
	30-59 msec	1 (6.7%)	0 (0.0%)	1 (7.1%)
	≥60 msec	0 (0.0%)	0 (0.0%)	0 (0.0%)
QT (msec)	<30 msec	13 (93.3%)	9 (90%)	12 (92.9%)
	30-59 msec	1 (6.7%)	1(10%)	1 (7.1%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In Adderall XR 20mg group, one subject whose overall ECG was normal at screening turned to abnormal (clinically significant atrial bigeminy) at the end of Part A study. However, a repeat ECG was normal and his cardiologist didn't restrict him from his previous stimulant-based medication after completion of the study. Otherwise, the sponsor reports there is no marked outliers in Adderall XR groups from ECG analysis.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were conducted. Tanner staging was not performed for the studies in this submission.

7.1.10 Immunogenicity

Not available.

7.1.11 Human Carcinogenicity

No human carcinogenicity data was provided in this application .

7.1.12 Special Safety Studies

No special safety studies were done for this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor reports that no adverse drug withdrawal effect observed in any subject who discontinued treatment in the studies included in this submission.

Amphetamine is know to have abuse potential. However, no updated information on this or relevant issues is available in this submission.

7.1.14 Human Reproduction and Pregnancy Data

Human reproduction and pregnancy data are not available in this submission.

7.1.15 Assessment of Effect on Growth

Like other psychostimulants, Adderall XR has effects on reducing weight and suppresses growth. The sponsor analyzed mean changes of weight from baseline to endpoint and utilized z-score according to the CDC Growth Chart of weight, height, and BMI for age. Based on the z-score the sponsor created the following three subgroups: Subgroup 1 is defined as at greater than 75 percentile, Subgroup 2 is defined as at 25-75 percentiles, and Subgroup 3 is defined as at less than 25 percentile.

The following table provides the mean changes of weight from baseline to endpoint in Part A of Study SLI381-314. No change in height or BMI reported by the sponsor for this part of the study.

Table 24. Mean Changes of Weight from Baseline to Endpoint in Primary Cohort of Part A of Study SLI381-314 (LOCF)

Weight (lbs)	Adderall XR				Placebo	p-Value
	10mg	20mg	30mg	40mg		
	N=54	N=54	N=58	N=61	N=52	
Baseline (SD)	125.9(22.2)	125.3(20.4)	128.6(18.8)	125.3(22.3)	131.5(18.1)	
Endpoint (SD)	124.6(23.3)	121.6(20.4)	124.5(17.5)	121.3(22.8)	133.1(18.9)	
Mean Change	-1.1	-2.8	-4.0	-4.1	1.5	
p-Value	0.0001	<0.0001	<0.0001	<0.0001		<0.0001

Table 25. Mean Changes of Weight from Baseline to Endpoint in Secondary Cohort of Part A of Study SLI381-314 (LOCF)

Weight (lbs)	Adderall XR		Placebo	p-Value
	50mg	60mg		
	N=15	N=10	N=15	
Baseline (SD)	189.6 (35.2)	191.1 (15.0)	190.5 (35.2)	<0.0001
Endpoint (SD)	182.5 (21.2)	181.6 (14.5)	191.0 (34.5)	
Mean Change	-7.1	-9.5	0.5	
p-Value	0.0001	<0.0001		

Z-scores of weight, height, and body mass index (BMI) from the six-month open-label study, Part B of Study SLI381-314 show significant decrease of weight and BMI in all three subgroups as defined above. Significant change in BMI is probably secondary to the change of weight because z-score of height was not significantly changed among subgroups 2 and 3. There was some significant decrease of z-score of height in subgroup 1. Thus, those whose height at 75

percentile or greater are more affected by the drug than those whose height was even smaller. The following table presents mean changes of weight, height, and BMI in z-scores from baseline to endpoint of Part B of Study SLI381-314.

Table 26. Mean Changes of Z-scores of Weight, Height, and BMI from Baseline to Endpoint of Part B of Study SLI381-314

	Subgroup 1	Subgroup 2	Subgroup 3	Total
Weight z-score				
N	59	62	17	138
Baseline mean (SD)	1.3 (0.5)	0.1 (0.4)	-1.1 (0.5)	0.5 (0.9)
Endpoint mean (SD)	0.8 (0.6)	-0.2 (0.4)	-1.3 (0.5)	0.1 (0.9)
Change mean (SD)	-0.4 (0.3)	-0.3 (0.3)	-0.2 (0.3)	-0.4 (0.3)
p-value[a]	<0.0001	<0.0001	0.0099	<0.0001
Height z-score				
N	26	71	41	138
Baseline mean (SD)	1.3 (0.4)	-0.1 (0.4)	-1.3 (0.6)	-0.2 (1.0)
Endpoint mean (SD)	1.2 (0.5)	-0.1 (0.5)	-1.1 (0.6)	-0.2 (0.9)
Change mean (SD)	-0.1 (0.3)	0.0 (0.2)	0.1 (0.8)	0.0 (0.5)
p-value[a]	0.0268	0.2840	0.2404	0.8801
BMI z-score				
N	70	53	15	138
Baseline mean (SD)	1.3 (0.4)	0.0 (0.4)	-1.1 (0.3)	0.6 (0.9)
Endpoint mean (SD)	0.7 (0.6)	-0.2 (0.4)	-1.4 (0.6)	0.1 (0.9)
Change mean (SD)	-0.6 (0.4)	-0.3 (0.4)	-0.3 (0.4)	-0.4 (0.4)
p-value[a]	<0.0001	<0.0001	0.0081	<0.0001

[a] P-value is based on a one-sample t-test of change from baseline=0.

Though Tanner Staging was mentioned in the FDA WR, it was not required for this submission and the sponsor plans to measure it in the 24-month open-label trial (SLI381-315).

7.1.16 Overdose Experience

The sponsor reports no non-clinical studies relevant to overdose have been performed and no overdose in any of the clinical studies in this submission. As of July 26, 2004, there were seven spontaneous case reports of overdose (see Table 9 in Appendix). Symptoms of acute overdose include various gastrointestinal symptoms such as nausea, vomiting, abdominal cramps, and diarrhea, arrhythmia, dysregulation of blood pressure, circulation collapse, restlessness, tremor, hyperreflexia, hyperpyrexia, rapid respiration, panic states, confusion, hallucinations, agitation, assultiveness, convulsion, and rhabdomyolysis. If severe enough, coma and death can occur.

There is no specific antidote for amphetamine. Treatment for overdose is symptomatic and supportive, including gastric lavage, charcoal and cathartic administration, and sedation. Acidification of urine increases amphetamine excretion but is believed to increase risk of acute renal failure if myoglobinuria is present. Caution should be given to a gradual drop in blood pressure when sufficient sedation is achieved.

7.1.17 Postmarketing Experience

The sponsor reports that Canada (for children 6-12 year-old) is the only country marketed with Adderall XR outside the U.S. (which is for both adults and children 6-12 year-old). since January 21, 2004. The surveillance report extends to September 17 , 2004. From the list of foreign postmarketing experience reports provided, no death is seen. The sponsor didn't provide dosages of these cases or any more detailed information other than patients' age, reported events, and the preferred terms of these events. The consequences of these cases are unknown, including if anyone was hospitalized.

The sponsor didn't present domestic postmarketing experience in this submission. Last review of domestic postmarketing experience was conducted by both FDA ODS and our division safety team in August 2004 for questionable signal for drug related sudden death, stroke, or serious cardiovascular adverse events. The conclusion for that review was no evidence for such signal for these events that is above the background rates for these events. This review was in response to Dr. Glenn Mannheim's concern in his review dated September, 2003.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The pivotal study design and patient enumeration are adequate per FDA WR.

7.2.1.2 Demographics

Demographic distribution of the pivotal study is also adequate according to FDA WR.

Extent of exposure (dose/duration)

Per our request, the sponsor provided the following table illustrating the extent of exposure (maximum dose taken for the longest period that was not interrupted for more than two days) to Adderall XR in both Part A and Part B of Study SLI381-314:

Table 27. Enumeration of Subjects by Maximum Dose of Adderall XR and Duration of Exposure to that Dose in Study SLI381-314 (Parts A & B combined)

Number of Subjects / Days of Exposure	Placebo	Maximum Adderall XR Daily Dose					
		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg
0	1	2	0	0	0	0	0
1 - 7	2	7	9	5	35	8	4
8 - 14	2	5	3	25	14	5	4
15 - 21	1	1	16	15	1	0	1
22 - 28	16	15	12	1	0	1	0
29 - 35	14	10	1	7	2	1	0
36 - 65	2	0	1	3	2	0	2
66 - 95	0	0	1	5	7	1	0
96 - 125	0	0	3	3	5	2	2
126 - 155	0	0	1	5	5	2	2
156 - 185	0	0	11	9	4	2	1
Total	38	40	58	78	75	22	16

In my opinion, the range of dosage studied is sufficient. However, only a small number of adolescent patients have received Adderall XR for an extended duration in these studies. No patients received their maximum dose for longer than 185 days. Only 40 patients received a maximum dose of 40mg or greater for at least 29 days. For the recommended dose of 20 mg/day, 90 patients received a maximum dose of 20 mg/day or higher for at least 29 days. For the purpose of safety evaluation, the sponsor still needs to complete the long term study for safety which requires study treatment of 24 consecutive months.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The only study currently ongoing to evaluate safety at this point is SLI381-315 that will be done for 24 consecutive months. The sponsor provides 4-month Safety Update which is reviewed in Section 7.2.9.

7.2.2.2 Postmarketing experience

As mentioned about in Section 7.1.17, the sponsor provides cases for foreign postmarketing experience from Canada with the cut-off date of Sept. 2004 but didn't present domestic postmarketing experience in this submission. The cases reviewed by Dr. Mannheim were submitted by the sponsor in July, 2003, and those submitted to our division safety team for review had the cut-off date of December 31, 2003.

Thus, foreign postmarketing surveillance needs to be more detailed with case narratives.

7.2.2.3 Literature

The sponsor provided the listing of literature search, but only submitted the following information in the response to our filing letter. In this subsequent submission, the sponsor reports that a member of the US Shire Medical Information Team conducted literature review. The search used Medline and Embase databases and only queried literature of North America. The sponsor explains this is because Adderall XR is only marketed in the U.S. and Canada. The search terms include "Adderall, Adderall XR, mixed amphetamine salts, mixed salts of a single-entity amphetamine sulphate, amphetamine aspartate, dextroamphetamine, amphetamine aspartate." The sponsor states that publications regarding the illicit use of amphetamines were excluded. However, the sponsor still hasn't provided the warrant conclusion from literature search. (See Vol. 8, Page 96-101.)

7.2.3 Adequacy of Overall Clinical Experience

The sponsor fulfilled the requested studies in this population as per FDA WR with the exception of the requirement for 24 month safety data, which will be generated by their ongoing study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This section is not applicable for this NDA supplement.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor has conducted appropriate clinical laboratory testing except for no serum Creatinine and analysis of urinalysis data is incomplete. Thus, we can't know the function of the kidneys from the trial data. Though up to date, renal function has not been a major concern with the use of Adderall XR in other population, and the metabolism of Adderall XR mostly goes through liver, I'd recommend that serum creatinine be added in the future trials (esp. long term ones) for thorough assessment of renal function.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See above Section regarding renal function and serum creatinine. The sponsor needs to submit tables for outliers of laboratory tests and more detailed analysis of urinalysis data if collected.

For detailed information on metabolism and clearance workup, please refer to the review by FDA biopharmaceuticals reviewer, Kofi Kumi, PhD.

According to FDA WR, drug-drug interaction study result was not requested for this submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable as this is not a new drug.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the study design meets the requirement of the FDA WR except for the pending 24-month safety information. However, the following items in the submission are still not properly completed or analyzed:

1) In the literature search, the sponsor doesn't have conclusion and warrant for their literature review nor the timeframe for the literature search. The searched literature is just listed.

2) Demographic analysis of common adverse events is not properly conducted (See Section 7.1.5.6).

3) The sponsor doesn't provide explanation on why serum creatinine was not done and only very limited analysis of the urinalysis data is submitted (see Review of Urinalysis).

4) The sponsor only provides the subject listing of outliers of laboratory tests but not summarized table providing the proportion of patients with outlying values by treatment group.

5) The sponsor didn't mention domestic postmarketing exposure in this submission though I was able to find out from our previous analysis with data cut-off date of December 31, 2003.

6) The sponsor submitted a total of 19 Case Report Forms. One of them is very hard to read the copies of laboratory test results clearly.

7) The sponsor has not submitted case report forms and narratives for subjects who dropped out of the ongoing study in the Safety Update (see next section).

7.2.9 Additional Submissions, Including Safety Update

The Four-Month Safety Update includes the same safety date that were submitted for this sNDA and the interim safety data from an ongoing study, Study SLI-381-315, "a phase III, multi-center, 24-month, safety, tolerability, and efficacy study of Adderall XR in adolescents with ADHD." The following review is focused on death, SAEs, and AEs lead to dropout.

The sponsor reports that no death in this new study up to the cut-off date, September 23, 2004. There have been two subjects in the ongoing study reported nonfatal serious adverse events.

1) Subject # 27-002, a 14 year-old female who rolled over from Part A of SLI-381-314, developed major depressive disorder (COSTART term: depression) during the second month of treatment while on 40mg of Adderall XR. The subject discontinued from the study due to this event, but the sponsor reports it was resolved without sequelae and considers this as unrelated to the drug. I don't think the drug-relatedness can be ruled out here.

2) Subject # 56-003, a 13 year-old female who rolled over from Part B of SLI-381-314, developed suicidal ideation (COSTART term: depression) and was hospitalized two months after

entering the new study while on 30mg of Adderall XR. As the above subject, despite this discontinued from the study due to this event, the sponsor reports it was resolved without sequelae and considers this as unrelated to the drug. Again, I don't think the drug-relatedness can be ruled out here.

Up to 11 subjects have dropped out from Study SLI381-315 by the time of Safety Update submission. Together with Part A and Part B of Study SLI381-314, it totals 25 subjects and all of them were from Adderall XR group (only Part A is placebo-controlled double-blind study). In SLI381-315, the most common reason for discontinuation are depression (3, one of them with suicidal ideation and hospitalized—see above narratives) and weight loss (3). (Patients with depression were on 30-40mg and those with weight loss were on 20-30mg.) Somnolence, twitching, irritability, fever with nausea, and abnormal ECG each happened in one subject.

The sponsor provides narratives for SAEs in the Safety Update but hasn't provided narratives or case report forms for dropout cases.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As mentioned above, the demographic analysis of common adverse events is not properly done; Neither serum creatinine nor full urinalysis is provided making it difficult to assess renal function from the trial data; even among those who had proteinuria (all of them were in Adderall XR group), no more detailed related information provided; Finally, only subject listing of outliers of laboratory tests is submitted, instead of summarized table of enumeration of outliers by treatment group. In the Safety Update, the sponsor provides narratives for SAEs but hasn't provided narratives or case report forms for dropout cases.

In my opinion, the sponsor must correct these deficiencies before this NDA can be approved.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Most of the review data for safety is from the pivotal study conducted according to FDA WR. However, serious adverse events and deaths as well as drop-outs during adverse events were reviewed from the PK study, pivotal study (Part A of SLI381-314), as well as the six-month open-label part of the study (Part B) and the 4-Month Safety Update.

7.4.1.2 Combining data

See above Section 7.4.1.1. Data for safety review were not combined for common adverse events and labs, vital signs, and ECG data analysis.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Changes of vital signs, laboratory findings, and ECG as well as adverse events in different dose groups are summarized in Section 7.1.

7.4.2.2 Explorations for time dependency for adverse findings

The sponsor provides information on changes of vital signs, laboratory findings, and ECG. Summaries of these changes from baseline to endpoint are in Section 7.1.7.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor provides information on drug-demographic interaction for those AEs that were reported at >5% and with greater incidence than placebo in both Part A and Part B of Study SLI381-314. Essentially comparison is made based on percentages between the placebo group and the whole Adderall XR group regardless doses. The sponsor didn't separate the dose groups for these demographic analyses and didn't analyze the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

7.4.2.4 Explorations for drug-disease interactions

There is no explorations for drug-disease interactions. ADHD is the only indicated disease for treatment studied. No study regarding subjects with any organ disease or failure is presented.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interaction studies were done for this submission. The sponsor has no additional new information for drug-drug interaction in the proposed labeling.

7.4.3 Causality Determination

In this review, adverse events of 5% or more and twice of the incidence of placebo group are considered drug-related.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

It can be concluded that dosing regimen for adolescents can be started from 10mg/day, then increase to 20mg/day as needed. From the trial data, dosing beyond 20mg does not show additional clinical benefit but increased risks of adverse events.

8.2 Drug-Drug Interactions

See Section 7.4.2.5.

8.3 Special Populations

The sponsor didn't have study report on patients with renal or liver or other organ system disease or failure.

8.4 Pediatrics

This submission is specifically for adolescents with ADHD.

8.5 Advisory Committee Meeting

No advisory committee meeting was planned or conducted regarding this submission.

8.6 Literature Review

The sponsor provides the list of references but no warrant or conclusions.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

8.8 Other Relevant Materials

See review of the Four-Month Safety Update in Section 7.2.9.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor conducted the PK and pivotal study according to FDA WR and the studies fulfilled the WR.

9.2 Recommendation on Regulatory Action

I recommend the agency to take approvable action on the use of 20mg of Adderall XR for treatment of ADHD in adolescents age 13-17 years old. The sponsor needs to submit the information which satisfactorily address the above deficiencies for review before the approval action can be granted. These include the items mentioned in Section 7.2.8: Assessment of Quality and Completeness of Data.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended at this point.

9.3.2 Required Phase 4 Commitments

Continue the ongoing study to demonstrate long term study for safety and tolerability: Study SLI381-315.

9.3.3 Other Phase 4 Requests

As mentioned in previous sections, I would like to recommend monitoring serum creatinine in the future studies because this gives the thorough assessment for renal function.

9.4 Labeling Review

The labeling review here is focused on clinical issues (see Appendix for details). The sponsor needs to do the following:

1) The sponsor must revise the sentences (b) (4) at the bottom of the page 2-6 in Vol 4.2 (b) (4)

2) The sponsor must remove the sentence on the next page, from lines 3-4, that states, (b) (4)

3) The sponsor should revise Table 2 on page 2-12 (Vol 4.2) (b) (4)

9.5 Comments to Applicant

Thanks for your submission. For future references, I recommend including thorough analysis of outlier data, instead of just listings of data for submissions.

10 APPENDICES

10.1 Tables referenced in the review text.

Table 1. Principal Investigators and the Numbers of Subjects Recruited for SLI381-314

Principal Investigators	Location	N in Part A	N in Part B
Scott T. Aaronson, MD	Baltimore, MD 20214	-	-
Howard Abikoff, PhD	New York, NY 10016	2	-
Valerie Arnold, MD	Memphis, TN 38119	15	9
Louise M. Beckett, MD	Oklahoma City, OK 73103	15	10
John C. Burnside, MD	San Antonio, TX 78247	9	1
Regina Bussing, MD	Gainesville, FL 32610	5	-
John Cecil, MD	Paducah, KY 42001	9	4
Mark Chandler, MD	Chapel Hill, NC 27514	11	6
Edward Cherlin, MD	El Centro, CA 92243	10	5
Daniel Coury, MD	Columbus, OH 43205	7	4
Jeanette Cueva, MD	New York, NY 10011	-	-
Andrew J. Cutler, MD	Winter Park, FL 32789	5	-
Robert Dahmes, MD	New Orleans, LA 70114	10	4
Anthony P. Dietrich, MD	Woodstock, VT 05091	6	1
Bradley Diner, MD	Little Rock, AR 72223	5	2
Catherine Ducommun-Nagy, MD	Jenkintown, PA 19046	2	-
David Duesenberg, MD	Chesterfield, MO 63017	11	6
John Gilliam, MD	Richmond, VA 23294	6	1
Lawrence Ginsberg, MD	Houston, TX 77090	4	3
Michael Greenbaum, MD	Libertyville, IL 60048	8	-
James T. Grimm, MD	Eugene, OR 97401	9	-
Howard Hassman, MD	Clementon, NJ 08021	9	5
James Hedrick, MD	Bardstown, KY 40004	12	7
Alexander Horwitz, MD	Salem, OR 97301	6	1
Rakesh Jain, MD	Lake Jackson, TX 77566	2	2
James Knutson, MD	Kirkland, WA 98033	8	1
Elly Lee, MD	Irvine, CA 92618	4	1
James E. Lee, MD	Charlotte, NC 28226	3	2
Robert Lehman, MD	Baltimore, MD 21208	-	-
Alan Levine, MD	Boulder, CO 80304	5	1
David E. Linden, MD	Oklahoma City, OK 733118	6	5
Robert S. Lipetz, DO	Spring Valley, CA 91978	1	-
Frank Lopez, MD	Maitland, FL 32751	16	12
Veena Luthra, MD	Bala Cynwyd, PA 19004	3	-

Table 1. Principal Investigators and the Numbers of Subjects Recruited for SLI381-314 (Continued)

Jeffrey Mattes, MD	Princeton, NJ 08540	3	-
Craig M. McCarthy, MD	Mesa, AZ 85210	4	-
Janice L. Miller, MD	West Palm Beach, FL 33407	10	6
Mario Molina, MD	Hialeah, FL 33016	7	3
Eliot Moon, MD	Temecula, CA 92591	7	-
Kamalesh Pai, MD	Jacksonville, FL 32216	6	3
Anil S. Patel, MD	San Marcos, CA 92078	-	-
Robert A. Riesenberg, MD	Atlanta, GA 30308	4	-
Leon I. Rosenberg, MD	Moorestown, NJ 08057	4	-
Keith E. Saylor, PhD	Bethesda, MD 20814	8	6
Ward T. Smith, MD	Portland, OR 97201	4	-
Craig A. Spiegel, MD	Bridgeton, MO 63044	3	-
William Terry, MD	Boise, ID 83704	8	-
Kathleen Toups, MD	Lafayette, CA 94549	5	3
Bradley Vince, DO	Overland Park, KS 66211	18	13
Richard H. Weisler, MD	Raleigh, NC 27609	2	-
Scott West, MD	Orlando, FL 32806	6	6
Mark Wolraich, MD	Oklahoma City, OK 73117	1	2
Daniel Wynn, MD	Northbrook, IL 60062	1	-
Kashinath G. Yadalam, MD	Lake Charles, LA 70601	4	2

Table 2. Clinician Version of ADHD-Rating Scale-IV (ADHD-RS-IV) Used in the Trials.

Check the box that **BEST DESCRIBES** this subject's behavior in the last week.

	Never or rarely	Sometimes	Often	Very Often
1. Fails to give close attention to details or makes careless mistakes in work	0❑	1❑	2❑	3❑
2. Fidgets with hands or feet or squirms in seat	0❑	1❑	2❑	3❑
3. Has difficulty sustaining attention in tasks or play activities	0❑	1❑	2❑	3❑
4. Leaves seat in classroom or in other situations in which seating is expected	0❑	1❑	2❑	3❑
5. Does not seem to listen when spoken to directly	0❑	1❑	2❑	3❑
6. Runs about or climbs excessively in situations in which it is inappropriate	0❑	1❑	2❑	3❑
7. Does not follow through on instructions and fails to finish work	0❑	1❑	2❑	3❑
8. Has difficulty playing or engaging in leisure activities quietly	0❑	1❑	2❑	3❑
9. Has difficulty organizing tasks and activities	0❑	1❑	2❑	3❑
10. Is "on the go" or acts as if "driven by a motor"	0❑	1❑	2❑	3❑
11. Avoids tasks (e.g., schoolwork, homework) that require sustained mental effort	0❑	1❑	2❑	3❑
12. Talks excessively	0❑	1❑	2❑	3❑
13. Loses things necessary for tasks or activities	0❑	1❑	2❑	3❑
14. Blurts out answers before questions have been completed	0❑	1❑	2❑	3❑
15. Is easily distracted	0❑	1❑	2❑	3❑
16. Has difficulty awaiting turn	0❑	1❑	2❑	3❑
17. Is forgetful in daily activities	0❑	1❑	2❑	3❑
18. Interrupts or intrudes on others	0❑	1❑	2❑	3❑

Table 3. Common Adverse Events Reported by ≥ 2% in Any Adderall XR Dose Groups in Primary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	Adderall XR				Placebo
	10mg N=56	**20mg** N=56	**30mg** N=58	**40mg** N=63	N=54
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total AEs	35 (62.5)	43 (76.8)	45 (77.6)	49 (77.8)	32 (59.3)
Body as a whole					
Abdominal Pain	5 (8.9)	3 (5.4)	6 (10.3)	11 (17.5)	1 (1.9)
Accidental Injury	1 (1.8)	4 (7.1)	1 (1.7)	5 (7.9)	3 (5.6)
Asthenia	2 (3.6)	1 (1.8)	2 (3.4)	1 (1.6)	0
Flu Syndrome[2]	2 (3.6)	0	1 (1.7)	1 (1.6)	1 (1.9)
Headache[4]	8 (14.3)	7 (12.5)	14 (24.1)	9 (14.3)	12 (22.2)
Infection (unspecified)[4]	0	0	2 (3.4)	1 (1.6)	1 (1.9)
Infection (Viral)[1]	0	4 (7.1)	1 (1.7)	2 (3.2)	6 (11.1)
Pain[3]	0	4 (7.1)	0	0	2 (3.7)
Cardiovascular System					
Tachycardia	0	2 (3.6)	0	1 (1.6)	0
Gastroenterology System					
Anorexia	13 (23.2)	19 (33.9)	26 (44.8)	25 (39.7)	1 (1.9)
Diarrhea	0	1 (1.8)	3 (5.2)	0	0
Dry Mouth	1 (1.8)	3 (5.4)	3 (5.2)	3 (4.8)	0
Dyspepesia	2 (3.6)	2 (3.6)	1 (1.7)	2 (3.2)	0
Nausea	3 (5.4)	1 (1.8)	2 (3.4)	1 (1.6)	0
Vomiting	1 (1.8)	3 (5.4)	3 (5.2)	1 (1.6)	0
Metabolic & Nutritious Status					
Weight Loss	1 (1.8)	5 (8.9)	8 (13.8)	8 (12.7)	0
Central Nervous System					
Depression	0	2 (3.6)	1 (1.7)	0	0
Dizziness[1]	3 (5.4)	2 (3.6)	4 (6.9)	4 (6.3)	4 (7.4)
Emotional Lability	2 (3.6)	1 (1.8)	4 (6.9)	0	0
Insomnia	5 (8.9)	8 (14.3)	4 (6.9)	11 (17.5)	2 (3.7)
Nervousness[3]	3 (5.4)	6 (10.7)	2 (3.4)	3 (4.8)	3 (5.6)
Somnolence	2 (3.6)	1 (1.8)	2 (3.4)	6 (9.5)	2 (3.7)
Respiratory System					
Cough Increased	0	2 (3.6)	0	2 (3.2)	1 (1.9)
Pharyngitis[3]	4 (7.1)	9 (16.1)	4 (6.9)	3 (4.8)	5 (9.3)
Rhinitis[3]	2 (3.6)	4 (7.1)	1 (1.7)	2 (3.2)	3 (5.6)
Skin Diseases					
Acne[4]	0	0	2 (3.4)	0	0
Herpes Simplex	2 (3.6)	0	0	1 (1.6)	0
Urogenital					
Albuminuria	0	1 (1.8)	0	3 (4.8)	0

[1]These adverse events are higher in the placebo group: Dizziness, viral infection.
[2]These adverse events are higher than placebo group only in the 10mg group: Flu syndrome,
[3]These adverse events are higher than placebo group only in the 20mg group: Rhinitis, Pharyngitis, nervousness.
[4] These adverse events are higher than placebo group only in the 30mg group: Headache, unspecified infection, acne.

Table 4. Common Adverse Events that ≥ 2% in Any Adderall XR Dose Groups in Primary Cohort of Part B of Study SLI381.314

Adverse Events (Preferred Terms)	Adderall XR		Placebo
	50mg N=15	**60mg** N=10	N=15
	N (%)	**N (%)**	**N (%)**
Total AEs	12 (80.0)	7 (70.0)	10 (66.7)
Body as a whole			
Abdominal Pain	2 (13.3)	2 (20.0)	1 (6.7)
Accidental Injury	1 (6.7)	0	0
Asthenia	1 (6.7)	0	1 (6.7)
Headache	5 (33.3)	3 (30.0)	3 (20.0)
Pain	1 (6.7)	0	0
Infection (Viral)	1 (6.7)	2 (20.0)	0
Cardiovascular System			
Syncope	1 (6.7)	0	0
Tachycardia	1 (6.7)	0	0
Gasterenterology System			
Anorexia	6 (40.0)	5 (50.0)	2 (13.3)
Dry Mouth	2 (13.3)	0	0
Dyspepsia	1 (6.7)	0	0
Gastroenteritis	1 (6.7)	0	0
Increased Appetite	1 (6.7)	0	1 (6.7)
Nausea	0	1 (10.0)	0
Stomach Ulcer	0	1 (10.0)	0
Tooth Disorder	1 (6.7)	0	0
Metabolic & Nutritious Disease			
Weight Loss	3 (20.0)	1 (10.0)	0
Muscularskeletal System			
Tendon Disorder	1 (6.7)	0	0
Central Nervous System			
Anxiety	0	2 (20.0)	0
Dizziness	4 (26.7)	2 (20.0)	0
Insomnia	4 (26.7)	4 (40.0)	0
Nervousness	3 (20.0)	3 (30.0)	0
Paresthesia	1 (6.7)	0	0
Somnolence	1 (6.7)	1 (10.0)	1 (6.7)
Tremor	1 (6.7)	0	0
Vertigo	0	1 (10.0)	0
Respiratory System			
Cough Increased	0	1 (10.0)	0
Lung Disorder	1 (6.7)	0	0
Pharyngitis	0	1 (10.0)	1 (6.7)

Rhinitis	1 (6.7)	1 (10.0)	3 (20.0)
Skin Disease			
Rash	0	1 (10.0)	1 (6.7)
Urogenital			
Albuminuria	0	1 (10.0)	0
Dysmenorrhea	0	1 (10.0)	0

Table 5. Common Drug-Related Adverse Events in Primary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	**Adderall XR**				**Placebo**
	10mg	**20mg**	**30mg**	**40mg**	
	N=56	N=56	N=58	N=63	N=54
Gasterenterology System					
Abdominal Pain	5 (8.9%)	3 (5.4%)	6 (10.3%)	11 (17.5%)	1 (1.9%)
Anorexia	13 (23.2%)	19 (33.9%)	26 (44.8%)	25 (39.7%)	1 (1.9%)
Diarrhea	0	1 (1.8%)	3 (5.2%)	0	0
Dry Mouth	1 (1.8%)	3 (5.4%)	3 (5.2%)	3 (4.8%)	0
Nausea	3 (5.4%)	1 (1.8%)	2 (3.4%)	1 (1.6%)	0
Vomiting	1 (1.8%)	3 (5.4%)	3 (5.2%)	1 (1.6%)	0
Central Nervous System					
Emotional Lability	2 (3.6%)	1 (1.8%)	4 (6.9%)	0	0
Insomnia	5 (8.9%)	8 (14.3%)	4 (6.9%)	11 (17.5%)	2 (3.7%)
Somnolence	2 (3.6%)	1 (1.8%)	2 (3.4%)	6 (9.5%)	2 (3.7%)
Metabolic and Nutritious Disease					
Weight Loss	1 (1.8%)	5 (8.9%)	8 (13.8%)	8 (12.7%)	0 (0%)

Table 6. Common Drug-Related Adverse Events in Secondary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	**Adderall XR**		**Placebo**
	50mg	**60mg**	
	N=15	N=10	N=15
Body as a whole			
Accidental Injury	1 (6.7%)	0	0
Pain	1 (6.7%)	0	0
Infection (Viral)	1 (6.7%)	2 (20.0%)	0
Cardiovascular System			
Syncope	1 (6.7%)	0	0
Tachycardia	1 (6.7%)	0	0
Gasteroenterology System			
Abdominal Pain	2 (13.3%)	2 (20.0%)	1 (6.7%)
Dry Mouth	2 (13.3%)	0	0
Dyspepsia	1 (6.7%)	0	0
Gastroenteritis	1 (6.7%)	0	0
Nausea	0	1 (10.0%)	0
Stomach Ulcer	0	1 (10.0%)	0
Tooth Disorder	1 (6.7%)	0	0
Muscularskeleton System			
Tendon Disorder	1 (6.7%)	0	0
Central Nervous System			
Anxiety	0	2 (20.0%)	0
Dizziness	4 (26.7%)	2 (20.0%)	0
Insomnia	4 (26.7%)	4 (40.0%)	0
Nervousness	3 (20.0%)	3 (30.0%)	0
Paresthesia	1 (6.7%)	0	0
Tremor	1 (6.7%)	0	0
Vertigo	0	1 (10.0%)	0
Respiratory System			
Cough Increased	0	1 (10.0%)	0
Lung Disorder	1 (6.7%)	0	0
Urogenital			
Albuminuria	0	1 (10.0%)	0
Dysmenorrhea	0	1 (10.0%)	0

Table 7. Summary of Treatment-Emergent Adverse Events by Body System and Preferred Term in Primary Cohort (All Randomized Subjects) of Study SLI381-314 are in the next 4 pages:

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
Total	32 (59.3%)	63	35 (62.5%)	77	43 (76.8%)	124	45 (77.6%)	128	49 (77.8%)	130	204 (71.1%)	522
BODY AS A WHOLE	20 (37.0%)	30	18 (32.1%)	25	22 (39.3%)	37	21 (36.2%)	32	25 (39.7%)	37	106 (36.9%)	161
ABDOMINAL PAIN	1 (1.9%)	1	5 (8.9%)	5	3 (5.4%)	7	6 (10.3%)	6	11 (17.5%)	13	26 (9.1%)	32
ACCIDENTAL INJURY	3 (5.6%)	3	1 (1.8%)	1	4 (7.1%)	6	1 (1.7%)	1	5 (7.9%)	5	14 (4.9%)	16
ALLERGIC REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ASTHENIA	0 (0.0%)	0	2 (3.6%)	2	1 (1.8%)	1	2 (3.4%)	2	1 (1.6%)	1	6 (2.1%)	6
BACK PAIN	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
CHEST PAIN	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
CHILLS	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
FEVER	1 (1.9%)	1	1 (1.8%)	1	2 (3.6%)	2	0 (0.0%)	0	0 (0.0%)	0	4 (1.4%)	4
FLU SYNDROME	1 (1.9%)	1	2 (3.6%)	2	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	5 (1.7%)	5
HEADACHE	12 (22.2%)	15	8 (14.3%)	11	7 (12.5%)	9	14 (24.1%)	19	9 (14.3%)	12	50 (17.4%)	66
INFECTION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (3.4%)	2	1 (1.6%)	1	4 (1.4%)	4
INFECTION FUNGAL	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
NECK RIGIDITY	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PAIN	2 (3.7%)	2	0 (0.0%)	0	4 (7.1%)	4	0 (0.0%)	0	1 (1.6%)	1	7 (2.4%)	7
PHOTOSENSITIVITY REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
VIRAL INFECTION	6 (11.1%)	6	0 (0.0%)	0	4 (7.1%)	4	1 (1.7%)	1	2 (3.2%)	2	13 (4.5%)	13
CARDIOVASCULAR SYSTEM	2 (3.7%)	2	0 (0.0%)	0	4 (7.1%)	4	3 (5.2%)	4	1 (1.6%)	1	10 (3.5%)	11
ELECTROCARDIOGRAM ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
MIGRAINE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	2	0 (0.0%)	0	1 (0.3%)	2
PALPITATION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
POSTURAL HYPOTENSION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
TACHYCARDIA	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	1 (1.6%)	1	3 (1.0%)	3
VASODILATATION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
DIGESTIVE SYSTEM	2 (3.7%)	2	18 (32.1%)	22	25 (44.6%)	30	32 (55.2%)	39	32 (50.8%)	38	109 (38.0%)	131
ANOREXIA	1 (1.9%)	1	13 (23.2%)	13	19 (33.9%)	19	26 (44.8%)	26	25 (39.7%)	28	84 (29.3%)	87
APHTHOUS STOMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
DIARRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	3 (5.2%)	3	0 (0.0%)	0	4 (1.4%)	4
DRY MOUTH	0 (0.0%)	0	1 (1.8%)	1	3 (5.4%)	3	3 (5.2%)	3	3 (4.8%)	3	10 (3.5%)	10

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
DYSPEPSIA	0 (0.0%)	0	2 (3.6%)	2	2 (3.6%)	3	1 (1.7%)	1	2 (3.2%)	2	7 (2.4%)	8
GASTRITIS	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
INCREASED APPETITE	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
MELENA	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
NAUSEA	0 (0.0%)	0	3 (5.4%)	3	1 (1.8%)	1	2 (3.4%)	2	1 (1.6%)	1	7 (2.4%)	7
STOMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
VOMITING	0 (0.0%)	0	1 (1.8%)	1	3 (5.4%)	3	3 (5.2%)	3	1 (1.6%)	1	8 (2.8%)	8
ENDOCRINE SYSTEM	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPOTHYROIDISM	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HEMIC AND LYMPHATIC SYSTEM	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	3 (5.2%)	3	1 (1.6%)	1	5 (1.7%)	5
ANEMIA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ECCHYMOSIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
ERYTHROCYTES ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
LYMPHADENOPATHY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	2 (0.7%)	2
METABOLIC AND NUTRITIONAL DISORDERS	1 (1.9%)	1	2 (3.6%)	2	5 (8.9%)	5	9 (15.5%)	11	8 (12.7%)	8	25 (8.7%)	27
DEHYDRATION	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
SGOT INCREASED	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
SGPT INCREASED	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
WEIGHT GAIN	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
WEIGHT LOSS	0 (0.0%)	0	1 (1.8%)	1	5 (8.9%)	5	8 (13.8%)	8	8 (12.7%)	8	22 (7.7%)	22
MUSCULOSKELETAL SYSTEM	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
MYALGIA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
NERVOUS SYSTEM	9 (16.7%)	12	11 (19.6%)	17	16 (28.6%)	25	15 (25.9%)	26	21 (33.3%)	28	72 (25.1%)	108
AGITATION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ANXIETY	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
DEPRESSION	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
DIZZINESS	4 (7.4%)	5	3 (5.4%)	3	2 (3.6%)	2	4 (6.9%)	6	4 (6.3%)	5	17 (5.9%)	21

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, QUINTILES (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
EMOTIONAL LABILITY	0 (0.0%)	0	2 (3.6%)	2	1 (1.8%)	1	4 (6.9%)	4	0 (0.0%)	0	7 (2.4%)	7
HALLUCINATIONS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERKINESIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERTONIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
INSOMNIA	2 (3.7%)	2	5 (8.9%)	5	8 (14.3%)	8	4 (6.9%)	5	11 (17.5%)	12	30 (10.5%)	32
NERVOUSNESS	3 (5.6%)	3	3 (5.4%)	3	6 (10.7%)	7	2 (3.4%)	2	3 (4.8%)	4	17 (5.9%)	19
PARESTHESIA	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
SOMNOLENCE	2 (3.7%)	2	2 (3.6%)	2	1 (1.8%)	1	2 (3.4%)	3	6 (9.5%)	6	13 (4.5%)	14
TREMOR	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	2 (0.7%)	2
TWITCHING	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
RESPIRATORY SYSTEM	9 (16.7%)	11	7 (12.5%)	7	14 (25.0%)	17	6 (10.3%)	6	7 (11.1%)	9	43 (15.0%)	50
COUGH INCREASED	1 (1.9%)	1	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	2 (3.2%)	2	5 (1.7%)	5
DYSPNEA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
EPISTAXIS	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
HYPOVENTILATION	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
PHARYNGITIS	5 (9.3%)	5	4 (7.1%)	4	9 (16.1%)	9	4 (6.9%)	4	3 (4.8%)	3	25 (8.7%)	25
RHINITIS	3 (5.6%)	3	2 (3.6%)	2	4 (7.1%)	5	1 (1.7%)	1	2 (3.2%)	2	12 (4.2%)	13
SINUSITIS	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
SKIN AND APPENDAGES	2 (3.7%)	2	3 (5.4%)	3	1 (1.8%)	1	4 (6.9%)	5	3 (4.8%)	3	13 (4.5%)	14
ACNE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (3.4%)	3	0 (0.0%)	0	2 (0.7%)	3
CONTACT DERMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HERPES SIMPLEX	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	3 (1.0%)	3
HERPES ZOSTER	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PRURITUS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
RASH	1 (1.9%)	1	0 (0.0%)	0	1 (1.8%)	1	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
SKIN BENIGN NEOPLASM	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
SWEATING	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
SPECIAL SENSES	1 (1.9%)	1	1 (1.8%)	1	2 (3.6%)	2	0 (0.0%)	0	1 (1.6%)	1	5 (1.7%)	5
ABNORMAL VISION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
EAR PAIN	1 (1.9%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b)(4) (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
OTITIS EXTERNA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
TINNITUS	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
UROGENITAL	1 (1.9%)	1	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	4 (6.3%)	4	8 (2.8%)	8
ALBUMINURIA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	3 (4.8%)	3	4 (1.4%)	4
DYSMENORRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	1 (1.7%)	1	1 (1.6%)	1	3 (1.0%)	3
METRORRHAGIA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) (US) 16-MAR-2004 09:47

Table 8. Summary of Treatment-Emergent Adverse Events by Body System and Preferred Term in Secondary Cohort (All Randomized Subjects) of Study SLI381-314

Body System Preferred Term (Costart)	Placebo (N=15) #(%) Subj	Placebo (N=15) # AEs	Adderall XR 50 mg (N=15) #(%) Subj	Adderall XR 50 mg (N=15) # AEs	Adderall XR 60 mg (N=10) #(%) Subj	Adderall XR 60 mg (N=10) # AEs	Total (N=40) #(%) Subj	Total (N=40) # AEs
Total	10 (66.7%)	20	12 (80.0%)	45	7 (70.0%)	37	29 (72.5%)	102
BODY AS A WHOLE	5 (33.3%)	6	9 (60.0%)	11	5 (50.0%)	9	19 (47.5%)	26
ABDOMINAL PAIN	1 (6.7%)	1	2 (13.3%)	2	2 (20.0%)	3	5 (12.5%)	6
ACCIDENTAL INJURY	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
ASTHENIA	1 (6.7%)	1	1 (6.7%)	1	0 (0.0%)	0	2 (5.0%)	2
FLU SYNDROME	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
HEADACHE	3 (20.0%)	3	5 (33.3%)	5	3 (30.0%)	4	11 (27.5%)	12
PAIN	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
VIRAL INFECTION	0 (0.0%)	0	1 (6.7%)	1	2 (20.0%)	2	3 (7.5%)	3
CARDIOVASCULAR SYSTEM	0 (0.0%)	0	2 (13.3%)	2	0 (0.0%)	0	2 (5.0%)	2
SYNCOPE	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
TACHYCARDIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
DIGESTIVE SYSTEM	5 (33.3%)	5	8 (53.3%)	12	5 (50.0%)	7	18 (45.0%)	24
ANOREXIA	2 (13.3%)	2	6 (40.0%)	6	5 (50.0%)	5	13 (32.5%)	13
DIARRHEA	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
DRY MOUTH	0 (0.0%)	0	2 (13.3%)	2	0 (0.0%)	0	2 (5.0%)	2
DYSPEPSIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
GASTROENTERITIS	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
GASTROINTESTINAL DISORDER	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
INCREASED APPETITE	1 (6.7%)	1	1 (6.7%)	1	0 (0.0%)	0	2 (5.0%)	2
NAUSEA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
STOMACH ULCER	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
TOOTH DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
HEMIC AND LYMPHATIC SYSTEM	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
ECCHYMOSIS	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0%)	0	3 (20.0%)	3	1 (10.0%)	1	4 (10.0%)	4
WEIGHT LOSS	0 (0.0%)	0	3 (20.0%)	3	1 (10.0%)	1	4 (10.0%)	4

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=15) #(%) Subj	# AEs	Adderall XR 50 mg (N=15) #(%) Subj	# AEs	Adderall XR 60 mg (N=10) #(%) Subj	# AEs	Total (N=40) #(%) Subj	# AEs
MUSCULOSKELETAL SYSTEM	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
TENDON DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
NERVOUS SYSTEM	2 (13.3%)	2	7 (46.7%)	14	5 (50.0%)	14	14 (35.0%)	30
ANXIETY	0 (0.0%)	0	0 (0.0%)	0	2 (20.0%)	2	2 (5.0%)	2
DIZZINESS	0 (0.0%)	0	4 (26.7%)	4	2 (20.0%)	2	6 (15.0%)	6
EMOTIONAL LABILITY	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
INSOMNIA	0 (0.0%)	0	4 (26.7%)	4	4 (40.0%)	4	8 (20.0%)	8
NERVOUSNESS	0 (0.0%)	0	3 (20.0%)	3	3 (30.0%)	4	6 (15.0%)	7
PARESTHESIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
SOMNOLENCE	1 (6.7%)	1	1 (6.7%)	1	1 (10.0%)	1	3 (7.5%)	3
TREMOR	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
VERTIGO	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
RESPIRATORY SYSTEM	3 (20.0%)	5	2 (13.3%)	2	1 (10.0%)	3	6 (15.0%)	10
COUGH INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
LUNG DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
PHARYNGITIS	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
RHINITIS	3 (20.0%)	4	1 (6.7%)	1	1 (10.0%)	1	5 (12.5%)	6
SKIN AND APPENDAGES	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
RASH	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
UROGENITAL	0 (0.0%)	0	0 (0.0%)	0	2 (20.0%)	2	2 (5.0%)	2
ALBUMINURIA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
DYSMENORRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b)(4) (US) 16-MAR-2004 09:47

Table 9. Spontaneously Reported Cases of Overdose on Adderall XR as of July, 2004

Subjects	Demographics and Doses	Symptoms & Signs	Outcome
US-02-044-00	A 10 year-old boy with diagnosis of ADHD, bipolar disorder NOS on Remeron 30mg/day, Wellbutrin SR 200mg/day and *Adderall XR 40mg/day*.	Tremor and hallucinations, angry	Continued on Adderall XR 40mg/day according to the report.
US-02-123-00	A 16 year-old male overdosed *a half bottle of 20mg of Adderall XR*. He was also on creatine and other unspecified over-the-counter products.	Psychosis (hallucinations)	Hospitalized for couple of days
US-02-296-00	A 16 year-old female patient was despondent and impulsively overdosed on *28 tablets of 20mg Adderall XR*. She was also on unspecified antidepressant.	Subsequent increased fidgeting, impulsivity, and clenching of the jaw.	Hospitalized in psychiatric hospital for a week after gastric lavage and treatment. Antidepressant was increased in the hospital.
US-02-323-00	A 12 year-old female took an overdose of 4 capsules of Adderall XR 20mg.	The sponsor reports this patient had "no symptoms".	Multiple follow-ups failed.
SUS1-2003-00072	A 19 year-old male with ADHD and a history of alcohol and substance abuse. He was on venlafaxine together with Adderall immediate release 10mg Bid. Possibly, he overdosed on Adderall 10mg tablets(of unspecified numbers) and other medications.	Amphetamine in the urine. Otherwise, no detailed description.	Admitted to the hospital.
SUS1-2003-00346	A 5 year-old boy had an overdose from a medication error by a pharmacy that filed the 5mg Adderall XR prescription with 30mg capsules. Thus, he took *30mg Adderall XR.*	Non-stop talking, stuttering, not eating stomach ache, rash on face, nervous, mood swings, and headache	Treated with valium in the hospital.
SUS1-2003-	A 17 year-old male overdosed on multiple drugs including	Pulmonary congestion, terminal aspiration of	Completed suicide

00510	Adderall XR, Seroquel, Lamotrigine, Effexor, carbamazepine, and sertraline in foster home. Some were prescribed but Adderall XR was given by a friend.	gastric contents, cerebral edema. Blood level of amephetamine at 2.2mcg/ml which is the only medication reached and was higher than its lethal level (1.0mcg/ml).	

10.2 Review of Individual Study Reports

Since there is only one efficacy study, it is integrated in the Section of Integrated Review of Efficacy.

10.3 Line-by-Line Labeling Review

The sponsor submits the annotated labeling in Vol. 4.2. The review of labeling here is focused on clinical aspect. Please see other disciplinary reviews for their comments.

1) In Vol 4.2, page 2-6, the sponsor inserts a section for adolescents, at the bottom of the page, in which it states, (b) (4) .

2) Continuing on the next page, from lines 3-4, the sponsor states, (b) (4) the sponsor must remove this sentence.

3) On page 2-12, the sponsor lists common adverse events in adolescents from this trial in Table 2. (b) (4)

All other clinically related changes are appropriate.

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

/s/

June Cai
2/24/05 04:58:00 PM
MEDICAL OFFICER

Paul Andreason
3/1/05 10:37:31 AM
MEDICAL OFFICER
I agree that this supplement is approvable. Please see my memo to the file dated March 1, 2005.